Microwave tissue ablation of primary and secondary lung cancer

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Assessment report

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The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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CONTENTS

TABLES

BOXES

FIGURES

EXECUTIVE SUMMARY

Main issues for MSAC consideration:

- Clinical input suggests that approximately 90 per cent of lung microwave tissue ablation (MTA) procedures conducted in Australia are for early stage non-small cell lung cancer (NSCLC), and 10 per cent are for oligometastatic disease. Clinical input also suggests that stereotactic body radiation therapy (SBRT) is the main comparator to ablative technologies, as both SBRT and MTA are primarily offered to patients who are not eligible for surgical resection.
- The evidence for lung MTA in patients with inoperable early stage NSCLC, and in patients with pulmonary oligometastatic disease in whom the primary cancer is under control, was comprised entirely of retrospective Level IV (case series) studies with small sample sizes. The evidence base for the comparator interventions – radiofrequency ablation (RFA), radiotherapy and surgical resection – was also limited by study design (predominantly Level IV case series).
- These limitations introduced significant uncertainty in the clinical evidence, and precluded any direct or indirect comparison of the clinical benefits of lung MTA relative to the comparators. Therefore, statistical tests of non-inferiority of lung MTA relative to the comparator interventions could not be performed.
- Pneumothorax was the most common adverse event associated with MTA (median 30%, range 8–64%, 20 studies), a proportion of which require chest tube placement (median 10%, range 0–29%). Other adverse events were reported variably. Procedure-related deaths were rare (0.2%, 2/916, 23 studies).
- Due to the uncertain clinical benefit associated with lung MTA, the economic evaluation was conducted using a cost-minimisation approach. Similarly, the economic evaluation reflects clinical input regarding the main comparator and the breakdown of patients by indication.
- The cost of lung MTA is affected by the choice of treatment modality, i.e. whether it is performed as an inpatient or outpatient procedure, and whether the service is provided through general or local anaesthetic. If the procedure were reimbursed, there may be a shift of service to increased numbers of outpatient procedures and the use of local anaesthesia.
- Clinical input has suggested that lung MTA is not currently used for palliative therapy in Australia, as patients would be more likely to receive systemic therapies. This advice is reflected in the economic evaluation of lung MTA, which does not include this group of patients.
- In the base case of the economic evaluation, SBRT is the least costly intervention ($5,372.95 over three months for less than three lesions), followed by MTA ($7,843.83), with surgery (for population two) being the most expensive option ($19,472.05). In terms of financial impact, annual net Medicare Benefits Schedule costs will decrease over the 5-year horizon, related to a substitution of SBRT, which has a higher rebate, and with an increasing capacity of provision of lung MTA services over time.

APPLICATION 1403: MICROWAVE TISSUE ABLATION FOR PRIMARY AND SECONDARY LUNG CANCER

This contracted assessment examines the evidence to the support listing of microwave tissue ablation (MTA) on the Medicare Benefits Schedule (MBS). The service would be used in the inpatient setting, and potentially in the outpatient setting, for the treatment of primary and secondary lung cancer. The applicant has claimed that the successful listing of the technology in the proposed target populations and setting will lead to MTA being used as an additional therapeutic option.

Alignment with agreed protocol

This assessment report deviates from the protocol that was ratified by the Protocol Advisory Sub Committee (PASC) in two key ways. First, it was not possible to stratify the analysis by primary tumour type as suggested in the protocol, due to limitations in the identified evidence. Second, it was not possible or appropriate to undertake a cost-effectiveness analysis as suggested in the protocol, because the clinical literature identified was not suitable for statistical tests of non-inferiority of MTA relative to the comparators. Rather, a cost minimisation approach has been used.

Proposed medical service

MTA is an ablative therapy which destroys cancerous cells through the percutaneous delivery of high-frequency electromagnetic radiation (Dupuy 2009). In Australia, MTA is typically performed in an inpatient setting under general anaesthesia. Patients undergo a computed tomography (CT) scan of the ablation zone at one-, four- and 24-hours after the procedure to monitor treatment success and adverse events. MTA is not currently reimbursed under the MBS and is largely performed within the public system.

Proposal for public funding

The application requests the listing of six new 'Category 3 – Therapeutic Procedures' items on the MBS (Table 1). The proposed items are graduated based on the number of ablated lesions, and are intended to cover the cost of pre-, intra- and post-operative imaging. This includes a limited planning scan, intra-operative image guidance, and a post-ablation control scan. The proposed fee has been adopted from Application 1402 (MTA of liver tumours). Application 1402 states:

> *"A $1300 fee for ablation of 2–3 lesions, a $1600 fee for ablation of 4–5 lesions and a $2000 fee for ablation of >5 lesions. The higher fee for >5 lesions reflects the increased risk to the patients such as collateral damage as well as more skill, time and expertise required of the physician to ensure better patient outcomes."*

Table 1 Proposed MBS items for microwave tissue ablation of lung cancer

Category 3 – THERAPEUTIC PROCEDURES
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00

Proposed population(s)

There are three proposed populations eligible for MTA of primary or secondary lung cancers:

1. Patients with early stage non-small cell lung cancer (NSCLC) who are not eligible for surgical resection, and who are receiving treatment with curative intent. Prevalence is difficult to estimate for this population. For the economic evaluation, it has been estimated that 31 per cent of NSCLC is localised at diagnosis (Barton 2013), or approximately 2250 cases in 2014.

2. Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease). Because this

population includes patients with lung metastases from any primary cancer, it is not possible to estimate of the number of patients who might be eligible for MTA in this group.

3. Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment. Because this population is broad, no estimates of population size can be determined. Australian clinicians have indicated that MTA is not currently used for palliation.

Comparator details

The number and type of comparators to MTA depends on the population, as illustrated in Table 2. The relevant MBS item descriptor/s for the relevant comparator/s is summarised in Section A.5.

Table 2 Comparator(s) to MTA in the proposed populations

Population	Comparator(s)
Population one (early stage non-small cell lung cancer)	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy
Population two (oligometastatic disease)	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy 3) Surgical resection
Population three (palliative therapy)	1) Conventional palliative therapy without microwave ablation

Clinical management algorithm(s)

In population one (NSCLC), MTA is intended to be a direct replacement for radiofrequency ablation (RFA), and an additional therapeutic option to current best practice radiotherapy with or without chemotherapy. In population two (oligometastases), MTA is intended to be a direct replacement for RFA, and an additional therapeutic option to surgical resection or current best practice radiotherapy with or without chemotherapy. In population three (palliative), MTA is intended to be an additional treatment option to conventional palliative treatments for NSCLC and pulmonary metastases. The current and proposed algorithms are shown in section A.6.

Key differences in the delivery of the proposed medical service and the main comparator

The main differences in the delivery of MTA and the comparators are:

- RFA may require longer anaesthesia time than MTA, owing to increased ablation times.
- Conventional radiotherapy regimens are delivered over 30-45 sessions, while stereotactic body radiotherapy (SBRT) is delivered over 1–10 sessions. In contrast, MTA is usually performed in a single session. However, radiotherapy is provided on an outpatient basis and an overnight hospital stay is not required. SBRT also requires pre-treatment simulation with

a standard high-resolution CT scan, magnetic resonance imaging (MRI), angiography or positron emission tomography (PET) scan.

- Surgical resection is associated with an extended recovery period, requiring hospitalisation in all cases.

Clinical claim

Population one: The applicant claims that MTA offers superior effectiveness compared to RFA, and equivalent effectiveness compared to radiotherapy, with an acceptable safety profile.

Population two: In patients who are not eligible for surgery, the applicant claims that MTA offers superior effectiveness compared to RFA, and equivalent effectiveness compared to radiotherapy or chemoradiotherapy, with an acceptable safety profile. In patients who are eligible for surgery, the applicant claims that MTA has equivalent effectiveness to resection with acceptable safety.

Population three: MTA may improve symptom relief compared to conventional palliative therapy.

APPROACH T*aken to the* E*vidence* A*ssessment*

A systematic review of published literature was undertaken to identify all studies of MTA in the proposed populations. No studies that directly or indirectly compared MTA to a relevant comparator were identified. As a result, the evidence base was insufficient to inform the Medical Services Advisory Committee (MSAC) on the comparative safety, effectiveness and cost effectiveness of MTA. As MTA and RFA are technologically similar (both thermal ablative technologies), high quality comparative data for RFA compared to current MBS listed comparator services (SBRT and surgery) could inform a funding decision on MTA. Therefore, a second systematic search was conducted to identify all studies on RFA. No direct or indirect comparative evidence was identified, and as such, no form of meta-analysis or indirect comparison across interventions could be undertaken.

In order to contextualise the evidence base for MTA and RFA, pragmatic searches were executed to identify evidence for the remaining comparators—current best practice radiotherapy and surgical resection—across the three defined populations. The approach to searches is depicted in Figure 1. Section B.1 gives a more detailed explanation of searches and rationale. Full details of search strategies and databases searched are provided in Appendix B.

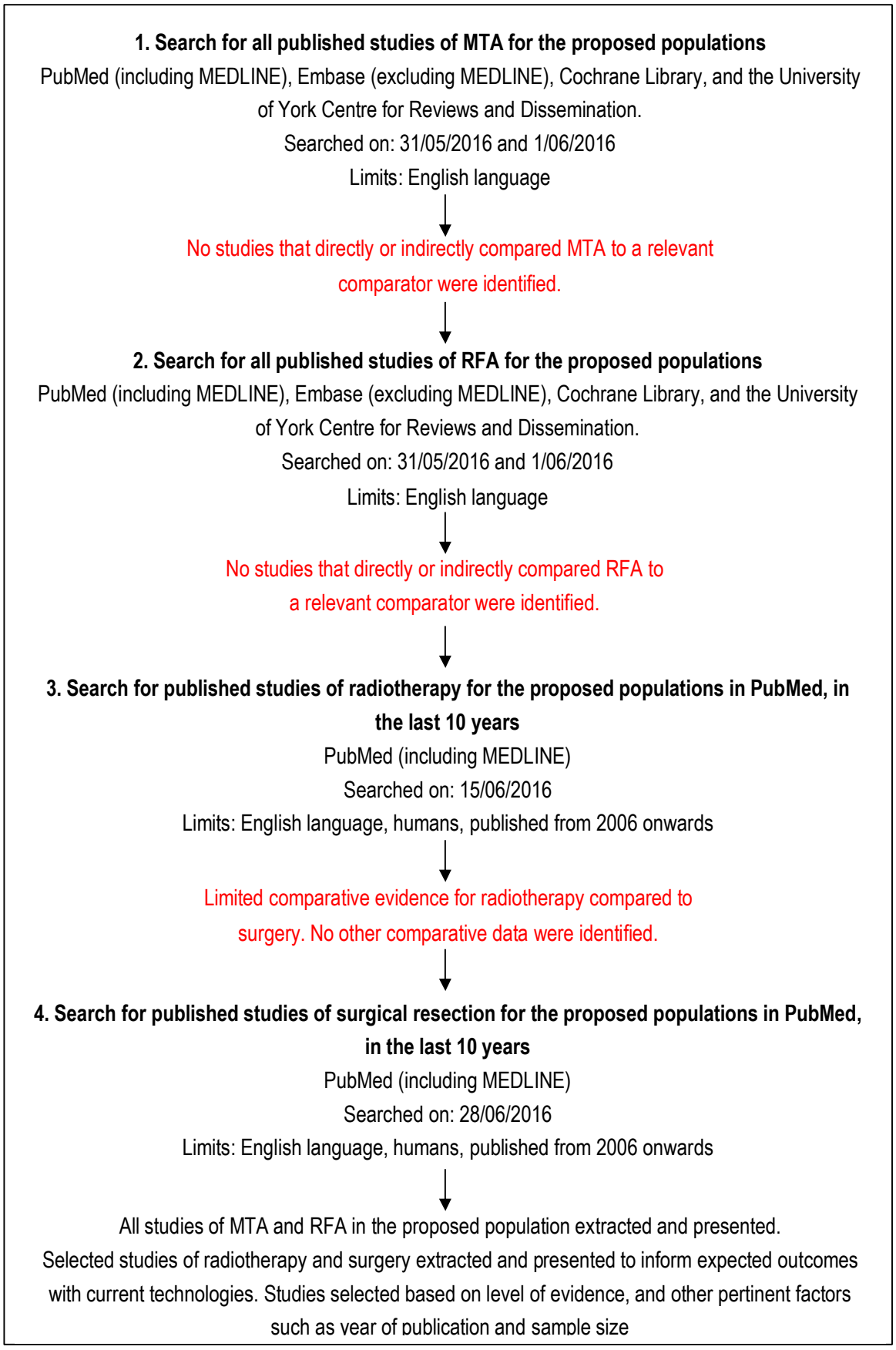

Figure 1 **Depiction of the step-wise approach to literature searches**

The level of evidence of included studies was ranked according to the National Health and Medical Research Council (NHMRC) levels of evidence (Merlin et al 2009). The quality of systematic reviews was evaluated using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool (Shea et al 2007). Randomised and non-randomised studies were evaluated using the Downs and Black checklist (Downs and Black 1998). Single arm case series were evaluated using the 'Quality Appraisal Checklist for Case Series Studies' developed by the Institute of Health Economics (Guo et al 2016). The overall quality of evidence for each outcome, across studies, was assessed using the GRADE methodology (Guyatt et al). Integration of this evidence to draw conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice is presented in Section B.8.

CHARACTERISTICS OF THE EVIDENCE BASE

No direct or indirect comparative trials of MTA were identified for population one and two, despite an extensive review of the published literature. Eight studies of MTA in the proposed populations were identified. An additional 15 case series studies were included for the safety of MTA, but which did not meet the inclusion criteria for effectiveness due to mixed populations. The evidence base for the intervention and its comparators is at a high risk of bias due to study design (predominantly Level IV case series), quality concerns, and poor reporting. Section B.3 and B.4 of the main report provides a comprehensive assessment of the characteristics of the evidence base. A summary of the number and type of identified studies for each intervention in presented in Table 3.

Table 3 Number and type of included studies for each intervention, in each study population

Intervention	Included studies (P1)	Included studies (P2)	Included studies (P3)
MTA	3 Level IV case series	2 Level IV case series	2 Level III-2 cohort 1 Level IV case series
RFA*	1 Level III-3 cohort 7 Level IV case series	11 Level IV case series **	1 Level IV case series
Radiotherapy	2 Level II RCT 1 Level III-1 cohort 1 Level III-2 cohort 1 Level III-3 historical control	3 Level III-2 cohort 14 Level IV case series	1 systematic review of 13 RCTs
Surgery	NA	2 systematic reviews 5 Level IV case series	NA

< NA = not applicable; MTA = microwave tissue ablation; RCT = randomised controlled trial; RFA = radiofrequency ablation >

* An existing systematic review published in 2008 was included for safety outcomes. It did not identify any prior studies of effectiveness that were relevant to the current evaluation.

** Yan et al 2006 and Yan et al 2007 reported different outcomes from the same sample population, over the same period. These publications have been reported as a single publication in the report.

Results

Limitations in the study design; sample size, and reporting of included studies for both the intervention and comparators have resulted in significant uncertainty in the clinical evidence, and precluded any direct or indirect comparison of the clinical benefits of MTA relative to the comparator interventions. Results across interventions are presented for context; conclusions regarding the comparative effectiveness or safety of interventions cannot be drawn.

Safety

Due to limited evidence, the overall safety of each comparator is described for treating lung cancer as a whole. The overall safety outcomes are summarised in Table 4.

Safety of MTA in the treatment of lung cancer

No comparative studies of the safety of MTA relative to the comparator interventions were identified for population one or population two. As a result, the inclusion criteria for MTA were broadened to include studies with mixed populations (i.e. primary or secondary cancer) to provide the MSAC with a more complete understanding of the safety profile of the technique.

Twenty-three studies, including two Level III-2 and 21 Level IV studies, reported the safety of MTA. Procedure-related mortality was rare, occurring in less than one per cent of all patients (2/916, <1%). Mortality within 30 days was also very low, occurring in less than one per cent of all patients (1/739, <1%). Serious adverse events were rarely reported. Pneumothorax was the most frequent adverse event associated with MTA, reported in 27 per cent of ablation sessions (median 30%, range 8–64%). Across studies, chest tube drainage or other intervention was required after 12 per cent (median 10%, range 0–29%) of ablation sessions. The majority of pneumothorax cases were self-limiting. Other adverse events included pneumonia (median 4%, range 3–15%), haemoptysis (48/545, 8.8%), pleural effusion (79/649, 12.2%), skin burns (6/325, 1.8%), post-ablation syndrome (32/285, 11.2%) and bronco-pleural fistula (4/360, 1.1%). The severity of adverse events was not consistently reported across studies.

Safety of RFA in the treatment of lung cancer

Nineteen studies reported the safety of RFA, of which one was Level III-3 and 18 were Level IV. Similar to MTA, the procedure-related mortality (1/1,259, 0.08%) and 30-day mortality (2/810, 0.25%) associated with RFA were very low. Pneumothorax was the most commonly reported adverse event, reported after 45 per cent of RFA sessions (median 24%, range 9–67%). Chest tube placement was required after 22 per cent of RFA sessions (median 9%, range 2–39%). Other adverse events were reported variably across studies, and as a result, it is difficult to summarise the

incidence of major and minor adverse events associated with RFA. Additional details regarding adverse events are provided in Section B.6.

Safety of current best practice radiotherapy in the treatment of lung cancer

Twenty-two studies reported the safety of radiotherapy in population one and two, including two Level II studies, five Level III-2 studies, one Level III-3 study, and 14 Level IV studies. There were two cases of procedure-related mortality across all included studies (2/887, 0.2%). Serious adverse events arising from radiotherapy were rare, such that the overall sample size for each population was too small to meaningfully represent the likelihood of key adverse events in each population. The majority of adverse events were reported according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, and were scored as grade 1 ("mild") or 2 ("moderate") in severity. The majority of studies reported no grade 3 ("severe") or higher adverse events. Thirty-four per cent (346/877) of patients experienced a grade 1 or 2 event across studies (median 42.5%, range 3–120%), while 3.3 per cent (34/887) of patients experienced a grade 3 event (median 0%, range 0–33%).

The relative safety of palliative radiotherapy regimens was recently summarised by a Cochrane review of 14 randomised controlled trials (RCTs). The review authors found no significant difference between rates of oesophagitis (mean 22% vs 26%, RR 1.23, 95% CI 0.81–1.87), radiation myelopathy (mean 0.3% vs 0.4%, RR 1.29, 95% CI 0.37–4.51), or radiation pneumonitis (mean 4% vs 2.4%, RR 0.62, 95% CI 0.23–1.66) for SBRT with less fractions compared to more fractions.

Safety of surgical resection in the treatment of lung cancer

Five Level IV studies and one recent systematic review reported safety of surgery (Table 4). The review by Pfannschmidt et al (2007) identified four of 20 included studies that reported postoperative mortality, which ranged from 0 to 2.5 per cent of patients. In the case series studies, immediate procedure-related mortality did not occur in any patients (0/365, 0%, 2 studies), and thirty day mortality occurred in 10 of 1,499 patients (0.67%, 4 studies). Adverse events were reported in 99 of 776 thoracotomies (13%) by Younes et al (2009), and in 83 of 532 patients (15.6%) by Rodriguez-Fuster et al (2014). Specific adverse events are reported in Section B.6 of the report.

Table 4 Safety outcomes relevant to all populations

Outcome and intervention/comparator	№ of patients Level of evidence	Summary	Quality of the evidence (GRADE)
Procedure-related mortality			
MTA F/U range 6–30 months	N = 916 1 Level III-2 studies 19 Level IV studies	2/916 (0.22%)[1]	⊕⊙⊙⊙ VERY LOW
RFA F/U range 10–46 months	N = 1259 1 Level III-3 study 16 Level IV studies	1/1259 (<0.1%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy F/U range 13–82 months	N = NA 2 Level II studies 2 Level III-2 studies 12 Level IV studies	2/778 (0.26%)[2]	⊕⊙⊙⊙ VERY LOW
Surgery F/U NA	N = NA 1 Level I study 2 Level IV studies	Pfannschmidt et al (2007) Range 0–3% of patients (4/20 studies) Renaud et al (2014), Kitano et al (2012) 0/365 (0%)	⊕⊙⊙⊙ VERY LOW
30-Day mortality			
MTA F/U range 6–30 months	N = 739 16 Level IV studies	1/739 (0.14%)	⊕⊙⊙⊙ VERY LOW
RFA F/U range 10–36 months	N = 810 1 Level III-3 study 7 Level IV studies	2/810 (<0.1%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy F/U range 13–82 months	N = NA 2 Level II studies 2 Level III-2 studies 12 Level IV studies	0/778 (0.0%)	⊕⊙⊙⊙ VERY LOW
Surgery F/u: NA	N = 1,499 4 Level IV studies	10/1,499 (0.67%)	⊕⊙⊙⊙ VERY LOW
Pneumothorax			
MTA F/U range 6–30 months	N = 1025 (sessions) 2 Level III-2 studies 20 Level IV studies	280/1025 (27.3%) Median: 30.2 (8.3–63.8%)	⊕⊙⊙⊙ VERY LOW
RFA F/U range 12–46 months	N = 1497 (sessions) 1 Level III-3 study 18 Level IV studies	Per ablation: 674/1497 (45%), median 24% (9–67%) Per patient: 46/262 (18%), median 17.5% (5–36%)	⊕⊙⊙⊙ VERY LOW

Outcome and intervention/comparator	№ of patients Level of evidence	Summary	Quality of the evidence (GRADE)
Pneumothorax with intervention			
MTA F/U range 6–30 months	N = 985 (sessions) 2 Level III-2 studies 18 Level IV studies	122/985 (12.4), median 10.3 (0–28.6%)	⊕⊙⊙⊙ VERY LOW
RFA F/U range 12–46 months	N = 1497 (sessions) 1 Level III-3 study 18 Level IV studies	Per ablation 335/1497 (22%), median 9% (2–39%) Per patient 29/262 (11%), median 10% (3–24%)	⊕⊙⊙⊙ VERY LOW

< F/U = follow-up; NA = not applicable >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ **Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. One death was delayed (occurring eight months after the procedure).
2. Videtic et al (2015) reported one death 319 days after the procedure due to respiratory failure. Oh et al (2012) reported one death from respiratory failure five months after receiving SBRT.

EFFECTIVENESS

No comparative studies were identified to inform an assessment of comparative effectiveness of MTA. The evidence for both the intervention and its comparators is largely characterised by Level IV evidence with variable outcome measures and incomplete reporting. The claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by published evidence. For a more complete discussion of the contextual interpretation of the evidence, see Section B.8.

The tables below (Table 5, Table 6, and Table 7) provide a summary of findings for selected outcomes that were reported across multiple comparators. Other effectiveness outcomes are reported in Section B.6. It is important to note that information for comparators should not be directly compared with MTA, as data in tables is drawn largely from case series studies.

Table 5 Effectiveness outcomes relevant to population one

Outcome and intervention/comparator	№ of studies Level of evidence	Summary	Quality of the evidence (GRADE)
Overall survival rate			
MTA Assessed with: Kaplan-Meier estimate (95% CI not reported) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 1-year 91.7%, 2-year 76.5%, 3-year 47.9% and 4-year 47.9% Yang et al (2015) [2] 1-year 89%, 2-year 63%, 3-year 43%, and 5-year 16%	⊕⊙⊙⊙ VERY LOW [1]
RFA Assessed with: Kaplan-Meier estimate (95%CI not reported) F/U range 19 to 46 months	1 Level III-3 study 7 Level IV studies	Median survival rate, pooled 1-year 86.3% (range 83–100%) 2-year 74% (range 69.8–86%) 3-year 62.8% (range 40–74%) 5-year 28% (range 14–61%)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Assessed with: varied instruments F/U range 21 to 30.2 months	1 Level II study 1 Level III-1 study[5]	Videtic et al (2015) *1-year survival* 34/1 GY SBRT = 48.6% (95% CI 68.9–92.8%) 48/4 GY SBRT = 91.1 (95% CI 78.0–96.6%) *2-year survival* 34/1 GY SBRT = 61.3% (95% CI 44.2–74.6%) 48/4 GY SBRT = 77.7% (95% CI 62.5–87.3%) Koshy et al (2015) *3-year survival* No therapy = 28% , Conventional radiotherapy = 36%, SBRT = 48% A propensity-matched cohort reported 3 year overall survival with SBRT of 48% and with conventional radiotherapy of 40% (p = 0.001).	⊕⊕⊙⊙ LOW
Median survival time			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 35.0 months (95%CI 22.3–47.7) Yang et al (2014) 33.8 months (95%CI 31.9–35.7) [2]	⊕⊙⊙⊙ VERY LOW [5]

Outcome and intervention/comparator	№ of studies Level of evidence	Summary	Quality of the evidence (GRADE)
RFA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 19 to 37 months	6 Level IV studies	Median overall survival 42.8 months (range: 33.4–67)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Not reported	0 studies	NA	NA
Time to local progression			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 28.0 months (95%CI 17.7–38.3) Yang et al (2015) 45.5 months (95%CI: 28.8–61.8)	⊕⊙⊙⊙ VERY LOW [6,7]
RFA Assessed with: Kaplan-Meier estimate (95%CI) F/U 19 to 46 months	1 Level III-3 study[8] 3 Level IV studies	Ambrogi et al (2011) Median of 39 months (range NR) Lanuti et al (2012) mean (SD) of 12 (10) months, range 1–44 Liu et al (2012) mean (SD): 25 (11) months, range 4–35 Safi et al (2015) 11.9 ± 8.1 (1–24) months with RFA and 6.0 ± 3.0 (1–46) months with radiotherapy, p = 0.36 for test of significance	⊕⊙⊙⊙ VERY LOW [9]
Radiotherapy Not reported	0 studies	NA	NA

< F/U = follow-up; CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; RFA = radiofrequency ablation; SD = standard deviation; ± = SD; SBRT= stereotactic body radiotherapy >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊕⊙⊙ **Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Neither Han et al (2015) nor Yang et al (2015) provide confidence intervals associated with the point estimates, therefore the precision of these estimates is unclear. Similarly only Yang et al (2015) report maximum follow-up of >60 months (5 years).
2. Note that: Yang et al (2015) examined a subgroup of patients with tumours > 3.5 cm versus ≤ 3.5 cm and found that tumours ≤ 3.5 cm were associated with better survival than were tumours >3.5 cm (p = 0.016). The distribution in number of patients with tumours >3.5 cm across the two studies will affect the consistency of outcomes.
3. There is a wide range of survival rates reported with reporting becoming more and more limited over time. This should be a relatively homogenous group in terms of cancer stage and extent of disease. There is substantial concern that outcomes have been measured very differently across studies. For example Hiraki et al (2011) has a 5-year survival of 61% whilst Ridge et al (2014) reports only 14%.
4. Koshy et al (2015) is a Level III-1 retrospective propensity-matched cohort, Videtic et al (2015) is Level II study.
5. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95% CI than

Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.

6. It has been observed that authors appear to use the term recurrence/progression interchangeably. Han et al (2015): A focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage was considered local recurrence if technical success had been confirmed. Yang et al (2015): Local progression was referred to as the contrast enhancement by CT scans in the site of ablation.
7. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95% CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.
8. Safi et al (2015) is a Level III-3 retrospective cohort study that compared RFA and radiotherapy.
9. Estimates across different studies are markedly different, it may be due to differences in measurement, reporting or outcome.

Table 6 Effectiveness outcomes relevant to population two

Outcome and intervention/comparator	№ of Studies and level of evidence	Summary	Quality of the evidence (GRADE)
Overall survival rate			
MTA Assessed with: n/N (%) at 1 and 2 years Median F/U 9 months	1 Level IV study	Vogl et al (2015) 12 month survival 91% (73/80 patients alive), 24 month survival 75% (60/80 patients alive). Survival greater than 24 months NR.	⊕⊙⊙⊙ VERY LOW
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U range 12 to 38 months	10 Level IV studies	Median survival rate, pooled 1-year 87.8% (range 73.4–100%) 2-year 59.3% (range 41.1–94%) 3-year 53.0% (range: 30–85%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy Assessed with: Kaplan-Meier estimate (95%CI) F/U range 13 to 55 months	3 Level III-2 studies 14 Level IV studies	Median survival rate, pooled 1-year 86.0% (60.5–98%) 2-year 65.1% (31.2–86%) 3-year 61.5% (50.1–73%) 5-year 46.2% (39–56.2%)	⊕⊙⊙⊙ VERY LOW [1]
Surgery assessed with: varied measures Minimum F/U 30 days	2 Level I studies (of Level IV evidence) 2 Level IV studies	Young et al (2015) Meta-analysis of 5 year overall survival from 11 studies (387 patients) : 29.1% (95%CI; 24.1–35.3); I2 =0%, p = 0.462, d.f = 10 Pfannschmidt et al (2007) Median 5-year survival 48%, range 41%–56% Reza et al (2014) 3-year 48%, 5-year 42%, 10-year 31% Kitano et al (2012) 2-year 53.9%, 5-year 40.9%	⊕⊙⊙⊙ VERY LOW
Median survival time			
MTA Not reported	0 studies	NA	NA

Outcome and intervention/comparator	№ of Studies and level of evidence	Summary	Quality of the evidence (GRADE)
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U range 12 to 38 months	10 Level IV studies	Median overall survival 44 months (range 21–67)	⊕⊙⊙⊙ VERY LOW [2]
Radiotherapy Assessed with: Kaplan-Meier estimates (95%CI) F/U range 13 to 55 months	1 Level III-2 study 10 Level IV studies	Median overall survival 27.8 months (range 12–42.8)	⊕⊙⊙⊙ VERY LOW [2]
Surgery assessed with: Kaplan-Meier estimate (95 % CI) F/U not reported	3 Level IV studies	Renaud et al (2014) No lymph node involvement: 94 months (95%CI, 76.3–111.7) positive lymph node involvement: 42 months (95%CI, 30.1–53.9; p<0.0001) Hilar location of lymph node involvement: 47 months (95%CI, 29.9–64.1) Mediastinal location of lymph node involvement: 37 months (95%CI, 14.0–60.0; p>0.05) Solitary pulmonary metastasis: 81 months (95%CI, 60.8–101.2) Multiple metastases: 55 months (95%CI, 35.1–74.9; p<0.01) Hepatic metastases: 47 months (95%CI, 21.6–72.4) No hepatic metastases: 74 months (95%CI, 60.7–87.3;. p<0.01) Reza et al (2014) 35 months (95%CI 23–61) Kitano et al (2012) 26.5 months (range: 0.7–165)	⊕⊙⊙⊙ VERY LOW [2]
Time to local progression			
MTA Assessed with: Mean time in months (range) F/U range 9 to 14 months	2 Level IV studies	Qi et al (2015) 7.2 months (range 4–20) Vogl et al (2015) 6 months (range: 1–18)	⊕⊙⊙⊙ VERY LOW
RFA Assessed with: mean (range) months/Kaplan-Meier estimate (95%CI) F/U range 12 to 38 months	5 Level IV studies	Median time to local progression 12 months (range: 8.2–15 months)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Assessed with: median months until progression	1 Level III-2 study 6 Level IV studies	Median time to local progression 10.8 months (range: 5–18)	⊕⊙⊙⊙ VERY LOW [3]

Outcome and intervention/comparator	№ of Studies and level of evidence	Summary	Quality of the evidence (GRADE)
F/U range 15 to 24 months			
Surgery Not reported	0 studies	NA	NA

< CI = confidence interval; F/U = follow up; MTA = microwave tissue ablation; NA = not applicable; RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Studies report a large range of survival rates with many studies not providing any indication of the variance associated with point estimates. At later time points less results are available.
2. Studies included investigated a range of prognostic factors and different studies reported on patients with different primary cancers. This is likely to have affected the overall survival time of included patients.
3. Studies report a range of time to progression estimates and it is not clear whether they were measured in a consistent manner.

Table 7 Effectiveness outcomes relevant to population three

Outcome and intervention/comparator	№ of Studies and level of evidence	Summary	Quality of the evidence (GRADE)
1 year survival			
MTA versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U range 6 to 35 months	1 Level III-2 study (Sun et al 2015)	MTA: 9/18 (50%) MTA + chemotherapy: 17/22 (77.3%)	⊕⊙⊙⊙ VERY LOW[1,2]
2-year survival			
MTA versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U range 6 to 35 months	1 Level III-2 study (Sun et al 2015)	MTA: 5/18 (27.7%) MTA + chemotherapy: 13/22 (79.1%)	⊕⊙⊙⊙ VERY LOW[1,2]
Median survival time			
Chemotherapy versus MTA + chemotherapy Assessed with: Kaplan-Meier estimate F/U median 21 months	1 Level III-2 study (Wei et al 2015)	MTA + chemotherapy: 23.9 (95%CI15.2–32.6) months Chemotherapy: 17.3 (95%CI 15.2–19.3) months, difference p = 0.140	⊕⊙⊙⊙ VERY LOW[1,3,4]
MTA alone Assessed with: Median and range F/U median 17.7 months	1 Level III-2 study (Wei et al 2015)	Median OS: 17.7 months (range of 5–45) and from the time of MTA until death it was 10.6 months (range: 3.1–36.2).	⊕⊙⊙⊙ VERY LOW[1,5]

< CI = confidence interval; F/U = follow-up; MTA = microwave tissue ablation; NA = not applicable >

GRADE Working Group grades of evidence (Guyatt et al., 2013),

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Based on the results of one study with 22patients in one arm and 18 in the other, study reporting quality was low.
2. Measures of variance are not available. The small sample size reduces the reliability of the outcomes
3. Wei et al (2015) reports on small sample sizes and inherent drawbacks in study design are problematic
4. Measures of variance show wide confidence intervals associated with OS. The small sample size reduces the reliability of the outcomes.
5. Due to inherent limitations in case series evidence

Summary of the clinical evidence

Based on the evidence identified, the MSAC should consider the following:

- In **population one (early stage, inoperable NSCLC)**, MTA has uncertain safety and effectiveness compared to RFA and current best practice radiotherapy.
- In **population two (oligometastatic lung disease)**, MTA has uncertain safety and effectiveness compared to current best practice radiotherapy and RFA. MTA appears to have superior procedure-related mortality and uncertain effectiveness compared to surgery.
- In **population three (palliative care)**, MTA has uncertain safety and uncertain effectiveness compared to best supportive therapy.

Translation issues

The claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by any published studies. As such it was not necessary or appropriate to undertake any translation of the evidence presented in Section B for the purposes of an economic evaluation.

Economic evaluation

A cost-minimisation analysis was undertaken to examine the cost implications of MTA, versus SBRT in populations one and two, and also against surgery in population two. MSAC (2016) noted that where an intervention is proven to be no worse than its main comparators in terms of both effectiveness and safety (i.e. there is no clear efficacy benefit) a cost minimisation approach should be employed.

This type of approach has been undertaken in the past for an assessment of radiotherapy technology where the evidence base was limited. For example, in the case of IGRT, MSAC (2015) concluded that due to the lack of evidence (the quality of the available studies was deemed to be poor with inconsistent evidence of safety and clinical effectiveness) for any significant benefit in clinical outcomes between IGRT and non-IGRT, a cost minimisation analysis was appropriate.

Model inputs

Costs for MTA, RFA and surgery were obtained from MBS, the applicant, and the National Hospital Cost Data Collection Australia Public Hospitals Cost Report Round 18. They are specified for patients with < 3 lesions and 3–5 lesions as the protocol proposed a graduated fee structure for MTA based on this lesion grouping. Discussion with clinicians indicated that patients with more than five lesions and those undergoing palliative care would rarely receive MTA. Costs are not estimated for these patients.

Model results

The total average costs for MTA, SBRT and surgery are presented as the cost per patient over the course of 3 months of treatment. They are presented in Table 8 for populations one and two, by lesion grouping. It is evident that the total average cost of SBRT is less than that of MTA for populations one and two across all included lesion groupings. For less than three lesions, the average cost of MTA is $2,471 higher than for SBRT. The key items driving increased costs are the costs of the disposable applicator and the overnight hospital stay. In the case of the applicator this cost is $2,960 and the hospital stay is $873 per night. In the longer term, the MTA procedure may be delivered on an outpatient basis, which would reduce the cost margin.

Table 8 Health care costs per patients (3 months) for base-case analysis

Resource item description	MTA	SBRT	Incremental cost of MTA vs SBRT	Surgery	Incremental cost of MTA vs Surgery
Population and Lesions	Population 1 and 2, <3 lesions			Population 2 , <3 lesions	
Specialist services – screening prior to intervention	1,557.55	1,557.55	0.00	1,557.55	0.00
Specialist services – intervention (MBS supported)[1]	1,866.68	3,168.90	-1,302.22	2,814.33	-947.65
Specialist services – intervention (Hospital)	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	293.50	2,916.50	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	7,843.83	5,372.95	2,470.88	19,472.05	-11,628.22
	Population 1 and 2, <3–5 lesions			Population 2 , <3–5 lesions	
Specialist services – screening prior	1,557.55	1,557.55	0.00	1,557.55	0.00

Resource item description	MTA	SBRT	Incremental cost of MTA vs SBRT	Surgery	Incremental cost of MTA vs Surgery
to intervention					
Specialist services – intervention (MBS supported)	2,166.68	3,494.90	-1,328.22	2,814.33	-647.65
Specialist services – intervention (Hospital)	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	329.62	2,880.38	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	8,143.83	5,735.07	2,408.76	19,472.05	-11,328.22

< MTA = microwave tissue ablation; SBRT= stereotactic body radiotherapy >

[1] Total average cost including MBS fee and gap. MBS reimbursement implications are outlined in Section E.

A similar result was observed for the MTA and SBRT comparison for 3–5 lesions. Surgery is costlier when compared to MTA across both lesion groupings. Sensitivity analysis was undertaken for key parameters used in the economic evaluation for the MTA and SBRT comparison. Unsurprisingly, the model was shown to be most sensitive to hospital costs, inclusion of adverse events for MTA and the cost of the probe. Even with a 10 per cent variation in many of these items MTA is still costlier when compared to SBRT. The complete removal of the hospital overnight stay still results in MTA being more expensive, albeit at lesser margin. MTA was found to be less expensive compared to surgery across the range of variation in all key parameters.

Estimated extent of use and financial implications

Within Australia it is expected that 3,215 patients in year one will have early stage NSCLC and 1,833 of them will be ineligible for, or not elect, surgery, increasing to 2,031 patients in year five. Additionally, a smaller number of patients with pulmonary metastases, in whom the primary tumour is under control, will be eligible for MTA under the proposed MBS items. This is estimated to be equivalent to 10 per cent of the early stage eligible population. An uptake rate of 10% for MTA among these patients has been assumed for the first 5 years to account for developing treatment capacity and educating radiologists. A total of 202 MTA procedures are estimated in Year 1 increasing to 1,117 in Year 5.

The number of MTA procedures is disaggregated by lesion groupings. Discussions with clinical experts indicated most ablation would involve less than 3 lesions. Correspondingly, 90% of the 202 MTA procedures forecast for Year 1 will involve the proposed fee associated with less than three lesions. While 181 MTA procedures are estimated for <3 lesions, around 10% of all MTA procedures,

or 20, are estimated for 3–5 lesions. No MTA procedures are estimated for patients with more than 5 lesions. The cost to the MBS from MTA uptake is estimated to be $0.61 million in year one, increasing to $3.41 million in year 5 based on these projections. MTA would largely replace SBRT, which entails a higher MBS rebate. Consequently, there is an annual net MBS cost saving of $0.30 million in Year 1 to a saving of $1.64 million in Year 5. These budget impacts are outlined in Table 9.

Table 9 Total estimated additional costs to MBS of changes in services ($)

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake estimate	10%	20%	30%	40%	50%
Anticipated total number of MTA procedures per year	202	414	636	871	1,117
Procedures by Lesion Grouping					
1–3total cost per patient (90%)	181	372	573	784	1,005
3–5 lesions total cost per patient (10%)	20	41	64	87	112
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	202	414	636	871	1,117
MTA MBS Costs by Lesion Grouping					
1–3total cost per patient (90%)	549,161	1,126,565	1,733,634	2,371,868	3,042,840
3–5 lesions total cost per patient (10%)	65,554	134,480	206,946	283,133	363,228
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	614,715	1,261,044	1,940,581	2,655,001	3,406,068
SBRT MBS Costs by Lesion Grouping (Item 15600)					
1–3total cost per patient (90%)	815,107	1,672,134	2,573,194	3,520,509	4,516,418
3–5 lesions total cost per patient (10%)	96,829	198,638	305,678	418,213	532,779
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	911,937	1,870,773	2,878,872	3,938,722	5,049,197
Net MBS Costs	-296,546	-608,343	-936,160	-1,280,805	-1,643,129

MBS = Medicare benefits schedule; MTA = microwave tissue ablation for primary and secondary lung cancer.

The costs of the MTA machine, and probes are borne by private health funds, patients or hospitals (state and territory budget). The base case estimate assumes the number of MTA patients increases from 202 to 1,117 per year, leading to a total cost of the machines of $0.05 million in year one increasing to $0.28 million in year five. The cost of probes and hospital stays also increase. Probes are the largest cost item – increasing from $0.60 million in Year 1 to $3.31 million in Year 5. The total

cost to private health funds and hospitals in year five is $13.42 million. This is substantially more than the net impact to the MBS. Variables such as the proportion of lung cancer that is NSCLC, the relative size of population one and two patient numbers, and assumed uptake have an impact on net MBS expenditures. Increases in these parameters generally increase the MBS net cost savings, as a higher number of SBRT procedures are being substituted.

ACRONYMS AND ABBREVIATIONS

AHRT	Accelerated hypofractionated radiotherapy
AIHW	Australian Institute of Health and Welfare
AMSTAR	A Measurement Tool to Assess Systematic Reviews
ARTG	Australian Register of Therapeutic Goods
CHART	Continuous hyperfractionated accelerated radiation therapy
COPD	Chronic obstructive pulmonary disease
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDG	Fludeoxyglucose (18F)
FRANZCR	Fellow of the Royal Australian and New Zealand College of Radiologists
HCC	Hepatocellular carcinoma
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IGRT	Image-guided radiation therapy
IHE	Institute of Health Economics
IQR	Interquartile range
MBS	Medicare Benefits Schedule
MD	Mean difference
MeSH	Medical subject heading
MSAC	Medical Services Advisory Committee
MTA	Microwave tissue ablation

NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NHMRC	National Health and Medical Research Council
NSCLC	Non-small cell lung cancer
NSW	New South Wales
OL	Open label (unblinded)
OS	Overall survival
PASC	Protocol Advisory Sub-Committee
PET	Positron emission tomography
PF	Progression-free
PFS	Progression free survival
PICO	Population, Intervention, Comparator, Outcome
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFA	Radiofrequency ablation
RT	Radiotherapy
RTOG	Randomised controlled trial Radiation Therapy Oncology Group
SBRT	Stereotactic body radiation therapy
SCLC	Small cell lung cancer
TACE	Transarterial chemoembolization
TGA	Therapeutic Goods Administration
TTLP	Time to local progression
US	Ultrasound
VEGF	Serum vascular endothelial growth factor
WHO	World Health Organisation

SECTION A CONTEXT

This contracted assessment of microwave tissue ablation (MTA) for the treatment of primary and secondary lung cancer is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

ASERNIP-S of the Royal Australasian College of Surgeons has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of MTA for the treatment of primary and secondary lung cancer. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded. Appendix A provides a list of the people involved in the development of this assessment report.

The proposed use of MTA in Australian clinical practice was outlined in a protocol that was presented to, and accepted by, the PICO Confirmation Advisory Sub-Committee (PASC). The protocol was released for public comment on 5 October 2016.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This contracted assessment addresses most of the PICO elements that were pre-specified in the protocol that was ratified by the PASC. However, the protocol advises that the assessment should stratify population two into two groups with respect to their primary tumours: those with sarcoma (bone and soft tissue) and those with non-sarcoma primary cancers. Unfortunately, the published literature was not amenable to such stratification. Additionally, because the clinical literature identified is not suitable for a statistical test of non-inferiority of MTA as compared to any of its comparators in any of the populations it was not possible or appropriate to undertake the cost-effectiveness analysis suggested by the protocol. Rather a cost minimisation approach has been used.

A.2. PROPOSED MEDICAL SERVICE

MTA for primary or secondary lung cancer has not previously been assessed by MSAC.

Description of the proposed service

MTA is a thermo-ablative technique that uses high frequency electromagnetic energy to produce large ablation volumes in short procedure times (up to ten minutes per ablation cycle), with high accuracy and predictability (Dupuy 2009). Microwaves are the part of the electromagnetic spectrum with frequencies ranging from 900 to 2450 MHz, lying between infrared radiation and radio waves (Banik et al 2003). Microwave is a non-ionising radiation and therefore does not contain sufficient energy per quantum to ionise (or completely remove an electron from) atoms or molecules. Consequently, microwave does not induce DNA damage in individual cells (Banik et al 2003; Ong et al 2009). Microwave radiation causes water molecules in tissue to oscillate between two to five billion times per second, generating heat from the friction and subsequently leading to cell death through coagulation necrosis (Lu et al 2012b; Ong et al 2009; Simon et al 2005).

In the clinical application of MTA, a thin microwave antenna is positioned in the centre of the tumour (Ong et al 2009). These antennae are straight applicators with active tips ranging in length from 0.6 to 4.0 cm. They can be single, dual or triple antennae which are simultaneously activated, and have either a straight or looped configuration affecting ablation volume (Meredith et al 2005; Yu et al 2006).

A microwave generator then emits electromagnetic waves at a frequency of up to 2.45 GHz, with powers ranging from 20W to 140W through the non-insulated portion of the antenna to surrounding tissue (Dong et al 2003; Seki et al 2000). The microwave field allows for direct and uniform deposition of energy into tissue several centimetres from the antenna, rather than relying upon current flow and resistive heating. Tumours in this field are treated to over 60°C to achieve coagulation necrosis (Swan et al 2012). The average ablation duration ranges between 60 and 300 seconds (Kuang et al 2007). Lower frequency microwave radiation at 0.915 GHz can theoretically be applied at a power of 45W, requiring longer duration of ablation (Simon et al 2005; Yu et al 2006).

In the context of pulmonary lesions, MTA is administered percutaneously with computed tomography (CT). Ultrasound guidance is suitable for chest wall tumours, or tumours with broad pleural contact (He et al 2006a). However, it is rarely used and for the purposes of this application MTA is considered to be administered with CT. Within Australia, available MTA systems are either 902–928 MHz or 2400–2500 MHz. Independent clinical feedback has indicated that both systems have the same indication profile, but that high powered systems are considered superior owing to their ability to conduct larger ablations in shorter times.

Clinical input suggests that MTA of lung tumours is ideally suited to tumours that do not exceed 4.5 to 5.0 cm, which accounts for a 0.5 cm circumferential safety margin. In terms of the maximum number of lesions suitable for MTA per-procedure, a soft rule of maximally 5 lesions per hemithorax has been widely adopted; (Gillams et al 2013; Smith and Jennings 2015) however, the best long-term

survival rates are achieved in patients with up to two pulmonary metastases no larger than 3cm in diameter (de Baere et al 2015b).

Proposed clinical setting

The intervention is proposed to be delivered in an inpatient or outpatient setting in tertiary centres. Major complications of MTA procedures are a rare occurrence but may lead to severe consequences. In order to effectively manage major complications, vascular interventional radiology, cardiothoracic surgery and intensive care units should be accessible. These services are typically only available in specialised tertiary centres, and are not accessible in stand-alone private radiology clinics. Therefore, MTA is provided in radiology departments within larger public or private hospitals, with patients either being kept overnight or in a day surgery setting. A chest X-ray is required within 3–4 hours after the procedure to monitor complications. If no complications are observed patients may be discharged on the same day. Patients may be admitted as inpatients for overnight observation to monitor perioperative complications. If patients remain stable they can be discharged the following day. Local expert feedback has advised that MTA is usually provided as an inpatient service in Australia, with patients remaining in hospital overnight for monitoring.

Service delivery

Percutaneous MTA is provided by interventional radiologists familiar with pulmonary interventions. Interventional radiology is a clinical subspecialty of radiology, which involves the conduct of minimally invasive procedures under image guidance. Radiologists completing the Fellowship of the Royal Australian and New Zealand College of Radiologists (FRANZCR) qualification are considered competent to perform interventional radiology procedures. The Interventional Radiology Society of Australia (IRSA) defines two tiers of intervention radiology competence (Interventional Radiology Society of Australasia (IRSA) 2015):

- Tier A: includes basic diagnostic angiography and interventional techniques including angiography, nephrostomy, abscess drainage and biopsy. Tier A falls within the scope of requirements of RANZCR Fellowship training and any individual with FRANZCR may perform them.
- Tier B: includes a number of more complex interventional procedures such as neuro-interventional procedures and oesophageal and duodenal stent placement etc. For these procedures accreditation is based on proof of a certain number of procedures performed at IRSA/RANZCR accredited sites.

No formal requirements beyond FRANZCR are currently required to perform MTA procedures. However, hospitals may apply their own credentialing standards to determine that the radiologist is suitably trained, competent, has the required clinical team support, and permitted to perform these procedures in the local setting. It is preferable, but not formally required, that interventional radiologists wishing to conduct MTA procedures conduct prior bench work or observation of procedures.

The pre-procedure patient preparation is similar to that for a CT-guided lung biopsy, added by the requirement of booking an overnight bed. Patients may be contraindicated for MTA if they have tumours abutting the hilum, large blood vessels or bronchi, severe coagulation disorders, or recently used anticoagulants (Schneider et al 2013; Simon et al 2005).

MTA is administered percutaneously, under CT image guidance to localise and position a thin microwave antenna into the centre of the target tumour (Simon et al 2005). A microwave generator emits electromagnetic waves at 915 MHz or 2.45 GHz through the non-insulated portion of the antenna to the surrounding tissue, with the consequent heat leading to cell death. During the procedure patients may receive conscious sedation or general anaesthesia.

The size, shape, location and vascular supply of the target lesion have an influence on the power and time required to complete an ablation. A single ablation is usually performed in less than 8 minutes, while overlapping ablations required in larger target lesions may add up to a total ablation time of 15–20 minutes. The procedure as a whole – including patient positioning and anaesthesia – typically takes between 1–1.5 hours.

A routine follow-up chest X-ray is performed 3–4 hours after the procedure, generally followed by a limited CT scan of the ablated area the morning after the procedure. The limited CT scan aims to assess the final thermal damage at the ablation site and potential salient complications (described in section 8.2); this scan is the baseline scan for comparison of future. Without complications requiring further action, the patient can be discharged after this CT scan.

Clinical feedback recommends routine CT imaging follow-up be performed at three, six and 12 months after ablation and yearly thereafter (Liu and Steinke 2013a). However, a recent literature review conducted by Cancer Australia concluded that optimal post-operative follow-up remain contentious (Cancer Australia 2013).

Marketing status of device / technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if the device is not listed on the ARTG. Items on the ARTG that are relevant to this application are shown in Table 10. There are four microwave ablation systems available in Australia:

- The Acculis MTA system (N Stenning & Co Pty Ltd, ARTG 174513, 195697, 1754514, 157722). This device uses 2.45GHz microwave energy.

- The Avecure Microwave Ablation / Coagulation System (Aurora BioScience Pty Ltd ARTG ID 200325). This device uses 902–928 MHz microwaves, and 32W.

- The Emprint™ Ablation System with Thermosphere™ Technology (by Covidien Pty Ltd, ARTG 226598, 178369, 152044). This system uses 1.4–1.5 GHz and 100W.

- The Amica microwave hyperthermia system (Culpan Medical Pty Ltd, 212509, 212510). The system uses 2.45 GHz and 20–140W.

Table 10 Microwave tissue ablation devices listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
200325	NA	Avecure Microwave Ablation / Coagulation System	Medical Device Class IIb	Aurora BioScience Pty Ltd
226598	NA	Emprint™ Ablation System with Thermosphere™	Medical Device Class IIb	Covidien Pty Ltd
178369	NA	Hyperthermia applicator, microwave, intracorporeal	Medical Device Class IIb	Covidien Pty Ltd
152044	NA	Hyperthermia system, microwave	Medical Device Class IIb	Covidien Pty Ltd
212509	NA	Hyperthermia system, microwave	Medical Device Class IIb	Culpan Medical Pty Ltd
212510	NA	Hyperthermia applicator, microwave, intracorporeal	Medical Device Class IIb	Culpan Medical Pty Ltd
157722	NA	Hyperthermia system, microwave	Medical Device Class IIb	N Stenning & Co Pty Ltd
174513	NA	Probe, hyperthermia, temperature monitoring	Medical Device Included Class IIa	N Stenning & Co Pty Ltd
174514	NA	Hyperthermia applicator, microwave, intracorporeal	Medical Device Included Class IIb	N Stenning & Co Pty Ltd
195697	NA	Trolley, general-purpose	Medical Device Included Class 1	N Stenning & Co Pty Ltd

< ARTG = Australian register of therapeutic goods; NA = not applicable >

Source: Therapeutic Goods Administration, accessed 14 June 2016, Link to TGA.gov.au

Other indications

MTA can also be used for the ablation of tissue in other sites. In particular it has been used to ablate tumours of the liver. Ablation of liver lesions may be more established within Australian practice than ablation in the lung.

Current funding arrangements

The intervention is not currently funded under the MBS and no other ablative technologies such as radiofrequency ablation (RFA) are associated with MBS items for lung tumours. However, ablative procedures are currently provided at a number of tertiary sites around Australia. In particular it has been reported that pulmonary RFA has been conducted at the Royal Perth Hospital and the Royal Brisbane and Women's Hospital. For private patients it is understood that private health funds typically cover the cost of the consumables; however, gap-payments may be charged in addition to consumable costs. MTA is currently available at the Royal Adelaide Hospital and Royal Brisbane and Women's Hospital, funded through the public health system.

A.3. PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 11. The current application requests the listing of six new 'Category 3 – Therapeutic Procedures' items on the MBS (Table 11). The proposed items are targeted to three defined populations (described in the following section) graduated based on the number of ablated lesions, and are intended to cover the cost of pre-, intra- and post-operative imaging. This includes a limited planning scan, intra-operative image guidance, and a post ablation CT scan. The proposed fee has been adopted from Application 1402 (MTA of liver tumours). Application 1402 states:

> *"A $1300 fee for ablation of 2–3 lesions, a $1600 fee for ablation of 4–5 lesions and a $2000 fee for ablation of >5 lesions. The higher fee for >5 lesions reflects the increased risk to the patients such as collateral damage as well as more skill, time and expertise required of the physician to ensure better patient outcomes."*

According to the applicant, the number of tumours treated alters the complexity of the procedure. A graduated fee structure for the number of tumours treated should be supported by evidence of increased complexity and increased clinical benefits. To determine the value of a graduated fee, PASC has advised that the assessment phase should include a stratified survival analysis based on the number of ablated lesions.

As there is no Medicare item for lung RFA, the maximum rebate that can be received in private practice is $470.00 (MBS item 57341 for CT-guided interventions). The fee for RFA services for liver [both percutaneous and open/laparoscopic (50952)] is $817.10. It should be noted, the application

claims MTA has a faster ablation time which would result in less time overall spent in the radiology suite, and may impact on the cost of the procedure.

Table 11 Proposed MBS item descriptors for microwave tissue ablation of lung cancer

Category 3 – THERAPEUTIC PROCEDURES
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00

A.4. PROPOSED POPULATION(S)

Lung cancer is a major contributor to cancer-related mortality and burden of disease in Australia. It was the leading cause of cancer-related mortality in 2014 – accounting for 18.3 per cent of all cancer deaths (8,630 deaths) – and was the fifth most common primary cancer in Australia (excluding non-melanoma skin cancers) (Australian Institute of Health and Welfare (AIHW) 2014a). Lung cancer was responsible for 9.4 per cent of new cancer diagnoses in 2014 (11,580 cases), with an estimated age-standardised incidence rate of 54.8 cases per 100,000 men and 33.2 cases per 100,000 women (Australian Institute of Health and Welfare (AIHW) 2014a).

The high mortality rate associated with lung cancer is reflected in the current estimates of 5-year relative survival. In 2007–2011, the 5-year relative survival at diagnosis was 14.3 per cent (Australian Institute of Health and Welfare (AIHW) 2014a). There is a strong correlation between age and relative survival, with a sharp decline in 5-year relative survival between patients aged 15–24 (76%) and 25–44 (29%), followed by a more gradual decline towards patients aged 75+ (8.7%) (Australian Institute of Health and Welfare (AIHW) 2014a). However, the relative survival of lung cancer depends on the aetiology of the lesion.

Primary lung cancer

There are two broad categories of primary lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLCs accounted for 12.3 per cent (1,140 cases) of all lung cancers in 2007, and are derived from neuroendocrine precursor cells in the bronchi and bronchioles. They are characterised by aggressive progression and spread throughout the body (Australian Institute of Health and Welfare (AIHW) 2011a). Due to the manner in which SCLC progresses, patients with this form of cancer may not be suitable candidates for surgical resection and are often managed with palliative care. As a result, patients with SCLC are not considered to be appropriate candidates for MTA and are not included in the eligible patient populations.

In contrast, NSCLC accounted for 62.6 per cent (6,095 cases) of lung cancers in 2007, and may be derived from a range of bronchial epithelial progenitor cells. The main forms of NSCLC include squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (Australian Institute of Health and Welfare (AIHW) 2011a). They are characterised by slower growth and metastatic spread compared to SCLC (Australian Institute of Health and Welfare (AIHW) 2011a). Due to their slower rate of progression, NSCLC may be amenable to curative treatments, including surgical resection, radiotherapy, and chemoradiotherapy. Based on data from the United States, it is estimated that 16.1 per cent of NSCLC in males and 19.6 per cent of NSCLC in females remains localised at the time of diagnosis (Australian Institute of Health and Welfare (AIHW) 2011a).

Secondary lung cancer

Secondary lung cancers are metastases from primary malignancies found elsewhere in the body. The lungs are the second most common site of metastases. Breast, colorectal, lung, kidney, head and neck, and uterine cancers are the most common primary tumours leading to lung metastasis at autopsy (Seo et al 2001). Colorectal cancer, which accounts for 10 per cent of all cancers, accounts for 15 per cent of all cases of pulmonary metastases (Hirakata et al 1993). In total, 20 per cent of metastatic disease is isolated to the lungs.

The presence of pulmonary metastases tends to indicate advanced, disseminated disease; however, it can occasionally be an isolated event. The patients' prognosis depends on the primary tumour and whether it is under control as well as whether the pulmonary metastatic spread is an isolated event or part of disseminated disease. The applicant has suggested that sarcomas and thyroid, renal, head and neck cancers tend to metastasise predominantly or exclusively to the lung. In the setting of metastases confined to the lung with the primary tumour under control, the patient may be eligible for curative therapy.

There are three proposed population groups eligible for MTA of primary or secondary lung cancers. These groups include:

- Patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.
- Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease).
- Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment.

MTA is primarily intended to be used in patients with early stage NSCLC who are not candidates for surgical resection. This group includes 15 per cent of all NSCLC patients and 30 per cent of NSCLC patients over the age of 75 (Dupuy 2013). As lung cancer patient demographics are changing, with increasing age at time of diagnosis, invasive and costly therapies are becoming less attractive (Dupuy 2013). MTA may also be used in patients with pulmonary metastases where the number and site of metastases, or previous lung surgery, precludes them from further surgery (Hiraki and Kanazawa 2012).

It is necessary to specify different clinical management algorithms and PICO criteria for each of these populations as the appropriate comparator for each group differs according to disease stage and treatment intent. This has flow on effects for the expected health outcomes of each patient group.

A.5. COMPARATOR DETAILS

There are several comparators to MTA including radiofrequency ablation (RFA), current best practice radiotherapy and surgery. The number, and type, of comparators to MTA depends on the population, this is illustrated in Table 12.

Table 12 Comparator(s) in the three populations

Population	Comparator(s)
Patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy
Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease)	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy 3) Surgical resection
Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment	1) Conventional palliative therapy without MTA

For patients with early stage inoperable NSCLC being treated with curative intent the comparators include RFA and current best practice radiotherapy with or without chemotherapy. For patients with lung metastases, in whom the primary tumour is under control and who are receiving treatment with curative intent the comparators include RFA, surgical resection by any technique, and, current best practice radiotherapy with or without chemotherapy. For patients with NSCLC or lung metastases who are receiving treatment with palliative intent the comparator is conventional palliative therapy without MTA.

The MBS item descriptors for the relevant comparators are summarised below; clinical input has suggested a range of items could be used for stereotactic body radiation therapy (SBRT) (See Table 13 and Table 14) and that the item code for SBRT 15600 is rarely used for lung disease and is generally reserved for intracranial neoplasm. RFA is not widely diffused in the Australian healthcare system and is not currently associated with an MBS item.

Table 13 Radiotherapy treatments for lung cancer currently listed on the MBS

Category 3 – Therapeutic Procedures
MBS item 15215 RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (lung). Fee: $57.40; Benefit: 75% = $43.05; 85% = $48.80

Category 3 – Therapeutic Procedures
MBS item 15230 RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (lung). The fee for item 15215 plus for each field in excess of 1, an amount of $36.50.
MBS item 15555 SIMULATION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT), with or without intravenous contrast medium, if: 1. treatment set-up and technique specifications are in preparations for three-dimensional conformal radiotherapy dose planning; and 2. patient set-up and immobilisation techniques are suitable for reliable CT-image volume data acquisition and three-dimensional conformal radiotherapy; and 3. a high-quality CT-image volume dataset is acquired for the relevant region of interest to be planned and treated; and 4. the image set is suitable for the generation of quality digitally-reconstructed radiographic images. Fee: $710.55 Benefit: 75% = $532.95 85% = $631.05
MBS item 15565 Preparation of an IMRT DOSIMETRY PLAN, which uses one or more CT image volume datasets, if: (a) in preparing the IMRT dosimetry plan: (i) the differential between target dose and normal tissue dose is maximised, based on a review and assessment by a radiation oncologist; and (ii) all gross tumour targets, clinical targets, planning targets and organs at risk are rendered as volumes as defined in the prescription; and (iii) organs at risk are nominated as planning dose goals or constraints and the prescription specifies the organs at risk as dose goals or constraints; and (iv) dose calculations and dose volume histograms are generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded in the plan; and (v) a CT image volume dataset is used for the relevant region to be planned and treated; and (vi) the CT images are suitable for the generation of quality digitally reconstructed radiographic images; and (b) the final IMRT dosimetry plan is validated by the radiation therapist and the medical physicist, using robust quality assurance processes that include: (i) determination of the accuracy of the dose fluence delivered by the multi-leaf collimator and gantryposition (static or dynamic); and (ii) ensuring that the plan is deliverable, data transfer is acceptable and validation checks are completed on a linear accelerator; and (iii) validating the accuracy of the derived IMRT dosimetry plan in a known dosimetric phantom; and (iv) determining the accuracy of planned doses in comparison to delivered doses to designated points within the phantom or dosimetry device; and (c) the final IMRT dosimetry plan is approved by the radiation oncologist prior to delivery. Fee: $3,313.85 Benefit: 75% = $2,485.40 85% = $3,234.35

Category 3 – Therapeutic Procedures
MBS item 15275 RADIATION ONCOLOGY TREATMENT with IGRT imaging facilities undertaken: (a) to implement an IMRT dosimetry plan prepared in accordance with item 15565; and (b) utilising an intensity modulated treatment delivery mode (delivered by a fixed or dynamic gantry linear accelerator or by a helical non C-arm based linear accelerator), once only at each attendance at which treatment is given. Fee: $182.90 Benefit: 75% = $137.20 85% = $155.50
MBS item 15254 RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site for diseases and conditions not covered by items 15245, 15248 or 15251 Fee: $59.65 Benefit: 75% = $44.75 85% = $50.75
MBS item 15715 RADIATION ONCOLOGY TREATMENT VERIFICATION of planar or volumetric IGRT for IMRT, involving the use of at least 2 planar image views or projections or 1 volumetric image set to facilitate a 3-dimensional adjustment to radiation treatment field positioning, if: (a) the treatment technique is classified as IMRT; and (b) the margins applied to volumes (clinical target volume or planning target volume) are tailored or reduced to minimise treatment related exposure of healthy or normal tissues; and (c) the decisions made using acquired images are based on action algorithms and are given effect immediately prior to or during treatment delivery by qualified and trained staff considering complex competing factors and using software driven modelling programs; and (d) the radiation treatment field positioning requires accuracy levels of less than 5mm (curative cases) or up to 10mm (palliative cases) to ensure accurate dose delivery to the target; and (e) the image decisions and actions are documented in the patient's record; and (f) the radiation oncologist is responsible for supervising the process, including specifying the type and frequency of imaging, tolerance and action levels to be incorporated in the process, reviewing the trend analysis and any reports and relevant images during the treatment course and specifying action protocols as required; and (g) when treatment adjustments are inadequate to satisfy treatment protocol requirements, replanning is required; and (h) the imaging infrastructure (hardware and software) is linked to the treatment unit and networked to an image database, enabling both on line and off line reviews Fee: $76.60 Benefit: 75% = $57.45 85% = $65.15

Category 3 – Therapeutic Procedures
MBS item 15562 DOSIMETRY FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 3 COMPLEXITY - where: (a) dosimetry for a three or more phase three dimensional conformal treatment plan using CT image volume dataset(s) with at least one gross tumour volume, three planning target volumes and one organ at risk defined in the prescription; or (b) dosimetry for a two phase three dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, and (i) two planning target volumes; or (ii) two organ at risk dose goals or constraints defined in the prescription. or (c) dosimetry for a one phase three dimensional conformal treatment plan using CT image volume datasets with at least one gross tumour volume, one planning target volume and three organ at risk dose goals or constraints defined in the prescription; or (d) image fusion with a secondary image (CT, MRI or PET) volume dataset used to define target and organ at risk volumes in conjunction with and as specified in dosimetry for three dimensional conformal radiotherapy of level 2 complexity. All gross tumour targets, clinical targets, planning targets and organs at risk as defined in the prescription must be rendered as volumes. The organ at risk must be nominated as planning dose goals or constraints and the prescription must specify the organs at risk as dose goals or constraints. Dose volume histograms must be generated, approved and recorded with the plan. A CT image volume dataset must be used for the relevant region to be planned and treated. The CT images must be suitable for the generation of quality digitally reconstructed radiographic images Fee: $1,120.75 Benefit: 75% = $840.60 85% = $1,041.25
MBS item 15550 SIMULATION FOR THREE DIMENSIONAL CONFORMAL RADIOTHERAPY without intravenous contrast medium, where: (a) treatment set up and technique specifications are in preparations for three dimensional conformal radiotherapy dose planning; and (b) patient set up and immobilisation techniques are suitable for reliable CT image volume data acquisition and three dimensional conformal radiotherapy treatment; and (c) a high-quality CT-image volume dataset must be acquired for the relevant region of interest to be planned and treated; and (d) the image set must be suitable for the generation of quality digitally reconstructed radiographic images Fee: $658.60 Benefit: 75% = $493.95 85% = $579.10
MBS item 15710 RADIATION ONCOLOGY TREATMENT VERIFICATION - volumetric acquisition, when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15705 - each attendance at which treatment involving three fields or more is verified (ie maximum one per attendance). (see para T2.5 of explanatory notes to this Category) Fee: $76.60 Benefit: 75% = $57.45 85% = $65.15

Table 14 Stereotactic radiosurgery treatments for lung cancer currently listed on the MBS

Category 3 – Therapeutic Procedures
MBS item 15215 RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (lung). Fee: $57.40; Benefit: 75% = $43.05; 85% = $48.80

Table 15 Surgical treatments for lung cancer currently listed on the MBS

Category 3 – Therapeutic Procedures
MBS item 38418 THORACOTOMY, exploratory, with or without biopsy Multiple Services Rule (Anaes.) (Assist.) Fee: $922.10
MBS item 38421 THORACOTOMY, with pulmonary decortication Multiple Services Rule (Anaes.) (Assist.) Fee: $1,473.95
MBS item 38438 PNEUMONECTOMY or LOBECTOMY or SEGMENTECTOMY not being a service associated with a service to which Item 38418 applies Multiple Services Rule (Anaes.) (Assist.) Fee: $1,473.95 Benefit: 75% = $1,149.00
MBS item 38440 LUNG, wedge resection of Multiple Services Rule (Anaes.) (Assist.) Fee: $1,103.75 Benefit: 75% =
MBS item 38441 RADICAL LOBECTOMY or PNEUMONECTOMY including resection of chest wall, diaphragm, pericardium, or formal mediastinal node dissection Multiple Services Rule (Anaes.) (Assist.) Fee: $1,746.40 Benefit: 75% = $1,361.40

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

The following algorithm, Figure 2, shows the current management of unresectable, early stage NSCLC. MTA is shown as an alternative to RFA and current best practice radiotherapy with or without chemotherapy. In the proposed algorithm, Figure 3, MTA is shown as an alternative to current best practice radiotherapy with or without chemotherapy.

Figure 4 shows the current clinical management algorithm for the management of pulmonary metastases in patients with the primary cancer under control. In this algorithm MTA is an alternative to RFA and radiotherapy with or without platinum-based chemotherapy in patients who are not eligible for surgical resection. Figure 5, the proposed algorithm shows MTA as a comparator both to radiotherapy with or without chemotherapy and as a comparator to surgery in both bilateral and unilateral disease.

Figure 6 and Figure 7 show the current and proposed clinical management algorithms for the palliative management of NSCLC and pulmonary metastases respectively. MTA is shown as an additional treatment option to conventional palliative treatments for NSCLC and pulmonary metastases.

