Cryotherapy for Recurrent Prostate Cancer and Renal Cancer

Part A – Salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Part B – Cryotherapy for renal cancer

September 2009

MSAC application 1124

Assessment report

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Minister for Health and Ageing 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.

This report was prepared by Ms Zhaohui Liufu, Ms Skye Newton and Professor Janet Hiller from Adelaide Health Technology Assessment (AHTA), Discipline of Public Health, the University of Adelaide, with the assistance of an Advisory Panel of experts. The report was commissioned by the Department of Health and Ageing on behalf of the Medical Services Advisory Committee (MSAC). It was edited by Ms Jo Mason, Mason Edit, South Australia.

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Executive summary

The procedure

Cryotherapy is a procedure that can be used for recurrent or persistent prostate cancer after radiotherapy. In the past 20 years there have been large advances in cryoablative technology, including the use of transrectal ultrasound guidance and urethral warming, as well as the transition from liquid nitrogen-driven to argon gas-based systems, to reduce the occurrence of post-procedural adverse events. Both second- and third-generation cryotherapy take advantage of these technologies, the only difference between them being the cryoprobe diameter. During a cryotherapy procedure, cryoprobes are placed into the prostate gland. Argon gas expands in the chamber at the end of the probe, reducing the temperature through the Joule-Thomson process, generating an ice ball. Helium gas is then delivered to the needle to induce active thawing. Cancer cells are ruptured and killed through the freeze/thaw cycle. A second cycle is highly recommended to ensure complete destruction of malignant cells.

Neoadjuvant hormone therapy (NHT) may be prescribed to a proportion of patients before salvage cryotherapy, with the intent of improving the clinical outcomes of cryotherapy by shrinking the gland size, reducing tumour extension and decreasing positive surgical margins.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Adelaide Health Technology Assessment, in the Discipline of Public Health, School of Population Health and Clinical Practice within the University of Adelaide, was engaged to conduct a systematic review of literature on cryotherapy for recurrent or persistent prostate cancer after radiotherapy. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC on the safety, effectiveness and cost-effectiveness of cryotherapy for recurrent or persistent prostate cancer after radiotherapy.

MSAC's assessment of cryotherapy

Clinical need

Salvage cryotherapy is indicated for patients with biopsy-confirmed recurrent or persistent prostate cancer after radiotherapy, with no clinical evidence of extraprostatic extension or metastases, and with tolerance for spinal or general anaesthesia. In current clinical practice in Australia, an extremely large proportion of patients (>95%) who fit the selection criteria for salvage cryotherapy receive non-curative ongoing hormone therapy or watchful waiting. Other salvage treatment options, such as radical

prostatectomy, high-intensity focused ultrasound (HIFU) and brachytherapy, are rarely performed.

Prostate cancer is the second most common malignant tumour in Australian males, preceded only by non-melanoma skin cancer. In 2004, a total of 15 759 new cases of prostate cancer were diagnosed in Australia, corresponding to an annual age-standardised incidence rate of 163 per 100 000. Using data from the United States, it is estimated that 37.3 per cent of patients with prostate cancer undergo radiotherapy as their primary treatment. Given the incidence of prostate cancer in Australia, it is expected that the number of primary radiotherapy cases in Australia would be 5878 per year. The literature indicated that between 10.0 and 57.4 per cent of patients treated by primary radiotherapy would develop histologically confirmed recurrent or persistent prostate cancer; therefore, the number of patients with radiation failure would range between 588 and 3374 per year. Expert advice from the Advisory Panel and the applicant suggest that between 10 and 33 per cent of those patients with recurrent prostate cancer may be assumed to be suitable for salvage cryotherapy. It is expected that the number of salvage cryotherapy procedures performed in Australia would therefore be between 59 and 1113 per year.

Safety

In order to assess the safety of argon-based salvage cryotherapy (±neoadjuvant hormone therapy (NHT)) for the treatment of recurrent or persistent prostate cancer after radiotherapy, the procedure was compared to other potentially curative salvage treatments: salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT). However, no studies comparing the safety of salvage cryotherapy (±NHT) with these alternative treatments were identified. Eighteen uncontrolled case series and one case study reported on the safety of cryotherapy.

No procedure-related death or life threatening events were reported as a consequence of cryotherapy. Recto-urethral fistula was the most serious adverse event reported, with incidence rates ranging between 0 and 7.1 per cent during follow-up periods of between 8.3 and 72.5 months. Between 60 and 100 per cent of patients with potency before salvage cryotherapy suffered impotence post-procedurally. Rates of urethral damage have decreased with the use of urethral warming during cryotherapy procedures. Less than one-third of patients developed urinary incontinence after cryotherapy. Urethral sloughing, urethral stricture, bladder neck obstruction and urethral ulcer were also observed as adverse consequences from salvage cryotherapy in up to 11.1 per cent of patients.

Pain in the pelvis and/or perineal and/or rectum was the most common minor complication resulting from salvage cryotherapy, with incidence rates of between 0 and 39.6 per cent reported during various follow-up periods. Other minor adverse events included urinary tract infection, scrotal swelling, transient haematuria, penile tingling and/or numbness, and proctitis.

There was no evidence indicating that the smaller cryoneedles (17-G) used for third-generation cryotherapy systems would result in better safety outcomes, when compared with the 2.4 mm or 3 mm probes used in second-generation cryotherapy.

Overall, without direct comparative data, it is not possible to draw a conclusion on the safety of salvage cryotherapy (±NHT) relative to other salvage procedures. However,

naïve comparisons with evidence from studies identified through non-systematic searching strategies and the expert opinion of the Advisory Panel suggests that salvage cryotherapy (±NHT) is likely to be as safe as or safer than salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT). In addition, cryotherapy, as an invasive procedure, is unlikely to be as safe as conservative treatments such as stand-alone hormone therapy and watchful waiting.

Effectiveness

Twenty-one uncontrolled case series were identified that investigated the effectiveness of salvage cryotherapy (±NHT). None of the follow-up periods reported by these studies were ideal (≥10 years): one followed patients for approximately 6 years; two reported a mean follow-up period of longer than 2 years (25 months and 39 months); and the remaining 18 studies followed patients for no more than 2 years.

The overall survival rates ranged between 92 and 100 per cent with mean follow-up periods of between 8.3 and 39 months. As reported in one study, 5-year and 8-year overall survival rates were 97 per cent and 92 per cent, respectively, in those patients who were followed up longer than 5 years or 8 years. No more than 5 per cent of patients died from prostate cancer after salvage cryotherapy during follow-up periods ranging from 8.3 to 24 months.

Biopsy-confirmed disease-free survival was achieved in 83.4 to 94.1 per cent of patients who underwent routine biopsies and 50.0 to 100 per cent of patients who had a biopsy after having abnormal results in prostate specific antigen (PSA) testing. Two-year PSA control rates were reported as between 38 and 79 per cent by various studies, where different definitions of biochemical recurrence-free survival (BRFS) were used. If 0.5 ng/mL was defined as the PSA cut-off value, 7-year PSA control was achieved in 59 per cent of patients. Risk factors for biochemical recurrence after salvage cryotherapy included a PSA level of above 10 ng/mL, a Gleason score of more than 6, and a clinical stage of higher than 2b before primary radiotherapy. Local lymph node involvement and distant metastases developed in 0 to 15.8 per cent of patients following salvage cryotherapy.

Patients recovered from salvage cryotherapy quickly and were required to stay in hospital for no more than 1 day. Although post-procedure urinary and sexual dysfunction or discomfort was expressed, patients reported good health status and quality of life (QoL) in general after cryotherapy.

Based on the available evidence, salvage cryotherapy (±NHT) appears to be effective in the short term for the treatment of recurrent or persistent prostate cancer after radiotherapy. Its long-term effectiveness is still waiting to be proved. As no data compared salvage cryotherapy (±NHT) against salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT), it was impossible to draw any conclusions as to the comparative effectiveness of the procedure. However, as a curative treatment, salvage cryotherapy is expected to be more effective than conservative stand-alone hormone therapy and watchful waiting.

Economic considerations

As there was no evidence comparing salvage cryotherapy (±NHT) with salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), it was impossible to determine if the procedure is as effective as, or more effective than, its comparators. Therefore, only a financial incidence analysis was performed to identify the likely cost impact of salvage cryotherapy, if it was to be listed on the Medicare Benefits Schedule (MBS). Since ongoing hormone therapy and watchful waiting are currently the major treatments for radiation failure, their costs are considered when estimating the financial implications of salvage cryotherapy, even though stand-alone hormone therapy and watchful waiting are not appropriate comparators for the assessment of the safety and effectiveness of cryotherapy. On the contrary, salvage radical prostatectomy, salvage HIFU and salvage brachytherapy are not included in the financial analysis because these procedures are performed in very few patients with recurrent or persistent prostate cancer after radiotherapy; and their cost impact on both the government and the society is relatively insignificant.

The estimate of the financial impact of salvage cryotherapy relied on the following assumptions: that all patients with radiation failure would otherwise be managed either by stand-alone hormone therapy (80%) or watchful waiting (20%); that 50 per cent of patients that undergo hormone therapy are treated with Goserelin and the remaining 50 per cent with Leuprorelin; and that ongoing hormone therapy and watchful waiting take place in private health care settings.

The expenditures related to salvage cryotherapy were calculated in separate scenarios: where various proportions (10% and 33%) of patients with recurrent or persistent prostate cancer after radiotherapy undergo salvage cryotherapy; where different numbers (20 and 500) of cryotherapy procedures are performed per machine per year; and where varied public to private patient splits (75:25 and 50:50) were used. The financial incidence analysis was complicated further—the costs of cryotherapy relative to hormone therapy vary over different time frames, as the expenditures on hormone therapy drugs for an additional year greatly exceed those on follow-up visits and PSA testing after cryotherapy. The analyses were simplified by employing the base case where 2000 patients develop recurrent or persistent prostate cancer after radiotherapy per year, rather than using the wide range of 588 to 3374 (see the 'Clinical need' section).

It was estimated that the unit cost per cryotherapy procedure (including the costs of work-up and post-procedural care) would be $16 727 in the first year if 20 procedures are performed annually on one cryotherapy machine (based on the expected use for this indication in one centre); and $13 973 when the annual volume of procedures reached 500 (if the cryotherapy equipment is used at maximum efficiency). The high cost of cryotherapy is mainly attributable to the expensive disposable Cryokit and gases ($8700). The costs of follow-up after cryotherapy would be approximately $55 in the second year and each year thereafter. The costs to the Australian Government for each cryotherapy procedure would be $2809 for the first year, then approximately $40 for each additional year.

Overall, a cost *saving* to the government of salvage cryotherapy would range between $688 608 and $2 739 439 in the first year, in different scenarios where various numbers (50, 100, 165 and 330) of cryotherapy procedures would be carried out in a private healthcare setting. By the end of the second year, the cost *saving* would be about twice as much as that in the first year. If 5-year disease-specific survival of 100 per cent is

achieved in patients who are treated by cryotherapy, the government would *save* $3 309 892 to $11 416 442 over the 5-year horizon.

The cost to the Australian healthcare system is estimated to be between $2 794 510 and $11 039 556 in the first year, incurring an *additional* cost of $1 712 230 to $7 468 032 relative to ongoing hormone therapy and watchful waiting. The cost difference would become narrower in the second and the third years. After that, cryotherapy would result in cost savings. There would be a *saving* of $454 151 to $3 316 370 over 5 years if all the patients receiving cryotherapy lived longer than 5 years without experiencing treatment failure.

It should be highlighted that the above cost implications of cryotherapy for recurrent or persistent prostate cancer after radiotherapy are estimated assuming *100 per cent* of patients who receive salvage cryotherapy are disease free during follow-up periods. Otherwise, additional costs would be incurred to both the Australian Government and the healthcare system overall for the treatment of recurrence after salvage cryotherapy.

Expert opinion

It is the opinion of the Advisory Panel that, in current clinical practice in Australia, a vast majority of patients with recurrent or persistent prostate cancer after radiotherapy receive non-curative ongoing hormone therapy and watchful waiting, due to concerns over the safety of salvage radical prostatectomy, salvage HIFU and salvage brachytherapy as well as the unavailability of these curative treatments in some healthcare settings. The Advisory Panel indicated that salvage cryotherapy would be a preferred treatment for patients who meet the selection criteria. In current clinical practice, salvage cryotherapy procedures after radiation failure are only performed in one centre in Australia.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of cryotherapy, a therapeutic intervention for recurrent or persistent prostate cancer. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for cryotherapy for recurrent or persistent prostate cancer after radiotherapy.

Rationale for assessment

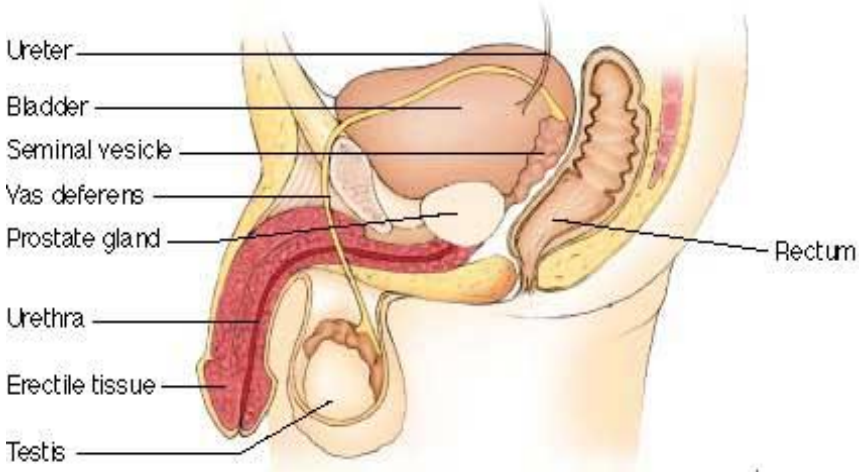
Scanmedics Pty Ltd has submitted an application to the MSAC to have an assessment undertaken of the safety, effectiveness and cost-effectiveness of cryotherapy for recurrent or persistent prostate cancer after radiotherapy.

Background

Prostate cancer

The prostate is a walnut-shaped compound tubuloalveolar exocrine gland of the male reproductive system. It is located at the base of the urinary bladder, anterior to the rectum. The prostate gland wraps around the first part of the urethra, which allows the passage of urine and semen out of the penis (see Figure 1). The gland has two functions: to produce part of the nutrients (including calcium, zinc, citric acid, acid phosphatase and albumin) in semen and to control urination by pressing directly against part of the urethra (Braunwald et al 2001).

Figure 1 Prostate gland



Source: Strax 2006; used with permission

Prostate cancer is the abnormal growth of malignant cells in the prostate gland. Localised prostate cancer is usually asymptomatic, but also may present with symptoms such as urinary retention, incontinence, haematuria (blood in the urine), pelvic pain, and urethral or bowel obstruction (Braunwald et al 2001). As the cancer advances, the tumour invades tissues surrounding the prostate gland, or metastasises to distant locations in the body, such as the bones, lungs and liver. Patients with advanced prostate cancer often develop urinary symptoms (painful urination, urgency, frequency, hesitation, straining, dribbling or haematuria), other local symptoms (constipation, low back pain or pelvic bone pain) or general symptoms (unexplainable weight loss, loss of appetite, anaemia, recurring fevers and so on) (Braunwald et al 2001).

Prostate cancer generally develops and progresses slowly. Therefore, a great number of younger patients with prostate cancer detected in its early stage have a long life expectancy after treatment, while a large proportion of older patients die from diseases other than prostate cancer (Brenner & Arndt 2005; Kessler & Albertsen 2003). It is estimated that between 30 and 40 per cent of men aged over 50 years would have evidence of prostate cancer if biopsied. However, only one in four of these cancers would become symptomatic in their lifetime and just one in 14 would be the cause of death (Abbas & Scardino 1997). Since it is still not possible to differentiate clinically significant tumours from non-life-threatening prostate cancers, screening for prostate cancer using either a prostate specific antigen (PSA) test or a digital rectal examination

(DRE) has been widely debated. Currently, population-based prostate cancer screening is not recommended by the Australian Prostate Cancer Collaboration, the Urological Society of Australia and New Zealand or any Cancer Council in Australia, given a lack of definitive evidence of beneficial effects of such screening on patient outcomes, such as mortality rates from prostate cancer and patients' quality of life (QoL) (Ilic et al 2008; MacKenzie et al 2007; The Cancer Council Australia 2007). However, the PSA test has been highly promoted at a community level, resulting in a high uptake level in general practice. In 2007 the Australian Government reimbursed the cost of 1 379 029 PSA tests, of which 860 704 (62.4%) were for screening and case finding (Medicare Australia 2008a).