Although MTA is proposed as a replacement for RFA in each algorithm, there is currently no MBS item for RFA, and in practice, clinical input suggests that patients would more frequently be referred for current best practice radiotherapy than ablative procedures in each of the populations. In particular, clinical input has suggested that SBRT is currently the preferred radiotherapy option for populations one and two and hence from a reimbursement perspective SBRT would be the main comparator to MTA.

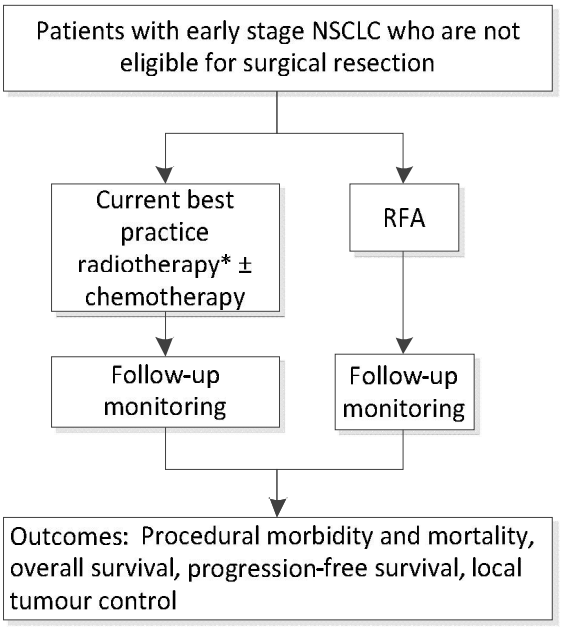

Figure 2 **Current clinical management algorithm for the management of unresectable, early stage NSCLC with curative intent (population one)**

< NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy >
*Stage IIA patients are considered to be unsuitable for SBRT.

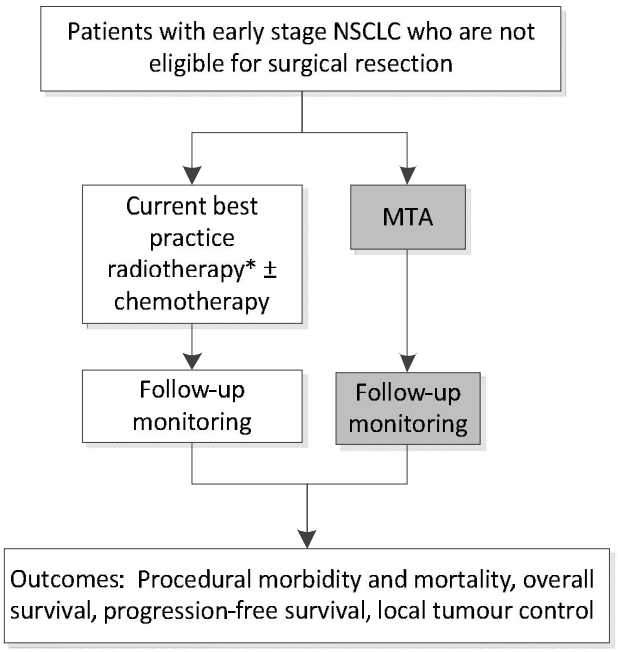

Figure 3 **Proposed clinical management algorithm for the management of unresectable, early stage NSCLC with curative intent (population one)**

<MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiotherapy >
*Stage IIA patients are considered to be unsuitable for SBRT.

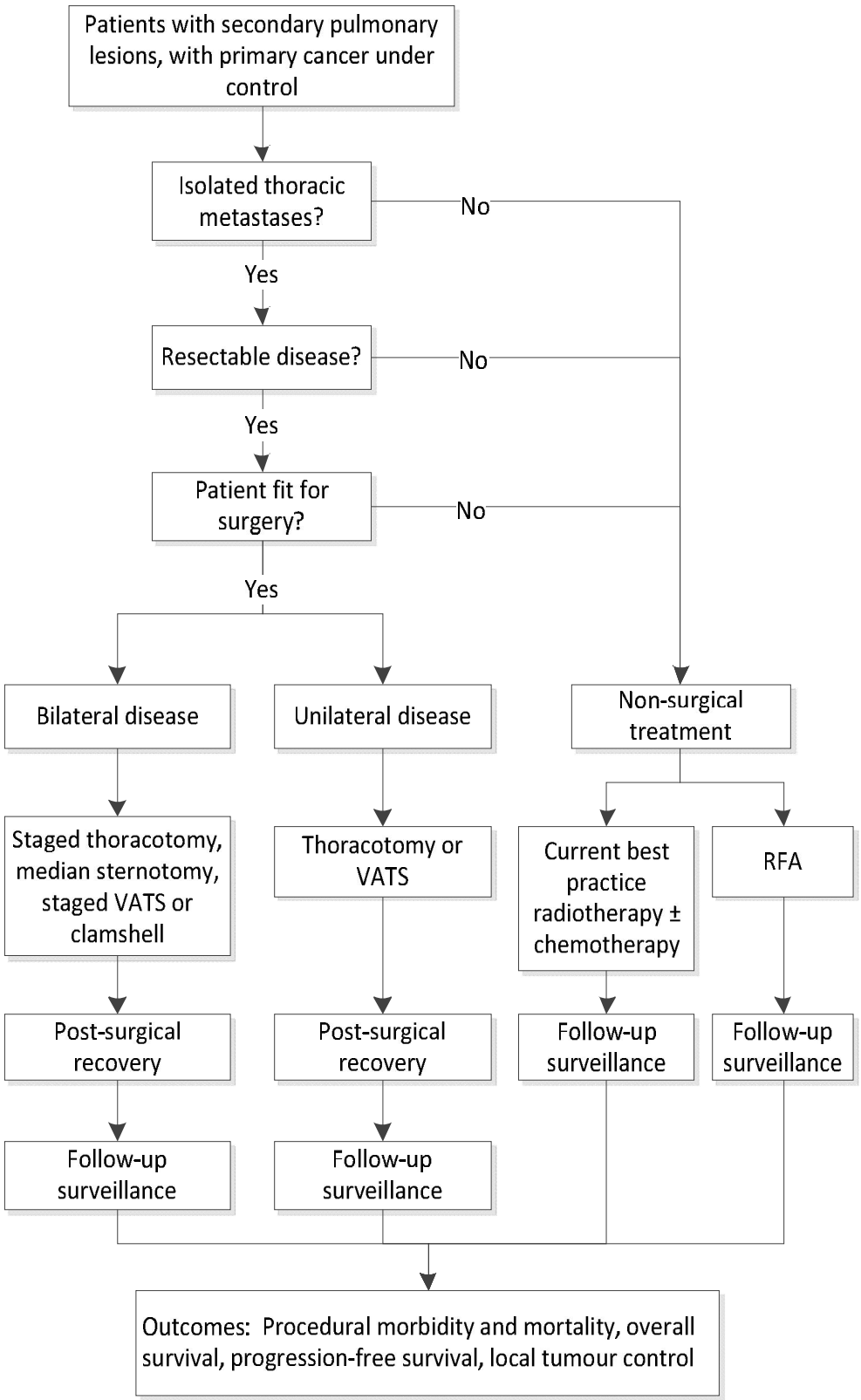

Figure 4 **Current clinical management algorithm for the management of pulmonary metastases in patients with the primary cancer under control (population two)**

< RFA = radiofrequency ablation; VATS = Video-assisted thoracoscopic surgery >

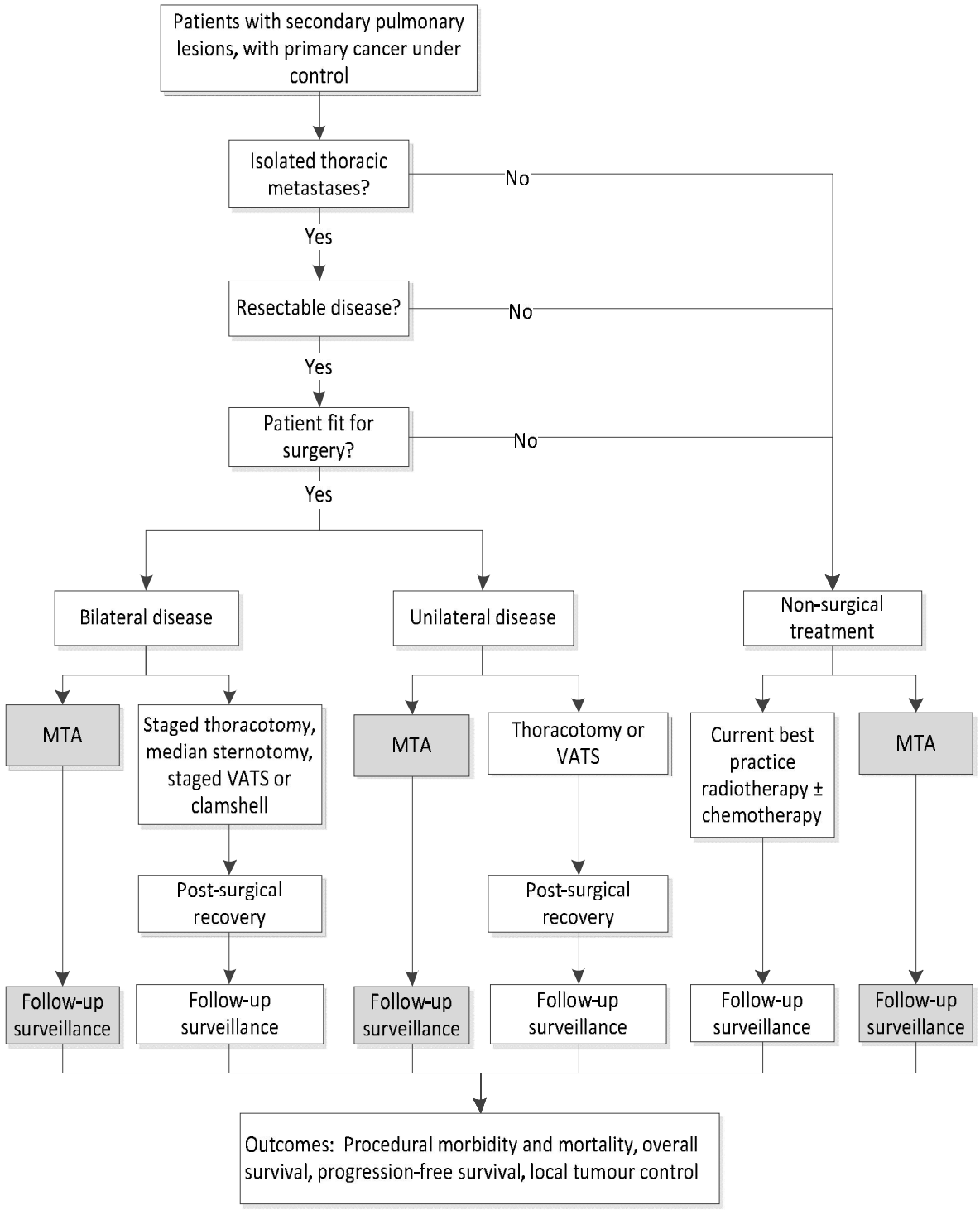

Figure 5 **Proposed clinical management algorithm for the management of pulmonary metastases with curative intent in patients with the primary cancer under control (population two)**

< MTA = microwave tissue ablation; VATS = video-assisted thorascopic surgery >

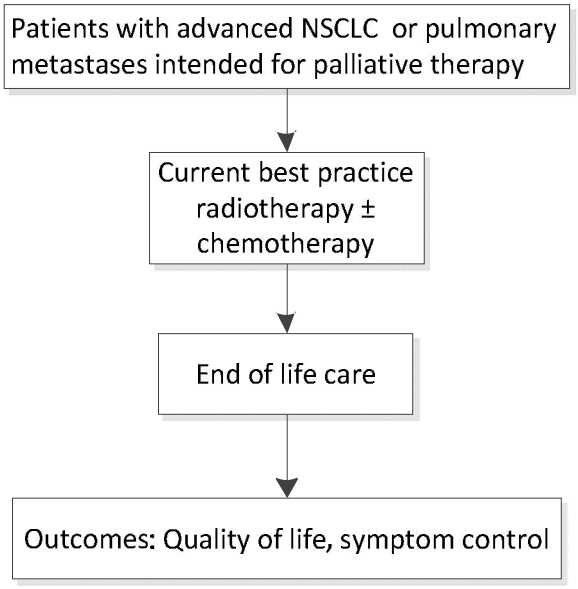

Figure 6 **Current clinical management algorithm for the palliative management of NSCLC and pulmonary metastases (population three)**

< NSCLC = non-small cell lung cancer >

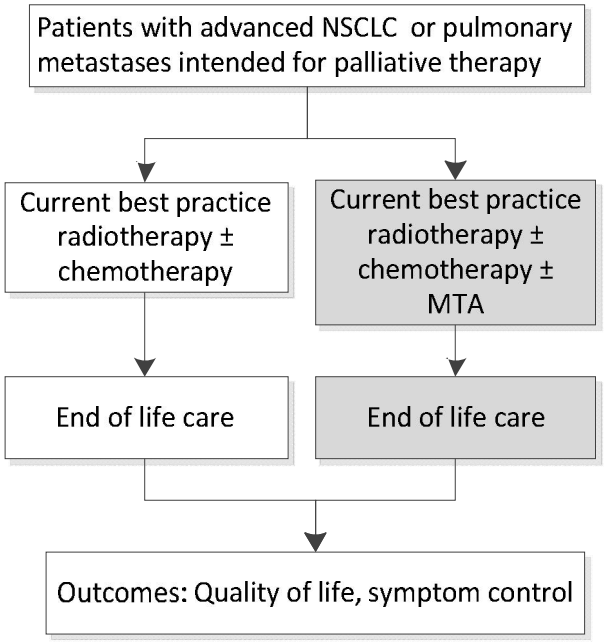

Figure 7 **Proposed clinical management algorithm for the palliative management of NSCLC and pulmonary metastases (population three)**

< MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer >

A.7. KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

Before patients are referred for the intervention or any of its comparators patients would generally have seen a GP, a respiratory physician and have had several diagnostic studies performed including one or more of:

- A computed tomography(CT) scan of lungs and centre of the chest (mediastinum), liver and adrenals for staging.
- A PET scan to evaluate distant spread including to bones.
- A bronchoscopy to confirm malignancy.

Following diagnosis and staging, therapeutic options are discussed at a multidisciplinary team meeting. The multidisciplinary team considers the appropriate treatment options, bearing in mind factors such as location of the lesions and comorbidities of the patient. Following this meeting the treating physician presents treatment options to the patient. The main differences in the delivery of the proposed service and the comparators are:

- The delivery of RFA and MTA are very similar, RFA may require longer anaesthesia time owing to increased ablation times. However, follow-up imaging and the mode of care requiring an overnight stay is the same. Both interventions are provided by an Interventional radiologist.
- The delivery of SBRT requires several steps including simulation, dosimetry, treatment and verification. Prior to treatment, the patient undergoes imaging procedures to determine the size, shape and location of the tumour. A simulation study begins with a standard high-resolution CT scan; however other imaging techniques, such as MRI, angiography or PET, may also be used. Depending on the treatment plan SBRT might be delivered in a single or multiple fractions and patients may need to attend a number of planning and treatment appointments. In contrast MTA is usually performed in a single session. However, SBRT is provided on an outpatient basis and an overnight hospital stay is not required. Similarly, SBRT is not followed by an immediate, four hour or 24 hour CT.
- Surgical resection differs from the delivery of MTA in that patients have an extended recovery period requiring hospitalisation in all cases. Treatment is provided by a thoracic surgeon.

A.8. CLINICAL CLAIM

The clinical claim associated with this application depends upon the intended use of, and available treatment alternatives to MTA.

Clinical claim in patients with early stage inoperable NSCLC who are receiving treatment with curative intent (population one)

The applicant has indicated that MTA has a role in the definitive treatment of early stage inoperable NSCLC. In these patients, guidelines recommend the use of radiotherapy including SBRT or radical radiotherapy and chemoradiotherapy. MTA is intended to be offered as an alternative to these therapies in selected patients. It is understood that the clinical claim associated with the application for this patient group is that MTA offers equivalent effectiveness outcomes to radiotherapy or chemoradiotherapy with an acceptable safety profile.

Clinical claim in patients with lung metastase(s), in whom the primary tumour is under control and who are receiving treatment with curative intent (population two)

In these patients the potential treatments for lung metastases depends on whether the patient is suitable for surgical resection. In patients who are not suitable for surgical resection the clinical claim is that MTA offers equivalent effectiveness to radiotherapy or chemoradiotherapy with an acceptable safety profile.

In patients who are eligible for surgical resection the applicant has indicated that MTA can be considered in selected operable patients with unilateral or bilateral disease, as it is less invasive, more tissue-sparing, repeatable and can be performed in an outpatient setting or with an overnight stay, having the least negative impact on quality of life. Hence, the clinical claim associated with patients in this group eligible for surgical resection is that MTA demonstrates equivalent effectiveness to surgical resection with an acceptable safety profile. Further to this the applicant claims that MTA offers certain benefits over surgical resection in terms of invasiveness, repeatability and quality of life.

Clinical claim in patients with NSCLC who are not eligible for surgical resection and patients with pulmonary metastases who are receiving treatment with palliative intent (Population Three)

MTA may have a role in treating patients with NSCLC with palliative intent. In these patients chemotherapy and radiotherapy are the main treatment options. MTA may be offered as an adjunct to radiotherapy and/or chemotherapy in these patients, as a means of de-bulking prominent tumours for symptom relief. In this population, MTA may improve symptom relief as opposed to conventional palliative therapies without MTA.

Clinical claim with respect to RFA in all patient groups

The applicant suggests there are significant treatment advantages of MTA over RFA, especially in the setting of lung tumour ablation. MTA is arguably more controllable and considered a safer procedure. MTA also offers larger, faster, more predictable ablation zones and higher temperatures during ablation. This may result in lower local recurrence rates and better patient-relevant health outcomes. Hence, in all the patient groups the applicant has suggested that RFA is a treatment option and that MTA is superior to RFA in terms of effectiveness for all patient groups and is associated with an acceptable safety profile.

A.9. SUMMARY OF THE PICO

The guiding framework of a protocol is recommended by MSAC for each assessment. The protocol describes current clinical practice and reflects the likely future practice with the proposed medical service. The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1, Box 2, Box 3, Box 4, Box 5, and Box 6.

Box 1 Criteria for identifying and selecting studies to determine the safety of MTA in patients with early stage inoperable NSCLC

<table>
<tr><th>Selection criteria</th><th>Description</th></tr>
<tr><td>Population</td><td>Patients with early stage, inoperable NSCLC.
Include those studies in which patients are said to have ‘early stage’ NSCLC, stage I NSCLC or stage IIa NSCLC. Alternatively, for studies reporting staging as TNM, early stage includes:
<table>
<tr><td>Stage</td><td>T</td><td>N</td><td>M</td></tr>
<tr><td>0</td><td>Tis</td><td>N0</td><td>M0</td></tr>
<tr><td>IA</td><td>T1a
T1b</td><td>N0
N0</td><td>M0
M0</td></tr>
<tr><td>IB</td><td>T2a</td><td>N0</td><td>M0</td></tr>
<tr><td>IIA</td><td>T1a
T1b
T2a
T2b</td><td>N1
N1
N1
N0</td><td>M0
M0
M0
M0</td></tr>
</table>
Include those studies which state that patients are not candidates for surgery for any reason.
Pre-planned subgroups
Studies containing mixed populations outcomes will be included only for those patients with known early stage NSCLC. For patient cohorts that are mixed and where patient outcomes are not reported according to disease stage these studies will be reported separately.</td></tr>
<tr><td>Intervention</td><td>Percutaneous MTA, guidance may be CT or US</td></tr>
<tr><td>Comparators</td><td>Percutaneous RFA
Current best practice radiotherapy with or without chemotherapy:
Radical radiotherapy
Image guided radiotherapy
Intensity modulated radiotherapy
Stereotactic body radiotherapy
Continuous hyperfractionated accelerated radiotherapy</td></tr>
<tr><td>Outcomes</td><td>Critical for decision making: Any immediate or delayed adverse event or mortality related to the procedure or anaesthesia
Important, but not critical for decision making: Not applicable
Low importance for decision making: Not applicable</td></tr>
<tr><td>Systematic review question</td><td>What is the safety profile of microwave tissue ablation in patients with early stage inoperable NSCLC as compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy?</td></tr>
</table>

< CT = computed tomography; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; US = ultrasound >

Box 2 Criteria for identifying and selecting studies to determine the effectiveness of MTA in patients with early stage, inoperable NSCLC

<table>
<tr><th>Selection criteria</th><th>Description</th></tr>
<tr><td>Population</td><td>Patients with early stage, inoperable NSCLC.
Include those studies in which patients are said to have ‘early stage’ NSCLC, stage I NSCLC or stage IIa NSCLC. Alternatively, studies reporting staging as TNM, early stage includes:
<table>
<tr><td>Stage</td><td>T</td><td>N</td><td>M</td></tr>
<tr><td>0</td><td>Tis</td><td>N0</td><td>M0</td></tr>
<tr><td>IA</td><td>T1a
T1b</td><td>N0
N0</td><td>M0
M0</td></tr>
<tr><td>IB</td><td>T2a</td><td>N0</td><td>M0</td></tr>
<tr><td>IIA</td><td>T1a
T1b
T2a
T2b</td><td>N1
N1
N1
N0</td><td>M0
M0
M0
M0</td></tr>
</table>
Include those studies that state that patients are not candidates for surgery for any reason.
Pre-planned subgroups
Studies containing mixed populations outcomes will be included only for those patients with known early stage NSCLC. For patient cohorts that are mixed and where patient outcomes are not reported according to disease stage these studies will be reported separately.</td></tr>
<tr><td>Intervention</td><td>Percutaneous MTA, guidance may be CT or US</td></tr>
<tr><td>Comparators</td><td>Percutaneous RFA
Current best practice radiotherapy with or without chemotherapy:
Radical radiotherapy
Image guided radiotherapy
Intensity modulated radiotherapy
Stereotactic body radiotherapy
Continuous hyperfractionated accelerated radiotherapy</td></tr>
<tr><td>Outcomes</td><td>Critical for decision making: Overall survival, relative survival at 1, 2, 3 and 5-years, recurrence free survival period, recurrence free survival rates and cancer related mortality
Important, but not critical for decision making: Local recurrence rates or time to local recurrence, 1-year local control rates, metastatic disease, tumour progression, patient reported outcomes, quality of life
Low importance for decision making: Procedural time, length of hospital stay and recovery time</td></tr>
<tr><td>Systematic review question</td><td>What is the effectiveness of microwave tissue ablation in patients with early stage inoperable NSCLC as compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy?</td></tr>
</table>

<CT = computed tomography; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; US = ultrasound >

Box 3 Criteria for identifying and selecting studies to determine the safety of MTA in patients with lung metastases in whom the primary tumour is under control, and who are receiving treatment with curative intent

Selection criteria	Description
Population	Patients with lung metastases in whom the primary tumour is under control, treated with curative intent. Include studies which state that patients had lung metastases with primary tumour of any other origin and where the primary tumour was reported to be under control (or controllable), definitively treated or completely resected (etc). Include studies which state that no extra thoracic disease was present or which state that extra thoracic disease was controlled or controllable. Include studies which state that patients were treated with curative intent. If it is unclear, studies will be included if they report outcomes that suggest patients were treated with curative intent, such as 1, 2, 3 and 5 year survival and/or progression or recurrence free periods. If there is still significant uncertainty regarding the treatment intent clinical expertise may be sought on the inclusion of the study. Pre-planned subgroups Studies reporting only on patients with sarcoma (bone and soft tissue) will be reported separately. Where possible outcomes for patients in studies reporting mixed populations will be stratified according to sarcoma and non-sarcoma primary cancers.
Intervention	Percutaneous MTA, guidance may be CT or US
Comparators	Percutaneous RFA Surgical resection by any technique Current best practice radiotherapy with or without chemotherapy: • Radical radiotherapy • Image guided radiotherapy • Intensity modulated radiotherapy • Stereotactic body radiotherapy • Continuous hyperfractionated accelerated radiotherapy
Outcomes	Critical for decision making: Any immediate or delayed adverse events or mortality related to the procedure or anaesthesia Important, but not critical for decision making: Not applicable Low importance for decision making: Not applicable
Systematic review question	What is the safety profile of microwave tissue ablation in patients with lung metastases in whom the primary tumour is under control, treated with curative intent?

< CT = computed tomography; MTA = microwave tissue ablation; RFA = radiofrequency ablation; US = ultrasound >

Box 4 **Criteria for identifying and selecting studies to determine the effectiveness of MTA in patients with lung metastases in whom the primary tumour is under control, and who are receiving treatment with curative intent**

Selection criteria	Description
Population	Patients with lung metastases in whom the primary tumour is under control, treated with curative intent. Include studies which state that patients had lung metastases with primary tumour of any other origin and where the primary tumour was reported to be under control (or controllable), definitively treated or completely resected (etc). Include studies which state that no extra thoracic disease was present or which state that extra thoracic disease was controlled or controllable. Include studies which state that patients were treated with curative intent. If it is unclear, studies will be included if they report outcomes that suggest patients were treated with curative intent, such as 1, 2, 3 and 5 year survival and/or progression or recurrence free periods. If there is still significant uncertainty regarding the treatment intent clinical expertise may be sought on the inclusion of the study. Pre-planned subgroups Studies reporting only on patients with sarcoma (bone and soft tissue) will be reported separately. Where possible outcomes for patients in studies reporting mixed populations will be stratified according to sarcoma and non-sarcoma primary cancers.
Intervention	Percutaneous MTA, guidance may be CT or US
Comparators	Percutaneous RFA Surgical resection by any technique Current best practice radiotherapy with or without chemotherapy: • Radical radiotherapy • Image guided radiotherapy • Intensity modulated radiotherapy • Stereotactic body radiotherapy • Continuous hyperfractionated accelerated radiotherapy
Outcomes	Critical for decision making: Overall survival, relative survival at 1, 2, 3 and 5-years, recurrence free survival period, recurrence free survival rates and cancer related mortality Important, but not critical for decision making: Local recurrence rates or time to local recurrence, 1-year local control rates, metastatic disease, tumour progression, patient reported outcomes, quality of life Low importance for decision making: Procedural time, length of hospital stay and recovery time
Systematic review question	What is the effectiveness of microwave tissue ablation in patients with lung metastases in whom the primary tumour is under control, treated with curative intent?

< CT = computed tomography; MTA = microwave tissue ablation; RFA = radiofrequency ablation; US = ultrasound >

Box 5 Criteria for identifying and selecting studies to determine the safety of MTA in patients with NSCLC or pulmonary metastases, who are receiving palliative treatment

Selection criteria	Description
Population	Patients with NSCLC or lung metastases being treated with palliative intent. Include studies which state that patients were treated with palliative intent. Include studies reporting that patients had advanced NSCLC or advanced primary cancers. Include studies which report on outcomes relevant to palliative care only such as symptom relief/control and quality of life. If there is still significant uncertainty regarding the treatment intent clinical expertise may be sought on the inclusion of the study.
Intervention	Percutaneous MTA, guidance may be CT or US
Comparators	Conventional palliative therapy which may include palliative chemotherapy, radiotherapy, RFA or best supportive care
Outcomes	Critical for decision making: Any immediate or delayed adverse events or mortality related to the procedure or anaesthesia Important, but not critical for decision making: Not applicable Low importance for decision making: Not applicable
Systematic review question	What is the safety profile of microwave tissue ablation in patients with NSCLC or lung metastases being treated with palliative intent?

< CT = computed tomography; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; US = ultrasound >

Box 6 **Criteria for identifying and selecting studies to determine the effectiveness of MTA in patients with NSCLC or pulmonary metastases who are receiving palliative treatment**

Selection criteria	Description
Population	Patients with NSCLC or lung metastases being treated with palliative intent. Include studies which state that patients were treated with palliative intent. Include studies reporting that patients had advanced NSCLC or advanced primary cancers. Include studies which report on outcomes relevant to palliative care only such as symptom relief/control and quality of life. If there is still significant uncertainty regarding the treatment intent clinical expertise may be sought on the inclusion of the study.
Intervention	Percutaneous MTA, guidance may be CT or US
Comparators	Conventional palliative therapy which may include palliative chemotherapy, radiotherapy, RFA or best supportive care
Outcomes	Critical for decision making: Symptom relief/control, quality of life, median survival times Important, but not critical for decision making: Relative survival rates at 1-,2-,3- and 5- years, procedural time, length of hospital stay, recovery time, patient discomfort Low importance for decision making: Not applicable
Systematic review question	What is the effectiveness of microwave tissue ablation in patients with NSCLC or lung metastases being treated with palliative intent?

< CT = computed tomography; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation; US = ultrasound >

A.10. CONSUMER IMPACT STATEMENT

No significant feedback was received during the public consultation period of the protocol for this application.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

A step-wise approach to literature searching was necessary in order to accommodate the limitations of the peer-reviewed literature pertaining to the intervention. In the first instance, a systematic literature search was conducted to identify all studies on MTA. No studies that directly or indirectly compared MTA to a relevant comparator were identified. As a result, the evidence base was insufficient to inform the MSAC assessment. As MTA and RFA are technologically similar (both thermal ablative technologies), high quality comparative data for RFA compared to current MBS listed comparator services (SBRT and surgery) could inform a funding decision on MTA. A second systematic search was conducted to identify all studies on RFA. No direct or indirect comparative evidence was identified. As no comparative data were identified, meta-analysis and indirect comparison across multiple interventions could not be undertaken.

In order to contextualise the evidence base for MTA and RFA, and to provide some idea of potential results with ablative therapies, additional pragmatic searches were executed. These aimed to identify evidence for the remaining comparators—current best practice radiotherapy and surgical resection—across all three defined populations. These searches were not designed to be comprehensive systematic reviews. A systematic approach is not justified based on the paucity of evidence available for ablative therapies, including MTA. Rather, these searches were designed to enable the selection of high quality evidence on these interventions that is reflective of current practice. These searches were executed in PubMed only, and evidence was selected preferentially in order of quality. The approach taken is described below (Table 16). Full details of search strategies and databases searched are provided in Appendix B.

Table 16 Summary of searches undertaken to identify studies regarding the intervention and comparators

Intervention	Databases searched, search date(s) and limits	Pearling
Microwave tissue ablation	PubMed (including MEDLINE), Embase (excluding MEDLINE), Cochrane Library, and the University of York Centre for Reviews and Dissemination. Searched on: 31/05/2016 and 1/06/2016 Limits: English language, humans	Yes
Radiofrequency ablation	PubMed (including MEDLINE), Embase (excluding MEDLINE), Cochrane Library, and the University of York Centre for Reviews and Dissemination Searched on: 31/05/2016 and 1/06/2016 Limits: English language, humans, published from 2006 onwards	Yes

Intervention	Databases searched, search date(s) and limits	Pearling
Radiotherapy	PubMed (including MEDLINE) Searched on: 15/06/2016 Limits: English language, humans, published from 2006 onwards	No
Surgery	PubMed (including MEDLINE) Searched on:28/06/2016 Limits: English language, humans, published from 2006 onwards	No

Identifying literature on MTA and RFA

Four key biomedical databases were searched, including PubMed (including MEDLINE), Embase (excluding MEDLINE), the Cochrane Library, and the University of York Centre for Reviews and Dissemination. In addition, reference lists of included studies were hand searched for studies missed by the formal searches. Clinical experts were engaged to identify any studies that may be have been missed in the database searches. No date restrictions were applied to the search for MTA. The search for RFA was date limited from 2006 onwards owing to the existence of a comprehensive systematic review with a search date of November 2006 whose scope aligned with that of the current assessment (Zhu et al 2008a). Zhu et al (2008a) assessed the safety and efficacy of RFA for primary and metastatic lung tumours and included 16 studies of Level IV evidence.

A comprehensive search strategy was designed using relevant search terms, incorporating key words, Medical Subject Headings (MeSH), and Emtree terms. Additional search limits and filters for both technologies included English language, studies in humans and for the search for RFA, 2006 onwards. Search terms were developed based on the PICO criteria, and informed by an initial scoping search. The medical literature was searched on 31/05/2016 and 1/06/2016 for MTA and RFA, respectively. Detailed search strategies are shown in Appendix B. Ongoing clinical trials that are ongoing, or clinical trials that have been completed but not published, were identified by searching ClinicalTrials.gov (www.clinicaltrials.gov), the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), and the World Health Organisation International Clinical Trials Registry Platform (www.who.int).

Identifying literature on current best-practice radiotherapy

No comparative studies for either MTA or RFA for patients with lung cancer were identified in the initial searches. A third search strategy was developed in order to identify relevant literature on current best practice radiotherapy in populations one and two. In order to identify studies of current radiotherapy protocols only, this search was limited to the last 10 years of published literature and was executed in PubMed. This date restriction aligns with the dates of published evidence available

for MTA and RFA, and avoided the inclusion of older studies that are not reflective of current clinical practice which would bias the evidence-base. The volume of literature regarding current best practice radiotherapy and lung cancer is extensive. Consequently terms for the population and intervention were combined with terms for outcomes (see Appendix B for details). Supplementary scoping searches were executed to identify any systematic reviews or randomised controlled trials (RCTs) that may have been missed.

Identifying literature on surgical resection for population two

No high quality studies of radiotherapy compared to surgery were identified for population two. A fourth search strategy was developed to identify relevant literature on surgical resection in population two. In order to identify studies of current surgical practice and to align with the dates of the evidence available for MTA and RFA, this search was limited to the last 10 years of published literature and was executed in PubMed. The volume of literature regarding surgical resection and lung cancer is extensive. Consequently terms for the population and intervention were combined with terms for outcomes (see Appendix B for details). Supplementary targeted scoping searches were also executed in order to identify any systematic reviews or RCTs that may have been missed by this search.

B.2. RESULTS OF LITERATURE SEARCH

The results of the literature search are presented graphically in Figure 8, Figure 9, and Figure 10. The search results were imported into bibliographic management software (EndNote X7, Thompson Reuters). Each database was filtered to remove duplicate entries prior to formal study selection. Studies were screened for eligibility according to the relevant PICO criteria outlined in the review questions. Selection was initially undertaken by one reviewer, who screened eligible entries by title and abstract. Study selection was deliberately conservative, whereby full-texts were sought when there was any ambiguity in applying the selection criteria. One reviewer assessed each of the full-text articles for inclusion, and a second reviewer assessed a random sample of 25%. The bibliographies of all included studies for the intervention (MTA) and the comparator ablative technology (RFA) were hand-searched (pearling) for any relevant references missed in the database searches. Uncertainties or discrepancies between reviewers were resolved through discussion with a third reviewer.

Additional pre-specified criteria for excluding studies included conference abstracts and other publications that are not subject to peer-review. In the case of study overlap, i.e. two or more studies reporting on the same population, either the latest or most complete study was included. Studies that were excluded during full-text review are listed Appendix E, with reasons for exclusion. This includes studies that could not be retrieved or that met the inclusion criteria but contained

insufficient or inadequate data for inclusion. All other studies that met the inclusion criteria are listed in Appendix C.

For the comparator of surgical resection the same process was followed; however, a PRISMA flowchart is not provided because inclusion was not based on all studies meeting the inclusion criteria. A select number of studies were used which met the inclusion criteria and informed on specific elements of the comparison. Seventy-six case series studies and two systematic reviews were identified on surgical resection in oligometastatic disease. For the purposes of this report both systematic reviews were included. These reviews were supplemented with four case series with greater than 100 patients, and one case series (<100 patients) focusing on primary hepatocellular carcinoma. These studies were selected based on the primary cancers represented in the studies of MTA and RFA. Notably, although it is a widely established therapeutic option, surgical resection has not been the subject of any comparative trials in this population. Systematic reviews on the subject are comprised entirely of case series data. This assessment identified one currently recruiting clinical trial, the PULMICC trial (A Randomised Trial of Pulmonary Metastasectomy in Colorectal Cancer [PulMiCC], NCT01106261), a randomized multicentre controlled trial on resection versus conservative therapy for colonic lung metastases. This trial aims to assess whether surgery is beneficial in patients who have been deemed suitable for resection. The existence of this study illustrates the current, relatively uncertain, state of evidence for all therapies in this population.

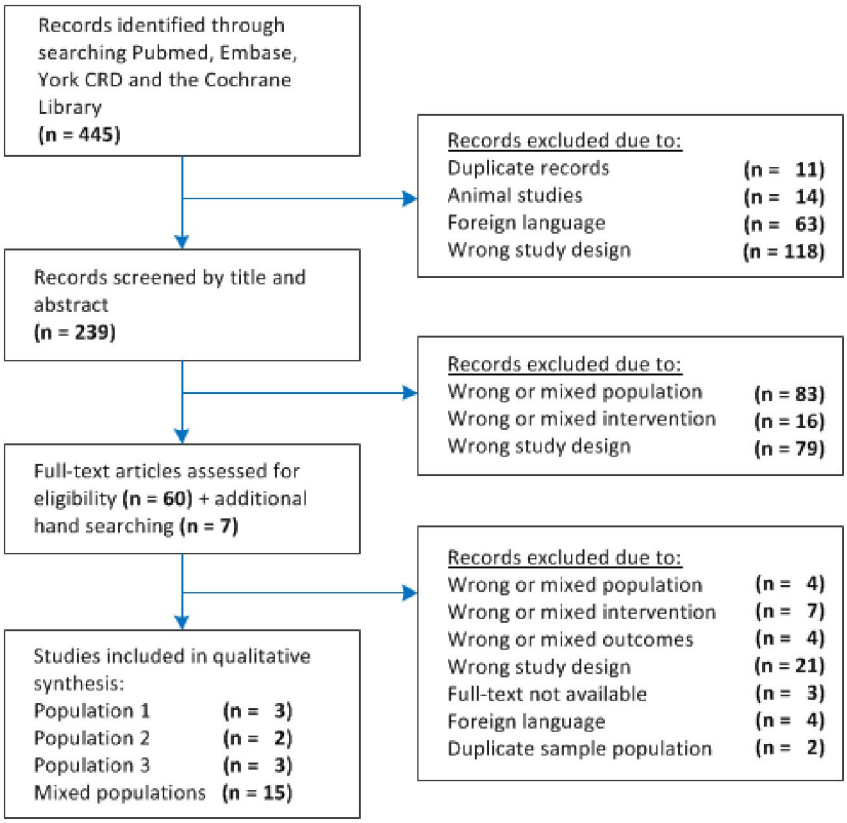

Figure 8 Summary of the process used to identify and select studies of MTA

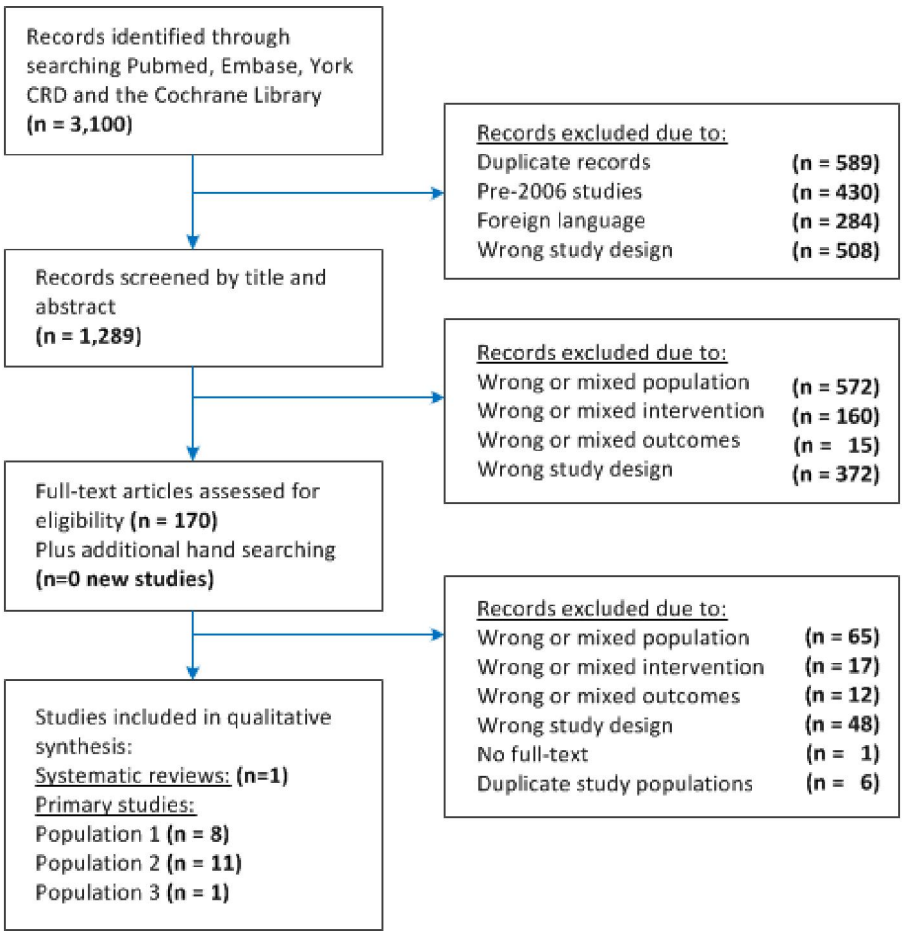

Figure 9 **Summary of the process used to identify and select studies of RFA**

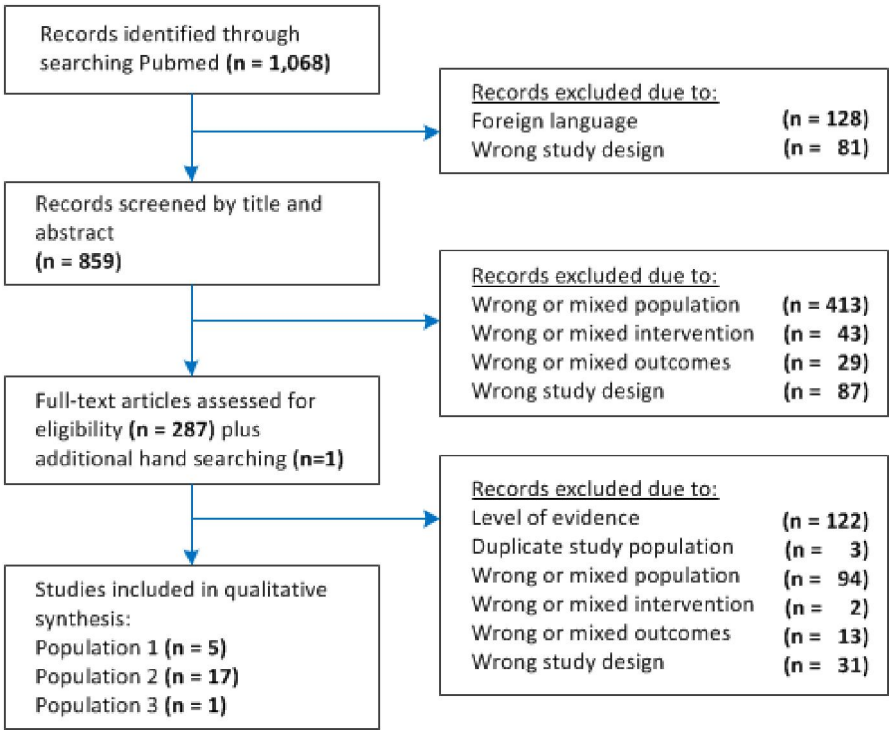

Figure 10 **Summary of the process used to identify and select studies of radiotherapy**

A profile of each included study is given in Appendix C. This study profile describes the authors, study ID, publication year, study design and quality (level of evidence and risk of bias), study location, setting, length of follow-up of patients, study population characteristics, description of the intervention, description of the comparator and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4. A search of clinical trials identified only one comparative trial of MTA that is currently recruiting (NCT02455843). This trial will compare MTA in combination with chemotherapy to chemotherapy alone for advanced NSCLC. A list of relevant clinical trials on all interventions in this population is provided at the end of Appendix F. Table 17 lists the number and type of included studies according to the intervention.

Table 17 Number and type of included studies for each intervention, in each study population

Intervention	Included studies (P1)	Included studies (P2)	Included studies (P3)
MTA*	3 Level IV case series	2 Level IV case series	2 Level III-2 cohort 1 Level IV case series
RFA**	1 Level III-3 cohort 7 Level IV case series	11 Level IV case series†	1 Level IV case series
Radiotherapy	2 Level II RCT 1 Level III-1 propensity-matched cohort 1 Level III-2 cohort 1 Level III-3 historical control	3 Level III-2 cohort 14 Level IV case series	1 systematic review of 13 RCTs
Surgery	NA	5 Level IV case series	NA

< MTA = microwave tissue ablation; RCT = randomised controlled trial; RFA = radiofrequency ablation >

* An additional 16 Level IV studies with mixed populations were included in the safety section.

** An existing systematic review published in 2008 was included for safety outcomes. It did not identify any prior studies of effectiveness that were relevant to the current evaluation.

† Yan et al 2006 and Yan et al 2007 reported different outcomes from the same sample population, over the same period. These publications have been reported as a single publication in the report.

Appraisal of the evidence

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review. Some risk of bias items were assessed for the study as a whole, while others were assessed at the outcome level (Section B.3). The risk of bias in included studies was evaluated across two domains—level of evidence (Merlin et al 2009), and quality of evidence (Mustafa et al 2013) —that collectively represent of the strength of the evidence of individual studies. The level of bias introduced by the study design, relative to the research question, was ranked according to the National Health and Medical Research Council (NHMRC) levels of evidence (Merlin et al 2009). The

quality of included studies was evaluated at the study level. Systematic reviews were evaluated using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool (Shea et al 2007). Randomised and non-randomised studies were evaluated using the Downs and Black checklist (Downs and Black 1998). Single arm case series investigations were evaluated using the 'Quality Appraisal Checklist for Case Series Studies' developed by the Institute of Health Economics (Guo et al 2016). Critical appraisal was conducted by one reviewer, and checked by a second reviewer for accuracy. Any disputes were settled through discussion.

Stage 2: Extraction of the pre-specified outcomes for this assessment, synthesising (using measures of central tendency when possible or otherwise a narrative synthesis) to determine an estimate of effect per outcome. Data were extracted by one reviewer and checked by a second using a piloted data extraction template developed a priori. Data was only extracted if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. Any disagreements or discrepancies in the extracted data were resolved through discussion, or referred to a third reviewer if agreement could not be reached (Sections B.6–7).

Stage 3: Rating the quality of the evidence per outcome across studies, based on study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and likelihood of publication bias. This was assessed using the GRADE methodology (Guyatt et al). The strength of the evidence supporting each summary estimate is reported according to risk of bias, imprecision, indirectness, inconsistency, and publication bias (Evidence profile tables, Appendix D). Based on the combined rating against these criteria, the quality of evidence contributing to each recommendation is given a score from low to high. The rating was determined by one reviewer and checked by a second with disagreements resolved through discussion. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice.

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6–8).

B.3. RISK OF BIAS ASSESSMENT

Summary – Risk of bias in the identified evidence base:

- No direct or indirect comparative evidence for MTA relative to the comparators was identified.
- The evidence base for MTA and its comparators has a high risk of bias due to limitations in study design (i.e. mostly retrospective case series) and quality of the included studies.
- The evidence prohibits inference regarding the comparative effectiveness of the intervention because there is no data available for:
    - direct comparison of MTA and relevant comparators; or
    - indirect comparison of MTA and relevant comparators, through a common reference arm; or
    - the natural history of patients with oligometastatic lung disease.
- There is considerable uncertainty regarding the consistency with which reported outcomes were defined, and the time points at which outcomes were measured.
- Due to the limitations in the evidence base, it is not appropriate to compare outcomes across studies, even within the same study populations.

Risk of bias within studies included for MTA

Risk of bias associated with study design

Evidence for the intervention (MTA) in populations one and two is limited to Level IV evidence (case series), with small patient numbers, which are largely retrospective in design (Alexander et al 2013a; Belfiore et al 2013; Carrafiello et al 2012; Carrafiello et al 2014; Chung et al 2014; Egashira et al 2016; He et al 2006b; Little et al 2013; Lu et al 2012a; Nour-Eldin et al 2011; Splatt and Steinke 2015; Sun et al 2015b; Vogl et al 2013; Wolf et al 2008; Yang et al 2015; Zheng et al 2014). Two Level III-2 non-randomised comparative trials were identified in population three (Sun et al 2015a; Wei et al 2015); however, these studies did not report the primary effectiveness outcomes relating to quality of life or symptom control. The evidence base is largely comprised of Level IV evidence, which prohibits any inference on the effect of the intervention as no data is available for comparison with other interventions. Furthermore, the lack of concurrent or historical comparison groups within studies raises concerns in comparing across Level IV studies of different interventions as the study populations may differ in the distribution of prognostic factors that could affect study outcomes. The Level IV studies included within this report were appraised individually using the 'Quality Appraisal Checklist for Case Series Studies' developed by the Institute of Health Economics (Guo et al 2016). All but one study were retrospective in design and reporting was of variable quality. Some key issues regarding bias are summarised in Table 18, in which the studies are grouped according to the population that they inform.

Selection bias

Inherent in the case series study design is risk of selection bias. In studies where it is unclear how patients were selected for the intervention and whether cases were included consecutively, there may be issues with selection bias. Most of the included studies reported both inclusion and exclusion criteria. However, it was usually unclear whether patient enrolment was consecutive or not. Subtle differences in inclusion criteria exist, such as limitations on lesion size, and may have a prognostic impact affecting the outcomes of patients and therefore the study conclusions. In general, studies did not adjust for potential confounders.

Performance bias and detection bias

In terms of outcome measures such as overall survival, although the outcome is dichotomous in nature, issues of performance bias may still be introduced in terms of co-interventions or post ablation therapies. The majority of the included studies are not explicit about treatments received post ablation. It is unclear whether other therapies may also have been delivered that could influence patient survival. Similarly, in terms of follow-up CT results, there is potential for detection bias as neither patients nor outcome assessors where blinded. This also applies to the two Level III-2 studies in population three.

Attrition bias and reporting bias

In general it is not clear within retrospective case series studies whether certain outcomes were omitted because they were not collected, or because they were incomplete. Reporting of outcomes across the case series evidence was not comprehensive and approach to losses to follow-up was often unclear.

Populations

Study populations are discussed in more detail in Section B.4 of the report.

Risk of bias across the reporting of outcomes

The available evidence is inconsistent—both in terms of which outcomes were measured and how they were assessed and reported within studies. This affects the quality of the studies when assessed using validated tools. For example, time to progression or recurrence was variably reported and measured. In one study this could be defined as: *a focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage was considered local recurrence if technical success had been confirmed* (Han et al 2015), or simply as *the contrast-enhancement by CT scans in the site of ablation* in another (Yang et al 2014). In this instance, it could be expected that the more liberal definition applied by Yang et al (2014) would be associated with poorer median

time to progression. In actuality, this is further complicated by results indicating details on the outcome measure were unreported. In fact, Yang et al (2014) reported median time to progression that was both longer than that reported by Han et al (2015) and longer than overall survival within their own study, suggesting that this outcome probably excluded deaths from the analysis of time to progression.

Uncertainties such as this, arising from limitations in study reporting, mean it was impossible to establish if inconsistency in study results within the same population was due to differences in prognostic factors between study populations or differences in the way outcomes were measured and reported. Both inherent limitations in the case series study design and study quality issues within studies contribute to the risk of bias across all included studies of MTA being attributed a value of 'high'.

Table 18 Risk of bias and quality appraisal for MTA

Intervention and population	Number of studies (patients), level of evidence	Reporting/quality concerns	Risk of bias
MTA for early stage NSCLC. Patients were ineligible for resection or refused surgery.	3 (90), Level IV	Studies predominantly retrospective in design and had poor reporting in relation to consecutive recruitment of patients, comprehensive eligibility criteria and follow-up. Study conclusions not supported by findings in two studies.	High
MTA for patients with lung metastases in whom the primary tumour is under control. Patients included those with primary nasopharyngeal carcinoma in one study and mixed primary cancers in another.	2 (159), Level IV	Retrospective study design in one, reporting of adverse events was incomplete for one study, poor reporting in relation to consecutive recruitment of patients, comprehensive eligibility criteria and follow-up.	High
MTA for patients with lung metastases or primary NSCLC treated with palliative intent.	3 (103), Level III-2 (2 studies), Level IV (1 study)	Studies did not allocate patients to interventions based on a randomisation procedure and patient demographics were variably reported.	High
MTA for mixed populations, included for an extended assessment of harms.	15 (977), Level IV	Reporting of adverse events was incomplete in k = 5/15. Poor reporting in relation to consecutive recruitment of patients, comprehensive eligibility criteria and follow-up was an issue.	High

< k = number of studies; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer >

Table 19 Quality appraisal of included case series investigations of MTA, according to the IHE Quality Appraisal of Case Series Studies

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
POPULATION 1																		
Han et al (2015)	✓	?	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	?	✓
Liu & Steinke (2015)	✓	×	×	?	✓	✓	✓	✓	•	×	✓	✓	✓	✓	✓	✓	✓	✓
Yang et al (2014)	✓	×	×	?	✓	✓	✓	✓	•	×	✓	✓	✓	×	✓	✓	?	×
POPULATION 2																		
Qi et al (2015)	✓	×	×	?	✓	✓	✓	✓	×	×	•	✓	✓	✓	×	•	×	✓
Vogl et al (2015)	✓	✓	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	•
POPULATION 3																		
Ni et al (2015)	✓	×	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	×

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Mixed																		
Alexander et al (2013)	✓	×	×	?	✓	•	×	✓	✓	×	✓	✓	✓	×	✓	•	✓	✓
Belfiore (2013)	✓	×	×	?	×	✓	×	✓	•	×	✓	✓	✓	×	✓	✓	✓	×
Carrafiello et al (2014)	✓	×	×	?	×	×	×	✓	✓	×	✓	✓	✓	×	✓	✓	✓	•
Carrafiello et al (2012)	✓	×	×	?	•	×	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	•
Chung et al (2014)	✓	×	×	?	•	×	×	✓	✓	×	✓	✓	×	×	✓	✓	?	✓
Egashira et al (2016)	✓	×	×	?	✓	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	×	•
He et al (2006)	✓	?	×	?	•	×	×	✓	•	×	✓	✓	✓	×	✓	✓	×	•
Little et al (2013)	✓	×	×	✓	•	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	•
Lu et al (2012)	✓	×	×	?	•	✓	×	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓
Nour-Eldin (2011)	✓	×	×	?	×	×	×	✓	✓	×	✓	✓	×	?	✓	•	✓	•

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Splatt & Steinke (2015)	✓	×	×	?	×	×	×	✓	×	×	✓	✓	?	?	✓	•	✓	•
Sun et al (2015)	✓	?	×	?	•	×	×	✓	✓	×	✓	✓	✓	✓	✓	✓	×	×
Wolf et al (2008)	✓	×	×	?	•	✓	×	✓	✓	×	✓	✓	✓	?	✓	✓	?	×
Yang et al (2015)	✓	?	×	?	•	×	×	✓	✓	×	✓	✓	×	×	✓	✓	✓	✓
Zheng et al (2014)	✓	×	×	✓	•	×	×	✓	✓	×	✓	✓	?	?	✓	•	✓	×

✓ = yes, × = no, • = partial, ? = unclear.

Note: The IHE quality appraisal tool has been modified to remove two questions that are not applicable to this review. These include: Were additional interventions (co-interventions) clearly described? And, were the relevant outcome measures made before and after the intervention?

Table 20 Quality appraisal of included comparative studies of MTA, according to the Downs and Black Checklist for Randomised and Non-Randomised Comparative Trials

Study ID	Reporting: Hypothesis	Reporting: Outcomes	Reporting: Patient characteristics	Reporting: Intervention	Reporting: Confounders	Reporting: Main findings	Reporting: Random variability in results	Reporting: Adverse events	Reporting: Losses to follow-up	Reporting: Actual probabilities	Validity: Invited sample representative	Validity: Participating sample representative	Validity: Facilities representative	Bias: Subjects blinded	Bias: Measurements blinded	Bias: Data dredging	Bias: Length of follow-up accounted for	Bias: Statistical tests appropriate	Bias: Compliance with intervention	Bias: Outcomes were accurate	Confounding: Recruitment same population	Confounding: Recruitment same time	Confounding: Randomisation	Confounding: Randomisation blinded	Confounding: Adjustment for confounders	Confounding: Losses to follow-up	Power: Power reported
Sun et al (2015)	1	1	0	1	0	1	1	0	1	0	0	0	1	0	0	1	0	1	1	1	1	1	0	NA	0	1	0
Wei et al (2015)	1	1	1	1	1	1	1	0	1	1	0	0	1	0	0	1	1	1	1	1	1	1	0	NA	1	1	0

1 = yes, 0 = no, NA = not applicable.

Risk of bias for studies of RFA

Risk of bias associated with study design

Nineteen of the published studies of RFA for the treatment of lung cancer were case series, and one was a non-randomised historical control trial of early stage NSCLC. A summary of the overall risk of bias according to each population is presented in Table 21. Detailed quality appraisal scores for each study are presented in Table 22 and Table 23.

Selection bias

The majority of studies were conducted retrospectively (k = 16) through case note review. There were no apparent discrepancies between the number of included patients and the total number of patients reported in the analysis.

Performance bias and detection bias

Due to the retrospective nature of the included studies, treatment with RFA was the main study inclusion criteria, but pre- or post-RFA treatments were often not considered. Chemotherapy was the most common pre-RFA treatment for pulmonary metastases. Due to the lack of uniformity in pre- and post-RFA treatment strategies, the reported survival effects could not be attributed to RFA alone. Similarly, the diverse patients in the included studies introduced uncertainty whether survival effects were related to RFA therapy or the natural history of the patients.

Attrition bias and reporting bias

Five of the included studies accounted for patients that were excluded from the study (Fanucchi et al 2016; Hiraki et al 2011b; Lu et al 2015a; Ridge et al 2014; Yan et al 2007), whereas the other studies did not report any losses to follow-up. It is unknown whether patients with incomplete case notes were excluded from analysis.

Populations

The included patients for population two were highly diverse, even after accounting for the strict study inclusion criteria of this assessment. The observed variation in sample populations across studies was largely related to the stage of primary disease, type of primary disease, male: female distribution, age distribution, number of lesions and, most importantly, treatment strategies for pulmonary metastases before and after RFA. Study populations are discussed in more detail in Section B.4 of the report.

Risk of bias across the outcome reporting

Safety outcomes were reported inconsistently across studies, with the exception of procedure-related mortality and pneumothorax. Other outcomes were reported variably, and definitions for adverse events were mixed. Two studies reported adverse events as major or minor (Ambrogi et al 2011; Liu et al 2015), six reported adverse events according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria (Dupuy et al 2015; Fanucchi et al 2016; Hiraki et al 2011a; Matsui et al 2015; Ridge et al 2014; Simon et al 2007), and nine studies did not adequately define how adverse events were recorded in the case notes (De Baere et al 2015a; Koelblinger et al 2014; Li et al 2012; Lu et al 2015a; Lu et al 2015b; Safi et al 2015; Viti et al 2014; Von Meyenfeldt et al 2011; Yan et al 2007).

Table 21 Risk of bias and quality appraisal for RFA

Intervention and population	Number of studies (patients) and level of evidence	Reporting/quality concerns	Risk of bias
RFA for early stage NSCLC. Patients were ineligible for resection or refused surgery	1 (25), Level III-3 7 (283), Level IV	Single-arm (k = 7/8), retrospective studies (k = 6/8) Pre- and post-RFA therapies were diverse Safety outcomes reported variably or not defined	High
RFA for patients with limited lung metastases in whom the primary tumour is under control	10* (997), Level IV	Single-arm (k = 10/10), retrospective studies (k = 9) Heterogeneous populations Pre- and post-RFA therapies were diverse Safety outcomes reported variably or not defined	High
RFA for patients with lung metastases or primary NSCLC treated with palliative intent	1 (21), Level IV	Single-arm, retrospective study	High

< k = number of studies; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation >

*Note, two studies reported different outcomes from the same population, therefore the true number of published studies was 11.

Table 22 Quality appraisal of included case series investigations of RFA, according to the Downs and Black Checklist for Randomised and Non-Randomised Comparative Trials

Study ID	Reporting: Hypothesis	Reporting: Outcomes	Reporting: Patient characteristics	Reporting: Intervention	Reporting: Confounders	Reporting: Main findings	Reporting: Random variability in results	Reporting: Adverse events	Reporting: Losses to follow-up	Reporting: Actual probabilities	Validity: Invited sample representative	Validity: Participating sample representative	Validity: Facilities representative	Bias: Subjects blinded	Bias: Measurements blinded	Bias: Data dredging	Bias: Length of follow-up accounted for	Bias: Statistical tests appropriate	Bias: Compliance with intervention	Bias: Outcomes were accurate	Confounding: Recruitment same population	Confounding: Recruitment same time	Confounding: Randomisation	Confounding: Randomisation blinded	Confounding: Adjustment for confounders	Confounding: Losses to follow-up	Power: Power reported
Safi et al (2015)	1	1	1	0	1	1	1	1	1	0	NA	1	1	0	0	1	1	1	1	1	0	1	0	NA	0	0	0

1 = yes, 0 = no, NA = not applicable.

Table 23 Quality appraisal of included case series investigations of RFA, according to the IHE Quality Appraisal of Case Series Studies (Guo et al 2016)

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
POPULATION 1																		
Ambrogi et al (2011)	✓	?	?	?	✓	•	✓	✓	✓	×	✓	✓	✓	×	•	✓	✓	✓
Dupuy et al (2015)	✓	✓	✓	?	✓	•	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	✓
Hiraki et al (2011)	✓	×	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	×	✓	✓	•
Lanuti et al (2012)	✓	×	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	•	•	✓	•
Liu et al (2015)	✓	×	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	•
Ridge et al (2014)	✓	×	?	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓	•	✓	✓	•
Viti et al (2014)	✓	×	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	•	✓	✓	✓
POPULATION 2																		
de Baere et al (2015)	✓	×	✓	✓	•	•	?	✓	✓	×	✓	✓	✓	×	✓	•	×	✓

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Fanucchi et al (2016)	✓	×	×	?	•	✓	?	•	✓	×	•	✓	✓	✓	✓	✓	✓	✓
Hiraki et al (2011)	✓	×	✓	×	•	✓	?	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	•
Koelblinger et al (2014)	✓	×	?	?	×	•	?	✓	✓	×	•	✓	×	N/A	×	•	✓	•
Li et al (2012)	•	×	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	N/A	✓	•	×	✓
Lu et al (2015a)	×	✓	×	✓	•	✓	?	•	•	×	•	✓	✓	×	✓	•	•	×
Lu et al (2015b)	✓	?	×	?	•	✓	?	•	•	×	•	✓	×	×	✓	✓	✓	×
Matsui et al (2015)	✓	×	×	✓	•	✓	?	✓	✓	×	✓	✓	✓	N/A	✓	✓	✓	•
von Meyenfeldt (2011)	•	×	×	✓	•	•	?	✓	✓	×	•	✓	✓	×	✓	✓	✓	•
Yan (2006 + 2007)	✓	✓	×	✓	✓	✓	✓	✓	•	×	•	✓	✓	✓	•	•	✓	×

✓ = yes, × = no, • = partial,? = unclear.

Note: The IHE quality appraisal tool has been modified to remove two questions that are not applicable to this review. These include: Were additional interventions (co-interventions) clearly described? And, were the relevant outcome measures made before and after the intervention?

Risk of bias for studies of radiotherapy

Risk of bias associated with study design

The overall risk of bias in the included radiotherapy studies is summarised in Table 24. Detailed quality appraisal scores for each study are presented in Table 25 and Table 26.

In population one, two RCTs and four non-randomised controlled trials of current best practice radiotherapy for early stage NSCLC were identified. Included studies investigated SBRT compared to conventional radiotherapy and no therapy, single-fraction SBRT compared to multi-fraction SBRT, and radical radiotherapy compared to radical radiotherapy plus chemotherapy. The results of the comparative data give a more reliable estimate of the effectiveness and safety of radiotherapy compared to case series evidence, but cannot directly inform the relative effectiveness or safety of radiotherapy compared to MTA or RFA.

In population two, the majority of the identified studies that reported safety and effectiveness were case series (k = 14/17). The risk of bias in case series studies is inherently high, due to the lack of comparison to an alternate therapy. Three comparative studies were also identified, which compared single- and multi-fraction SBRT schedules (Siva et al 2015), or compared SBRT and surgery (Widder et al 2013; Yu et al 2014).

In the Cochrane review of palliative radiotherapy for lung cancer (population three), risk of bias was ranked according to the Cochrane risk of bias tool (Higgins et al 2011). Studies were evaluated according to random sequence generation, blinding, incomplete outcome data, selective reporting and other biases. Blinding of patients and treating physicians to treatment allocation was not included as a quality criteria, as it was unlikely to affect the risk of bias in reported outcomes (Stevens et al 2015). Overall, the risk of bias across included studies was low.

Selection bias

Most of the included studies reported both inclusion and exclusion criteria and there were a number of RCTs and comparative trials. However, within the case series evidence, differences in inclusion criteria that may have a prognostic impact may have contributed to variation in the outcomes. Most studies did not adjust for potential confounders in the analysis.

Performance bias and detection bias

None of the reported trials included for population one reported the method of randomisation (if relevant), nor whether the subjects or assessors were blinded to the intervention. Case series studies were predominantly retrospective. Concerns with reporting limited interpretation of the relationship between the intervention and outcomes.

Attrition bias and reporting bias

In general, it is not clear within retrospective case series studies whether certain outcomes were omitted because they were not collected, or because they were incomplete. Reporting of outcomes across the case series evidence was not comprehensive and approach to losses to follow-up was often unclear. Similarly, losses to follow up were also poorly reported in comparative trials.

Populations

Study populations are discussed in more detail in Section B.4.

Risk of bias across the outcome reporting

The available evidence is inconsistent both in terms of which outcomes were measured and how they were assessed and reported within studies. Price et al (2012), Videtic et al (2015) and Lucas et al (2015) reported adverse events according to the NCI-CTCAE, while Jeppsen et al (2013) did not define how adverse events were recorded. Ten case series investigations reported adverse events according to the NCI-CTCAE criteria (k = 10), two reported adverse events according to the Randomised controlled trial Radiation Therapy Oncology Group (RTOG) criteria, and two reported adverse events according to both NCI-CTCAE and RTOG criteria.

Table 24 Risk of bias and quality appraisal for Radiotherapy studies

Intervention and population	Number of studies (patients), level of evidence	Reporting/quality concerns	Risk of bias
Radiotherapy for early stage NSCLC. Patients were ineligible for resection or refused surgery	2 (195), Level II 1 (1,502), Level III-1 3* (13,282), Level III-2 1 (132), Level III-3	2 randomised, 1 propensity-matched, 4 non-randomised studies. No studies reported blinding of patients, treating physicians or outcome assessors to treatments.	Moderate
Radiotherapy for patients with lung metastases in whom the primary tumour is under control	3 (233), Level III-2 14 (575), Level IV	All non-randomised, 13/17 studies were retrospective. No studies reported blinding of patients, treating physicians or outcome assessors to treatments.	High
Radiotherapy for patients with lung metastases or primary NSCLC treated with palliative intent	14 (3,576), Level I	Cochrane systematic review, included RCTs only. Most studies did not report their random sequence generation (selection bias), or blinding for symptom control (performance bias and detection bias). 7/14 studies had incomplete data for symptom control.	Low

< NSCLC = non-small cell lung cancer; OS = overall survival; PS = performance status; RCT = randomised controlled trial >
*Note: the 1502 patients from the Level III-1 group overlapped with the Level III-2 study.

Table 25 **Quality appraisal of included comparative studies of radiotherapy, according to the Downs and Black Checklist for Randomised and Non-Randomised Comparative Trials**

Study ID	Reporting: Hypothesis	Reporting: Outcomes	Reporting: Patient characteristics	Reporting: Intervention	Reporting: Confounders	Reporting: Main findings	Reporting: Random variability in results	Reporting: Adverse events	Reporting: Losses to follow-up	Reporting: Actual probabilities	Validity: Invited sample representative	Validity: Participating sample representative	Validity: Facilities representative	Bias: Subjects blinded	Bias: Measurements blinded	Bias: Data dredging	Bias: Length of follow-up accounted for	Bias: Statistical tests appropriate	Bias: Compliance with intervention	Bias: Outcomes were accurate	Confounding: Recruitment same population	Confounding: Recruitment same time	Confounding: Randomisation	Confounding: Randomisation blinded	Confounding: Adjustment for confounders	Confounding: Losses to follow-up	Power: Power reported or sufficient
POPULATION 1																											
Price (2012)	1	1	0	1	1	1	0	1	0	0	NA	?	1	0	0	0	1	1	1	1	?	1	1	0	0	1	1
Videtic (2015)	1	1	1	1	1	1	1	1	0	NA	NA	?	1	0	0	0	1	1	1	1	?	1	0	0	0	0	0
Koshy (2015)	1	1	1	0	1	1	1	0	0	1	NA	?	1	0	0	0	1	1	1	1	1	0	0	NA	0	0	1
Jeppsen (2013)	1	1	1	1	1	1	0	0	0	1	NA	?	1	0	0	0	1	1	1	1	1	0	0	NA	0	0	0
Lucas (2015)	0	0	1	1	1	1	1	0	0	1	NA	?	1	0	0	0	1	1	1	0	0	1	0	NA	0	0	0
POPULATION 2																											
Siva (2015)	1	1	0	1	1	1	1	0	0	1	NA	?	1	0	0	0	1	1	1	1	1	1	0	NA	0	0	0
Widder (2013)	1	1	0	1	1	1	1	0	0	1	NA	?	1	0	0	0	1	1	1	1	1	1	0	NA	0	0	0

Yu (2014)	1	1	0	1	1	1	0	0	0	0	NA	?	1	0	0	0	1	1	1	1	1	1	0	NA	0	0	0

CA = cannot answer; 1 = yes, 0 = no, NA = not applicable.