Primary treatment and treatment failure

Major primary treatments for prostate cancer include radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy; the latter two are jointly termed radiotherapy. Chemotherapy, hormone therapy, high-intensity focused ultrasound (HIFU), cryotherapy and watchful waiting are other potential primary treatment options. Post-treatment PSA level has been widely recognised as an appropriate measure of treatment response (Kuriyama et al 1981). The detection of biochemical failure after radical prostatectomy is relatively straightforward, in that the source of PSA production, the prostate gland, has been removed during the treatment. Therefore, the biochemical recurrence after radical prostatectomy is generally defined as a detectable PSA level during follow-up (Nielsen & Partin 2007). However, the definition of biochemical failure following radiotherapy is more complicated, because current radiotherapy technology cannot remove all functioning prostatic epithelium (Nielsen & Partin 2007).

A lack of consensus on biochemical failure after radiotherapy prompted the American Society for Therapeutic Radiology and Oncology (ASTRO), in its 1996 Consensus Conference, to formulate a standard definition of biochemical failure after radiotherapy as 'three consecutive rises in PSA level after the PSA nadir, backdating to the point halfway between the nadir and the first rise' (American Society for Therapeutic Radiology and Oncology Consensus Panel 1997). Accumulated clinical experience since has noted the inherent limitations of this consensus definition, such as delays in the diagnosis of treatment failures, difficulties in interpreting PSA results when hormone therapy is given as an adjuvant treatment, and biases in estimating event-free survival through Kaplan-Maier survival analysis (Dudderidge et al 2007; Nielsen & Partin 2007). Therefore, the second Consensus Conference, sponsored by ASTRO and the Radiation Therapy Oncology Group (RTOG) in 2005, revised the definition of radiotherapy failure to 'a rise of 2 ng/mL or more above the PSA nadir, with the date of failure being determined at call' (Roach et al 2006). Once biochemical failure occurs, a prostate biopsy should always be carried out to seek histological evidence of prostate cancer before local salvage treatments are considered. Other investigations, such as bone scan, abdominal and pelvic magnetic resonance imaging (MRI), computed tomography (CT) and pelvic lymph node dissection, are usually prescribed to rule out distant metastases or regional lymph node involvement, as local salvage treatments are no longer suitable for these cases (Dudderidge et al 2007; Galosi et al 2007).

The procedure

Cryotherapy is a method of killing cancer cells through a process of rapid freeze and thaw cycles (Pareek & Nakada 2005). It was first used to treat prostate cancer in the

1960s using a single liquid nitrogen probe (Gonder et al 1966). Early methods of cryotherapy were associated with high rates of complications, such as incontinence, urethral sloughing[1], and recto-urethral fistula formation (Lam & Belldegrun 2004). Current methods of cryotherapy (Table 1) have greatly reduced the rate of complications through the use of transrectal ultrasound (TRUS) for treatment planning and real-time monitoring of the placement of needles and the freezing process, and a urethral warming catheter (39–43 °C) to reduce the rate of urethral sloughing (Pareek & Nakada 2005). Furthermore, the change of freezing agent from liquid nitrogen to argon gas has allowed the use of smaller diameter needles in second- and third-generation cryotherapy (2.4 mm and 1.47 mm, respectively). The thinner probes used in argon-based cryotherapy systems allow for a direct transperineal placement of cryoprobes into the prostate gland (through an interstitial radiotherapy or brachytherapy template). There is no need for an incision kit or dilating sheaths, which are necessary for the liquid nitrogen-based cryotherapy system (Galosi et al 2007; Scanmedics Pty Ltd, 2007) (see Figure 2).

Argon gas is delivered under pressure into a chamber at the end of the needle, where it expands and cools to below –40 °C. This is known as the Joule-Thomson effect, where different gasses undergo temperature changes when depressurised (Lam & Belldegrun 2004). An ice ball forms around the needle, freezing the prostate and the tumour within it (Figure 2). Second- and third-generation cryotherapy then employ helium gas to produce active thawing, which ruptures and kills the cells in the prostate. This freeze/thaw cycle (FTC) is repeated to ensure that all the cancer cells are destroyed (Moreno et al 2007). Patients have a urinary catheter inserted, in case of any temporary incontinence, which is normally removed after several days. Cryotherapy can be performed as an outpatient procedure but is usually associated with 2 days of hospitalisation (Scanmedics Pty Ltd 2007).

Table 1 Generations of cryotherapy (since 1995)

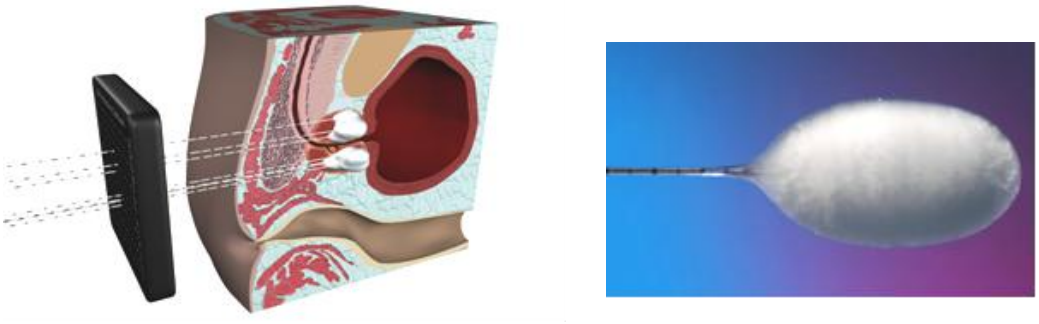
Generation	Cryogen	Thawing	Probe diameter	Probe placement	New characteristics
First	Liquid nitrogen	Passive thawing	3 mm	Requires tract dilation	TRUS-guided and monitored Urethral warming
Second	Argon gas	Helium gas	3 mm / 2.4 mm	Direct puncture with 2.4 mm probe	Template guidance Computerised planning system Auto freeze control Variable freezing length probe
Third	Argon gas	Helium gas	1.47 mm (17-G)	Direct puncture	Smaller probes

Source: Shinohara 2007

TRUS: transrectal ultrasound

[1] urethral sloughing = necrotic tissue from the prostate entering the urinary tract

Figure 2 Cryotherapy for prostate cancer



a b

Source: Galil Medical Inc 2007; used with permission
a: The prostate cryotherapy procedure; b: The ice ball

Intended purpose

Indications

Salvage cryotherapy is a local curative treatment and is indicated for patients:

- with biopsy-confirmed recurrent or persistent prostate cancer after radiotherapy
- with no evidence of extraprostatic extension or metastases
- who are fit for spinal or general anaesthetic

(Dudderidge et al 2007; Galosi et al 2007; Moreno et al 2007; Scanmedics Pty Ltd 2007).

A PSA level less than or equal to 10 ng/mL and a Gleason score[1] less than 8 are suggested as elective indications for salvage cryotherapy after radiation failure, in that patients who do not fall into this category have a high risk of concomitant or subsequent unidentified micro-metastatic diseases and therefore a high possibility of salvage treatment failure (Dudderidge et al 2007; Galosi et al 2007).

Relative contraindications to salvage cryotherapy include:

- extensive defect of prostate tissue after previous transurethral prostate surgery
- large prostate gland (over 50 cm^3)
- significant symptoms of urinary obstruction before treatment
- history of abdominoperineal resection for major rectal diseases, such as rectal cancer or rectal stenosis

[1] The Gleason score is the sum of the differentiation grade scores of cancer cells from two sections of a prostate cancer. The scale goes from 2 (well differentiated, least aggressive) to 10 (undifferentiated, most aggressive) (Che & Grignon 2002).

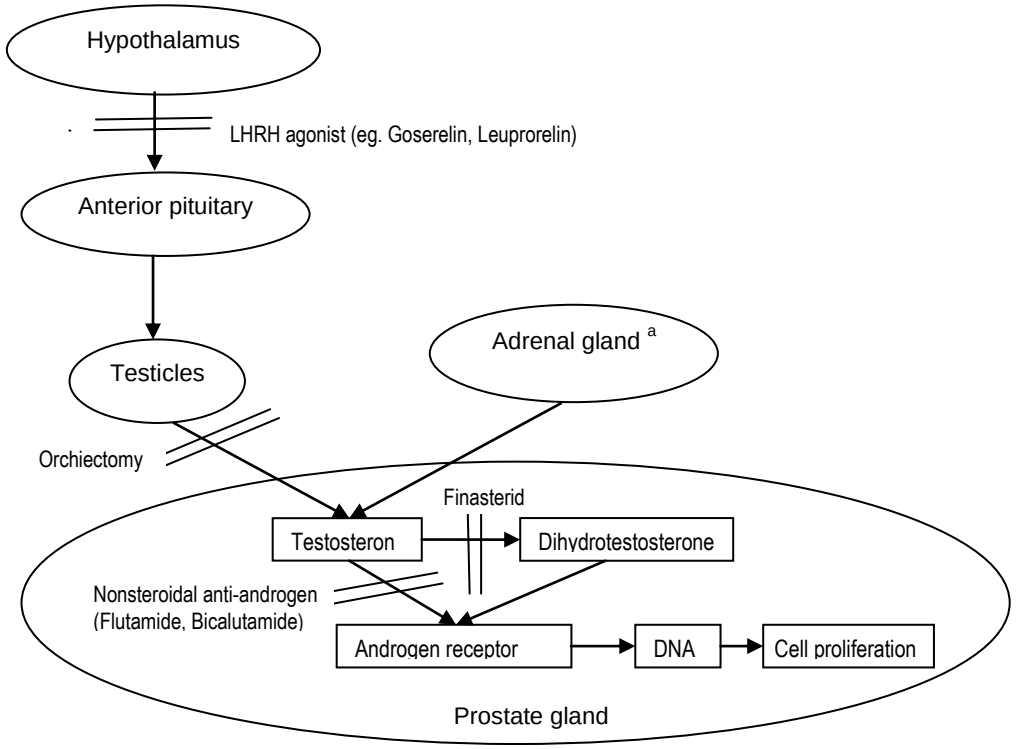
- presence of fistula from inflammatory bowel diseases

(Cooperberg et al 2006; Galosi et al 2007 ; Scanmedics Pty Ltd 2007).

Neoadjuvant hormone therapy

Neoadjuvant hormone therapy (NHT) may be prescribed in combination with salvage treatments, including cryotherapy, especially for those patients with large prostate glands (over 50 cm^3). NHT contrasts with traditional adjuvant hormone therapy in that NHT is usually given before, not after, salvage treatments, and does not continue during or after mainstay treatments (Garnick & Fair 1997). The typical duration of NHT is 3 months. It is prescribed for the purpose, through androgen deprivation, of improving the clinical outcomes of mainstay treatments by diminishing the size of the prostate gland, decreasing extracapsular extension, and reducing the number of positive surgical margins (Aus et al 1998; Meyer et al 2001; Schulman et al 2000; Soloway et al 2002). A variety of drugs, targeting different levels of glands in the endocrine system, can be used in NHT to achieve androgen deprivation, in either a single-agent or double-agent regimen (Figure 3) (Garnick & Fair 1997; Hellerstedt & Pienta 2002; Patel et al 2006).

Figure 3 Levels for androgen deprivation



Source: Hellerstedt & Pienta 2002

[a] The adrenal gland produces 10% of the body's testosterone.

LHRH: luteinizing hormone-releasing hormone; DNA: deoxyribonucleic acid

Existing procedures

The clinical decision-making process concerned with the use of salvage cryotherapy in the management of recurrent or persistent prostate cancer is presented in Figure 4 (page 15).

Radical prostatectomy after radiation failure is a local treatment modality with the longest history among all salvage treatments (Lam & Belldegrun 2004). For patients with large prostate glands, NHT is usually given in combination with salvage prostatectomy. By removing the prostate gland, radical prostatectomy has the ability to eradicate the local tumour, providing long-term disease-specific survival (Lam & Belldegrun 2004). However, in clinical practice the surgical procedure is a challenging operation and has poor acceptance due to significant peri- or post-treatment morbidity (Lam & Belldegrun 2004). The primary radiotherapy-related tissue fibrosis and the merging of tissue planes used for dissection complicate the salvage radical prostatectomy operation, resulting in longer surgery time and more complications such as rectal injury, incontinence, impotence and bladder neck stricture (Nguyen et al 2007).

HIFU is another potential option for salvage treatment of recurrent or persistent prostate cancer (Bong & Keane 2007; Dudderidge et al 2007; Galosi et al 2007). This procedure kills cancer cells by using a lethal rise in temperature in the targeted prostate gland (Dudderidge et al 2007). The reported promising treatment effectiveness and acceptable morbidity indicate that HIFU may potentially be a curative treatment option after radiation failure (Dudderidge et al 2007). Salvage HIFU has become increasingly diffuse in clinical practice in Australia (expert opinion of the Advisory Panel).

Salvage brachytherapy (re-irradiation) is a newly available treatment option for recurrent or persistent prostate cancer after radiotherapy (Bong & Keane 2007; Dudderidge et al 2007; Galosi et al 2007). Although several studies have reported the promising effectiveness of salvage brachytherapy, it is not possible to make definitive statements regarding its value, since its effectiveness may be offset by the relatively high risk of grade 3 or 4 genitourinary and lower gastrointestinal toxicity[1] incurred by re-irradiation (Bong & Keane 2007; Dudderidge et al 2007; Nguyen et al 2007). Salvage brachytherapy is still in its embryonic stage and not well established in clinical practice.