Table 26 **Quality appraisal of included case series investigations of radiotherapy, according to the IHE Quality Appraisal of Case Series Studies (Guo et al 2016)**

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Agolli (2015)	✓	×	×	?	✓	✓	✓	✓	✓	×	✓	✓	✓	×	×	•	•	•
Baschnagel (2013)	✓	•	×	?	•	✓	?	✓	✓	×	✓	✓	✓	✓	×	✓	•	×
Garcia-Cabezas (2015)	✓	×	×	✓	•	✓	?	•	✓	×	•	✓	✓	×	×	•	•	•
Filippi (2015)	•	×	×	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	•	✓	•
Gamsiz (2014)	✓	×	×	?	•	✓	?	✓	✓	×	✓	✓	✓	×	×	•	×	•
Kim (2009)	✓	×	×	?	•	✓	?	✓	✓	×	✓	✓	✓	×	•	✓	✓	•

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Navarria (2014)	✓	✓	×	✓	•	✓	?	✓	✓	×	•	✓	✓	×	×	•	✓	✓
Navarria (2015)	•	✓	×	✓	•	✓	?	✓	✓	×	•	✓	✓	×	✓	•	✓	✓
Norihisa (2008)	•	×	×	?	•	✓	?	•	✓	×	✓	✓	✓	×	×	✓	×	✓
Nuyttens (2015)	✓	✓	×	?	•	✓	?	•	✓	×	✓	✓	✓	×	✓	✓	✓	•
Oh (2012)	•	×	×	?	•	✓	?	✓	✓	×	✓	✓	✓	×	×	•	•	•
Osti (2013)	✓	✓	×	?	•	✓	?	✓	✓	×	✓	✓	✓	×	×	•	✓	•
Ricardi (2011)	✓	×	×	?	•	✓	?	✓	✓	×	✓	✓	✓	×	×	•	•	•
Takahashi (2014)	✓	×	×	✓	•	✓	?	✓	✓	×	✓	✓	✓	×	✓	•	×	•

✓ = yes, × = no, • = partial, ? = unclear, NA = not applicable.

Note: The IHE quality appraisal tool has been modified to remove two questions that are not applicable to this review. These include: Were additional interventions (co-interventions) clearly described? And, were the relevant outcome measures made before and after the intervention?

Risk of bias in the included studies for surgery

The studies identified for surgical resection in population two were selected to give an idea of the outcomes associated with surgical resection in patients with oligometastatic disease. Two systematic reviews were identified and included because they represent a synthesis of a large volume of patient data; however, neither included any comparative data. Information from these systematic reviews was supplemented with the results of large, recent studies. No randomised comparative trials, or any other comparative trials were identified in this population and the evidence base is comprised entirely of Level IV studies. The two systematic reviews were appraised using the AMSTAR tool and the case series were appraised using the 'Quality Appraisal Checklist for Case Series Studies' developed by the Institute of Health Economics (Guo et al 2016). Some important issues regarding risk of bias in the included studies are summarised in Table 27. The AMSTAR appraisal of the two systematic reviews is presented in Appendix C to this report and is not reproduced within this section.

Risk of bias associated with study design

Evidence for surgical resection in population two is limited to Level IV evidence (case series) and systematic reviews of Level IV evidence. This evidence cannot be used to inform estimates of comparative effectiveness. Of the two systematic reviews, that by Pfanschmidt (2007) was of particularly poor quality. In both systematic reviews, the included studies were comprised entirely of Level IV evidence. Reporting of complications in both the primary studies and the systematic reviews was poor. Only one study reported on complications in a comprehensive fashion (Roudriguez-Fuster et al 2014). In general only 5-year overall survival was reported.

Selection bias

Inherent in the case series study design is risk of selection bias. In studies where it is unclear how patients were selected for the intervention, or whether cases were included consecutively, there may be issues with selection bias. The eligibility criteria were usually only partially reported in the Level IV studies and it was unclear whether patients were consecutive or not. Of particular concern, with respect to patients selected for surgical resection, is the issue of 'survivor bias'; the confounding effect of selecting patients who are likely to survive longer (Fiorentino et al 2010; Treasure et al 2012). Many studies of surgical resection in this population aim to characterise the prognostic factors related to better outcomes after surgical resection and thereby refine selection criteria accordingly. However, the findings of many studies are contradictory and underpowered for the identification of such influences. Without data on the natural history of this disease state it is unclear what benefit surgical resection offers.

Performance bias and detection bias

In terms of outcome measures such as overall survival, the majority of the included studies are not explicit about treatments received post-surgery. Therefore, it is unclear whether other therapies may also have been delivered that could affect patient survival. The issue of 'survivor bias' will also have contributed to performance bias in both primary studies and systematic reviews.

Attrition bias and reporting bias

In general, it is not clear within retrospective case series studies whether certain outcomes are omitted because they were not collected, or not complete. Reporting of outcomes across the case series evidence was not comprehensive and approach to losses to follow-up was often unclear. Systematic reviews tended to report only 5-year survival and neglected complications and safety issues. In general, complications were not well reported. Additionally, given the invasive nature of surgical resection *and* its impact on patient lung volume it would be reasonable to expect studies to include outcomes related to quality of life and activities of daily living post resection. However, the systematic reviews did not identify this outcome and no primary studies reporting on these outcomes were identified through the search of the literature.

Populations

Study populations are discussed in more detail in Section B.4. In order to provide data on the outcomes of surgical resection across a range of primary cancers, large studies of specific populations were selected. Renaud et al (2014) reported on 320 patients with colorectal primary cancers, Younes et al (2009) reported on 529 patients with mixed primary cancers, Reza et al (2014) reported on 118 patients with sarcoma, Rodriguez-Fuster (2014) reported on 532 patients with primary colorectal carcinoma, and Kitano et al (2012) reported on patients with hepatocellular carcinoma. The systematic reviews included one of patients with head and neck cancers and one of patients with colorectal cancer. Given the diversity of primary cancers included in studies of MTA and RFA, it was deemed appropriate to include a similar spectrum for surgery. Regarding the potential prognostic impact of primary cancer type on survival following metastasectomy, results from these studies should be considered with respect to the population treated.

Risk of bias across the outcome reporting

The available evidence has studies largely 5-year survival following resection and 1, 2 and 3-year survival is typically not available. Time to progression and data concerning local control and complications were sparsely reported. There was inconsistency across studies in terms of which outcomes were measured and how they were assessed.

Table 27 Summary of the risk of bias concerns within studies of surgical resection

Intervention and population	Number of studies (patients) and level of evidence	Reporting/quality concerns	Risk of bias
Surgical resection for patients with lung metastases in whom the primary tumour is under control	2 systematic reviews of Level IV studies	Both systematic reviews included only Level IV evidence in their analysis. Only one performed a meta-analysis. Pfannschmidt et al 2007 was of particularly low quality reporting and provided only narrative synthesis of the data. The meta-analysis reported in Young et al 2015 is of a better reporting quality; however, it is still limited by the level of primary evidence (IV) which is at a high risk of bias.	High
Surgical resection for patients with lung metastases in whom the primary tumour is under control	5 Level IV studies	Retrospective study designs, reporting of adverse events was incomplete for one study, poor reporting in relation to consecutive recruitment of patients, comprehensive eligibility criteria and follow-up	High

Table 28 Quality appraisal of included case series investigations of surgical resection, according to the IHE Quality Appraisal of Case Series Studies

Study ID	Was the objective of the study clearly stated?	Was the study conducted prospectively?	Were the cases collected in multiple centres?	Were patients recruited consecutively?	Were patient characteristics described?	Were the eligibility criteria clearly stated?	Did patients enter the study at a similar point in the disease?	Was the intervention clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention?	Were outcomes measured using appropriate methods?	Were the statistical tests appropriate?	Was follow-up long enough to capture important events and outcomes?	Were losses to follow-up reported?	Did the study provide estimates of random variability in the data analysis?	Were the adverse events reported?	Were the conclusions of the study supported by results?	Were competing interests and sources of support reported?
Kitano et al (2012)	✓	×	×	✓	✓	•	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	•
Renauld et al (2014)	✓	×	✓	?	✓	✓	✓	✓	✓	×	✓	✓	✓	×	✓	✓	✓	•
Roudriguez-Fuster et al (2014)	✓	✓	✓	?	✓	•	✓	✓	✓	×	✓	✓	✓	✓	✓	✓	✓	✓
Reza et al (2009)	✓	×	×	?	✓	•	✓	✓	✓	×	✓	✓	✓	×	✓	×	✓	•
Younes et al (2009)	✓	×	×	?	✓	•	✓	✓	✓	×	✓	✓	✓	✓	•	✓	✓	×

✓ = yes, × = no, • = partial, ? = unclear.

Note: The IHE quality appraisal tool was modified to remove two questions that are not applicable to this review. These include: Were additional interventions (co-interventions) clearly described? And, were the relevant outcome measures made before and after the intervention?

B.3. CHARACTERISTICS OF THE EVIDENCE BASE

Characteristics of the studies included for MTA

See Appendix C for details on the individual studies included in the evidence base. A total of eight studies meeting the inclusion criteria were identified (Table 29, Table 30, Table 31, Table 32). In all but population three, these studies were Level IV case series evidence. As a consequence of the study design all studies are rated as having a high risk of bias due to the inherent weaknesses of case series evidence. This does not imply that all studies were of a poor quality, but rather that the methodological design of the available evidence is at a high risk of bias. The proposed populations are considered separately below in terms of applicability for reimbursement.

Population one

In practice, this population is likely to account for the majority of ablations that would be performed if the procedure were reimbursed. Clinicians currently providing the service in public hospitals state that this population accounts for upwards of 90 per cent of ablation procedures. The included studies of MTA in this population are well aligned with the proposed population in that: patients were ineligible for surgical resection, had a range of comorbidities, tended to be in their sixth or seventh decade of life and had early stage NSCLC. Only two of the included studies contribute data on primary effectiveness outcomes.

In terms of study size, each of the included studies had less than 50 patients and in total only 90 patients and those patients differed across studies in terms of the proportion of patients with potential prognostic factors such as tumour size and peripheral versus central tumours. In Han et al (2015) lesion size was predominantly less than 35 mm and in Liu & Steinke (2015) an inclusion criteria of lesion size being less than 40 mm was applied. However, Yang et al (2014) had approximately half of the ablated lesions greater than 35 mm and included only peripheral NSCLC. It is not clear what the breakdown of such factors would be in practice; however, taken together the studies likely cover the spectrum of patients who might be treated.

Table 29 Characteristics of the included evidence for MTA in population one

Trial/Study	N (lesions)	Design; Duration [a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Han et al (2015)	28 (28)	Retrospective CS, Median 22.5 (4–53) months	High	Stage I NSCLC (> 75 years) and not candidates for resection	Overall survival, local efficacy, adverse events	Not used
Liu & Steinke (2015)	15 (16)	Retrospective CS, Median 12 (6–18) months	High	Stage Ia or Ib NSCLC, medically inoperable	Treatment outcome, adverse events within 24 hours	Not used
Yang et al (2015	47 (47)	Retrospective CS, Median 30 (7–70) months	High	Stage Ia or Ib peripheral NSCLC, medically inoperable or declined surgery	Overall survival, local control, TTLP, cancer-specific survival, adverse events, length of hospital stay	Not used
Meta-analysis/pooling	90 3 studies			Not applicable, outcomes could not be standardised or were not reported by all studies		Not used

< CS = case series; NSCLC = non-small cell lung cancer; OS = overall survival; TTLP = time to local progression >

[a] reported as median (range) unless otherwise stated.

Population two

Population two, patients with oligometastatic disease in the lung, are a heterogeneous group and there is debate in the literature regarding the criteria for selecting patients for potentially curative local therapies. Many studies have attempted to characterise a range of prognostic markers such as number and size of lesions, tumour histology, origin of the primary cancer, disease free interval and others that might be used to select patients likely to benefit (Cho et al 2015; Meimarakis et al 2014; Sclafani et al 2013; Veronesi et al 2007; Younes et al 2012). More fundamentally, some authors question whether the current state of evidence for such interventions (non-comparative, case series or cohort studies) can distinguish between the therapeutic effects of the intervention in terms of extended survival and the confounding effect of selecting patients who are likely to survive longer (effect of 'survivor bias') (Fiorentino et al 2010; Treasure et al 2012).

Overall there is a general consensus within the literature that oligometastatic disease involving the lung is characterised by lesions limited in number; cancer at the primary site that is eradicated, controlled or amenable to control; there is no extra thoracic metastases, or if there is, it is eradicated or controlled; and, that the patient is well enough to undergo the proposed treatment (Treasure et al 2012). That is, this patient group is characterised by a certain profile of disease presentation. This means that identifying the number of patients potentially eligible for such therapy is very challenging as cancer registries do not routinely collect detailed information on metastases. In this respect the heterogeneity amongst the included studies for MTA reflects this population in a broad sense. However, the volume of published literature for other interventions within this population *and* clinical input suggests that, in practice, metastases to the lung from colorectal cancers might comprise the majority of patients eligible for 'curative' local therapy. Within the MTA studies there were a total of 40 patients with colorectal carcinoma as the primary treated disease.

Table 30 Characteristics of the included evidence for MTA in population two

Trial/Study	N (lesions)	Design; Duration [a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Qi et al (2015)	17 (29)	Retrospective CS, Median 14 (3–24) months	High	Lung metastases from nasopharyngeal carcinoma, primary tumour controlled	Treatment response, local control, new recurrence, adverse events	Not used
Vogl et al (2015)	80 (130)	Retrospective CS, Median 9 (6–24) months	High	Surgically unresectable lung metastases or recurrence, primary tumour controlled[b]	Local tumour control, survival rate, adverse events, re-ablation,	Not used
Meta-analysis/pooling	97 2 studies			Not applicable, it is not appropriate to undertake pooling for two studies		Not used

< CS = case series; MTA = microwave tissue ablation; NSCLC = non-small cell lung cancer; TTLP = time to local progression >

[a] reported as mean (range) unless otherwise stated.

[b] primary tumour (patients/lesions): colorectal carcinoma (40/58), breast carcinoma (20/32), hepatocellular carcinoma (10/30), renal cell carcinoma (5/5), bronchogenic carcinoma (5/5).

Population three

Population three includes patients who would be eligible for MTA as a palliative therapy with the primary aim of relieving symptoms, improving quality of life and minimising tumour burden (Ye et al 2015). This population is heterogeneous in the sense that the primary cancer could be NSCLC or any other, patients in this group are characterised by prognosis and tumour burden within the lung. The

three studies included in this review included only patients with advanced stage primary NSCLC. None of the three studies included in this population provided any information regarding the effects of treatment on symptoms or quality of life. Two of the included studies were non-randomised comparative trials which investigate MTA in combination with chemotherapy compared to chemotherapy alone (Wei et al 2015), and MTA in combination with chemotherapy compared to MTA alone (Sun et al 2015a). Thus there was some heterogeneity in terms of the intervention; however, given the nature of palliative interventions this is appropriate. The weakness in this evidence is that no data on quality of life or symptom control is provided.

Table 31 Characteristics of the included evidence for MTA in population three

Trial/Study	N (lesions)	Design; Duration [a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Ni et al (2015)	35 (39)	Retrospective CS, Median 18 (6–45) months	High	Stage IIIB-IV NSCLC who had had prior treatment and who had partial response or stable disease	Response to MTA (complete/incomplete ablation), technical efficacy, survival and complications	Not used
Sun et al (2015)	40 (46)	Retrospective NR comparative, Range: 6–35 months	High	Stage IIIB-IV NSCLC	Local efficacy, modified RECIST criteria, disease control, 1-year and 2-year survival rates, adverse events	Not used
Wei et al (2015)	74 (NR)	Retrospective NR comparative, Median 21 (5–39) months	High	Stage IIIB-IV NSCLC	Treatment response (complete / incomplete ablation), TTLP, progression free survival, overall survival, complications	Not used
Meta-analysis/pooling	149 3 studies			Not applicable, outcomes could not be standardised or were not reported by all studies		Not used

< CS = case series; MTA = microwave tissue ablation; NR = non-randomised; NSCLC = non-small cell lung cancer; OS = overall survival; RECIST = Response Evaluation Criteria in Solid Tumours; TTLP = time to local progression >

[a] reported as median (range) unless otherwise stated.

Studies of microwave ablation of lung tumours not meeting inclusion criteria for effectiveness but included to inform the safety profile of MTA

In order to provide the MSAC with a more complete safety profile of MTA used in the lung, all studies of MTA for primary or secondary lung cancer which did not meet the inclusion criteria were extracted and appraised separately. These studies include:

- Studies with mixed primary and secondary lung lesions that meet inclusion criteria but for whom demographic data and results are not separable.
- Studies of patients with primary or secondary lung lesions for whom there is insufficient demographic or other data to establish whether they meet the inclusion criteria for the review.
- Studies of patients treated with MTA or RFA for whom results are separable but demographic data is not separable.

It was not appropriate to include these studies for an assessment of effectiveness as they do not meet the inclusion criteria. However, where possible adverse events associated with MTA have been extracted and contribute to Section B.6. All studies are at a high risk of bias.

Table 32 Additional studies of MTA included for safety

Trial/Study	N (lesions)	Design; Duration[a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Alexander et al (2013)	163 (195)[b]	Retrospective CS, Mean 20 (SD 15) months	High	Lung neoplasms treated with MTA and/or RFA	Incidence of rib fracture	Not used
Belfiore et al (2013)	58 (69)	Retrospective CS, NR	High	Inoperable primary or secondary lung cancer	Adverse events	Not used
Carafiello et al (2014)	24 (26)	Retrospective CS Mean 10 (range 2–26) months	High	NSCLC stages I-IV, or metastases, inoperable or refused surgery	Adverse events	Not used
Carafiello et al (2012)	45 (53)[c]	Retrospective CS NR	High	Inoperable primary or secondary lung tumours treated by MTA or RFA	Adverse events	Not used

Trial/Study	N (lesions)	Design; Duration[a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Chung et al 2014	39 (63)	Retrospective CS NR	High	Lung tumours treated by MTA	Adverse events	Not used
Egashira et al 2016	44 (87)	Retrospective CS Median 15 (6.2–29.5) months	High	Pulmonary tumours of primary or secondary origin[d]	Adverse events	Not used
He et al (2006)	12 (16)	Retrospective CS Mean: 20 (6–40) months	High	Primary cancer not suitable for resection and patients with oligometastatic lung lesions	Adverse events	Not used
Little et al (2013)	23 (29)	Retrospective CS Median 6 (3–19) months	High	Primary cancer not suitable for resection and oligometastatic lung lesions	Adverse events	Not used
Lu et al (2012)	69 (93)	Retrospective CS NR	High	Stage IIIB NSCLC or pulmonary metastases, inoperable	Adverse events	Not used
Nour-eldin et al (2011)	164[e] (NR)	Retrospective CS NR	High	Primary NSCLC or secondary lung tumours, inoperable	Adverse events	Not used
Sun et al (2014)	29 (39)	Retrospective CS Median 25 (3–45) months	High	Primary or metastatic lung cancer	Adverse events	Not used
Splatt & Steinke (2015)	51 (70)	Retrospective CS NR	High	Primary pulmonary malignancies or secondary metastases	Adverse events	Not used
Vogl et al (2012)	57 (91)	Retrospective CS mean (range): 10.2 (6.0–29.2) months	High	Primary or oligometastatic secondary lung cancer	Adverse events	Not used

Trial/Study	N (lesions)	Design; Duration[a]	Risk of bias	Patient population	Key outcome(s)	Result used in economic model
Wolf et al (2008)	82 (NR)	Retrospective CS mean (SD): 10 (6.8) months	High	Primary or secondary lung cancer, medically inoperable or refusing surgery	Adverse events	Not used
Yang et al (2015)	36 (40)	Retrospective CS Patients had at least one 6 month follow-up	High	Primary or secondary lung cancer who underwent MTA with or without induction of an artificial pneumothorax	Adverse events	Not used
Zheng at al (2014)	184 (253)	Retrospective CS NR	High	Primary or secondary lung cancer, medically inoperable or refusing surgery	Adverse events	Not used
Meta-analysis/pooling	Not calculable 16 studies			Where possible n/N (%) for adverse events has been calculated across all studies. Measures of central tendency and associated measures of variance have been reported if applicable		Not used

< CS = case series; MTA = microwave tissue ablation; n/N (%) = number with event/ total (percentage); NR = not reported; NSCLC = non-small cell lung cancer; RFA = radiofrequency ablation >

[a] reported as median (range) unless otherwise stated.

[b] 113 tumours treated by RFA, 74 tumours treated by MTA, 8 tumours treated by RFA and MTA in separate sessions.

[c] 29 patients (36 lung lesions) were treated with RFA; 16 patients (17 lung lesions) were treated with MTA.

[d] performed under normal respiration under conscious sedation (NR-CS) or high-frequency jet ventilation under general anaesthesia (HFJV-GA).

[e] 248 ablations in 164 patients were RFA ablations in 200 and MTA ablations in 48, number of patients: NR.

Characteristics of the studies included for RFA

One existing systematic review of reasonable quality was identified that reported the safety and effectiveness of RFA in patients with primary and secondary lung cancer, with search results up to 2006 (Zhu et al 2008a). The review conducted a comprehensive search, which identified only two studies that investigated primary NSCLC, and one that investigated metastases. The remaining 14 studies included in the review were from mixed population studies, which may have included patients from all three populations relevant to this assessment.

See Appendix C for details on the individual studies on RFA included in the evidence base. A summary is provided in Table 33 to Table 35.

Population one

Eight case series and one retrospective cohort study involving a total of 387 patients met the inclusion criteria for population one. The included patients presented with homogenous disease (inoperable stage IA-IB NSCLC), of similar mean size (median 21 mm, range 14–32 mm), similar median age (median 74.7 years, range 70–78 years), and similar gender (median 50% male, range 40–90%). The types of pre- and post-RFA therapies varied between patients. Between 37 and 58 per cent of patients had prior surgery for either an existing cancer (either NSCLC or other), with or without radiotherapy. Other significant comorbidities were not reported.

Table 33 Characteristics of the included evidence for RFA in population one

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Ambrogi et al (2011)	57 (59)	CS 46 (12–82) months	High	Stage IA-IB NSCLC, inoperable or refused surgery, diameter ≤ 50 mm, lesions > 10 mm from large vessels and airways	Overall, disease free, cancer specific survival, adverse events	Not used
Dupuy et al (2015)	51 (51)	prospective CS *24 (NR) months	High	Stage IA NSCLC, inoperable or refused surgery, lesion diameter ≤ 30 mm	Overall, PF survival, adverse events	Not used
Hiraki et al (2011)	50 (52)	Retrospective CS 37 (2–88) months	High	Stage IA-IB NSCLC, inoperable or refused surgery,	Overall, cancer-specific, disease-free survival, adverse events	Not used
Lanuti et al (2012)	45 (55)	Retrospective CS 32 (2–75) months	High	Stage IA-IB NSCLC, inoperable or refused surgery, lesion diameter < 50 mm, no disease outside involved lobe	Overall, disease-free survival, adverse events	Not used
Liu et al (2015)	29 (29)	Retrospective CS 19 (2–75) months	High	Stage IA-IB NSCLC, inoperable or refused surgery, ECOG status ≤ 2	Overall, cancer-specific survival, adverse events	Not used
Ridge et al (2014)	29 (29)	Retrospective CS 30 (12–85) months	High	Stage IA-IIA NSCLC, no prior in-field RT or resection, no chemo 12 months prior	Overall, PF survival, adverse events	Not used

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Safi et al (2015)	RFA 25 (NR) RT 49 (NR)	Retrospective cohort 10–13 (NR) months	Moderate	Stage IA-IB NSCLC	Overall, PF survival, adverse events	Not used
Viti et al (2014)	22 (24)	Retrospective CS Mean 30 (NR) months	High	Stage IA-IB NSCLC, inoperable or refused surgery, lesion diameter ≤ 35 mm	Overall, disease-free survival, adverse events	Not used
Yoo et al (2011)	30 (30)	Prospective CS 12[a] (range NR) months	High	Stage IA NSCLC, inoperable or high risk for surgery, ECOG status ≤ 2	Event rate (death, repeat ablation, progression)	Not used
Zhu et al (2008)	833 k = 16	Systematic review of CS	Moderate	Narrative analysis with descriptive statistics	Adverse events	Not used
Meta-analysis/ pooling	387 9 studies			Where possible n/N (%) for adverse events has been calculated across all studies. Measures of central tendency and associated measures of variance have been reported if applicable		Not used

< CS = case series; ECOG = Eastern Cooperative Oncology Group; mm = millimetres; n/N (%) = number with event/ total (percentage); NR = not reported; NSCLC = non-small cell lung cancer; PF = progression-free; RFA = radiofrequency ablation; RT = radiotherapy >

a unclear if median or mean reported.

Population two

Ten case series studies involving 997 patients met the inclusion criteria for population two. The included sample populations were diverse, even after accounting for the strict study inclusion criteria. The high degree of variation was due to differences in the stage of primary disease (T1–T4), type of primary cancer (liver, colorectal, sarcoma, breast, kidney, other), median age distribution (median 62 years, range 48–75 years), and importantly, treatment strategies for pulmonary metastases pre- and post-RFA. The lack of uniformity in pre-RFA treatment strategies was indicative of the retrospective nature of the included studies, in which RFA was not typically used as a first-line therapy, but after surgery was refused or deemed non-feasible. Due to these key differences between studies, it is difficult to determine whether the estimated survival rates can be attributed to treatment effects from RFA, pre- or post-RFA therapies, or if they reflect the natural history of this highly selected population (i.e. limited metastases, primary under control, good performance status,

etc.). Due to the presence of significant confounders that have not been adjusted for in the primary studies, the impact of RFA on survival is unclear based on the included evidence.

Table 34 Characteristics of the included evidence for RFA in population two

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Population	Key outcome(s)	Result used in economic model
de Baere et al (2015)	566 (1037)	Retrospective CS 36 (IQR 20–55) months	High	Lung metastases, inoperable or refused surgery, amenable to curative therapy	Overall, PF survival, adverse events	Not used
Fanucchi et al (2016)	61 (86)	Retrospective CS 28 (2–126) months	High	Lung metastases, controlled or absent extra thoracic disease, size < 50 mm	Overall, PF survival, adverse events	Not used
Hiraki et al (2011)	32 (83)	Retrospective CS 21 (4–98) months	High	HCC lung metastases, size < 40 mm	Overall survival, adverse events	Not used
Koelblinger et al (2014)	22 (55)	Retrospective CS 12 (4–54) months	High	Sarcoma lung metastases, amenable to curative therapy	Overall, PF survival, adverse events	Not used
Li et al (2012)	29 (68)	Retrospective CS 23 (6–70) months	High	HCC lung metastases, inoperable, controlled primary, size ≤ 50 mm, ≤ 5 lesions	Overall, PF survival, adverse events	Not used
Lu et al (2015)	67 (115)	Prospective CS 24 (3–39) months	High	Lung oligometastses, inoperable or refused surgery, absent or controlled primary, size < 50 mm	Overall, PF survival, adverse events	Not used
Lu et al (2015b)	35 (67)	CS (enrolment unclear) F/U NR	High	Breast cancer lung metastases, inoperable or refused surgery, absent or controlled extra thoracic disease, prior systemic chemotherapy, size < 40 mm	Overall survival, adverse events	Not used
Matsui et al (2015)	84 (172)	Retrospective CS 38 (5–130) months	High	CRC lung metastases, inoperable or refused surgery, primary lesion resected, amenable to curative therapy	Overall, PF survival, adverse events	Not used
von Meyenfeldt et al (2011) [a]	46 (90)	Retrospective CS 22 (2–65) months	High	Limited (recurrent) lung metastases with peripheral locations, < 5 lesions per patient	Overall, PF survival, adverse events	Not used

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Population	Key outcome(s)	Result used in economic model
Yan et al (2006 + 2007)	55 (NR)	Prospective CS 24 (6–40) months	High	CRC lung metastases, inoperable or refused surgery, primary cancer resected, 3–5 lesions, size ≤ 50mm	Overall, PF survival, adverse events	Not used
Zhu et al (2008)	833 k = 16	Systematic review of CS	Moderate	Narrative analysis with descriptive statistics	Adverse events	Not used
Meta-analysis/ pooling	997 10 studies			Where possible n/N (%) for adverse events has been calculated across all studies. Measures of central tendency and associated measures of variance have been reported if applicable		Not used

< CRC = colorectal cancer; CS = case series; HCC = hepatocellular carcinoma; IQR = interquartile range; k = number of studies; mm = millimetres; n/N (%) = number with event/ total (percentage); NR = not reported; PF = progression-free >

a While not explicitly stated in the inclusion criteria, the authors state in the introduction that patients with lung metastases are only treated at their institution if the primary cancer is under control.

Population three

One case series study including 21 patients was identified that reported palliative therapy. The study investigated long-term patient survival, local tumour progression, complication rates and symptom improvement related to RFA in lung cancer patients. There were two groups – a local control group of stage I NSCLC and stage IV metastatic cancer, and a palliation group involving stage IV metastatic cancer only. Patients were assigned to each group based on their symptoms (symptomatic or asymptomatic). The local control group included a mix of patients from population one and population two, and was therefore not included in this report. The palliation group included in this report was representative of the population outlined in the PICO criteria.

Table 35 Characteristics of the included evidence for RFA in population three

Study	N (lesions)	Design Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Simon et al (2007)	21 (27)	Level IV retrospective CS 21 (3–74) months	High	Advanced lung cancer, inoperable or refused surgery, refractory to treatment	Symptom improvement and relapse, adverse events	Not used

< CS = case series >

Characteristics of the studies included for radiotherapy

See Appendix C for details on the individual studies of radiotherapy included in the evidence base. A summary is provided in Table 36 to Table 38.

Population one

No studies were identified that directly or indirectly compared MTA to current best practice radiotherapy in population one. Two Level II studies, two Level III-2 studies and one Level III-3 study, involving a combined total of 6,635 patients that received radiotherapy, met the inclusion criteria for population one. In addition, one study included a control group of 6,888 patients that received no treatment, and reported a propensity-matched subgroup analysis of SBRT compared to RT (Level III-1) (Koshy et al 2015).

The included studies compared SBRT to accelerated hypofractionated radiotherapy (AHRT) (Lucas et al 2014), radical RT to radical RT with chemotherapy (Price et al 2012), SBRT to conventional RT and/or no treatment (Jeppesen et al 2013; Koshy et al 2015), and single-fraction SBRT to multi-fraction SBRT (Videtic et al 2015). In the absence of direct evidence for radiotherapy compared to MTA, comparative data for radiotherapy provides a more representative indication of the safety and effectiveness than single arm trials. In the trial that compared SBRT to AHRT, patients were selected for each treatment based on tumour size, which is likely to have introduced systematic bias into the results (Lucas et al 2014). SBRT patients were significantly older, more likely to be Caucasian, had more squamous cell carcinoma, smaller tumours, earlier stage, and peripherally located lesions.

Sample populations in the randomised and non-randomised comparative trials of radiotherapy were relatively homogenous in terms of disease stage (Stage I-IIB NSCLC), gender distribution (median 49% males, range 40–68%), and median age (median 75 years, range 69–76 years). Prior treatments were only reported in one study (Lucas et al 2014), making it unclear if prior treatment was a confounding factor. Overall, there were limited applicability issues regarding the included studies relative to the PICO criteria.

Table 36 Characteristics of the included evidence for radiotherapy in population one

Study	Intervention (N)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Koshy et al (2015)	SBRT (751) RT (751)	Retrospective propensity-matched cohort 21 (IQR 11–43) months	Low	Stage I NSCLC who did not undergo surgery	Overall survival	Not used

Study	Intervention (N)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Koshy et al (2015)	SBRT (773) RT (5375) NT (6888)	Retrospective cohort 21 (IQR 11–43) months	Moderate	Stage I NSCLC who did not undergo surgery	Overall survival	Not used
Price et al (2012)	RT (56) RT + C (55)	RCT OL MC Follow-up NR	Moderate	Inoperable stage IA-IIB NSCLC	Overall + PF survival, adverse events	Not used
Videtic et al (2015)	Single-FX SBRT(39) Multi-FX SBRT(45)	RCT OL MC Median 30.2 months	Moderate	Stage IA-IIA NSCLC, ≤ 50 mm, medically inoperable or refused surgery	Overall + disease-free survival, adverse events	Not used
Jeppsen et al (2013)	SBRT(100) RT (32)	Historical control 82 (9–173) months	High	Inoperable stage IA-IIA NSCLC	Adverse events	Not used
Lucas et al (2015)	SBRT (81) AHRT (79)	Retrospective cohort 24 (IQR 11–40) months	High	Inoperable stage IA-IIA NSCLC	Adverse events	Not used
Meta-analysis/ pooling	487 4 studies			Where possible n/N (%) for adverse events has been calculated across all studies. Measures of central tendency and associated measures of variance have been reported if applicable		Not used

< AHRT = accelerated hypofractionated radiotherapy; C = chemotherapy; FX = fraction; IQR = interquartile range; MC = multicentre; n/N (%) = number with event/ total (percentage); NR = not reported; NSCLC = non-small cell lung cancer; NT = no therapy; OL = open label (unblinded); PF = progression-free; RCT = randomised-controlled trial; RT = radiotherapy; SBRT = stereotactic body radiotherapy >

Population two

No studies were identified that directly or indirectly compared MTA to current best practice radiotherapy in population two. Three Level III-2 and 14 Level IV studies, involving 709 patients that received radiotherapy and 99 patients that received surgery, met the inclusion criteria for population two. The comparative trials investigated the safety and effectiveness of single- versus multi-fraction SBRT (Siva et al 2015), and SBRT compared to pulmonary metastectomy (Widder et al 2013; Yu et al 2014).

As with the evidence for RFA in population two, the identified studies of radiotherapy for lung oligometastases included a diverse population group. The main differences across studies were related to the type of primary cancer (colorectal, lung, liver, sarcoma, breast, other), median age (median 66 years, range 46–74 years), gender distribution (median 64% male, range 43%–86%), and pre- and post-radiotherapy treatments. Only two studies reported the T-stage of the primary cancer site. Due to the presence of significant confounders that have not been reported or adjusted for in the primary studies, the impact of radiotherapy on survival is unclear based on the included evidence.

Table 37 Characteristics of the included evidence for radiotherapy in population two

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Siva et al (2015)	41 (49) 24 (33)	Retrospective cohort 25 months	Moderate	1–3 lung metastases, ≤ 50 mm, extra thoracic disease treated definitively	Overall survival, adverse events	Not used
Widder et al (2013)	42 (NR) 68 (NR)	Retrospective cohort 43 (IQR 36–60) months	Moderate	1–5 lung metastases treated with curative intent (all visible lesions amenable to treatment), primary tumour curatively resected	Overall, PF survival	Not used
Yu et al (2014)	27 (NR) 31 (NR)	Retrospective cohort 30 (5–96) months	High	Osteosarcoma lung metastases, no other sites, complete resectability of metastases	Overall, PF survival, adverse events	Not used
Agolli et al (2015)	22 (29)	Retrospective CS 18 (4–53) months	High	1–4 lung metastases with primary under control, and no other active sites of distant metastasis	Overall, cancer-specific, PF survival, adverse events	Not used
Baschnagel et al (2013)	32 (47)	Retrospective CS 28 (8–57) months	High	1–3 lung metastases, controlled extra thoracic disease, inoperable or refused surgery	Overall survival, adverse events	Not used
Garcia-Cabezas et al (2015)	44 (53)	Retrospective CS 13 (4–46) months	High	Lung oligometastases, 1–5 lesions, ≤ 50 mm, controlled primary disease	Overall, cancer-specific, PF survival, adverse events	Not used
Filippi et al (2015)	40 (59)	Retrospective CS 20 (3–72) months	High	1–5 colorectal lung metastases, primary resected, absent or controlled extra thoracic disease	Overall, PF survival, adverse events	Not used

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Gamsiz et al (2014)	20 (31)	Retrospective CS 14 (range NR) months	High	1–5 pulmonary metastases, < 70 mm, controlled primary	Overall, disease-free survival, adverse events	Not used
Kim et al (2009)	31 (134)	Retrospective CS 13 (3–23) months	High	Lung oligometastases, no extrapulmonary metastases	Overall, PF survival, adverse events	Not used
Navarria et al (2014)	76 (118)	Prospective CS 18 (6–45) months	High	1–5 lung metastases, controlled primary tumour, no progressive disease longer than 6 months, medically inoperable	Overall, cancer-specific PF survival, adverse events	Not used
Navarria et al (2015)	28 (51)	Prospective CS 21 (8–20) months	High	1–4 lung metastases, slow-progressing disease, controlled primary tumour, progressive disease after chemo ± surgery	Overall survival, adverse events	Not used
Norihasa et al (2008)	34 (43)	Retrospective CS 27 (10–80) months	High	1–2 pulmonary metastases, ≤ 40 mm, locally controlled primary tumour, no other metastatic sites	Overall, disease-free survival, adverse events	Not used
Nuyttens et al (2015)	30 (57)	Prospective CS 36 (4–60) months	High	1–5 lung metastases, inoperable or refused surgery, primary under control	Overall, disease-free survival, adverse events	Not used
Oh et al (2012)	57 (67)	Retrospective CS 21 (3–107) months	High	1–4 lung metastases, < 50 mm, with a controlled primary tumour	Overall survival, adverse events	Not used
Osti et al (2013)	66 (103)	Prospective CS 15 (3–45) months	High	1–2 lung metastases, < 50 mm, controlled extra thoracic disease	Overall, cancer-specific, PF survival, adverse events	Not used
Ricardi et al (2011)	61 (77)	Retrospective CS 20 (3–77) months	High	Patients with 1–3 lung metastases, <50mm, absent or controlled extra thoracic disease	Overall, cancer-specific, PF survival, adverse events	Not used
Takahashi et al (2014)	34 (44)	Retrospective CS 24 (6–167) months	High	Colorectal lung metastases, resected primary, inoperable, no other metastases	Overall survival, adverse events	Not used

Study	N (lesions)	Design; Median follow up (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Meta-analysis/ pooling	808 17 studies			Where possible n/N (%) for adverse events has been calculated across all studies. Measures of central tendency and associated measures of variance have been reported if applicable		Not used

< CS = case series; IQR = interquartile range; mm = millimetres; n/N (%) = number with event/ total (percentage); NR = not reported; PF = progression-free >

Population three

A recently published Cochrane review was identified that evaluated the safety and effectiveness of different palliative radiotherapy regimens in lung cancer patients (Stevens et al 2015). The search was conducted in January 2014, and identified 14 randomised controlled trials involving 3,756 patients. Patients included those with locally advanced or metastatic NSCLC with thoracic symptoms. In order to identify the treatment effects attributable to different radiotherapy regimens, studies that included radiotherapy plus chemotherapy were excluded. As a result, the studies included are not completely reflective of the patients that are likely to receive palliative radiotherapy for lung cancer in Australia, but provide a good representation of the effect of radiotherapy for palliation.

Table 38 Characteristics of the included evidence for radiotherapy in population three

Study	N (lesions)	Design; Follow up duration (range)	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Stevens et al (2015)	3576 k = 14	Systematic review of CS	Moderate	Narrative analysis with descriptive statistics	Overall survival, adverse events	Not used
Meta-analysis/ pooling	3576 14 studies			Random effect model, overall pooled and subgroup analyses for oesophagitis, radiation myelopathy, pneumonitis, 1-yr overall survival		Not used

< CS = case series; k = number of studies >

Characteristics of the included studies for surgery

See Appendix C for details on the individual studies included in the evidence base. A summary is provided in Table 39.

Population two

Studies on surgical resection are only applicable in population two, patients with oligometastatic disease in the lung. Given the heterogeneity of primary cancers in studies of MTA and RFA studies of surgical resection were sought across a range of primary cancers as shown in the tables below. The literature on surgical resection for oligometastatic disease is voluminous and it is neither informative nor feasible to include all studies of surgical resection in this population. The evidence for this intervention is comprised entirely of Level IV studies and as pointed out by other authors there is little to be gained by continuing to compile and report on further uncontrolled studies. Therefore, the approach to providing an overview of potential outcomes expected in this group has been based on the selection of systematic reviews supplemented by large, recent case series data.

Overall the studies include patients that are broadly representative of the population under assessment in that they conform to the general consensus on what constitutes oligometastatic disease.

Table 39 Characteristics of the included evidence for surgical resection, systematic reviews

Study	N studies	Design; Follow up duration (range)	Risk of bias	Results	Key outcome(s)	Result used in economic model
Pfannschmidt et al 2007	2,320 k = 20	Systematic review of CS	High	Narrative analysis with descriptive statistics	Overall survival with analysis of prognostic factors	Not used
Young et al 2015	403 k = 13	Systematic review of CS	Moderate	Meta-analysis of 5-year overall survival	Overall survival with analysis of prognostic factors	Not used

< CS = case series; k = number of studies >

Table 40 Characteristics of the included case series evidence for surgical resection

Trial/Study	N (lesions)	Design/ duration [a]	Risk of bias	Inclusion criteria	Key outcome(s)	Result used in economic model
Renaud et al 2014	320 (NR)	Retrospective CS, 21.6 months (0–192)	High	CRC Lung metastases, resection with curative intent	Overall survival, Prognostic factors, postoperative death	Not used
Younes et al 2009	529 (NR)	Retrospective CS, NR	High	Patients had primary malignant solid tumours and who subsequently underwent surgical resection of lung nodules[b]	Complications, overall survival rate, univariate and multivariate analyses of factors affecting overall survival	Not used
Reza et al 2014	118 (NR)	Retrospective CS, 17.7 (6–45) months	High	Pulmonary metastasectomy for sarcoma involving complete resection of their metastatic disease	Survival, recurrence and repeat resection, analysis of prognostic factors affecting survival	Not used
Rodriguez-Fuster et al 2014	532 (NR)	Retrospective CS, 30 days	High	CRC pulmonary metastases, primary cancer under control, absence of extra pulmonary disease	Complications	Not used
Kitano et al 2012	45 (NR)	Retrospective CS, 17.6 months (0.7–165)	High	Pulmonary metastastasectomy for HCC [d]	Overall survival and disease-free survival	Not used
Meta-analysis/pooling	1544 5 studies			Not applicable, outcomes could not be standardised or were not reported by all studies.		Not used

< CS = case series; CRC = colorectal carcinoma; HCC = hepatocellular carcinoma; SD = standard deviation >

[a] reported as median (range) unless otherwise stated.

[b] In the context of suspected or diagnosed metastatic lesions, patients eligible for resection included those with the following characteristics: 1) primary tumour controlled or controllable, 2) nodules confined to the lung parenchyma, 3) nodules that were amenable to surgical, 4) pulmonary function and clinical condition that were compatible with the planned operation, 5) predictable remaining lung function after resection that would allow for adequate postoperative quality of life, 6) non-availability of a more suitable treatment option for the metastases.

[c] 0-12 years: 38/529 (7.2%); 13-40 years: 155/529 (29.3%); 65 years: 231/529 (43.7%); 70 years: 105/529 (19.8%).

[d] With 1) the possibility of complete resection, 2) no evidence of uncontrolled intrahepatic or extrapulmonary lesions at the time of the lung surgery and 3) adequate general physical condition for the pulmonary resection.

B.4. OUTCOME MEASURES AND ANALYSIS

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results. The comparative safety and effectiveness presented in this assessment draws upon unadjusted and non-comparative data from (largely) low quality evidence. The results should be interpreted with caution. This is reflected in the GRADE assessment presented in summary tables in Section B.8.

Meta-analysis and statistical analysis of the included studies

The main issue in terms of outcome measures and analysis in the included studies stems from a lack of any comparative data for populations one and two. Some comparative evidence for radiotherapy was identified; however, comparisons were generally concerned with different radiotherapy regimes and could not be used to inform the comparative effectiveness of ablative therapies and radiotherapy. Rather, these studies, being of a higher level of evidence simply have a decreased risk of bias and uncertainty associated with summary effects. Because studies on ablative therapies do not contain any comparisons, no benefit with respect to other treatment options (direct or indirect) was tested by the included studies. Also, information given on patient details within studies was scarce and measured in variable units. This was also true of outcome measures; meaning that data was not amenable to pooling with a view to undertaking any synthesis such as propensity matched adjustment that would allow for pseudo randomisation (Bosco et al 2010). Because of these limitations no statistical comparisons could be made across the studies of different interventions. Authors of MTA studies were contacted in an effort to obtain raw data; however, low response rates and the format of data received precluded its use.

When possible, measures of central tendency across studies including the mean and or median from the data as well as an indication of variance have been provided. Studies of MTA are both scarce and of low quality, raising concerns about their suitability for assessment. These issues are also prevalent amongst studies of other interventions used in these populations. Although a greater number of studies have been published on radiotherapy, surgical resection and RFA the vast majority of these studies are also retrospective case series studies with similar issues in terms of reporting of outcome measures. The evidence base, including outcome measures, for all interventions is characterised by a low level of evidence (of varying quantity), poor reporting of outcome definitions, and un-quantifiable levels of uncertainty regarding the impact of patient prognostic factors or the effect of the intervention on study results.

Safety

The International Working Group on Image-guided Tumour Ablation has defined major complications, minor complications and side effects and make recommendations regarding the reporting of those outcomes. According to this working group a major complication is an event leading "*to substantial morbidity and disability, increasing the level of care, or results in hospital admission or substantially lengthened hospital stay*". All other complications are considered minor, whilst side effects are defined as "*expected undesired consequences of the procedure that, although occurring frequently, rarely if ever result in substantial morbidity*". For example, in these populations, pneumothorax requiring chest tube drainage would be considered a major complication whilst pneumothorax that resolves spontaneously would be considered a minor complication. Side effects may include pain, post ablation syndrome and asymptomatic pleural effusion. The working group recommends that complications should be reported on a per-session basis.

The included studies infrequently reported the classification of the adverse events and, owing to limited reporting, it was often difficult to distinguish features of the adverse event that may have required additional treatment. For example, differentiating pleural effusion into major and minor pleural effusions was largely not possible. Similarly the retrospective nature of the majority of the included studies meant that it is not possible to know whether no adverse events occurred or whether no adverse events were reported. In the event that studies made explicit statements such as "no other complications or side effects occurred" events that were not reported were assumed to be nil. However, most events have been recorded as not reported rather than assumed to be nil. Resultantly, pooled estimates of adverse events are largely inappropriate. For the outcome of mortality and pneumothorax a pooled event rate has been calculated as this was reported by the vast majority of studies. However, for other outcomes reporting en masse is given as a measure of central tendency and an associated range as these outcomes are more sparsely reported and less amenable to pooling.

Overall and relative survival outcomes (primary effectiveness)

Survival outcomes are intended to speak to the underlying aim of prolonging life through cure or reduction in disease burden. Within studies of MTA survival outcomes were reported, typically, as Kaplan-Meier estimates with 95 per cent confidence intervals. These were reported as median overall survival time as well as survival rates at 1-, 2-, 3- and 5- years post procedure. In some studies the cancer-specific survival for patients was also reported, although this was infrequent. There are several issues to consider with respect to outcome measures for survival in retrospective case series data:

- The majority of included studies did not report approach to losses to follow-up or if there were any. This will have affected censoring of patients. However, this may be tempered by the fact that retrospective studies probably selected only those patients with available records which introduces some selection bias.

- Small sample size and retrospective study design means that differences in prognostic factors within study groups are likely to contribute to differences in point estimates. For example, certain tumour factors such as size greater than 35 mm in diameter might be associated with a poorer prognosis; however, subgroup analysis with respect to such factors was not routinely undertaken.

- Sample sizes were generally small (<50 patients), which reduces the reliability of the estimates.

Progression free survival and time to progression (secondary effectiveness)

There are a range of outcomes used to report on the local control of tumours including progression free survival and time to local progression. The terms 'recurrence' and 'progression' are frequently used interchangeably. In practice, it is not usually possible to distinguish between an incompletely treated viable tumour that continued to grow (recurrence), or a new tumour which is growing at the treated site (Goldberg et al 2005). The term 'progression' is used preferentially within this report. Progression is usually defined as enhancement on CT following treatment, and definitions for what constitutes enhancement varies substantially across studies making it difficult to compare across the evidence base.

Progression free survival (PFS), in general, is calculated from time of treatment until progression at the treatment site, distant disease or death. However, time to local progression (TTLP) is generally calculated from the time of treatment to progression at the treatment site and does not include deaths or distant disease. A complication for the comparison of PFS and TTLP across studies (for any intervention) is variation in:

- definitions of progression at the local site;

- whether deaths or distant disease are included in measures of PFS; and

- lack of clarity in reporting definitions.

These issues largely preclude the pooling of study reports. Where measures of central tendency across studies are provided, any uncertainty around definitions or potential explanations of inconsistency in results has been noted.

Local control (secondary effectiveness)

Local control measures act as a surrogate measure of effectiveness in that they evaluate the mechanism of effect, i.e. destruction of the tumour and durability of that treatment. A range of local control outcomes were reported within the included studies which vary in terms of the definition of the measure and in terms of time points at which the outcome was measured.

Local recurrence rate could include the number of patients at the end of a study with local recurrence, the number of patients with local recurrence at a particular time point such as at the 6 month CT, or it could be reported as the number of patients with local recurrence at 1, 2, 3 years etc. In addition to differences in reporting time points some studies also reported *local recurrence rates* as Kaplan-Meier estimates.

Tumour progression (secondary effectiveness)

Tumour progression was a measure of local control reported in some studies and it was generally based on the modified response evaluation criteria in solid tumour (RECIST) (Therasse et al 2000). The RECIST criteria are generally measured relatively soon after procedures. Variability in reporting of this outcome, and its uncertain relationship with patient relevant outcomes such as survival, resulted in the decision not to report this local control outcome within the body of the report.

Patient reported outcomes, symptom relief or quality of life (primary effectiveness for population three)

No studies reporting these outcomes were identified and therefore no information regarding the potentially benefits or harms of MTA for patient relevant factors can be provided.

B.5. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS MTA FOR ABLATION OF LUNG CANCER SAFE?

Summary – Research questions were:

What is the safety of MTA in patients with early stage inoperable NSCLC as compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy?

What is the safety of MTA in patients with lung metastases in whom the primary tumour is under control, treated with curative intent as compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy or surgical resection?

What is the safety of MTA in patients with NSCLC or lung metastases being treated with palliative intent?

No comparative studies of MTA were identified to inform these research questions.

Due to the low numbers of studies available for each defined population, safety results are provided for MTA for lung cancer as a whole (including studies with a mixed population base) to provide a more robust evidence base. Due to the limited evidence-base and variability in reporting of safety outcomes, is not possible to comment on safety outcomes for each of the three defined populations separately.

Procedure-related mortality is a rare adverse event associated with MTA, occurring in less than 1 per cent of all patients (2/916, 0.22%). Mortality within 30 days is also very low, occurring in less than 1 per cent of all patients (1/739, 0.14%). The mortality profile with RFA is similar and in studies of radiotherapy, procedure-related mortality is a rare event. Surgery is associated with the highest rates of mortality; however, it is still an infrequent outcome.

Pneumothorax following microwave ablation is a relatively frequent complication; however, not all instances of pneumothorax require subsequent intervention such as chest tube drainage. Across studies reporting pneumothorax, a median of 9.3 per cent required chest tube drainage or other interventions and this ranged from nil to 28.6 per cent. Similar to MTA, pneumothorax was the most commonly reported adverse event associated with RFA therapy. Serious adverse events arising from radiotherapy were rare. The majority of studies reported no grade three ("severe") or higher adverse events. Thirty-four per cent of patients experienced a grade 1 ("mild") or 2 ("moderate") event across studies, while 3.3 per cent of patients experienced a grade three event.

Adverse events associated with surgery are generally not well reported; although when reported, complications occurred in greater than 10 per cent of thoracotomies.

No comparative studies were identified to inform this research question. Owing to the paucity of evidence on MTA, as it pertains to the populations specified in the PICO, the assessment of safety for MTA in the setting of lung cancer took into account all studies of MTA in the lung in order to provide the MSAC with a more complete understanding of the safety profile of MTA when used in the lung. Overall the safety assessment for MTA in the lung is comprised of 22 studies of which 20 are Level IV evidence and two are Level III-2 evidence. What follows is a summary of the harms associated with

MTA based on data from studies that included a total of 1,160 patients. The following table outlines the outcomes that were reported by more than two studies and gives an overview of the number of studies contributing to assessment of each harm.

Procedure-related mortality

Procedure-related mortality is a rare adverse event associated with MTA, occurring in less than 1 per cent of all patients (Table 40). There were two instances of definite procedure-related mortality reported across studies of MTA in patients with lung tumours and one instance of death within 30 days, which may or may not have been procedure-related. Procedure related deaths were reported by Wolf et al (2008) and Zheng et al (2014). In one instance a patient died 8 months and 14 days post-procedure due to infection of the cavity lesion that caused fatal haemoptysis (Wolf et al 2008). In a second instance, one patient died 41 hours after the procedure (Zheng et al 2014). The patient's chest X-ray showed a large pneumothorax with a good-sized pleural effusion. Chest tube placement and thoracic drainage alleviated the respiratory failure, but the patient died of sudden ventricular fibrillation. The death within 30 days was reported by Splatt & Steinke (2015) who state that a patient died suddenly during the night two days after ablation. The cause was not identified.

Table 41 Procedure related mortality reported in studies of MTA

Study ID	Level of evidence/ Quality rating of summary estimate	Procedure-related mortality n/N (%), per patient	30-day mortality n/N (%), per patient
Belfiore et al (2013)	IV	0/56 (0%)	NR
Carafiello et al (2012)	IV	0/17 (0%)	NR
Carrafiello et al (2014)	IV	0/24 (0%)	0/24 (0%)
Chung et al (2014)	IV	0/39 (0%)	0/39 (0%)
Egashira et al (2016)	IV	0/44 (0%)	0/44 (0%)
Han et al (2015)	IV	0/28 (0%)	0/28 (0%)
He et al (2006)	IV	0/12 (0%)	0/12 (0%)
Little et al (2013)	IV	0/23 (0%)	0/23 (0%)
Liu & Steinke (2015)	IV	0/15 (0%)	0/15 (0%)
Lu et al (2012)	IV	0/69 (0%)	0/69 (0%)
Ni et al (2015)	IV	0/35 (0%)	0/35 (0%)
Qi et al (2015)[a]	IV	0/17 (0%)	0/17 (0%)
Song et al (2014)[a]	IV	0/29 (0%)	0/29 (0%)
Splatt & Steinke (2015)[a]	IV	0/51 (0%)	1/51 (2%)
Sun et al (2015)	III-2	0/40 (0%)	NR

Study ID	Level of evidence/ Quality rating of summary estimate	Procedure-related mortality n/N (%), per patient	30-day mortality n/N (%), per patient
Vogl et al (2015)[a]	IV	0/80 (0%)	0/80 (0%)
Wolf et al (2006)	IV	1/50 (0%)[b]	0/50 (0%)
Yang et al (2014)	IV	0/47 (0%)	0/47 (0%)
Yang et al (2015)	IV	0/36 (0%)	0/36 (0%)
Zheng et al (2014)[a]	IV	1/204 (0.5%)	NR
Pooled, n/N (%), per patient	⊕⊙⊙⊙ **VERY LOW**	2/916 (0.22%)	1/739 (0.14%)

< n/N (%) = number with event/ total (percentage); NR = not reported >

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a These studies were assessed through quality appraisal as being at risk of incomplete reporting of adverse events.

b Death was delayed, occurring 8 months after the procedure.

Pneumothorax

Pneumothorax following microwave ablation is a relatively frequent complication (Table 42); however, not all instances of pneumothorax require subsequent intervention such as chest tube drainage. Across the studies reporting rates of pneumothorax as a percentage of ablation sessions the median rate of any pneumothorax was 30.2 per cent with a range of 8.3 to 63.8 per cent. This includes all instances of pneumothorax irrespective of their seriousness. Across studies reporting pneumothorax, a median of 9.3 per cent required chest tube drainage or other interventions and this ranged from nil to 28.6 per cent.

Nour-Eldin et al (2011) retrospectively investigated the incidence of pneumothorax following RFA and MTA ablation at their institution. Of 200 RFA ablation sessions pneumothorax occurred in 45 (18.1%), pneumothorax consisted of 10 mild, 25 moderate and six severe cases. In patients treated by MTA, four of 48 ablation sessions (8.9%) resulted in pneumothorax, of those two were mild and two were moderate. The difference in the incidence of pneumothorax between RFA and MTA ablation was not significant (p = 0.59).

Table 42 Results of key patient-relevant outcome across the studies

Study ID	Level of evidence; Quality rating of	Pneumothorax n with event/N ablation	Pneumothorax requiring intervention[a]

	summary estimate	sessions (%)	n with event/N ablation sessions (%)
Belfiore et al (2013)	IV	18/56 (32.1)	8/56 (14.3)
Carafiello et al (2012)	IV	4/17 (23.5)	0/17 (0)
Carrafiello et al (2014)	IV	9/24 (37.5)[b]	NR
Chung et al (2014)	IV	13/46 (28.3)	4/46 (8.7)
Egashira et al (2016)	IV	12/62 (19.4)	12/62 (16.1)
Han et al (2015)	IV	14/28 (50.0)	8/28 (28.6)
He et al (2006)	IV	1/12 (8.3)	0/12 (0)
Little et al (2013)	IV	10/23 (43.5)	3/23 (13.0)
Liu & Steinke (2015)	IV	10/16 (62.5)	NR
Lu et al (2012)	IV	13/69 (18.8)	5/69 (7.2)
Ni et al (2015)	IV	8/39 (20.5)	3/39
Nour-Eldin et al (2011)	IV	4/48 (8.3)	2/48 (4.2)
Qi et al (2015)	IV	2/17 (11.8)	0/17 (0)
Song et al (2014)	IV	5/29 (17.2)	1/29 (3.4)
Splatt & Steinke (2015)	IV	9/70 (12.9)[c]	9/70 (12.9)
Sun et al (2015)	III-2	13/40 (32.5)	4/40 (10.0)
Vogl et al (2015)	IV	11/30 (36.7)	5/30 (16.7)
Wei et al (2015)	III-2	18/46 (39.1)	3/46 (6.5)
Wolf et al (2006)	IV	26/66 (39.1)	8/66 (12.1)
Yang et al (2014)	IV	30/47 (63.8)	5/47 (10.6)
Yang et al (2015)	IV	18/36 (50.0)	10/36 (27.8)
Zheng et al (2014)	IV	32/204 (15.7)[c]	32/204 (15.7)
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	280/1025 (27.3) 30.2 (8.3–63.8)	122/985 (12.4 10.3 (0– 28.6)

< n/N (%) = number with event/ total (percentage); NR = not reported >

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Intervention includes any additional resources including chest tubes, thoracentesis etc. includes moderate and severe pneumothorax.

[b] Did not report severity of pneumothorax.

[c] Reported only severe pneumothorax.

Pneumonia

Pneumonia was reported by five studies of MTA (Ni et al 2015; Yang et al 2014; Yang et al 2015; Zheng et al 2014) and is reported separately as it is an unexpected adverse event with potentially serious repercussions. It is not clear what relationship there is, whether causative, associative or incidental, between the MTA procedure and incidence of pneumonia in studies reporting it. Overall, it is likely to be an uncommon event as studies not reporting pneumonia are likely not to have

observed any cases of pneumonia. In studies in which pneumonia is reported, it occurs after a median of 3.6 per cent of ablation sessions with a range of 2.8 per cent to 14.9 per cent.

Other adverse events reported

Other adverse events reported by more than two studies include haemoptysis, skin burns, broncho-pleural fistula, infection, pleural effusion and post-ablation syndrome. The large range in reported rates of these outcomes makes it difficult to conclude with what frequency these outcomes might be expected in practice. However, a brief summary of these results is provided in

Table 43. In most instances the percentage of patients with that adverse event had a range from nil up to 35.9 per cent, reflecting substantial variation across studies in terms of the frequency of events.

One study (Alexander et al 2013a) undertook a review of 163 patients treated by RFA, MTA or both to identify the incidence of rib fracture. The authors found that patients treated with RFA were more likely to experience a rib fracture than those who had MTA ($p = 0.0396$). Similarly patients treated with RFA and MTA were more likely to experience a rib fracture than those who had MTA alone ($p<0.049$). Across aspects of baseline patient demographics, females were associated with a higher rate of rib fracture, and ablation zones close to the chest wall were associated with a higher probability of fracture. This was the only study to report rib fracture. The Kaplan-Meier estimate of probability of a rib fracture at one year was 2.7 per cent (95%CI 0.7–10.4) for patients treated with MTA.

In addition to these, there were two reported instances of technical events related to MTA device failure that did not result in reported harm to patients. In one patient the ceramic coating of microwave antennae was lost in the pleural space (Liu and Steinke 2013b) and in another a needle tip fractured and was left in the lesion that had been ablated (Little et al 2013).

Table 43 Other adverse events reported

Study ID	Level of evidence	n with event/N ablation sessions (%)
Haemoptysis		
Carrafiello et al (2014)	IV	1/24 (4.2)
Chung et al (2014)	IV	3/46 (6.5)
Egashira et al (2016)	IV	0/44 (0)
Han et al (2015)	IV	1/28 (3.6)
Liu & Steinke (2015)	IV	1/16 (6.3)
Lu et al (2012)	IV	5/69 (7.3)
Ni et al (2015)	IV	1/39 (2.6)
Vogl et al (2015)[a]	IV	6/130 (4.6)
Wolf et al (2006)	IV	4/66 (6.1)
Yang et al (2014)	IV	15/47 (31.9), 7 occurring during ablation
Yang et al (2015)	IV	11/36 (30.6)
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	48/545 (8.8) 6.1 (0–31.9)
Infection		
Carafiello et al (2012)	IV	0/46 (0)
Little et al (2013)	IV	0/23 (0)
Splatt & Steinke (2015)[a]	IV	2/70 (2.9)
Sun et al (2015)	IV	7/40 (17.5)
Vogl et al (2015)[a]	IV	0/130 (0)
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	9/309 (2.9) 0 (0–17.5)
Pleural effusion		
Carafiello et al (2012)	IV	4/46 (8.7)
Carrafiello et al (2014)	IV	1/24 (4.2)
Chung et al (2014)	IV	14/46 (30.4)
Egashira et al (2016)	IV	0/62 (0)
Ni et al (2015)	IV	6/39 (15.4)
Song et al (2014)a	IV	2/29 (6.9)

Study ID	Level of evidence	n with event/N ablation sessions (%)
Splatt & Steinke (2015)[a]	IV	4/70 (5.7)
Wei et al (2015)	IV	15/46 (32.6)
Yang et al (2015)	IV	11/36 (30.6)
Yang et al (2014)	IV	16/47 (34)
Zheng et al (2014)	IV	6/204 (2.9)
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	79/649 (12.2) 8.7 (0–34.0)
Skin burns		
Carrafiello et al (2014)	IV	0/24 (0)
He et al (2006)	IV	1/12 (8.3)
Little et al (2013)	IV	1/23 (4.3)
Splatt & Steinke (2015)[a]	IV	1/70 (1.4)
Vogl et al (2015)[a]	IV	1/130 (0.8) grade 3 burn
Wolf et al (2006)	IV	2/66 (3.0) in 2 patients, both required treatment
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	6/325 (1.8) 2.2 (0–8.3)
Post-ablation syndrome		
Carafiello et al (2012)	IV	2/17 (11.8)
Carrafiello et al (2014)	IV	0/24 (0)
Little et al (2013)	IV	0/23 (0)
Lu et al (2012)	IV	0/69 (0)
Ni et al (2015)	IV	14/39 (35.9)
Wolf et al (2006)	IV	1/66 (1.5) with signs and symptoms resolving in 3–4 days
Yang et al (2014)	IV	15/47 (31.9)
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	32/285 (11.2) 1.5 (0–35.9)
Broncho-pleural fistula		
Ni et al (2015)	IV	1/39 (2.6)
Splatt & Steinke (2015)[a]	IV	1/70 (1.4) delayed broncho-pleural fistula (related to pneumothoraces)

Study ID	Level of evidence	n with event/N ablation sessions (%)
Yang et al (2014)	IV	1/47 (2.1)
Zheng et al (2014)[a]	IV	1/204 (0.5) which caused pneumothorax
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	4/360 (1.1) 1.8 (0.5–2.6)

< n/N (%) = number with event/ total (percentage); NR = not reported >

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a These studies were assessed through quality appraisal as being at risk of incomplete reporting of adverse events.

IS RADIOFREQUENCY ABLATION OF LUNG CANCER SAFE?

No trials of MTA compared to RFA were identified. In the absence of relevant comparative data, adverse events reported in the included RFA studies are reported to provide some indication of the safety of RFA for consideration by the MSAC.

Only one comparative trial of RFA compared to a relevant comparator (radiotherapy) in early stage NSCLC was identified (Safi et al 2015). No comparative studies on RFA for lung metastases or palliative therapy were identified. As per the previous section on MTA, the safety outcomes for RFA are grouped for all populations, to provide MSAC with an understanding of the main safety issues associated with RFA of the lung. In total, one Level III-3 and 18 Level IV studies of RFA, which included a combined total of 1,354 patients, were included. As RFA and MTA are technologically similar devices, Table 44 presents a summary of the key MTA safety outcomes reported in studies of RFA. The evidence has been presented in this way to enable a rudimentary comparison of the relative safety of MTA and RFA, noting that the level of evidence identified does not allow definitive comparisons to be drawn.

Procedure-related mortality

Similar to MTA, the procedure-related mortality associated with RFA is very low (Table 44). From a combined sample of 1,259 patients, there was only one procedure-related death reported. In this case, the patient died three months after RFA from repeated infection and pulmonary deterioration associated with the therapy (Von Meyenfeldt et al 2011). Two patients died within 30 days of RFA therapy, due to unrelated causes (De Baere et al 2015a). In these patients, one died at 21 days from decompensate cardiorespiratory function, and the other at 16 days from cerebral stroke.

Table 44 Procedure related mortality reported in 17 studies of RFA

Study ID	Level of evidence/ Quality of summary estimates	Procedure-related mortality n/N (%), per patient	30-day mortality n/N (%), per patient
Ambrogi et al (2011)	IV	0/57 (0)	NR
De Baere et al (2015)	IV	0/566 (0)	2/566 (0.3)
Dupuy et al (2015)	IV	0/51 (0)	NR
Fanucchi et al (2016)	IV	0/61 (0)	0/61 (0)
Hiraki et al (2011a)	IV	0/50 (0)	NR
Hiraki et al (2011b)	IV	0/32 (0)	0/32 (0)
Li et al (2012)	IV	0/29 (0)	NR
Liu et al (2015)	IV	0/29 (0)	0/29 (0)
Lu et al (2015a)	IV	0/67 (0)	NR
Lu et al (2015b)	IV	0/35 (0)	NR
Matsui et al (2015)	IV	0/84 (0)	NR
Ridge et al (2014)	IV	0/29 (0)	0/29 (0)
Safi et al (2015)	III-3	0/25 (0)	0/25 (0)
Simon et al (2007)	IV	0/21 (0)	NR
Viti et al (2014)	IV	0/22 (0)	0/22 (0)
von Meyenfeldt et al (2011)	IV	1/46 (2)	0/46 (0)
Yan et al (2006+ 2007)	IV	0/55 (0)	NR
Pooled, n/N (%), per patient	⊕⊙⊙⊙ **VERY LOW**	1/1259 (<0.1)	2/810 (<0.1)

< n/N (%) = number with event/ total (percentage); NR = not reported; RFA=radiofrequency ablation>

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Pneumothorax

Similar to MTA, pneumothorax was the most commonly reported adverse event associated with RFA therapy. The incidence of pneumothorax was reported as either a percentage of ablation sessions, or total patients. In total, pneumothorax occurred in 45 per cent of ablation sessions, and 18 per cent of patients (Table 45). The severity of pneumothorax was reported according to those that spontaneously resolved without intervention, and those that required chest tube placement. Intervention with a chest tube was required in 50 per cent of sessions that led to pneumothorax. In contrast, 63 per cent of patients that had a pneumothorax needed a chest tube placed.

Table 45 Pneumothorax reported in 19 studies of RFA, per-session and per-patient

Study ID	Level of evidence/ Quality of summary estimates	Pneumothorax n with event/N (%)	Pneumothorax requiring intervention n with event/N (%)
Ambrogi et al (2011)	IV	9/80 (11)	4/80 (5)
De Baere et al (2015)	IV	430/642 (67)	250/642 (39)
Fanucchi et al (2016)	IV	9/99 (9)	8/99 (8)
Hiraki et al (2011a)	IV	25/52 (48)	3/52 (6)
Hiraki et al (2011b)	IV	38/65 (58)	15/65 (23)
Koelblinger et al (2014)	IV	3/30 (10)	1/30 (3)
Lanuti et al (2012)	IV	10/55 (18)	1/55 (2)
Li et al (2012)	IV	5/56 (9)[a]	5/56 (9)
Liu et al (2015)	IV	8/33 (24)	3/33 (9)
Matsui et al (2015)	IV	59/113 (52)	15/113 (13)
Simon et al (2007)	IV	52/183 (28)	18/183 (10)
Viti et al (2014)	IV	4/24 (17)	3/24 (13)
von Meyenfeldt et al (2011)	IV	22/65 (29)	9/65 (14)
Pooled, n/N (%), per session **Median (rage), per session**	⊕⊙⊙⊙ **VERY LOW**	**674/1497 (45)** **24% (9–67)**	**335/1497 (22)** **9% (2–39)**
Dupuy et al (2015)	IV	2/51 (4)	2/51 (4)
Lu et al (2015a)	IV	8/67 (12)	2/67 (3)
Lu et al (2015b)	IV	3/35 (9)	2/35 (6)
Ridge et al (2014)	IV	8/29 (28)	7/29 (24)
Safi et al (2015)	III-3	9/25 (36)	7/25 (28)
Yan et al (2006+ 2007)	IV	16/55 (29)	9/55 (14)
Pooled, n/N (%), per patient **Median % (range), per patient**	⊕⊕⊙⊙ **LOW**	**46/262 (18)** **17.5% (5–36)**	**29/262 (11)** **10% (3–24)**

< n/N (%) = number with event/ total (percentage) >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a 10/56 additional patients had minor self-limiting complications including pneumothorax and cough, but the total number of each type of complication was not reported.