Androgen deprivation as a stand-alone treatment modality is not prescribed with curative intent, so it is therefore reserved for men who are not fit for, have no access to, or decline more invasive salvage treatments (Lam & Belldegrun 2004; Izawa et al 2002). Likewise, watchful waiting is another conservative management option for recurrent or persistent prostate cancer after radiotherapy. In clinical practice an extremely large proportion of patients (>95%) with radiotherapy failure undergo hormone therapy or watchful waiting, since salvage treatments are inaccessible to them (expert opinion of the

[1] Genitourinary toxicity: grade 3: frequency with urgency and nocturia hourly or more frequently; dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic; gross haematuria with/without clot passage; grade 4: haematuria requiring transfusion; acute bladder obstruction not secondary to clot passage, ulceration or necrosis

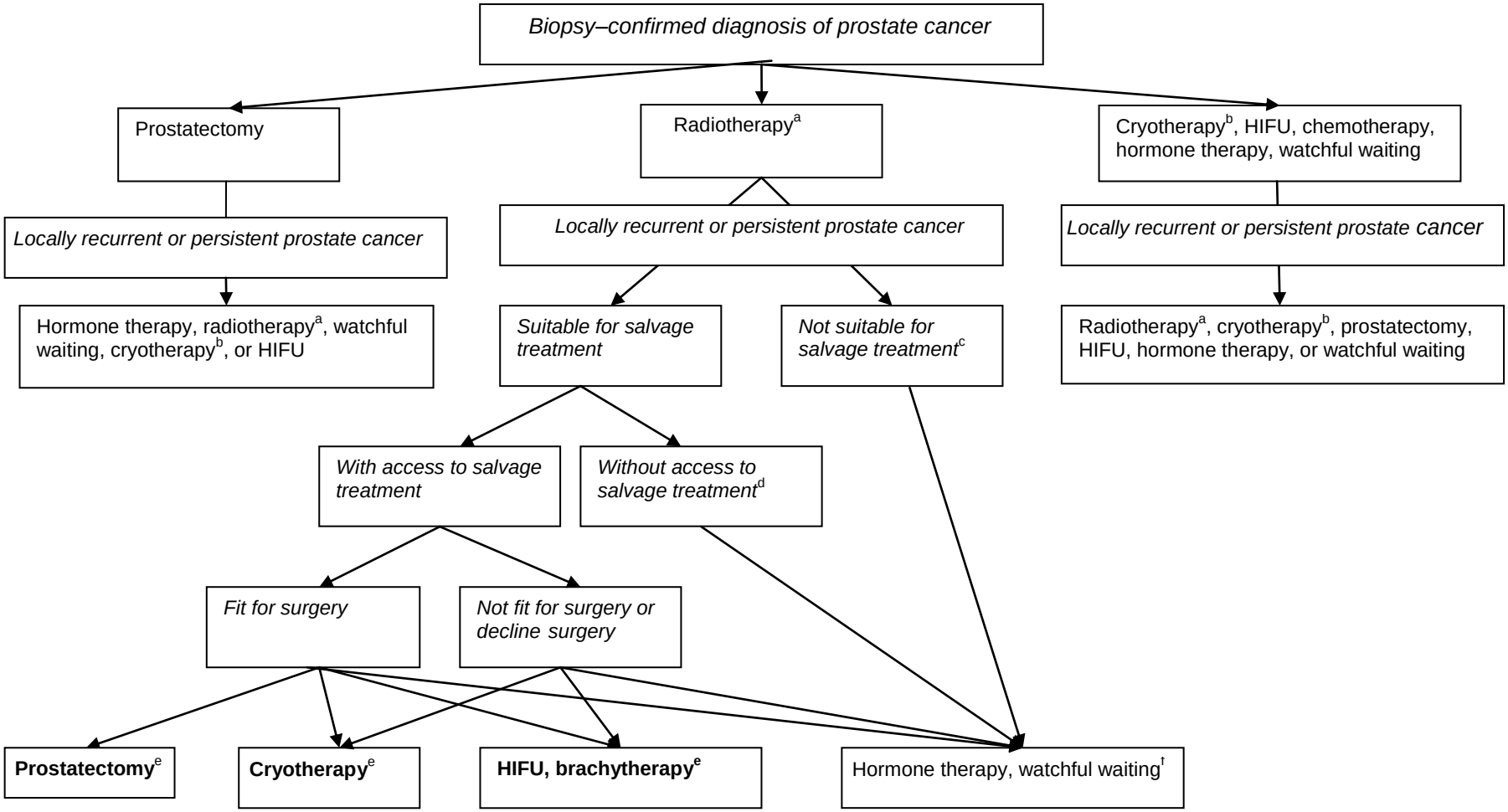
Lower gastrointestinal toxicity: grade 3: diarrhoea requiring parenteral support; severe mucous or blood discharge necessitating sanitary pads; abdominal distention (flat plate radiograph demonstrates distended bowel loops); grade 4: acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion (Radiation Therapy Oncology Group 2008).

Advisory Panel). Some of these patients are expected to resort to salvage cryotherapy if this procedure becomes more widely diffused in Australia. However, due to their non-curative nature, androgen deprivation and watchful waiting are not deemed as appropriate comparators when assessing the safety and effectiveness of salvage cryotherapy.

Comparators

The aim of this report is to evaluate the evidence of the safety, effectiveness and cost-effectiveness of salvage cryotherapy (± NHT) in the management of recurrent or persistent prostate cancer after radiotherapy compared with salvage radical prostatectomy (± NHT), salvage HIFU (± NHT) and salvage brachytherapy (± NHT).

Figure 4 Clinical decision tree for localised prostate cancer



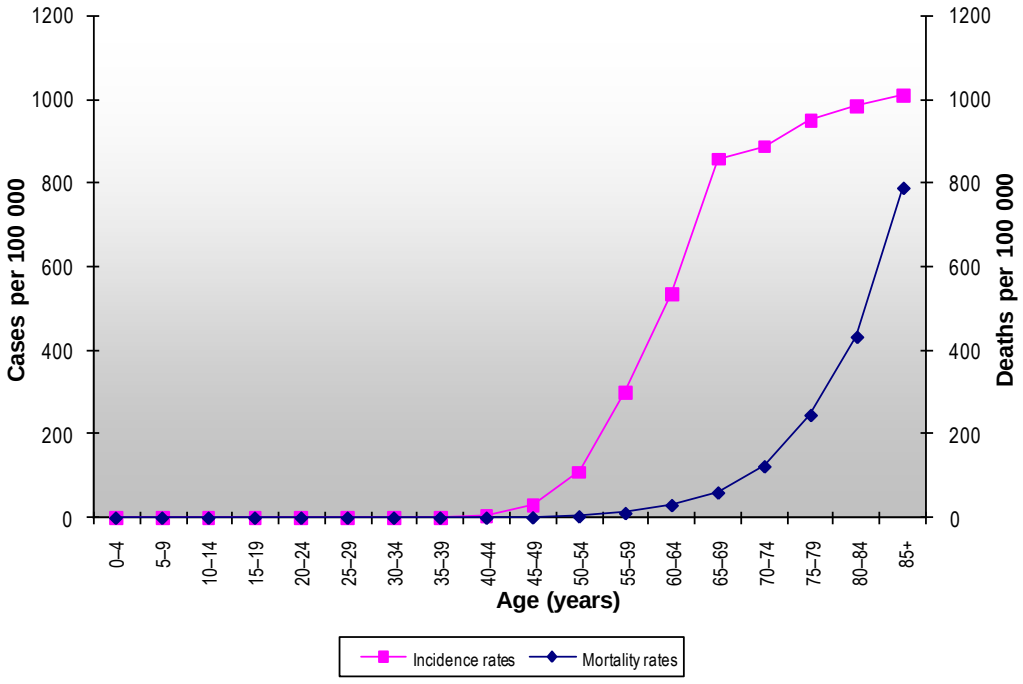
[a] External beam radiation therapy or brachytherapy; [b] The current application is not seeking reimbursement for patients who have not received primary radiation; [c] Patients not suitable for salvage treatment include those who cannot tolerate anaesthesia for major surgery, have co-morbidities, that make them unfit for surgery, or decline salvage treatment options; [d] If cryotherapy is accessible to these patients, hormone therapy and watchful waiting might be replaced by cryotherapy; [e] NHT may be given in combination with these treatment options; [f] Hormone therapy and watchful waiting are not prescribed with curative intent and, therefore, are not considered as appropriate comparators for salvage cryotherapy.

HIFU: high-intensity focused ultrasound

Clinical need for the procedure

In Australia prostate cancer is one of the eight cancers on which the National Health Priority Area Cancer Control Initiative has focused (AIHW 2007b). Prostate cancer is, apart from non-melanoma skin cancer, the most common cancer diagnosed in Australian males and the second leading cause of cancer deaths in males, preceded only by lung cancer (AIHW 2007b). In 2004 there were 15 759 new cases diagnosed in Australia and 2792 deaths due to prostate cancer (AIHW 2007a). These figures represented 28.7 per cent of all male cancers and 12.9 per cent of all male cancer deaths for that year. In Australia in 2004 the age-standardised incidence and mortality rates were 163 per 100 000 and 33 per 100 000, respectively (AIHW 2007a). The incidence of prostate cancer increases with age, with the average age at first diagnosis being 69.5 years in Australian males in 2004. Prostate cancer is very rare in men younger than 55 years of age; the incidence rate increases greatly after that age, reaching 1011 per 100 000 in men aged 85 years or older. The mortality rate from prostate cancer has the same trend as the incidence, reaching 788 per 100 000 in males equal to or older than 85 years of age (AIHW 2007a) (Figure 5).

Figure 5 Age-specific incidence and mortality for prostate cancer, Australia, 2004



Data source: AIHW 2007a

No data were identified on treatment rates of primary prostate cancer in Australia. The Cancer-Aging Linked Database of the United States (US) showed that, of all 10 179 men with incident prostate cancer diagnosed between 1999 and 2001, a total of 3795 (37.3%) underwent primary radiotherapy, including 2328 (22.9%) EBRT cases and 1467 (14.4%) brachytherapy cases (Zhou et al 2008). Using the US data to estimate treatment rates in Australia, it is assumed that 37.3 per cent of the 15 759 new cases of prostate cancer each year (5878 men) may receive radiotherapy.

The biopsy-confirmed recurrence rates for prostate cancer after radiotherapy vary substantially between series. Older studies reported significant biopsy-positive rates up to 93 per cent (Kabalin et al 1989). More recent studies indicate that between 10.0 and 57.4 per cent of patients receiving primary radiotherapy experience biopsy-confirmed radiation failure (Crook et al 2000; Pollack et al 2002; Pucar et al 2005; Zelefsky et al 2001). Crook and colleagues attributed the reduction in biopsy-positive rates over time to better understanding and more prudence in interpreting ambiguous post-radiotherapy biopsies (Crook et al 1995, 1997a, 1997b, 2000). Changes in patient selection criteria for primary radiotherapy over time and advances in radiotherapy technology may also account for the decrease in biopsy-confirmed radiotherapy failure (Erlichman et al 1999). Using the estimated 5878 patients who undergo primary radiotherapy per year in Australia, the number with recurrent prostate cancer after radiotherapy is therefore estimated to be between 588 and 3374. From 10 to 33 per cent of those patients with recurrent prostate cancer are assumed to be suitable for salvage cryotherapy (expert opinion of the Advisory Panel; Scanmedics Pty Ltd 2007). It is therefore expected that between 59 and 1113 patients would be candidates for salvage cryotherapy for recurrent prostate cancer after radiotherapy.

Marketing status of the technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). One argon-based cryosurgical unit (manufactured by Gilil Medical, Yokneam, Israel) is registered on the ARTG under the following item:

ARTG no.	Product no.	Product description	Sponsor
144069	231903	Cryosurgical unit, general-purpose	Scanmedics Pty Ltd

Source: Therapeutic Goods Administration 2008

Current reimbursement arrangement

Currently, there is no listing on the Medicare Benefits Schedule (MBS) for cryotherapy for prostate cancer. The MBS items for the comparative potentially curative procedures, prostatectomy and brachytherapy, are listed in Table 2. HIFU for prostate cancer is not on the MBS list.

Table 2 Relevant MBS items for recurrent or persistent prostate cancer

MBS item	Descriptor	Fee	Benefit
37210	PROSTATECTOMY, radical, involving total excision of the prostate, sparing of nerves around the bladder and bladder neck reconstruction, not being a service associated with a service to which item 35551, 36502 or 37375 applies (Anaes.) (Assist.)	$1 439.00	$1 179.25
15338	PROSTATE, radioactive seed implantation of, radiation oncology component, using transrectal ultrasound guidance, for localised prostatic malignancy at clinical stages T1 (clinically inapparent tumour not palpable or visible by imaging) or T2 (tumour confined within prostate), with a Gleason score of less than or equal to 7 and a prostate specific antigen (PSA) of less than or equal to 10 ng/ml at the time of diagnosis. The procedure must be performed at an approved site in association with a urologist.	$864.35	$648.30

Source: Medicare Australia 2008b

Some forms of NHT drugs are subsidised through the Pharmaceutical Benefits Scheme (PBS) (Table 3). They may be used in a single-agent or a two-agent modality. Many of the

drugs are available in different concentrations and different forms (ie tablet or solution). and are produced by different manufacturers. Only a single form of each drug has been described below. The cost of these treatments is likely to vary between patients, as drug regimens will be tailored to individual needs.

Table 3 Potentially relevant PBS items for recurrent or persistent prostate cancer

Descriptor		Example of form and quantity	Dispensed price for max. quantity
LHRH agonist	Goserelin acetate	Subcutaneous implant 3.6 mg (base) in pre-filled injection syringe	$332.57
	Leuprorelin acetate	IM injection (modified release), powder for injection 7.5 mg with diluent in pre-filled dual-chamber syringe	$419.77
Nonsteroidal anti-androgen	Flutamide	250 mg x 100 tablets	$212.60
	Nilutamide	150 mg x 30 tablets	$236.13
	Bicalutamide	50 mg x 28 tablets	$194.99
Steroid	Cyproterone acetate	100 mg x 50 tablets	$169.33

Source: Medicare Australia 2008c

LHRH: luteinizing hormone-releasing hormone

Approach to assessment

Objectives

To determine whether there is sufficient evidence, in relation to safety, effectiveness and cost-effectiveness, to have argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer after radiotherapy failure listed on the Medicare Benefits Schedule.

Research questions

Safety

1. What is the safety of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?

2. What is the safety of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

Effectiveness

3. What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?

4. What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

Cost-effectiveness

5. What is the cost-effectiveness of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?

6. What is the cost-effectiveness of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

Expert advice

An advisory panel with expertise in urology, radiology, medicine oncology, and consumer issues was established to evaluate the evidence and provide advice to the MSAC from a

clinical perspective. In selecting members for advisory panels, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the Advisory Panel associated with this application is provided at Appendix A.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period between 1995 (or, if inception of the database was later, from that date) to November 2008, as cryotherapy using the argon–helium system was first used in clinical practice in the middle of the 1990s (Ahmed et al 2005). Appendix B describes the electronic databases that were used for this search and other sources of evidence that were investigated. Grey literature[4] was included in the search strategy. Unpublished literature, however, was not canvassed as it is difficult to search for this literature exhaustively and systematically; and trials that are difficult to locate are often smaller and of lower methodological quality (Egger et al 2003). It is, however, possible that these unpublished data could impact on the results of this assessment.

The search terms used to identify literature in electronic bibliographic databases on the safety, effectiveness and cost-effectiveness of using cryotherapy for recurrent or persistent prostate cancer after radiotherapy are also presented in Appendix B.

Inclusion/exclusion criteria

In general, studies were excluded if they:

- did not address the research question;
- assessed salvage cryotherapy for recurrence or persistence of prostate cancer after a primary prostatectomy rather than primary radiotherapy;
- used liquid nitrogen-based cryotherapy;
- did not report what generation of cryotherapy was used;
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes (in some instances a study was included to assess one or more outcomes but had to be excluded for other outcomes due to data inadequacies);
- were in other languages and were of a lower level of evidence than that available in English; or
- did not have the appropriate study design.

[4] Literature that is difficult to find including published government reports, theses, technical reports, non-peer-reviewed papers etc.

If the same data were duplicated in multiple articles, results from the most comprehensive or most recent article only were included.

The inclusion criteria relevant to each of the research questions posed in this assessment are provided in Box 1, Box 2 and Box 3 in the 'Results' section of this report.

Search results

The process of study selection for this report went through six phases:

1. All reference citations from all literature sources were collated into an Endnote 8.0.2 database.

2. Duplicate references were removed.

3. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. All other studies were retrieved for full-text assessment.