Other adverse events

Other adverse events were reported variably across the included studies, and were rarely reported according to standardised grading criteria for severity. As a result, it is difficult to summarise the incidence of major and minor adverse events that occurred across the included studies. Table 46 describes the overall rate of adverse events that were directly related to RFA therapy, as reported by at least two studies. The pneumonitis group included cases of pneumonitis, infection, and pneumonia. Pneumonia was a rare event in the RFA studies, which occurred in three patients in one study (Von Meyenfeldt et al 2011). Pain (median 9.0%, range 7.3%–27.6%) was the second most commonly reported adverse event behind pneumothorax, followed by haemoptysis (median 8.8%, range 8.6%–9.0%), and pleural effusion (median 5.9%, range 2.0%–16.0%). Post-ablation syndrome was not reported in any study. Brachial and phrenic neuropathies were reported in 3/113 (2.7%) and 2/113 (1.8%) patients respectively, across two studies (Matsui et al 2015; Ridge et al 2014).

In addition to the adverse events listed in Table 46, a range of studies reported additional adverse events not detected in the other studies. These included:

- one case of dyspnoea (Dupuy et al 2015);
- one case of hypoxia (Dupuy et al 2015);
- one case of broncho-pleural fistula (Hiraki et al 2011a);
- four cases of minor skin burns (De Baere et al 2015a);
- one case of pneumomediastinum (Viti et al 2014);
- one case of worsening stridor (Ridge et al 2014)
- two cases of self-liming aerodermectasia (Lu et al 2015a); and
- one case of vomiting (Lu et al 2015a).

Table 46 Adverse events reported in studies of RFA (per-session or per-patient)

Study ID	Level of evidence	n / N (%)
Haemoptysis (per session)		
Ambrogi et al (2011)	IV	2/80 (2.5) sessions
Hiraki et al (2011b)	IV	1/65 (1.5) sessions
Li et al (2012)	IV	0/56 (0.0) sessions
Lu et al (2015a)	IV	5/185 (2.7) sessions
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 8/384 (2.1) Median 2.0 (0.0–2.7)
Haemoptysis (per patient)		
Lu et al (2015b)	IV	6/67 (9.0) patients

Study ID	Level of evidence	n / N (%)
Simon et al (2007)	IV	3/35 (8.6) patients
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 9/102 (8.8) Median 8.8 (8.6–9.0)
Pneumonitis/infection (per patient)		
Dupuy et al (2015)	IV	1/51 (2.0) patients
Hiraki et al (2011a)	IV	2/50 (4.0) patients
Koelblinger et al (2014)	IV	1/22 (4.5) patients
Li et al (2012)	IV	0/29 (0.0) patients
Matsui et al (2015)	IV	1/84 (1/2) patients
Simon et al (2007)	IV	2/21 (9.5) patients
von Meyenfeldt et al (2011)	IV	4/46 (8.7) patients
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 11/303 (3.6) Median 4.0 (0.0–9.5)
Pleural effusion (per session)		
Ambrogi et al (2011)	IV	3/80 (3.8) sessions
Fanucchi et al (2016)	IV	2/99 (2.0) sessions
Hiraki et al (2011a)	IV	11/65 (16.9) sessions
Hiraki et al (2011b)	IV	1/52 (1.9) sessions
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 17/296 (5.7) Median 2.9 (1.9–16.9)
Pleural effusion (per patient)		
Dupuy et al (2015)	IV	1/51 (2.0) patients
Koelblinger et al (2014)	IV	1/22 (4.5) patients
Lu et al (2015b)	IV	2/67 (3.0) patients
Ridge et al (2014)	IV	3/29 (10.3) patients
Safi et al (2015)	III-3	4/25 (16.0) patients
Yan et al (2006+ 2007)	IV	4/55 (7.3) patients
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 15/249 (6.0) Median 5.9 (2.0–16.0)
Pain		
Ambrogi et al (2011)	IV	5/57 (8.8) patients

Study ID	Level of evidence	n / N (%)
Liu et al (2015)	IV	8/29 (27.6) patients
Lu et al (2015a)	IV	6/67 (9.0) patients
Lu et al (2015n)	IV	4/35 (11.4) patients
Yan et al (2006+ 2007)	IV	4/55 (7.3) patients
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 27/243 (11.1) Median 9.0 (7.3–27.6)
Pulmonary bleeding		
Ambrogi et al (2011)	IV	1/57 (1.8) patients
Hiraki et al (2011b)	IV	1/32 (3.1) patients
Li et al (2012)	IV	0/29 (0.0) patients
Matsui et al (2015)	IV	5/113 (4.4) sessions
Safi et al (2015)	III-3	1/25 (4.0) patients
von Meyenfeldt et al (2011)	IV	4/46 (8.7) patients
Yan et al (2006 +2007)	IV	5/55 (9.1) patients
Pooled n/N (%) Median % (range)	⊕⊙⊙⊙ **VERY LOW**	Total 17/357 (4.8) Median 4.0% (0.0–9.1)

<n/N (%)= number with event/ total (percentage)>

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

IS CURRENT BEST PRACTICE RADIOTHERAPY FOR LUNG CANCER SAFE?

No trials of MTA compared to current best practice radiotherapy were identified. In the absence of relevant comparative data, adverse events reported in the included radiotherapy studies are reported to provide some indication of the safety of radiotherapy for consideration by the MSAC.

In population one, two Level II studies, one Level III-2 study, and one Level III-3 study reported safety outcomes from a total sample of 487 patients. In population two, three Level III-3 studies and 14 Level IV studies reported safety outcomes from a total sample of 643 patients. The safety of radiotherapy in population three is summarised by a recent Cochrane review of 14 RCTs. Due to the small number of comparative studies identified in population one and two, and the nature of the comparisons, it was not appropriate to conduct a meta-analysis of the available randomised and non-randomised studies. In lieu of meta-analysis, adverse event rates across studies have been reporting with simple descriptive statistics.

Serious adverse events arising from radiotherapy were rare, such that the overall sample size of each population was too small to meaningfully represent the likelihood of key adverse events in each population. In addition, 14 of 20 included studies were retrospective, observational case note reviews, in which it was unclear whether relevant adverse events were formally monitored. The prospective RCT by Price et al (2012) did not report which adverse events were formally monitored, or how relevant adverse events were defined.

Due to limitations in the available evidence base, it was not possible or informative to report safety outcomes separately for population one and population two. Therefore, the safety results have been combined for population one and two to give an indication of the safety of radiotherapy for the treatment of lung cancer more broadly.

Severity of adverse events

The majority of adverse events were reported according to the NCI-CTCAE criteria, and were scored as grade 1 ("mild") or 2 ("moderate") in severity. The majority of studies reported no grade 3 ("severe") or higher adverse events. As reported in Table 47, 34 per cent of patients experienced a grade 1 or 2 event across studies, while 3.3 per cent of patients experienced a grade 3 event.

Table 47 Adverse events reported in radiotherapy studies, stratified by event grade*

Study	Grade 1-2 Events / patients (%)	Grade 3 Events / patients (%)	Grade 4 Events / patients (%)	Grade 5 Events / patients (%)
Agolli et al (2015)	15/111 (72.7)	0/111 (0.0)	0/111 (0.0)	0/111 (0.0)
Baschnagel et al (2013)	2/32 (6.3)	5/32 (15.6)	0/32 (0.0)	0/32 (0.0)
Garcia-Cabezas et al (2015)	4/44 (9.1)	0/44 (0.0)	0/44 (0.0)	0/44 (0.0)
Filippi et al (2015)	10/40 (25.0)	0/40 (0.0)	0/40 (0.0)	0/40 (0.0)
Gamsiz et al (2014)	24/20 (120.0)[a]	2/20 (10.0)	0/20 (0.0)	0/20 (0.0)
Kim et al (2009)	18/31 (58.1)	0/31 (0.0)	0/31 (0.0)	0/31 (0.0)
Navarria et al (2014)	61/67 (80.3)	0/76 (0.0)	0/76 (0.0)	0/76 (0.0)
Navarria et al (2015)	18/28 (64.3)	0/28 (0.0)	0/28 (0.0)	0/28 (0.0)
Norihisa et al (2008)	27/34 (79.4)	1/34 (2.9)	0/34 (0.0)	0/34 (0.0)
Nuyttens et al (2015)	10/30 (33.3)	0/30 (0.0)	0/30 (0.0)	0/30 (0.0)
Oh et al (2012)	4/57 (7.0)	0/57 (0.0)	0/57 (0.0)	1/57 (1.8)
Osti et al (2013)	4/66 (6.1)	2/66 (3.0)	0/66 (0.0)	0/66 (0.0)
Ricardi et al (2011)	2/61 (3.3)	1/61 (1.6)	0/61 (0.0)	0/61 (0.0)
Takahashi et al (2014)	33/34 (97.1)	0/34 (0.0)	0/34 (0.0)	0/34 (0.0)

Yu et al (2014)	9/27 (33.3)	0/27 (0.0)	0/27 (0.0)	0/27 (0.0)
Videtic et al (2015)	58/84 (69.0)	9/84 (10.7)	0/84 (0.0)	1/84 (1.2)
Lucas et al (2014)	25/160 (15.6)	4/160 (2.5)	0/160 (0.0)	0/160 (0.0)
Pooled, n/N (%) **Median % (range)**	**346/877 (34)** **42.5 (3.3–120)**	**34/887 (3.3)** **0.0 (0.0–33.3)**	**0/887 (0.0)** **NA**	**2/887 (0.2)** **0.0 (0.0–1.8)**

<n/N (%) = number with event/ total (percentage); NA = not applicable>
a Patients had multiple events.

Procedure-related mortality

A total of 15 included studies reported no procedure-related mortality, or mortality from any cause within 30 days (n = 778). There were two cases of procedure-related mortality across all included studies. Videtic et al (2015) reported the death of one patient who received 48 Gy radiation in 4 fractions. The patient died 319 days after the procedure due to respiratory failure. The cause of respiratory failure was judged directly related to SBRT. The other death was reported by Oh et al (2012), in whom a patient with a long history of chronic obstructive pulmonary disease (COPD), and who had received left pneumonectomy and postoperative RT for NSCLC prior to SBRT. The patients died from respiratory failure 5 months after receiving SBRT. The respiratory failure was related to grade 5 pneumonitis brought on after SBRT treatment. Takahashi et al (2014) report one case of bacterial pneumonitis resulting in death but it is unclear whether it was procedure-related.

Specific adverse events

A summary of the specific adverse events that occurred in patients receiving radiotherapy for primary NSCLC or oligometastases is reported in Table 48. All but two studies reported the total number of events that were grade 3 or higher. In contrast, minor adverse events were reported inconsistently, as represented by a high degree of variation in the median ranges of grade 1–2 adverse events across included studies. Due to the retrospective nature of most studies, and apparent selective reporting, it was often unclear whether an adverse event did not occur, or was not reported. This made it difficult to determine the total rate of minor adverse events. Therefore, only studies that specifically reported an adverse event having occurred or not occurred are reported in Table 48. Pneumonitis was the most common adverse event, followed by rash and dyspnoea. Adverse events that of grade 3 or higher were rarely reported.

Table 48 Adverse events reported in at least two studies of radiotherapy

	Grade 1–2 events		Grade 3 events		
Adverse event	**Number of studies**	**Pooled, n/N (%)** **Median % (range)**	**Number of studies**	**Pooled, n/N (%)** **Median % (range)**	**Quality of estimates**
Pneumonitis	9 studies	Total 57/532 (10.7)	18 studies	Total 7/887 (0.8)	⊕⊕⊙⊙

		Median 7.2% (0.0–48.4)		Median 0.0 (0.0–3.3)	LOW
Dyspnoea [a]	2 studies	Total 9/62 (14.5) Median 14.2 (3.3–25.0)	18 studies	Total 5/887 (0.6) Median 0.0 (0.0–13.3)	⊕⊙⊙⊙ VERY LOW
Oesophagitis [b]	5 studies	Total 10/230 (4.3) Median 4.5 (0.0–6.3)	18 studies	Total 3/887 (0.3) Median 0.0 (0.0–2.7)	⊕⊙⊙⊙ VERY LOW
Pericardial effusion	3 studies	Total 3/92 (3.3) Median 3.2 (0.0–5.9)	18 studies	Total 0/887 (0.0) Median NA	⊕⊙⊙⊙ VERY LOW
Pain [c]	4 studies	Total 12/118 (10.2) Median 9.2 (3.3–17.6)	18 studies	Total 2/887 (0.2) Median 0.0 (0.0–6.7)	⊕⊙⊙⊙ VERY LOW
Rib facture [d]	5 studies	Total 14/225 (6.2) Median 2.9 (0.0–12.5)	18 studies	Total 1/887 (0.1) Median NA	⊕⊙⊙⊙ VERY LOW
Rash [e]	5 studies	Total 23/157 (14.6) Median 20.6 (0.0–30.0)	18 studies	Total 0/887 (0.0) Median NA	⊕⊙⊙⊙ VERY LOW
Fatigue	3 studies	Total 18/146 (12.3) Median 13.1 (9.4–26.7)	18 studies	3/887 (0.6) Median 0.0 (0.0–10.0)	⊕⊙⊙⊙ VERY LOW
Cough	2 studies	Total 10/62 (16.0) Median 16.0 (13.3–18.8)	18 studies	Total 1/887 (0.1) Median N/A	⊕⊙⊙⊙ VERY LOW

<n/N (%) = number with event/ total (percentage); NA = not applicable>

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a Note: one additional study reported three cases of "serious" dyspnoea. Due to incomplete reporting, this study was not included in the pooled estimates.

b Note: one additional study reported one case of "severe" esophagitis that required treatment. Due to incomplete reporting, this study was not included in the pooled estimates.

c Note: two additional studies reported two cases of non-descript pain each. Due to incomplete reporting, these studies were not included in the pooled estimates. Another study reported generic musculoskeletal adverse events (including pain), and is described in the "other events" section.

d Note: four additional studies reported additional rib fractures, including: four cases of non-descript rib facture, one case of "serious" rib fracture, and 9/67 lesions that had a rib fracture adjacent to the SBRT volume.

e Note: one additional study reported one case of "serious" rash. Due to incomplete reporting, this study was not included in the pooled estimates.

Other events

Across the included studies, minor adverse events that were only reported by a single study included one case of grade 2 pneumomediastinum (Kim et al 2009), one case of grade 2 myositis (Baschnagel et al 2013), one case of grade 1 temporal liver dysfunction (Norihisa et al 2008), eleven cases of grade 1/2 unspecified musculoskeletal disorders (Videtic et al 2015). Price et al (2012) reported a number of "serious" adverse events (not graded according to NCI-CTCAE) that were not reported in other studies, including: 1/56 (2%) myocardial infarction, 1/56 (2%) perforated viscus, 1/55 (2%)

hypotension, 1/55 (2%) COPD exacerbation, 1/55 (2%) pneumothorax, 1/55 (2%) subcutaneous reaction, and 1/55 (2%) transient ischaemic attack. Lucas et al (2014) reported 1/79 (1.3%) case of "serious" bleeding (grade NR). Lung fibrosis was reported in two studies (Agolli et al 2015; Price et al 2012), but due to poor quality reporting, it was not appropriate to report event numbers across studies. Price et al (2012) detected two cases of "serious" lung fibrosis in the radiotherapy + chemo group, and Agolli et al (2015) reported 10/22 (45%) patients had minor grade 1–2 lung fibrosis.

Safety of palliative radiotherapy

The safety of palliative radiotherapy regimens was comprehensively evaluated in a 2015 Cochrane review (Stevens et al 2015). The review sought to assess the impact of different radiotherapy regimens on symptom relief and overall survival in patients with NSCLC who were not suitable for radical radiotherapy delivered with curative intent. The main safety outcomes identified in the review, and corresponding quality of evidence (GRADE), are reported in Table 49.

Table 49 Safety results and quality of evidence for palliative radiotherapy regimens (Stevens et al 2015)

Outcomes	Illustrative risks*	Comparative (95% CI)	Relative effect (95% CI)	No of patients (studies)	Quality of the evidence (GRADE)	Comments
	Less fractions	More fractions				
Oesophagitis (grade 3 to 4)	Mean 22.3% (0–50%)	Mean 25.7% (0–56%)	RR 1.23 (0.81–1.87)	1302 (8 studies)	⊕⊕⊙⊙ LOW	NR in all trials, mixed patient- and physician-reported toxicity
Radiation myelopathy (any grade)	Mean 0.30% (0–1.4%)	Mean 0.38% (0–1.6%)	RR 1.29 (0.37–4.51)	2663 (11 studies)	⊕⊕⊕⊙ MODERATE	Reported in most studies but not all. Not graded and most not confirmed post-mortem
Radiation pneumonitis (any grade)	Mean 3.9% (2.8–6.0%)	Mean 2.4% (1.6–4.0%)	RR 0.62 (0.23–1.66)	533 (3 studies)	⊕⊕⊙⊙ LOW	Not reported in majority of studies, not graded

<CI = confidence interval; NR = not reported; RR = relative risk.>

IS SURGICAL RESECTION OF LUNG METASTASES SAFE?

Only one of the two systematic reviews reported on any safety data. Pfannschmidt et al (Pfannschmidt et al 2007) reported postoperative mortality; and found that within the 20 included studies it was only reported by four studies and ranged from nil to 2.5 per cent of patients. Nine studies reported perioperative mortality within an undefined time period in which the cause (n = 8)

was reported by five studies to be pulmonary embolism (n = 3), pneumonia (n = 3), respiratory failure (n = 1) and cardiac failure (n = 1). No other safety outcomes were reported.

Within the included case series studies immediate procedure-related mortality was reported in two studies (Kitano et al 2012; Renaud et al 2014), and occurred in no patients (0/365, 0%). Thirty day mortality was reported in four of the five studies (Renaud et al 2014; Reza et al 2014; Rodriguez-Fuster et al 2014; Younes et al 2009), and occurred in 10 of 1,499 patients (0.67%); only one study reported the causes of death [sepsis in one, and ventricular fibrillation in one (Rodriguez-Fuster et al 2014)].

Overall rates of adverse events were reported by two studies (Rodriguez-Fuster et al 2014; Younes et al 2009) and was 99 complications in 776 thoracotomies (13%) in the study by Younes et al (2009) and was 83 complications in 532 patients (15.6%) in the study by Rodriguez-Fuster (2014). Other adverse events that were reported are shown in Table 50. No pooling was possible due to uncertainty across studies around whether an adverse event did not occur or was not reported.

Table 50 Adverse events reported in the Level IV studies on surgical resection

Study ID	Mortality, n/N (%)	Adverse events, n/N (%) Reported out of thoracotomies unless otherwise state
Renaud et al (2014)	Procedure related: 0/320 (0) 30-day: 5/320 (1.7)	Laryngeal nerve palsy: 16/320 patients (5)
Younes et al (2009)	Procedure related: NR 30-day: 2/529 (0.4))	Infection: 19/776 (2.4) Atelectasis: 29/776 (3.7) Cardiac arrhythmia: 18/776 (2.3) Stroke: 2/776 (0.3) Prolonged air leak: 28/776 (3.6)
Reza et al (2014)	Procedure related: NR 30-day: 1/118 (0.8)	NR
Rodriguez-Fuster et al (2014)	Procedure related: NR 30-day: 2/532 (0.4)	Air leaks > 7 days: 18/532 patients (3.4) Atelectasis: 12/532 (2.3) Pneumonia: 13/532 (2.3) Paralytic ileum 12/532 (2.3) Arrhythmias: 9/532 (1.7) Acute respiratory distress syndrome: 4/532 (0.8) Pleural cameras: 16/532 (3.0) Urinary infection: 5/532 (0.9) Renal insufficiency: 3/532 (0.6) Phrenic paralysis: 2/532 (0.4)

Study ID	Mortality, n/N (%)	Adverse events, n/N (%) Reported out of thoracotomies unless otherwise state
		Congestive heart failure: 2/532 (0.4) Oedema post-pneumonectomy: 1/532 (0.2) Broncho-pleural fistula: 1/532 (0.2)
Kitano et al (2012)	Procedure related: 0/45 (0) 30-day: NR	Empyema due to prolonged air leakage: 1/45 patients (2)

< n/N (%) = number with event/ total (percentage); NR = not reported >

IS MTA EFFECTIVE IN PATIENTS WITH EARLY STAGE NSCLC AND WHO ARE NOT ELIGIBLE FOR SURGICAL RESECTION?

Summary – What is the effectiveness of microwave tissue ablation in patients with early stage inoperable NSCLC as compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy?

The evidence for both the intervention and its comparators is by and large characterised by Level IV evidence with variable outcome measures and incomplete reporting. The mechanism of action of thermal ablative technologies in terms of tumour destruction is intuitively appealing; however, the comparative benefit of this form of tumour destruction over existing treatment options is unknown. It is important to note that in the context of a reimbursement decision the claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by published studies.

Patients with early stage NSCLC are likely to present with localised, technically resectable disease; however, a substantial proportion of these patients will not be candidates for surgical resection due to significant comorbidities or age. Consequently, these patients are traditionally offered definitive radiotherapy. The effectiveness of treatments for early stage NSCLC in patients that are not eligible for surgical resection is evaluated by survival outcomes and measures of local control.

Head to head trials comparing newer radiotherapy options (SBRT) to surgery in operable patients have been terminated early due to slow accrual (Chang et al 2015). However, retrospective data indicates that SBRT may have comparable local control and survival outcomes to surgery when analyses are adjusted for comorbidities and age (Chang et al 2015; Crabtree et al 2010; Nanda et al 2015; Shirvani et al 2012). These studies did not meet the formal inclusion criteria for this review as they report on comparisons that are not appropriate for the research questions for this review. However, they provide general context for SBRT as a therapy in early stage NSCLC. Additionally, a large retrospective study examining the effect of SBRT versus observation identified a survival benefit in patients treated with SBRT (the median overall survival was 29 months with SBRT versus 10 months with observation alone, P<.001). No such comparative trials of MTA are available for this population; however, results from Level IV studies are presented, and some crude comparisons are discussed, herein. The MSAC should consider that it is not possible to statistically test for differences in prognostic factors across studies or for differences in effects. Outcomes reported from case series studies are subject to a high risk of bias, and it is not possible to quantify the impact of bias or confounding factors.

Overall and cancer-specific survival time

No studies were identified that directly or indirectly compared overall survival time for MTA to the relevant comparators. Three case series studies of MTA were identified for patients with early stage

NSCLC who are not eligible for surgical resection. Only two of those reported overall survival outcomes (Han et al 2015; Yang et al 2014). In both studies the median overall survival and the lower bound of the confidence interval was greater than 20 months (Table 51). The studies of MTA include a very small number of patients and although crude comparisons can be drawn to estimates presented in studies of a similar population, it is not possible to provide an estimate of comparative effectiveness.

In terms of prognostic factors affecting survival, Yang et al (2014) found that tumours ≤ 35 mm in diameter were associated with better survival than tumours >35 mm ($p = 0.016$). The distribution of patients with tumours >35 mm across the two studies will affect the consistency of outcomes if tumour size is indeed a prognostic factor. In the study by Han et al (2015) seven patients (25%) had tumours greater than 35 mm in diameter (subgroup analyses were not reported) whereas in Yang et al (2014) 51 per cent of patients had tumours greater than 35 mm in diameter. It is not clear whether the distribution of tumours larger than 35 mm in the study by Yang or Han might be more reflective of the general spectrum of patients that might be expected to receive MTA.

Five included case series studies of RFA reported a median overall survival time, and two reported cancer-specific survival time, in patients treated for inoperable early stage NSCLC. A summary of the median overall and cancer-specific survival times are reported in Table 51. The studies of RFA included small numbers of patients, were not adjusted for confounding factors, and did not have a relevant comparator arm. Therefore, the existing evidence cannot provide a reliable estimate for the comparative effectiveness across studies, only an indicative estimate of the observed survival in patients that were treated with RFA.

Overall survival was not reported in the included radiotherapy studies for population one.

Table 51 Overall and cancer-specific survival time in patients with inoperable early stage NSCLC

Trial/Study	N (lesions)	Median overall survival time (95%CI) *Cancer specific survival time (95% CI)*	Subgroup analyses
MTA			
Han et al (2015)	28 (28)	35.0 months (22.3–47.7) *41.9 months (38.8–49.9)*	NA
Liu & Steinke (2015)	15 (16)	NR	NR
Yang et al (2014)	47 (47)	33.8 months (31.9–35.7) *47.4 months (25.7–69.1)*	Tumours ≤ 35 mm associated with better survival (p = 0.016)
Pooled analysis	75 (75)	Pooling not possible Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	NA
RFA			
Ambrogi et al (2011)	57 (59)	33.4 months *41.4 months*	NA
Hiraki et al (2011)	50 (52)	67 months (mean: 59 months)	NA
Lanuti et al (2012)	45 (55)	44.3 months	NA
Liu et al (2015)	29 (29)	57 (95% CI, 44–70) months *63 (95%CI, 50–75) months*	Stage IA: 65 (51–79) months Stage IB 65 (51–79) months
Viti et al (2014)	22 (24)	36.5 months	NA
Ridge et al (2014)	29 (29)	41.3 months	T1a and T1b not significantly different, nor first primary and synchronous tumours
Pooled analysis	175 (189)	Median overall survival: 42.8 months (range: 33.4–67) Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	NA

< CI = confidence interval; MTA = microwave thermal ablation; NA = not applicable; NR = not reported; RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1-, 2-, 3-, 4- or 5- year survival

Only Han et al (2015) and Yang et al (2014) reported survival rates associated with MTA in population one. Yang et al (2014) reported slightly lower one and two-year survival. Three-year survival was reported more consistently cross studies. Han et al (2015) did not report survival beyond 4 years although in the study by Yang et al (2014) survival drops substantially to 16 per cent at 5 years. It is important to note that the maximum follow-up of any patient in either study did not exceed six years and therefore predicting survival beyond this point is challenging. Given that follow-up in such studies is determined both by the time point at which historical records are accessed *and* the times at which patients died it is often unclear which the follow-up represents.

Eight included RFA studies reported the overall 1-, 2-, 3- or 5-year survival rates in early stage inoperable NSCLC patients. Survival rates in NSCLC patients treated with RFA are presented in Table 100 (Appendix E). The overall survival rates, particularly those reported by Ridge et al (2014), Liu et al (2015) and Hiraki et al (2011a), are especially favourable, but it is not clear why as these studies are lacking in adjustment for confounders or a relevant comparator arm. With the exception of Safi et al (2015), the RFA studies included small numbers of patients, were not adjusted for confounding factors, and did not have a relevant comparator arm.

Three comparative trials reported the overall survival of radiotherapy in population one. Koshy et al (2015) compared conventional radiotherapy, SBRT and no treatment in a study of 13,036 patients. This study only provided 3-year survival rates and analysed raw treatment data and a propensity-matched cohort in order to compare SBRT to conventional radiotherapy. In patients who did not receive any treatment the 3-year survival rate was 28 per cent; with treatment this was in the range of 36 (conventional radiotherapy) to 48 (SBRT) per cent. The propensity-matched cohort of SBRT and conventional radiotherapy gave a 3-year overall survival with SBRT of 48 per cent and with conventional radiotherapy of 40 per cent ($p = 0.001$). This result and those from other randomised controlled trials of different radiotherapy regimes are summarised in Table 101 (Appendix E). The studies of MTA include a very small number of patients and did not report any estimates of random variability around survival rates. Therefore, although similar to reported 3-year survival rates from a large study, it is not possible to infer that the results are comparable.

As no direct or indirect comparative data was identified, it is difficult to draw meaningful comparisons across interventions. With this limitation in mind, the 1-, 2-, 3-, and 5-year overall survival rates are presented in Figure 11. This figure visually represents the variability in reported survival rates within the evidence base for each intervention, and is not intended to be used to draw comparisons across interventions.

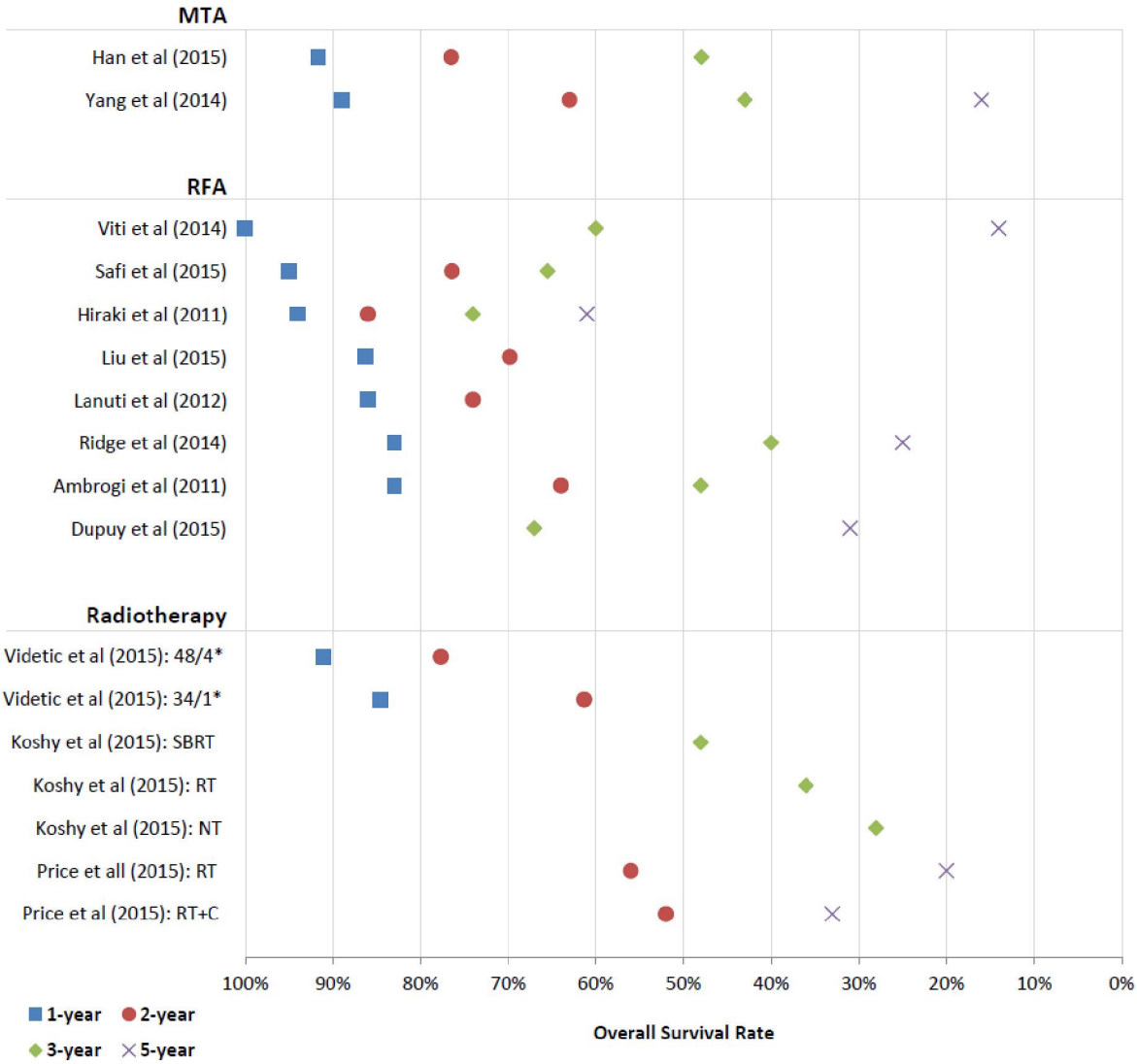

Figure 11 **Overall survival rates of MTA, RFA and radiotherapy in patients with inoperable early stage NSCLC. Both interventions in the comparative radiotherapy studies are presented.**

< C = chemotherapy; NT = no therapy; RT = conventional radiotherapy; SBRT = stereotactic body radiotherapy. * = SBRT >

Median time to local progression

Of the included MTA studies, only Han et al (2015) and Yang et al (2014) reported median time to local progression (Table 52). However, it should be noted that the studies defined local progression differently. Yang et al (2014) did not include deaths in the median time to local progression, as the median overall survival time was shorter than the median time to local progression. Han et al (2015) included death or progression in this measure, and as such, the outcomes are not comparable.

Time to local progression was reported in four of the included RFA studies in population one (Table 52). Time to progression was defined and reported variably, and as such, it was not appropriate to provide pooled estimates across studies. In the only comparative trial, patients treated with RFA had a longer time to local progression compared to radiotherapy, but the significance was not tested.

The included radiotherapy studies for population one did not report time to local progression (Koshy et al 2015; Price et al 2012; Videtic et al 2015).

Table 52 Median time to local progression in patients with inoperable early stage NSCLC

Trial/Study	Intervention	N (lesions)	Median time to local progression (95%CI)
MTA			
Han et al (2015)	RFA	28 (28)	28.0 months (17.7–38.3)
Liu & Steinke (2015)	RFA	15 (16)	NR
Yang et al (2014)	RFA	47 (47)	45.5 months (28.8–61.8)
Pooled analysis	NA	75 (75)	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ VERY LOW
RFA			
Ambrogi et al (2011)	RFA	57 (59)	Median 39 months
Lanuti et al (2012)	RFA	45 (55)	mean (SD): 12 (10) range:1–44 months
Liu et al (2012)	RFA	29 (29)	mean (SD): 25 (11) range: 4–35 months
Safi et al (2015)	RFA	25 (25)	11.9 ± 8.1 (1–24) [a]
	RT	49 (49)	6.0 ± 3.0 (1–46) [b]
Pooled analysis	NA	205 (324)	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ **VERY LOW**

< MTA = microwave thermal ablation; NA = not applicable; NR = not reported; RFA = radiofrequency ablation; RT = radiotherapy; SD = standard deviation; ± = SD >

GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Primary tumour recurrence: 8.8 ± 7.5 (1–27), locoregional recurrence: 10.1 ± 8.1 (1–47), distance recurrence: 11.4 ± 7.3 (3–21)

[b] Primary tumour recurrence: 6.8 ± 3.3 (1–46), locoregional recurrence: 8.7 ± 7.0 (1–46), distance recurrence: 6.7 ± 6.7 (1–22), p = 0.36.

Local control and Local progression

Local control rates were reported in two included MTA studies (Han et al 2015; Yang et al 2014), two RFA studies (Dupuy et al 2015; Hiraki et al 2011a), and one radiotherapy study (Videtic et al 2015). Local progression was reported in three MTA studies (Han et al 2015; Liu and Steinke 2013b; Yang et al 2014), seven RFA studies (Ambrogi et al 2011; Dupuy et al 2015; Hiraki et al 2011a; Lanuti et al 2012; Liu et al 2015; Ridge et al 2014; Viti et al 2014), and two radiotherapy studies (Price et al 2012; Videtic et al 2015). Reported rates of local control and local progression are presented in Table 53.

Local control was defined as no focal or diffuse enlargement of the ablated lesion (Lanuti et al 2012), a decrease in the longest tumour diameter of at least 30 per cent with no evidence of peripheral tumour growth (Ridge et al 2014), or the absence of local failure (Videtic et al 2015). Other studies did not report, or did not define, local control, making it difficult to draw comparisons across studies.

Local progression or recurrence was defined as contrast-enhancement on CT at the site of ablation (Liu et al 2015; Yang et al 2014), focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage (Han et al 2015), recurrence in the same lobe or hilum (Dupuy et al 2015), recurrence in the same lobe but away from the ablation zone (Hiraki et al 2011a), interval increase in size or Fludeoxyglucose (FDG) uptake (Ridge et al 2014), and tumour recurrence in the former resection line or at the ablation site (Safi et al 2015). Local tumour response, including progression, was defined according to the RECIST criteria in a minority of studies (Liu and Steinke 2013b; Videtic et al 2015; Yang et al 2014). Outcomes for local control and local progression are difficult to compare across studies, because the definition of control and progression, and the time points at which they were reported, varied across studies.

Table 53 Local control of MTA, RFA and radiotherapy in patients with inoperable early stage NSCLC

Trial/Study	Intervention	N (lesions)	Local control rate n/N (%)	Local progression n/N (%)
MTA				
Han et al (2015)[a]	MTA	28 (28)	1-year NR (81) 2-year NR (74) 3-year NR (22) 4-year NR (22)	9/28 (32)
Liu & Steinke (2015)[b]	MTA	15 (16)	NR	5/16 (31)
Yang et al (2014)[c]	MTA	47 (47)	1-year NR (96) 3-year NR (64) 5-year NR (48)	13/47 (28)
Pooled analysis	NA	90 (91)	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ VERY LOW	Median 31% (28-32) Quality of the evidence ⊕⊙⊙⊙ VERY LOW

Trial/Study	Intervention	N (lesions)	Local control rate n/N (%)	Local progression n/N (%)
RFA				
Ambrogi et al (2011)	RFA	57 (59)	NR	13/59 (22)
Dupuy et al (2015)	RFA	51 (51)	1-year NR (69) 2-year NR (60)	19/51 (37)
Hiraki et al (2011)	RFA	50 (52)	40/52 (77) at last follow-up	16/52 (31) at median 15 months after RFA
Lanuti et al (2012)	RFA	45 (55)	NR	15/45 (33)
Liu et al (2012)	RFA	29 (29)	NR	7/33 (21) at median 25 months after RFA [d]
Ridge et al (2014)	RFA	29 (29)	NR	7/29 (24) at median 9 months after RFA
Viti et al (2014)	RFA	22 (24)	NR	6/24 (25)
Pooled analysis	NA	283 (299)	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ VERY LOW	Median 25% (range 21–33) Quality of the evidence ⊕⊙⊙⊙ VERY LOW
Radiotherapy				
Price et al (2012)	XRT	56 (NR)	NR	14/55 (25)
	XRT + gemcitabine	55 (NR)	NR	9/50 (18)
Videtic et al (2015)	34/1 GY SBRT	39 (NR)	1-year 33/34 (97)	2-year NR (2.6)
	48/4 GY SBRT	45 (NR)	1-year 41/44 (93)	2-year NR (2.2)
Pooled analysis	NA	NA	Pooling not possible Quality of the evidence ⊕⊕⊙⊙ LOW	Pooling not possible Quality of the evidence ⊕⊕⊙⊙ LOW

< CI = confidence interval; MTA = microwave thermal ablation; NA = not applicable; NR = not reported;NSCLC = non-small cell lung cancer; n/N (%) = number with event/ total (percentage); RFA = radiofrequency ablation; SBRT = stereotactic body radiotherapy; XRT = radical radiotherapy >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] No definition of local control was provided. A focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage was considered local recurrence (progression) if technical success had been confirmed.

[b] RECIST criteria=CR: 9/16 (56.3%), PR: 2/16 (12.5%), PD: 5/16 (31.3%).

[c] No definition of local control was provided. Local progression was referred to as the contrast-enhancement by CT scans in the site of ablation. Patients were requested to have serial repeat contrast-enhanced CT (CECT) scans at 3-, 6-, 9-, and 12-month intervals.

[d] denominator = number of treatments.

IS MTA EFFECTIVE IN PATIENTS WITH LUNG METASTASES IN WHOM THE PRIMARY TUMOUR IS UNDER CONTROL, AND WHO ARE RECEIVING TREATMENT WITH CURATIVE INTENT (OLIGOMETASTATIC DISEASE)?

Summary – What is the effectiveness of microwave tissue ablation in patients with lung metastases in whom the primary tumour is under control, treated with curative intent compared to radiofrequency ablation or current best practice radiotherapy with or without chemotherapy or surgical resection?

The evidence for both the intervention and its comparators is by and large characterised by Level IV evidence with variable outcome measures and incomplete reporting. The comparative benefit of this form of tumour destruction over existing treatment options is unknown. The claim of non-inferiority for the comparative effectiveness of MTA as compared to other interventions remains untested by any published studies.

Patients with oligometastatic disease in the lung are a heterogeneous group. Only two studies that investigated the use of MTA in oligometastatic pulmonary disease were identified (Qi et al 2015; Vogl et al 2011). These studies included oligometastases from nasopharyngeal carcinoma (n = 17) colorectal carcinoma (n = 40), breast carcinoma (n = 20), hepatocellular carcinoma (n = 10), renal cell carcinoma (n = 5), bronchogenic carcinoma (n = 5). Patients with oligometastatic disease are defined primarily by the curative intent of therapy, and outcomes of interest in this population include both survival and progression. The comparators to MTA include RFA, current best practice radiotherapy and surgery. However, no comparative trials are available to inform an assessment of comparative effectiveness. Very few relevant outcomes were reported by the included MTA studies.

Assessing the effectiveness of MTA is further complicated by uncertainty regarding the benefit of treatments for patients with oligometastatic pulmonary metastases (Treasure et al 2012). There is currently no reliable estimate of baseline survival in patients with oligometastatic lung disease (Ashworth et al 2013), and therefore, in the absence of direct comparative data it is difficult to quantify the benefits associated with treatments for oligometastatic lung disease. Authors of large case series studies examining interventions for pulmonary metastases almost uniformly conclude that intervention prolongs survival without undertaking any analysis to support such a claim. This issue is further confounded by debate around appropriate criteria for selecting patients for intervention and whether different primary cancers are associated with better or worse survival profiles. The MSAC should consider that it is not possible to statistically test for differences in prognostic factors across studies or for differences in effects. Outcomes reported from case series studies are subject to high risk of bias for a number of reasons and it is not possible to quantify the impact of bias or confounding effects within the included evidence.

Overall survival

Overall survival was reported by one study of MTA (Vogl et al 2011). The authors reported on a series of 80 patients with lung metastases from a range of primary cancers. At 12 months the survival rate was 91 per cent (73/80 patients alive) and at 24 months it was 75 per cent (60/80 patients alive). Survival greater than 24 months was not reported. The authors categorised ablations as complete successful ablation or failed ablation; where failure was defined by tumour residue or recurrence at follow-up (occurred in 35/130, 27%). The authors report a statistically significant difference in survival after complete versus failed ablations (p = 0.001) with complete ablation conferring a survival advantage. Qi et al (2015) does not report survival outcomes; however, reports that 11/17 (64%) of patients were disease free at the time of writing.

Overall survival outcomes reported by studies of MTA, RFA and radiotherapy are presented in Figure 12, and ranges of overall survival are presented in Table 54. As no direct or indirect comparative data was identified, it is difficult to draw meaningful comparisons across interventions. With this limitation in mind, the 1-, 2-, 3-, and 5-year overall survival rates are presented in order to demonstrate the large degree of variability in reported survival rates for each intervention, and should not be used to draw comparisons across interventions. The raw data on overall survival outcomes are presented in Table 102 and Table 103 (Appendix E).

Table 54 Overall survival reported in studies of RFA and radiotherapy in population two

Intervention	1-year OS (№ studies)	2-year OS (№ studies)	3-year OS (№ studies)	5-year OS (№ studies)
RFA	Median 88% Range 73–100% (10 studies)	Median 59% Range 41–94% (7 studies)	Median 52% Range 14–85% (10 studies)	Median NR Range 45–52% (3 studies)
Radiotherapy	Median 86% Range 61–98% (10 studies)	Median 65% Range 31–86% (15 studies)	Median 62% Range 50–73% (4 studies)	Median 46% Range 39–56% (5 studies)

< NR = not reported; OS = overall survival; RFA = radiofrequency ablation >

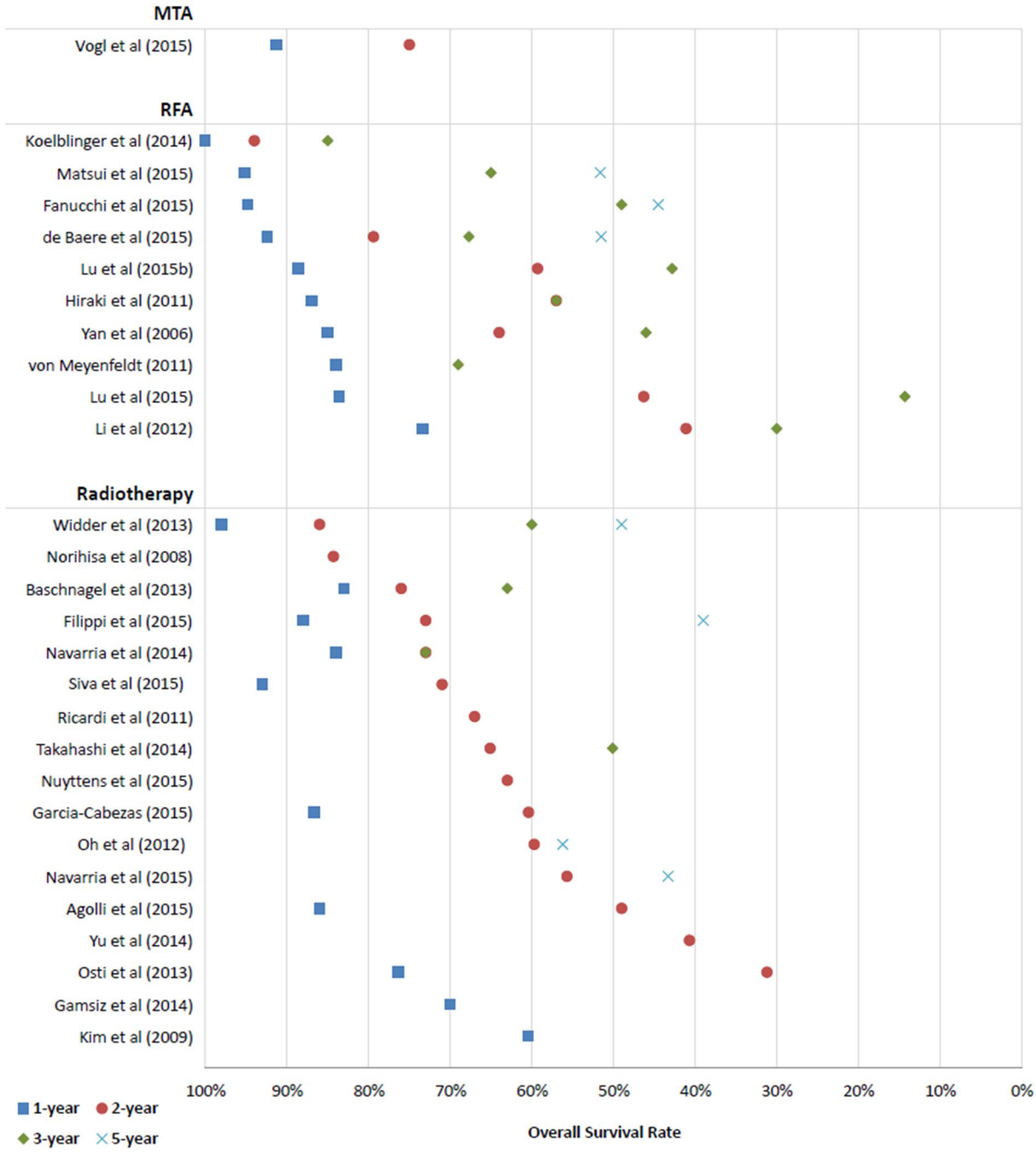

Figure 12 Overall survival rates reported in studies of MTA, RFA and radiotherapy for population two

Overall survival and survival rates reported in studies of surgical resection

There is a large volume of Level IV case series evidence published on surgical resection in the setting of oligometastatic disease. Therefore, inclusion was limited to systematic reviews and supplemented by the addition of several case series that were recent, had large sample size or represented a population with primary tumour histology included in studies of MTA and RFA. Overall results are varied.

Overall survival time was infrequently reported and in one study was only reported according to a number of variables. Reza et al (2014) reported on a series of patients with sarcoma (N = 118) and found median overall survival was 35 months. This was associated with a wide confidence interval ranging from 23 to 61 months. In the study by Kitano et al (2012) the median overall survival of 45 patients with Hepatocellular carcinoma (HCC) was 26.5 months with a range of 0.7 to 165 months. Renaud et al (2014) studied 320 patients with lung metastases from colorectal cancer and found a statistically significant difference in overall survival in patients with no lymph node involvement (versus positive lymph node involvement); solitary pulmonary metastases (versus multiple); and no hepatic involvement (versus hepatic metastases).

Survival rates were rarely reported at less than five years and are shown in Table 104 (Appendix E). Young et al (2015) reported the results of a meta-analysis of 387 patients with head and neck cancers. This review reported a 5-year survival rate of 29.1 per cent (95%CI 24.1–35.3%). Young et al (2015) also reported prognostic factors from primary studies:

- Two papers reported significantly worse 5-year survival rates in patients with oral head and neck squamous cell carcinoma compared with other sites.
- Two papers reported that the presence of cervical lymph node metastases at diagnosis of the primary tumour significantly worsened 5-year survival rates following pulmonary metastasectomy.
- Other poor prognostic factors for survival included incomplete pulmonary resection (reported by one study) and the presence of multiple pulmonary nodules (also reported by one study).

The systematic review by Pfannschmidt et al (2007), which included 20 studies (2,320 patients) of patients with lung metastases from colorectal cancer reported a median 5-year survival rate of 48 per cent (range: 41–56%). The authors did not conduct any meta-analysis or undertake any formal analysis of prognostic factors. However, studies reporting complete (called R0) resections either for the whole study population or for subgroups of patients had median 5-year survival rate of 39.6 per cent (range: 24–6%). Three studies reporting 5-year survival for non-radical resection had a median 5-year survival rate of 0% (range: 0–21%). Three studies reported 5-year survival exclusively for patients who had pulmonary and hepatic resection, those studies had a median 5-year survival rate of 31 per cent (range: 30–38%).

Time to progression and local progression

Time to local progression in patients treated with MTA was reported by both Qi et al (2015) and Vogl et al (2015). The average time to local progression was similar in both studies (7 and 6 months), as was the rate of local progression (29% and 27%).

The median time to local progression reported in the included RFA studies was 12 months (range 4–15 months), and the median rate of local progression was 15% (range 12–28%). In the included radiotherapy studies, the median time to local progression was 11 months (range 5–18 months), and the median rate of local progression was 10% (4–23%). One study compared surgery to SBRT, in which the median time to progression was eight and five months, respectively (Yu et al 2014). No other studies reported time to local progression for surgery. However, one study that described a series of surgically treated lung metastases from colorectal cancer reported that 110/320 patients (34%) underwent at least two thoracic procedures for pulmonary recurrence (Renaud et al 2014).

Both time to local progression and the local progression rate are likely to be influenced by differences in reporting across studies. As in population one, the definition of local progression varied across studies, and the time at which the rate was calculated was rarely reported. Hence, differences in reported outcomes across studies may be due to differences in unadjusted confounding factors in the study populations (due to Level IV evidence), differences in the effectiveness of the interventions, or differences in outcome measures and analysis.

Table 55 Median time to local progression and local progression rate (population 2)

Trial/Study	N (lesions)	Median time to local progression (range)	Local progression rate, n/N (%)
MTA			
Qi et al (2015)	17 (29)	7 (4–20) months	5/17 (29)[a]
Vogl et al (2015)	80 (130)	6 (1–18) months	35/130 (27)
Pooled analysis	97 (159)	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ VERY LOW	Pooling not possible Quality of the evidence ⊕⊙⊙⊙ VERY LOW
RFA			
De Baere et al (2015)	566 (1037)	NR	82/566 (15)
Fanucchi et al (2015)	61 (86)	NR	7/61 (12)
Hiraki et al (2011)	32 (83)	NR	NR
Koelbinger et al (2014)	22 (55)	12 months[b]	NR
Li et al (2012)	29 (68)	14 months (2–56)	4/29 (14)
Lu et al (2015)	67 (115)	NR	NR
Lu et al (2015b)	35 (67)	NR	NR
Matsui et al (2015)	84 (172)	8 ± 8 months (3–44)	18/84 (21)

Trial/Study	N (lesions)	Median time to local progression (range)	Local progression rate, n/N (%)
Von Meyenfeldt et al (2011)	46 (90)	4 months (95% CI 2.7–5.3)[b]	25/90 (28)
Yan et al (2006)	55 (NR)	15 (3–40) months[b]	NR
Pooled analysis	997 (1828)	Median 12 (4–15) months Quality of the evidence ⊕⊙⊙⊙ VERY LOW	Median 15% (12–28) Quality of the evidence ⊕⊙⊙⊙ VERY LOW
Radiotherapy			
Agolli et al (2015)	22 (29)	18 (NR) months	4/22 (18)
Fillipi et al (2015)	40 (59)	8 (NR) months	3/40 (8)[c]
Kim et al (2009)	31 (134)	11 (SD 1.25) months	3/31 (10)
Navirra et al (2014)	76 (118)	10 (range: 3–19) months	3/76 (4)
Norihisa et al (2008)	34 (43)	NR	3/34 (9)
Nuytens et al (2015)	30 (57)	NR	7/30 (23)
Osti et al (2013)	66 (103)	10 (NR) months	10/103 (10) lesions
Ricardi et al (2011)	61 (77)	12 (NR) months	9/61 (15)
Takeshi et al (2014)	34 (44)	11 (NR) months	NR
Yu et al (2014)	27 (NR)	5 (NR) months	NR
Pooled analysis	421 (691)	Median 10.5 (5–18) months Quality of the evidence ⊕⊙⊙⊙ VERY LOW	Median 10% (4–23) Quality of the evidence ⊕⊙⊙⊙ VERY LOW

< MTA = microwave thermal ablation; N = number; n/N (%)= number with event/ total (percentage); NR = not reported; RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Five patients had new metastases inside the lung and the other patient had thoracic vertebral metastases 1 year postoperatively.

[b] Reported as disease-free survival period.

[c] failure at SBRT site, SBRT = stereotactic body radiotherapy.

IS MTA EFFECTIVE IN PATIENTS WITH LUNG METASTASES OR PRIMARY LUNG CANCER WHO ARE BEING TREATED WITH PALLIATIVE INTENT?

Summary – What is the effectiveness of microwave tissue ablation in patients with NSCLC or lung metastases being treated with palliative intent?

For patients treated with palliative intent the main outcomes of interest relate to symptom control and quality of life; however, no data on these outcomes was reported by the literature on ablation. Three studies of MTA in this population were identified of which two were non-randomised comparative trials. These studies found a benefit in terms of survival for patients who received MTA in combination with chemotherapy over those receiving either therapy alone. However, the magnitude of this benefit (in terms of months gained) could not be calculated.

Three studies of MTA in patients being treated with palliative intent were identified; however, none reported primary effectiveness outcomes related to quality of life or symptom control. Only secondary effectiveness outcomes were assessed. Two non-randomised comparative trials compared treatment strategies involving MTA and chemotherapy regimes in a palliative population. Sun et al (2015) included patients with advanced NSCLC and compared the therapeutic strategies of MTA alone (n = 22) or MTA in combinations with chemotherapy (n = 18). Wei et al (2015) included patients with advanced NSCLC and compared MTA in combination with chemotherapy (n = 46) to chemotherapy alone (n = 28). A third study by Ni et al (2015) is a retrospective case series study of patients with stage IIIB-IV NSCLC (n = 35) who had received prior treatment (including chemotherapy, targeted therapy, concurrent chemo-radiation followed by chemotherapy), and, who had partial response or stable disease. In both comparative studies combination therapy as opposed to single therapy (MTA alone or chemotherapy alone) confers a statistically significant advantage in terms of survival outcomes. However, as previously mentioned no outcomes relevant to symptom relief or quality of life were reported.

Sun et al (2015): MTA versus MTA and chemotherapy

Sun et al (2015) reported the 1- and 2-year survival and the disease control rate. The authors report one year survival in patients treated with MTA alone as 50 per cent, which dropped to 28 per cent at two years. In the group treated with MTA and chemotherapy 1-year survival was 77 per cent dropping to 59 per cent at two years. A statistically significant difference was reported by the authors in 2-year overall survival but not 1-year overall survival. The disease control rate was measured using the RECIST criteria and was defined as the number of patients with complete response, partial response and stable disease. In the MTA alone group this was 44 per cent (8/18 patients) and in the MTA and chemotherapy group this was 77 per cent (17/22 patients); this result was statistically significant ($p<0.05$). No other relevant effectiveness outcomes were reported.

Wei et al (2015): MTA and chemotherapy versus chemotherapy alone

Wei et al (2015) reported median overall survival time, progression free survival time and the rate of local progression and distant metastases. In the patients treated by combination therapy the median overall survival (95% CI) was 23.9 months (15.2–32.6) in comparison with 17.3 months (15.2–19.3) in the patients treated with chemotherapy alone. The difference was not statistically significant. The difference in median progression free survival between groups is reported to be statistically significant with patients treated with combination therapy having a longer progression free interval (10.9 months, 95%CI 5.1–17.7 versus 4.8 months, 95%CI 3.9–5.8; p = 0.001). All patients in the chemotherapy alone group experienced local progression as compared to 9 (19.6%) in the combined group. Similarly, all patients in the chemotherapy group had distant metastases develop in contrast to 30 (65.2%) of patients in the combination group. No other relevant effectiveness outcomes were reported.

Ni et al (2015): MTA

Ni et al (2015) report median overall survival following MTA as well as local progression rate, incidence of distant metastases and median time to progression. Overall the median overall survival time for the 35 included patients was 17.7 months (range of 5–45) and from the time of MTA until death it was 10.6 months (range: 3.1–36.2). The median time to progression was 11.8 months (3.2–44.7) and from the time of MTA it was 5.4 months (range: 0.7–35.3); five (14.3%) of patients had local progression and 20 (57%) developed distant metastases. At the end of the follow-up nine patients (25%) were living without progression and 14 patients had died due to intrapulmonary progression (n = 5), distant metastases (n = 8) or respiratory causes (n = 1). No other effectiveness outcomes were reported.

Effectiveness of RFA for palliation of advanced-stage lung cancer

One primary study was identified that investigated the impact of RFA in population three. Simon et al (2007) conducted a retrospective study of RFA for symptom palliation involving 21 patients with stage IV metastatic lung cancer. The results of this small, single-arm case series are presented in Table 56. The majority of symptoms improved following RFA (26/27 lesions); however, 37 per cent (10/27 lesions) experienced a recurrence in symptoms. As lesions were the base unit of measurement for symptom relief, it is unclear how many patients benefited from symptom improvement, or experienced a subsequent recurrence. For example, one of the patients treated for cough may have had three lesions ablated without recurrence, which would have biased the 25 per cent recurrence rate. In addition to symptom control, authors reported a median estimated survival time of 6 months (95% CI 2–10 months), which was associated with 1-year survival of 28 per cent, and 2-year of six per cent.

Table 56 Symptom improvement in lung cancer patients treated palliatively with RFA (Simon et al 2007)

Symptom	№ of lesions treated	№ of lesions with symptom improvement	№ of lesions with symptom recurrence (%)
Pain	20	19	7 (37)
Haemoptysis	3	3	2 (67)
Cough	4	4	1 (25)

Effectiveness of radiotherapy for palliation of advanced-stage lung cancer

The effectiveness of radiotherapy for palliative treatment of advanced stage lung cancer was recently reported in a Cochrane review by Stevens et al (2015). The review included 13 RCTs that compared the effects of radiotherapy fractionation schedules on symptom improvement and overall survival. The authors noted that all of the included studies reported a benefit of radiotherapy on symptom improvement, but concluded that no strong evidence for higher doses were associated with better or longer lasting palliation.

Quality of life

The overall survival in patients who have good or poor performance status, with quality of evidence ratings for the reported relative effect, are presented in Table 57.

Table 57 Effectiveness and quality of evidence for palliative radiotherapy regimens (Stevens et al 2015)

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	No of patients (studies)	Quality of the evidence (GRADE)	Comments
	Less fractions	More fractions				
1-year overall survival in patients of good performance status	Mean 25.6% (9.4–45.7%)	Mean 33.3% (11.4–46.2%)		1,081 (8 studies)	⊕⊕⊙⊙ LOW	NO summary statistic due to heterogeneity, incomplete data – unable to source missing data from authors
1-year overall survival in patients of poor performance status	Mean 14.6% (1.3–29.5%)	Mean 17.5% (9.1–28.6%)	RR 0.96 (0.91 to 1.02)	911 (7 studies)	⊕⊕⊕⊙ MODERATE	Incomplete data - unable to source missing data from authors

< CI = confidence interval; NR = not reported; RR = relative risk >

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊕⊕⊙ **Moderate quality**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

B.6. EXTENDED ASSESSMENT OF HARMS

All of the relevant information of safety for the intervention is contained within Section B.6.

B.7. INTERPRETATION OF THE CLINICAL EVIDENCE

Overall, the clinical evidence for MTA in all of the proposed populations for reimbursement is limited in quantity and quality. This issue also pervades the clinical literature for the main comparators, and is likely to impact the availability of high quality comparative evidence for therapy in these populations for some time. The evidence for both the intervention and its comparators is largely characterised by Level IV evidence with variable outcome measures and incomplete reporting. The mechanism of action of thermal ablative technologies in terms of tumour destruction is intuitively appealing; however, the comparative benefit of this form of tumour destruction over existing treatment options is unknown. It is important to note that in the context of a reimbursement decision the claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by any published studies. The main safety concern associated with MTA is pneumothorax; however, the majority of pneumothorax that occurs appears to be mild and does not require further intervention. Thermal ablation in the literature is frequently performed under local anaesthesia but this may not be representative of Australian clinical practice. Physicians undertaking MTA in Australia have indicated that the procedure is done almost exclusively under general anaesthesia. Hence, risks associated with anaesthesia may not have been captured by the published literature although these are not likely to add substantially to the risk profile of MTA.

NOTE on summary of findings tables: only selected outcomes that were reported across multiple comparators are summarised in the tables that follow. More complete reporting of outcomes is provided in the main body of the report (B.6).

Population one

Based on the evidence profile (summarised in Table 58 and Table 61), it is suggested that, relative to current best practice radiotherapy, the intervention has uncertain safety and uncertain effectiveness. For patients with early stage NSCLC who are not eligible for surgery radiotherapy, SBRT has become the treatment option of choice. Attempts to conduct head-to-head trials of SBRT versus surgery have failed due to slow accrual and hence the best available evidence for radiotherapy comes from retrospective, database analysis. Studies in this area have found a survival benefit of radiotherapy over observation; and, of SBRT over conventional radiotherapy. However, the question of how ablative therapies compare to either conventional radiotherapy or SBRT has not been addressed by any retrospective or prospective studies. Furthermore, it was not feasible to undertake any statistical tests of non-inferiority between thermal ablation and radiotherapy. Although authors of papers on ablative technologies continue to assert the benefit of such technologies and suggest that they provide a viable treatment alternative to radiotherapy, the claim of non-inferiority remains untested. Notably, although an apparently safe technology, thermal ablation does appear on face value to be associated with a greater frequency of adverse events than SBRT. However, there are instances in which SBRT may be inappropriate due to the location of the tumour and clinical advice suggests that MTA may be a complimentary technology for patients who cannot have SBRT.

Table 58 Balance of clinical benefits of MTA, relative to its comparators, and as measured by the patient-relevant outcomes in the key studies for population one

Outcome and intervention/comparator	№ of studies, level of evidence	Quality of the evidence (GRADE)	Summary
Survival rates at 1-,2-,3- and 4 or 5-years			
MTA Assessed with: Kaplan-Meier (95% CI NR) F/U: range 22.5 months to 30 months	2 Level IV studies	⨁⊙⊙⊙ VERY LOW[1,2]	Han et al (2015): 1-year: 91.7%, 2-year: 76.5%, 3-year: 47.9% and 4-year: 47.9% Han et al (2015) cancer-specific: cancer-specific survival rate was 1-year: 94.7%, 2-year: 73.9%, 3-year: 64.7% and 4-year: 64.7% Yang et al (2015): 1-year: 89%, 2-year 63%, 3-year 43%, and 5-year: 16% [3]
RFA Assessed with: Kaplan-Meier (95%CI NR) F/U: range 19 months to 46 months	1 Level III-3 study 7 Level IV studies	⨁⊙⊙⊙ VERY LOW[1,4]	Median survival rate, pooled 1-year: 86.3% (range 83–100%) 2-year: 74% (69.8–86%) 3-year: 62.75% (40–74%) 5-year: 28% (14–61%)

Outcome and intervention/comparator	№ of studies, level of evidence	Quality of the evidence (GRADE)	Summary
Radiotherapy Assessed with: varied instruments F/U: range 21 months to 30.2 months	1 Level II study 1 Level III-1 study[5]	⊕⊕⊙⊙ LOW	Koshy et al (2015) compared conventional radiotherapy, SBRT and no treatment in a study of 13,036 patients. No treatment 3-yr survival was 28%; SBRT was 48%; conventional radiotherapy was 36%. A propensity-matched cohort of SBRT and conventional radiotherapy gave a 3-yr overall survival with SBRT of 48% and with conventional radiotherapy of 40 % (p = 0.001). Videtic et al (2015) reported 1-year survival with 34/1 GY SBRT and 48/4 GY SBRT as 48.6% (09% CI 68.9–92.8%) and 91.1 (78.0–96.6%) respectively. For 2-year survival it was: 61.3% (44.2–74.6%) versus 77.7% (62.5–87.3).
Median overall survival			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U: range 22.5 months to 30 months	2 Level IV studies	⊕⊙⊙⊙ VERY LOW[1,6]	Han et al (2015): 35.0 months (95%CI 22.3–47.7) Yang et al (2014): 33.8 months (95%CI 31.9–35.7)[3] Han et al (2015): cancer specific 41.9 months (95% CI 38.8–49.9) Yang et al (2014): cancer specific 47.4 months (25.7–69.1)
RFA Assessed with: Kaplan-Meier estimate (95%CI) F/U: range 19 months to 37 months	6 Level IV studies	⊕⊙⊙⊙ VERY LOW [1,4]	Median overall survival: 42.8 months (range: 33.4–67)
Radiotherapy Not reported	0 studies	NA	NA
Median time to local progression			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U: range 22.5 months to 30 months	2 Level IV studies	⊕⊙⊙⊙ VERY LOW[1,7,8]	Han et al (2015) time to local progression: 28.0 months (95%CI 17.7–38.3) Yang et al (2015) time to first recurrence: 45.5 months (95%CI: 28.8–61.8)
RFA Assessed with: Kaplan-Meier estimate (95%CI)	1 Level III-3 study[9] 3 Level IV	⊕⊙⊙⊙ VERY LOW [1,10]	Ambrogi et al (2011): Median of 39 months (range NR) Lanuti et al (2012): mean (SD) of 12 (10) months, range 1–44

Outcome and intervention/comparator	№ of studies, level of evidence	Quality of the evidence (GRADE)	Summary
F/U: range 19 months to 46 months	studies		Liu et al (2012): mean (SD): 25 (11) months, range 4–35 Safi et al (2015): 11.9 ± 8.1 (1–24) months with RFA and 6.0 ± 3.0 (1–46) months with radiotherapy, p = 0.36 for test of significance
Radiotherapy Not reported	0 studies	NA	NA

< F/U = follow-up; MTA = microwave tissue ablation; NA = not applicable; RFA = radiofrequency ablation; SD = standard deviation; ± = SD; SBRT= stereotactic body radiotherapy >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. Due to inherent limitations in study design and from quality concerns with the included studies.
2. Neither Han et al (2015) nor Yang et al (2015) provide confidence intervals associated with the point estimates, and therefore it isn't clear how precise estimates are. Similarly only Yang et al (2015) report maximum follow-up of >60 months (5 years).
3. Note that: Yang et al (2015) examined a subgroup of patients with tumours > 3.5 cm versus ≤ 3.5 cm and found that tumours ≤ 3.5 cm were associated with better survival than were tumours >3.5 cm (p = 0.016). The distribution in number of patients with tumours >3.5 cm across the two studies will affect the consistency of outcomes.
4. There is a wide range of survival rates reported with reporting becoming more and more limited over time. This should be a relatively homogenous group in terms of cancer stage and extent of disease. There is substantial concern that outcomes have been measured very differently across studies. For example Hiraki et al (2011) has a 5-year survival of 61% whilst Ridge et al (2014) reports only 14%.
5. Koshy et al (2015) is a Level III-1 retrospective propensity-matched cohort, Videtic et al (2015) is Level II study.
6. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95% CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.
7. It has been observed that authors appear to use the term recurrence/progression interchangeably. Han et al (2015): A focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage was considered local recurrence if technical success had been confirmed. Yang et al (2015): Local progression was referred to as the contrast-enhancement by CT scans in the site of ablation.
8. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95% CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.
9. Safi et al (2015) is a Level III-3 retrospective cohort study that compared RFA and radiotherapy.
10. Estimates across different studies are markedly different, it may be due to differences in measurement, reporting or outcome.

Population two

Based on the evidence profile (summarised in Table 59 and Table 61) it is suggested that, relative to current best practice radiotherapy, the intervention has uncertain safety and uncertain effectiveness. Relative to surgical resection, the intervention has superior safety and uncertain effectiveness.