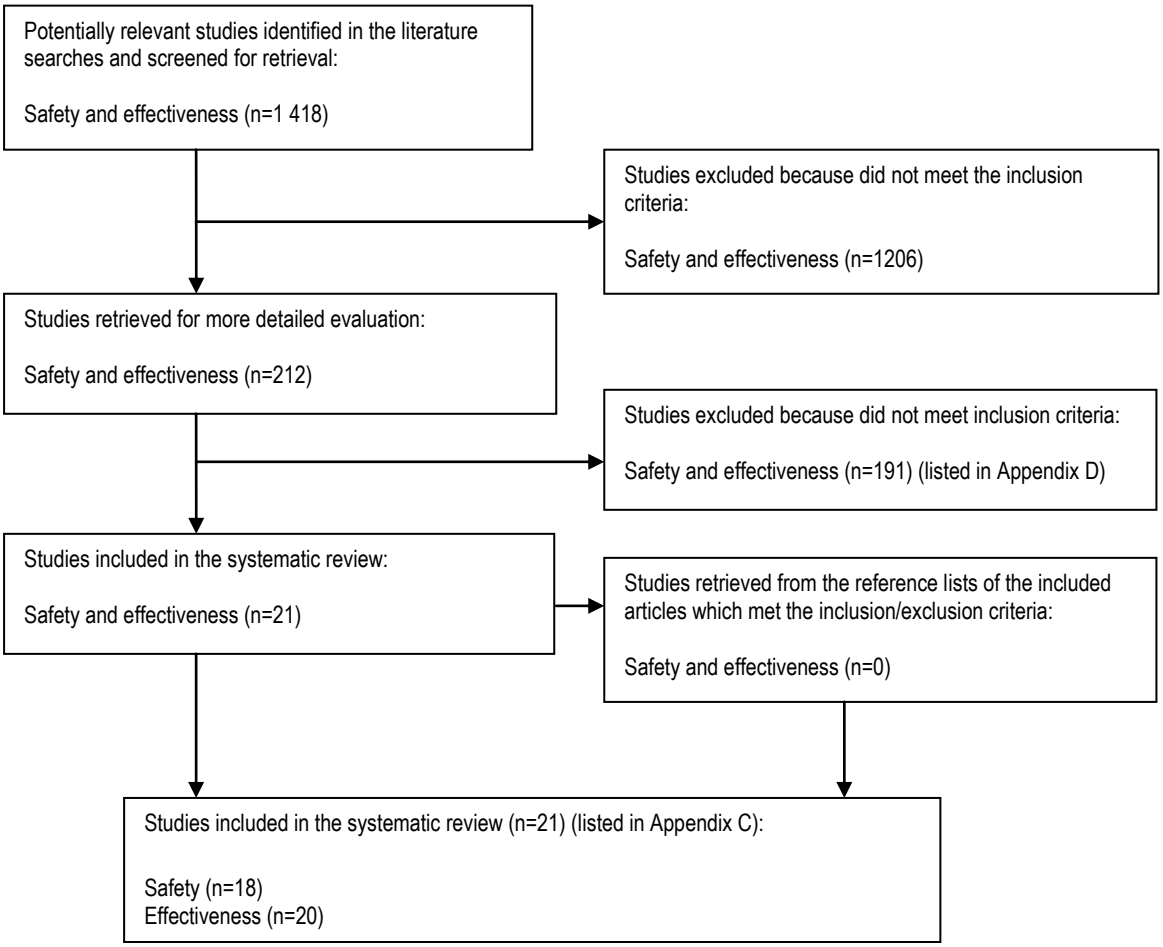
4. Studies were included to address the research questions if they met the pre-specified criteria applied by the reviewer on the full-text articles. Those articles meeting the criteria formed part of the evidence-base. The remainder provided background information.

5. The reference lists of the included articles were pearled for additional relevant studies. These were retrieved and assessed according to phase 4.

6. The evidence-base consisted of articles from phases 4 and 5 that met the inclusion criteria.

Any doubt concerning inclusions at phase 4 was resolved by consensus between the two reviewers, with a third reviewer available (although not required) for adjudication. The results of the process of study selection are provided in Figure 6.

Figure 6 Summary of the process used to identify and select studies for the assessment of cryotherapy for recurrent or persistent prostate cancer



Source: adapted from Moher et al 1998

Data extraction and analysis

A profile of key characteristics was developed for each included study (Appendix C). These study profiles described authors, publication year, location, the level of evidence, quality assessment, study design, study population characteristics, type of intervention, inclusion/exclusion criteria, outcomes assessed and follow-up period for each included study.

Studies that were unable to be retrieved or initially appeared to meet the inclusion criteria but contained insufficient or inadequate data for inclusion are provided in Appendix D.

Definitions of all technical terms and abbreviations are provided in the Glossary. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 4) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 4 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 5

Strength of the evidence

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 5.

Level

A study comparing different generations of cryotherapy is still ranked level IV interventional evidence, because the comparator used in the study is not salvage prostatectomy, brachytherapy or HIFU as specified in the listed research questions.

Table 5 Designations of levels of interventional evidence

Level	Intervention[a]
I[b]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial[c] Cohort study Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single-arm studies [d] Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: NHMRC 2005

[a] Definitions of these study designs are provided in NHMRC 2000, pp 7–8; [b] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence; [c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie utilising A vs B and B vs C to determine A vs C); [d] Comparing single-arm studies (ie case series from two studies).

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Quality

Study quality was assessed using the critical appraisal checklists provided in Table 6. The appraisal of comparative intervention studies pertaining to treatment safety and effectiveness would have been undertaken using a checklist developed by the NHMRC (2000). This checklist would have been used for systematic reviews / health technology assessment (HTA) reports, randomised controlled trials, cohort studies and case-control studies (if they were available). Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the United Kingdom National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001).

Table 6 Quality checklists

Study type	Checklists
Systematic reviews / HTA reports	NHMRC Checklist Table 1.4 (NHMRC 2000)
Randomised controlled trials	NHMRC Checklist Table 1.4 (NHMRC 2000)
Cohort study	NHMRC Checklist Table 1.4 (NHMRC 2000)
Case-control	NHMRC Checklist Table 1.4 (NHMRC 2000)
Intervention case series	NHS CRD Quality Assessment Scale (Khan et al 2001)

Statistical precision

Statistical precision was determined using standard statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real and not attributable to chance (NHMRC 2000).

Size of effect

For intervention studies on salvage cryotherapy it was important to assess whether statistically significant differences are also clinically important. The size of the effect needs to be determined, as well as whether the 95 per cent confidence interval includes only clinically important effects. Rank scoring methods were used to determine the clinically important benefit of the size of the effect in studies, as well as the clinical relevance of the evidence in controlled studies (NHMRC 2000).

Relevance of evidence in individual studies

Similarly, the outcome being measured in the studies should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000). When assessing the safety and effectiveness of salvage cryotherapy, rank scoring methods were used to determine the clinical relevance of the outcome being assessed in any controlled studies (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2005). Five components are considered essential by the NHMRC when judging the body of evidence:

- the volume of evidence – which includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogenous findings
- the potential clinical impact – appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test
- the generalisability of the evidence to the target population
- the applicability of the evidence – integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 7) (NHMRC 2008). Once the results of the studies had been synthesised, the overall conclusion as derived from the body of evidence was presented to answer each clinical question – see the 'Discussion' section (page 65).

Table 7 Body of evidence assessment matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review / multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population	Population(s) studied in body of evidence are similar to the target population	Population(s) studied in body of evidence differ to target population but it is clinically sensible to apply this evidence to target population	Population(s) studied in body of evidence are different to target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC 2008

Results of assessment

Is it safe?

Argon-based cryotherapy for treatment of recurrent or persistent prostate cancer after radiotherapy was assessed in terms of possible patient harms that may result from the procedure. Box 1 outlines the inclusion criteria determined a priori for the assessment of the safety of using salvage cryotherapy. We excluded studies where an overlap of results was evident, but there may still be some remaining overlap in study populations in studies from the same co-authors or institutions.

Box 1 Inclusion criteria for studies assessing the safety of salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Research question	
1. What is the safety of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?	
2. What is the safety of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?	
Characteristics	**Criteria**
Population	1. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery 2. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery
Intervention	Salvage cryotherapy (argon-based) (±NHT)
Comparators	1. Salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT) 2. Salvage HIFU(±NHT) or salvage brachytherapy(±NHT)
Outcome	Primary – major treatment-induced complications, eg fatality, renal failure, fistula, change in continence, change in potency, urethral sloughing, urethral stricture, bladder neck contracture, haemorrhage, major infection, anaemia, liver problems, enlarged breasts, blood clots Secondary – minor treatment-induced complications, eg probe site pain, scrotal swelling, haematuria, bleeding not requiring transfusion, minor infection, transient incontinence
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials, animal, in-vitro and laboratory studies were excluded.
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.

Complications were classified as either primary or secondary, based on the severity of the adverse events (Box 1).

This review does not include a systematic assessment of the safety of salvage radical prostatectomy, salvage HIFU or salvage brachytherapy. The safety of argon-based cryotherapy for recurrent or persistent prostate cancer after radiotherapy failure relative to the comparators was initially planned, but no comparative studies were identified. An overview of the safety considerations concerning the alternative salvage treatments for recurrent or persistent prostate cancer after radiotherapy, informed by articles identified during the process of study selection and by expert opinion of the Advisory Panel, is presented in the section 'Other relevant considerations' (page 66).

Primary safety outcomes

Major complications

There were no comparative studies identified that fitted the selection criteria determined a priori for assessing the safety of argon-based cryotherapy as a treatment for recurrent or persistent prostate cancer after radiotherapy.

A total of 18 uncontrolled post-test case series (level IV intervention evidence) reported on major complications as a result of argon-based cryotherapy for recurrent or persistent prostate cancer after radiation failure (Table 8); studies are listed in order of cryotherapy generation, quality, and then sample size). NHT was used in combination with salvage cryotherapy in all but three case series (Clarke et al 2007; Cytron et al 2003; Eisenberg & Shinohara 2008). The third-generation cryotherapy with thinner cryoneedles (17-G) was investigated in eight studies. Another three case series included both third- and second-generation cryotherapy. Second-generation cryotherapy was given to patients following radiation failure in the remaining seven case series, among which three studies had a minority of patients who underwent liquid nitrogen-based instead of argon-based cryotherapy. This includes the largest case series identified, which involved 187 cryotherapy procedures, reported by Ng et al (2007) in a good-quality study. Those case series investigating third-generation cryotherapy were relatively small, with the largest sample being 55 procedures in Ismail et al's study (2007). One case report was also identified providing results in terms of major complications following third-generation cryotherapy. The study profiles for all included studies are listed in Appendix C.

There were no deaths or life-threatening events (such as cerebral vascular accident, renal failure, sepsis or deep vein thrombosis) reported as a direct result of the argon-based cryotherapy procedure.

Peri-operative significant complications were reported by Cresswell et al (2006) in a moderate-quality study involving 20 procedures. In their study one case of significant haematuria occurred immediately after the third-generation cryotherapy procedure. This patient was sent back to the operating theatre for a cystoscopic bladder washout.

The major direct post-treatment complications reported by included studies were recto-urethral fistula, incontinence, impotence, urethral sloughing, urethral stricture, bladder obstruction and urethral ulcer. Fistula is the most serious complication of salvage cryotherapy for prostate cancer following radiation failure. The rates of recto-urethral fistula after cryotherapy ranged from 0 to 7.1 per cent. In Ng et al's good-quality case series (2007) of 187 salvage cryotherapy procedures, three cases of recto-urethral fistula (2.1%), indicating an open repairing operation, were observed after second- or first-generation cryotherapy. Ismail et al (2007) compared the rates of complications between third- and second-generation cryotherapy in a high-quality case series. No significant difference was observed in the rates of recto-urethral fistula between patients treated by third-generation cryotherapy and those who underwent second-generation cryotherapy (1.8% vs 0%, p=0.550). In a high-quality case series Gowardhan et al (2007) explored the relationship between the incidence of post-salvage treatment recto-urethral fistula and the primary radiotherapy modality. During a follow-up period of 19 months, a total of three cases of recto-urethral fistula (7.1%) were reported as a result of the third-generation cryotherapy procedure. Of the three patients, two had brachytherapy as their primary treatment, making the recto-urethral fistula incidence 20.0 per cent in this patient group. This figure was significantly higher than the 3.1 per cent fistula rate in patients

who underwent EBRT as their primary treatment, suggesting that previous brachytherapy may be a risk factor for recto-urethral fistula following salvage cryotherapy. A total of ten studies (Clarke et al 2007; Cresswell et al 2005; Cytron et al 2003; de la Taille et al 2000a, 2000b; Eisenberg & Shinohara 2008; Ghafar et al 2001; Han et al 2003, 2004; Zisman et al 2001) did not observe any case of recto-urethral fistula as a major complication after cryotherapy. However, their relatively small sample sizes (none involved more than 50 patients) should be taken into account when interpreting the absence of recto-urethral fistula. Vesico-urethral fistula beyond the external sphincter was reported in 0.8 per cent of patients in one study (Chin et al 2001).

Impotence was very common after salvage cryotherapy, with incidence rates ranging from 80 to 100 per cent. The largest case series reporting impotence after salvage cryotherapy procedure was Ismail et al (2007). In this high-quality case series, the authors observed that 84 out of 100 patients (84%) experienced impotence after argon-based cryotherapy. In addition, this study also reported a higher incidence of rate of impotence for third-generation than second-generation cryotherapy (90.9% vs 80.0%, respectively, p=0.042). However, caution should be exercised when drawing a conclusion from this result, as no data on the incidence rates of impotence before the salvage cryotherapy procedure were provided. Therefore, it is impossible to ascertain whether the difference was attributable to the generation of cryotherapy systems or to the type of primary radiotherapy. A total of three case series of moderate quality reported the incidence rates of impotence before salvage cryotherapy (Chin et al 1998; Eisenberg & Shinohara 2008; Han et al 2003). Authors of these studies observed extremely high rates of impotence, ranging from 71.7 per cent to 100 per cent, before salvage cryotherapy was carried out. After the procedure, 60 to 100 per cent of patients who had potency before salvage cryotherapy developed impotence. The results demonstrated that both primary radiotherapy and salvage cryotherapy were significant risk factors for impotence. Therefore, the high rate of impotence after salvage cryotherapy was attributable to the cumulative influence of these two treatments.

The incidence of incontinence varies when different definitions are used. Using 'the loss of urinary control, which indicates at least one pad within 24 hours or further incontinence-related medical and/or surgical intervention' as the criteria for incontinence, between 0 and 33.3 per cent of patients experienced incontinence after salvage cryotherapy. In a high-quality case series with the largest sample size, Ng et al (2007) observed that five out of 187 patients (2.7%) lost their continence after salvage cryotherapy. All five patients needed an artificial urinary sphincter inserted to regain their urine control capacity. The second largest study included was by Chin et al (2001). A total of 118 patients were recruited in this moderate-quality study, with 107 patients undergoing an argon-based cryotherapy procedure and another 11 cases undergoing liquid nitrogen-based cryotherapy. However, the data on incontinence rate for each generation of cryotherapy was not available. Therefore, it is impossible to infer whether the high rate of incontinence (33.3%) from this study was attributable to first- or second-generation cryotherapy (or both).

One case series compared the incidence rates of incontinence between two argon-based cryotherapy systems using different sizes of cryoneedles (Ismail et al 2007). The authors reported a 7.3 per cent incontinence incidence rate in patients who underwent third-generation cryotherapy with thinner cryoneedles. This figure was relatively lower than the 20 per cent incidence rate of incontinence in patients who were given second-generation cryotherapy, but these results were not statistically significant (p=0.057). Potential treatment options (apart from open surgical insertion of an artificial urinary sphincter)

for patients experiencing incontinence after salvage cryotherapy following radiation failure include cystoscopy surgery, transurethral collagen injection and conservative medical therapy. It is noteworthy that none of the studies included in the systematic review reported the incontinence rate after primary radiotherapy; therefore, change in continence before and after salvage cryotherapy was undetermined. However, it was reported that incontinence was not a common complication after EBRT or brachytherapy (Liu et al 2004; Machtens et al 2006; Mols et al 2009; Potosky et al 2004).

Urethral sloughing was another major complication following argon-based cryotherapy procedure. Ten studies reported a range of incidence rates of urethral sloughing from 0 to 11.1 per cent. Chin et al (2001), authors of the largest case series of the ten studies, observed that a total of six out of 118 patients developed urethral sloughing after salvage cryotherapy, resulting in an incidence rate of 5.1 per cent. Ismail et al (2007) found that there was no significant difference in urethral sloughing incidence rates between third- and second-generation cryotherapy (0% vs 5.1%, p=0.770), although both of the two urethral sloughing cases occurred in patients who received second-generation cryotherapy.

Likewise, between 0 and 11.1 per cent of patients experienced urethral stricture after an argon-based cryotherapy procedure. In a good-quality case series involving 187 salvage cryotherapy procedures, Ng et al (2007) observed one case (0.5%) of urethral stricture following salvage cryotherapy. Urethral dilation was indicated for this patient to resolve the urethral stricture.

Bladder neck obstruction was observed as an adverse consequence in 0 to 10.0 per cent of patients having salvage cryotherapy after radiation failure. Ng et al (2007) reported that a total of three cases (1.6%) of bladder neck obstruction occurred after a salvage cryotherapy procedure, all of which required a bladder neck incision to get rid of the obstruction.