For this heterogeneous population, predominantly defined by the curative intent of treatment, there is no available evidence comparing treatment with different interventions. This review identified one

currently recruiting clinical trial, the PULMICC trial (NCT01106261), which is a randomized multicentre controlled trial on resection versus conservative therapy for colonic lung metastases. This trial aims to address the issue of whether or not surgery is beneficial in patients who have been deemed suitable for resection which illustrates the current, relatively uncertain, state of evidence for all therapies in this population. Patients with oligometastatic disease in the lung may be offered resection, SBRT or thermal ablation. There is, at present, no data amenable to comparison across treatment strategies. Thermal ablation is purported to have benefit in this population; however, only two studies of MTA were identified and the limited outcomes reported are not sufficient to compare across interventions in terms of effectiveness. As compared to surgical resection, however, MTA is associated with a shorter recovery time and procedure-related mortality is expected to be a rare outcome of MTA. Clinical advice is that the decision of how to treat patients with oligometastatic disease would be considered by a multidisciplinary team. The potential benefits and harms of each option would differ according to the patients' individual situation. MTA has been described as having potential advantages over surgery or radiotherapy in terms of its repeatability and minimal impact on surrounding lung tissue. This might make MTA an attractive option for patients who cannot tolerate the loss of any further lung volume or who cannot receive further doses of radiation. Where there is uncertainty regarding the benefit of surgery for certain patients, some physicians may have a preference for less invasive therapies such as SBRT or thermal ablation over resection.

Table 59 Balance of clinical benefits of MTA, relative to its comparators, and as measured by the patient-relevant outcomes in the key studies for population two

Outcome and intervention/comparator	№ of Studies and level of evidence	Quality of the evidence (GRADE)	Summary
Survival rates at 1-,2-,3- and 4 or 5-years			
MTA Assessed with: n/N (%) at 1 and 2 years F/U: median 9 mths	1 Level IV study	⊕⊙⊙⊙ VERY LOW [1]	Vogl et al (2015) At 12 months the survival rate was 91.3 per cent (73/80 patients alive) and at 24 months it was 75 per cent (60/80 patients alive). Survival greater than 24 months was not reported.
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U: range 12 months to 38 months	10 Level IV studies	⊕⊙⊙⊙ VERY LOW [1]	Median survival rate, pooled 1-year: 87.8% (range 73.4–100%) 2-year: 59.3% (range 41.1–94%) 3-year: 53 % (range: 30–85%) 5-year: Not estimable
Radiotherapy Assessed with: Kaplan-	3 Level III-2 studies	⊕⊙⊙⊙ VERY LOW [1,3]	Median survival rate, pooled 1-year: 86 % (60.5–98%)

Outcome and intervention/comparator	№ of Studies and level of evidence	Quality of the evidence (GRADE)	Summary
Meier estimate (95%CI) F/U: range 13 months to 55 months	14 Level IV studies[2]		2-year: 65.1% (31.2–86%) 3-year: 61.5% (50.1–73%) 5-year: 46.2 %(39–56.2%)
Surgery Assessed with: varied measures F/U: minimum follow-up was 30 days months	2 Level I studies (of Level IV evidence) 2 Level IV studies	⊕⊙⊙⊙ VERY LOW [1,3]	Young et al (2015): Meta-analysis of 5 year overall survival from 11 studies (387 patients) : 29.1% (95%CI; 24.1–35.3); I2 = 0%, p = 0.462, d.f.= 10 Pfannschmidt et al (2007): All studies reported overall survival of 5 years for all patients undergoing resection of pulmonary metastases (median: 48%, range: 41.1% to 56%). Reza et al (2014): 3-year: 48%, 5-year: 42%, 10-year: 31%. Kitano et al (2012): 2-year: 53.9%, 5-year: 40.9%
Median overall survival			
MTA Not reported	0 studies	NA	NA
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U: range 12 months to 38 months	10 Level IV studies	⊕⊙⊙⊙ VERY LOW [1,4]	Median overall survival: 44 months (range: 21–67)
Radiotherapy Assessed with: Kaplan-Meier estimates (95%CI) F/U: range 13 months to 55 months	1Level III-2 study 10 Level IV studies [6]	⊕⊙⊙⊙ VERY LOW [1,4]	Median overall survival: 27.8 months (range: 12–42.8)
Surgery Assessed with: Kaplan-Meier estimate (95 % CI) F/U: median Not reported months	3 Level IV studies	⊕⊙⊙⊙ VERY LOW [1,5]	Renaud et al (2014): No lymph node involvement: 94 months (95%CI, 76.27–111.72) positive lymph node involvement: 42 months (95%CI, 30.06–53.93; p<0.0001) Hilar location of lymph node involvement: 47 months (95%CI, 29.89–64.10) Mediastinal location of lymph node involvement: 37 months (95%CI, 13.98–60.01; p>0.05) Solitary pulmonary metastasis: 81 months (95%CI, 60.8–101.19) Multiple metastases: 55 months (95%CI, 35.14–74.86; p<0.01) Hepatic metastases: 47 months (95%CI, 21.6–72.39) No hepatic metastases: 74 months (95%CI,

Outcome and intervention/comparator	№ of Studies and level of evidence	Quality of the evidence (GRADE)	Summary
			60.74–87.26;. p<0.01) Reza et al (2014): 35 months (95%CI 23–61) Kitano et al (2012): 26.5 months (range: 0.7–165)
Median time to local progression			
MTA Assessed with: Mean time in months (range) F/U: range 9 months to 14 months	2 Level IV studies	⊕⊙⊙⊙ VERY LOW[1]	Qi et al (2015): 7.2 months (range 4–20) Vogl et al (2015): 6 months (range: 1–18)
RFA Assessed with: mean (range) months/Kaplan-Meier estimate (95%CI) F/U: range 12 months to 38 months	5 Level IV studies	⊕⊙⊙⊙ VERY LOW [1,6]	Median time to local progression: 12 months (range: 8.2–15 months)
Radiotherapy Assessed with: median months until progression F/U: range 15 months to 24 months	1 Level III-2 study 6 Level IV studies[8]	⊕⊙⊙⊙ VERY LOW [1,6]	Median time to local progression: 10.8 months (range: 5–18)
Surgery Not reported	0 studies	NA	NA

< CI = confidence interval; F/U = follow-up; MTA = microwave tissue ablation; n/N (%) = number with event/ total (percentage); NA = not applicable; RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Due to inherent limitations in study design as well as quality issues.
2. There were the following other study designs: Siva et al (2015) Level III-2 retrospective cohort study, Yu et al (2014) Level III-2 retrospective cohort study, Widder et al (2013) Level III-2 retrospective cohort study.
3. Studies report a large range of survival rates with many studies not providing any indication of the variance associated with point estimates. At later time points less results are available.
4. There were the following other study designs: Siva et al (2015) Level III-2 retrospective cohort study, Yu et al (2014) Level III-2 retrospective cohort study.
5. Studies included investigated a range of prognostic factors and different studies reported on patients with different primary cancers. This is likely to have affected the overall survival time of included patients.
6. Studies report a range of time to progression estimates and it is not clear whether they were measured in a consistent manner.

Population three

Based on the evidence profile (Table 60 and Table 61), it is suggested that the intervention has uncertain safety and uncertain effectiveness. For patients treated with palliative intent the main outcomes of interest relate to symptom control and quality of life. No data on these outcomes was reported by the literature on ablation. Three studies of MTA in this population were identified, of which two were non-randomised comparative trials. These studies found a benefit in terms of survival for patients who received MTA in combination with chemotherapy over those receiving either therapy alone. However, the magnitude of this benefit (in terms of months gained) could not be calculated. These studies indicate that MTA could be an additional option for patients who are being treated with a palliative intent; however, the impact of MTA on symptoms and quality of life in this population is uncertain. Clinical advice has indicated that patients are not currently treated with MTA for this indication in Australia, as they would more often receive systemic therapies.

Table 60 Balance of clinical benefits of MTA, relative to its comparators, and as measured by the patient-relevant outcomes in the key studies for population three

Outcome and intervention/comparator	№ of Studies and level of evidence	Quality of the evidence (GRADE)	Summary
1 year survival (Sun et al 2015)			
MTA alone versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U: range 6 months to 35 months	1 Level III-2 study	⊕⊙⊙⊙ VERY LOW [1,2]	MTA alone: 9/18 (50%) MTA and chemotherapy: 17/22 (77.3%)
2-year survival (Sun et al 2015)			
MTA alone versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U: range 6 months to 35 months	1 Level III-2 study	⊕⊙⊙⊙ VERY LOW [1,2]	MTA alone: 5/18 (27.7%) MTA and chemotherapy: 13/22 (79.1%)
Median overall survival (Wei et al 2015)			
MTA+ chemotherapy versus chemotherapy alone	1 Level III-2 study	⊕⊙⊙⊙ VERY LOW [1,3,4]	MTA+chemotherapy: 23.9 (95%CI15.2–32.6) months

Outcome and intervention/comparator	№ of Studies and level of evidence	Quality of the evidence (GRADE)	Summary
Assessed with: Kaplan-Meier estimate F/U: median 21 months			Chemotherapy: 17.3 (95%CI 15.2–19.3) months, difference p = 0.140
MTA alone Assessed with: Median and range F/U: median 17.7 months	1 Level III-2 study	⊕⊙⊙⊙ VERY LOW [1,5]	Median OS: 17.7 months (range of 5–45) and from the time of MTA until death it was 10.6 months (range: 3.1–36.2).

<CI = confidence interval; F/U = follow-up; MTA = microwave tissue ablation; n/N (%) = number with event/ total (percentage) >
GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. This is based on the results of one study with 22patients in one arm and 18 in the other, study reporting quality was low.
2. Measures of variance are not available. The small sample size reduces the reliability of the outcomes
3. Wei et al (2015) reports on small sample sizes and inherent drawbacks in study design are problematic
4. Measures of variance show wide confidence intervals associated with OS. The small sample size reduces the reliability of the outcomes.
5. Due to inherent limitations in case series evidence

Table 61 Balance of clinical harms associated with MTA relative to its comparators, and as measured by the patient-relevant outcomes in the key studies

Outcome and intervention/comparator	№ of patients (studies)	Summary	Quality of the evidence (GRADE)
Procedure-related mortality			
MTA F/U: range 6–30 months	N = 916 1 Level III-2 studies 19 Level IV studies	2/916 (0.22%)[1]	⊕⊙⊙⊙ VERY LOW
RFA F/U: range 10–46 months	N = 1259 1 Level III-3 study 16 Level IV studies	1/1259 (<0.1%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy F/U: range 13–82 months	N = NA 2 Level II studies 2 Level III-2 studies 13 Level IV studies	2 cases of procedure-related mortality across all included 17 studies.[2]	⊕⊙⊙⊙ VERY LOW[3]
Surgery F/U: NA	N = NA 1 Level I study 2 Level IV studies	Pfannschmidt et al (2007): 4/20 studies reported mortality, range 0–3% of patients Renaud et al (2014) and Kitano et al (2012): 0/365 (0%)	⊕⊙⊙⊙ VERY LOW

Outcome and intervention/comparator	№ of patients (studies)	Summary	Quality of the evidence (GRADE)
30 day mortality			
MTA F/U: range 6–30 months	N = 739 16 Level IV studies	1/739 (0.14%)	⊕⊙⊙⊙ VERY LOW
RFA F/U: range 10–36 months	N = 810 1 Level III-3 study 7 Level IV studies	2/810 (<0.1%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy F/U: range 13–82 months	N = NA 2 Level II studies 2 Level III-2 studies 13 Level IV studies	No deaths within 30 days were reported by any study.	⊕⊙⊙⊙ VERY LOW
Surgery F/U: NA	N = 1,499 4 Level IV studies	10/1,499 (0.67%)	⊕⊙⊙⊙ VERY LOW
Pneumothorax			
MTA F/U: range 6–30 months	N = 1025 (sessions) 2 Level III-2 studies 20 Level IV studies	280/1025 (27.3) Median: 30.2 (8.3–63.8)	⊕⊙⊙⊙ VERY LOW
RFA F/U: range 12–46 months	N = 1497 (sessions) 1 Level III-3 study 18 Level IV studies	Per ablation: 674/1497 (45%), median 24% (9–67%) Per patient: 46/262 (18%), median 17.5% (5–36%)	⊕⊙⊙⊙ VERY LOW
Pneumothorax with intervention			
MTA F/U: range 6–30 months	N = 985 (sessions) 2 Level III-2 studies 18 Level IV studies	122/985 (12.4), median 10.3 (0–28.6%)	⊕⊙⊙⊙ VERY LOW
RFA F/U: range 12–46 months	N =1497 (sessions) 1 Level III-3 study 18 Level IV studies	Per ablation: 335/1497 (22%), median 9% (2–39%) Per patient: 29/262 (11%), median 10% (3–24%)	⊕⊙⊙⊙ VERY LOW

< F/U = follow-up, MTA = microwave thermal ablation; NA = not applicable; N = number; n/N (%) = number with event/ total (percentage); RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. One death was delayed (occurring eight months after the procedure).
2. Videtic et al (2015) reported one death 319 days after the procedure due to respiratory failure. Oh et al (2012) reported one death from respiratory failure five months after receiving SBRT.

SECTION C TRANSLATION ISSUES

Because the claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by any published studies it was not necessary or appropriate to undertake any translation of the evidence presented in Section B for the purposes of an economic evaluation.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The key research question outlined in the protocol is what is the safety, effectiveness and cost effectiveness of single treatment percutaneous MTA compared to RFA and current best practice radiotherapy with or without chemotherapy in (i) patients with early stage NSCLC who are not eligible for surgical resection and who are receiving treatment with curative intent (population one), (ii) among patients with pulmonary metastases for the above comparators and surgery (population two) and in (iii) palliative care (population three) for best current palliative treatment.

The protocol suggests the economic evaluation for the proposed service be informed by clinical claims: of superior safety and effectiveness compared to RFA in population one and two, non-inferior effectiveness and superior safety compared to surgery (population two) and current best practice radiotherapy with or without chemotherapy (population one and two).

This section provides an economic evaluation of these claims starting with an overview of the evaluation method chosen, and review of the economic literature relating to MTA and associated procedures, then presentation of the evaluation and results. The section concludes with sensitivity analyses which investigate the robustness of results in line with the major assumptions.

Type of economic evaluation

MSAC (2016) encourage that the base case for an economic evaluation be a cost-utility analysis where there is a clear efficacy benefit. It is noted that MSAC has a strong preference for evidence derived from direct randomised trials, although all levels of evidence will be considered. Where an intervention is proven to be no worse than its main comparators in terms of both effectiveness and safety (i.e. there is no clear efficacy benefit) a cost minimisation approach should be employed.

The MSAC guidelines matrix for preferred economic approach based on comparative effectiveness and safety is presented in Table 62. An overview of evidence of effectiveness and safety for each of the three assessment populations is summarised in Table 63, based on findings in Section B. MSAC (2016) also highlight that where there is uncertainty around conclusions an assessment should be made about the impact of this information gap on key modelling assumptions and parameters in the economic evaluation. As noted, the section is concluded with sensitivity analyses of the intervention against key comparators in relevant populations.

Table 62 Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
-	**Inferior**	**Uncertain**	**Non-inferior**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

< CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis >

POPULATION ONE

The applicant suggests MTA is indicated for the treatment of early stage NSCLC with curative intent – which includes NSCLC T1a-T2b, N0, M0 (up to and including stage IIa). For patients with unresectable NSCLC, treatment options are dependent upon the stage of cancer and patient characteristics. Treatments can be stand alone or multimodal and generally comprise radiotherapy alone or in combination with chemotherapy. The evidence-base for effectiveness and safety is limited.

Head to head trials comparing newer radiotherapy options (SBRT) to surgery in operable patients have been terminated early due to slow accrual (Chang et al 2015). However, retrospective data indicates that they may have comparable local control and survival outcomes when analyses are adjusted for comorbidities and age (Chang et al 2015; Crabtree et al 2010; Nanda et al 2015; Shirvani et al 2012). Additionally, a large retrospective study examining the effect of SBRT versus observation identified a survival benefit in patients treated with SBRT (the median overall survival was 29 months with SBRT versus 10.1 months with observation alone, p<0.001 (Nanda et al 2015).

No comparative trials of MTA have been identified for this population. However, results from Level IV observational studies are reported in Section B. Only three studies of MTA in population one were identified and only two reported overall survival outcomes for a total of 75 patients: Han et al (2015) reported median overall survival of 35.0 months (95%CI 22.3–47.7) and Yang et al (2014) reported overall survival of 33.8 months (95%CI 31.9–35.7). For the five Level IV studies reporting overall survival in patients who had RFA the median was 44.3 months (range: 36.5–67.0). Overall survival in other comparative trials comparing radiotherapy regimes was not reported. Similarly, for other

outcomes such as 1-, 2-, 3- and 5- year survival rates, progression free survival and local progression reporting was variable and sparse. In the context of a reimbursement decision the claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy or RFA remains untested by any published studies. Because of the paucity of literature and its low quality it was not feasible to undertake any statistical tests of non-inferiority between thermal ablation and radiotherapy for population one. On the basis of the evidence, a cost-minimisation analysis is appropriate for comparing MTA with other treatment options within population one: patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.

Table 63 Summary of evidence for MTA versus comparator(s)

Population	Comparative effectiveness	Comparative safety
Patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.	Limited evidence of superior effectiveness compared to RFA and non-inferior effectiveness compared to current best practice radiotherapy with or without chemotherapy	Limited evidence of superior safety of RFA and current best practice radiotherapy with or without chemotherapy
Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease)	No evidence of superior effectiveness compared to RFA and non-inferior effectiveness compared to surgery and current best practice radiotherapy with or without chemotherapy	Limited evidence of superior safety of RFA, surgery and current best practice radiotherapy with or without chemotherapy
Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment	Limited evidence of superior effectiveness compared to conventional palliative therapy without MTA (as an adjunct to radiotherapy and/or chemotherapy)	Limited evidence of superior safety compared to conventional palliative therapy without MTA

< MTA= Microwave tissue ablation. NSCLC= Non-small cell lung cancer. RFA= Radiofrequency ablation >

POPULATION TWO

Population two includes patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease). PASC feedback was that population two should be stratified into two groups at the assessment phase with respect to their primary tumours: those with sarcoma (bone and soft tissue) and those with non-sarcoma primaries. The applicant has indicated that MTA has a role in the definitive treatment of patients with lung metastases in whom the primary tumour is under control. In this patient group comparators include RFA, surgical resection and current best practice radiotherapy with or without chemotherapy.

For this heterogeneous population, that is predominantly defined by the curative intent of treatment, there is no available evidence comparing different interventions. Patients may be offered

resection, SBRT or thermal ablation. There is, at present, no data amenable to comparison across treatment strategies. Thermal ablation is purported to have benefit in this population; however, only two studies of MTA were identified and the limited outcomes reported are not sufficient to compare across interventions in terms of effectiveness. Overall survival time was not reported, and rates of survival were reported by only one study and were limited to 24 months. With RFA, median overall survival was 44.45 months (range 21–67). As compared to surgical resection, however, MTA is associated with a shorter recovery time and procedure related mortality is expected to be a rare outcome of MTA. There is insufficient clinical evidence to suggest that MTA has superior effectiveness to RFA. The safety appears equivalent between MTA and RFA. There were insufficient comparative studies with surgery to make a claim regarding patient benefits. Because of the paucity of literature, and its low quality it was not feasible to undertake any statistical tests of non-inferiority between thermal ablation and RFA, radiotherapy and surgery for population two. On the basis of the evidence, a cost-minimisation analysis is appropriate for assessing MTA for population two.

POPULATION THREE

Population three consists of patients with NSCLC who are not eligible for surgical resection and patients with pulmonary metastases who are receiving treatment with palliative intent. MTA may have a role in treating patients with NSCLC with palliative intent. In this group, MTA may assist with symptom control and decrease tumour burden in metastatic disease. For these patients the key comparator to MTA is conventional palliative therapy. MTA may be offered as an adjunct to de-bulk prominent tumours for symptom relief. Limited evidence of effectiveness and safety was found for MTA in palliative populations. Three studies of MTA in patients being treated with palliative intent were identified; however, none reported primary effectiveness outcomes related to quality of life or symptom control. Only secondary effectiveness outcomes were assessed. There were two non-randomised comparative trials that compared treatment strategies involving MTA and chemotherapy regimes in a palliative population. In both comparative studies combination therapy as opposed to a single therapy (MTA alone or chemotherapy alone) confers a statistically significant advantage in terms of survival outcomes. Although the magnitude of this benefit (in terms of months gained) could not be calculated clinical advice has indicated that patients are not currently treated with MTA for this indication as they would more often receive systemic therapies. Therefore, for the purposes of the evaluation, costs are estimated for populations one and two.

The drawback of the evidence base being largely comprised of Level IV evidence is that it prohibits inference regarding the effect of the intervention because there is no data available for comparison with other strategies. Furthermore, the lack of concurrent or historical comparison groups within studies then raises concerns in comparing across level IV studies of different interventions because the study populations may differ in the distribution of prognostic factors that could affect outcomes. Based on low grade evidence, the clinical claims associated with the proposed medical service remain untested. For the purposes of an economic evaluation an assumption has been made that

the proposed medical service is non-inferior (equivalent) to the main comparator across populations one and two. As such, MSAC (2016) recommend that cost-minimisation analysis is the appropriate economic evaluation approach and should be presented in an abbreviated Section D.

The remainder of this section focuses on the costs of delivery of MTA, SBRT and surgery in populations one and two. This approach has been taken for radiotherapy technology assessment in the past, where the evidence base was limited. For example, in the case of image-guided radiation therapy (IGRT), MSAC (2015) concluded that due to the lack of evidence (the quality of the available studies was deemed to be poor with inconsistent evidence of safety and clinical effectiveness) for any significant benefit in clinical outcomes between IGRT and non-IGRT, a cost minimisation analysis was appropriate. MSAC considered the frequency of verification scans is uncertain and the budgetary impact of publicly funding IGRT, even on a cost minimisation basis, is also uncertain.

D.2. POPULATIONS AND SETTINGS

There were 11,580 cases new cases of lung cancer diagnosed across Australia in 2014, equivalent to an incidence rate of 54.8 cases per 100,000 men and 33.2 cases per 100,000 women (AIHW 2014). SCLC accounted for around 12.3 per cent of lung cancer incidence in 2007 and NSCLC 62.6 per cent (Australian Institute of Health and Welfare (AIHW) 2011b). AIHW (2014b) projected 12,203 new lung cancer cases in 2016 based on an age-standardised incidence rate of 43 cases per 100,000 persons (54 for males and 34 for females). The proportion of lung cancers specified as small cell carcinoma was 11 per cent for males and 13 per cent for females in 2007, with other carcinoma and unspecified malignant neoplasm accounting for 25 per cent of lung cancers in males and 26 per cent in females (Australian Institute of Health and Welfare (AIHW) 2011b). New cases of primary lung carcinoma at the Liverpool and Macarthur Cancer Therapy Centre (CTC) in NSW between 1 December 2005 and 21 December 2006 were reviewed by Kang et al (Kang et al 2012). Around 13.8 per cent of cases where SCLC, which broadly reflect AIHW estimates.

Data from New South Wales (Vinod et al 2004), collected between 1995 and 2004, suggests that 29.6 per cent of staged lung cancers are localised. A retrospective survey of lung cancer reported in the Victorian Cancer Registry from 1 January to 30 June 2003, and followed up for 5 years, recorded that 35.4 per cent of NSCLC were stage I, IA and IB cases (Mitchell et al 2013). This is higher than the proportions in the USA, where less than 20 per cent of NSCLC cases in males and females were localised at the time of diagnosis (Australian Institute of Health and Welfare (AIHW) 2011a).

Barton et al (2013) assumed that around 31 per cent of staged lung cancers are stage I-II when determining radiotherapy demand. This assumption is included in the financial assessment as it is within the range of the Vinod et al (2004), USA and Kang et al (Kang et al 2012)studies. Barton et al (2013) assumed that around 43 per cent of early stage NSCLC would be subject to resection when

determining radiotherapy demand in Australia. Pearson (Pearson 1994) concludes patients in whom a complete resection is anticipated should be selected for surgery. These cases include TI to T4 stages, NO and Ni tumours, and selected N2 cases.

Zhu et al (2008b)noted that many patients presenting with lung cancer have advanced disease at the time of diagnosis and, therefore, are not eligible for surgical resection (Dienemann 2001; Hoffman et al 2000). Many present with comorbidities which limits the feasibility of surgery (Pearson 1994). Barton (2013) specified that the patient population not electing or suitable for surgery includes those with NSC Stage I-II showing good performance that do not undergo surgery (10% of all lung cancer cases) and NSC Stage I-II cases with poor performance (5% of all lung cancer cases). A proportion of these patient groups would be suitable for MTA where tumour size or other factors hinder surgical resectability.

Clinical input suggests that MTA of lung tumours is ideally suited to primary tumours that do not exceed 4.5 to 5.0 cm, with 5 lesions per hemithorax (Gillams et al 2013; Smith and Jennings 2015). This patient grouping, denoted population one in the assessment, includes tumour staging NSCLC T1a-T2b, N0, M0 (up to and including stage IIa). Comparators to MTA in this group include RFA and current best practice radiotherapy with or without chemotherapy. MTA would be delivered on an inpatient basis and radiotherapy in an outpatient setting. The population group is further stratified by lesion number as a graduating fee scale based on lesion groupings of <3 lesions, 3–5 and more than 5 has been proposed. The comparators remain constant across these lesion groupings as per Table 64.

Table 64 Populations and comparators

Population	Stratification by Number of Lesions and Tumour Size	Comparator
Patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.	<3 lesions. Clinical input suggests that MTA of lung tumours is ideally suited to tumours that do not exceed 4.5 to 5.0 cm, which accounts for a 0.5 cm circumferential safety margin 3–5 lesions. 5> lesions. Maximally 5 lesions per hemithorax has been widely adopted;(Gillams et al 2013; Smith & Jennings 2015)	Radiotherapy or RFA
Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease)	Clinical input suggests that MTA of lung tumours is ideally suited to tumours that do not exceed 4.5 to 5.0 cm, which accounts for a 0.5 cm circumferential safety margin 3–5 lesions A soft rule of max 5 lesions per hemithorax, per MTA procedure, has been widely adopted (Gillams et al 2013; Smith & Jennings 2015)	Radiotherapy, surgery or RFA

Population	Stratification by Number of Lesions and Tumour Size	Comparator
Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment	Not included in economic evaluation	

< MTA= Microwave tissue ablation; NSCLC= Non-small cell lung cancer; RFA= Radiofrequency ablation; SBRT= Stereotactic body radiation therapy >

In addition to primary cancers, the lung parenchyma is the second most frequent site for metastases. Secondary lung cancers are metastases from primary malignancies elsewhere in the body. The applicant has suggested that sarcomas, thyroid, renal, and head and neck cancers tend to metastasise predominantly or exclusively to the lung. In the setting of metastases confined to the lung with the primary tumour under control, the patient may be eligible for curative therapy.

As outlined in Section B.6, patients with oligometastatic disease in the lung are a heterogeneous group and only two studies reporting MTA of oligometastatic disease were identified. These studies included oligometastases from nasopharyngeal carcinoma (n = 17) colorectal carcinoma (n = 40), breast carcinoma (n = 20), hepatocellular carcinoma (n = 10), renal cell carcinoma (n = 5), bronchogenic carcinoma (n = 5). The comparators to MTA include RFA, current best practice radiotherapy and surgery. However, no comparative trials are available to inform an assessment of comparative effectiveness. Very few relevant outcomes were reported by both studies of MTA. Authors of large case series examining interventions for pulmonary metastases almost uniformly conclude that intervention prolongs survival without undertaking any analysis to support such a claim.

Engstrom et al (2003) note all metastatic patients should be carefully evaluated with adequate imaging before surgery, and meet the criteria of resection being technically feasible; the patient being able to tolerate surgery; control of the primary tumour is warranted; and no extra thoracic lesion is detectable. Only 2–3 per cent of patients with pulmonary metastases, that is, 1 in 30–50 patients, elected metastasectomy in an examination of case series in Spain (Embun et al 2013).

The numbers electing surgery as a proportion of oligometastatic cases across Australia are unclear, although selected studies indicate a similar proportion. For example, a retrospective cohort study of patients with mCRC (metastatic colorectal cancer) submitted to the South Australian mCRC registry found 2.9 per cent (66) of 2289 patients with metastases from colorectal cancer had surgical resection (Hocking et al 2014), which is similar to Spain. This provides an indication that the patient group for population two is limited.

The RFA review of 17 centres by Zhu et al (2008b) found all except three facilities included both primary and secondary lung tumour treatment. The median number of patients was 33 across the 17

centres, with a median of 12 patients having primary (population one) and 19 (population two) secondary tumours. The ratio of patients between these populations does not appear to be as balanced in Australia. Most clinicians indicated that primary cancer patients account for the largest share of MTA and SBRT procedures.

MTA may also have a role in treating patients with NSCLC with palliative intent. In this group, MTA may assist with symptom control and decrease tumour burden in metastatic disease. Discussions with clinicians indicate this population group is very small in number, as systemic treatments are generally favoured. Estimated population sizes and uptake are presented in Section E. In summary, MTA is primarily intended to be used in patients with early stage NSCLC who are not candidates for surgical resection.

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table D.3.1.

Table 65 Summary of the economic evaluation

Characteristics	Details
Perspective	Australian health system
Comparator	SBRT (population one and two), surgery (population two)
Type of economic evaluation	Cost-minimisation
Sources of evidence	Case series
Time horizon	3 months
Outcomes	Not applicable
Software packages used	Excel

< SBRT=Stereotactic body radiation therapy>

Literature review

A search of PubMed, EMBASE, Global Health, and the Cochrane Library, was conducted with no limit on publication date for economic studies related to MTA, RFA, radiotherapy and surgery. The aim of this review was to identify economic models that could inform the economic evaluation of MTA in the proposed MBS populations. Details of the search is provided in Appendix B. Based on the results of the search, the economics of treating primary and secondary lung tumours with the above approaches appears to have an emerging evidence base. No studies were identified that investigated the application of MTA to patients with primary lung cancer that are ineligible for surgery.

A total of 11 studies were identified that economically evaluated RFA, SBRT and/or surgery, and are summarised in Table 66. A discussion of the methods is provided, although the methodologies used are not deemed appropriate for this analysis. The limited comparative evidence outlined in Section B is the key factor constraining the economic evaluation in this assessment to cost minimisation, as opposed to cost-effectiveness analysis using Markov modelling which is used to evaluate other potential treatment options within the identified economic evaluations. The characteristics and results of these studies are summarised in Table 66 and discussed in the accompanying text**.**

Radiofrequency ablation

A selected number of RFA economic studies were identified in the literature. Alexander et al (Alexander et al 2013b; Australian Institute of Health and Welfare (AIHW) 2014b) undertook a costing study of RFA in the USA. They noted that the treatment is better tolerated than surgery and can be performed in an outpatient setting under conscious sedation. The medical records of 84 patients older than 65 years of age with stage IA or IB NSCLC undergoing RFA or surgical resection were reviewed–with costs estimated from the perspective of the payer, Medicare.

Lower medical costs and shorter hospital stays were identified in the series of RFA cases compared to surgery. The median cost per month lived was USD$620.74 for a patient treated with RFA, compared with USD$1,195.92 for a patient treated surgically. The patient population is not directly comparable with populations being investigated in the assessment, as stage IA or IB NSCLC patients are eligible for resection. Resection is an option for population two of the assessment; and is found to be considerably more expensive for the above mentioned rationale.

Sher et al (2011) developed a Markov model to compare SBRT, 3DCRT, and radiofrequency ablation (RFA) for 65 year old men with medically inoperable NSCLC. Data sources for the decision model were extracted from the published literature. Costs accruing to each health state were largely derived from publicly available 2009 USA Medicare payment schedules. Average costs of RFA for eradiation of pulmonary tumour and guidance were USD$5,879, while a SBRT cost of USD$14,741 included simulation, planning and treatment.

The model includes utility measures. The authors noted there were no data explicitly evaluating patient utility values after treatment with SBRT, 3D-CRT, or RFA. However, a study published by Doyle et al (Doyle et al 2008) that elicited patient utility values for several health care states associated with NSCLC was used in the analysis. Utility weights included no disease 0.712, pneumonitis 0.576, chest wall pain 0.557 and local, nodal, and distant recurrence 0.461. The incremental cost-effectiveness ratio (ICER) for SBRT over 3DCRT was USD$6,000/QALY and USD$14,100/QALY for SBRT over RFA.

The major variable driving outcome was the local recurrence risk of RFA and tumour size governed failure rates.

Kwan et al (2014) compared ablation and surgery medical costs for a matched-pair cohort of Medicare patients. The cohort included 128 patients of at least 65 years of age with stage IA/IB NSCLC in the USA. Ablation had a mean cost of $50,682 over 24 months, while surgery had a mean cost of $57,994 over a similar period. The applicant has suggested that RFA is the appropriate comparator; however, this technology is not widely diffused in the Australian healthcare system and is not currently associated with an MBS item. Therefore, SBRT and surgical treatments for patients with primary and secondary lung cancer are considered comparators to MTA for the purposes of this economic evaluation.

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Table 66 Summary of published economic evaluation of MTA, RFA, surgery and RT to treat lung cancer

Reference	Time Horizon	Country and Population	Intervention Cost	Comparator Costs	Type of analysis	Perspective	Results
Sher et al. (2011)	A lifetime horizon	65-year-old men with medically inoperable NSCLC in USA	RFA treatment for eradiation of pulmonary tumour and guidance cost of $5,879.62	SBRT cost of $14,741.13 includes simulation, planning and treatment	Markov model comparing RFA, SBRT and 3DCRT	Payer	SBRT had an ICER of $6,000/QALY compared to 3DCRT and $14,100/QALY for SBRT relative to RFA.
Alexander et al (2013b)	9 years	84 patients older than 65 years of age with stage IA or IB non–small-cell lung cancer in the USA	Median cost per month lived was $620.74 for RFA	Median cost of $1,195.92 per month for a patient treated surgically	Patient health histories and billing charges converted to 2009 Medicare reimbursement fees.	Payer	RFA patients were calculated to have a cost per month of life of $620.74, compared to $1,195.92 for surgery
Kwan et al (2014)	2 years	Matched cohort of 128 patients of at least 65 years of age with stage IA/IB NSCLC in USA	Ablation had a mean cost of $50,682 over 24 months	Surgery had a mean cost of $57,994 over 24 months	Compared medical costs for a matched-pair cohort of Medicare patients.	Payer	Thermal ablation had lower treatment and medical costs at 1 month, 3 months, and 12 months relative to sub-lobar resection
Grutters et al (2010)	5-year	Inoperable and operable stage I NSCLC. Model based on clinical data from Japan for operable and Dutch meta-analysis for inoperable patients.	Carbon-ion and proton therapy	CRT and SBRT	Decision-analytic Markov model	Health system	Carbon-ion therapy costed €67.257 per quality-adjusted-life-year gained compared to SBRT for inoperable stage I NSCLC.

Reference	Time Horizon	Country and Population	Intervention Cost	Comparator Costs	Type of analysis	Perspective	Results
Shah et al (2013)	Lifetime	65-year-old patient with medically operable stage I NSCLC in USA. Local recurrence rate for SBRT obtained from a 3-year study of potentially operable patients in the Netherlands	SBRT had mean cost and quality-adjusted life expectancy of $42,094/8.03 - $40,107/8.21	Wedge resection, and lobectomy had a mean cost and quality-adjusted life expectancy of $51,487/7.93 and $49,093/8.89.	Markov model developed to compare the cost-effectiveness of SBRT with wedge resection and lobectomy for clearly and marginally operable patients	Payer	SBRT was the cost-effective strategy for marginally operable patients. Lobectomy was most cost-effective in clearly operable patients,
Lester-Coll et al (2014)	10 years, using 3% discount rate	Study undertaken at the Department of Therapeutic Radiology, Yale University School of Medicine, and so USA perspective assumed. Cohort entry age not specified, although tracked for 10 years.	10 year cost of SBRT was $1,286,700	Patients underwent SBRT or systemic therapy (FOLFIRI or Ipilimumab). FOLFIRI and had a 10-year cost of $1,733,293	Markov model to study a hypothetical cohort of patients with oligometastatic colon cancer or melanoma with 1–3 pulmonary metastases.	Payer	The ICER for SBRT over systemic therapy was $95,879/quality adjusted life month (QALM) for colon cancer
Lanni et al (2011)	6 years	86 patients with Stage I (TI-2 N0) NSCLC in the USA	$13,639 for EBRT	$10,616 for SBRT	Cost calculated using 2010 Medicare hospital-based ambulatory payment and hospital-based physician fee screen reimbursement rates.	Payer	SBRT was less costly when compared to standard fractionated EBRT, It was also found to have superior local control and overall survival

Reference	Time Horizon	Country and Population	Intervention Cost	Comparator Costs	Type of analysis	Perspective	Results
Porter et al (2004)	12 months	Data from 1124 Canadian patients with pulmonary metastases from soft tissue sarcoma	Mean cost of resection $C 20,339 dollars per patient	Mean cost of 6 cycles of chemo was C$ 99,033 dollars per patient	Decision tree to model the outcomes of treatment	Payer	ICERS of $14,357 per life-year for pulmonary resection, $104,210 for systemic chemotherapy, and $51,159 for pulmonary resection and systemic chemotherapy were calculated.
Puri et al (2012)	5 years	Medical records of 114 patients (57 each for SBRT and surgery) with stage I NSCLC at Washington University from 2000 to end 2006	SBRT $14,153	Surgery $17,629	Markov decision model with propensity matching	Payer	SBRT was less expensive than surgery, surgery was more cost-effectiveness due to greater survival time
Smith et al (2015)	5 years	Local NSCLC identified in the USA Surveillance, Epidemiology, and End Results Medicare population-based database between 2003–2009, USA.	$55,120 for SBRT treatment	$77,964 with sub lobar resection	Costs of SBRT and surgery compared over 5 years using Wilcoxon rank-sum test	Payer	Lobectomy was more cost-effective compared to SBRT
Lester-Coll et al (2016)	10 years, using 3% discount rate	Melanoma; NSCLC adenocarcinoma without an EGFR mutation (NSCLC AC); NSCLC with an EGFR mutation (NSCLC EGFRm AC); NSCLC squamous cell carcinoma (NSCLC SCC); and colon cancer.	-	-	Markov modeling approach was used to compare average cumulative costs, quality adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs)	Payer	The most cost-effective strategies were SBRT for patients with NSCLC AC ($156,725/0.80), paclitaxel/carboplatin for patients with NSCLC, SCC ($123,799/0.48), and erlotinib for NSCLC, EGFRm AC ($147,091/1.90).

<CRT= conventional radiotherapy; ICER = incremental cost effectiveness ratio; MTA= Microwave tissue ablation; NSCLC= Non-small cell lung cancer; QALY = quality adjusted life year; RFA= Radiofrequency ablation; SBRT= Stereotactic body radiation therapy>

Stereotactic radiotherapy

No Australian studies were identified in the literature search that examined the economics of SBRT. A trial to assess the safety and efficacy profiles of single and multi-fraction SBRT for pulmonary oligometastases is currently underway. Siva et al (2016) described the study which includes fractionation schedules in the SAFRON phase II study. The primary endpoint is safety of SBRT as measured by the incidence of toxicities. Secondary endpoints include quality of life using EQ-5D and MDASI-LC, local efficacy, resource use, and costs associated with treatment (Siva et al 2016).

Grutters et al (2010) developed a decision-analytic Markov model with a 5-year time frame to examine Carbon-ion and proton therapy against conventional radiotherapy (CRT) and SBRT in Europe. The model was based on clinical data from Japan for operable patients and a Dutch meta-analysis for inoperable stage I NSCLC patients. This population is in line with population one in this assessment. Carbon-ion therapy cost €67.257 per quality-adjusted-life-year gained compared to SBRT. The authors concluded that limited data is available on the effectiveness of particle therapy. SBRT was, however, identified as the most cost-effective strategy under base economic modelling assumptions.

Lanni et al (2011) compared the clinical and cost outcomes of SBRT, 3-dimensional conformal radiotherapy (3DCRT), and intensity modulated radiation therapy (IMRT) for the treatment of medically inoperable NSCLC. The treatment cost included technical and professional components. The estimated costs were USD$55,705 for 35 fractions of IMRT, and USD$52,471 for 4 fractions of SBRT. Shah et al (2013) compared SBRT and wedge resection for patients who were marginally operable (MO) and suitable for surgery (SO). The efficacy of SBRT was assumed to be the same in both comparisons; however, the risk of toxicity was substantially greater in the marginally operable population. Model parameters were based on studies in The Netherlands (Lagerwaard et al 2012). In patients who are marginally operable SBRT was the dominant strategy and most cost-effective. For patients who are suitable for surgery, lobectomy was the most cost-effective treatment intervention (ICER $13,200/QALY).

Lester-Coll et al (2014) developed a Markov model to study the cost-effectiveness of SBRT compared to systemic therapy (FOLFIRI or Ipilimumab) in a hypothetical cohort of patients with oligometastatic colon cancer or melanoma with 1–3 pulmonary metastases. Event rates, costs and utilities were derived from the published literature.

The incremental cost effectiveness ratio for SBRT over systemic therapy was $95,879/quality adjusted life month (QALM) for colon cancer and $528,433/QALM for melanoma. In summary, SBRT appeared to be a cost-effective strategy across a range of comparators, unfortunately none of which were MTA.

Surgery for population two

Patients with stage I NSCLC are typically treated using is lobectomy (Shah et al 2013). Both lobectomy and wedge resection are generally costlier than SBRT. Lester-Coll et al (Lester-Coll et al 2014) undertook a cost-effectiveness analysis using Markov modelling approach to compare wedge resection, SBRT, and systemic therapy among melanoma, non-small cell lung cancer adenocarcinoma without an EGFR mutation (NSCLC AC), NSCLC with an EGFR mutation (NSCLC EGFRm AC); NSCLC squamous cell carcinoma (NSCLC SCC); and colon cancer patients. The most cost-effective strategy depended on patient characteristics, such as having EGFR mutation or not.

Puri et al (2012) compared the cost-effectiveness of surgical intervention and SBRT in high-risk patients with stage I NSCLC. A Markov decision model was developed from a payer's perspective and data for the efficacy of surgical intervention and SBRT were obtained through a review of medical records in Washington, USA. SBRT was less expensive, however, surgery was deemed to be cost-effectiveness due to longer expected overall survival.

Smith et al (2015) examined the cost-effectiveness of SBRT as an alternative to lobectomy or sublobar resection for early lung cancer. Lobectomy was found to be more cost-effective compared to SBRT, however, sublobar resection is not dominant due to different health outcomes and costs. Although not focussing on population two for this assessment, these results indicate that costlier surgery may be more economically attractive when health outcomes are included in the evaluation framework –due to factors such as longer survival time. In summary, SBRT provides a cost-effective and clinically effective option for patients with NSCLC compared to conventional treatments, where surgery is not feasible (Bijlani et al 2013). When survival is considered in a cost-effective framework SBRT may be dominated by surgical options.

Structure of the economic evaluation

The economic evaluation was conducted using Excel 2010. A description of key structural parameters, assumptions and sources of data is provided in

Table 67. Further details are provided in the following sections. The economic model employs 3-month cycle length.

The economic analysis takes the perspective of the Australian health system. For clinical events directly associated with MTA, AR-DRG (Australian Refined Diagnosis Related Groups) costs are from public hospitals.

Table 67 Summary of key structural parameters and assumptions used

Parameter	Value	Source
Intervention of interest	Microwave tissue ablation	-
Comparators	SBRT	Section B
Perspectives	Australian health system	MSAC guidelines (2016)
Time horizon	3 months	-

< MTA= Microwave tissue ablation; SBRT= Stereotactic body radiation therapy >

D.4. INPUTS TO THE ECONOMIC EVALUATION

The costs of MTA, SBRT and surgery are outlined in this section. They are specified for up to 3 lesions and for 3–5 lesions, as the applicant has proposed fees by lesion number. Costs for each procedure are outlined for screening prior to the procedure, the procedure itself and at 3-month follow-up.

Costs of MTA

Screening Prior to the Intervention

The protocol notes that pre-procedure patient preparation is similar to that for a CT-guided lung biopsy. Costs included within pre-procedure preparation include the visit with a medical oncologist and diagnostics. The Cancer Council of Victoria (2014) indicates that a CT scan of lungs and centre of the chest is generally used as part of staging. The cost of this procedure is included using MBS Item 5634. A PET scan could also be undertaken to add additional information about distant spread including to bones, along with a test of a respiratory function.

MTA Equipment

The system is comprised of a microwave control unit, which generates energy, and an applicator that delivers the energy to the tissue. The generator emits electromagnetic waves at 915 MHz or 2.45 GHz through the non-insulated portion of the antenna to the surrounding tissue. The single-use, sterile, disposable applicator is supplied in a sterile pack that contains the applicator. In the case of the Sulis system, the pack includes two temperature probes, an integrated 2.5 metre microwave cable, and the connector to the control unit. Each applicator may be used to coagulate up to 10 separate areas of target tissue for each patient, and is available in two sizes.

Optional temperature probes are single-use, sterile, disposable instruments used to monitor the temperature of adjacent tissues, vital structures, ducts, vessels, or nerves. They may be used to monitor the temperature of key vessels near the area to be coagulated, or to confirm when the heating zone has reached the volume required (HospiMedica International 2009). The protocol

outlines an average cost of the control unit to be $50,000 and a disposable applicator $2,960. The optimal temperature probe is estimated to cost $960 and is not included in base economic costs. The applicant estimates that around 20–35 procedures would be undertaken per machine per year. Over a 10-year life it is assumed that the capital cost per procedure is $250 (using straight line amortisation and no discount rate) using the lower end estimate of utilisation.

Table 68 Resources associated with MTA

Resource	Setting for delivery	Cost per unit of resource	Quantity	Source
Medical services – screening prior to intervention				
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	As outpatient	202.00	1	MBS Item 56347
Whole body FDG PET study, performed for evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	As outpatient	953.00	1	MBS Item 61523
Respiratory function test	As outpatient	138.65	1	MBS Item 11503
Medical oncologist consultation	As outpatient	263.90	1	MBS Item 132
Medical services – intervention				
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of 1–3by MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	1,300.00	1	Applicant.
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	1,600.00	1	Applicant
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of >5 lesions, by MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	2,000.00	1	Applicant
Pre-anaesthesia consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.48	1	Mean for MBS items 17610, 17615, 17620, 17625

Resource	Setting for delivery	Cost per unit of resource	Quantity	Source
Referred consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.48	1	Mean of MBS items 17640, 17645, 17650, 17655
Initiation of management of anaesthesia, for computerised axial tomography scanning, magnetic resonance scanning, digital subtraction angiography scanning	Anaesthesiologist, delivered to inpatient	138.60	1	MBS item 21922
Administration of anaesthesia, 56 MINUTES TO 1:00 HOUR	Anaesthesiologist, delivered to inpatient	79.20	1	MBS Item 22025
Anaesthesia modifier for patients over 70	Anaesthesiologist, delivered to inpatient	19.80	1	MBS Item 25015
Blood pressure monitoring	Anaesthesiologist, delivered to inpatient	59.40	1	MBS Item 22012
CHEST (lung fields) by direct radiography (NR)	Radiologist, delivered to inpatient	35.35	2	MBS Item 58500
Medical services – post intervention follow-up				
Medical oncologist consultation	Outpatient	75.50	1	MBS Item 116
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	Radiologist, as outpatient	202.00	1	MBS Item 56347
Hospital services				
Nurse assistant – Year 2, $847.00 per week (July 2016). Hourly rate of $22.30 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $22.3 based on average 1-hour input	Assist with theatre, analgesia	22.30	1	NSW Public Health System Awards and Determinations, July 2016
Registered nurse (RN) – Year 5, $1,399.30 per week $36.80 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $36.8 based on average 1-hour	Assist with theatre, analgesia	36.80	1	NSW Public Health System Awards and Determinations,

Resource	Setting for delivery	Cost per unit of resource	Quantity	Source
input				July 2016
Hospital accommodation is the average of shared ward and single ward accommodation costs calculated in Victoria for 2015–16, surgical or obstetric patient first 14 days	Hospital	873.00	1	Average actual cost per bed day 2015–16.
Prostheses costs				
MTA machine	Prostheses	50,000.00	0.005	Applicant. Assumes 10–year life and 20 procedures per year
Probe	Prostheses	2,960.00	1	Applicant
Adverse events				
Averaged DRG-E68A. Pneumothorax W Catastrophic or Severe CC and DRG-E68B. Pneumothorax W/O Catastrophic or Severe CC	Hospital, some MBS	7,793.50	0%	AR-DRG VERSION 7.0, Round 18 (2013–14) inflated to 2016 using ABS CPI
Total : 1–3 lesions total cost per patient				**7,843.83**
Total : 3–5 lesions total cost per patient				**8,143.83**
Total: >5 lesions total cost per patient				**8,543.83**

< ABS= Australian Bureau of Statistics; CPI = consumer price index; FDG- PET= Fludeoxyglucose (18F) Positron Emission Tomography; MBS= medicare benefits schedule; MTA = microwave thermal ablation; NSW = New South Wales >

MTA procedure

MTA is administered percutaneously, under CT image guidance to localise and position a thin microwave antenna into the centre of the target tumour (Simon et al 2005). The size, shape, location and vascular supply of the target lesion have an influence on the power and time required to complete an ablation. Promotional material indicates that a 4.5 x 5.5 cm ablation can be undertaken in 6 minutes (Angiodynamics 2016). Discussions with clinicians indicated that a large part of procedural time is associated with preparing anaesthetic and placing the patient. A single ablation is usually performed in less than 8 minutes, while overlapping and additional ablations required in larger target lesions may add up to an ablation time of 15–20 minutes per lesion. The entire procedure takes from around 1 to 1.5 hours.

The MTA procedure is led by an interventional radiologist. Angiodynamics, the manufacturer of the Acculis MTA System, note that it is designed to be used by physicians who are trained in the use and application of image-guided ablation procedures, intraoperative ultrasound and/or CT guided needle placement (Angiodynamics 2016). According to the applicant the number of tumours treated alters the complexity of the procedure. The proposed fee has been adopted from MSAC Application 1402 (MTA of liver tumours). A "$1300 fee for ablation of 2–3 lesions, a $1600 fee for ablation of 4–5 lesions and a $2000 fee for ablation of >5 lesions. The higher fee for >5 lesions reflect the increased risk to the patients such as collateral damage as well as more skill, time and expertise required of the physician to ensure better patient outcomes". Discussions with clinicians indicate that more than 5 lesions are rarely treated and resultantly this cost is not included.

The proposed descriptor reads 'NON-RESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of lesions, by percutaneous MTA with curative or palliative intent, including any associated imaging services'. Imaging is presumed to be associated with MTA guidance, rather than follow-up scans and X-rays. Two follow-up chest X-rays are performed after the procedure, generally followed by a limited CT scan of the ablated area the morning after the procedure. A CT scan aims to assess the final thermal damage at the site of ablation. Discussions with clinicians indicate that CT scans should be performed after the overnight stay when the damage to the tumour is more apparent. MBS fees for CHEST (lung fields) by direct radiography of $35.35 per X-ray (MBS Item 58500) and COMPUTED TOMOGRAPHY (MBS Item 56347) of $202 for scan of the chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium are included for imaging are included in the overall cost of the procedure.

During the procedure, patients may receive conscious sedation or general anaesthesia. In a review of ablation studies prior to November 2006 by Zhu et al (2008), a total of 17 treatment centres were identified. Of these centres, 13 preferred conscious sedation with local anaesthesia, three used general anaesthesia alone (Fernando et al 2005; Gadaleta et al 2004; Herrera et al 2003; Kang et al

2004), two used conscious sedation with local anaesthesia or general anaesthesia (de Baere et al 2006; VanSonnenberg et al 2005) and one used conscious sedation with local anaesthesia or epidural anaesthesia. Discussions with a MTA clinician indicated that general anaesthesia is preferred in the Australian setting. Patients often exhibit poor performance, have comorbidities and are elderly. A range of items is included for general anaesthesia within hospital, and are listed in the above table. Mean times across item numbers were used for base costing. A local anaesthesia using lidocaine could also be administered at the site of insertion. This cost is not included in the base costing.

As the procedure occurs in a hospital and involves overnight stay, dedicated nursing staff and hospital resources are involved. They are costed using a nurse assistant—year 2, $847.00 per week (July 2016) and registered nurse (RN) — year 5, $1,399.30 per week providing an average 1-hour input across the lesion groupings. Because the intervention involves a fixed cost associated with anaesthesia and placing the patient, this cost will not vary substantially with the addition of two lesions. Hospital accommodation is the average of shared ward and single ward accommodation costs calculated in Victoria for 2015–2016, surgical or obstetric patient first 14 days.

Follow-up

The protocol notes that CT imaging follow-up can be performed at 3, 6 and 12 months after ablation and yearly thereafter (Liu and Steinke 2013). The cost minimisation analysis is undertaken up to 3 months post-intervention and includes an additional CT scan and follow-up consultation with a medical oncologist.

Adverse Events

As a proportion of ablation procedures from included studies in Section B a median of 32% of procedures are associated with pneumothorax (range: 8.3–63.8%), with 30.3 per cent (range 0–66.7%) being severe (i.e. require chest tube drainage). This translates into 9.6 per cent of all MTA procedures requring chest drainage. Using the mean from included studies, as opposed to the median, the proportions are similar. A total of 31.4 per cent of MTA procedures would have associated pneumothorax (standard deviation [SD] 17.2%) and of those 27.4 per cent would be severe (SD 18.6%). This equates to a total mean proportion of 8.6 per cent of MTA procedures requring a chest drain.

The average costs of pneumothorax are collected as part of the Australian public hospital AR-DRG series. The protocol notes that MTA is provided in radiology departments within larger public or private hospitals, with patients either being kept overnight or in a day surgery setting. Given the

absence of an MBS number or the current location of MTA practitioners, most MTA appears to be delivered in public settings.

Public hospital costs for this adverse event includes DRG-E68A, Pneumothorax W Catastrophic or Severe CC, with an average cost per separation of $10,035 Round 18 (2013–2014) inflated to 2016 using Australian Beaureau of Statistics consumer price index (ABS CPI) and DRG-E68B. Pneumothorax W/O Catastrophic or Severe CC has an average cost per separtion of $5,098 inflated to 2016 using CPI. Discussions with clincians indicate that this adverse event is rare in their practice, possibly due to the intervention being delivered in an inpatient setting. The cost is not included in the base cost estimate, but included in a sensitivitity analysis.

Table 69 Summary of the key assumptions relating to major adverse events

Major adverse events	Base case	Reference
Proportion of patients experiencing Pneumothorax	32%, with 30% being severe enough to warrant chest drainage	Han et al (2015), Liu & Steinke and Yang et al (2014) for population one, Qi et al (2015) and Vogl et al (2015) for population two and Sun et al (2015), Wei et al (2015) and Ni et al (2015) for population three.

A number of other adverse events were observed across included studies; however, they are less comprehensively reported when compared to pneumothorax. For haemoptysis, the median was 6.2 per cent (0–31.9%), reported by nine studies. Skin burns was 2.2 per cent (0–8.3%), reported by six studies. Broncho-pleural fistula was 1.8 per cent (0.5–2.6%), reported in four studies. Post ablation syndrome was 6.9 per cent (0–35.9%) reported by six studies. Subcutaneous emphysema was 17.4 per cent (3.6–29.8%), reported by three studies. Pleural effusion was 11.2 per cent (0–34%) reported by ten studies. And, pneumonia was 4 per cent (2.8–14.9%), reported by four studies.

Two reports of adverse events related to the device itself, one being the ceramic of microwave antennae being lost in the pleural space: 1/16 (6.3%) and the other was needle -tip fracture: 1/23 (4.3%) where the needle tip was left in the lesion which had been ablated. Drawing conclusions about the prevalence is difficult as, due to a lack of systematic recording of adverse events, just because studies did not report them occurring may not mean they did not occur. As the occurrence of pneumothorax is the most comprehensively reported, this event is included in the financial cost minimisation analyses sensitivity analysis.

Total Costs per MTA Procedure

The overall total cost for up to three lesions per patient using MTA is $7,843.83 and for 3–5 lesions $ 8,183.83. Pre-procedural costs account for around 20 per cent of the total cost and follow-up costs

(to 3 months) account for 4 per cent of the total costt. MTA procedures associated with MBS (current and proposed) account for around a quarter of the total cost. The largest component cost related to the disposable probe which costs $2,960, excluding the optional thermometer. This item accounts for around 38 per cent of the overall cost.

Costs of RFA

The protocol notes that the pre-procedure patient preparation is the same as for MTA or similar to that for a CT-guided lung biopsy, added by the requirement of booking an overnight bed. The cost of RFA machines and probes differ to that of MTA. Widespread RFA systems include the CooltipTM system (Covidien, Mansfield, Massachusetts, USA), RF 3000® (Boston Scientific Corporation, Natick, Massachusetts, USA), and Model 1500X RF generator (AngioDynamics, Latham, New York, USA). The protocol estimated an average machine cost of $52,500 and probe of $2,200 for RFA compared to $50,000 and $2,960 for MTA.

The protocol, however, notes that MTA has a steeper temperature gradient when compared to RFA, with tissue temperatures reaching > 200 degrees Celsius, and faster conduction than RFA (Simo et al 2013). This allows for larger ablation volumes in faster times of 4–6 minutes in contrast to 12–20 minutes for single ablations required for RFA (Swan et al 2013). The key delivery cost difference between RFA and MTA is associated with the longer time to deliver the procedure. The lower probe cost results in a procedure cost of RFA that is around 90 per cent of MTA, if all other intervention costs were the same.

Zhu et al (2008) reviewed the rates of pneumonia, pulmonary abscess, haemothorax, intrapulmonary bleeding, haemoptysis, pleuritic chest pain, cough and fever ranged from 6–12 per cent. RFA has a similar adverse events profile to that of MTA except for burns. The protocol notes RFA uses electricity or grounding pads which has a risk of pad site burns and potential malfunction of implanted cardiac devices (Lee et al 2013; Schutt et al 2009).

Costs of SBRT

SBRT is the delivery of high dose radiation in an extremely hypofractionated treatment (typically up to five fractions) and is also called stereotactic ablative radiotherapy; however, within this document it is referred to as SBRT. Bertolaccini et al (2015) noted the standard of care of early stage NSCLC patients is generally lobectomy, however, a significant proportion are not suitable for surgery. These patients are the target for SBRT.

SBRT Equipment

Lievens et al (2015) estimated the costs of delivering SBRT using a range of techniques and for differing equipment in Belgium. Annual equipment costs were obtained by dividing the actual purchase price by the number of useful years which ranged for 5 years for software and 10 for all other equipment

Purchase costs for equipment were expressed in Euros and ranged from 1,988,248 € for linear accelerators to dedicated SBRT machines of 4,414,950 €. Conventional simulators purchase costs averaged 768,775 €, and CT simulators 680.668 €. Annual external maintenance contracts were also included and estimated for linear accelerators to be 115,510 € per year and conventional simulators 29,737 €.

Radiotherapy is supported in Australia through Radiation Oncology Health Program Grants (ROHPG), which reimburses the cost of expensive eligible radiation oncology equipment to facilities.

The Australian National Audit Office has undertaken a performance audit of the ROHPG program (Australian National Audit Office, 2016). Reimbursement rates for each equipment category are set out in the Scheme Guidelines. Funding for the Scheme in 2014–15 was $68.5 million and associated radiation oncology MBS payments equalled $343 million. More than 400 items of equipment are currently funded under the Scheme. These are mainly linear accelerators, although planning workstations, simulators, and brachytherapy machines are included. Capital allowance costs for SBRT delivery under the ROHPG program were derived following discussions with clinicians.

Table 70 Resources associated with SBRT

Resource	Provider of resource	Fee per unit of resource	Quantity	Source
Medical services – screening prior to intervention				
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	As outpatient	202.00	1	MBS Item 56347
Respiratory function test	As outpatient	138.65	1	MBS Item 11503
Whole body FDG PET study, performed for evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	As outpatient	953.00	1	MBS Item 61523

Resource	Provider of resource	Fee per unit of resource	Quantity	Source
Medical consultation	As outpatient	263.90	1	MBS Item 132
Medical services – intervention (Non IMRT Course, not Department of Veterans Affairs)				
SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL - professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred	As outpatient	85.55	1	MBS Item 104
SIMULATION FOR THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY	As outpatient	658.60	1	MBS Item 15550
DOSIMETRY FOR THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 3 COMPLEXITY	As outpatient	1,120.75	1	MBS Item 15562
RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site for diseases and conditions not covered by items 15245, 15248 or 15251	As outpatient	59.65	4	MBS Item 15254 1F (primary field)
RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - to a maximum of 5 additional fields treatment delivered to primary site (lung)	As outpatient	37.95	20	MBS Item 15260 5F (Secondary Field)
RADIATION ONCOLOGY TREATMENT VERIFICATION - volumetric acquisition, when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15705 - each attendance at which treatment involving three fields or more is verified (ie maximum one per attendance).	As outpatient	76.60	4	MBS Item 15710
RPG - Linac				
15254 Primary treatment field	As outpatient	36.12	4	RPG
15550 Simulation	As outpatient	65.2	1	RPG
15562-Level 6-Plan	As outpatient	83.82	1	RPG

Resource	Provider of resource	Fee per unit of resource	Quantity	Source
Medical services – post intervention follow-up				
Medical consultation (1-month toxicity, 3 month CT)	As outpatient	75.50	2	MBS Item 116
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	Radiologist, as outpatient	202.00	1	MBS Item 56347
Total: 1–3total cost per patient (4 fractions)	-	-	-	5,372.95
Total: 3–5 lesions total cost per patient (5 fractions)	-	-	-	5,735.07

<CT = computed tomography; FDG-PET = fludeoxyglucose Positron Emission Tomography; IMRT = intensity modulated radiotherapy; MBS=medicare benefits schedule; SBRT = stereotactic body radiotherapy>

SBRT Procedure

Cancer Voices (2011) note that most centres use the usual rebates for 3D conformal treatment planning when costing SBRT. The Royal Australian and New Zealand College of Radiologists (2012) suggests Medicare data demonstrates that more than 80 per cent of all radiotherapy services are charged at the MBS fee or less, so co-payment is possibly limited.

The procedure involves simulation, dosimetry, treatment and verification. Prior to treatment, the patient undergoes imaging procedures to determine the size, shape and location of the tumour using CT scan. This is followed by the generation of a treatment plan and then delivery of the treatment. MBS items are used to cost these various items. It is assumed that <3 lesions would be treated in 4 fractions and 3–5 lesions in 5 fractions. Costs outlined at the bottom of Table 70 reflect this assumption.

The Royal Australian and New Zealand College of Radiologists notes the current single fraction Medicare rebate for SBRT grossly under-reimburses the cost of providing stereotactic radiosurgery, when considered in terms of cost in capital outlays and time taken for planning and treatment. Discussions with clinicians also supported this view. Lievens et al (2015) estimated SR delivery costs in Belgium.

The overall treatment average costs (in 2011 Euro) of lung SBRT were 6221€ (range by centre: 3104€–12,649€), of standard fractionated 3D-CRT: 5919€ (4557€–6564€) and IMRT: 7379€ (5054€–8733€); of hypofractionated 3D-CRT: 3993€ (3674€-4380€) and IMRT: 4730€ (single centre). Based

on a $A to Euro conversion of 1.33 in 2011, the average treatment cost in this year was $8,274. This is substantially more than the estimated cost of SBRT in this assessment. Comparison with MTA is problematic using MBS item numbers if this is the case. Costs are increased within sensitivity analysis to determine the robustness of the cost difference between MTA and SBRT. As noted, the SBRT code 15600 is rarely used (usually for brain) and costs have been developed using conventional item numbers following discussions with SBRT clinicians.

Radiation oncology treatment may also involve a number of indirect costs for the patient in addition to the treatment costs. These include travel costs and time away from work. SBRT is delivered over multiple treatments as opposed to one for MTA. The cost savings associated with less travel and lost productive time are not explored in the cost minimisation analysis.

Adverse Events

Early and later stage adverse events are associated with treatment. Early stage issues may include skin reactions and difficulty swallowing. Later stage issues may include chest wall pain, which is an uncommon side effect of lung SBRT. Larger tumour size is a significant predictor of ≥Grade 2 chest wall pain (Murray et al 2016). Rib fracture can also occur, but is very uncommon. The costs of these adverse effects are not included in the cost analysis.

Follow-up

Clinical feedback recommends routine CT imaging follow-up be performed at three months after treatment. An additional visit at one-month post intervention is also included to review toxicity.

Costs of resection in population two

Pfannschmidt et al (2007) noted that surgery is a key treatment for patients with isolated pulmonary metastases. Potentially curative operations are feasible when the metastases are technically resectable, the primary tumour is controlled, and no extra thoracic lesions are detected. The authors note that no randomized trials comparing surgical resection versus no surgery have been conducted. In a synthesis of 1,684 patient case series conducted by Pfannschmidt et al (2007) using 17 different studies it was demonstrated that resection of colorectal pulmonary metastases can be performed safely. Wedge resection was most commonly used for patients with pulmonary metastectomy (single metastases). Wedge resection is included in the cost analysis using MBS Item 38440.

The operative approach for wedge resection is costed using MBS Item 38418 (Thoracotomy, exploratory, with or without biopsy). Video-assisted thoracoscopic techniques are utilised for pulmonary resections including regional lymph node assessment (Australian Cancer Network Management of Lung Cancer Guidelines Working Party 2004).

Table 71 Costs associated with lung wedge surgery for pulmonary oligometastases

Resource	Provider of resource	Price per unit of resource	Quantity	Source
Medical services – screening prior to intervention				
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	As outpatient	202.00	1	MBS Item 56347
Whole body FDG PET study, performed for evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	As outpatient	953.00	1	MBS Item 61523
Respiratory function test	As outpatient	138.65	1	MBS Item 11503
Medical oncologist consultation	As outpatient	263.90	1	MBS Item 132
Medical services – intervention				
LUNG, wedge resection of	Surgeon to inpatient	1,147.20	1	MBS Item 38440
THORACOTOMY, exploratory, with or without biopsy	Surgeon to inpatient	958.40	1	MBS Item 38418
INTERCOSTAL DRAIN, insertion of, not involving resection of rib	Surgeon to inpatient	133.55	1	MBS Item 388–6
Intra-arterial cannulation when performed in association with the administration of anaesthesia	Anaesthesiologist, delivered to inpatient	79.20	1	MBS Item 22025
Pre-anaesthesia consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.49	1	Mean for MBS items 17610, 17615, 17620, 17625
Referred consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.49	1	Mean of MBS items 17640, 17645, 17650, 17655
Initiation of management of anaesthesia, for computerised axial tomography scanning,	Anaesthesiologist, delivered to inpatient	138.60	1	MBS item 21922

Resource	Provider of resource	Price per unit of resource	Quantity	Source
magnetic resonance scanning, digital subtraction angiography scanning				
Administration of anaesthesia, 56 MINUTES TO 1:00 HOUR	Anaesthesiologist, delivered to inpatient	79.20	1	MBS Item 23043
Anaesthesia modifier for patients over 70	Anaesthesiologist, delivered to inpatient	19.80	1	MBS Item 25015
Blood pressure monitoring	Anaesthesiologist, delivered to inpatient	59.40	1	MBS Item 22012
Medical services – post intervention follow-up				
Medical oncologist consultation	Outpatient	75.50	1	MBS Item 116
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	Radiologist, as outpatient	202.00	1	MBS Item 56347
Hospital services				
Nurse assistant – Year 2, $847.00 per week (July 2016). Hourly rate of $22.30 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $22.3 based on average 1-hour input	Assist with theatre, analgesia	22.30	1	NSW Public Health System Awards and Determinations, July 2016
Registered nurse (RN) – Year 5, $1,399.30 per week $36.80 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $36.8 based on average 1-hour input	Assist with theatre, analgesia	36.80	1	NSW Public Health System Awards and Determinations, July 2016
Major Chest Procedures W/O Catastrophic CC, AR-DRG E01B net other medical costs	Hospital	14,763.57	1	AR-DRG, round 18 (2013–14) inflated to 2016 using ABS CPI. Net of other costed elements.
Total				**19,472.05**

<ABS CPI = Australian bureau of statistics consumer price index; FDG-PET = Fludeoxyglucose positron emission tomography; MBS = Medicare benefits schedule; NSW = New South Wales>

Overall Cost

Pre-intervention and follow-up costs are assumed to be the same as MTA; costing $1,596.95 and $277.50 respectively. The costs of screening, the intervention and follow-up are outlined in Table 71. The overall cost of surgery is $19,472.05, which is higher than MTA and SBRT due to the hospital stay. The AR-DRG E01B for Major Chest Procedures W/O Catastrophic CC had an estimated national average cost per separation of $17,124, which is adjusted by 1.03 to be $17,637 in current prices.

The average length of stay associated with this AR-DRG is 6.53 days which is likely to be greater than average stay for lung resection when VATs is used. Discussions with a clinician indicated hospital stays of 2–3 days are most likely associated with this procedure, so hospital costs included in the costing are overstated. The AR-DRG E02B has an average length of stay of 3.47 days, and an average cost of $9,123. Overall costs for lung resection are probably more in line with this overall cost, and $17,637 would be at the higher end of the cost for lung resection. Aggregation of different lung surgery procedures in AR-DRG E01B makes costing for this specific procedure difficult. Despite this issue, the overall cost of procedures with average length of stay of 3–4 days are more expensive when compared to MTA and SBRT.

D.5. RESULTS OF THE ECONOMIC EVALUATION

The total average costs for MTA, SBRT and surgery are presented as the cost per patient over the course of three months of treatment. They are presented in Table 72 in a disaggregated form for <3 lesions for populations one and two, and for population two in the case of surgery. As the costing is estimated over a three month period discounting is not appropriate.