One case of urethral ulcer was reported by Eisenberg and Shinohara (2008) in a moderate-quality study with a small sample of 19 patients. This complication was resolved after 6 months of suprapubic catheter drainage.

Case reports may be useful for describing rare complications. In general, they provide less information than uncontrolled case series since it is impossible to determine the denominator, ie how many patients received salvage cryotherapy after radiation failure and were at risk of harm but did not necessarily have any adverse events. No major complication was observed after salvage cryotherapy following primary radiotherapy failure in the one case report included (Mouraviev et al 2006).

Table 8 Major complications resulting from cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Major complications
3rd generation			
(Clarke et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	47	Recto-urethral fistula: 0/47 Impotence: Before cryotherapy: 47/47 (100%) After cryotherapy: 47/47 (100%) Incontinence: 0/47 Urethral sloughing: 0/47 Bladder neck obstruction: 0/47
(Gowardhan et al 2007)[a]	Level IV Quality: 4.5/6 Prospective case series	42 EBRT: 32 Brachytherapy: 10	Recto-urethral fistula: 3/42 (7.1%) EBRT: 1/32 (3.1%) Brachytherapy: 2/10 (20.0%) Impotence: Before cryotherapy: n/a After cryotherapy: EBRT: 17/17 (100%) Brachytherapy: 4/5 (80.0%)
(Zisman et al 2001)	Level IV Quality: 4.5/6 Retrospective case series	17	Recto-urethral fistula: 0/17 Incontinence: 0/17 Urethral sloughing: 1/17 (5.9%) Bladder neck obstruction: 0/17
(Cresswell et al 2005)[a]	Level IV Quality: 4/6 Prospective case series	20	Peri-operative significant complication: 1/20 (5.0%) Recto-urethral fistula: 0/20 Impotence: Before cryotherapy: 16/20 (80.0%) After cryotherapy: 20/20 (100%) Incontinence: 2/20 (10.0%) Bladder neck obstruction: 2/20 (10.0%).
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	Recto-urethral fistula: 0/19 Impotence: Before cryotherapy: n/a After cryotherapy: 3/5 (60.0% for patients with potency before cryotherapy) Incontinence: 1/19 (5.3%) Urethral stricture: 1/19 (5.3%) Urethral ulcer: 1/19 (5.3%)
(Han et al 2003)[b]	Level IV Quality: 4/6 Prospective case series	18	Recto-urethral fistula: 0/18 Impotence: Before cryotherapy: n/a After cryotherapy: 12/14 (85.7% for patients with potency before cryotherapy) Incontinence: 2/18 (11.1%) Urethral sloughing: 2/18 (11.1%) Urethral stricture: 0/18
(Cytron et al 2003)	Level IV Quality: 3.5/6 Prospective case series	5	Recto-urethral fistula: 0/5
(Han et al 2004)[b]	Level IV Quality: 3/6 Prospective case series	29	Recto-urethral fistula: 0/29 Incontinence: 2/29 (6.9%)

3rd or 2nd generation						
(Ismail et al 2007)	Level IV Quality: 4.5/6 Prospective case series	100 3rd generation: 55 2nd generation: 45		3rd generation	2nd generation	p-value
			Recto-urethral fistula	1/55 (1.8%)	0/45	0.550
			Impotence (after cryotherapy)	50/55 (90.9%)	36/45 (80.0%)	0.042
			Incontinence	4/55 (7.3%)	9/45 (20.0%)	0.057
			Urethral sloughing[d]	0/55	2/45 (4.4%)	0.770
(Bahn et al 2003)	Level IV Quality: 4.5/6 Retrospective case series	59	Recto-urethral fistula: n/a (3.4%) Incontinence: n/a (4.3%) Urethral sloughing: 0/59 Urethral stricture: 0/59 Bladder obstruction: 0/59			
(Donnelly et al 2005)	Level IV Quality: 4/6 Prospective case series	46 3rd generation: 6 2nd generation: 40	Recto-urethral fistula: 1/46 (2.2%) Impotence: Before cryotherapy: 33/46 (71.7%) After cryotherapy: 39/46 (84.8%) Incontinence: 3/46 (6.5%) Urethral sloughing: 3/46 (5.6%)			
2nd generation						
(Ng et al 2007)[d]	Level IV Quality: 4.5/6 Retrospective case series	187[e]	Recto-urethral fistula: 4/187 (2.1%) Incontinence: 5/187 (2.7%) Urethral stricture: 1/187 (0.5%) Bladder neck obstruction: 3/187 (1.6%)			
(Chin et al 2001)[d]	Level IV Quality: 4/6 Retrospective case series	118[e]	Recto-urethral fistula: 4/118 (3.3%) Vesico-urethral fistula beyond external sphincter: 1/118 (0.8%) Incontinence: 8/118 (33.3%) Urethral sloughing: 6/118 (5.1%) Bladder neck obstruction: 10/118 (8.5%)			
(Chin et al 1998)[d]	Level IV Quality: 4/6 Retrospective case series	45[e]	Impotence: Before cryotherapy: n/a After cryotherapy: n/a (100% for patients with potency before cryotherapy)			
(Ghafar et al 2001)[c]	Level IV Quality: 4/6 Prospective case series	38	Recto-urethral fistula: 0/38 Incontinence: 3/38 (7.9%) Urethral sloughing: 0/38 Urethral stricture: 0/38 Bladder neck obstruction: 0/38			
(de la Taille et al 2000a)[c]	Level IV Quality: 3.5/6 Prospective case series	19	Recto-urethral fistula: 0/19 Incontinence: 2/19 (10.5%) Urethral sloughing: 0/19 Urethral stricture: 0/19 Bladder obstruction: 0/19			
(de la Taille et al 2000b)[c]	Level IV Quality: 4/6 Retrospective case series	18	Recto-urethral fistula: 0/18 Incontinence: 2/18 (11.1%) Urethral sloughing: 0/18 Urethral stricture: 0/18 Bladder neck obstruction: 0/18			

(Anastasiadis et al 2003)[c]	Level IV Quality: 3.5/6 Prospective case series	42	Impotence: Before cryotherapy: n/a After cryotherapy: n/a (90%) Incontinence: n/a (10%)
Case report			
(Mouraviev et al 2006)	Case report	1	No complication observed

[a] May be overlap between patient series; [b] May be overlap between patient series; [c] May be overlap between patient series; [d] May be overlap between patient series; [e] Eleven patients underwent nitrogen-based cryotherapy instead of argon-based cryotherapy.

n/a: not available; EBRT: external beam radiotherapy

Secondary safety outcomes

Minor complications

Ten descriptive studies reported minor complications following argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer after radiotherapy (Table 9). They are all level IV intervention evidence of moderate to good quality. One case report was also identified as reporting the result of minor complications after salvage cryotherapy. The study profiles for all the included studies are shown in Appendix C.

Pelvic and/or perineal and/or rectal pain occurred in 0 to 39.6 per cent of patients who underwent argon-based cryotherapy. Ng et al (2007), in a good-quality case series involving 187 salvage cryotherapy procedures, reported that a total of 25 patients (13.4%) presented with post-treatment pelvic and/or perineal and/or rectal pain. Ismail et al (2007) compared the incidence rates of pelvic and/or perineal and/or rectal pain between third- and second-generation cryotherapy and found no significant difference (3.6% vs 4.4%, p=0.610). All cases of pelvic and/or perineal and/or rectal pain reported by studies identified in the literature were not serious and could be managed with medication such as analgesic drugs. Cytron et al (2003) reported a zero incidence of pelvic and/or perineal and/or rectal pain after the third-generation cryotherapy procedure. However, since there were only five patients involved in this study, the generalisability of the results from this study is unknown.

Another minor complication after salvage cryotherapy for prostate cancer is a urinary tract infection (UTI), which occurred in 2.1 per cent to 9.6 per cent of patients. The largest good-quality case series which reported the frequency of UTIs following cryotherapy was by Ng et al (2007). In their study 18 out of 187 patients (9.6%) receiving salvage cryotherapy experienced a UTI after the procedure.

Transient haematuria developed in 2.2 per cent to 11.2 per cent of patients who underwent argon-based salvage cryotherapy. Ng et al (2007), in their high-quality case series involving 187 cryotherapy procedures, observed a total of 21 cases of haematuria (11.2%) following cryotherapy.

Between 10.5 per cent and 11.1 per cent of patients experienced scrotal swelling after argon-based cryotherapy following radiation failure. However, the four studies reporting rates of scrotal swelling were all small case series, with sample sizes of no more than 40 patients (de la Taille et al 2000a, 2000b; Ghafar et al 2001; Han et al 2003).

Penile tingling and/or numbness were reported as a minor complication in Han et al's study (2003), with an incidence rate of 5.9 per cent (1/18). The symptom could be successfully resolved by conservative methods. In addition, proctitis after salvage

cryotherapy was reported in one out of 46 patients in a case series (2%; Donnelly et al 2005).

No minor complication was reported in the included case report (Mouraviev et al 2006).

Table 9 Minor complications resulting from cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Minor complications
3rd generation			
(Clarke et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	47	UTI: 1/47 (2.1%) Haematuria: 2/47 (4.3%)
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	Pelvic/perineal/rectal pain: 1/19 (5.3%)
(Han et al 2003)	Level IV Quality: 4/6 Prospective case series	18	Pelvic/perineal/rectal pain: 1/19 (5.6%) Scrotal swelling: 2/19 (11.1%) Penile tingling/numbness: 1/19 (5.9%)
(Cytron et al 2003)	Level IV Quality: 3.5/6 Prospective case series	5	Pelvic/perineal/rectal pain: 0/5
3rd or 2nd generation			
(Ismail et al 2007)	Level IV Quality: 4.5/6 Prospective case series	100 3rd generation: 55 2nd generation: 45	Pelvic/perineal/rectal pain: 3rd generation: 2/55 (3.6%) 2nd generation: 2/45 (4.4%), p=0.610
(Donnelly et al 2005)	Level IV Quality: 4/6 Prospective case series	46 3rd generation: 6 2nd generation: 40	Pelvic/perineal/rectal pain: 8/46 (17.4%) UTI: 4/46 (8.7%) Haematuria: 1/46 (2.2%) Proctitis: 2/46 (4.3%)
2nd generation			
(Ng et al 2007)	Level IV Quality: 4.5/6 Prospective case series	187 [b]	Pelvic/perineal/rectal pain: 25/187 (13.4%) UTI: 18/187 (9.6%) Haematuria: 21/187 (11.2%)
(Ghafar et al 2001)[a]	Level IV Quality: 4/6 Prospective case series	38	Pelvic/perineal/rectal pain: 15/38 (39.6%) UTI: 1/38 (2.6%) Haematuria: 3/38 (7.9%) Scrotal swelling: 4/38 (10.5%)
(de la Taille et al 2000b)[a]	Level IV Quality: 4/6 Retrospective case series	18	Pelvic/perineal/rectal pain: 7/18 (38.9%) UTI: 1/18 (5.6%) Haematuria: 1/18 (5.6%) Scrotal swelling: 2/18 (11.1%)
(de la Taille et al 2000a)[a]	Level IV Quality: 3.5/6 Prospective case series	19	Pelvic/perineal/rectal pain: 7/19 (36.8%) UTI: 1/19 (5.3%) Haematuria: 1/19 (5.3%) Scrotal swelling: 2/19 (10.5%)
Case report			
(Mouraviev et al 2006)		1	No minor complication observed

[a] May be overlap between patient series; [b] Eleven patients underwent nitrogen-based cryotherapy instead of argon-based cryotherapy
UTI: urinary tract infection

Summary – What is the safety of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?

– What is the safety of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

No data were identified reporting on the comparative safety of salvage cryotherapy (±NHT) against salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT).

A total of 18 case series (level IV evidence) and one case report were identified, reporting complications as a result of argon-based cryotherapy for recurrent or persistent prostate cancer after radiotherapy. Three studies involving liquid nitrogen-based cryotherapy procedures were also included for assessment, since only a minority of the recruited patients in these studies underwent cryotherapy using liquid nitrogen as the freezing agent.

There were no deaths or life-threatening events caused by argon-based cryotherapy procedures. Only one case of peri-operative complication, haematuria, was observed among all identified articles.

Recto-urethral fistula was one of the most serious, although not common, complications following the argon-based cryotherapy procedures. An open repair operation was indicated. Previous brachytherapy was regarded as a potential risk factor for fistula following salvage cryotherapy. The extremely high incidence rate of impotence after salvage cryotherapy was due to the accumulative damage from primary radiation and subsequent cryotherapy. The salvage cryotherapy procedure itself accounted for a high risk of impotence. Incontinence was the second most common adverse event after salvage cryotherapy, preceded only by impotence. However, the real effect of salvage cryotherapy on patients' continence is unknown, since no data on pre-cryotherapy rates of incontinence were identified. Other major complications with relatively low incidence rates were urethral sloughing, bladder neck obstruction, urethral stricture and urethral ulcer.

The majority of minor complications reported, including pelvic and/or perineal and/or rectal pain, UTI, scrotal swelling, transient haematuria, penile tingling and/or numbness, and proctitis, were self-limiting and did not require medical therapy.

One study compared complication rates after third-generation cryotherapy to those following second-generation cryotherapy, and reported no difference between the two groups except for post-cryotherapy incidence rate of impotence. However, it is impossible to determine whether the difference in the frequency of impotence was related to the generations of the cryotherapy, since no data on the pre-cryotherapy impotence rates were available (Ismail et al 2007).

Is it effective?

Studies were included in this assessment of the effectiveness of salvage argon-based cryotherapy according to the criteria outlined in Box 2. We excluded studies where an overlap of results was evident, but there may still be some remaining overlap in study populations in studies from the same co-authors or institutions.

Box 2 Inclusion criteria for studies assessing the effectiveness of salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Research question

1. What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?
2. What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

Characteristics	Criteria
Population	1. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery 2. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery
Intervention	Salvage cryotherapy (argon-based) (±NHT)
Comparators	1. Salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT) 2. Salvage HIFU (±NHT) or salvage brachytherapy (±NHT)
Outcome	Primary – overall survival or mortality rate, disease-specific survival Secondary – disease-free survival (biopsy-confirmed), duration of PSA control, progression-free survival, quality of life, symptom control (eg pain, bleeding, urination), length of hospital stay, operative time
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials; animal, in-vitro and laboratory studies were excluded.
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they provided a higher level of evidence than the English language articles identified.

The effectiveness of argon-based cryotherapy for recurrent or persistent prostate cancer after radiotherapy relative to the comparators was initially planned, but no comparative studies were identified. An overview of the effectiveness considerations concerning salvage radical prostatectomy, salvage HIFU and salvage brachytherapy following radiation failure informed by expert opinion is presented in the section 'Other relevant considerations' (page 66).

Primary effectiveness outcomes

A total of five descriptive studies (level IV interventional evidence) were identified that reported on the primary effectiveness outcomes of argon-based cryotherapy for treatment of recurrent or persistent prostate cancer after radiotherapy. The study profiles for all the included studies are listed in Appendix C.

Overall survival

Four descriptive studies reported on the overall survival rates after salvage cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy (Table

10). The case series investigated by Ng et al (2007) had the largest population (187 patients) as well as the longest follow-up period (mean: 39 months). In this good-quality study it was reported that the 5-year and 8-year survival rates were 97 per cent and 92 per cent, respectively, in those patients who were still followed up 5 years or 8 years after salvage cryotherapy. However, the data on loss to follow-up were not provided.

In a moderate-quality case series involving 46 patients, Robinson et al (2006) reported that a total of three patients died within 2 years after salvage cryotherapy, resulting in a 2-year survival rate of 93.5 per cent. The other two small studies, with mean follow-up periods of less than 12 months, reported survival rates ranging from 95 to 100 per cent.

Table 10 Overall survival after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Follow-up period: overall survival
3rd generation			
(Cresswell et al 2006)	Level IV Quality: 4/6 Prospective case series	20	9 months (mean): 19/20 (95.0%)
3rd or 2nd generation			
(Robinson et al 2006)	Level IV Quality: 3.5/6 Prospective case series	46	24 months: 43/46 (93.5%)
2nd generation			
(Ng et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	187[a]	5 years: n/a (97%) 8 years: n/a (92%)
(de la Taille et al 2000a)	Level IV Quality: 3.5/6 Prospective case series	19	8.3 months (mean): 19/19 (100%)

[a] Eleven patients underwent nitrogen-based cryotherapy instead of argon-based cryotherapy.
n/a: not available

Disease-specific survival

Four descriptive studies reported on disease-specific survival rates after salvage argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy (Table 11). It is noteworthy that the follow-up periods of the four case series were either short (less than 2 years) or unknown. None of the studies with long follow-up periods reported disease-specific survival rates. Of the four studies which did, two case series with small sample sizes (less than 20 participants) did not observe any disease-specific deaths. The other two studies reported high disease-specific survival rates of equal to or more than 95.0 per cent, with one case of disease-specific death in each of the case series. One prostate cancer-related death after salvage cryotherapy was observed by Cresswell et al (2005). This patient had a rapidly rising PSA level, from 20.1 ng/mL before cryotherapy to 122.6 ng/mL at 3 months after the procedure. The existence of metastatic disease was proven by a positive MRI result. The patient failed subsequent systemic treatment and died from metastatic prostate cancer 9 months after salvage cryotherapy. Robinson et al (2006) reported the other case of death attributable to prostate cancer. In their moderate-quality case series of 46 patients, one patient died from prostate cancer following salvage cryotherapy failure 24 months after the procedure.

Table 11 Disease-specific survival after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Follow-up period: disease-specific survival
3rd generation			
(Cresswell et al 2006)	Level IV Quality: 4/6 Prospective case series	20	9 months (mean): 19/20 (95.0%)
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	18 months (median): 19/19 (100%)
3rd or 2nd generation			
(Robinson et al 2006)	Level IV Quality: 3.5/6 Prospective case series	46	24 months: 45/46 (97.8%)
2nd generation			
(de la Taille et al 2000a)	Level IV Quality: 3.5/6 Prospective case series	19	8.3 months (mean): 19/19 (100%)

Secondary effectiveness outcomes

Biopsy-confirmed disease-free survival

Eight descriptive studies reported their biopsy yields after salvage cryotherapy following radiation failure (Table 12). Routine post-treatment biopsy on all patients who underwent cryotherapy was not common. Biopsies were undertaken on all patients, or on patients who could be followed up in the institution where cryotherapy procedures were performed, in four case series. It is notable that all these studies were from the same institution and may include some of the same patients. In a good-quality study involving the largest number of patients (n=187), 156 patients (83.4%) were negative at biopsy during a mean follow-up period of more than 3 years (39 months) (Ng et al 2007). Another two case series with populations of more than 100 patients also demonstrated high biopsy-confirmed disease-free survival rates of above 80 per cent during their follow-up periods (3–53 months and up to 43 months, respectively) (Chin et al 2001, 2003). In a small moderate-quality case series, Chin et al (1998) detected three biopsy-positive cases from a total of 31 patients who returned for follow-up, yielding a biopsy-confirmed disease-free survival rate of 90.3 per cent during a follow-up period ranging from 1 to 30 months.

In the other three case series, a biopsy was carried out in patients with rising PSA levels or with PSA levels above certain cut-off points. Bahn et al (2003), in their good-quality case series of 59 patients, reported a 100 per cent biopsy-negative rate among patients with PSA levels higher than 0.5 ng/mL or rising PSA levels during a mean follow-up period of 20.7 months. Donnelly et al (2005), authors of a moderate-quality study involving 46 argon-based cryotherapy procedures, also showed a 100 per cent biopsy-confirmed disease-free survival rate among patients with PSA levels more than 4.0 ng/mL or rapidly rising PSA levels within a median follow-up period of 20 months. The highest biopsy-positive result was reported by Cresswell et al (2005) in a moderate-quality case series of 20 patients. A total of four patients with rising PSA levels received a biopsy examination. Two of the patients were positive for disease, resulting in a biopsy-positive rate as high as 50 per cent within a follow-up period of less than 1 year.

Eisenberg and Shinohara (2008) reported that, at 12 months after salvage cryotherapy, one out of ten patients who underwent a biopsy had a positive result for prostate cancer after the procedure. However, the patient population in whom biopsies were carried out was not clearly described.

Table 12 Biopsy-confirmed disease-free survival after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Population in whom biopsies were carried out	Follow-up period: biopsy-confirmed disease-free survival
3rd generation				
(Cresswell et al 2005)	Level IV Quality: 4/6 Prospective case series	20	Patients with a rising PSA level	9 months (mean)[a]: 2/4 (50.0%)
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	n/a	12 months: 9/10 (90.0%)
3rd or 2nd generation				
(Bahn et al 2003)	Level IV Quality: 4.5/6 Retrospective case series	59	Patients with a rising PSA level or PSA level >0.5 ng/mL	20.7 months (mean)[a]: n/a (100%)
(Donnelly et al 2005)	Level IV Quality: 4/6 Prospective case series	46 3rd generation: 6 2nd generation: 40	Patients with a PSA level >4.0 ng/mL or rapidly rising PSA level	20 months (median)[a]: n/a (100%)
2nd generation				
(Ng et al 2007)[b]	Level IV Quality: 4.5/6 Retrospective case series	187[c]	All patients	39 months (mean): 156/187 (83.4%)
(Chin et al 2003)[b]	Level IV Quality: 4.5/6 Retrospective case series	106[c]	All patients	3–43 months (range): 91/106 (85.8%)
(Chin et al 2001)[b]	Level IV Quality: 4/6 Retrospective case series	118[c]	All patients	18.6 months (median): 111/118 (94.1%)
(Chin et al 1998)[b]	Level IV Quality: 4/6 Retrospective case series	45[c]	Patients who returned for follow-up	1–30 months (range)[a]: 28/31 (90.3%)

[a] Follow-up period refers to all patients involved in the study; data on the follow-up period in the subgroup of patients who underwent biopsy was not available; [b] May be overlap between patient series; [c] Eleven patients underwent 1st generation instead of 2nd generation cryotherapy.
n/a: not available; PSA: prostate specific antigen

Duration of PSA control

In the evaluation of the effectiveness of prostate cancer treatment, the duration of PSA control is one of the essential surrogate outcome measures for clinical disease control. It is alternatively called biochemical recurrence-free survival (BRFS). Both terms refer to a span of time in which the PSA level is below a specific cut-off point. At present, no consensus has been achieved on the definition of biochemical recurrence of prostate cancer after cryotherapy. Cut-off values for the diagnosis of biochemical recurrence could be an increase of PSA level above the PSA nadir (ie 0.2 ng/mL, 0.3 ng/mL or 2.0 ng/mL above PSA nadir), a specific PSA level (ie 0.3 ng/mL, 0.4 ng/m, 0.5 ng/mL 2.0 ng/mL or 4.0 ng/mL) or three consecutive rises in the PSA level. Apart from differences in definitions of biochemical recurrence, heterogenous baseline PSA levels

and different follow-up periods complicate the analysis and synthesis of clinical data on PSA control derived from distinct studies in the literature.

A total of 17 descriptive case series investigated the duration of PSA control after argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer (Table 13). Seven studies reported on BRFS following third-generation cryotherapy with thinner cryoneedles. Another four case series included either third-generation or second-generation cryotherapy as their interventions. Second-generation cryotherapy was used for patients with radiation failure in the other six studies, three of which had a minority of patients who underwent cryotherapy using liquid nitrogen instead of argon gas as the freezing agent.

The overall 1-year and 2-year BRFS rates, as reported by the 17 studies described in Table 13, ranged from 44 to 89 per cent and from 38 to 79 per cent, respectively. The largest study identified in the literature was by Ng et al (2007). It was a good-quality case series of 187 cryotherapy procedures, with a mean follow-up period of 39 months. The PSA levels before salvage cryotherapy were in the range 0–36.4 ng/mL, with a median level of 4.9 ng/mL. A definition of biochemical recurrence of equal to, or more than, 2.0 ng/mL above the PSA nadir was used in this case series. A total of 105 patients (56.1%) were in PSA control during the follow-up period.

The largest study investigating third-generation cryotherapy after recurrent or persistent prostate cancer was carried out by Clarke et al (2007) in a good-quality case series of 47 patients. The mean baseline PSA level before salvage treatment was 9.0 ng/mL. A BRFS of 80.9 per cent during a mean follow-up period of 25 months was reported by the authors, using a PSA cut-off value of 0.5 ng/mL.

Ismail et al (2007) reported their results on PSA control after either third- or second-generation cryotherapy in a total of 100 patients. The median PSA level before cryotherapy was 5.4 ng/mL. Biochemical recurrence was defined as a PSA level of 0.5 ng/mL or above. The overall BRFS rate was 72 per cent at 2 years after salvage cryotherapy, with no difference in BRFS rates between third- and second-generation cryotherapy ($p=0.54$). Furthermore, this study also stratified its results on the duration of PSA control into three risk groups according to patients' PSA level, Gleason score and clinical stage[5] before primary radiotherapy. Patients in the low-risk group were those with a PSA level of 10 ng/mL or less, a Gleason score of 6 or lower and a clinical stage of 2b or below. Patients were classified into the intermediate-risk group if they had one of the following unfavourable risk factors: more than 10 ng/mL in PSA level, equal to or more than 7 in Gleason score, or more than stage 2b in clinical stage. The high-risk group included patients with two or more unfavourable risk factors. The authors found the 5-year BRFS rate for the low-risk group was 73 per cent, which was significantly higher than that for both the intermediate-risk group (45%) and the high-risk group (11%) ($p<0.01$).

The study with the longest follow-up period was reported by Bahn et al (2003). It was a high-quality case series of 59 argon-based cryotherapy procedures with a mean follow-up period of 72.5 months. The baseline PSA levels were in the range 0–57 ng/mL, with a

[5] In the past, prostate cancer was divided into four T-stages – T1, T2, T3 and T4. T1: non-palpable prostate cancer; T2: organ-confined prostate cancer (T2 stage was divided further into three substages – T2a: palpable prostate cancer involving 50 per cent or less of one lobe of the prostate; T2b: palpable prostate cancer involving more than 50 per cent of one lobe; T2c: palpable prostate cancer involving both lobes); T3: prostate cancer penetrating through the prostate capsule; T4: prostate cancer with local invasion (Braunwald et al 2001).

median of 5.6 ng/mL. The authors observed a BRFS rate of 59 per cent at 7 years after salvage cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy, using the PSA cut-off value of 0.5 ng/mL as the definition of biochemical recurrence.

Gowardhan et al (2007) reported a case series with the highest pre-cryotherapy PSA level among all the studies identified in the literature. The mean baseline PSA levels for the EBRT group and the brachytherapy group were 31.6 ng/mL and 13.5 ng/mL, respectively. The follow-up periods ranged from 6 weeks to 36 months, with a mean of 19.2 months. Biochemical-free recurrence rates were similar between patients who had received EBRT and brachytherapy as their primary treatment at 6 months (48.1% vs 50%) and 9 months (47.1% vs 50%).

Table 13 Biochemical disease-free survival after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Definition of biochemical recurrence-free	Pre-treatment PSA level	Follow-up period: biochemical recurrence-free survival
3rd generation					
(Clarke et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	47	PSA <0.5 ng/mL	Mean: 9.0 ng/mL	25 months (mean): 24/33 (72.7%)
(Gowardhan et al 2007)[a]	Level IV Quality: 4/6 Prospective case series	EBRT: 32	PSA ≤0.5 ng/mL	Mean: 31.6 ng/ml Range: 2.2–85.0 ng/mL	6 months: 13/27 (48.1%) 9 months: 8/17 (47.1%) 12 months: 7/16 (43.8%) 18 months: 5/10 (50.0%)
		Brachytherapy: 10	PSA ≤0.5 ng/mL	Mean: 13.5 ng/mL Range: 4.8–32.2 ng/mL	6 months: 5/10 (50.0%) 9 months: 3/6 (50.0%) 12 months: 4/5 (80.0%) 18 months: 3/4 (75.0%) 24 months: 1/1 (100%)
(Cresswell et al 2005)[a]	Level IV Quality: 4/6 Prospective case series	20	PSA <0.5 ng/mL	Median: 7.0 ng/mL Range: 2.5–21.1 ng/mL	6 weeks: 12/18 (66.7%) 3 months: 10/15 (66.7%) 12 months: 4/6 (66.7%)
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	Without three consecutive rises in PSA level	Mean: 3.3 ng/mL Range: 0.3–9.0 ng/mL	12 months: n/a (89%) 24 months: n/a (67%) 36 months: n/a (50%)
			PSA ≤2 ng/mL above the nadir	Mean: 3.3 ng/mL Range: 0.3–9.0 ng/mL	12 months: n/a (89%) 24 months: n/a (79%) 36 months: n/a (79%)
(Han et al 2003)[b]	Level IV Quality: 4/6 Prospective case series	18	PSA ≤0.4 ng/mL	n/a	3 months: 14/17 (82.3%) 12 months: 13/17 (76.5%)
(Cytron et al 2003)	Level IV Quality: 3.5/6 Prospective case series	5	PSA ≤0.5 ng/mL	Mean: 6.4 ng/mL Range: 4.7–8.4 ng/mL	9 months: 3/5 (60.0%) 12 months: 3/5 (60.0%) 15 months: 3/5 (60.0%)

(Han et al 2004)[b]	Level IV Quality: 3/6 Prospective case series	29	PSA ≤0.4 ng/mL	n/a	12 months: 13/18 (72.2%)
3rd or 2nd generation					
(Ismail et al 2007)	Level IV Quality: 4.5/6 Prospective case series	100 3rd generation: 55 2nd generation: 45	PSA <0.5 ng/mL	Median: 5.4 ng/mL	12 months: n/a (83%) 24 months: n/a (72%) (p=0.54 between the 3rd and 2nd generations) 36 months: n/a (59%) 60 months: n/a (55%) Low-risk group: n/a (73%) Intermediate-risk group: n/a (45%) High-risk group: n/a (11%) (p<0.001)
(Bahn et al 2003)	Level IV Quality: 4.5/6 Retrospectiv e case series	59	PSA <0.5 ng/mL	Median: 5.6 ng/mL Range: 0–57 ng/mL	6 months: n/a (85%) 12 months: n/a (80%) 24 months: n/a (75%) 60 months: n/a (59%) 84 months: n/a (59%)
(Donnelly et al 2005)[c]	Level IV Quality: 4/6 Prospective case series	46 3rd generation: 6 2nd generation: 40	PSA ≤0.3 ng/mL	Median: 5.6 ng/mL Range: 0.1–16.1 ng/mL 3rd generation: Median: 4.3 ng/mL Range: 1.7–7.5 ng/mL 2nd generation: Median: 5.2 ng/mL Range: 2.4–10.6 ng/mL	6 weeks: 33/46 (71.7%) 3rd generation: 3/6 (50.0%) 2nd generation: 30/40 (75.0%) 12 months: n/a (51%) 24 months: n/a (44%)
(Robinson et al 2006)[c]	Level IV Quality: 4/6 Prospective case series	46	PSA <0.3 ng/mL	0–10 ng/mL: 40 patients 11–20 ng/mL: 6 patients	12 months: 25/39 (64.1%) 24 months: 16/31 (51.6%)
2nd generation					
(Ng et al 2007)[d]	Level IV Quality: 4.5/6 Retrospective case series	187[e]	PSA ≤2.0 ng/mL above the nadir	Median: 4.9 ng/mL Range: 0–36.4 ng/mL	39 months (mean): 105/187 (56.1%)
(Chin et al 2001)[d]	Level IV Quality: 4/6 Retrospective case series	118[e]	PSA <0.5 ng/mL	<5 ng/mL: 60 ≥5 ng/mL: 58	3 months: n/a (75%) 12 months: n/a (50%) 24 months: n/a (38%)
			PSA <2.0 ng/mL	<5 ng/mL: 60 patients ≥5 ng/mL: 58 patients	3 months: n/a (85%) 12 months: n/a (70%) 24 months: n/a (62%)
			PSA <4.0 ng/mL	<5 ng/mL: 60 patients ≥5 ng/mL: 58 patients	3 months: n/a (90%) 12 months: n/a (80%) 24 months: n/a (72%)
(Chin et al 1998)[d]	Level IV Quality: 4/6 Retrospective	45[e]	PSA <0.5 ng/mL	n/a	6 months: 10/20 (50.0%)

	case series				
(Ghafar et al 2001)[f]	Level IV Quality: 4/6 Prospective case series	38	PSA <0.3 ng/mL above the nadir	Mean: 7.5 ng/mL Range: 0.4–28 ng/mL	3 months: n/a (100%) 6 months: n/a (100%) 12 months: n/a (86%) 24 months: n/a (74%)
(de la Taille et al 2000b)[f]	Level IV Quality: 4/6 Retrospective case series	18	PSA <0.2 ng/mL above the nadir	n/a	6 months: n/a (79%) 12 months: n/a (66%)
(de la Taille et al 2000a)[f]	Level IV Quality: 3.5/6 Prospective case series	19	PSA <0.2 ng/mL above the nadir	Mean: 5.9 ng/mL Range: 0.6–25 ng/mL	3 months: n/a (93%) 6 months: n/a (93%) 9 months: n/a (85%)

[a] May be overlap between patient series; [b] May be overlap between patient series; [c] May be overlap between patient series; [d] May be overlap between patient series; [e] Eleven patients underwent 1st generation instead of 2nd generation cryotherapy; [f] May be overlap between patient series

n/a: not available; PSA: prostate-specific antigen; EBRT: external beam radiotherapy

Local lymph node involvement and distant metastases

A total of six studies reported on local lymph node involvement and distant metastases after argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy (Table 14). Two case series investigated third-generation cryotherapy, and the other four studies reported on second-generation cryotherapy.