It is evident that the total average cost of SBRT is less than that of MTA for populations one and two across all included lesion groupings. For <3 lesions the average cost of MTA is $2,632 higher than for SBRT. The key items driving increased costs are the costs of the disposable applicator and the cost of the overnight hospital stay. In the case of the applicator this cost is $2,960 (the MTA equipment cost of $3,210 in the following table includes a $250 per service capital cost allowance for the generator) and the hospital stay is $873 per night. In the longer term the MTA procedure may be delivered on an outpatient basis. The potential cost reduction from this change in setting for delivery is explored in the sensitivity analysis.

Table 72 Health care costs per patients (3 months) for base-case analysis

Resource item description	MTA	SBRT	Incremental cost of MTA over SBRT	Surgery	Incremental cost of MTA over Surgery

	Populations one and two, <3 lesions			Population two, <3 lesions	
Specialist services – screening prior to intervention	1,557.55	1,557.55	0.00	1,557.55	0.00
Specialist services – intervention (MBS supported)	1,866.68	3,168.90	-1,302.22	2,814.33	-947.65
Specialist services – intervention (Hospital) [a]	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	293.50	2,916.50	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	**7,843.83**	**5,372.95**	**2,470.88**	**19,472.05**	**-11,628.22**
	Populations one and two, 3–5 lesions			**Population two, 3–5 lesions**	
Specialist services – screening prior to intervention	1,557.55	1,557.55	0.00	1,557.55	0.00
Specialist services – intervention (MBS supported)	2,166.68	3,494.90	-1,328.22	2,814.33	-647.65
Specialist services – intervention (Hospital)	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	329.62	2,880.38	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	**8,143.83**	**5,735.07**	**2,408.76**	**19,472.05**	**-11,328.22**

< MBS = Medicare benefits schedule; MTA = microwave thermal ablation; SBRT = stereotactic body radiotherapy>

a Total average cost including MBS fee and gap. MBS reimbursement implications are outlined in Section E.

There is uncertainty over the cost of adverse events from MTA, as these events are rare and the severity will vary, affecting the cost estimate. Median prevalence of pneumothorax was derived from the case series summarised in Section B and calculated to be 31.4 per cent of MTA procedures having pneumothorax (SD 17.2%) and of those 27.4 per cent would be severe (SD 18.6%). This equates to a total median proportion of 9.6 per cent of MTA procedures requring a chest drain. The average costs of pneumothorax are collected as part of the Australian public hospital AR-DRG series. This cost is included in the sensitivity analysis, and makes the procedure marginally more costly.

The inclusion of the proposed graduated fee for 3–5 lesions of $1,600 increases the relative cost of MTA when compared to SBRT. Surgery is option for pulmonary metastases, as is MTA. The cost of

resection is expensive due to the cost of a number of days in hospital following the surgery. On a cost basis, MTA is a more economic option for population two patients when compared to surgery. To determine cost-effectiveness a stratified survival analysis is required to determine the degree to which any extension is survival or quality life years offsets the increase in resources associated with this procedure.

The major conclusion of the base-case economic evaluation is that MTA is costlier when compared to SBRT, but less than surgery. There is a degree of uncertainty around the presented incremental costs, due to contention about whether the current MBS fees for SBRT reflects true cost and if MTA were to be delivered on an outpatient basis in the future. Even with these considerations, there currently is a significant gap between MTA and SBRT delivery costs. The robustness to results to changes in key assumptions are outlined Section D.6.

D.6. SENSITIVITY ANALYSES

Univariate sensitivity analyses are outlined in this section for cost model variables. Table 73 presents univariate sensitivity analysis of key parameters used in the economic evaluation for the MTA and SBRT comparison in population one patients with <3 lesions. It is unsurprising that the model was shown to be most sensitive to hospital costs, inclusion of adverse events for MTA and the cost of the probe. Even with a 10 per cent variation in many of these items MTA is still costlier when compared to SBRT. The complete removal of the hospital overnight stay still results in MTA being more expensive, albeit at a lesser margin.

Table 73 Average costs one-way sensitivity analysis of MTA versus SBRT, populations one and two, <3 lesions

Parameter	Analysis	Change in Base Incremental cost
Destruction of 1–3by MTA – proposed fee ($1,300)	10%	130.00
	-10%	-130.00
MTA hospital accommodation, under base ($873 per night)	10%	87.30
	-10%	-87.30
MTA machine ($50,00)	10%	25.00
	-10%	-25.00
MTA probe ($2,960)	10%	296.00
	-10%	-296.00
SBRT simulation fee ($658)	10%	-65.86
	-10%	65.86
SBRT dosimetry fee ($1120.75)	10%	-112.08
	-10%	112.08
SBRT treatment fee, MBS Item 15260 5F ($37.95)	10%	-75.90
	-10%	75.90
Inclusion of pneumothorax at rate of 9.6% of MTA procedures	Included	748.18

< MBS= Medicare benefits schedule; MTA = microwave thermal ablation; SBRT = stereotactic body radiotherapy >

Similarly, as for <3 lesions, a significant cost difference exists between MTA and SBRT across all parameters that are varied for the comparison of SBRT and MTA for 3–5 lesions. The larger cost items have the more substantial impact on the increased cost of MTA over SBRT. Key items again include adverse event inclusion, the probe and hospital stay. MSAC (2016) indicates that the base-case economic evaluation should capture changes in the cost of health care resources and supplementary analyses used to accommodate any impacts on non-health care resources and non-health outcomes.[1] It is stated that the costs of social services such as home help, day care, or private

[1] MSAC (2016) noted requests have been made to include non-health process attributes such as convenience of use, and any other externalities, but these need to be judged on their merits and impact of direction on the base-case economic evaluation.

travel may be considered in some circumstances.

MTA treatment involves fewer visits to health facilities when compared to SBRT. These savings are, however, not quantified due to paucity of travel cost data. Travel and other non-health costs are likely to be lower. Shukla et al (2015) cite a range of overseas studies on the impact of distance and travel on radiotherapy treatment utilisation. For example, Madelaine et al (2002)reported lower treatment rates for rural lung cancer patients in Europe and Greenberg et al (1988) asserted that remote and rural Americans with lung cancer were more likely to undergo surgery relative to radiotherapy or chemotherapy.

Table 74 Average costs one-way sensitivity analysis of MTA versus SBRT, populations one and two, and 3–5 lesions

Parameter	Analysis	Change in Base Incremental cost
Destruction of up to three lesions, by MTA – proposed fee ($1,600)	10%	160.00
	-10%	-160.00
MTA hospital accommodation, under base ($873 per night)	10%	87.30
	-10%	-87.30
MTA machine ($50,00)	10%	25.00
	-10%	-25.00
MTA probe ($2,960)	10%	296.00
	-10%	-296.00
SBRT simulation fee ($658)	10%	-65.86
	-10%	65.86
SBRT dosimetry Fee ($1120.75)	10%	-112.08
	-10%	112.08
SBRT treatment fee, MBS Item 15260 5F ($37.95)	10%	-94.88
	-10%	94.88
Inclusion of pneumothorax at rate of 9.6% of MTA procedures	Included	748.18

< MBS= Medicare benefits schedule; MTA = microwave thermal ablation; SBRT = stereotactic body radiotherapy >

Sensitivity analysis of surgery compared to MTA amongst population two (pulmonary metastases) indicates surgery is costlier across all variations included in the analyses. As mentioned, the high cost of the hospital stay makes surgery a costlier intervention when compared to MTA.

Table 75 Average costs one-way sensitivity analysis of MTA versus surgery, population two, <3 lesions

Parameter	Analysis	Incremental cost
Destruction of up to three lesions, by MTA – proposed fee ($1,300)	+10%	-130.00
	-10%	130.00
MTA Hospital accommodation, under base ($873 per night)	+10%	-87.30
	-10%	87.30
MTA machine ($50,00)	+10%	-25.00
	-10%	25.00
MTA Probe ($2,960.00)	+10%	-296.00
	-10%	296.00
Lung Wedge Fee ($1147)	+10%	114.70
	-10%	-114.70
Other Hospital Costs ($14,763.57)	+10%	1476.00
	-10%	-1476.00
Inclusion of Pneumothorax at rate of 10% of MTA procedures	Included	-748.18

< MTA = microwave thermal ablation >

Note: Numbers surrounded by round parentheses are negative value

The modelled results were most sensitive to variations in the largest cost items involved in the delivery of the MTA, SBRT and surgery. In the case of MTA compared to SBRT, the cost of the probe and hospital stay have the largest impact. Reductions in the cost for these items would most significantly reduce the cost difference between the interventions.

Table 76 Key drivers of the economic model

Description	Method/Value	Impact
Probe cost	$2,960, disposable	High, does not favours intervention
Hospital costs associated with inpatient delivery of MTA	MTA hospital accommodation ($873 per night)	High, does not favours intervention
Cost of SBRT	MBS Item numbers used for non-IMRT course	High. Current value of MBS fees may be lower than actual delivery costs, which does not favour the intervention.

< IMRT= intensity modulated radiotherapy; MTA = microwave thermal ablation; SBRT = stereotactic body radiotherapy >

SECTION E FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

This section of the contracted assessment presents the estimated financial impact of MTA use in patients using an epidemiologic approach. First, the numbers of patients eligible for MTA in each of the three target sub-populations are estimated, and then the financial implications to the MBS and broader health system are determined based on the uptake of services in the target population. The estimation methods and the majority of assumptions employed in the following analyses follow from the cost minimisation analysis provided in Section D.

The majority of data used to develop the financial estimate of MTA reimbursement are sourced from lung cancer indicence data provided to the AIHW (Australian Institute of Health and Welfare (AIHW) 2011a; Australian Institute of Health and Welfare (AIHW) 2014a; Australian Institute of Health and Welfare (AIHW) 2016) This section summarises the current burden of lung cancer in Australia as well as the current practice of treating the condition and the associated adverse events. Table 77 outlines the key assumptions used in the financial impact assessment. Further discussion and justification of these assumptions is provided in the sections that follow.

Table 77 Summary of the key assumptions used in the financial impact assessment

Parameter	Base case	Sensitivity analysis	Reference
Incidence of lung cancer cases in Australian males in 2016	7,130	-	AIHW 2016. An age-standardised incidence rate of 43 cases per 100,000 persons (54 for males and 34 for females) was projected for 2016.
Incidence of lung cancer cases in Australia females 2016	5,073	-	AIHW 2016. An age-standardised incidence rate of 43 cases per 100,000 persons (54 for males and 34 for females) was projected for 2016.
Annual growth of female lung cancer cases in Australia	4.26%	-	Projection of annual growth rates in male and female lung cancer incidence estimated by AIHW (2016) between 2000 and 2012
Annual growth of male lung cancer cases in Australia	1.37%	–	Projection of annual growth rates in male and female lung cancer incidence estimated by AIHW (2016) between 2000 and 2012
NSCLC proportion of lung cancer cases	85.0%	63%	Barton et al (2013), AIHW (2011) proportion of lung cancer cases in 2007

Parameter	Base case	Sensitivity analysis	Reference
Incidence of NSCLC cases in Australia for 2016	10,373	-	Based on NSCLC accounting for 85 per cent (AIHW, 2011) of lung cancer cases in 2007
Proportion of NSCLC in Stage I-II	31%	-	Barton et al (2013)
Patients with early stage NSCLC in 2016	3,215	-	Between 1995 and 2004, around 29.6 per cent of staged lung cancers in NSW were localised (AIHW 2011). In the United States, it was estimated that 16.1 per cent of NSCLC in males and 19.6 per cent of NSCLC in females remains localised at the time of diagnosis (AIHW 2011). Estimated 31% of NSCLC incidence
Proportion of NSCLC stage I-II not suited to surgery	57%	-	Barton et al (2013) assumed 60% of NSCLC stage I-II not suited to surgery, or 15% of all lung cancer incident cases. In the future this proportion could increase with the availability of ablative technologies such as MTA
Patients with early stage NSCLC who are not suitable for surgical resection (population 1).	1833	-	Proportion of patients with early stage NSCLC estimated by experts to be not suited for surgical resection.
Equivalent proportion of patients with pulmonary metastases, in whom the primary tumour is under control, curative intent and suitable for MTA (as % population 1)	10%	100%	Assumed to be 10% of primary tumour population following discussions with experts. A range of estimates were provided, as high as 100%
Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent and suitable for MTA (population 2)	183	-	At higher end estimate a total of 1833 would be in population 2.
Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment (population 3) and suitable for MTA	0	-	Only limited numbers of MTA procedures are being provided to this population. The population is deemed more suitable for systemic therapies

< ABS, the Australian Bureau of Statistics. AIHW, Australian Institute of Health and Welfare; MTA=microwave thermal ablation; NSCLC = non small cell lung cancer >

The cost mininisation analysis includes the cost of major adverse events related to the MTA procedure. The assumptions related to the proportion of patients undergoing the MTA procedure likely to experience major adverse events, based on studies outlined in Section B, are provided in Table 78**.** The key adverse event requiring treatment is pneumothorax.

As a proportion of ablation procedures from included studies in Section B a median of 32 per cent of procedures are associated with pneumothorax (range: 8.3%–63.8%), with 30.3 per cent (range 0–66.7%) being severe (i.e. require chest tube drainage). This translates into 9.6 per cent of all MTA prcedures requring chest drainage. Using the mean from included studies, as opposed to the median, the proportions are similar. A total of 31.4 per cent of MTA procedures would have associated pneumothorax (SD 17.2%) and of those 27.4 per cent would be severe (SD 18.6%). This equates to a total mean proportion of 8.6 per cent of MTA procedures requiring a chest drain.

Table 78 Summary of the key assumptions relating to major adverse events

Major adverse events	Base case	Reference
Proportion of patients experiencing pneumothorax	32%, with 30% being severe enough to warrant chest drainage	Han et al (2015), Liu & Steinke and Yang et al (2014) for population 1, Qi et al (2015) and Vogl et al (2015) for population 2 and Sun et al (2015), Wei et al (2015) and Ni et al (2015) for population 3.

A number of other adverse events were observed across included studies; however, they are less comprehensively reported when compared to pneumothorax. For haemoptysis the median was 6.2 per cent (0–31.9%), reported by nine studies. Skin burns was 2.2 per cent (0–8.3%), reported by six studies. Broncho-pleural fistula was 1.8 per cent (0.5–2.6%), reported in four studies. Post ablation syndrome was 6.9 per cent (0–35.9%) reported by six studies. Subcutaneous emphysema was 17.4 per cent (3.6–29.8%), reported by three studies. Pleural effusion was 11.2 per cent (0–34%) reported by ten studies. And, pneumonia was 4 per cent (2.8–14.9%), reported by four studies.

Two reports of adverse events related to the device itself, one being ceramic coating of microwave antennae being lost in the pleural space: 1/16 (6.3%) and the other was needle-tip fracture: 1/23 (4.3%) where the needle tip was left in the lesion which had been ablated. Drawing conclusions about the prevalence of these technical events is difficult as just because studies did not report them occurring may not mean they did not due to a lack of systematic recording of adverse events. As the occurrence of pneumothorax is the most comprehensively reported, this event is included in the financial assessment and cost minimisation analyses.

E.2. USE AND COSTS OF MTA

The current and future population with lung cancer has been estimated using a combination of statistics from the AIHW and the general literature. Table 79 summarises the current and future population estimates.

Prevalence of primary and secondary lung cancer

The AIHW (2016) reported that the number of new lung cancers diagnosed each year increased from 4,692 in 1982 to 6,462 males in 2012, however, a greater relative increase was observed in females from 1,261 to 4,464 over the same period (Figure 13). Age-standardised incidence rates have decreased for males by 32 per cent (from 85 to 58 per 100,000) between 1982 and 2012, but increased in females by 83 per cent (from 18 to 33 per 100,000). Differences in time series incidence rates between males and females reflects the earlier decline in smoking rates among men.

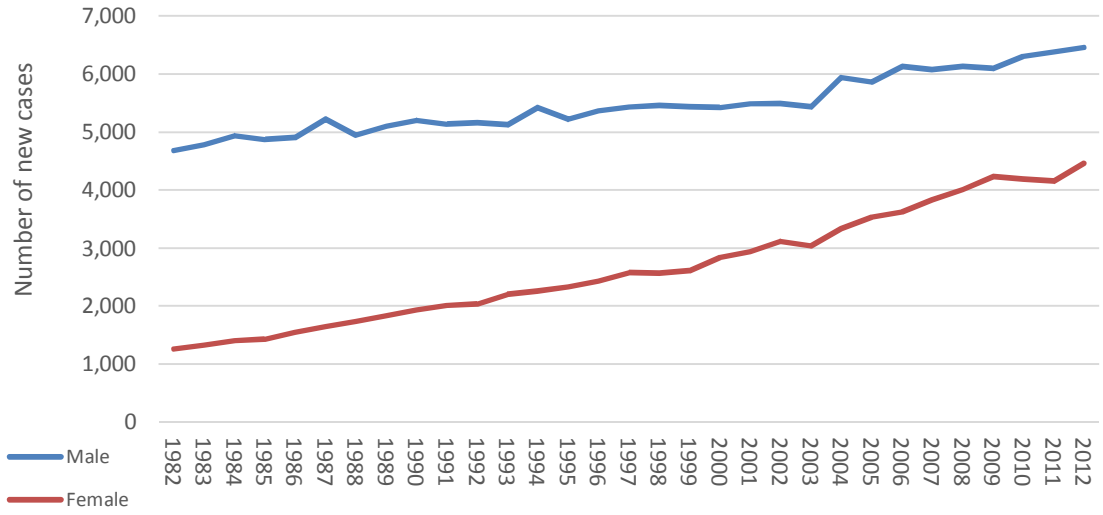

Figure 13 Incidence of Lung Cancer, Australia 1982–2012 (AIHW 2016)

The AIHW (2016) projected 12,203 new lung cancer cases in 2016 based on an age-standardised incidence rate of 43 cases per 100,000 persons (54 for males and 34 for females). This translates into 7,130 and 5,073 male and female incident cases on lung cancer in this year. Average annual rates of increase for males and females between 2000 and 2016 from AIHW (2016) have been used to project for the next five years in the base financial projections. The proportion of lung cancers specified as small cell carcinoma was 11 per cent for males and 13 per cent for females in 2007, with other carcinoma and unspecified malignant neoplasm accounting for 25 per cent of lung cancers in males and 26 per cent in females (AIHW, 2011). Barton et al (2013) assumed a proportion of 15 per cent of incident lung cancer in Australia as being small cell carcinoma when determining radiotherapy demand. This proportion is included in base financial projections in this assessment. Non-small cell incidence is assumed to be 85 per cent of national incidence, which includes other

carcinoma and unspecified malignant neoplasm. A lower bound sensitivity assumption of 63 per cent incident lung cancer which excludes other carcinoma and unspecified malignant neoplasm is provided in the concluding part of this section.

Data from New South Wales (Vinod et al 2004) collected between 1995 and 2004, suggests that 29.6 per cent of staged lung cancers are localised. A retrospective survey of lung cancer reported in the Victorian Cancer Registry from 1 January to 30 June 2003, and followed up for 5 years, recorded that 35.4 per cent of NSCLC were stage I, IA and IB cases (Mitchell 2013). This is higher than the proportions in the USA, where between 16.1 per cent of NSCLC in males and 19.6 per cent of NSCLC in females were localised at the time of diagnosis (AIHW 2011). Barton et al (2013) assumed that around 31 per cent of staged lung cancers are stage I-II when determining radiotherapy demand. This assumption is included in the financial assessment.

Barton et al (2013) assumed that around 43 per cent of early stage NSCLC would be subject to surgery when determining radiotherapy demand in Australia. This corresponds with surgery rates found by Currow et al (2014) in an extracted data set for 3040 patients from the NSW Central Cancer Registry between January 2003 and December 2007. The surgery rate was estimated to be between 38 per cent and 43 per cent, which is similar to that calculated by Barton et al (2013). Surgery rates declined with age. Rates by age group in the NSW study were: <60 years, 490 patients, 52.7 per cent of cases resected, 60–69, 832 patients, 48.3 per cent of cases resected, 70–79, 1091 patients, 37.2 per cent of cases resected and 80 or over, 627 patients, 16.3 per cent of cases resected (Currow et al 2014).

Based on incident calculation for 2016, a total of 1833 patients with early stage NSCLC would not be suited or would not elect surgical resection. Barton et al (2013) specified that this patient population includes those with NSC stage I-II showing good performance that do not undergo surgery (10% all incident lung cancer cases) and NSC stage I-II cases with poor performance (5% of lung cancer cases). A proportion of these patient groups would be suitable for MTA where tumour size or other factors hinder surgical resectability.

Primary tumours in other parts of the body metastasise to the lungs as secondary malignancies. The lungs account for approximately 20 per cent of metastatic disease (Hirakata et al 1993). In cases where the primary tumour is under control, the patient may be eligible for curative therapy. The applicant has suggested that sarcomas, thyroid, renal, head and neck cancers tend to metastasise predominantly or exclusively to the lung. AIHW (2011) noted that there is no national requirement for collection of data on lung cancer stage so no Australia-wide data on staging of lung cancer are available.

Consequently, there is considerable uncertainty about the proportion of NSCLC cases which are secondary malignancies for which the primary tumour is being controlled or those patients with

metastatic disease receiving palliative care. Discussions with experts indicate the number of eligible patients associated with this population would be less than those with primary tumours, or population one patients in this assessment. An assumption that this population is equivalent to 10 per cent of population one patient numbers estimate is included in the base case scenario. A range of assumptions about uptake in these populations are included in the sensitivity analyses to examine the impact on overall MBS costs.

For population three patients the use of palliative radiotherapy can relieve pain and ease obstructive symptoms (Vinod 2013). Barton et al (2013) estimated that around 83 per cent of stage IV NSCLC patients would be eligible for palliative radiotherapy. The feedback from experts is that palliative radiotherapy is done relatively infrequently and not in a large number of centres. Experts indicated that the use of MTA and RFA in these populations would be limited and patients would be more likely to use systemic therapies. No patients are included for palliative treatment in the financial analyses.

Number of MTA of eligible patients

MTA is primarily intended to be used in patients with early stage NSCLC who are not candidates (or do not elect) surgery or those with oligometastatic disease (secondary malignancies in the lung). Figure 14 illustrates the incidence of lung cancer in Australia by sub-population of interest and follows the discussion in the previous sub-section. Around 15 per cent of lung cancer cases, along with those diagnosed from previous years — that have not progressed — would be eligible for MTA as population one patients should resection not be an option. The number of non-incident cases contributing to this population is likely to be limited. AIHW (2011) use 'limited-duration prevalence' as a prevalence measure for the number of people alive who were diagnosed with lung cancer when reporting Australian lung cancer prevalence.

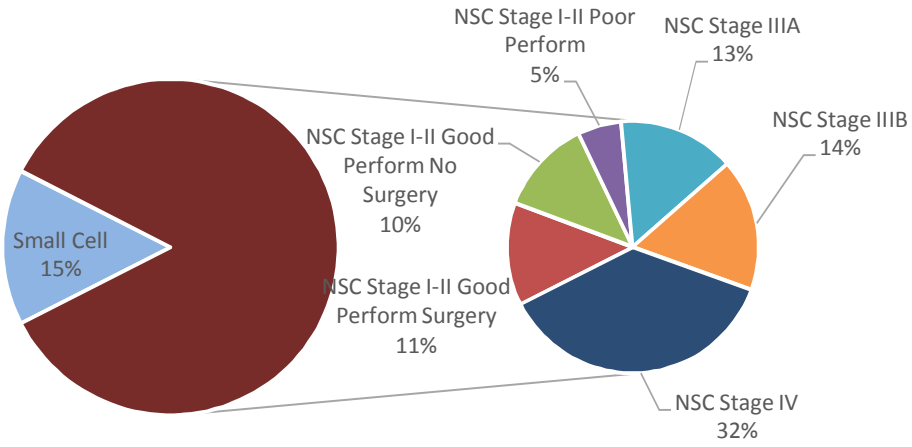

Figure 14 Incidence of lung cancer in Australia by sub-population of interest (Barton et al 2013)

At the end of 2007, some 7,417 males and 5,189 females were alive who had been diagnosed with lung cancer in the previous 5 years. Based on this data, national prevalence is similar to the number of incident cases which were 5,948 in males and 3,755 in females in the same year (AIHW, 2011). This reflects low relative survival, as people diagnosed with lung cancer were 13 per cent as likely to live 5 years after diagnosis as their counterparts in the general population, although five-year relative survival was higher in females (15%) than males (11%) (AIHW, 2011).

For the purposes of this assessment it is assumed the equivalent of 57 per cent of incident cases with early stage NSCLC are ineligible or not suited for surgical resection. There is uncertainty surrounding this estimate. Lower and upper patient population estimates were calculated using an assumption of 40 and 70 per cent of patients with early stage NSCLC estimated by experts to be ineligible for surgical resection. MTA may also be used in patients with pulmonary metastases where the number and site of metastases, or previous lung surgery, precludes them from further surgery. These populations are estimated to be small as discussions with clinicians indicated 90 per cent of current MTA practice targeting early stage tumours within the assessment's population one. It is estimated that later stage treatment is equivalent to 10 per cent of early stage NSCLC who are not candidates for surgical resection. Lower and upper patient population estimates were also calculated

Total population eligible for MTA in Australia

Applying the asssumptions as described above, the total population eligible for MTA in Australia in 2016—2020 is estimated and presented in Table 79.

Table 79 Population eligible for MTA in Australia

	Epidemiology assumption	Calc.	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
A	Female Lung Cancer Cases	Annual growth 4.26% since 2000	5,073	5,289	5,514	5,749	5,994
B	Male Lung Cancer Cases	Annual growth 1.37% since 2000	7,130	7,228	7,327	7,427	7,529
C	Total Lung Cancer Cases	A +B	12,203	12,517	12,841	13,176	13,523
D	NSCLC Cases	C × 85%	10,373	10,639	10,915	11,200	11,495

	Epidemiology assumption	Calc.	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
E	Early Stage NSCLC Cases	D x 31%	3,215	3,298	3,384	3,472	3,563
F	Early Stage NSCLC Cases Ineligible for Resection	E x 61%	1833	1880	1929	1979	2031
G	Later Stage NSCLC Cases Suitable for MTA	F x 10%	183	188	193	198	203
H	All Cases Suitable for MTA	G + F	2016	2068	2122	2177	2234

< MTA= microwave tissue ablation; NSCLC= non-small cell lung cancer >

Uptake of MTA in the potential patient population

In the absence of recurrence or failure, MTA is a one-time procedure. Correspondingly, it is assumed that there is only one intervention per patient. Furthermore, given that the intervention will be delivered in a limited number of tertiary facilities with radiologists who need to be educated in how to undertake the procedure, only a proportion of eligible patients would receive MTA over the next five years.

It is expected that in year 1, 3,215 patients will have early stage NSCLC and 1,833 of them will be ineligible or would not elect surgery, increasing to 2,174 patients in year five. Additionally, a smaller number of patients with pulmonary metastases, in whom the primary tumour is under control, will be eligible for MTA. This is estimated to be equivalent to 10 per cent of the early stage eligible population.

The protocol notes it is unclear how often either MTA or RFA are used in current clinical practice as there is no current MBS, AIHW Procedure or AR-DRG item for these procedures of the lung. The closest description of a procedure was found to be item 90181–00: destruction procedures on lung. In total 127 procedures were undertaken in 2011–1202, 135 in 2012–13, and 148 in 2013–2014.

Expert clinical advice is that the MTA procedure is likely to substitute for stereotactic radiosurgery of the lung. Stereotactic radiosurgery allows non-invasive ablative treatment that is used for tumours and other lesions that would be inaccessible or inappropriate for open surgery (Timmerman et al 2010).

Stereotactic radiosurgery is usually referred to as fractionated stereotactic radiation therapy (SRT), when more than two treatments are given and SBRT when treatment is given to areas other than the head. Like MTA, the procedures are alternatives to invasive surgery, including for tumours and abnormalities that are hard to reach and located close to vital organs (Royal Australian and New Zealand College of Radiologists (RANZCR) 2016). Treatment is generally safe for peripheral smaller tumours (Timmerman et al 2006).

Following discussion with experts it is assumed that MTA would largely replace the current use of SBRT in Stage I inoperable patients with NSCLC and to a lesser extent in pulmonary oligometastases.

The machines used by Radiation Oncologists for SBRT provide precision in association with guidance systems that allows treatment to be delivered in 3–5 events using high dosage, as opposed to 20–30 treatments with conventional radiotherapy. Cancer Voices Australia (2011) highlighted that no data is available which examine savings in resource utilisation —such as reductions in travel and delivery cost—from treating with a small number of stereotactic treatments compared with more numerous conventional treatments.

Currently there is a once-off single item number (15600) covering stereotactic radiosurgery that bundles medical consultation, planning, simulation, dosimetry and treatment. The number of SBRT procedures reported using MBS online for this item number between 2000 and 2015 are limited. Most procedures are delivered in NSW, although until recently less than 100 procedures were delivered per year in this state, and the national number of services is around 500 per year. Discussions with experts and Cancer Voices (2011) indicated that this item number is rarely used for SBRT. MBS items for SBRT treatment of lung cancer are itemised using MBS item numbers for a non-IMRT course derived following discussions with the billing clinicians. These item numbers are outlined were outlined in Section D and the MBS components calculated later in this section.

The applicant estimates that 20–35 pulmonary ablations would be expected to be performed per site, per year. This estimate is based on data from large tertiary hospitals currently conducting pulmonary RFA, including the Royal Perth Hospital and the Royal Brisbane and Women's Hospital. It is unclear how many sites would need to be considered in estimates of overall utilisation if the proposed service received MBS funding.

An uptake rate of 10 per cent has been assumed for the first 5 years to account for developing treatment capacity and educating radiologists. The number of interventions increases by nearly 200 procedures per year which reflects an increase in capacity of 10 machines per year. The base case estimates for number of anticipated MTA procedures per year based on these uptake rates are provided in Table 80**.**

A total of 202 procedures are estimated in Year 1 increasing to 1117 in Year 5. The estimated number of MTA procedures in Year 1 is calculated as 10 per cent of 2,016 eligible MTA patients from

Table 80. This uptake linearly increases until 50 per cent of the Year 5 number of MTA patients of 2,234, or 1,117 patients are estimated to receive MTA treatment in this year.

The number of MTA procedures is diaggregated by lesion groupings. Discussions with clinicial experts indicated most ablatation would involve less than 3 lesions. Correspondingly, 90 per cent of the 202 MTA procedures forecast for Year 1 will involve the proposed fee associated with less than three lesions. While 181 MTA procedures are estimated for <3 lesions, around 10 per cent of all MTA procedures, or 20, are estimated for 3–5 lesions. No MTA procedures are estimated for patients with more than 5 lesions.

Table 80 Estimated uptake of the MTA procedure

	Year 1	Year 2	Year 3	Year 4	Year 5
All Cases Suitable for MTA	2,016	2,068	2,122	2,177	2,234
Uptake estimate	10%	20%	30%	40%	50%
Anticipated total number of MTA procedures per year	202	414	636	871	1117
Procedures by Lesion Grouping					
1–3 lesions total per patient (90%)	181	372	573	784	1005
3–5 lesions total per patient (10%)	20	41	64	87	112
>5 lesions total per patient (0%)	0	0	0	0	0
Total	202	414	636	871	1117

< MTA= Microwave tissue ablation >

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

The disaggregateted costs and resources associated with the MTA procedure have been described previously in Section D, however the unit costs are provided again for ease of reference (Table 81). The costs of the machine and probe and the cost of the hospital admission are borne by private health funds; and, as such are excluded from the total additional MBS cost per MTA procedure. The proportion of each cost element that can be claimed under the MBS is listed for each item and combined to generate a total MBS cost for the procedure.

Table 81 Costs and services associated with MTA procedure

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Medical services – screening prior to intervention						
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	As outpatient	202.00	202.00	85%	1	MBS Item 56347
Respiratory function test	As outpatient	138.65	138.65	85%	1	MBS Item 11503
Whole body FDG PET study, performed for evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	As outpatient	953.00	953.00	92% [A]	1	MBS Item 61523
Medical oncologist consultation	As outpatient	263.90	263.90	85%	1	MBS Item 132
Medical services – intervention						
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	1,300.00	1,300.00	75%	1	Applicant
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	1,600.00	1,600.00	75%	1	Applicant

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of >5 lesions, by percutaneous MTA with curative or palliative intent, including any associated imaging services	Radiologist, delivered to inpatient	2,000.00	2,000.00	75%	1	Applicant
Pre-anaesthesia consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.49	99.49	75%	1	Mean for MBS items 17610, 17615, 17620, 17625
Referred consultation. Consultations comprise 4 time-based items utilising 15 minute increments up to and exceeding 45 minutes	Anaesthesiologist, delivered to inpatient	99.49	99.49	75%	1	Mean of MBS items 17640, 17645, 17650, 17655
Initiation of management of anaesthesia, for computerised axial tomography scanning, magnetic resonance scanning, digital subtraction angiography scanning	Anaesthesiologist, delivered to inpatient	138.60	138.60	75%	1	MBS item 21922
Administration of anaesthesia, 56 MINUTES TO 1:00 HOUR	Anaesthesiologist, delivered to inpatient	79.20	79.20	75%	1	MBS Item 23043
Anaesthesia modifier for patients over 70	Anaesthesiologist, delivered to inpatient	19.80	19.80	75%	1	MBS Item 25015
Blood pressure monitoring, (central venous, pulmonary arterial, systemic arterial or cardiac intracavity), by indwelling catheter	Anaesthesiologist, delivered to inpatient	59.40	59.40	75%	1	MBS Item 22012
CHEST (lung fields) by direct radiography (NR)	Radiologist, delivered to inpatient	35.35	35.35	75%	2	MBS Item 58500

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Medical services – post intervention follow-up						
Medical oncologist consultation	Outpatient	75.50	75.50	85%	1	MBS Item 116
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	Radiologist, as outpatient	202.00	202.00	85%	1	MBS Item 56347
Hospital services						
Nurse assistant – Year 2, $847.00 per week (July 2016). Hourly rate of $22.30 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $22.3 based on average 1-hour input	Assist with theatre, analgesia	22.30	0.00	0.00	1	NSW Public Health System Awards and Determinations, July 2016.
Registered nurse (RN) – Year 5, $1,399.30 per week $36.80 based on ordinary hours of work for each full time employee being 228 hours balanced over a six-week period. Cost: $36.8 based on average 1-hour input	Assist with theatre, analgesia	36.80	0.00	0.00	1	NSW Public Health System Awards and Determinations, July 2016
Hospital accommodation is the average of shared ward and single ward accommodation costs calculated in Victoria for 2015–16, surgical or obstetric patient first 14 days	Hospital	873.00	0.00	0.00	1	Average actual cost per bed day 2015–16.
Prostheses costs						
MTA machine	Prostheses	50,000.00	0.00	0.00	0.005	Assumes 10-year life and 20 procedures per year

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Probe	Prostheses	2,960.00	0.00	0.00	1	Applicant
Adverse events						
Averaged DRG-E68A. Pneumothorax W Catastrophic or Severe CC and DRG-E68B. Pneumothorax W/O Catastrophic or Severe CC estimated cost weights	Hospital, some MBS	7,793.50	Not in base calculation		0.0%	AR-DRG VERSION 7.0, Round 18 (2013–14) inflated to 2016 using ABS CPI.
Total : 1–3 lesions total cost per patient	-	-	-	-	-	**7,843.83**
Total : 3–5 lesions total cost per patient	-	-	-	-	-	**8,143.83**
Total : >5 lesions total cost per patient	-	-	-	-	-	**8,543.83**

< ABS= Australian bureau of statistics; CPI = consumer price index; MTA = microwave tissue ablation; NSW = New South Wales; PET= Positron emission tomography >

[A] Typically, 85% of MBS fee is reimbursed in outpatient settings. The online published reimbursement is $873.50, or 92% of fee at the 85% level.

The total MBS cost for up to three lesions per patient is $3,027. They are summarised in Table 93 and include follow up up 3 months, but excludes adverse events. The MBS cost increases to $3,252 and $3,551 per patient for three–five lesions and greater than five lesions. As previously noted, the number of patients receiving treatment for more than five lesions would be very limited. Most would have up to three lesions.

Table 82 Summary of Costs by Payer associated with the MTA procedure

	MBS	Hospital	Patient/ Insurance	Total
1–3 lesions total cost per patient	3,026.51	932.10	3,885.22	**7,843.83**
3–5 lesions total cost per patient	3,251.51	932.10	3,960.22	**8,143.83**
>5 lesions total cost per patient	3,551.51	932.10	4,060.22	**8,543.83**

< MBS=Medical Benefits Scheme; MTA = microwave tissue ablation >

Patients with private insurance would receive 75 per cent of the MBS fee for hospital delivered procedures. A total of 13,409,297 persons held some form of private health insurance in 2015. The proportion of the Australian population with hospital cover was 47.2 per cent and 55.8 per cent have general treatment cover. Private Healthcare Australia (Private Healthcare Australia 2016) estimated about 75 per cent of subacute and non-acute separations from public hospitals were for public patients, and private health insurance funded 82 per cent of subacute and non-acute separations from private hospitals. Around 54 per cent of all subacute and non-acute separations covered by private insurance. (Australian Institute of Health and Welfare (AIHW) 2014a). Those taking up MTA are assumed to have private cover. MBS rebates calculated in the above table assume 85[2] per cent of outpatient and 75 per cent of inpatient fees are claimable under the MBS. Discussions with the Australian Government Department of Health indicated the convention for MSAC applications is that the scheduled fee is used as an indication of the patient's out of pocket costs.[3] Omission of co-payment data is likely to understate Extended Medicare Safety Net impacts. Correspondingly, these have not been calculated.

Discussions with clincians indicated further a range of diagnostic procedures could occur during work up. This includes whole body FDG PET study, performed for the staging of proven NSCLC, where curative surgery or radiotherapy is planned. This procedure has an MBS listed fee of $953.00 and benefits of 75% = $714.75 or 85% = $873.50. It should be noted that any patient being considered for any kind of therapy (MTA, RFA, resection or SBRT), would all receive imaging under the base assumptions, so no incremental difference accrues to any intervention.

Discussions with clincians delivering MTA within Australian hospitals indicated that adverse events are rare. Overseas, the procedure is undertaken out-of-hospital and adverse events are documented in Section B. From the published evidence, pneumothorax is a key adverse event, with 9.6 per cent of MTA proceures requiring insertion of chest drain and requiring hospital stay. Average costs for DRG-E68A, Pneumothorax W Catastrophic or Severe CC and DRG-E68B. Pneumothorax W/O Catastrophic or Severe CC were calculated as part of the Round 18 of the Australian national hospital collection.

These costs are indexed to 2016 prices using CPI. The total health price index (THPI) is the AIHW's index of annual ratios of estimated total national health expenditure at current prices, which is generally used to index health sector costs. It is not available for 2016 adjustments, however, CPI most closely tracks THPI when compared to other indices. For example over the 2004–2013 period

[2] Except footnoted selected items

[3] Correspondence with the DoH, 11 August 2016.

average CPI (Australian Bureau of Statistics 2016) annual change has been 2.7 per cent per year and the THPI also 2.7 per cent (Australian Institute of Health and Welfare (AIHW) 2014a).

An index numbers 108.2 in March 2016 compared with 105 for 2013–2014 is used to adjust Round 18 hospital costs to 2016 levels (AIHW, 2015). It is evident that the costs of treating pneumothorax per separation vary from $10,238 to $5,144 in current estimated prices–depending on severity. A proportion of these costs would be borne by the MBS. Ward medical and imaging costs comprise around 30 per cent of the overall cost, or $2,338 per separation. If 9.6 per cent of MTA results in pneumothorax, then the procedure would cost an average additional $224 per intervention. This additional cost is included in the sensitivity analysis.

The results presented in Table 83 indicate that the cost to the MBS is estimated to be $0.65 million in year one, increasing to $3.41 million in year 5 following base case estimates. Most cost is associated with ablation of up to three lesions in total per patient.

Table 83 Total estimated additional costs to MBS of changes in services

	Unit	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake estimate		**10%**	**20%**	**30%**	**40%**	**50%**
Anticipated total number of MTA procedures per year	No.	202	414	636	871	1,117
Procedures by Lesion Grouping						
1–3 total cost per patient (90%)	No.	181	372	573	784	1,005
3–5 lesions total cost per patient (10%)	No.	20	41	64	87	112
>5 lesions total cost per patient (0%)	No.	0	0	0	0	0
Total	**No.**	**202**	**414**	**636**	**871**	**1,117**
MTA MBS Costs by Lesion Grouping						
1–3 lesions total cost per patient (90%)	$	549,161	1,126,565	1,733,634	2,371,868	3,042,840
3–5 lesions total cost per patient (10%)	$	65,554	134,480	206,946	283,133	363,228
>5 lesions total cost per patient (0%)	$	0	0	0	0	0
Total	**$**	**614,715**	**1,261,044**	**1,940,581**	**2,655,001**	**3,406,068**

<MTA= microwave tissue ablation for primary and secondary lung cancer; MBS= Medicare benefits schedule >

E.4. FINANCIAL IMPLICATIONS FOR THE MBS

The applicant has advised that MTA is currently used in both the public and private settings as a substitute for RFA; however, there is no current MBS service for either MTA or RFA in the proposed populations. Use of both MTA and RFA is therefore limited. If subsidised, MTA is likely to primarily replace SBRT, which is more commonly used to treat stage I NSCLC patients who are unsuitable for, or who refuse, surgery. The protocol notes that Guidelines from the Alberta health services define a role for SBRT in stage I NSCLC who cannot undergo surgery. These guidelines recommend SBRT for tumours five or less cm in size.

Stage I NSCLC patients who are unsuitable for, or who refuse, surgery are estimated to be the largest population group suitable for the MTA intervention. In 2016, the MTA eligible population is estimated to be 1,833 patients, followed by 183 patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent. Patients within the pulmonary oligometastases population could also receive radiotherapy or surgery, so MTA uptake would substitute for these MBS supported interventions amongst this group.

Those patients with pulmonary oligometastases availing MTA over surgery are likely to have poor lung performance or other co-morbidities, so the degree of substitution between these interventions is likely to be limited. There are no statistics about the number of patients with pulmonary metastases, in whom the primary tumour is under control who receive surgery; however, even if these patients account for half of the population with pulmonary metastases population estimated to uptake MTA, they represent less than 100 patients per year. That is, 50 per cent of the estimated 183 patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent.

Consequently, substitution of MTA with currently listed MBS procedures is limited to SBRT within the base case financial analysis. The cost of surgery was explored in Section D. Most of the cost is associated with hospital services borne by state and territory budgets.

Radiofrequency Ablation (RFA)

Radiofrequency ablation can be performed in patients under conscious sedation, by using medications similar to those used with any other interventional radiology procedure (Tatli et al 2012). Discussions with Australian clinicians indicated the procedure that is currently delivered within hospitals has a similar pre and follow-up procedural cost to MTA. The cost of RFA machines and probes differ to that of MTA. Widely available RFA systems include CooltipTM system (Covidien, Mansfield, Massachusetts, USA), RF 3000® (Boston Scientific Corporation, Natick, Massachusetts, USA), and Model 1500X RF generator (AngioDynamics, Latham, New York, USA). The protocol estimated an average machine cost of $52,000 and probe of $2,000 for RFA compared to $50,000

and $2,960 for MTA. The lower probe cost results in a procedure cost of RFA that is 88 per cent of MTA, if all other intervention costs were the same.

The protocol, however, notes that MTA has a steeper temperature gradient when compared to RFA, which allows for larger ablation volumes in faster times of 4–6 minutes in contrast to 12–20 minutes for single ablations required for RFA (Swan et al 2013). The key cost difference between RFA and MTA is associated with the longer time to deliver to procedure. A similar adverse event profile is reported for RFA and MTA. Pulmonary RFA ablation has an overall major complication rate ranging between 8–12 per cent (Okuma et al 2010), with pneumothorax being the most common complication.

Stereotactic Body Radiation Therapy (SBRT)

SBRT has emerged as a technology that can improve the delivery of external beam radiotherapy. As discussed, SBRT may reduce the number of attendances compared to other forms of radiotherapy. The number of delivered fractions depends on factors such as histology, clinical stage, surgical clearance of the tumour margin, patient fitness or performance status, presence or absence of symptoms, and outcome of previous treatments (Delaney et al 2003).

Rusthoven et al (2009) indicated that high-dose radiation can be focally administered without excessive risk of radiation pneumonitis, provided sufficient normal lung can be spared. Chest wall pain and rib fractures are potential toxicities following SBRT, although this risk can be minimised by adjusting fractionation in relation to tumour location (Bongers et al 2011). The MBS and other costs associated with SBRT are included in the following table without costs of treating adverse events – such as chest wall pain.

Table 84 Costs and services associated with SBRT

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Medical services – screening prior to intervention						
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	As outpatient	202.00	202.00	85%	1	MBS Item 56347

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Respiratory function test	As outpatient	138.65	138.65	85%	1	MBS Item 11503
Whole body FDG PET study, performed for evaluation of a solitary pulmonary nodule where the lesion is considered unsuitable for transthoracic fine needle aspiration biopsy, or for which an attempt at pathological characterisation has failed	As outpatient	953.00	953.00	92%[A]	1	MBS Item 61523
Medical consultation	As outpatient	263.90	263.90	85%	1	MBS Item 132
Medical services – intervention (Non IMRT Course, not Department of Veterans Affairs)						
SPECIALIST, REFERRED CONSULTATION - SURGERY OR HOSPITAL - professional attendance at consulting rooms or hospital by a specialist in the practice of his or her specialty where the patient is referred	As outpatient	85.55	85.55	85%	1	MBS Item 104
SIMULATION FOR THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY	As outpatient	658.60	658.60	88%[B]	1	MBS Item 15550
DOSIMETRY FOR THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY OF LEVEL 3 COMPLEXITY	As outpatient	1,120.75	1,120.75	93%[C]	1	MBS Item 15562
RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site for diseases and conditions not covered by items 15245, 15248 or 15251	As outpatient	59.65	59.65	85%	4	MBS Item 15254 1F (primary field)

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - to a maximum of 5 additional fields treatment delivered to primary site (lung)	As outpatient	37.95	37.95	85%	20	MBS Item 15260 5F (Secondary Field)
RADIATION ONCOLOGY TREATMENT VERIFICATION - volumetric acquisition, when prescribed and reviewed by a radiation oncologist and not associated with item 15700 or 15705 - each attendance at which treatment involving three fields or more is verified (ie maximum one per attendance).	As outpatient	76.60	76.60	85%	4	MBS Item 15710
RPG - Linac						
15254 Primary treatment field	As outpatient	36.12	0.00	0.00	4	RPG
15550 Simulation	As outpatient	65.2	0.00	0.00	1	RPG
15562-Level 6-Plan	As outpatient	83.82	0.00	0.00	1	RPG
Medical services – post intervention follow-up						
Medical consultation (1-month toxicity, 3 month CT)	As outpatient	75.50	75.50	85%	2	MBS Item 116
COMPUTED TOMOGRAPHY - scan of chest, including lungs, mediastinum, chest wall and pleura, with or without scans of the upper abdomen, with intravenous contrast medium	Radiologist, as outpatient	202.00	202.00	85%	1	MBS Item 56347

Resource	Provider of resource	Fee per unit of resource	MBS Fee	% of fee MBS claimable	Quantity	Source
Total: 1–3total cost per patient (4 fractions)	-	-	-	-	-	5,372.95
Total: 3–5 lesions total cost per patient (5 fractions)	-	-	-	-	-	5,735.07

< IMRT = intensity modulated radiotherapy; MBS = Medicare benefits schedule>

A Typically, 85% of MBS fee is reimbursed in outpatient settings. The MBS online published reimbursement is $873.50, or 92% of fee.

B The MBS online published reimbursement is $579.10, or 88% of fee at the 85% level. Discussions with radiotherapy billing departments indicated that this amount is received.

C The MBS online published reimbursement is $1,041.25, or 93% of fee at the 85% level. Discussions with radiotherapy billing departments indicated that this amount is received.

SBRT is delivered on an outpatient basis, so 85 per cent of MBS fees are claimable for most services delivered as well as during screening and follow-up. Stereotactic radiosurgery is covered under MBS item 15600 for the brain which includes consultation, planning, simulation, dosimetry and treatment. As already noted, Cancer Voices (2011) indicate that most centres use the usual rebates for 3D conformal treatment planning for SBRT. Item numbers were identified during consultations with clinicians. They are included in Table 84 by item and aggregated by payer in Table 85.

Table 85 Summary of Costs by Payer associated with the SBRT procedure ($)

	MBS	Hospital	Patient/ Insurance	ROHPG	Total
1–3 lesions total cost per patient	4,492.18	0.00	587.27	293.50	5,372.95
3–5 lesions total cost per patient	4,802.77	0.00	602.68	329.62	5,735.07

< MBS= Medicare benefits schedule; ROHPG= Radiation Oncology Health Program Grants >

MBS rebates account for $4,492.18 of the three-month treatment cost for SBRT on up to three lesions of the lung. When ROHPG grants are taken from the total, MBS rebates accounts for 85 per cent of treatment costs. Given SBRT is delivered on an outpatient basis this is to be expected. Discussions with clinicians indicated that MBS fees for SBRT are possibly below costs of delivery.

Low unit costs for radiation oncology items on the MBS was implicated by the Royal Australian and New Zealand College of Radiologists (RANZCR) (2015) for the increasing level of funding for these services through the Medicare Safety Net where $49.9 million (or almost 13%) of the total $389.9 million in MBS funding for radiation oncology in 2014 was spent through the Safety Net (Australian

Government Department of Health, 2015). Average co-payments have not been included in the assessment report, but could be significant when private delivery of SBRT is considered. Base unit costs in the draft assessment were derived from the public health system. The MBS item numbers used in base financial calculations are outlined in Table 85.

Uptake of MTA would result in cost savings for the MBS, as the MBS rebate for MTA is lower at $3,027 for patients with less than 3 lesions, when compared to the cost of SBRT which is $4,492.

Costs to MBS if MTA procedure is adopted

This section provides an overview of MTA replacing SBRT focussing on the financial implications in terms of MBS rebates. The costs to the MBS only include the costs associated with the procedure; the costs of the machines, probes and hospital stay are borne by private health funds. It is evident that annual net MBS costs decrease from a saving of $0.30 million in Year 1 to a saving of $1.65 million in Year 5. The overall saving to the MBS over 5 years is $4.78 million.

Table 86 Total estimated additional costs to MBS of changes in services ($)

Uptake estimate	**Year 1 10%**	**Year 2 20%**	**Year 3 30%**	**Year 4 40%**	**Year 5 50%**
Anticipated total number of MTA procedures per year	202	414	636	871	1,117
Procedures by Lesion Grouping					
1–3total cost per patient (90%)	181	372	573	784	1,005
3–5 lesions total cost per patient (10%)	20	41	64	87	112
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	202	414	636	871	1,117
MTA MBS Costs by Lesion Grouping					
1–3total cost per patient (90%)	549,161	1,126,565	1,733,634	2,371,868	3,042,840
3–5 lesions total cost per patient (10%)	65,554	134,480	206,946	283,133	363,228
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	614,715	1,261,044	1,940,581	2,655,001	3,406,068

Uptake estimate	Year 1 10%	Year 2 20%	Year 3 30%	Year 4 40%	Year 5 50%
SBRT MBS Costs by Lesion Grouping					
1–3total cost per patient (90%)	815,107	1,672,134	2,573,194	3,520,509	4,516,418
3–5 lesions total cost per patient (10%)	96,829	198,638	305,678	418,213	536,520
>5 lesions total cost per patient (0%)	0	0	0	0	0
Total	911,937	1,870,773	2,878,872	3,938,722	5,052,938
Net MBS Costs	**-297,221**	**-609,728**	**-938,292**	**-1,283,721**	**-1,646,870**

< MBS= Medicare benefits schedule; MTA= microwave tissue ablation; SBRT = stereotactic body radiotherapy>

E.5. FINANCIAL IMPLICATIONS FOR GOVERNMENT HEALTH BUDGETS

Implementing the proposed MBS items has financial implications for other parts of the Australian Government's health budget. There are also impacts on state and territory Government health budgets, including public hospitals, and private insurance.

Costs to the PBS

The protocol notes that NICE recommends the consideration of chemoradiotherapy for patients with stage II or III NSCLC who are not suitable for surgery (The National Institute for Health Care and Excellence (NICE) 2011). Both SBRT and MTA treated patients could utilise chemoradiotherapy, therefore net impacts on the PBS are likely to be minimal.

State and Territory Health and Private Insurance Budgets

The costs of the MTA machine, and probes are borne by private health funds, patients or hospitals (state and territory budget). The base case estimate assumes the number of MTA patients increases from 202–1,117 per year, leading to a total cost of the machines of $0.05 million in year 1 increasing to $0.28 million in year five. The cost of probes and hospital stays also increase. Probes are the largest cost item —increasing from $0.60 million in Year 1 to $3.31 million in Year 5. The total cost to private health funds and hospitals in year 5 is $13.42 million.

Table 87 Total Costs of the MTA Machine and Probes and Hospital Stay

	Unit	Year 1	Year 2	Year 3	Year 4	Year 5
Number of MTA procedures	No.	202	414	636	871	1,117
Hospital stay costs	$	187,922	385,508	593,246	811,648	1,041,254
Cost of probes	$	596,769	1,224,230	1,883,928	2,577,491	3,306,631
Cost of MTA machines	$	50,403	103,398	159,116	217,694	279,276
Total Costs to private health funds	**$**	**835,094**	**1,713,136**	**2,636,290**	**3,606,833**	**4,627,162**

< MTA = microwave tissue ablation >

E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

The budget impact model presented in this section provided a base case with a relatively high estimate of early stage NSCLC as a proportion of overall lung cancer. The high estimate was justified based on the study by Barton et al (2013) and provided an upper bound on financial impact. Using a lower proportion of 63 per cent decreases the MBS cost savings to $1.22 million in Year 5, compared to $1.65 million for the base case (85%). Financial impacts are relatively small, just as increasing uptake of patients with primary and secondary cancer. If both populations one and two were equivalent in size, the number of MTA procedures would be 2,031 patients per year by Year 5. The net MBS cost saving in Year 5 would be $2.99 million.

Table 88 Sensitivity analysis

	Year 1	Year 2	Year 3	Year 4	Year 5
Base case					
Number of MTA procedures per year	202	414	636	871	1,117
Total cost associated to MBS Services	-297,221	-609,728	-938,292	-1,283,721	-1,646,870
Total costs toprivate and hospitals	835,094	1,713,136	2,636,290	3,606,833	4,627,162
63% of lung cancer NSCLC					

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of MTA procedures per year	149	307	472	645	828
Total cost associated to MBS Services	-220,293	-451,916	-695,440	-951,464	-1,220,621
Total costs to private and hospitals	618,952	1,269,736	1,953,956	2,673,300	3,429,543
Populations 1 and 2 equivalent					
Number of MTA procedures per year	367	752	1,157	1,583	2,031
Total cost associated to MBS Services	-540,402	-1,108,597	-1,705,985	-2,334,039	-2,994,309
Total costs to private and hospitals	1,518,353	3,114,792	4,793,254	6,557,878	8,413,021
75% uptake					
Number of MTA procedures per year	302	620	955	1,306	1,676
Total cost associated to MBS Services	-445,832	-914,593	-1,407,437	-1,925,582	-2,470,305
Total costs to private and hospitals	1,252,641	2,569,703	3,954,434	5,410,250	6,940,742
Adverse events					
Number of MTA procedures per year	202	414	636	871	1,117
Total cost associated to MBS Services	-251,969	-516,897	-795,436	-1,088,274	-1,396,133
Total costs to private and hospitals	940,682	1,929,743	2,969,619	4,062,878	5,212,215

< MBS= Medicare benefits schedule; MTA= microwave tissue ablation; NSCLC = non=small cell lung cancer >

SECTION F OTHER RELEVANT CONSIDERATIONS

RFA PLUS RADIOTHERAPY OR BRACHYTHERAPY

The systematic literature search identified three Level IV studies that investigated the combined use of RFA or MTA with radiotherapy and/or brachytherapy in patients with inoperable early stage NSCLC (Chan et al 2011; Dupuy et al 2006; Grieco et al 2006). While these studies did not meet the inclusion criteria for this review, they represent plausible scenarios in Australian clinical practice. Combined RFA plus brachytherapy or radiotherapy resulted in 2-year overall survival rates of 50–73% (median 53%). The study characteristics and results of these trials are outlined in Table 89.

Table 89 Studies of RFA plus adjuvant RT or brachytherapy in patients with early stage inoperable NSCLC

	Dupuy et al (2006)	Grieco et al (2006)	Chan et al (2011)
Study design	Level IV retrospective CS Risk of bias: High Median follow-up 26.7 months	Level IV retrospective CS Risk of bias: High Median follow-up 19.5 months	Level IV retrospective CS Risk of bias: High Median follow-up 22 months
Population	Early stage inoperable NSCLC N = 24 Male 10 (42%):Female 14 (58%) Mean age 76 (58–85) years	Early stage inoperable NSCLC N = 41 Male 24 (59%):Female 17 (41%) Median age 76 (55–81) years	Early stage inoperable NSCLC N = 17 Male 7 (41%):Female 10 (59%) Mean age 74 ± 8.8 years
Intervention	CT-guided RFA Local anaes + conscious sedation Average 6.8 min per ablation (range 1–12 min) Radiotherapy RT dose 66 Gy in 33 fractions	CT-guided RFA Local anaes + conscious sedation RFA average time 6 min (range 1–12 min), Power 128.8 W RT (n = 27) or brachytherapy (n = 14) RT dose 66 Gy in 33 fractions Brachytherapy dose 18–20 Gy	CT-guided RFA Local anaes + conscious sedation Average 2 ablations per session (range 1–5 ablations), average 7 min per ablation (range 1–12 min) Brachytherapy Single-dose, median dose 18 (range 14.4–20) Gy
Comparator	N/A	N/A	N/A
Outcomes	Safety Pneumothorax 7/24 Chest tube 3/24 Acute respiratory distress 0/24 Self-limiting haemoptysis 1/24 Acute RT toxicity 0/24 Asymptomatic RT fibrosis 2/24	Safety Pneumothorax 15/41 Chest tube 9/41 Empyema 1/41 Acute respiratory distress 2/41 Self-limiting haemoptysis 2/41 Effectiveness	Safety Pneumothorax 11/17 Chest tube 5/17 Pleural effusion 3/17 Empyema 1/17 Pneumonia 1/17 (died <30 days) Radiation pneumonitis 0/17

	Dupuy et al (2006)	Grieco et al (2006)	Chan et al (2011)
	Effectiveness 1-year survival 85% 2-year survival 50% 5-year survival 39% Median survival NR	1-year survival 87% 2-year survival 70% 3-year survival 57% Median survival 42 ± 5 months	Intrapulmonary haemorrhage 0/17 Treatment-related mortality 0/17 Effectiveness 2-year survival 53% Median survival 21 months

< Anaes = anaesthetic. CS = case series. CT = computed tomography. MTA = microwave tissue ablation. N/A = not applicable. NR = not reported. NSCLC = non-small cell lung cancer. RFA = radiofrequency ablation. RT = radiotherapy >

ETHICAL ISSUES

The absence of prospective RCTs identified in this review is reflective of the ethical challenges of conducting research on patients with lung cancer. The concept of clinical equipoise – i.e. the presence of genuine uncertainty around the benefits of one treatment over another – underpins arguments against RCTs in this group (Freedman 1987). Conducting RCTs on new therapies for lung cancer is contentious due to a perceived lack of clinical equipoise (Allmark and Tod 2016), whereby the benefits of existing therapies, surgery and SBRT, are thought to be superior to other ablative therapies. In the context of this review, this argument does not appear to be substantiated by the presence of high-level data for current therapies. While there is changing opinion that RCTs have now become necessary to inform the appropriate management of lung cancer (Fiorentino et al 2010), the perceived lack of clinical equipoise remains a significant barrier to prospective research. Authors of prospective trails have also noted difficulties recruiting patients into studies that compare such drastically different interventions such as MTA, surgery and radiotherapy (Falk et al 2015). Consequently, the lack of RCTs comparing MTA and RFA to established therapies has resulted in significant uncertainty regarding their clinical effectiveness.

In the context of such uncertainty, the short-term risks of approving a service with limited evidence should be considered against the delay of waiting for more robust data (Siebert et al 2013). However, the present application is complicated by weaknesses in the evidence base for both the proposed intervention and existing services. While this review was not intended to systematically review the available evidence for surgery and radiotherapy in isolation, targeted searches identified a paucity of RCT evidence for any intervention, including both diffused and emerging services.

For primary cancer, current practice reflects treatment goals of cure or prolonged survival, and, surgical resection is believed to offer patients their best chance at both. The limited evidence available for early stage NSCLC shows that treatment is better than no treatment in terms of overall survival time from diagnosis (Koshy et al 2015). However, for patients who are not eligible for surgical therapy there are a range of non-invasive treatment options that have not been robustly

compared against one another, or to surgery. Therapies such as radiotherapy have become accepted based on physician experience with these modalities, results of small, uncontrolled trials and the understanding of the impact of not intervening.

In the setting of oligometastatic disease in the lung, even the benefit of surgery is uncertain (Fiorentino et al 2010), and searches did not identify any comparative evidence. Equally important is a dearth of any information regarding patient wellbeing after resection, particularly as patients often undergo repeated resections. Local opinion from a cardiothoracic surgeon suggests that patient lung function and quality of life are not materially impacted following wedge resection of the lung. Following from the assumption that intervention is associated with prolonged survival, radiotherapy has also become an accepted therapy in the management of oligometastatic disease.

The relevant considerations in the context of this assessment are:

- First, it is assumed that randomised trials are unlikely due to the accepted effectiveness of established therapies. However, randomised or pseudo-randomised trials are the best available methods by which to validate accepted, but unproven, treatments. Without such evidence, it is difficult to establish the comparative benefits or harms of current or future services.
- Second, although the volume of evidence for MTA is extremely limited it is not necessarily of a poorer quality than the evidence available for other currently accepted services. The intervention is a potentially attractive therapeutic option for patients in terms of convenience, no or limited requirement for repeat intervention, short recovery times and limited side effects.
- Third, cancer is a life-threatening disease. Treatments that pose little harm with uncertain effectiveness do not necessarily need high quality evidence to form a strong recommendation for use. However, once therapies become established without strong evidence it is not clear how emerging technologies should be evaluated in comparison. The limitations within the clinical evidence prohibit robust engagement with the comparative therapeutic performance of each intervention.

POLICY CONSIDERATIONS

As noted in Section E, the number of patients likely to use MTA if listed on the MBS is difficult to define. MTA is not widely used in Australian clinical practice. Several reasons have been posited by clinical experts, including a lack of MBS funding, perceived inferior effectiveness compared to SBRT, or inappropriate/small numbers of eligible patients.

Estimates based on clinical input suggest it is currently used in approximately 20 sites across the country, on 20–50 patients per year in large centres. It is possible that MBS listing of the technology may increase its utilisation rate; however, this ultimately depends on a number of factors. Clinical input suggests that MTA is currently used in patients who are not ideal candidates for radiotherapy or surgery. Reasons might include the location of their tumour(s), comorbidities precluding surgery or patients having reached maximum radiation exposure. In this sense, MTA is providing a therapeutic option to patients who have limited alternatives, and could be seen as a complimentary or adjunctive treatment. Further to this, the literature search also identified experimental studies in which thermal ablation was combined with radiotherapy (Dupuy et al 2006; Grieco et al 2006). These studies showed that there was no added toxicity or morbidity from combining the treatments. This was also confirmed by a later study combining RFA with brachytherapy (Chan et al 2011). It is not clear how the use of thermal ablation technologies would change in the setting of reimbursement.

In practice, it appears that decisions regarding treatment approaches are generally made by multi-disciplinary teams who take into account the expected benefits and harms of each treatment option. The approach of these teams to treatment may be affected by the reimbursement status of thermal ablative options. Currently, the use of MTA seems to be largely confined to the public system; however, this would be expected to change if the treatment was listed on the MBS.

A further consideration is the management of oligometastatic disease. There is a range of opinion presented in the peer-reviewed literature on:

- whether oligometastases should be treated aggressively;
- under what conditions oligometastases are amenable to potential cure; and
- the best treatment options for oligometastatic disease.

The literature reflects changes in practice that favour the aggressive treatment of metastases in the lung in patients with one to five lesions, a primary cancer that is controlled or amenable to control and absent or controlled extra thoracic metastases (Treasure 2012; Treasure et al 2012). As the oligometastatic state becomes an increasingly accepted indication for treatment of lung cancer in Australia and internationally, it is expected that demand for SBRT, surgical resection and potentially other therapies such as MTA will increase (The Tripartite Committee 2012).

It should also be considered that although the proposed service for public funding is MTA, and the evidence for this technology is limited, the evidence base for thermal ablation as a whole (including RFA and MTA) is more voluminous. The clinical benefits of MTA compared to RFA are not borne out in the evidence base due to a lack of comparative data, but they appear to have a similar safety profile. However, clinicians suggest MTA is the preferred tool for thermal ablation in the lung because it offers interventionists larger, more predictable ablation volumes in shorter times.

NON-CLINICAL BENEFITS AND PATIENT ACCESS

A key non-clinical benefit of MTA compared to radiation therapy is the duration of treatment, i.e. one treatment session versus multiple. However, the duration of radiation therapy depends on the type of therapy offered. Clinical feedback indicates that SBRT is the preferred radiotherapy modality in patients with lung cancer. Compared to conventional radiotherapy, SBRT offers higher radiation doses in significantly fewer sessions (1–10 versus 30–45 sessions), and with a higher degree of tissue sparing. However, the delivery of SBRT requires a highly specialised workforce and expensive infrastructure. According to the Tripartite National Strategic Plan for Radiation Oncology 2012–2022, SBRT is offered in 11 centres (21%) in Australia (The Tripartite Committee 2012). The majority (82%) of stereotactic equipment is located in public sector facilities, with the remainder (18%) located at privately owned facilities. According to the report, the Australian Capital Territory, Northern Territory and Tasmania do not offer any stereotactic services.

Radiation therapy may involve greater indirect costs compared to MTA due to the increased number of treatment sessions, particularly for patients who live in rural or remote areas or who do not have access to SBRT. These include childcare, accommodation, travel, and time away from work. The cost savings associated with less travel and lost productive time are not explored in the cost minimisation analysis. However, it may be that MTA could be made available to patients more easily and may have significant benefits over conventional radiotherapy treatments in terms of these indirect costs. Where SBRT is not available, the convenience offered by MTA may be seen as an important benefit compared to conventional radiotherapy.

ONGOING CLINICAL TRIALS

A search of clinical trials identified one comparative trial of MTA (NCT02455843), and one single arm trial of MTA (NCT02673021) that are current recruiting:

1. NCT02455843, Microwave Plus Chemotherapy Versus Chemotherapy for Advanced NSCLC. This trial is currently recruiting participants and is a multicentre, randomised, open-label phase III trial comparing MTA with chemotherapy versus chemotherapy alone in patients with advanced NSCLC.
2. NCT02673021, MARK 1A Series: Percutaneous Microwave Ablation for Patients With Lung Tumor(s) (MARK 1A). This trial is currently recruiting participants and is a single arm trial enrolling patients with lung cancer who are at a high risk for surgery.

Appendix A Clinical Experts and Assessment Group

ASSESSMENT GROUP

Name	Position
Alun Cameron	Research Manager, Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S), Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Robyn Lambert	Senior Research Officer, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Thomas Vreugdenburg	Senior Research Officer, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Ross McLeod	Director, eSYS Development Pty Limited, Sydney, New South Wales, Australia
Yasoba Atukorale	Research Officer, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Meegan Vandepeer	Research Officer, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Nicholas Marlow	Team Leader, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia
Anje Scarfe	Research Officer, ASERNIP-S, Royal Australasian College of Surgeons, Adelaide, South Australia, Australia

CLINICAL EXPERTS

During the course of the assessment clinical input was obtained from a range of local experts in the fields of oncology, interventional radiology, radiation oncology and cardiothoracic surgery.

CONFLICTS OF INTEREST

The review authors and clinical experts have no conflicts of interest to disclose.