The incidence rates of local lymph node involvement and distant metastases ranged from 0 to 15.8 per cent in the six studies. The largest high-quality case series was reported by Ng et al (2007). Among 187 patients who underwent salvage cryotherapy, a total of 24 patients (12.8%) developed clinically evident metastatic diseases during a mean follow-up period of 39 months. Chin et al (2001) were the authors of the other study with a population of more than 100, which observed local lymph node involvement and distant metastases. This study reported ten cases of metastases (8.5%) in the bones, liver or pelvic lymph nodes during a mean follow-up period of 18.6 months. In another moderate-quality case series, Chin et al (1998) discovered three cases of bone metastatic diseases (6.7%), one case of liver metastasis (2.2%) and one case of pelvic lymph node involvement (2.2%) during a follow-up period of up to 43 months. It was not possible to determine conclusively whether there was any overlap among patient populations in the above three case series, although, given the relatively low rates of metastatic disease, it is likely that the patient series was duplicated to some extent. The case series by de la Taille et al (2000a), like the previous three studies, also included the incidence of metastatic disease; however, the authors did not discover any cases of either local lymph node involvement or distant metastases in 19 patients during a mean follow-up period of 8.3 months.

Of the two small moderate-quality case series reporting metastatic diseases following third-generation cryotherapy, Cresswell et al found that a total of two patients (10.0%) had developed metastases during a mean follow-up period of 9 months, while Eisenberg and Shinohara (2008) reported a metastasis incidence rate of 15.8 per cent during a mean follow-up period of 18 months among their 19 patients.

Table 14 Local lymph node involvement and distant metastases after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Follow-up period: local lymph node involvement and distant metastases
3rd generation			
(Cresswell et al 2006)	Level IV Quality: 4/6 Prospective case series	20	9 months (mean): Lymph node involvement: 1/20 (5.0%) Distant metastases: 1/20 (5.0%)
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	18 months (mean): Distant metastases: 3/19 (15.8%)
2nd generation			
(Ng et al 2007)[a]	Level IV Quality: 4.5/6 Retrospective case series	187[b]	39 months (mean): Distant metastases: 24/187 (12.8%)
(Chin et al 2001)[a]	Level IV Quality: 4.5/6 Retrospective case series	118[b]	18.6 months (mean): Distant metastases: 10/118 (8.5%)
(de la Taille et al 2000a)	Level IV Quality: 4.5/6 Prospective case series	19	8.3 months (mean): Distant metastases: 0
(Chin et al 1998)[a]	Level IV Quality: 4/6 Retrospective case series	45[b]	0–43 months (range): Lymph node involvement: 1/45 (2.2%) Distant metastases: 4/45 (8.9%)

[a] May be overlap between patient series; [b] Eleven patients underwent nitrogen-based cryotherapy instead of argon-based cryotherapy.

Symptom control

In the literature the International Prostate Symptom Score (IPSS) is the most widely used measure of symptom control among men undergoing treatment for prostate cancer. The IPSS was derived from the American Urological Association Symptom Index. It is a self-administered questionnaire consisting of seven urinary symptom questions and one quality of life question (Appendix F). Each question is assigned points from 0 to 5, indicating an increase in the severity of each symptom. The total score therefore ranges from 0 to 35 (from asymptomatic to severely symptomatic) (Barry et al 1992). The IPSS was primarily designed for assessing treatment outcomes in benign prostatic hyperplasia. Now, the use of this instrument has broadened to measuring symptom severity and response among patients after treatment for prostate cancer. The IPSS has proven to have good internal consistency (Cronbach's α[6] = 0.86) and excellent test–retest reliability (r = 0.92). In addition, the scores derived from the IPSS questionnaire are highly correlated with patients' global ratings of the severity of their urinary problems (r = 0.65–0.72) (Barry et al 1992).

There were two case series reporting IPSS results of argon-based cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy (Table 15). Ismail et al (2007), in their good-quality study, compared IPSSs before and after second-generation cryotherapy in a total of 100 patients. The median baseline IPSS before the cryotherapy procedure was 7 (range = 1–27). At 6 weeks after the treatment the median

[6] Cronbach's α: a coefficient indicating reliability or consistency. It measures the extent to which a set of variables can be treated as measuring a single, unidimensional latent variable (Hatcher 1994)

IPSS rose to 13, with the highest score being 34. A decrease in median IPSSs was observed after that period, reaching a score of 9 at 12 months. Although this figure was higher than the baseline score of 7, neither statistically (p=0.133) nor clinically[7] significant differences were observed between IPSSs before and 1 year after the salvage procedure. This indicated that salvage cryotherapy neither improves nor significantly worsens urinary tract symptoms among patients with recurrent or persistent prostate cancer after radiotherapy. The other study was reported by Cresswell et al (2005). In this moderate-quality case series involving 20 argon-based cryotherapy procedures, the median IPSS increased from 6 before the procedure to 11 at 9 months after the salvage treatment. However, the statistical significance of this change was not tested.

Table 15 IPSS before and after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	IPSS	
			Before cryotherapy	After cryotherapy
3rd generation				
(Cresswell et al 2005)	Level IV Quality: 4/6 Prospective case series	20	Median: 6 Range: 1–20	9 months: Median: 11 Range: 6–29
3rd or 2nd generation				
(Ismail et al 2007)	Level IV Quality: 4.5/6 Prospective case series	100 3rd generation: 55 2nd generation: 45	Median: 7 Range: 1–27	6 weeks: Median: 13 (p=0.133) Range: 0–34 12 months: Median: 9 (p=0.133) Range: 0–32

IPSS: International Prostate Symptom Score

Quality of life

Two case series reported on quality of life (QoL) after argon-based cryotherapy for patients with radiation failure (Table 16). The EORTC-QLQ-C30, a health-related QoL instrument developed by the European Organization for Research and Treatment of Cancer (EORTC), was administered in both of the studies. Another more specific instrument, the Prostate Cancer Index (PCI), was used in one of the two case series.

The EORTC-QLQ-C30 is a self-administered standardised multiscale questionnaire measuring health-related QoL that is relevant to the experience of cancer. It consists of nine multi-item scales: five functional scales (physical activity, emotional state, role function, social interaction and cognitive function), three symptom scales (fatigue, pain and nausea/vomiting) and one global health and QoL scale. In addition, six single items (insomnia, appetite loss, constipation, diarrhoea, dyspnoea and financial difficulties) are included in the EORTC-QLQ-C30 (Appendix F). A high score in functional scales or in the global health and QoL scale represents a healthy level of functioning and a good health status / QoL, respectively; while a high score for a symptom scale or item represents a high level of health problems (Aaronson et al 1993). The EORTC-QLQ-C30 has high reliability in different clinical research settings, with Cronbach's $\alpha \geq 0.70$ on all scales or items except the role functional scale. The good validity of the EORTC-QLQ-C30 as a measure of QoL in cancer patients is demonstrated in three parts: the

[7] Clinically significant difference in IPSS: IPSS increases or decreases >3 (Barry & O'Leary 1995)

substantial interscale correlation ($p<0.01$); clear differences in functional scales (physical, role and cognitive) and symptom scales among patients with varied clinical status ($p<0.05$); and significant changes ($p<0.05$) in functional scales (physical and role), the global health and QoL scale, and symptom scales corresponding to patients' performance status during treatment (Aaronson et al 1993).

In a moderate-quality case series, Robinson et al (2006) followed up a total of 46 patients after the salvage cryotherapy procedure, with a 2-year follow-up rate of 83.8 per cent. The authors observed slight decreases in all functional scores and in the global health and QoL score within 3 months after cryotherapy, compared with baseline scores. In addition, there was a minor increase in the symptom scores as well as in the single item scores immediately after the cryotherapy procedure. However, there were no statistically significant differences between baseline scores and the scores at 24 months after salvage cryotherapy across any of the domains in the EORTC-QLQ-C30, with the exception of the pain scale, in which the score was higher at 2 years after cryotherapy than before the procedure. Overall health-related QoL was high at 2 years after treatment, with a score of 80 for the global health and QoL scale, scores above 85 for the five functional scales, and scores below 20 for all of the three symptom scales. These results are not clinically significantly different[8] to those in the normal population aged 50 years or older (Schwarz & Hinz 2001). The other study reporting the results on EORTC-QLQ-C30 was carried out by Anastasiadis et al (2003). At 6 months after salvage cryotherapy the mean scores on the global health and QoL scale and the five functional scales ranged from 73 to 91, whereas the scores for the three symptom scales and the six single item scales were low. However, the actual effect of cryotherapy on patients' QoL cannot be determined in this study due to the lack of baseline QoL scores.

The PCI is a questionnaire that measures QoL specific to prostate cancer. It includes 20 self-report questions assessing the function and level of discomfort in three organ systems: urinary, sexual and bowel (Appendix F). It was developed by the University of California, Los Angeles, USA, as a health-related QoL measurement for men treated for early stage prostate cancer (Litwin et al 1998). The PCI performs well in older adults with or without prostate cancer, with test–retest reliability and internal consistency ranging from 0.66 to 0.93 and 0.65 to 0.93, respectively. The measures of function and discomfort correlate significantly with each other in the urinary, sexual and bowel domains ($r = 0.65–0.73$, $p<0.001$). In addition, expected worsening in the measures of function and discomfort in the three disease-specific domains are observed in patients receiving prostatectomy or radiotherapy for the treatment of prostate cancer (Litwin et al 1998).

One case series by Robinson et al (2006) reported post-cryotherapy disease-specific QoL using the PCI. This study showed that the mean urinary function score significantly decreased from above 90 at baseline to below 60 at 24 months after the salvage cryotherapy procedure ($p<0.001$). The proportion of patients reporting moderate-to-severe problems with sexual functioning increased from 0 per cent at baseline to 40.6 per cent at 6 weeks after cryotherapy, with long-term effects in 29 per cent of the men at 24 months. There was a significant decline (>30 points) from the baseline mean sexual function score to that at 24 months ($p<0.001$). A significant amount of sexual

[8]Clinically significant difference in EORTC-QLQ-C30: an increase or decrease of score ≥10 (Osoba et al 1998)

discomfort was reported by 35.6 per cent of the patients before salvage cryotherapy, with the percentage climbing to 51.9 per cent at 2 years after the treatment. Although the mean score for bowel function decreased at 6 weeks after cryotherapy, it returned to the baseline score by 24 months.

Table 16 QoL after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Mean QoL scores			
EORTC-QLQ-C30 instrument						
(Robinson et al 2006)	Level IV Quality: 3.5/6 Prospective case series	46	Items	Baseline (n=46)	24 months (n=31)	
			Global health and QoL score	Around 80	Around 80[a]	
			Function scores	85–100	85–100[a]	
			Symptom scores	0–15	0–20[b]	
			Shortness of breath	2.2	0	
			Insomnia	9.4	9.7	
			Appetite loss	2.3	0	
			Constipation	2.3	3.2	
			Diarrhoea	4.4	0	
(Anastasiadis et al 2003)	Level IV Quality: 3.5/6 Prospective case series	42	6 months (mean score): Global health and QoL score: 73 Function scores: Physical function score: 91 Role function score: 86 Emotional function score: 84 Cognitive function score: 89 Social function score: 75 Symptom scores: low Single item scores: <25			
PCI instrument						
(Robinson et al 2006)	Level IV Quality: 3.5/6 Prospective case series	46	Items	Baseline	6 weeks	24 months
			Urinary function score (mean)	>90	60	<60 (p<0.01)
			Sexual function score (mean)	Around 30	<5	<10 (p<0.01)
			Bowel function score (mean)	Around 85	around 75	Return to baseline score
			Urinary bother (% with moderate-to-severe problems)	0	40.6%	29.0%
			Sexual bother (% with moderate-to-severe problems)	35.6%	54.8%	51.9%

[a] No statistical difference between the baseline scores and post-procedure scores; [b] With statistical difference only in the pain scale

QoL: quality of life; PCI: Prostate Cancer Index

Length of hospital stay

A total of 14 moderate-to-high quality case series reported on length of hospital stay after argon-based cryotherapy for recurrent or persistent prostate cancer following radiation failure (Table17). In general, the hospital stay after salvage cryotherapy was very short:

patients in all except two studies were discharged on the day of procedure or one day after that. Cresswell et al (2005) reported lengths of hospital stay from 1 to 3 days after third-generation cryotherapy, without providing any reason for the comparatively long hospital stay in this case series. In another study involving 46 cryotherapy procedures, Donnelly et al (2005) observed a median hospital stay of 1 day, with only two patients staying in hospital for another day, and this was due to a lack of home support rather than clinical need.

Table17 Length of hospital stay after cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Evidence level and quality	Number of patients	Length of hospital stay
3rd generation			
(Clarke et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	47	Median: 0 day
(Zisman et al 2001)	Level IV Quality: 4.5/6 Prospective case series	17	Range: 0–1 day
(Cresswell et al 2005)	Level IV Quality: 4/6 Prospective case series	20	Median: 2 days Range: 1–3 days
(Eisenberg & Shinohara 2008)	Level IV Quality: 4/6 Retrospective case series	19	Median: 0 day
(Han et al 2003)	Level IV Quality: 4/6 Prospective case series	18	Median: 1 day
3rd or 2nd generation			
(Ismail et al 2007)	Level IV Quality: 4.5/6 Prospective case series	100 3rd generation: 55 2nd generation: 45	Range: 0–1 day
(Bahn et al 2003)	Level IV Quality: 4/6 Retrospective case series	59	Median: 1 day
(Donnelly et al 2005)	Level IV Quality: 4/6 Prospective case series	46 3rd generation: 6 2nd generation: 40	Median: 1 day Range: 1–2 days
2nd generation			
(Ng et al 2007)[b]	Level IV Quality: 4.5/6 Retrospective case series	178[c]	Median: 1 day
(Chin et al 2001)[b]	Level IV Quality: 4/6	118[c]	Median: 1 day
(Ghafar et al 2001)[b]	Level IV Quality: 4/6 Prospective case series	38	Median: 1 day
(de la Taille et al 2000b)[a]	Level IV evidence Quality: 4/6 Retrospective case series	18	Range: 0–1 day
(Anastasiadis et al 2003)[a]	Level IV Quality: 3.5/6 Prospective case series	42	Median: 1 day

(de la Taille et al 2000a)[a]	Level IV evidence Quality: 3.5/6 Prospective case series	19	Range: 0–1 day

[a] May be overlap between patient series; [b] May be overlap between patient series; [c] Eleven patients underwent 1st generation instead of 2nd generation cryotherapy.