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
Embase	Search for MTA and RFA: inception – 01/06/2016
Medline (via PubMed)	Search for MTA and RFA: inception – 01/06/2016 Search for radiotherapy: 01/01/2006 – 15/06/2016 Search for surgery: 01/01/2006 – 28/06/2016
The Cochrane Library (CDSR, Central, DARE, HTA, HEED)	Search for MTA and RFA: inception – 01/06/2016
The University of York Centre for Reviews and Dissemination	Search for MTA and RFA: inception – 01/06/2016

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
Australian Clinical Trials Registry	www.anzctr.org.au
ClinicalTrials.gov	www.clinicaltrials.gov
the World Health Organisation International Clinical Trials Registry Platform	www.who.int/ictrp/en

SEARCH STRATEGIES

Search 1: Microwave ablation executed in PubMed, Embase, The Cochrane Library (CDSR, Central, DARE, HTA, HEED), and The University of York Centre for Reviews and Dissemination

Population terms were combined with intervention terms using the AND function

Element of clinical question	Search terms
Population	#1 Lungs [MeSH and Emtree] #2 Pulmonary #3 Lung* #4 Pneumo* #5 #1 OR #2 OR #3 OR #4 #6 Neoplasms [MeSH and Emtree]

Element of clinical question	Search terms
	#7 Cancer* #8 #6 OR #7 #9 #5 AND #8 #10 Neoplasm metastasis [MeSH], Emtree = metastasis #11 Metastasis #12 Metastases #13 #10 OR #11 OR #12 #14 #5 AND #13 #15 Lung neoplasm [MeSH], Emtree = lung tumor #16 Carcinoma, non small cell lung [MeSH], Emtree = Non small cell lung cancer #17 Non-small cell lung cancer #18 Non small cell lung cancer #19 #9 OR #14 OR #15 OR #16 OR #17 OR #18
Intervention	#20 Ablation #21 Ablative #22 Coag* #23 #20 OR #21 OR #22 #24 Ablation, catheter [MeSH], Emtree = Ablation therapy OR tumor ablation OR ablation catheter OR catheter ablation OR ablation #25 #23 OR #24 #26 Microwave [MeSH], Emtree= Microwave OR microwave radiation #27 Microwave #28 MTA #29 MWA #30 #26 OR #27 OR #28 OR #29 #31 #25 AND #30
Comparator (if applicable)	NA
Outcomes (if applicable)	NA
Limits	English language

Search 2: Radiofrequency ablation executed in PubMed, Embase, The Cochrane Library (CDSR, Central, DARE, HTA, HEED), The University of York Centre for Reviews and Dissemination

Population terms were combined with intervention terms using the AND function

Element of clinical question	Search terms
Population	#1 Lungs [MeSH and Emtree] #2 Pulmonary #3 Lung* #4 Pneumo* #5 #1 OR #2 OR #3 OR #4 #6 Neoplasms [MeSH and Emtree] #7 Cancer* #8 #6 OR #7 #9 #5 AND #8 #10 Neoplasm metastasis [MeSH], Emtree = metastasis #11 Metastasis #12 Metastases #13 #10 OR #11 OR #12 #14 #5 AND #13 #15 Lung neoplasm [MeSH], Emtree = lung tumor #16 Carcinoma, non small cell lung [MeSH], Emtree = Non small cell lung cancer #17 Non-small cell lung cancer #18 Non small cell lung cancer #19 #9 OR #14 OR #15 OR #16 OR #17 OR #18
Intervention	#20 Ablation #21 Ablative #22 Coag* #23 #20 OR #21 OR #22 #24 Ablation, catheter [MeSH], Emtree = Ablation therapy OR tumor ablation OR ablation catheter OR catheter ablation OR ablation #25 #23 OR #24 #26 Radiofrequency #27 Radio-frequency #28 RFA #29 #26 OR #27 OR #28 #30 #25 AND #29
Comparator (if applicable)	NA

Element of clinical question	Search terms
Outcomes (if applicable)	NA
Limits	English language

Search 3: Radiotherapy executed in PubMED

Population terms were combined with intervention terms and outcome terms using the AND function

Element of clinical question	Search terms
Population	#1 Carcinoma, Non-Small-Cell Lung [mh and txt] #2 NSCLC #3 #1 OR #2 #4 early stage #5 stage I #6 stage IIa #7 #4 OR #5 OR #6 #8 #3 AND #7 #9 Neoplasm Metastasis [mh] #10 Metastasis OR metastases #11 oligometastases OR oligometastasis OR oligometastatic #12 #9 OR #10 OR #11 # 13 pulmonary OR lung #14 #12 AND #13 #15 #8 OR #14
Intervention	#1 Stereotactic AND radiotherapy #2 radiosurgery OR SBRT OR SABR) #3 CHART OR Continuous Hyperfractionated Accelerated Radio Therapy OR Continuous Hyperfractionated Accelerated radiotherapy #4 Radical AND radiotherapy #5 IGRT OR (image guided AND (radiation therapy OR radiotherapy)) #6 IMRT OR (intensity modulated AND (radiation therapy OR radiotherapy)) #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
Comparator (if applicable)	NA
Outcomes (if applicable)	#1 Surviv* #2 Recurrence

Element of clinical question	Search terms
	#3 Progression #4 Mortality #5 Discomfort #6 Time #7 Quality of life OR QoL OR HRQoL OR Health-related quality of life) OR (Patient reported outcomes OR PROM) #8 Local AND control #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
Limits	English language, published in the last 10 years

Search 4: Surgery executed in PubMED

Element of clinical question	Search terms
Population	#1 Neoplasm Metastasis [mh] #2 Metastasis OR metastases #3 oligometastases OR oligometastasis OR oligometastatic #3 #1 OR #2 OR #3 #4 pulmonary OR lung #5 #3 AND #4
Intervention	#1 Surg* AND resect* #2 pulmonary surgical procedures [mh and text] #3 Lobectomy #4 Wedge resection #5 Video-assisted thoracic surgery [mh and text] #6 Thoracotomy #7 Sternotomy #8 Clamshell #9 Metastasectomy #10 Sleeve resection #11 Segmentectomy #12 Thoracotomy #13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
Comparator (if applicable)	NA

Element of clinical question	Search terms
Outcomes (if applicable)	#1 Surviv* #2 Recurrence #3 Progression #4 Mortality #5 Discomfort #6 Time #7 Quality of life OR QoL OR HRQoL OR Health-related quality of life) OR (Patient reported outcomes OR PROM) #8 Local AND control #9 safety #10 complication #11 adverse event #12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
Limits	English language, published in the last 10 years

LITERATURE SEARCH TO INFORM THE ECONOMIC ANALYSES

Literature search strategies used to identify microwave economic studies

Search terms		MEDLINE Citations retrieved	EMBASE Citations retrieved	Global Health Citations retrieved
#1	exp microwave/	14566	18519	5151
#2	(Acculis or Sulis or Avecure or Amica or Emprint or Microsulis).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	38	167	5
#3	lung/ or lung metastasis/ or lung carcinoma/ or lung cancer/ or non small cell lung cancer/ or lung.mp. or squamous cell lung carcinoma/ or pulmonary.mp or lung neoplasm.mp. or exp lung tumor/	970657	1486743	82634
#4	exp economics/ or exp "costs and cost Analysis"/ or utility.mp or exp health economics or exp quality adjusted life year/ or exp QALY/ or cost utility analysis"/ or "cost benefit analysis"/ or "cost minimization analysis"/ or cost.mp. or "cost"/ or "cost effectiveness analysis"/ or "cost of illness"/	342525	941251	55008

Search terms		MEDLINE Citations retrieved	EMBASE Citations retrieved	Global Health Citations retrieved
#5	#1 OR #2	14544	18647	5156
	Microwave Ablation			
#6	#5 AND #4 AND #3	2	9	-
	Studies identified via checking references	-		
Inappropriate study type: the article did not report the structure or results or didn't consider MTA, RFA or Radiotherapy in an economic evaluation		2	9	-
Number of included publications		-	-	-

No studies were found that investigated the cost effectiveness of MTA.

Literature search strategies used to identify RFA economic studies

Search terms	MEDLINE Citations retrieved	EMBASE Citations retrieved	Global Health Citations retrieved	Search terms
#9	ablation.mp. or radiofrequency ablation device/ or ablation device/ or tumor ablation/ or ablation therapy/ or radiofrequency ablation/	67205	125620	1701
#10	#9 AND #4 AND #3	63	418	-
	Studies identified via checking references	-		
Inappropriate study type: the article did not report the structure or results or didn't consider MTA, RFA or Radiotherapy in an economic evaluation		60	418	-
Number of included publications		**3**	**4**	**-**

Literature search strategies used to identify radiotherapy economic studies

	Search terms	MEDLINE Citations retrieved	EMBASE Citations retrieved	Global Health Citations retrieved
#11	Radiosurgery/ or Radiotherapy/ or Stereotactic.mp.	201680	400,124	143,503
#12	#11 AND #4 AND #3	2236	2047	375
	Studies identified via checking references		-	
Inappropriate study type: the article did not report the structure or results or didn't consider MTA, RFA or Radiotherapy in an economic evaluation		2232	2038	375
Number of included publications		**4**	**9**	**-**

Literature search strategies used to identify surgery economic studies

	Search terms	MEDLINE Citations retrieved	EMBASE Citations retrieved	Global Health Citations retrieved
#13	resection or surgery or lobectomy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1,080,303	2,158,273	64,336
#14	#13 AND #4 AND #3	1384	5502	100
	Studies identified via checking references		-	
Inappropriate study type: the article did not report the structure or results or didn't consider MTA, RFA or Radiotherapy in an economic evaluation		1382		
Number of included publications		**2**	**8**	**-**

Between 2-8 studies were found on each database relating to RFA, radiotherapy or surgery. Many were duplicates, particularly for EMBASE and MEDLINE, or were economic analyses comparing the listed interventions. Eleven key studies are summarised in the main text of the report.

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Table 90 Profiles of studies on MTA included in the systematic literature review

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
POPULATION 1				
Han et al (2015) China	CS (enrolment NR) Level IV Risk of bias: High 22.5 (4–53) months	Patients with stage I NSCLC, aged > 75 years, inoperable N = 28 (28 lesions) Maximum tumour diameter > 35 mm in 7 (25%), maximum diameter ≤ 35 mm in 21 (75%) Males 18 (64%): Females 10 (46%) Mean age 77 (range NR) years Comorbidities: COPD (6, 21.4%); chronic cor pulmonale (1, 3.6%); hypertension (9/28, 32.1%); coronary heart disease (10, 35.7%); cardiovascular disease (3, 10.7%); diabetes (7, 25%); silicosis (1, 3.6%); declined surgery (3, 10.7%)	Intervention: CT-guided MTA Local anaesthesia 28 ablation sessions duration: NR Comparator: N/A	1. Overall survival: Kaplan-Meier test (for all survival outcomes) 2. Local efficacy: assessed using criteria outlined by Ye et al (2015) 3. Local recurrence: identified by CT, time point NR. 3. Adverse events: reported according to terminology outlined by Ahmed et al (2014)and Goldberg et al (2005)
Liu & Steinke (2015) Australia	Retrospective CS Level IV Risk of bias: High Hospital setting 12 (6–18) months	Patients with stage Ia or Ib NSCLC, medically inoperable and less than 40 mm in size N = 15 (16) Median tumour size (range): 24 (8–40) mm M/F ratio: 11:4 median age 73 (range 52–88) years Comorbidities: NR	Intervention: CT-guided MTA Conscious sedation with local anaesthesia Median duration (range): 2.5 (0.5–7) min/ablation Comparator: N/A	1. Treatment outcome: evaluated by RECIST criteria based on follow-up CT and PET-CT imaging. Judged by comparing the limited CT scan on the day post-ablation with follow-up imaging 2. Adverse events: NR

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Yang et al (2014) China	Retrospective CS Level IV Risk of bias: High Hospital setting 30 (7–70) months	Patients with stage Ia or Ib peripheral NSCLC, who were medically inoperable or declined surgery N = 47 (47) Maximum tumour sixe > 35 mm in 24, ≤ 35 mm in 23 Male/Female ratio: 29:18 Mean age 69.4 (range 56–82) years Comorbidities (n, %) were: pulmonary disease (19, 40.4%), cardiovascular disease (39, 83%), diabetes mellitus (16, 34%), renal insufficiency (2, 4.3%), refusal of surgery (1, 2.1%)	Intervention: CT-guided MTA Local anaesthesia Duration: preset ablation time was 6–8 minutes Comparator: N/A	1. Overall survival and local control: Kaplan-Meier test (for all survival outcomes) 2. Local progression: defined as the contrast enhancement by CT scans in the site of ablation 3. Therapeutic outcome of MTA: measured using the modified RECIST criteria 4. Adverse events: reported according to terminology outlined by Ahmed et al (2014) and Goldberg et al (2005)
POPULATION 2				
Qi et al (2015) China	Retrospective CS Level IV Risk of bias: High Hospital setting Mean: 14 (3–24) months	Patients with lung metastases (from nasopharyngeal carcinoma) whose primary lesions were in complete remission N = 17 (29) Tumour size: range: 8–42 mm Male/Female ratio: 15:2 Mean age 45.7 (range 28–65) years Prior treatments included (n, %): radical radiotherapy (all patients), neoadjuvant/adjuvant chemotherapy (14, (82%), failed systemic chemotherapy (10, 58.8%), recurrence after surgery (2, 11.8%)	Intervention: CT-guided MTA Anaesthesia: NR Duration: range of 5–10 minutes Comparator: N/A	1. Treatment response: ssessed by CT[d] 2. Local control: measured by number of new metastases inside the lung

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Vogl et al 2015 Germany	Prospective CS Level IV Risk of bias: High Hospital setting Mean: 9 (6–24) months	Patients with surgically unresectable lung metastases or recurrence after prior excision, whose primary lesions were under control N = 80 (130) Tumour volume: 2.9 mL range (0.25–8.2) Male/Female ratio: 30:50 Mean age 59.7 (range 48–68) years Primary tumour (patients/lesions): colorectal carcinoma (40/58), breast carcinoma (20/32), hepatocellular carcinoma (10/30), renal cell carcinoma (5/5), bronchogenic carcinoma (5/5), prior treatments (n, %): (5, 56.3%) surgical resection of primary cancer (45, 56.3%), systemic chemotherapy (45, 56.3%), radiation therapy for primary cancer (13, 16.3%), surgical resection of liver metastases (22, 27.5%) surgical resection of lung metastases (5, 6.3%), mastectomy (20, 25%), chemotherapy plus hormone therapy (7, 8.8%),lobectomy or segmentectomy (3, 3.8%), transarterial chemoablation, total or partial nephrectomy(5, 6.3%), radiation therapy non specified (3, 3.8%)	Intervention: CT-guided MTA Conscious sedation Duration: mean 15 minutes (range: 10–30) Comparator: N/A	1. Local tumour response: evaluated by measurements of maximal axial dimensions, tumour volumetric changes, and contrast enhancement patterns on follow-up images 2. Success or failure of ablation: the contrast enhancement pattern[d] 3. Survival times: Kaplan-Meier test. 4. Peri procedural adverse events: estimated by classifying pneumothorax[e]
POPULATION 3				

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Ni et al (2015) China	Retrospective CS Level IV Risk of bias: High Hospital setting 17.7 (6–45) months	Patients with stage IIIB-IV NSCLC who had had prior treatment including chemotherapy, targeted therapy, concurrent chemo-radiation followed by chemotherapy, and, who had partial response or stable disease N = 35 (39) Mean tumour size 30 mm (range 10–110) M/F ratio: 25:10 Mean age: 59 (range 34–71) years, Performance status: ECOG 0–1 in 22 and 2 in 13.	Intervention: CT-guided MTA following first-line chemotherapy[f] Local anaesthesia Duration: NR Comparator: N/A	1. Response to initial MTA: classified as complete ablation and incomplete ablation 2. Technical efficacy (local efficacy) was complete ablation of macroscopic tumour and/or symptoms relieved. If not achieved within four procedures or 3 months, it was classified as a technical failure 3. Adverse events: reported according to the Common Terminology Criteria for Adverse Events v4.03 of the National Cancer Institute 4. Overall survival: Kaplan–Meier analysis
Sun et al (2015) China	Prospective non-randomised comparative trial Level III-2 Risk of bias: High Hospital setting Range: 6–35 months	Patients with stage IIIB-IV NSCLC N = 22 intervention arm, N = 18 comparator arm Total number of lesions 46, mean maximum diameter: 36 mm (range 11–68) Male/Female ratio: 26/14 (all patients) Mean age: 64.25 (range 32–74) years Performance score (ECOG) 0–2 for all patients.	Intervention: CT-guided MTA Anaesthesia NR Duration: NR Comparator: CT-guided MTA in combination with chemotherapy[g] Anaesthesia NR Duration of MTA: NR	1. Local efficacy: classified as complete ablation and incomplete ablation according to Ye et al (2015) 2. 1 and 2-year survival: Kaplan-Meier test 3. Disease control: disease control rate (DCR) was equal to CR+PR+SD 4. Adverse effects of chemotherapy drugs were assessed in accordance with the WHO Anticancer Drugs Toxic Reaction Criteria

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Wei et al (2015) China	Retrospective non-randomised comparative trial Level III-2 Risk of bias: High Hospital setting 21.0 (5.1–39.2) months	Patients with stage IIIB-IV NSCLC N = 46 intervention, N = 28 comparator Total number of lesions: NR Mean maximum diameter intervention: 37 mm (range 10–70), comparator: 43 (12–110) Male/female ratio intervention: 27:19, comparator: 18:10 Mean age (intervention) < 60 in 19, > 60 in 27, mean age (comparator) <60 in 17 and > 60 in 11 years Performance score (intervention): ECOG 0–1 in 43 and 2 in 3, performance score (comparator): ECOG 0–1 in 26, 2 in 2	Intervention: CT-guided MTA in combination with chemotherapy[h] Duration of MTA: NR Comparator: Chemotherapy alone[i] Anaesthesia: NA Duration: NA	1. Response to chemotherapy: Classified as CR, PR, SD, and PD according to RECIST 1.1 2. TTLP: calculated from the time of ablation of primary tumours to local progression 3. PFS was calculated from the start of anticancer treatment, including chemotherapy and MTA, to disease progression, including progression in ablative sites, distant metastases, or death 4. Adverse events of MTA and chemotherapy were assessed according to the National Cancer Institute Common Toxicity Criteria version 3.0.
MIXED SAMPLES				
Alexander et al (2013) United States of America	Retrospective CS Level IV Risk of bias: High Hospital setting Mean (SD): 20.0 (15.2) months	Patients with lung neoplasms treated with MTA and/or RFA at a single institution N = 163 (195) Mean (range): 25.6 (6–76) mm M/F ratio: 85:78 Mean age (range): 73 (43–94) years Primary/metastatic: 131 had primary lung tumours, 32 had metastatic tumours	Intervention: MTA/RFA under CT guidance (113 tumours treated by RFA, 74 tumours treated by MTA, 8 tumours treated by RFA and MTA) Conscious sedation Duration: NR Comparator: N/A	1. Incidence of rib fracture: three board-certified Radiologists retrospectively reviewed CT and/or PET/ CT images after ablation for the presence of rib fractures in the vicinity of the ablation zone, not related to tumour invasion

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Belfiore et al (2013) Italy	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with primary or secondary lung cancer who were not suitable for surgical procedures due to tumour extension or concomitant disease N = 56 (69) Maximum diameter mean (SD): 30 (9) M/F ratio: 35:21 Mean age (SD): 61.5 (9.13) years 44 patients had lung cancer (31 adenocarcinomas, 10 squamous carcinomas, 3 small cell carcinomas). 12 patients had metastatic disease (9 had primary colorectal cancer and 3 had primary breast cancer)	Intervention: CT-guided MTA Conscious sedation Duration: 6–10 minutes Comparator: N/A	1. Adverse events: non-specified
Carafiello et al (2014) Italy	Retrospective CS Level IV Risk of bias: High Hospital setting mean (range): 9.9 months (3–26)	Patients with NSCLC stages IA-IV or metastases, all patients judged to be inoperable or refusing surgery N = 24 (26) Mean index of max diameter (range): 30.96 (8–100) mm M/F ratio: 15:9 Mean age (range): 71.7 (46–83) years Primary cancers were: 6 squamous cell, 7 adenocarcinomas, 1 neuroendocrine carcinoma. There were 11 metastases and 1 microcytoma.	Intervention: CT-guided MTA Conscious sedation Duration: NR Comparator: N/A	1. Safety: defined as the frequency of intra-, peri- and post-procedural adverse events. All patients were evaluated for the presence of post ablation syndrome. Pain was evaluated with VAS

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Carafiello et al (2012) Italy	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with primary or secondary lung tumours treated by MTA or RFA, Patients were judged to have inoperable disease or refused surgery N = 16 with MTA (17) Mean tumour size(range): 37.5 (28–47) mm M/F ratio: NR Mean age (range): 74.75 (40–84) years Reasons for inoperability: 9 based on advanced stage, 6 comorbidities, 1 with metastases from an advanced primary	Intervention: CT-guided MTA Conscious sedation Duration: total ablation time of 10 minutes Comparator: N/A	1. Adverse events: Classified as side effects and major and minor adverse events in accordance with the classification proposed by the Society of Interventional Radiology (SIR). Patients were evaluated for the presence of post ablation syndrome and pain was measured with VAS.
Chung et al 2014 United Kingdom	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with lung tumours treated by MTA underperformed with normal respiration under conscious sedation (NR-CS) or high-frequency jet ventilation under general anaesthesia (HFJV-GA) N = 39 (63) Mean (SD) tumour size NR-CS: 27.38 (14.73), HFJV-GA: 16.09 (9.21) M/F ratio: 24:15 Mean age HF JV-GA (range): 66.39 (12.20), NR-CS: 69.15 (15.59) years Other details NR	Intervention: Percutaneous MTA with HFJV under GA with CT guidance Anaesthesiologist time mean (SD): 27.78 (17.78) Comparator: Percutaneous MTA with NR under CS with CT guidance Anaesthesiologist time mean (SD): 21.08 (8.45)	1. Adverse events: defined according tothe standardization of terminology and reporting criteria set out by the International Working Group on Image- Guided Tumour Ablation

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Egashira et al 2016 United Kingdom	Retrospective CS Level IV Risk of bias: High Hospital setting 15 (6.2–29.5) months	Patients who underwent high-energy MTA of one or more pulmonary tumours of primary or secondary origin N = 44 (87) Tumour size median (range): 12 (6–45) M/F ratio: 21:23 Median age (range): 66(17–89) years Primary tumour: 23/44 (52.2%) sarcoma, 16/44 (36.4%) colorectal, 2/44 (4.5%) lung, 1/44 (2.3%) oesophagus, 1/44 (2.3%) breast, 1/44 (2.3%) bladder.	Intervention: CT-guided MTA Anaesthesia: NR Duration: median (range) 2 (1–9) minutes Comparator: N/A	1. Adverse events: defined based on the Society of Interventional Radiology (SIR) classification of adverse events
He et al (2006) China	Retrospective CS Level IV Risk of bias: High Hospital setting Mean: 20 (6–40) months	Patients with primary or secondary lung cancer who underwent MTA at a single centre N = 12 (16) Tumour size range: 20–60 mm M/F ratio: 7:5 Mean age (range): 47.5 (31–69) years Reasons for choosing MTA included refusal of surgery (5), poor cardiopulmonary reserve (3), severe side effects from prior chemotherapy and/or radiotherapy (4)	Intervention: US-guided MTA Local anaesthesia Duration: NR Comparator: N/A	1. Adverse events: non-specified

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Little et al (2013) United Kingdom	Retrospective CS Level IV Risk of bias: High Hospital setting 6 (3–19) months	Patients with primary cancer not suitable for resection and patients with oligometastatic lung lesions N = 23 (29) Tumour size- median (range): 19 (8–57) M/F ratio: 12:11 Mean age (range): 68 (30–87) years Primary cancers of the NSCLC patients (9 patients) were without evidence of nodal/metastatic disease. Patients with pulmonary metastases (14 patients) had primary tumours as follows: 5 colorectal, 5 sarcoma, 3 renal, 2 oesophageal, 3 adrenal, 1 melanoma, 1 digital papillary adenocarcinoma.	Intervention: CT-guided MTA Conscious sedation Duration: mean (range) 3.6 (1–9) min Comparator: N/A	1. Adverse events: non-specified
Lu et al (2012) China	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with stage IIIB NSCLC or metastatic pulmonary malignancies who were deemed medically inoperable and underwent MTA procedures N = 69 (93) Tumour size- mean (range): 22.3 (8–55) mm M/F ratio: 45:24 Mean (SD) age: 65 (15) years NSCLC patients: stage I 7/48 (14.6%), stage II 10/48 (20.8%), stage III 22/48 (45.8%), stage IV 9/48 (18.8%). Metastasis patients: breast cancer 3/21 (14.3%), prostate cancer 4/21 (19.1%), liver cancer 7/21 (33.3%), gastrointestinal cancer 7/21 (33.3%).	Intervention: CT-guided MTA Conscious sedation Duration: NR Comparator: N/A	1. Adverse events: within 30 days after ablation, and were classified in accordance with the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE)

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Nour-eldin et al (2011) Germany	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with primary NSCLC or secondary lung tumours deemed medically inoperable or where the patient had refused surgery. Patients with metastatic lung tumours were without evidence of extrapulmonary metastases N = 164 (NR, 248 ablation sessions) Tumour size: NR M/F ratio: 92:72 Mean (SD) age: 59.7 (9.8) years 20/248 (8.1%) of ablation sessions were for primary lesions, 228/248 (91.9%) were for metastatic lesions	Intervention: CT-guided MTA or RFA Conscious sedation Duration: NR Comparator: N/A	1. Pneumothorax: categorised as mild, moderate or severe
Sun et al (2014) China	Retrospective CS Level IV Hospital setting 25 (3–45) months	Patients with primary or metastatic lung cancer, primary cancers included stage I-IV lung cancer. Distant metastases of patients with stage IV cancer and primary tumours of patients with pulmonary metastases had achieved complete response or stable disease following prior therapy N = 29 (39) Tumour size - mean (range): 37 (15–58) mm M/F ratio: 12:12 Median (range) age: 63 (39–74) years Primary NSCLC patients: 7/15 (46.7%) stage I, 2/15 (13.3%) stage II, 4/15 (26.7%) stage III, 2/15 (13.3%) stage IV. Metastases patients: 8/14 (57.1%) intestinal adenocarcinoma, 4/14 (28.6%) liver cancer, 2/14 (14.3%) breast cancer.	Intervention: CT-guided MTA Conscious sedation Duration: mean (range): 8 (5–12) minutes Comparator: N/A	1. Adverse events: any associated symptoms occurring within 30 days following ablation were considered therapy-related complications

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Splatt & Steinke (2015) Australia	Retrospective CS Level IV Hospital setting NR, all patients had an overnight stay with a follow-up radiograph at 3 hours and CT at 24 hours	Patients with primary pulmonary malignancies or secondary metastases N = 51 (70) Tumour size - median (range): 24.4 (7–63) mm M/F ratio: 33:18 Mean (range) age: 71.2 (46–88) years Tumours: 62.9% were NSCLC, 37.1% were secondary. Of metastases 21.4% were colorectal, 8.6% were sarcoma, 4.3% were melanoma, 1.4% was breast and 1.4% was thyroid.	Intervention: CT-guided MTA Conscious sedation Duration: range was 2.5 minutes to 15 min Comparator: N/A	1. Major complications: defined as per the Society of Interventional Radiology as those causing permanent sequelae or death, or those requiring further management other than analgesia.
Vogl et al (2012) Germany	Retrospective CS Level IV Hospital setting mean (range): 10.2 (6.0–29.2) months	Patients with primary or secondary lung cancer with a maximal tumour diameter of 3 cm, primary tumour control in case of metastases and a maximum of five lesions. Patients were also inoperable or had refused surgery N = 57 (91) Tumour size - mean largest diameter was 18 (range, 5–30m) M/F ratio: 27:30 Mean (range) age: 57.5 (24.9–80.7) years Tumour of origin was primary bronchogenic carcinoma in 2/57 (3.5%), metastases from bronchogenic carcinoma in 7/57 (12.3%), colorectal carcinoma in 20/57 (35.1%), breast cancer 10/57 (17.5%), urothelial cancer 3/57 (5.3%), other 15/57 (26.3%).	Intervention: CT-guided MTA Conscious sedation Duration: mean (range) 17.7 (5–30) min Comparator: N/A	1. Adverse events: in accordance with those of the Society of Interventional Radiology Technology Assessment Committee and the International Working Group on Image-Guided Tumour Ablation

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Wolf et al (2008) United States of America	Retrospective CS Level IV Risk of bias: High mean (SD): 10 (6.8) months	Patients with primary or secondary lung cancer who were deemed medically inoperable or refused surgery N = 82 (NR) Tumour size – mean (SD): 35 (16) mm M/F ratio: 28:22 Mean (SD) age: 70 (15) years Primary NSCLC 27/50 (54%), metastases were 23/57 (46%) colorectal 9/23, breast 3/23, hepatocellular 2/23, head and neck 2/23, rhabdomyosarcoma 1/23, bladder 1/23, uterine 1/23, renal cell 1/23.	Intervention: CT-guided MTA Conscious sedation Dration: tumours had an average (SD) number of applications of 2 (1) and each application lasted 7–10 minutes Comparator: N/A	1. Adverse events: Immediate, peri procedural, and delayed complications were recorded on a per-treatment basis and were classified in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute
Yang et al (2015) China	Retrospective CS Level IV Risk of bias: High Hospital setting Patients had at least one 6 month follow-up	Patients with primary or secondary lung cancer who underwent MTA with or without induction of an artificial pneumothorax N = 36 (40) Tumour-size mean (SD): 29.4 (5.8) mm M/F ratio: 20:16 Mean (SD) age: 63.6 (10) years Primary lung cancer 8/17 (47.1%), metastatic with primaries from: breast cancer 4/17 (23.5%), colorectal cancer 4/17 (23.5%), kidney cancer 1/17 (5.9%) in patients with artificial pneumothorax, Primary lung cancer: 8/19 (42.1%), metastatic of which the primary was breast 6/19 (31.6%), colorectal cancer 5/19 (26.3%) in patients without artificial pneumothorax.	Intervention: CT-guided MTA with artificial pneumothorax Anaesthesia: unclear Duration: mean (SD) 5.9 (1.8) Comparator: Percutaneous MTA under CT guidance without artificial pneumothorax Anaesthesia: unclear Duration: mean (SD) 5.3 (1.9)	1. Adverse events: assessed according to the standards drafted by the International Working Group on Imagine‐Guided Tumor Ablation in 2005

Authors (Publication Year) Location	Study design, Level of evidence[a], and risk of bias assessment[b] Follow-up[c]	Study population characteristics, N (lesions), tumour size, male/female ratio, age, comorbidities/performance status/prior therapies	Description of Intervention and comparator	Relevant outcomes: measurement and methods of analysis
Zheng at al (2014) China	Retrospective CS Level IV Risk of bias: High Hospital setting NR	Patients with primary or secondary lung tumours treated by MTA who were considered unsuitable for surgery or who refused surgery N = 184 (253) Tumour size - mean (SD): 32.9 (19.3) mm M/F ratio: 117:67 Mean (range) age: 61.5 (19–85) years Primary cancer: 148/204 (72.5%) procedures, metastasis: 56/204 (27.5%) of procedures	Intervention: CT-guided MTA with artificial pneumothorax Conscious sedation Duration: range 4–8 minutes per site, mean (SD): 12.8 (11.13) minutes Comparator: N/A	1. Adverse events: evaluated on the basis of MTA procedures by reviewing medical records and CT images. They were reported in accordance with the classification proposed by the Society of Interventional Radiology

< COPD = chronic obstructive pulmonary disease; CS=case series; CT=computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; N = number; NSCLC = non-small cell lung cancer; mm = millimetres; MTA= microwave tissue ablation; N = number; NR = not reported; OS=overall survival;PET= positron emission tomography; PFS= progression free survival; RECIST = response evaluation criteria in solid tumours; RECIST criteria = complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD); TTLP = time to local progression; WHO= world health organisation; VEGF= serum vascular endothelial growth factor >

[a] Source:[b] Risk of bias as it relates to primary outcomes of the systematic review

[c] Median (range) unless otherwise stated.

[d] If no localized irregular enhancement of the lesions were shown on routine contrast‐enhanced CT after MTA, it was considered as complete response and success for MTA technology, thin symmetric rim of peripheral enhancement of <5 mm wide, observed up to 6 months after ablation was considered a sign of benign peritumoural enhancement and irregular focal soft‐tissue enhancement (>15 HU) was a sign of residual or recurrent disease.

e Pneumothorax was classified as follows: pneumothorax that complicated the ablation procedure as mild (causing lung surface retraction ≤ 2 cm from the pleural surface), moderate (causing retraction between 2 and 4 cm), or severe (causing lung surface retraction ≥ 4 cm, rapidly increasing with time, associated with mediastinal shift, and/or accompanied by respiratory or circulatory distress).

[f] Chemotherapy was platinum-doublet regimens that included cisplatin (75 mg/m2 intravenous [IV] on day 1) or carboplatin (with an area under curve of 5–6 on day 1) plus vinorelbine (25 mg/m2 IV on days 1 and 8, n = 1), gemcitabine (1,250 mg/m2 IV on days 1 and 8, n = 10), docetaxel (75 mg/m2 IV on day 1, n = 12), or pemetrexed (500 mg/m2 IV on day 1, n = 8). All chemotherapy regimens were repeated every 3 weeks for four or six cycles.

[g] Chemotherapy was whole-body chemotherapy seven days after ablation chosen based on histopathology and ECOG scores, chemotherapy regimens were completed for 4 cycles.

[h] All patients were treated with first-line, platinumbased doublet chemotherapy, 19 patients were treated with pemetrexed, 16 with docetaxel, 7 with gemcitabine, and 4 with paclitaxel. Twenty six patients received chemotherapy for four or more cycles. Chemotherapy was given after MTA in 35 (76.1%) of patients and before in 11 (23.9%).

[I] All patients received first-line, platinumbased doublet chemotherapy, 9 patients were treated with pemetrexed, 6 with docetaxel, 10 with gemcitabine, and 3 with paclitaxel. Twenty-two (78.6 %) patients received chemotherapy for four or more cycle.

Table 91 Profiles of studies on RFA included in the systematic literature review

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
POPULAITON	**1**			
Ambrogi et al (2011) Italy	CS (enrolment NR) Level IV Risk of bias: High 46 (12–82) months	Patients with stage IA-IB NSCLC, inoperable or refused surgery, lesion diameter ≤ 50 mm N = 57 (59 lesions) Mean size 26 (11–50) mm Males 45 (79%): Females 12 (21%) Mean age 74 (40–88) years Prior therapy: pulmonary metastectomy (20/57, 35%), chemotherapy + RFA (1/57, 2%)	Intervention: CT- or US-guided RFA Local anaesthesia + conscious sedation 71 ablation sessions Mean total procedure duration 39 mins (ablation duration 22 mins per lesion) Comparator: N/A	1. Overall survival: not defined (calculated with Kaplan-Meier method) 2. Cancer-free survival: not defined (calculated with Kaplan-Meier method) 3. Major adverse event: those resulting in readmission to the hospital for treatment 4. Minor adverse event: those resulting in no sequelae or needing nominal treatment
Dupuy et al (2015) USA	Prospective CS Level IV Risk of bias: High *24 (NR) months	Patients with stage IA NSCLC, inoperable or refused surgery, lesion diameter ≤ 30 mm N = 51 (51 lesions) Median size 21 (8–30) mm Males 23 (45%): Females 28 (55%) Median age 76 (60–89) years Prior therapy: NR	Intervention: CT-guided RFA Local anaesthesia + conscious sedation Single lesion/ablation session per patient Maximum 36 minutes per ablation Comparator: N/A	1. Overall survival: not defined (Kaplan-Meier) 2. Recurrence-free survival: time from RFA to death or recurrence (Kaplan-Meier method) 3. Local recurrence: recurrence in same lobe or hilum (based on CT scan) 4. Regional recurrence: recurrence within another lobe on the same side of ablation or within ipsilateral mediastinal or subcarinal nodes 5. Distant recurrence: recurrence within a contralateral, mediastinal node or distant metastatic disease (based on CT scan) 6. Adverse events: CTCAE v3.0

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Hiraki et al (2011) Japan	Retrospective CS Level IV Risk of bias: High 37 (2–88) months	Patients with stage IA-IB NSCLC, inoperable or refused surgery N = 50 (52 lesions) Mean size 21 (7–60) mm Males 29 (58%): Females 21 (42%) Mean age 75 (52–88) years Prior therapy: resection of extrapulmonary lesions (16/50, 32%)	Intervention: CT-guided RFA Local anaesthesia + conscious sedation 52 ablation sessions Ablation duration 12–15 mins per lesion Comparator: N/A	1. Overall survival: time from RFA to death (calculated with Kaplan-Meier method) 2. Cancer-specific survival: time from RFA to cancer-related death (calculated with Kaplan-Meier method) 3. Disease-free survival: time from RFA to death or cancer recurrence (calculated with Kaplan-Meier method) 4. Parenchymal recurrence: recurrence in the same lobe but away from ablation zone 5. Regional recurrence: recurrence in hilar and ipsilateral mediastinal lymph node 6. Distant recurrence: all other recurrences 7. Adverse events: CTCAE v 4.0
Lanuti et al (2012) USA	Retrospective CS Level IV Risk of bias: High 32 (2–75) months	Patients with stage IA-IB NSCLC, inoperable or refused surgery, lesion diameter < 50 mm, no disease outside involved lobe N = 45 (55 lesions) Mean size 20 (7–45) mm Males 18 (40%): Females 27 (60%) Median age 70 (51–89) years Prior therapy: resection of NSCLC (26/45, 58%)	Intervention: RFA (guidance NR) Local anaesthesia + conscious sedation 55 ablation sessions Ablation duration NR Comparator: N/A	1. Overall survival: not defined (calculated with Kaplan-Meier method) 2. Disease-free survival: not defined (calculated with Kaplan-Meier method) 3. Local control: no focal or diffuse enlargement of the ablated lesion on CT and no evidence of eccentric enhancement on PET at 3 or more months of follow-up. 4. Adverse events: not defined

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Liu et al (2015) China	Retrospective CS Level IV Risk of bias: High 19 (2–75) months	Patients with stage IA–IB NSCLC, inoperable or refused surgery, ECOG status ≤ 2 N = 29 (29 lesions) Mean size 31 (15–48) mm Males 18 (58%): Females 11 (42%) Median age 78 (56–85) years Prior therapy: NR	Intervention: CT-guided RFA Local anaesthesia + conscious sedation 33 ablation sessions Mean procedure duration 39 (15–120) mins [mean ablation duration 22 (12–32) mins] Comparator: N/A	1. Overall survival: time from RFA to death (calculated with Kaplan-Meier method) 2. Cancer-specific survival: not defined (calculated with Kaplan-Meier method) 3. Local progression: Focal enhancement of soft tissue compared with initial CT 4. Adverse events: puncture-related and ablation-related complications, minor complications, major complications
Ridge et al (2014) USA	Retrospective CS Level IV Risk of bias: High 30 (12–85) months	Patients with stage IA-IIA NSCLC, no prior in-field RT or resection, no chemo 12 months prior N = 29 (29 lesions) Median size 14 (10–26) mm Males 12 (41%): Females 17 (59%) Mean age 73 (55–86) years Prior therapy: resection ± radiotherapy for pulmonary lesions (14/29, 48%)	Intervention: CT-guided RFA General anaesthesia Number of sessions NR Ablation/procedure time NR Comparator: N/A	1. Overall survival: time from RFA to death or last follow-up (Kaplan-Meier) 2. Progression-free survival: time from RFA to disease progression or death (Kaplan-Meier) 3. Local control: decrease in tumour diameter of at least 30%, no evidence of peripheral tumour growth, loss of lesional FDG avidity on PET/CT 4. Local progression: interval increase in size or FDG uptake within the ablation lesion 5. Intrapulmonary recurrence: new lesion within treated lobe or adjacent pleura with increasing FDG uptake or increase size on follow-up 6. Distant recurrence: new metastasis at extralobar or extrathoracic site 7. Adverse events: CTCAE

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Safi et al (2015) Germany	Retrospective cohort study Level III-3 Risk of bias: High 10–13 months (range NR)	Patients with stage IA-IB NSCLC N = 25 [intervention] N = 49 [comparator] Mean size 22 (10–35) mm [intervention] Mean size 28 (10–50) mm [comparator] Males 52 (70%): Females 22 (30%) Mean age 71 (55–80) years [intervention] Mean age 74 (57–89) years [comparator] Prior therapy [intervention]: lung surgery (5/25, 20%), radiotherapy (2/25, 8%) Prior therapy [comparator]: NR	Intervention: CT-guided RFA General anaesthesia Number of sessions NR Ablation/procedure time NR Comparator: Radiotherapy 28/49 had SBRT, median 45 Gy in 3 fractions 21/49 had CRT, 66 Gy in 21 fractions	1. Overall survival: time of intervention to death (calculated with Kaplan-Meier method) 2. Progression-free survival: time of intervention to recurrence (calculated with Kaplan-Meier method) 3. Primary recurrence: tumour recurrence in the former resection line or at the ablation site (based on biopsy) 4. Locoregional recurrence: primary recurrence or tumour recurrence in the same lobe, ipsilateral hilar or ipsilateral mediastinal lymph nodes 5. Distant recurrence: any other recurrence 6. Adverse events: not defined
Viti et al (2014) Italy	Retrospective CS Level IV Risk of bias: High Mean FU 30 (NR) months	Patients with stage IA-IB NSCLC, inoperable or refused surgery, lesion diameter ≤ 35 mm N = 22 (24 lesions) Mean size 25 (11–34) mm Males 17 (77%): Females 5 (23%) Mean age 77 (70–84) years Prior therapy: lung surgery (11/22, 50%), heart surgery (4/22, 18%), abdominal surgery (3/22, 14%)	Intervention: CT-guided RFA Anaesthesia NR 24 ablation sessions Mean total procedure duration 25 (18–32) mins Comparator: N/A	1. Overall survival: time from RFA to death (calculated with Kaplan-Meier method) 2. Disease-free survival: not defined, but lower than overall survival so assumed death or progression (calculated with Kaplan-Meier method) 3. Adverse events: considered and recorded if further surgical procedures were needed or if hospitalisation was prolonged

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
POPULATION	**2**			
de Baere et al (2015) France	Retrospective CS Level IV Risk of bias: High 36 (IQR 20–55) months	Patients with lung metastases, inoperable or refused surgery, amenable to curative therapy N = 566 (1037 lesions) Median size 15 (4–70) mm Males 290 (51%): Females 276 (49%) Age 62.6 (17–92) years Prior therapy: NR Primary cancer: colorectal 293/566 (52%), kidney 68/566 (12%), 51/566 sarcoma (9%), 154/566 other (27%)	Intervention: CT-guided RFA General anaesthesia (n = 560), or local anaesthesia + conscious sedation (n = 6) 642 ablation sessions, duration NR Comparator N/A	1. Overall survival: time from first RFA session to death from any cause (calculated with Kaplan-Meier method) 2. Progression-free survival: time from RFA to disease progression anywhere inside or outside the lungs, or death from any cause (calculated with Kaplan-Meier method) 3. Adverse events: not defined
Fanucchi et al (2016) Italy	Retrospective CS Level IV Risk of bias: High 28 (2–126) months	Patients with lung metastases, controlled or absent extrathoracic disease, lesions size < 50 mm N = 61 (86 lesions) Median size 20 (5–50) mm Males 38 (62%): Females 23 (38%) Median age 75 (40–86) years Prior therapy: lung metastectomy 24/61 (39%) Primary cancer: colorectal 29/61 (48%), head/neck 8/61 (13%), sarcoma 5/61 (8%), kidney 4/61 (6%), other 15/61 (25%)	Intervention: CT- or US-guided RFA Local anaesthesia + conscious sedation 99 ablation sessions, duration 15–27 mins per lesion Comparator: N/A	1. Overall survival: time from RFA to death or last follow-up (calculated with Kaplan-Meier method) 2. Local progression-free survival: interval between RFA and evidence of local recurrence (death not included) (calculated with Kaplan-Meier method) 3. Local recurrence: evidence of tumour recurrence near to, in the site of thermal ablation, or within the same lobe 4. Adverse events: CTCAE

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Hiraki et al (2011) Japan	Retrospective CS Level IV Risk of bias: High 21 (4–98) months	Patients with HCC lung metastases, amenable to curative therapy, lesion size < 40 mm, ECOG status ≤ 2 N = 32 (83 lesions) Median size 11 (3–39) mm Males 24 (75%): Females 8 (25%) Mean age 62 (35–82) years Prior therapy: HCC resection 29/32 (91%), TACE ± RFA 3/32 (9%), pulmonary metastectomy 7/32 (22%), chemotherapy for metastases 6/32 (19%) Primary cancer: HCC 32/32 (100%)	Intervention: CT-guided RFA Local anaesthesia with conscious sedation 65 ablation sessions, duration 12 mins per lesion Comparator: N/A	1. Overall survival: time from RFA to death or last follow-up (calculated with Kaplan-Meier method) 2. Local progression: appearance of an irregular, scattered, nodular, or eccentric enhancement focus in the ablation zone, or when the ablation zone was circumferentially enlarged with contrast enhancement 3. Adverse events: measured against Society of Interventional Radiology guidelines
Koelblinger et al (2014) UK	Retrospective CS Level IV Risk of bias: High 12 (4–54) months	Patients with sarcoma lung metastases, amenable to curative therapy N = 22 (55 lesions) Median size 7 (5–20) mm Males 7 (32%): Females 15 (68%) Median age 48 (10–78) years Prior therapy: sarcoma resection 22/22 (10%), thoracotomy for metastases 15/22 (68%), systemic chemotherapy for metastases 9/22 (41%) Primary cancer: sarcoma 22/22 (100%)	Intervention: CT-guided RFA General anaesthesia, or local anaesthesia + conscious sedation 30 ablation sessions, duration NR Comparator: N/A	1. Overall survival: time from RFA to last follow-up (calculated with Kaplan-Meier method) 2. Progression-free survival: not defined (reported progression-free survival was shorter than overall survival, so likely includes death or progression [Kaplan-Meier method]) 3. Local progression: development of new tumour adjacent to ablation zone, focal nodular enhancement of part of the ablation zone, or enlargement of part of the ablation zone, or a change in shape of the ablation zone indicating focal enlargement 4. Adverse events: not defined

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Li et al (2012) China	Retrospective CS Level IV Risk of bias: High 23 (6–70) months	Patients with HCC lung metastases, inoperable, controlled intrahepatic primary, lesion size ≤ 50 mm, ≤ 5 lesions per patient, Karnofsky score > 80 N = 29 (68 lesions) Mean size 19 (5–50) mm Males 16 (55%): Females 13 (45%) Median age 56 (24–72) years Prior therapy: RFA 3/29 (10%), TACE 6 + RFA 7/29 (24%), liver transplant + TACE + RFA 9/29 (31%), hepatectomy + TACE + RFA 10/29 (35%) Primary cancer: HCC 29/29 (100%)	Intervention: CT-guided RFA General anaesthesia, or local anaesthesia with conscious sedation 56 ablation sessions, duration 12 mins per lesion Comparator: N/A	1. Overall survival: time from RFA to death or last follow-up (Kaplan-Meier) 2. Progression-free survival: time from RFA to either first recurrence or progression or death from any cause (Kaplan-Meier) 3. Local tumour progression: any detectable tumour activity in the ablation zone 4. Disease progression: evidence of new tumour located outside the treated region, (including intrahepatic and extrahepatic) 5. Adverse events: not defined
Lu et al (2015a) China	Prospective CS Level IV Risk of bias: High 24 (3–39) months	Patients with lung oligometastses, inoperable or refused surgery, absent or controlled primary tumour, lesion size < 50 mm N = 67 (115 lesions) Size NR Males 38 (57%): Females 29 (43%) Age > 65 years (n = 15), age ≤ 65 years (n = 52) Prior therapy: systemic chemotherapy for metastases 47/67 (70%) Primary cancer: colorectal 26/67 (39%), HCC 5/67 (8%), NSCLC 13/67 (19%), sarcoma 7/67 (10%), other 16/67 (24%)	Intervention: CT-guided RFA Anaesthesia NR # of sessions NR Duration NR Comparator: N/A	1. Overall survival: not defined, assumed measured from time of RFA to death (calculated with Kaplan-Meier method) 2. Progression-free survival: not defined (reported progression-free survival was longer than overall survival, i.e. likely does not include death, calculated with Kaplan-Meier method) 3. Local control: target lesions had not progressed during the follow-up period 4. Adverse events: not defined

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
Lu et al (2015b) China	CS (enrolment NR) Level IV Risk of bias: High Follow up NR	Patients with breast cancer lung metastases, inoperable or refused surgery, absent or controlled extrathoracic disease, prior chemotherapy, ECOG status ≤ 1, lesion size < 40 mm N = 35 (67 lesions) Size ≤ 20 mm (n = 20 patients, 39 lesions), > 20 mm (n = 15 patients 28 lesions) Males NR: Females NR Age > 65 years (n = 6), age ≤ 65 years (n = 29) Prior therapy: chemotherapy 35/35 (100%) Primary cancer: breast 35/35 (100%)	Intervention: CT-guided RFA Anaesthesia NR # of sessions NR Duration NR Comparator: N/A	1. Overall survival: not defined, assumed measured from time of RFA to death (calculated with Kaplan-Meier method) 2. Local control: target lesion had not progressed during follow-up period and each lesion was observed and judged 3. Adverse events: not defined
Matsui et al (2015) Japan	Retrospective CS Level IV Risk of bias: High 38 (5–130) months	Patients with CRC lung metastases, inoperable or refused surgery, primary resected, curative therapy N = 84 (172 lesions) Median size 15 (5–35) mm Males 46 (55%): Females 38 (45%) Median age 65 (31–94) years Prior therapy: colorectal resection 84/84 (100%), pulmonary metastectomy 34/84 (40%), systemic chemotherapy for metastases 24/84 (29%), metastectomy + chemotherapy 4/84 (5%), RFA 24/84 (29%), microwave ablation 1/84 (1%) Primary cancer: colorectal 84/84 (100%)	Intervention: CT-guided RFA Local anaesthesia + conscious sedation 113 ablation sessions, duration 12–15 mins per lesion Comparator: N/A	1. Overall survival: not defined, assumed time of RFA to death (Kaplan-Meier) 2. Progression-free survival: not defined (reported progression-free survival was longer than overall survival , i.e. likely does not include death, calculated with Kaplan-Meier method) 3. Local tumour progression: appearance of irregular, scattered, nodular, or eccentric focus in the ablation zone, or if the ablation zone was circumferentially enlarged 4. Adverse events: identified by follow-up CT, scored against CTCAE v4.0

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
von Meyenfeldt et al (2011) Netherlands	Retrospective CS Level IV Risk of bias: High 22 (2–65) months	Patients with limited recurrent lung metastases with peripheral locations, < 5 lesions per patient N = 46 (90 lesions) Tumour size < 20 mm (n = 62), ≥ 20 mm (n = 28) Males 19 (41%): Females 27 (59%) Median age 57 (32–78) years Prior therapy: NR Primary cancer: sarcoma 12/46 (26%), colorectal 14/46 (30%), kidney 4/46 (9%), breast 3/46 (7%), other 13/46 (28%)	Intervention: CT-guided RFA General anaesthesia (n = 3), or local anaesthesia + conscious sedation (n = 44) 65 ablation sessions, 12–25 mins per lesion Comparator: N/A	1. Overall survival: not defined, assumed time of RFA to death (Kaplan-Meier) 2. Progression-free survival: not defined, but assume aligned with death or "progression" as defined below, as progression-free survival was shorter than overall survival (Kaplan-Meier) 3. Progression: appearance of new lesions at any site, or growth in previously stable lesions 4. Local progression: any new or growing lesions in the ablation zone or within 1cm from this zone 5. Adverse events: not defined
Yan et al (2006 + 2007) Australia	Prospective CS Level IV Risk of bias: High 24 (6–40) months	Patients with colorectal lung metastases, inoperable or refused surgery, primary colorectal and liver metastases resected, 3–5 lesions either lung, lesion size ≤ 50mm N = 55 (lesions NR) Mean size 21 ± 11 mm Males 33 (60%): Females 22 (40%) Mean age 62 ± 11 years Prior therapy: hepatectomy 30/55 (55%), systemic chemotherapy 20/55 (36%) Primary cancer: colorectal 55/55 (100%)	Intervention: CT-guided RFA Local anaesthesia + conscious sedation 55 ablation sessions, median duration 2.5 (1.0–4.5) hours per patient Comparator: N/A	1. Overall survival: time from RFA to death (calculated with Kaplan-Meier method) 2. Recurrence: not defined 3. Disease progression: at least 20% increase in the largest diameter of the target lesion. 4. Local disease progression: disease progression at an original lung RFA site 5. Overall progression: disease progression at any systemic site 6. Adverse events: not defined

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
POPULATION	**3**			
Simon et al (2007) USA	Retrospective CS Level IV Risk of bias: High 21 (3–74) months	Patients with advanced lung cancer, inoperable or refused surgery, refractory to treatment N = 21 (27 lesions) Mean size 61 (15–190) mm Males 11 (53%): Females 10 (48%) Mean age 64 (46–77) years Prior therapy: NR Primary cancer: NSCLC 10/21 (48%), colorectal 3/21 (14%), other 8/21 (38%)	Intervention: CT-guided RFA Local anaesthesia + conscious sedation 129 ablations, mean 7 (1–15) minutes per ablation, mean 5 (2–9) ablations per lesion Comparator: N/A	1. Symptom improvement and relapse: based on medical record review and imaging reports, consensus by three authors 2. Adverse events: scored per-ablation session according to CTCAE

< CS = case series. CT = computed tomography. CTCAE = Common Terminology Criteria for Adverse Events. ECOG = Eastern Cooperative Oncology Group. FDG = Fludeoxyglucose (18F). Gy = gray. HCC = hepatocellular carcinoma. IQR = interquartile range. N= number. N/A = not applicable. NR = not reported. NSCLC = non-small cell lung cancer. PET = positron emission tomography. RFA = radiofrequency ablation. SBRT = stereotactic body radiotherapy. CRT = conventional radiotherapy. TACE = transarterial chemoembolization. US = ultrasound >

[A] Risk of bias as it relates to primary outcomes of the systematic review.

[B] Median (range) unless otherwise stated *unclear if median or mean reported.

Table 92 Profiles of studies on Radiotherapy included in the systematic literature review

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
POPULATION	**1**			
Koshy et al (2015) USA	Retrospective MC cohort study with propensity-matched subgroup analysis Level III-1/III-2 Risk of bias: Moderate Median 21 (IQR 11–43) months	Patients with stage I NSCLC who did not undergo surgery N = 13,036 (NR lesions) Size: NR Males 6531 (50%): Females 6505 (50%) Age 18–59 (8.5%), 60–69 (22.5%), 70–79 (40%), 85+ (29%) years Prior therapy: NR	Intervention: SBRT Dose and fractions NR Comparator: Conventional radiotherapy Minimum 60 Gy in 30 fractions Comparator: No treatment	1. Overall survival: not defined (calculated with Kaplan-Meier method)
Price et al (2012) UK	RCT OL MC Level II Risk of bias: Moderate Follow-up NR	Patients with stage IA-IIB NSCLC, age 18+, unfit for resection, performance status ≤ 2, no prior non-surgical treatment, no other malignancy in previous 5 years, not pregnant or breast feeding N = 56 (NR lesions) [intervention] N = 55 (NR lesions) [comparator] Median size 38 (3–89) mm [intervention] Median size 30 (3–55) mm [comparator] Males 38 (68%): Females 18 (32%) [intervention] Males 32 (58%): Females 23 (42%) [comparator] Median age 75 (range 49–88) years [intervention] Median age 74 (range 58–88) years [comparator] Prior therapy: NR	Intervention: Radical radiotherapy "majority" had 55 Gy in 20 fractions over 4 weeks Comparator: Radical radiotherapy + chemo "majority" had 55 Gy in 20 fractions over 4 weeks plus gemcitabine	1. Overall survival: Actuarial survival for 1-year and 2-year rates. Survival curve shown (calculated with Kaplan-Meier method) 2. Progression- or event-free survival: patients at the end of the trial that were alive and had not progressed - "progression" was note defined (calculated with Kaplan-Meier method) 3. Adverse events: CG-CTC v2.0 (assumed same as CTCAE from other studies

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Videtic et al (2015) USA	RCT OL MC Level II Risk of bias: Moderate Median 30.2 months	Patients with stage IA-IIA NSCLC, ≤ 50 mm, medically inoperable or refused surgery N = 39 (NR lesions) [intervention] N = 45 (NR lesions) [comparator] Max size median 20 (10–50) mm [intervention] Max size median 20 (8–43) mm [comparator] Males 16 (41%): Females 23 (59%) [intervention] Males 22 (49%): Females 23 (51%) [comparator] Median age 75 (57–89) years [intervention] Median age 75 (52–87) years [comparator] Prior therapy: NR	Intervention: Single-fraction SBRT 34 Gy in 1 fraction (n = 39/39 (100%) Comparator: Multi-fraction SBRT 48 Gy in 4 fractions (n = 45/45,100%)	1. Overall survival: time from enrolment to death (calculated with Kaplan-Meier method) 2. Disease-free survival: time from enrolment to death from any cause, treatment failure, distant metastasis, or second primary (calculated with Kaplan-Meier method) 3. Primary tumour control: absence of primary tumour failure - defined as post-SBRT tumour enlargement with proof of viability by PET, biopsy or both. 4. Adverse events: CTCAE v4.0 to define adverse events, and RTOG 0236 schema to define pulmonary function disorders
Jeppsen et al (2013) Denmark	Historical control study Level III-3 Risk of bias: High Median 82 (9–173) months	Patients with inoperable stage IA-IIA NSCLC N = 100 (NR lesions) [intervention] N = 32 (NR lesions) [comparator] Mean tumour volume 129 (7–650) mm^3 [I] Mean tumour volume 273 (30–1180) mm^3 [C]* Males 45 (45%): Females 55 (55%) [intervention] Males 22 (69%): Females 10 (31%) [comparator] Mean age 73 (52–88) years [intervention] Mean age 70 (51–87) years [comparator] Prior therapy: NR	Intervention: SBRT 45 Gy in 3 fractions (n = 32/100, 32%) 50 Gy in 3 fractions (n = 1/100, 1%) 66 Gy in 3 fractions (n = 67/100, 67%) Comparator: Conventional radiotherapy 80 Gy in 35 fractions, n = 20/32 (63%) 80 Gy in 40 fractions, n = 12/32 (37%)	1. Adverse events: not defined

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Lucas et al (2015) USA	Retrospective cohort Level III-2 Risk of bias: High Median 24 (IQR 11–40) months	Patients with inoperable stage IA-IIA NSCLC N = 81 (NR lesions) [intervention] N = 79 (NR lesions) [comparator] Median size 23 (IQR 16–29) mm [intervention] Median size 29 (IQR 20–42) mm [comparator]* Males 39 (48%): Females 46 (52%) [intervention] Males 54 (68%): Females 29 (37%) [comparator]* Median age 74 (IQR 66–78) years [intervention] Median age 69 (IQR 65–79) years [comparator] Prior therapy: Chemotherapy 5/81 (6.3%) [intervention], 6/81 (7.6%) [comparator] Lung surgery 19/81 (23.4%) [intervention], 2/81 (2.5%) [comparator] Radiation 1/81 (1.1%) [intervention], 0/81 (0.0%) [comparator]	Intervention: SBRT "majority" had 54 Gy in 3 fractions, range 36–60 Gy in 2–5 fractions Comparator: AHRT "majority" had 67.5 Gy in 25 fractions, range 60–72.3 Gy in 17–30 fractions	1. Adverse events: CTCAE v4.0
POPULATION	**2**			

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Siva et al (2015) Australia	Retrospective cohort Level III-2 Risk of bias: Moderate Median 25 months	Patients with 1–3 lung metastases, ≤ 50 mm, extrathoracic disease treated definitively N = 41 (49 lesions) [intervention] N = 24 (33 lesions) [comparator] Size NR Males 24 (59%): Females 17 (41%) [intervention] Males 14 (58%): Females 10 (42%) [comparator] Median age 70 (IQR 64–79) years [intervention] Median age 67 (IQR 51–76) years [comparator] Prior therapy [all patients]: 23 (40%) had prior pulmonary metastasectomy before SBRT. 13 (20%) had systemic chemotherapy for metastatic disease before SBRT. Of these, 2/13 had two lines of chemotherapy, whereas the remaining 11/13 patients had a single line of chemotherapy. Primary cancer [intervention]: colorectal 10/41 (24%), lung 16/41 (39%), bone and soft tissue 4/41 (10%), other 12/41 (29%)* Primary cancer [comparator]: colorectal 10 (43%), head and neck 7 (30%), other 6 (26%)	Intervention: Single-fraction SBRT 18 GY in 1 fraction (n = 1/40, 2%) 26 GY in 1 fraction (n = 39/40, 98%) Comparator: Multi-fraction SBRT 48 GY in 4 fractions (n = 14/24, 58%) 49 GY in 7 fractions (n = 1/24, 4%) 50 GY in 5 fractions (n = 9/24, 38%)	1. Overall survival: time from SBRT to death (calculated with Kaplan-Meier method) 2. Local control: failure defined as the combination of a CT demonstrable serially enlarging mass as per RECIST criteria, with the absence of air bronchograms and FDG avidity on PET scanning 3. Adverse events: CTCAE v4.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Widder et al (2013) Netherlands	Retrospective cohort Level III-2 Risk of bias: Moderate Median 43 (IQR 36–60) months	Patients with 1–5 lung metastases treated with curative intent (all visible lesions amenable to treatment), primary tumour curatively resected N = 42 (NR lesions) [intervention] N = 68 (NR lesions) [comparator] Mean largest size 17 (14–20) mm [intervention] Mean largest size 20 (17–24) mm [comparator] Males 27 (64%): Females 15 (36%) [intervention] Males 37 (54%): Females 31 (46%) [comparator] Median age 70 (49–89) years [intervention] Median age 61 (18–81) years [comparator]* Prior therapy [intervention]: Chemo 13/42 (31%)* Prior therapy [comparator]: Chemo 8/68 (12%) Primary cancer [intervention]: colorectal 31/42 (74%), NSCLC 6/42 (14%), other 5/42 (12%)* Primary cancer [comparator]: colorectal 39/68 (57%), sarcoma 18/68 (27%), other 11/68 (16%)	Intervention: SBRT 60 Gy in 3 fractions (n = 23/42, 55%) 60 Gy in 5 fractions (n = 9/42, 21%) 60 Gy in 8 fractions (n = 10/42, 24%) Comparator: Surgical resection Wedge resection (n = 52/68, 76%) Lobectomy (n = 15/68, 22%) Pneumonectomy (n = 1/68, 1%)	1. Overall survival: time from treatment to death by any cause (calculated with Kaplan-Meier method) 2. Progression-free survival: RECIST criteria or death measured as an event (calculated with Kaplan-Meier method)

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Yu et al (2014) China	Retrospective cohort Level III-2 Risk of bias: High Median 30 (5–96) months	Patients with osteosarcoma lung metastases, no other metastases, complete resectability N = 27 (NR lesions) [intervention] N = 31 (NR lesions) [comparator] Size NR Males 19 (70%): Females 8 (30%) [intervention] Males 22 (71%): Females 9 (29%) [comparator] Median age 21 (8–59) years Prior therapy [intervention]: amputation 11/27 (41%) limb salvage 16/27 (59%) Prior therapy [comparator]: amputation 15/31 (48%) limb salvage 16/31 (52%) Primary cancer: sarcoma (100%)	Intervention: SBRT Range 50 Gy in 10 fractions to 70 Gy in 10 fractions (n = 27/27, 100%) Comparator: Surgical resection Wedge resection (n = 14/31, 45%) Lobectomy (n = 17/31, 55%)	1. Overall survival: date of pulmonary metastases until death or last follow-up (calculated with Kaplan-Meier method) 2. Progression-free survival: date of pulmonary metastases until progress or last follow-up (calculated with Kaplan-Meier method) - progress defined by RECIST criteria v1.1 - explicit definition not provided 3. Adverse events: CTCAE v3.0, radiation reaction RTOG
Agolli et al (2015) Italy	Retrospective CS Level IV Risk of bias: High 18 (range NR) months	Patients with ≤ 4 lung metastases with primary under control, and no other active sites of distant metastasis N = 22 (29 lesions) Median maximal diameter 17 (9–45) mm Males 15 (68%): Females 7 (32%) Mean age 66 (52–85) years Prior therapy: surgery +/- chemoradiotherapy 13/22 (59%), definitive chemoradiotherapy 3/22 (14%), chemotherapy alone 5/22 (22%), SBRT 1/22 (5%) Primary cancer: adenocarcinoma 14/22 (64%), squamous cell carcinoma 7/22 (32%), NR 1/22 (4%)	Intervention: SBRT 23 Gy in 1 fraction (n = 10/29, 34%) 30 Gy in 1 fraction (n = 12/29, 41%) 45 Gy in 3 fractions (n = 7/29, 24%) Comparator: N/A	1. Overall survival: time from ablative therapy to death (calculated with Kaplan-Meier method) 2. Progression-free survival: time from therapy to local or distant progression (Kaplan-Meier) 3. Metastases-free survival: any site of distant progression (Kaplan-Meier) 4. Cancer-specific survival: date of death due to progression from NSCLC (Kaplan-Meier) 5. Local recurrence: in-field or marginal regrowth of disease 6. Adverse events: CTCAE v4.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Baschnagel et al (2013) USA	Retrospective (n = 23) and prospective (n = 9) CS Level IV Risk of bias: High 27.7 (7.6–57.1) months	Patients with 1–3 lung metastases, controlled extrathoracic disease, inoperable or refused surgery N = 32 (47 lesions) Median size 16 (7–52) mm Males: Females NR Median age 63 (21–87) years Prior therapy for primary: prior thoracic surgery 14/32 (44%), prior external beam radiation 4/32 (13%) Prior therapy for metastases: prior systemic therapy for any metastases (19/32 (59%) Primary cancer: colorectal 10/32 (31%), sarcoma 4/32 (13%), head and neck 4/32 (13%), melanoma 3/32 (9%), lung 2/32 (6%), renal cell 2/32 (6%), other 7/32 (22%)	Intervention: SBRT Median 60 Gy in 4 fractions 60 Gy in 5 fractions (n = 36/47, 77%) 48 Gy in 4 fractions (n = 7/47, 15%) 50 Gy in 5 fractions (n = 1/47, 2%) 60 Gy in 10 fractions (n = 2/47, 4%) 65 Gy in 10 fractions (n = 1/47, 2%) Comparator: N/A	1. Overall survival: not defined (calculated with Kaplan-Meier method) 2. Distant disease progression: not defined (calculated with Kaplan-Meier method) 3. Local control: not defined 4. Adverse events: CTCAE v3.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Garcia-Cabezas et al (2015) Spain	Retrospective CS Level IV Risk of bias: High 13.3 (3.6–46.2) months	Patients with lung oligometastases, ≤ 5 lesions, ≤ 50 mm, any histology, controlled primary disease) with no prior surgery and Karnofsky Index ≥ 70 N = 44 (53 lesions) Median maximum size 20 (range NR) mm Males 38 (86%): Females 6 (14%) Median age 74 (50–86) years Prior therapy: chemotherapy 27/44 (61%), radiotherapy 14/44 (32%), surgery 27/44 (61%) Primary cancer: colorectal 20/44 (45%), lung 10/44 (23%), head and neck 6/44 (14%), kidney 4/44 (9%), other 4/44 (9%)	Intervention: SBRT 60 Gy in 5 fractions (n = 35/53, 66%) 60 Gy in 8 fractions (n = 11/53, 21%) 50 Gy in 10 fractions (n = 7/53, 13%) Comparator: N/A	1. Overall survival: time from SBRT to death (calculated with Kaplan-Meier method) 2. Progression-free survival: not defined, but reported value was lower than overall survival so assumed time to death or progression (calculated with Kaplan-Meier method) 3. Local control: absence of progression in the treatment volume/field - assessed by PET/CT 4. Adverse events: CTCAE v3.0
Filippi et al (2015) Italy	Retrospective CS Level IV Risk of bias: High 20 (3–72) months	Patients with 1–5 colorectal lung metastases, primary treated with radical surgery, maximum diameter < 50 mm, absent or controlled extrathoracic disease, adequate pulmonary function, ECOG status 0–1 N = 40 (59 lesions) Median size 15 (10–40) mm Males 20 (50%): Females 20 (50%) Median age 70 (44–86) years Prior therapy: chemotherapy before SBRT 4/40 (10%), after SBRT 4/40 (10%) Primary cancer: Colorectal 40/40 (100%)	Intervention: SBRT 26 Gy in 1 fraction (n = 40/59, 68%) 45 Gy in 3 fractions (n = 11/59, 19%) 48 Gy in 4 fractions (n = 1/59, 2%) 55 Gy in 5 fractions (n = 5/59, 8%) 60 Gy in 8 fractions (n = 2/59, 3%) Comparator: N/A	1. Overall survival: time between SBRT and death from any cause (calculated with Kaplan-Meier method) 2. Progression-free survival: time between SBRT and relapse/progression at any site (calculated with Kaplan-Meier method) 3. Relapse/progression: CT scan showing either immediate tumour growth after treatment [progressive disease] or after initial shrinkage [complete/partial response] or stable disease 4. Adverse events: RTOG acute and late scores

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Gamsiz et al (2014) Turkey	Retrospective CS Level IV Risk of bias: High 14 (range NR) months	Patients with 1–5 pulmonary lesions, < 70 mm, controlled primary, Karnofsky status ≥ 70 N = 20 (31 lesions) Size NR Males 13 (65%): Females 7 (35%) Median age (24–81) years Prior therapy: NR Primary cancer: lung 10/20 (50%), soft tissue 3/20 (15%), rectum 2/20 (10%), breast 2/20 (10%), thyroid 1/20 (5%), colon 1/20 (5%), stomach 1/20 (5%)	Intervention: SBRT 30 Gy in 3 fractions (n = 3/20, 15%) 36 Gy in 3 fractions (n = 7/20, 35%) 60 Gy in 6 fractions (n = 1/20, 5%) 50 Gy in 5 fractions (n = 9/20, 45%) Comparator: N/A	1. Overall survival: time from SBRT to last day of follow-up (calculated with Kaplan-Meier method) 2. Disease-free survival: time from SBRT to local-regional or systemic recurrence (calculated with Kaplan-Meier method) 3. Local control: the absence of local progression evidenced by tumour growth or regrowth after initial shrinkage 4. Adverse events: CTCAE v4.0
Kim et al (2009) Republic of Korea	Retrospective CS Level IV Risk of bias: High 13 (3–23) months	Patients with lung oligometastases, no extrapulmonary metastases N = 31 (134 lesions) Size NR Males 18 (58%): Females 13 (42%) Median age 50 (17–81) years Prior therapy for primary cancer: surgery 23/31 (74%), embolization 5/31 (16%), chemotherapy 3/31 (10%) Prior therapy for lung metastases: chemotherapy 22/31 (71%) (all failed to control the disease) Primary cancer: liver 9/31 (3%), breast 7/31 (23%), lung 4/31 (13%), colon 3/31 (10%), thymoma 3/31 (10%), head and neck 2/31 (6%), pancreatic 1/31 (3.2%), soft tissue 1/31 (3.2%), renal cell 1/31 (3.2%)	Intervention: Helical tomotherapy Median dose 50 Gy in 10 fractions or 40 Gy in 10 fractions Comparator: N/A	1. Overall survival: time from SBRT to death (calculated with Kaplan-Meier method) 2. Local control: no progression of the individually treated lesion, i.e. included complete response, partial response and stable disease 3. Local failure: increase of 20% or more in tumour size within 80% of isodose volume 4. Regional failure: increase of 20% or more in tumour size within the ipsilateral lung parenchyma and bilateral mediatsium but outside the 80% isodose volume 5. Adverse events: CTCAE v3.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Navarria et al (2014) Italy	Prospective CS Level IV Risk of bias: High 21 (8–20) months	Patients with ≤ 5 lung metastases, controlled primary tumour, no progressive disease longer than 6 months, medically inoperable N = 76 (118 lesions) Size median total 6.5 cm3 (range 0.5 –100 cm3) Males 54 (71%): Females 22 (29%) Median age 68 (38–88) years Prior therapy: NR Primary cancer: colorectal 29/76 (38%), NSCLC 18/76 (24%), sarcoma 6/76 (8%), genitourinary 8/76 (11%), 'other' 15/76 (20%)	Intervention: SBRT 48 Gy in 12 fractions (n = 95/118, 80%) 60 Gy in 20 fractions (n = 7/118, 6% 60 Gy in 7.5 fractions (n = 16/118, 14%) Comparator: N/A	1. Overall survival: time from SBRT to death (calculated with Kaplan-Meier method) 2. Progression-free survival: not defined, but reported value was lower than overall survival so assumed time to death or progression (calculated with Kaplan-Meier method) 3. Disease specific survival: not defined (calculated with Kaplan-Meier method) 4. Adverse events: CTCAE v3.0
Navarria et al (2015) Italy	Prospective CS Level IV Risk of bias: High 55 (17–251) months	Patients with < 5 lung metastases, slow-progressing disease, controlled primary tumour, progressive disease after chemotherapy and/or surgical resection N = 28 (51 lesions) Size NR Males 12 (43%): Females 16 (57%) Median age 64 (23–89) years Prior therapy: chemotherapy 5/28 (18%), surgery 10/28 (36%), surgery and chemotherapy 7/28 (25%) Primary cancer: leiomyosarcoma 10/28 (36%), synovial sarcoma 4/28 (14%), spindle cell sarcoma 3/28 (11%), other sarcoma 11/28 (39%)	Intervention: SBRT 30 Gy in 1 fraction (n = 2/51, 4%) 60 Gy in 3 fractions (n = 7/51, 14%) 48 Gy in 4 fractions (n = 38/51, 74%) 60 Gy in 8 fractions (n = 4/51, 8%) Comparator: N/A	1. Overall survival: not defined (calculated with Kaplan-Meier method) 2. Treatment response: RECIST - not formally stated but same categories were reported; complete remission - disappearance of the lesions at CT scan; partial remission - a reduction greater than 30%; progression of disease - any growing lesions not clearly attributable to fibrosis. 3. Adverse events: CTCAE v4.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Norihasa et al (2008) Japan	Retrospective CS Level IV Risk of bias: High 27 (10–80) months	1–2 pulmonary metastases, ≤ 40 mm, locally controlled primary tumour, no other metastatic sites N = 34 (43 lesions) Size: <15 mm (n = 17/43, 40%), 15–30 mm (n = 22/43, 51%) >30 mm (n = 4/43, 9%) Males 22 (65%): Females 12 (35%) Median age 71 (30–80) years Prior therapy: most patients had previously undergone surgical resection and chemotherapy for their primary cancer Primary cancer: lung 15/34 (44%), colorectal 9/34 (26%), head and neck 5/34 (15%), kidney 3/34 (9%), bone 1/34 (3%), breast 1/34 (3%)	Intervention: SBRT 48 Gy in 4 fractions (n = 17/34, 50%) 48 Gy in 5 fractions (n = 1/34, 3%) 60 Gy in 5 fractions (n = 16/34, 47%) Comparator: N/A	1. Overall survival: time from SBRT to death or last follow-up (calculated with Kaplan-Meier method) 2. Local response: RECIST; complete response - disappearance of all target lesions, partial response - at least 30% decrease in the sum of the longest diameter of target lesions, stable disease - 30% decrease to 20% increase in the sum of the longest diameter of the target lesions, progressive disease - greater than 20% increase in the sum of the longest diameter of the target lesions 3. Adverse events: CTCAE v3.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Nuyttens et al (2015) Netherlands	Prospective CS Level IV Risk of bias: High 36 (4–60) months	Patients with 1–5 lung metastases, inoperable or refused surgery, limited to 2 organs, primary under control, not candidates for chemotherapy, min 6 months life expectancy N = 30 (57 lesions) Median size 13 (6–67)) mm Males 16 (53%): Females 14 (47%) Median age 66 (44–78) years Prior therapy: 15/30 (50%) patients had prior treatment for metastases (treatments not specified) Primary cancer: colorectal 19/30 (63%), breast carcinoma 2/30 (7%), lung 2/30 (7%), melanoma 2/30 (7%), sarcoma 2/30 (7%), other 3/30 (10%)	Intervention: SBRT 30 Gy in 1 fraction, n = NR 60 Gy in 3 fractions, n = NR 60 Gy in 5 fractions, n = NR 56 Gy in 7 fractions, n = NR Comparator: N/A	1. Overall survival: start of SBRT to death from any cause (calculated with Kaplan-Meier method) 2. Disease-free survival: time from SBRT to date of a local recurrence, regional or distant metastasis, or death from any cause (calculated with Kaplan-Meier method) 3. Local control: RECIST - measured from start of SBRT to date of diagnosis of a local recurrence - defined as a 20% increase in tumour size on CT scan compared with previous CT scan) 4. Adverse events: CTCAE v3.0, acute <4 months, late > 4 months
Oh et al (2012) Republic of Korea	Retrospective CS Level IV Risk of bias: High 21 (3–107) months	Patients with < 5 lung metastases, < 50 mm, with a controlled primary tumour, (if applicable, controllable extrapulmonary metastases) N = 57 (67 lesions) Size: <25 mm 58/67 (87%), ≥ 25 mm 9/67 (13%) Males 49 (86%): Females 8 (14%) Age: < 60 years 16/57 (28%), ≥ 60 years 41/57 (72%) Prior therapy: NR Primary cancer: lung 33/67 (49%), liver 9/67 (13%), colorectal 7/67 (10%), head and neck 11/67 (16%), others 7/67 (10%)	Intervention: SBRT 50 Gy in 5 fractions (n = 4/67, 6%) 60 Gy in 5 fractions (n = 44/67, 66%) 60 Gy in 4 fractions (n = 19/67, 28%) Comparator: N/A	1. Overall survival: date of SBRT to date of last follow-up or death (calculated with Kaplan-Meier method) 2. Tumour progression: increase in tumour size on two consecutive CT scans 3. Adverse events: CTCAE v3.0

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Osti et al (2013) Italy	Prospective CS Level IV Risk of bias: High 15 (3–45) months	Patients with 1–2 lung metastases, < 50 mm, controlled extrathoracic disease at ≤ 2 sites, adequate pulmonary function, ECOG score 0–1 N = 66 (103 lesions) Size: volume < 10 cc 64/103 (62%), volume ≥ 10 cc 39/103 (38%) Males 32 (48%): Females 34 (52%) Median age 68 (25–89) years Prior therapy: NR Primary cancer: NSCLC 12/66 (18%), colorectal 23/66 (35%), breast 11/66 (17%), other 20/66 (30%)	Intervention: SBRT 30 Gy in 1 fraction (n = 54/103, 52%) (peripheral tumours) 23 Gy in 1 fraction (n = 49/103, 48%) (central tumours) Comparator: N/A	1. Overall survival: death from any cause (calculated with Kaplan-Meier method) 2. Cancer-specific survival: death from cancer (calculated with Kaplan-Meier method) 3. Progression-free survival: local and/or systemic failure (calculated with Kaplan-Meier method) 4. Local control: absence of local progression and the presence of stable disease (based on CT scan) 5. Adverse events: RTOG morbidity scoring scale
Ricardi et al (2011) Italy	Retrospective CS Level IV Risk of bias: High 20.4 (3–77.4) months	Patients with 1–3 lung metastases, <50mm, absent or controlled extrathoracic disease, adequate pulmonary function, no prior radiotherapy, ECOG performance status 0–1 N = 61 (77 lesions) Median size 20 (7–45) mm Males 43 (70%): Females 18 (30%) Median age 70 (46–86) years Prior therapy: systemic therapy 7/61 (11%), pulmonary metastectomy 9/61 (15%) Primary cancer: lung cancer 34/61 (56%), colorectal 13/61 (21%), other 14/61 (23%)	Intervention: SBRT 26 Gy in 1 fraction (n = 51/77, 66%) 45 Gy in 3 fractions (n = 22/77, 29%) 36 Gy in 3 fractions (n = 4/77, 5%) Comparator: N/A	1. Overall survival: death from any cause (calculated with Kaplan-Meier method) 2. Cancer-specific survival: death from cancer (calculated with Kaplan-Meier method) 3. Progression-free survival: local and/or regional and/or systemic failure (calculated with Kaplan-Meier method) 4. Local control: the absence of local progression, evidenced by tumour growth or re-growth after initial shrinkage 5. Adverse events: RTOG acute radiation toxicity score - same as CTCAE

Authors (Year) Location	Study design Level of evidence Risk of bias [A] Follow-up [B]	Study population characteristics: N (lesions), tumour size, male/female ratio, age, prior therapy, primary site (P2/3 only)	Description of Intervention Dose (Gy)/ fraction	Relevant outcomes: measurement and methods of analysis
Takahashi et al (2014) Japan	Retrospective CS Level IV Risk of bias: High 23.7 (6.1–167.0) months	Patients with colorectal lung metastases, previously resected primary, no evidence of recurrence, not candidates for metastectomy, no other distant metastases, no systemic therapy within 1 month of radiotherapy, life expectancy >6 months N = 34 (44 lesions) Median size 18 (5–60) mm Males 20 (59%): Females 14 (41%) Median age 63 (34–79) years Prior therapy for primary cancer: resection of primary 34/34 (100%), 1 chemotherapy regimen before radiotherapy 18/34 (53%) Prior therapy for secondary cancer: pulmonary metastectomy for other oligo-recurrent lung lesions 10/34 (29%) Primary cancer: colorectal 34/34 (100%)	Intervention: Carbon ion radiotherapy Median total dose 60 Gy (range, 44–64.8 Gy) 60 Gy in 4 fractions (n = 31/44, 70%) Comparator: N/A	1. Overall survival: time from intervention to death (calculated with Kaplan-Meier method) 2. Local control rate: recurrence defined as continuous increase in opacity size on CT imaging, along with either increased maximum standardized uptake values ≥ 5 on PET/CT, or biopsy proof of disease. 3. Adverse events: CTCAE v3.0 (acute events), RTOG morbidity scoring scale (late events)

< AHRT = accelerated hypofractionated radiotherapy. CS = case series. CT = computed tomography. CTCAE = Common Terminology Criteria for Adverse Events. ECOG = Eastern Cooperative Oncology Group. FDG = Fludeoxyglucose (18F). Gy = gray. IQR = interquartile range. MC = multicentre. N = number; N/A = not applicable. NR = not reported. NSCLC = non-small cell lung cancer. OL = open label (unblinded). PET = positron emission tomography. RCT = randomised controlled trial. RECIST = Response Evaluation Criteria in Solid Tumours. RTOG = Radiation Therapy Oncology Group. SBRT = stereotactic body radiotherapy >

A risk of bias as it relates to primary outcomes of the systematic review

B median (range) unless otherwise stated

* Significant difference between study groups

Table 93 Profiles of studies on Surgery included in the systematic literature review

Author (Year) Location	Study design Level of evidence Risk of bias [A] Median follow-up [B]	Study population characteristics: N (lesions, tumour size, male/female ratio, age, prior therapy, primary cancer (P2/3 only)	Description of Intervention and Comparator	Relevant outcomes: measurement and methods of analysis
POPULAITON	**2**			
Renaud et al (2014)	Retrospective CS Level IV Risk of bias: High 21.6 months (0–192)	Lung metastases originating from a CRC who underwent resection with curative intent N = 320 (median number of resected lesions=2) Tumour size NR M/F ratio: 215:105 Median age: 63 (IQR: 13.75) years Primary cancer: colon - 164/320 patients (51%), rectum - 156/320 patients (49%)	Intervention: surgical resection Comparator: NA	1. Postoperative mortality: death occurring during hospitalisation or within 30 days of surgery 2. Overall survival: Kaplan-Meier test
Younes et al (2009)	Retrospective CS Level IV Risk of bias: High NR	Patients with primary malignant solid tumour, primary controlled or controllable, nodules confined to lung N = 529 (median resected: 1) Largest diameter: ≤ 1 cm 163/526 (31%); 1.1–3cm 256/526 (48.7%); >3cm 107/526 (20.3%) M/F ratio: 267:262 Age 0–12 years: 38/529 (7.2%); 13–40 years: 155/529 (29.3%); 65 years: 231/529 (43.7%); 70 years: 105/529 (19.8%) Primary tumours: Adenocarcinoma 154/528 (29.2%), osteosarcoma 86/528 (16.3%), squamous cell 81/528 (15.3%), soft tissue sarcoma 75/528 (14.2%), melanoma 48/528 (9.2%), other: 84/528 (15.9%)	Intervention: surgical resection Comparator: NA	1. Adverse events: not defined. 2. Overall survival rate: Kaplan-Meier test. 3. Prognostic factors: univariate and multivariate analyses.

Reza et al (2014)	Retrospective CS Level IV Risk of bias: High 17.7 (6–45) months	Pulmonary metastasectomies for sarcoma involving complete resection of their metastatic disease N = 118 (lesions: NR) Tumour size: 0–3 cm: 74/118 patients (62.7%), 3–5 cm: 20/118 patients (16.9%), > 5 cm: 24/118 patients (20.3%) M/F ratio: 62:56 Mean (SD): 46.5±15.4 years Primary tumour: unspecified sarcoma: 14/118 (12%), fibrosarcoma: 4/118 (3%), osteosarcoma: 19/118 (16%), Ewings sarcoma: 5/118 (4%), Synovial sarcoma: 16/118 (14%), spindle cell sarcoma: 6/118 patients (5%), leiomosarcoma: 29/118 (24%), peripheral nerve sheath: 3/118 (3%), chondrosarcoma: 6/118 (5%), rhabdomyosarcoma: 2/118 (2%), liposarcoma: 6/118 (5%), giant cell sarcoma: 3/118 (3%), other: 5/118 (4%)	Intervention: surgical resection Comparator: NA	1. Overall survival: assessed by Kaplan-Meier test. 2. Recurrence: not specified. 3. Repeat resection. 4. Prognostic factors: Cox proportional hazards modelling

Rodriguez-Fuster et al (2014)	Retrospective CS Level IV Risk of bias: High 30 days	Pulmonary metastases from colorectal carcinoma, primary under control, no extra pulmonary disease N = 532 (lesions median per patient: 1.78) Tumour size: < 3cm: 438/532 patients (82.3%), ≥ 3 cm: 94/532 patients (17.7%) M/F ratio: NR Age: No morbidity group mean ± SD (range): 67 ± 10 (35–91). Morbidity group mean ± SD (range): 68 ± 10 (42–85) Primary tumour: Colorectal in 100%, denocarcinoma: 524/532 patients (98.5%), carcinoma adenosquamous: 1/532 patients (0.2%), undifferentiated carcinoma: 2/532 patients (0.4%), no data: 5/532 patients (0.9%)	Intervention: surgical resection Comparator: NA	1. Complications: Patients were grouped as having presented (Group A), or not (Group B), postoperative complications. Variables in Groups A and B were compared with the Student's t-test or the Mann–Whitney U-test for continuous data according to the normal or non-normal distribution.
Kitano et al (2012)	Retrospective CS Level IV Risk of bias: High 17.6 months (0.7–165)	pulmonary metastastasectomy for HCC with 1) the possibility of complete resection, 2) no evidence of uncontrolled intrahepatic or extrapulmonary lesions at the time of the lung surgery and 3) adequate general physical condition for the pulmonary resection. N = 45 (lesions 1: 26/45 patients (58%), 2 to 3: 9/45 patients (20%) , more: 10/45 patients (22%)) Tumour size: median (range): 17 (2–70) mm M/F ratio: 33:12 Median age (range): 57 (26–80) years Primary tumour: hepatocellular in all	Intervention: surgical resection Comparator: NA	1. Overall survival: assessed by Kaplan-Meier test. 2. Prognostic factors: chi-square test, the Wilcoxon test, and Fisher's exact test, as appropriate.

<CS = case series. CT = computed tomography. CTCAE = Common Terminology Criteria for Adverse Events. ECOG = Eastern Cooperative Oncology Group. FDG = Fludeoxyglucose (18F). HCC = hepatocellular carcinoma. IQR = interquartile range. N/A = not applicable. NR = not reported. NSCLC = non-small cell lung cancer. PET = positron emission tomography. RFA = radiofrequency ablation. TACE = transarterial chemoembolization. US = ultrasound.>

[A] Risk of bias as it relates to primary outcomes of the systematic review

[B] Median (range) unless otherwise stated

Table 94 Study profile tables for the systematic reviews (all interventions) that were included in the systematic literature review

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intervention/ comparison	Summary of results	Conclusions/recommendation	Quality assessment
SURGERY						
Young et al (2015) *	To examine the survival rates of patients with metastatic head and neck squamous cell carcinoma who have undergone pulmonary squamous metastasectomies (population 2)	13 studies included (403 patients) Publication date range of included studies: 1986–2011	Study inclusion criteria Studies on patients with metastatic head and neck squaomous cell carcinoma who underwent pulmonary squamous metastasectomy. All patients had to have locoregional control of the primary tumour at the time of pulmonary metastasectomy without distant metastases elsewhere. All surgical approaches to pulmonary metastasectomy and both incomplete and complete resection were included as well as multiple or bilateral pulmonary nodules. Studies had to report survival outcome data on pulmonary metastasis from head and neck squamous cell carcinoma. Randomised controlled trials, prospective case series or case control studies were considered for inclusion. No language or publication date restrictions were imposed. Study exclusion criteria Studies of patients with metastatic pulmonary disease at the initial diagnosis of head and neck squamous cell carcinoma were excluded.	Meta-analysis of overall absolute 5-year survival rates Reported by 11 of the 13 studies with a total of 387 patients: 29.1% (95%CI; 24.1–35.3) I^2 = 0%, p = 0.462, d.f.= 10	Authors stated that the SR and meta-analysis demonstrated that certain carefully selected patients with lung metastasis following treatment for squamous cell carcinoma of the head and neck may benefit from pulmonary metastasectomy. They report that poor prognostic factors for pulmonary metatastectomy include the presence of lymph node metastasis at the diagnosis of the original tumour, squamous cell carcinoma of the oral cavity, incomplete pulmonary resection and the presence of multiple pulmonary nodules.	**MODERATE QUALITY** 1. Was an 'a priori' design provided? **YES** 2. Duplicate selection and extraction? **YES** 3. Comprehensive literature search? **YES** 4. Publication status (i.e. grey literature) used as an inclusion criterion? **YES** 5. List of studies provided? **NO** 6. Characteristics of included studies? **YES** 7. Scientific quality of the included studies assessed? **YES** 8. Scientific quality of the studies used in conclusions? **YES** 9. Methods used to combine the findings of studies appropriate? **YES** 10. Publication bias assessed? **YES** 11. Conflict of interest stated? **NO**

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intervention/ comparison	Summary of results	Conclusions/recommendation	Quality assessment
Pfannschmidt et al (2007) **	To assess the published evidence for the efficacy of pulmonary metastasectomy in patients with colorectal cancer (population 2)	20 studies included (2,320 patients) Publication date range of included studies: 1999–2006	Study inclusion criteria Studies on patients who underwent surgical resection with curative intent for colorectal pulmonary metastases. Patients who underwent repeat pulmonary resection and hepatic and pulmonary metastases resection were also included. Prospective and retrospective studies reporting the outcome of surgical resection with curative intent of colorectal pulmonary metastases. Restricted to studies published between 1995 and December 2006. Other criteria included at least 40 patients in the study, at least 30 days of follow-up after the operation for postoperative morbidity and mortality and at least 24 months for inclusion of survival data. English articles included. Study exclusion criteria NR	Overall 5-year survival: All studies reported overall survival of 5 years for all patients undergoing resection of pulmonary metastases (median: 48%, range: 41.1–56%)	Authors concluded there is a substantial body of evidence from retrospective case series demonstrating that resection of colorectal pulmonary metastases can be performed safely with a low mortality rate. For a subset of highly selected patients the overall 5-year actuarial survival rates ranged between 38.3% and 63.7% which the authors reported as being comparable with surgical resection for colorectal liver metastases.	**MODERATE QUALITY** 1. Was an 'a priori' design provided? **YES** 2. Duplicate study selection and data extraction? **CANNOT ANSWER** 3. Comprehensive literature search? **YES** 4. Publication status (i.e. grey literature) used as an inclusion criterion? **NO** 5. List of studies provided? **NO** 6. Characteristics of the included studies provided? **YES** 7. Scientific quality of the included studies assessed? **NO** 8. Scientific quality of the included studies used in conclusions? **NO** 9. Methods used to combine the findings of studies appropriate? **N/A** 10. Publication bias assessed? **N/A** 11. Conflict of interest stated? **NO**

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intervention/ comparison	Summary of results	Conclusions/recommendation	Quality assessment
RFA						
Zhu et al (2008)	To systematically review the safety and efficacy of RFA for primary and secondary lung cancers (safety outcomes from a mix of populations 2 and 3) Note: Efficacy data was mixed for populations 2 and 3	16 case-series studies included (833 patients) Publication date range of included studies: 2003–2006	Study inclusion criteria Studies that reported procedure-related morbidity and mortality, rates of complete tumor ablation, local recurrence and/or survival after RFA of primary or secondary lung tumors Study exclusion criteria Studies that looked at RFA plus radiotherapy, and RFA followed by surgery were excluded	Procedure-related mortality rate 0.0–5.6% (median 0%) [16 studies] Procedure-related morbidity rate 15.2–55.6% (median 35.7%) [16 studies] Complications (16 studies) **Pneumothorax**: 4.5–61.1% (median 28.0%) [13 studies], of which 3.3–38.9% (median 11.0%) required chest tube [11 studies] **Pleural effusion**: 3–60.0% (median 13.4%) [10 studies] **Pneumonia**: 6.0–12.0% (median 9.5%) [5 studies] **Pulmonary abscess**: 1.9–6.6% (median 6.4%) [3 studies] **Hemothorax**: 1.9–16.7% (median 4.3%) [4 studies] **Pulmonary bleed**: 0.0–11.0% (median 7.1%) [3 studies] **Hemoptysis**: 3.3–18.2% (median 11.1%) [7 studies] **Chest pain**: 2.3–24.0% (median 9.0%) [5 studies] **Cough**: 1.4–33.0% (median 3.7%) [3 studies] **Fever**: 6.6–22.2% (median 18.0%) [5 studies]	The authors reported that only limited, low level evidence is available on the clinical outcomes of RFA treatment of lung tumours (only observational studies) and thus cannot be considered a therapeutic equivalent to surgical resection. However, they state that it has a promising safety profile and may have a potential role in the treatment of non-resectable lung tumours.	**MODERATE QUALITY** 1. Was an 'a priori' design provided? **YES** 2. Duplicate study selection and data extraction? **YES** 3. Comprehensive literature search? **YES** 4. Publication status (i.e. grey literature) used as an inclusion criterion? **YES** 5. List of studies provided? **NO** 6. Characteristics of the included studies provided? **YES** 7. Scientific quality of the included studies assessed? **NO** 8. Scientific quality of the included studies used in conclusions? **YES** 9. Methods used to combine the findings of studies appropriate? **N/A** 10. Publication bias assessed? **N/A** 11. Conflict of interest stated? **YES**

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intervention/ comparison	Summary of results	Conclusions/recommendation	Quality assessment
RADIOTHERAPY						
Stevens et al (2015)	1.To assess the effects of different palliative radiotherapy regimens on improving thoracic symptoms in patients with locally advanced or metastatic non-small cell lung cancer who are not suitable for radical radiotherapy given with curative intent. 2. To assess the effects of radiotherapy dose on overall survival in patients with locally advanced or metastatic non-small cell lung cancer who are not suitable for radical RT given with curative intent.	14 RCTs included (3576 patients) Publication date range of included studies: 1985–2005	Study inclusion criteria RCTs fully published in journals and those identified from other sources for which full details were available. Patients were those with histologically or cytologically confirmed (or a high clinical likelihood of) lung cancer of non-small cell type, locally advanced or metastatic and with thoracic symptoms. Radiotherapy interventions included external beam, megavoltage to the chest given with palliative intent with a total tumour dose of less than 60 Gy in 2 Gy fractions or its radiobiological equivalent. Studies must have compared at least two radiation therapy dose/fractionation regimens. Study exclusion criteria Studies on radiotherapy with endobronchial brachytherapy and combination treatment with radiotherapy and chemotherapy were not considered. Studies comparing immediate versus delayed treatment were not considered.	1-year overall survival in patients with WHO performance status 0–1) Less fractions: mean 26% (9–46%) More fractions: mean 33% (11–46%) No summary estimate [1081 patients, 8 studies] 1-year overall survival in patients with WHO performance status 2–4) Less fractions: mean 15% (1–30%) More fractions: mean 18% (9–29%) RR (95%CI): 0.96 (0.91–1.02) [911 patients, 7 studies] Oesophagitis (grade 3 to 4) Less fractions: 22% (0–50%) More fractionated radiotherapy - mean (range): 27.5% (0–56%) RR (95%CI): 1.23 (0.81 to 1.87) [1301 patients, 8 studies] Radiation myelopathy (any grade) Less fractions: mean 0.3% (0–1.4%) More fractions: mean 0.4% (0–1.6%) RR (95%CI): 1.29 (0.37 to 4.51) [2663 patients, 11 studies] Radiation pneumonitis (any grade) Less fractions: mean 3.9% (3–6%) More fractions: mean 2.4% (1.6–4%)	The authors reported that their review showed that for most patients, a short course of radiotherapy with only one or two visits, improves common symptoms as effectively as longer courses, without more side effects. They state that there is no strong evidence to support the view that a longer course of radiotherapy may give a better chance of living for one or two years, but it does result in more immediate side effects, especially sore swallowing.	**HIGH QUALITY** 1. Was an 'a priori' design provided? **YES** 2. Duplicate study selection and data extraction? **YES** 3. Comprehensive literature search? **YES** 4. Publication status (i.e. grey literature) used as an inclusion criterion? **YES** 5. List of studies (included and excluded) provided? **YES** 6. Characteristics of the included studies provided? **YES** 7. Scientific quality of the included studies assessed? **YES** 8. Scientific quality of the included studies used in formulating conclusions? **YES** 9. Methods used to combine the findings of studies appropriate? **YES** 10. Publication bias assessed? **NO** 11. Conflict of interest

Author/Year	Objective of report	Number and publication dates	Population considered in included studies, Intervention/ comparison	Summary of results	Conclusions/recommendation	Quality assessment
				RR (95%CI): 0.6 (0.2–1.7) [533 patients, 3 studies]		stated? **YES**

<CS = case series. CT = computed tomography. CTCAE = Common Terminology Criteria for Adverse Events. ECOG = Eastern Cooperative Oncology Group. FDG = Fludeoxyglucose (18F). HCC = hepatocellular carcinoma. IQR = interquartile range. N/A = not applicable. NR = not reported. NSCLC = non-small cell lung cancer. PET = positron emission tomography. RFA = radiofrequency ablation. TACE = transarterial chemoembolization. US = ultrasound.>

***** Prognostic factors that influence 5-year survival: Two papers reported significantly worse 5-year survival rates in patients with oral head and neck squamous cell carcinoma compared with other sites (9.2% versus 32.4% and 15.4% versus 45.2%; p<0.05).Two papers reported that the presence of cervical lymph node metastases at diagnosis of the primary tumour significantly worsened 5-year survival rates following pulmonary metastasectomy (13.8% (N+) versus 32% (N0), and 24% (N+) versus 60% (N0); p<0.05).

****** Overall 5-year survival in studies that did not distinguish between resections being R0 or R1/2 or only presented with combined data for both types of resection (median: 52.5%, range: 38.3%–63.7%). Thirteen studies presented 5-year survival for patients undergoing R0 resections (either for the whole study population or for subgroups of patients) (median: 39.6%, range: 24–56.0%). Three studies reported 5-year survival for nonradical resection (median: 0%, range: 0–21%) Three studies reported 5-year survival exclusively for patients who had pulmonary and hepatic resection of colorectal metastases. (median: 31%, range: 30–38%). Postoperative mortality reported by four studies. Range: 0–2.5%. Analyses of prognostic factors that affect survival Stage of primary colorectal cancer: Nine studies analysed the stage of the primary tumour as a measurement for long term survival – only one confirmed statistical significance Distribution:Twelve studies reported on the distribution of lung metastases at the time of surgery. Unilateral or bilateral distribution could not be proven to be a prognostic factor for survival/ Carcinoembryonic antigen: In nine studies an elevated CEA level was a valuable prognostic measurement associated with poor prognosis. In seven studies CEA hand no significant prognosticator. Disease-free interval: The disease-free interval between resection of the primary tumour and pulmonary metastasectomy was reported in 19 studies. Median disease-free interval was between 20.0 and 37.5 months. Only in one study was disease free interval found to be a prognostic factor for survival. Surgical approach: Different surgical approaches were not found to have a significant effect on survival. Surgical procedures: The most common thoracic procedure reported in 14 studies was wedge resection or segmentectomy in 804 patients. In the majority of studies (n = 13) the type of lung resection was no prognosticator for survival. Radicality of resection: Of four studies that dealt with patients after complete and incomplete resection, two reported significantly improved long-term survival after achieving clear surgical margins. In three studies, in which the patients received incomplete resections, radicality of resection was not found to be an independent prognostic factor. Repeat pulmonary resection: Seven of the 10 studies with repeat pulmonary resection analysed patients with repeated resection separately for 5-year survival. No study found repeat pulmonary resection for local recurrent disease as an ominous prognostic factor. Effect of combined liver and lung resection: No significant difference in outcome was observed between patients with and without history of previously resected hepatic metastases at the time of pulmonary resection. Number and tumour size: The impact of the number of pulmonary metastases on long-term survival could not be proven by the majority of studies. Thoracic lymph node involvement: Lymph node involvement was not a prognostic factor for survival in studies in which lymph node dissection was not performed contemporary with all procedures, or lymph node dissection was carried out only in cases when node enlargement was detected by a CT scan. Neaoadjuvant and adjuvant therapy: Four studies reported on adjuvant chemotherapy after resection of the primary colorectal tumour. Eight studies reported on neoadjuvant of adjuvant therapy with pulmonary metastasectomy. In all studies chemotherapy was of no prognostic significance for long-term survival.

APPENDIX D EVIDENCE PROFILE TABLES

Table 95 Evidence profile table for population one

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
MTA									
Median OS Follow up: range 22.5 months to 30 months; assessed with: Kaplan-Meier estimate (95% CI)[1]	observational studies (k = 2)	serious [2]	not serious	not serious	serious [5]	none	Han et al (2015): 1.9 months (95% CI 38.8–49.9), Yang et al (2014): 41.9 months (95% CI 38.8–49.9) [4]	⨁⊙⊙⊙ VERY LOW	CRITICAL
Median cancer-specific OS Follow up: range 22.5 months to 30.0 months; assessed with: Kaplan-Meier estimate (95% CI)	observational studies (k = 2)	serious [2]	not serious	not serious	serious [5]	none	Han et al (2015): 1.9 months (95% CI 38.8–49.9), Yang et al (2014): 41.9 months (95% CI 38.8–49.9) [4]	⨁⊙⊙⊙ VERY LOW	CRITICAL
Survival rates at 1-,2-,3- and 4 or 5-years Follow up: range 22.5 months to 30 months; assessed with: Kaplan-Meier estimate (95% CI not reported)	observational studies (k = 2)	serious [2]	not serious	not serious	very serious [6]	none	Han et al (2015): 1-year: 91.7%, 2-year: 76.5%, 3-year: 47.9% and 4-year: 47.9% Han et al (2015) cancer-specific: cancer-specific survival rate was 1-year: 94.7%, 2-year: 73.9%, 3-year: 64.7% and 4-year: 64.7%; Yang et al (2015): 1-year: 89%, 2-year 63%, 3-year 43%, and 5-year: 16% [4]	⨁⊙⊙⊙ VERY LOW	CRITICAL
RFA									

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
Median OS Follow up: range 19 months to 37 months; assessed with: Kaplan-Meier estimate (95% CI)	observational studies (k = 5)	serious [2]	not serious	not serious	serious [8]	none	Median overall survival: 44.3 months (range: 36.5–67). This was generated from Kaplan-Meier estimates.	⨁⊙⊙⊙ VERY LOW	CRITICAL
Survival rates at 1-,2-,3- and 4 or 5-years with RFA Follow up: range 19 months to 46 months; assessed with: Kaplan-Meier estimate (95% CI not reported)9	observational studies (k = 8)	serious [2]	not serious	not serious	very serious [10]	none	1-year median survival rate: 86.3% (range 83–100%); 2-year: 74% (69.8–86%); 3-year: 62.75% (40–74%); 5-year: 28% (14–61%)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Median time to local progression or recurrence Follow up: range 19 months to 46 months; assessed with: Kaplan-Meier estimate (95% CI not reported)	observational studies (k = 4) [11]	serious [2]	not serious	not serious	very serious [12]	none	Ambrogi et al (2011): Median of 39 months (range NR); Lanuti et al (2012): mean (SD) of 12 (10) months, range 1–44; Liu et al (2012): mean (SD): 25 (11) months, range 4–35; Safi et al (2015): 11.9 ± 8.1 (1–24) months with RFA and 6.0 ± 3.0 (1–46) months with radiotherapy, p = 0.36 for test of significance	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Radiotherapy									
Survival rates at 1-,2-,3- and 4 or 5-years Follow up: range 21 months to 30.2 months; assessed with: Varied[13]	observational studies (k = 2) [14]	not serious	not serious	not serious	not serious	none	Koshy et al (2015) 3-year survival: SBRT = 48%, Conventional radiotherapy = 36%, no treatment = 28% 3-yr survival (propensity-matched): SBRT = 48%, conventional radiotherapy	⨁⨁⊙⊙ LOW	

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
							= 40 % (p = 0.001). Videtic et al (2015) 1-year survival 34/1 GY SBRT = 76% (60.3–87.3%) 48/4 GY SBRT = 91.1 % (60.3–87.3%) 2-year survival 34/1 SBRT = 61.3% (44.2–74.6%) 48/4 SBRT = 77.7% (62.5–87.3%)		

< CI = confidence interval, MTA = microwave thermal ablation; NA = not applicable, OS = overall survival, GY = gray, SBRT = stereotactic body radiotherapy, RFA = radiofrequency ablationk = number of studies >

GRADE Working Group grades of evidence (Guyatt et al., 2013).
⊕⊕⊙⊙ Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Han et al (2015) median (range) 22.5 (4–53) months; Yang et al (2015) median (range) 30 (7–70) months
2. Due to inherent limitations in study design and from quality concerns with the included studies
3. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95%CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision
4. Note that: Yang et al (2015) examined a subgroup of patients with tumours > 3.5 cm versus ≤ 3.5 cm and found that tumours ≤ 3.5 cm were associated with better survival than were tumours >3.5 cm (p = 0.016). The distribution in number of patients with tumours >3.5 cm across the two studies will affect the consistency of outcomes.
5. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially wider 95%CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision
6. Neither Han et al (2015) nor Yang et al (2015) provide confidence intervals for point estimates. It isn't clear how precise estimates are. Similarly only Yang et al (2015) report maximum follow-up of >60 months (5 years)
7. Ranged from 19 months in Liu et al (2015) to 37 months in Hiraki et al (2011)
8. There is a wide range of median OS reported by the included studies, from 36.5 months to 67 months. This should be a relatively homogenous group in terms of cancer stage and extent of disease.
9. Ranged from 19 months in Liu et al (2015) to 46 months in Ambrogi et al (2011)
10. There is a wide range of survival rates reported with reporting becoming more and more limited over time. This should be a relatively homogenous group in terms of cancer stage and extent of disease. There is substantial concern that outcomes have been measured very differently across studies. For example Hiraki et al (2011) has a 5-year survival of 61% whilst Ridge et al (2014) reports only 14%.
11. Safi et al (2015) is a Level III-3 retrospective cohort study that compared RFA and radiotherapy
12. Estimates across different studies are markedly different; it may be due to differences in measurement, reporting or outcome.
13. Median of 21 (IQR 11–43) months in Koshy (2015) and 30.2 (NR) months in Videtic et al (2015)
14. Koshy et al (2015) is a Level III-1 retrospective propensity-matched cohort, Videtic et al (2015) is Level II study

Table 96 Evidence profile table for population two

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
MTA									
Survival rate Follow up: median 9 months; assessed with: n/N (%) at 1 and 2 years	observational studies (k = 1)	serious [1]	not serious	not serious	not serious	none	At 12 months the survival rate was 91.3 per cent (73/80 patients alive) and at 24 months it was 75 per cent (60/80 patients alive). Survival greater than 24 months was not reported.	⨁⊙⊙⊙ VERY LOW	CRITICAL
Median time to local progression Follow up: range 9 months to 14 months; assessed with: Mean time in months	observational studies (k = 2)	serious [1]	not serious	not serious	not serious	none	Qi et al (2015): 7.2 months (range 4–20); Vogl et al (2015): 6 months (range: 1–18)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
RFA									
Median OS Follow up: range 12 months to 38 months; assessed with: Kaplan-Meier (95% CI)	observational studies (k = 10)	serious [1]	not serious	not serious	very serious [2]	none	Median overall survival: 44 months (range: 21–67)	⨁⊙⊙⊙ VERY LOW	CRITICAL
1,2,3,5-year survival Follow up: range 12 months to 38 months; assessed with: Kaplan-Meier estimates (95% CI)	observational studies (k = 10)	serious [1]	not serious	not serious	very serious [2]	none	1-year median survival rate: 87.8% (range 73.4–100); 2-year median survival rate: 59.3% (range 41.1–94); 3-year median survival rate: 53 % (range: 30–85); 5-year survival rate NR	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Median time to local progression with RFA Follow up: range 12 months to 38 months;	observational studies (k = 5)	serious [1]	not serious	not serious	serious [5]	none	Median time to local progression: 12 months (range: 8.2–15 months)	⨁⊙⊙⊙ VERY LOW	IMPORTANT

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
assessed with: mean (range) months/Kaplan-Meier estimate (95% CI)									
Radiotherapy									
Median OS Follow up: range 13 months to 55 months; assessed with: median months, Kaplan-Meier	observational studies [3] (k = 11)	serious [1]	not serious	not serious	serious [2]	none	Median overall survival: 27.8 months (range: 12–42.8)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
1,2,3,5-year survival Follow up: range 13 months to 55 months; assessed with: Kaplan-Meier estimate (95% CI)	observational studies [3] (k = 17)	serious [1]	not serious	not serious	very serious [4]	none	1-year median survival rate: 86 % (60.5–98); 2-year median survival rate: 65.1% (31.2–86); 3-year median survival rate: 61.5% (50.1–73); 5-year median survival rate: 46.2 % (39–56.2)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Median time to local progression Follow up: range 15 months to 24 months; assessed with: median months until progression	observational studies [6] (k = 7)	serious [1]	not serious	not serious	serious [5]	none	Median time to progression: 10.8 months (range: 5–18)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Surgery									
Median OS Follow up: median Not reported months; assessed with: Kaplan-Meier estimate (95 % CI))	observational studies (k = 3)	serious [1]	not serious	not serious	serious [4]	none	Renaud et al (2014): No lymph node involvement: 94 months (95% CI, 76.27–111.72) positive lymph node involvement: 42 months (95% CI, 30.06–53.93; p<0.0001) Hilar location of lymph node involvement: 47 months (95% CI, 29.89–64.10) Mediastinal location of	⨁⊙⊙⊙ VERY LOW	IMPORTANT

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
							lymph node involvement: 37 months (95%CI, 13.98–60.01; p>0.05) Solitary pulmonary metastasis: 81 months (95%CI, 60.8–101.19) Multiple metastases: 55 months (95%CI, 35.14–74.86; p<0.01) Hepatic metastases: 47 months (95%CI, 21.6–72.39) No hepatic metastases: 74 months (95%CI, 60.74–87.26;. p<0.01) Reza et al (2014): 35 months (95%CI 23–61); Kitano et al (2012): 26.5 months (range: 0.7–165)		
1,2,3,5-year survival Follow up: range 30 days to NA months; assessed with: varied measures	Observational studies (k = 4)	serious[1]	not serious	not serious	very serious[2]	none	Young et al (2015): Meta-analysis of 5 year overall survival from 11 studies (387 patients) 29.1% (95%CI; 24.1–35.3); I2 = 0%, p = 0.462, d.f. = 10 Pfannschmidt et al (2007): Median 5-year survival 48%, range: 41.1% to 56%). Reza et al (2014): 3-year: 48%, 5-year: 42%, 10-year: 31%. Kitano et al (2012): 2-year OS: 53.9%, 5-year OS: 40.9%	⨁⊙⊙⊙ VERY LOW	IMPORTANT

<CI = confidence interval, MTA = microwave tissue ablation; RFA = radiofrequency ablation; NA = not applicable, OS = overall survival, k = number of studies.>

GRADE Working Group grades of evidence (Guyatt et al., 2013).

⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Due to inherent limitations in study design as well as quality issues
2. Studies report a large range of overall survival times with many studies not providing any indication of the variance associated with point estimates.
3. There were the following other study designs: Siva et al (2015) Level III-2 retrospective cohort study, Yu et al (2014) Level III-2 retrospective cohort study.
4. Studies included investigated a range of prognostic factors and different studies reported on patients with different primaries. This is likely to have affected the overall survival time of included patients.
5. Studies report a range of time to progression estimates and it is not clear whether they were measured in a consistent manner

6. There were the following other study designs: Yu et al (2014) Level III-2 retrospective cohort study.

Table 97 Evidence profile table for population three

Outcome (units, follow-up)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results (e.g. publication bias)	Quality	Importance
MTA									
1 year survival of MTA versus MTA + chemo Follow up: range 6 months to 35 months; assessed with: % of patients living	Observational studies (k= 1)	serious [1]	not serious	not serious	serious [2]	none	MTA alone: 9/18 (50%) MTA and chemotherapy: 17/22 (77.3%)	⊕⊙⊙⊙ VERY LOW	IMPORTANT
2 year survival of MTA versus MTA + chemo Follow up: range 6 months to 35 months; assessed with: % of patients living	Observational studies (k=1)	serious [1]	not serious	not serious	serious [2]	none	MTA alone: 5/18 (27.7%) MTA and chemotherapy: 13/22 (79.1%)	⊕⊙⊙⊙ VERY LOW	IMPORTANT
Median OS (95%CI) with MTA + chemo versus chemo alone Follow up: median 21 months; assessed with: Kaplan-Meier estimate	Observational studies (k=1)	serious [3]	not serious	not serious	serious [4]	none	MTA+chemotherapy: 23.9 (15.2–32.6) months Chemotherapy: 17.3 (15.2–19.3) months, difference p = 0.140	⊕⊙⊙⊙ VERY LOW	IMPORTANT
Median OS (range) with MTA (follow up: median 17.7 months; assessed with: Median and range)	Observational studies (k=1)	observational studies	serious [5]	not serious	not serious	not serious	Median OS: 17.7 months (range of 5–45) and from the time of MTA until death it was 10.6 months (range: 3.1–36.	⊕⊙⊙⊙ VERY LOW	IMPORTANT

<CI = confidence interval, MTA= microwave thermal ablation, NA = not applicable, OS = overall survival, k = number of studies.>

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. This is based on the results of one study with 22patients in one arm and 18 in the other, study reporting quality was low.
2. Measures of variance are not available. The small sample size reduces the reliability of the outcomes.
3. Wei et al (2015) reports on small sample sizes and inherent drawbacks in study design are problematic
4. Measures of variance show wide confidence intervals associated with OS. The small sample size reduces the reliability of the outcomes.
5. Due to inherent limitations in case series evidence.

Table 98 Evidence profile table for safety outcomes

Outcome (units, follow-up, assessment)	No. of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Results	Quality	Importance
Procedure-related mortality									
MTA Follow up: range 6 – 30 mths Assessed with: n/N (%), per patient	Observational studies (k=20)	serious [1]	not serious	not serious	Not serious	none	2/916 (0.22%)[2]	⊕⊙⊙⊙ VERY LOW	CRITICAL
RFA Follow up: range 10 – 46 mths Assessed with: n/N (%), per patient	Observational studies (k=17)	serious [1]	not serious	not serious	Not serious	none	1/1259 (<0.1%)	⊕⊙⊙⊙ VERY LOW	IMPORTANT
Radiotherapy Follow up: range 13 – 82 mths Assessed with: number of patients who died	Observational studies (k=17)	serious [3]	not serious	not serious	not serious	none	There were two cases of procedure-related mortality across all included 17 studies.[4]	⊕⊙⊙⊙ VERY LOW	IMPORTANT
Surgery Follow up: NA Assessed with: number of patients who died	Observational studies (k=3)	serious [1]	not serious	not serious	not serious	none	Pfannschmidt et al (2007): postoperative mortality was reported by 4/20 studies, range 0.0 to 2.5 % Renaud et al (2014) and Kitano et al (2012): 0/365 (0%)	⊕⊙⊙⊙ VERY LOW	IMPORTANT

30-day mortality									
MTA Follow up: range 6 – 30 mths Assessed with: n/N (%), per patient	Observational studies (k=16)	serious [1]	not serious	not serious	not serious	none	1/739 (0.14%)	⨁⊙⊙⊙ VERY LOW	CRITICAL
RFA Follow up: range 10 – 36 mths Assessed with: n/N (%), per patient	Observational studies (k=8)	serious [1]	not serious	not serious	Not serious	none	2/810 (<0.1%)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Radiotherapy Follow up: range 13 – 82 mths Assessed with: number of patients who died	Observational studies (k=17)	serious [3]	not serious	not serious	not serious	none	No deaths within 30 days were reported by any study.	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Surgery Follow up: NA Assessed with: n/N (%), per patient	Observational studies (k=4)	serious [1]	not serious	not serious	not serious	none	10/1,499 (0.67%)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
Pneumothorax									
MTA Follow up: range 6 – 30 mths Assessed with: n/N (%), per ablations	Observational studies (k=22)	serious [1]	not serious	not serious	not serious	none	n/N (%): 280/1025 (27.3) Median: 30.2 (8.3 – 63.8)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
RFA Follow up: range 12 – 46 mths Assessed with: n/N (%), per ablations and per patient	Observational studies (k=19)	serious [1]	not serious	not serious	not serious	none	Per ablation: n/N (%):674/1497 (45%) Median: 24% (9–67%) Per patient: n/N (%): 46/262 (18%) Median: 17.5% (5–36%)	⨁⊙⊙⊙ VERY LOW	IMPORTANT

Pneumothorax requiring intervention									
MTA F/u: range 6 – 30 months Assessed with: n/N (%), per ablations	Observational studies (k=20)	serious [1]	not serious	not serious	not serious	none	n/N (%):122/985 (12.4) Median: 10.3 (0– 28.6)	⨁⊙⊙⊙ VERY LOW	IMPORTANT
RFA F/u: median f/u range 12 – 46 months Assessed with: n/N (%), per ablations and per patient	Observational studies (k=19)	serious [1]	not serious	not serious	not serious	none	Per ablation: n/N (%):335/1497 (22%) Median: 9% (2–39%) Per patient: n/N (%):29/262 (11%) Median: 10% (3–24%)	⨁⊙⊙⊙ VERY LOW	IMPORTANT

<CI=confidence interval, MTA = microwave tissue ablation, RFA = radiofrequency ablation, n/N (%)= number with event/ total (percentage), NA=not applicable, k=number of studies; F/u: follow-up; K=number of studies>

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⨁⨁⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⨁⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Due to inherent limitations in study design.
2. One death was delayed (occurring eight months after the procedure).
3. Studies of radiotherapy included a mix of Level IV, Level III-2, Level III-3 and Level II studies. However, overall there were a large number of Level IV studies.
4. Videtic et al (2015) reported the death of one patient who received 48 Gy radiation in 4 fractions. The patient died 319 days after the procedure due to respiratory failure. The other death was reported by Oh et al (2012), in whom a patient with a long history of COPD, and who had received left Pneumonectomy and postoperative RT for NSCLC prior to SBRT. The patients died from respiratory failure five months after receiving SBRT.

APPENDIX E STUDY OUTCOME TABLES

Table 99 Overall and cancer-specific survival rates at 1-, 2-, 3-, 4- and 5-years (MTA, population one)

Trial/Study	N (lesions)	1-year OS *Cancer specific*	2-year OS *Cancer specific*	3-year OS *Cancer specific*	4-year OS *Cancer specific*	5-year OS *Cancer specific*
Han et al (2015)	28 (28)	91.7% *94.7%*	76.5% *73.9%*	47.9% *64.7%*	47.9% *64.7%*	NR
Liu & Steinke (2015)	15 (16)	NR	NR	NR	NR	NR
Yang et al (2014)[a]	47 (47)	89%	63%	43%	NR	16%
Pooled analysis	75 (75)			Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW		

< CI = confidence interval; N = number; NR= not reported; OS= overall survival >

GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

a Overall 1-, 2-, 3-, and 5-year survivals, stratified by tumour size, were 91%, 72%, 59%, and 36% for tumours 3.5 cm, and 88%, 53%, 27%, and 0% for tumours >3.5 cm (p = 0.016)

Table 100 Overall and cancer-specific survival rates at 1-, 2-, 3- or 5-years (RFA, population one)

Trial/Study	N (lesions)	1-year OS (95% CI) *Cancer specific*	2-year OS (95% CI) *Cancer specific*	3-year OS (95% CI) *Cancer specific*	5-year OS (95% CI) *Cancer specific*
Ambrogi et al (2011)	57 (59)	83%	NR	40%	25%
Dupuy et al (2015)	51 (51)	86.3% (77.3–96%)	69.8% (58.0–83.9%)	NR	NR
Hiraki et al (2011)[a]	50 (52)	94% *100%*	86% *80%*	74% *80%*	61% *74%*
Lanuti et al (2012)	45 (55)	NR	NR	67%	31%
Liu et al (2012)[a]	29 (29)	95% (SD 6.4)	76.4 (SD 10.7)	65.5% (SD 13.6) *74.2% (SD 13.9)*	NR
Viti et al (2014)	22 (24)	83%	64%	48%	NR
Ridge et al (2014)[b]	29 (29)	100%	NR	60%	14%
Safi et al (2015)	25 (25)	NR *86%*	NR *74%*	NR	NR

Trial/Study	N (lesions)	1-year OS (95% CI) *Cancer specific*	2-year OS (95% CI) *Cancer specific*	3-year OS (95% CI) *Cancer specific*	5-year OS (95% CI) *Cancer specific*
Pooled analysis	308/324	Median: 86 (83–100) Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median: 74 (69.8–86) Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median: 63 (40–74) Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median: 28 (14–61) Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW

< CI = confidence interval; N = number; NR= not reported >

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Not significantly different between stages IA and IB

[b] 1-year survival 100% for all subgroups 3-year survival was 55 for first primary tumour, 63 for metachranous disease, 75 for synchronous tumours, 63 for T1a tumours and 60 for T1b tumours

Table 101 Overall survival rates at 1, 2-, 3- and 4-or 5- years (radiotherapy, population one)

Trial/Study	Intervention	N (lesions)	1-year OS (95% CI)	2-year OS (95% CI)	3-year OS (95% CI)	4-year OS (95% CI)	5-year OS (95% CI)
Koshy et al (2015)[a]	No treatment	6888 (NR)	NR	NR	28%	NR	NR
	Conventional radiotherapy	5375 (NR)	NR	NR	36%	NR	NR
	SBRT[b]	773 (NR)	NR	NR	48%	NR	NR
Price et al (2012)	XRT	56 (NR)	NR	56%	NR	NR	20%
	XRT+ gemcitabine	55 (NR)	NR	52%	NR	NR	33%
Videtic et al (2015)	34/1 Gy SBRT	39 (NR)	76% (60–87%)	61% (44–75%)	NR	NR	NR
	48/4 Gy SBRT	45 (NR)	91% (60–87%)	78% (63–87%)	NR	NR	NR
Pooled analysis		6,343 (NR)[c]	Pooling not possible				

<NR = not reported; OS = overall survival; SBRT = stereotactic body radiotherapy; XRT = radical radiotherapy>

[a] Significant difference between 3-year OS across interventions (p < 0.001)

[b] Propensity matched cohort of SBRT and conventional radiotherapy (n = 751 in both): 3-year survival: 40% versus 48% for conventional and SBRT respectively (p = 0.001)

[c] Excluded the no treatment arm in Koshy et al (2015)

Table 102 Overall survival rates at 1, 2-, 3- and 5- years (RFA, population two)

Trial/Study	N (lesions)	Median OS time	1-year OS (95% CI)	2-year OS (95% CI)	3-year OS (95% CI)	5-year OS (95% CI)
De Baere et al (2015)	566 (1037)	62 months	92% (SE 1.2)	79% (SE 1.9)	68% (SE 2.4)	52% (SE 3.3)
Fanucchi et al (2015)	61 (86)	65 months (95% CI 51–79)	95% (SE 0.03)	NR	49% (SE 0.07)	45% (SE 0.070)
Hiraki et al (2011)	32 (83)	37.7 months	87% (76–99)	57% (38–76)	57% (38–76)	NR
Koelbinger et al (2014)	22 (55)	51 months	100%	94%	85%	NR
Li et al (2012)	29 (68)	21 months (95% CI 9.7–32.3)	73%	41%	30%	NR
Lu et al (2015)	67 (115)	24 months (95% CI 8.2–29.8)	84%	46%	14%	NR
Lu et al (2015b)	35 (67)	33 months (95% CI 21.6 – 44.4)	89%	59%	43%	NR
Matsui et al (2015)	84 (172)	67.0 months	95% (91–100%)	NR	65 % (54–76%)	52% (40–64%)
Von Meyenfeldt et al (2011)	46 (90)	55 months (95% CI 26–84)	84%	NR	69%	NR
Yan et al (2006)	55 (NR)	33 months (range 4–40)	85%	64%	46%	NR
Pooled		Median: 44.45 months (range: 21–67) Certainty of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median 87.8 (range: 73.4–100) Certainty of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median 59.3 (range 41.1–94) Certainty of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Median 53 (range: 30–85) Certainty of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	

<CI = confidence interval; NA = not applicable; NR = not reported; OS = overall survival; SE = standard error>

GRADE Working Group grades of evidence (Guyatt et al., 2013)

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 103 Overall survival rates at 1-, 2-, 3- and 5- years (radiotherapy, population 2)

Trial/Study	Intervention	N (lesions)	Median OS time (range)	1-year OS (95% CI)	2-year OS (95% CI)	3-year OS (95% CI)	5-year OS (95% CI)
Agolli et al (2015)	SBRT	22 (29)	24 months (NR)	86%	49%	NR	NR
Baschnagel et al (2013)	SBRT	32 (47)	39 months (NR)	83%	76%	63%	NR
Fillipi et al (2015)	SBRT	40 (59)	46 months (NR)	88% (72–95%)	73% (53–86%)	NR	39% (14–64%)
Gamsiz et al (2014)	SBRT	20 (31)	NR	14-month 70%	NR	NR	NR
Garcia-Cabezas et al (2015)	SBRT	44 (53)	34 months (NR)	87%	60%	NR	NR
Kim et al (2009)	Helical tomotherapy	31 (134)	16 months (SD 2.2)	61%	NR	NR	NR
Navirra et al (2015)	SBRT	28 (51)	28 months (NR)	NR	56% ± 11%	NR	43% ± 12%
Navirra et al (2014)	SBRT	76 (118)	20 months (NR)	84%	73%	73%	NR
Norihisa et al (2008)	SBRT	34 (43)	NR	NR	84%	NR	NR
Nuytens et al (2015)	SBRT	30 (57)	NR	NR	63% (43–78%)	NR	NR
Oh et al (2012)	SBRT	57 (67)	NR	NR	60%	NR	56%
Osti et al (2013)	SBRT	66 (103)	12 months (NR)	76%	31%	NR	NR
Ricardi et al (2011)	SBRT	61 (77)	43 months (NR)	NR	67%	NR	NR
Siva et al (2015)	SBRT	65 (82)	NR	93% (87–100%)	71% (58–86%)	NR	NR
Takeshi et al (2014)	Carbon ion radiotherapy	34 (44)	37 months (NR)	NR	65% (47–84%)	50% (29–71%)	NR
Widder et al (2013)	SBRT	42 (NR)	NR	98% (84–100%)	86% (71–93%)	60% (42–73%)	49% (25–69%)
	Surgery	68 (NR)	NR	87% (76–93%)	74% (61–82%)	62% (49–73%)	41% (27–54%)
Yu et al (2014)	SBRT	27 (NR)	18 months (NR)	NR	40.7	NR	NR

	Surgery	31 (NR)	22 months (NR)	NR	48%	NR	NR
Pooled analysis			Median 28% (12–43%) ⊕⊙⊙⊙ VERY LOW	Median 86% (61–98%) ⊕⊙⊙⊙ VERY LOW	Median 65% (31–86%) ⊕⊙⊙⊙ VERY LOW	Median 62% (50–73%) ⊕⊙⊙⊙ VERY LOW	Median 46% (39–56%) ⊕⊙⊙⊙ VERY LOW

<CI = confidence interval; N = number; NR= not reported; ± = SD; OS = overall survival. SBRT=stereotactic body radiotherapy, GY=gray>

GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 104 Overall survival rates (surgery, population 2)

Trial/Study	N (lesions)	Overall survival time Median (range) or Kaplan-Meier estimate (95%CI) months	Survival rate
Young et al (2015)	13 included studies with 403 patients	NR	Meta-analysis of 5 year overall survival from 11 studies (387 patients) 29.1% (95% CI; 24.1–35.3) I^2 = 0%, p = 0.462, d.f. = 10
Pfannschmidt et al (2007)	20 included studies with 2,320 patients	NR	All studies reported overall survival of 5 years for all patients undergoing resection of pulmonary metastases (median: 48%, range: 41.1% to 56%)[a]
Renaud et al (2014)	320 (NR)	Overall NR[b]	NR
Younes et al (2009)	529 (NR)	NR	90 month overall survival rate for all patients: 30.4%
Reza et al (2014)	118 (NR)	35 months (95% CI, 23–61)	3-year: 48%, 5-year: 42%, 10-year: 31%
Rodriguez-Fuster et al (2014)	532 (NR)	NR	NR
Kitano et al (2012)	45 (NR)	26.5 (range: 0.7–165) months	2-year OS: 53.9%, 5-year OS: 40.9%
Pooled analysis	NA	Pooling not possible Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW	Pooling not possible Quality of the evidence (GRADE) ⊕⊙⊙⊙ VERY LOW

< CI = confidence interval; N = number; NR = not reported, OS = overall survival >

GRADE Working Group grades of evidence (Guyatt et al., 2013)
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a] Overall 5-year survival in studies that did not distinguish between resections being R0 or R1/2 or only presented with combined data for both types of resection (median: 52.5%, range: 38.3% to 63.7%). Thirteen studies presented 5-year survival for patients undergoing R0 resections (either for the whole study population or for subgroups of patients). Median: 39.6%, range: 24% to 56.0%. Three studies reported 5-year survival for nonradical resection. Median: 0%, range: 0% to 21%. Three studies reported 5-year survival exclusively for patients who had pulmonary and hepatic resection of colorectal metastases. Median: 31%, range: 30% to 38%

[b] No lymph node involvement: 94 months (95% CI, 76.27–111.72). Positive involvement: 42 months (95% CI, 30.06–53.93; p<0.0001). Hilar location of lymph node involvement: 47 months (95% CI, 29.89–64.10). Mediastinal location: 37 months (95% CI, 13.98–60.01; p>0.05). Solitary pulmonary metastasis: 81 months (95% CI, 60.8–101.19). Multiple metastases: 55 months (95% CI, 35.14–74.86; p<0.01). Hepatic metastases: 47 months (95% CI, 21.6–72.39). No hepatic metastases: 74 months (95% CI, 60.74–87.26; p<0.01)

APPENDIX F EXCLUDED STUDIES

Studies of MTA excluded based on full text review (n = 35)

Foreign language studies (n = 1)

Feng, W, Liu, W, Li, C, Li, Z, Li, R, Liu, F, Zhai, B, Shi, J & Shi, G 2002, 'Percutaneous microwave coagulation therapy for lung cancer', *Zhonghua zhong liu za zhi* [Chinese journal of oncology], vol.24(4), pp. 388-90.

Full text not retrievable (n = 1)

Computed tomography-guided percutaneous microwave ablation for lung nodules. Lansdale: HAYES, Inc. Healthcare Technology Brief Publication. 2014.

Inappropriate study design (n = 21)

Abbas, G 2011, 'Microwave Ablation', *Seminars in Thoracic and Cardiovascular Surgery*, vol.23(1), pp. 81-83.

Baisi, A, De Simone, M, Raveglia, F & Cioffi, U 2013, 'Thermal ablation in the treatment of lung cancer: Present and future', *European Journal of Cardio-thoracic Surgery*, vol.43(4), pp. 683-86.

Beland, M, Mueller, PR & Gervais, DA 2007, 'Thermal Ablation in Interventional Oncology', *Seminars in Roentgenology*, vol.42(3), pp. 175-90.

Boyer, MJ, Ricardi, U, Ball, D & Salama, JK 2016, 'Ablative Approaches for Pulmonary Metastases', *Thoracic Surgery Clinics*, vol.26(1), pp. 19-34.

Cardona, K, Williams, R & Movva, S 2013, 'Multimodality therapy for advanced or metastatic sarcoma', *Current Problems in Cancer*, vol.37(2), pp. 74-86.

Carrafiello, G, Lagana, D, Mangini, M, Fontana, F, Dionigi, G, Boni, L, Rovera, F, Cuffari, S & Fugazzola, C 2008, 'Microwave tumors ablation: Principles, clinical applications and review of preliminary experiences', *International Journal of Surgery*, vol.6(SUPPL. 1), pp. S65-S69.

Carrafiello, G, Mangini, M, De Bernardi, I, Fontana, F, Dionigi, G, Cuffari, S, Imperatori, A, Lagana, D & Fugazzola, C 2010, 'Microwave ablation therapy for treating primary and secondary lung tumours: technical note', *Radiol Med*, vol.115(6), pp. 962-74.

Ghaye, B 2013, 'Percutaneous ablation of malignant thoracic tumors', *Jbr-Btr*, vol.96(3), pp. 142-54.

Gillams, A 2008, 'Tumour ablation: Current role in the liver, kidney, lung and bone', *Cancer Imaging*, vol.8(SPEC. ISS. A), pp. S1-S5.

Healey, TT & Dupuy, DE 2012, 'Microwave ablation for lung cancer', *Medicine and health, Rhode Island*, vol.95(2), pp. 52-53.

Hernandez, JI, Cepeda, MF, Valdes, F & Guerrero, GD 2015, 'Microwave ablation: state-of-the-art review', *Onco Targets Ther*, vol.8pp. 1627-32.

Jones, GC, Kehrer, JD, Kahn, J, Koneru, BN, Narayan, R, Thomas, TO, Camphausen, K, Mehta, MP & Kaushal, A 2015, 'Primary treatment options for high-risk/medically inoperable early stage NSCLC patients', *Clinical Lung Cancer*, vol.16(6), pp. 413-30.

Oesch, A, Kuster, R & Schmid, RA 2012, 'Limited resection or radiofrequency ablation for high risk patients', *Therapeutische Umschau*, vol.69(7), pp. 429-32.

Pua, BB, Thornton, RH & Solomon, SB 2010, 'Ablation of pulmonary malignancy: Current status', *Journal of Vascular and Interventional Radiology*, vol.21(SUPPL. 8), pp. S223-S32.

Schneider, T, Heussel, CP, Herth, FJF & Dienemann, H 2013, 'Thermal ablation of malignant lung tumors', *Deutsches Arzteblatt international*, vol.110(22), pp. 394-400 and I and 8.

Sofocleous, CT, Sideras, P, Petre, EN & Solomon, SB 2011, 'Ablation for the management of pulmonary malignancies', American Journal of Roentgenology, vol.197(4), pp. W581-W89.

Solomon, SB, Thornton, RH, Dupuy, DE & Downey, RJ 2008, 'Protection of the Mediastinum and Chest Wall with an Artificial Pneumothorax during Lung Ablations', *Journal of Vascular and Interventional Radiology*, vol.19(4), pp. 610-15.

Sonntag, PD, Hinshaw, JL, Lubner, MG, Brace, CL & Lee, FT 2011, 'Thermal Ablation of Lung Tumors', *Surgical Oncology Clinics of North America*, vol.20(2), pp. 369-87.

Vogl, TJ, Naguib, NNN, Lehnert, T & Nour-Eldin, NEA 2011, 'Radiofrequency, microwave and laser ablation of pulmonary neoplasms: Clinical studies and technical considerations - Review article', *European Journal of Radiology, vol.77*(2), pp. 346-57.

Wasser, EJ & Dupuy, DE 2008, 'Microwave ablation in the treatment of primary lung tumors', *Seminars in Respiratory and Critical Care Medicine*, vol.29(4), pp. 384-94.

Zheng, A, Yang, X, Ye, X, Huang, G, Wei, Z, Wang, J, Han, X, Ni, X & Meng, M 2015, 'Bronchopleural fistula after lung ablation: Experience in two cases and literature review', *Indian Journal of Cancer*, vol.52(6), pp. e41-e46.

Studies in which the intervention was mixed and outcomes were not separable (n = 2)

Cheng, M, Fay, M & Steinke, K 2016, 'Percutaneous CT-guided thermal ablation as salvage therapy for recurrent non-small cell lung cancer after external beam radiotherapy: A retrospective study', Int J Hyperthermia, vol.pp. 1-8.

Grieco, CA, Simon, CJ, Mayo-Smith, WW, DiPetrillo, TA, Ready, NE & Dupuy, DE 2006, 'Percutaneous image-guided thermal ablation and radiation therapy: Outcomes of combined treatment for 41 patients with inoperable stage I/II non-small-cell lung cancer', *Journal of Vascular and Interventional Radiology*, vol.17(7), pp. 1117-24.

Studies without relevant outcomes (n = 3)

Erinjeri, JP, Thomas, CT, Samoilia, A, Fleisher, M, Gonen, M, Sofocleous, CT, Thornton, RH, Siegelbaum, RH, Covey, AM, Brody, LA, Alago Jr, W, Maybody, M, Brown, KT, Getrajdman, GI & Solomon, SB 2013, 'Image-guided thermal ablation of tumors increases the plasma level of interleukin-6 and interleukin-10', *Journal of Vascular and Interventional Radiology*, vol.24(8), pp. 1105-12.

Ierardi, AM, Petrillo, M, Xhepa, G, Lagana, D, Piacentino, F, Floridi, C, Duka, E, Fugazzola, C & Carrafiello, G 2016, 'Cone beam computed tomography images fusion in predicting lung ablation volumes: A feasibility study', *Acta Radiologica*, vol.57(2), pp. 188-96.

Pou Ucha, JL, Nogueiras Alonso, JM, Alvarez Paez, AM, Suarez Arfenoni, BA, Puig, AS, Lopez Lopez, AM, Barandela Salgado, J, Campos Villarino, LM, Casal Rivas, M & Guitian Iglesias, R 2012, 'Diagnostic yield of baseline and follow-up PET/CT studies in ablative therapy for non-small cell lung cancer', *Rev Esp Med Nucl Imagen Mol*, vol.31(6), pp. 301-7.

Studies of the wrong intervention (n = 2)

Gomez, FM, Patel, PA, Stuart, S & Roebuck, DJ 2014, 'Systematic review of ablation techniques for the treatment of malignant or aggressive benign lesions in children', *Pediatric Radiology*, vol.44(10), pp. 1281-89.

Palussiere, J, Lagarde, P, Auperin, A, Deschamps, F, Chomy, F & de Baere, T 2015, 'Percutaneous Lung Thermal Ablation of Non-surgical Clinical N0 Non-small Cell Lung Cancer: Results of Eight Years' Experience in 87 Patients from Two Centers', *Cardiovascular and interventional radiology*, vol.38(1), pp. 160-66.

Wrong population (n = 4)

Ryan, ER, Sofocleous, CT, Schoder, H, Carrasquillo, JA, Nehmeh, S, Larson, SM, Thornton, R, Siegelbaum, RH, Erinjeri, JP & Solomon, SB 2013, 'Split-dose technique for FDG PET/CT-guided percutaneous ablation: A method to facilitate lesion targeting and to provide immediate assessment of treatment effectiveness', *Radiology*, vol.268(1), pp. 288-95.

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