Summary – What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?

– What is the effectiveness of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?

No data were identified that compared the effectiveness of salvage cryotherapy (±NHT) against salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT). There were a total of 21 case series (level IV evidence) identified in the literature that met the inclusion criteria for this review, reporting effectiveness outcomes as a result of argon-based cryotherapy for recurrent or persistent prostate cancer after radiotherapy.

The majority of the articles included had follow-up periods ranging from 1 to 2 years. The case series with the longest follow-up period of 72.5 months was reported by Bahn et al (2003). Two other case series had a mean follow-up period longer than 2 years. Within the follow-up period after salvage argon-based cryotherapy, both the overall survival rate and the disease-specific survival rate were more than 90 per cent.

Biopsy was occasionally undertaken as a routine examination after salvage cryotherapy and was sometimes undertaken in patients with abnormal results on PSA testing. Biopsy-confirmed disease-free survival rates for patients undergoing routine biopsy and for those having selective biopsy were above 80 per cent and equal to or more than 50 per cent, respectively.

Two-year PSA control was achieved in 38 to 79 per cent of patients. The wide range in duration of PSA control between the case series was attributable to differences in pre-treatment PSA levels as well as various PSA cut-off values used for the definition of biochemical recurrence. The 7-year BRFS was reported as 59 per cent by Bahn et al (2003), using the definition of biochemical failure as a PSA level equal to or more than 0.5 ng/mL. Patients with good prognosis in PSA control were those with a PSA level of 10 ng/mL or less, a Gleason score of 6 or lower, and a clinical stage of 2b or below before the primary radiotherapy.

Local lymph node involvement and distant metastases were not common during the follow-up period, ranging from 0 to 15.8 per cent.

Although scores in functional scales and global health and QoL scale decreased immediately after the cryotherapy procedure, there was a return-to-baseline trend at 24 months after the cryotherapy procedure. In general, patients had a healthy level of functioning and were in a good health state and QoL after salvage cryotherapy.

Symptoms, especially in urinary and sexual organ systems, were more obvious after treatment. As reported by patients, urinary and sexual dysfunction or both were more serious after the cryotherapy compared to before the procedure.

After cryosurgery, patients recovered quickly and a short hospital stay of no more than 1 day was required following the procedure.

What are the economic considerations?

In its assessment of a new service, the MSAC is required to consider not only the comparative effectiveness and safety of the service but also the comparative cost and cost-effectiveness of the service. The purpose of the economic evaluation is to inform the decision made by the MSAC on the additional costs and additional gains (health or other socially relevant outcomes) of the proposed service over the comparator when used in the Australian healthcare system. This is to ensure that society's ultimately scarce resources are allocated to those activities from which it will get the most value. That is, it seeks to enhance economic efficiency.

When undertaking economic analyses, initially a systematic review (and/or meta-analysis) is produced to determine whether there is evidence that the intervention is comparatively effective (see 'Effectiveness' section page 36). An economic analysis is only undertaken if there is evidence that the procedure under consideration is as, or more, effective than the designated comparator(s). Due to the lack of comparative evidence, it is not possible to conclude whether or not salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy is as effective as, or more effective than, salvage prostatectomy. Therefore, only an analysis of the expenditures associated with the new procedure relative to the comparative procedures was conducted.

The cost data cover all non-trivial health system resources. Indirect costs, also known as productivity costs, were not considered. All cost data were converted to the single year 2008 and expressed in Australian dollars. Where a time horizon beyond 12 months was adopted, a discount rate of 5 per cent was used.

The costing exercise conducted is not intended for fee scheduling purposes, and is not a recommendation for funding at these levels.

Existing literature

Studies addressing the cost-effectiveness of salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy were assessed for inclusion in this report according to the criteria delineated a priori in Box 3.

Box 3 Inclusion criteria for studies assessing the cost-effectiveness of salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Research question	
1. What is the cost-effectiveness of salvage cryotherapy (±NHT), compared to salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery?	
2. What is the cost-effectiveness of salvage cryotherapy (±NHT), compared to salvage HIFU (±NHT) or salvage brachytherapy (±NHT), in patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery?	
Characteristics	**Criteria**
Population	1. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment and fit for surgery 2. Patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment but not fit for or decline surgery
Intervention	Salvage cryotherapy (argon-based) (±NHT)
Comparators	1. Salvage prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT) 2. Salvage HIFU (±NHT) or salvage brachytherapy (±NHT)
Outcome	Cost, cost per event avoided, cost per life year gained, cost per quality-adjusted life year or disability-adjusted life year, incremental cost-effectiveness ratio
Study design	Economic studies, decision analytic modelling studies, economic analyses
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.

No literature that met the inclusion criteria compared the cost-effectiveness of salvage cryotherapy (±NHT) against radical prostatectomy (±NHT), HIFU (±NHT) or brachytherapy (±NHT).

Financial incidence analysis

The purpose of the financial incidence analysis in this report is to estimate the cost impact of salvage cryotherapy when it is listed on the MBS. Stand-alone hormone therapy and watchful waiting, although not regarded as appropriate comparators when assessing the safety and effectiveness of cryotherapy, are considered in the financial analysis, since over 95 per cent of patients with recurrent or persistent prostate cancer after radiotherapy currently receive these two treatments. A proportion of these patients would choose salvage cryotherapy instead if this procedure was available, thus resulting in a financial impact on the Australian Government and the healthcare system overall. In comparison, the costs of salvage radical prostatectomy, salvage HIFU or salvage brachytherapy on the society and the government are negligible, as very few patients with radiation failure undergo these curative treatments (expert opinion of the Advisory Panel).

The financial analysis of salvage cryotherapy is performed under the assumption that *100 per cent* of patients with recurrent or persistent prostate cancer after radiation failure currently receive either hormone therapy or watchful waiting, in the ratio 80:20. The costs of salvage radical prostatectomy, salvage HIFU and salvage brachytherapy are not considered when calculating the comparative costs of cryotherapy to the Australian Government and to the Australian healthcare system overall. However, the unit costs of these procedures relative to salvage cryotherapy are still presented in this section.

Likely number of procedures in a typical year

As previously described in the section addressing clinical need/burden (page 16), between 588 and 3374 patients experience recurrent prostate cancer after radiotherapy per year in Australia. Based on the assumption that 80 per cent of patients with radiation failure are treated by androgen deprivation, and the remaining 20 per cent use watchful waiting, the numbers of patients who undergo these two treatments would be 470 to 2699 and 118 to 675, respectively. It is expected that between10 and 33 per cent of patients with locally recurrent or persistent prostate cancer following radiotherapy would be suitable for salvage cryotherapy; therefore, it is estimated that between 59 and 1113 salvage cryotherapy procedures would be performed annually across Australia (expert opinion of the Advisory Panel; Scanmedics Pty Ltd 2007).

Unit costs

The work-up for salvage cryotherapy, salvage HIFU and salvage brachytherapy is the same. Salvage radical prostatectomy following radiation failure requires more pre-procedural examinations, such as a blood crossmatch. A TRUS-guided prostate biopsy is carried out before all these salvage treatment procedures to provide the histological evidence of recurrent or persistent prostate cancer after radiotherapy. Chest X-rays and bone scans are also prescribed pre-procedurally to all patient candidates, so that patients with distant metastatic disease, who are unsuitable for salvage treatments, can be detected and excluded. Coagulation studies are carried out to rule out patients with bleeding disorders, who are considered not suitable for cryotherapy. A serum PSA test is highly recommended before salvage cryotherapy, radical prostatectomy, HIFU and brachytherapy in order to make possible a comparison between post-procedure PSA level and baseline PSA level, and thus give some indication of tumour response to salvage treatments. Furthermore, an elevated level of serum PSA suggests the existence of local extension or metastases. In that case, abdomen and pelvis CT is indicated.

The pre-treatment work-up for hormone therapy and watchful waiting is similar to that for salvage procedures, except for pre-anaesthetic consult and coagulation studies, which are not required for conservative treatments. The unit costs of the pre-treatment work-up are presented in Table 18.

Table 18 Unit costs of work-up for various treatments

Item	Schedule fee		Source of estimate
	CRYO, RP[a], HIFU and BT	HT and WW	
Specialist consult	$79	$79	MBS item 104
Pre-anaesthetic consult	$79	n/a	MBS item 17615
TRUS-guided prostate biopsy	$368	$368	MBS item 37219 and 55600
Chest X-ray	$47	$47	MBS item 58503
Bone scan	$497	$497	MBS item 61433
Serum PSA test	$21	$21	MBS item 66656
Coagulation studies	$43	n/a	MBS item 65129 and 65070
Abdomen and pelvic CT[b]	$385	$385	MBS item 56501
Total	**$1 519**	**$1 397**	

Source: Medicare Australia 2008b

[a] Salvage radical prostatectomy following radiation failure requires other pre-procedural examinations, such as blood crossmatch; [b] Item electively undertaken when there are clinical indications

BT: brachytherapy; CRYO: cryotherapy; CT: computed tomography; HIFU: high-intensity focused ultrasound; HT: hormone therapy; PSA: prostate-specific antigen; RP: radical prostatectomy; TRUS: transrectal ultrasound; WW: watchful waiting; n/a: not applicable

The post-procedural care and post-hospital costs are the same for both cryotherapy and other curative procedures. Five follow-up visits and PSA tests, usually at 6 weeks, 3 months, 6 months, 9 months, and 12 months post-operatively, are needed in the first post-procedural year. After that, a follow-up visit and PSA test take place once a year. Patients who undergo stand-alone hormone therapy or watchful waiting would visit a doctor and have PSA testing every 3 months in the first year, then twice per year. Annual blood tests, such as full blood count, liver function tests and kidney function tests, are also required for patients during ongoing hormone therapy (expert opinion of the Advisory Panel).

There are various hormone therapy (stand-alone or neoadjuvant) regimens. Single agents, either nonsteroidal anti-androgens or steroids, have been used, as have combinations of two agents, such as luteinizing hormone-releasing hormone (LHRH) agonists and nonsteroidal anti-androgens (Hellerstedt & Pienta et al 2002). In clinical practice in Australia the most commonly used hormone therapy drugs are Goserelin and Leuproprelin. Both of these drugs are listed on the PBS for the indication of stand-alone hormone therapy but not for NHT. Once stand-alone hormone treatment is started, patients will usually be on this for the rest of their lives. The duration of ongoing hormone therapy depends on their age, life expectancy, comorbidities and the occurrence of tumour progression or metastasis (expert opinion from the Advisory Panel). An NHT regime usually lasts 3 months. The unit costs of stand-alone hormone therapy and NHT are presented in Table 19.

Table 19 Unit costs of stand-alone hormone therapy and NHT

		Goserelin	Leuprorelin
Dispensed price for max. quantity		$332 (Goserelin acetate subcutaneous implant 3.6 mg)	$420 (Leuprorelin acetate IM injection 7.5 mg)
Stand-alone hormone therapy	Regimen	Goserelin acetate subcutaneous implant 3.6 mg/28 days x 13 per year	Leuprorelin acetate IM injection 7.5 mg/month x 12 per year
	Cost	**$4 316 per year**	**$5 040 per year**
Neoadjuvant hormone therapy	Regimen	Goserelin acetate subcutaneous implant 3.6 mg/28 days x 3	Leuprorelin acetate IM injection 7.5 mg/month x 3
	Cost	**$996**	**$1 260**

Source: Medicare Australia 2008c

The equipment costs of salvage cryotherapy are presented in Table 20. The unit cost is calculated in two scenarios: one where 20 salvage cryotherapy procedures are performed annually per machine; the other where efficient throughput for cryotherapy machines (2 procedures per day) is achieved, with an estimated procedure volume of 500 annually.

Table 20 Cost per unit of additional capital equipment and maintenance for salvage cryotherapy

Item	Estimate		Source of estimate
Equipment cost	$250 000	$250 000	Scanmedics Pty Ltd
Estimated clinical life of equipment	10 years	10 years	Scanmedics Pty Ltd
Annual equivalent cost of equipment	$32 376	$32 376	Annuity at 5% p.a. for 10 years
Annual maintenance costs	$25 000	$25 000	Scanmedics Pty Ltd
Total major capital equipment cost per year	$57 376	$57 376	
Estimated annual volume of procedures	20	500	Expert opinion of the Advisory Panel
Estimated cost per procedure	$2 869	$115	

The procedure costs of salvage cryotherapy, salvage radical prostatectomy, salvage HIFU and salvage brachytherapy are compared in Table 21, including all relevant costs regardless of the agency that bears them. The estimated costs per cryotherapy procedure would be $14 790 and $12 036, when the annual volumes of procedure are 20 and 500, respectively. In general, cryotherapy is more expensive than any of the other curative treatments: it will incur an additional cost of about $1550–$4500 per patient if compared with HIFU and brachytherapy; and the per procedure cost of cryotherapy is more than twice that of radical prostatectomy. The high unit cost of a cryotherapy procedure is mainly attributable to the expensive disposable Cryokit and gases.

A cost comparison among cryotherapy, hormone therapy and watchful waiting is presented in Table 22. An annual discount rate of 5 per cent was used when estimating various costs in the second year or thereafter. It was assumed that 10 per cent of patients would receive NHT, with a ratio between Goserelin and Leuprorelin of 50:50. The total cost per cryotherapy in the first year is estimated at $16 727 or $13 973 (in scenarios using different throughputs of a cryotherapy machine), which would be more than twice as much as the costs of stand-alone hormone therapy during the first year. After that, ongoing hormone therapy would result in a steadily substantial cost increase owing to the expenditures on androgen deprivation drugs; whereas the total cost of cryotherapy rises at a much slower speed because of the relatively low costs for follow-up visits and PSA tests. Somewhere between the third year and the fourth year, the total cost of hormone therapy would exceed that of cryotherapy. Cryotherapy would save about $4900–$11 000 relative to hormone therapy per procedure by the end of 5 years.

It should be highlighted that the cost comparison shown in Table 22 is based on the assumption that patients do not develop local recurrence or metastases during the period when the costs of cryotherapy and stand-alone hormone therapy are estimated; otherwise, additional downstream costs for the management of treatment failure would be incurred. Since no data on the long-term effectiveness of cryotherapy are currently available, caution should be taken when comparing the total costs between cryotherapy and hormone therapy in a long time period.

The unit cost comparison as displayed in Table 22 also demonstrates that watchful waiting would be understandably much cheaper than cryotherapy at any time during the follow-up period, but only if cancer recurrence does not occur.

Table 21 Procedural costs of salvage cryotherapy, radical prostatectomy, HIFU and brachytherapy in a private setting

Item	Cryotherapy	Cryotherapy	Radical prostatectomy	High-intensity focused ultrasound	Brachytherapy
Equipment cost	$2 869[a] (Table 20)	$115[b] (Table 20)	n/a	$7 000 (expert opinion of the Advisory Panel)	n/a
Cost of associated disposables / radiation seeds	$8 700 (Scanmedics Pty Ltd)	$8 700 (Scanmedics Pty Ltd)	n/a	$950 (EDAP TMS SA[c])	$7 000 (Prostheses List code ON003)[d]
Professional fee–surgeon[e]	$1 439 (MBS item 37210)	$1 439 (MBS item 37210)	$1 439 (MBS item 37210)	$959 (MBS item 37210)	$1 444 (MBS item 15338, 15539)
TRUS monitoring	$109 (MBS item 55600)	$109 (MBS item 55600)	n/a	n/a	$109 (MBS item 55600)
Anaesthesia initiation	$183 (MBS item 20845)	$183 (MBS item 20845)	$183 (MBS item 20845)	$183 (MBS item 20845)	$183 (MBS item 20845)
Anaesthesia time units[f]	$219 (MBS item 23063)	$219 (MBS item 23063)	$219 (MBS item 23063)	$110 (MBS item 23063)	$110 (MBS item 23063)
Surgical assistant	n/a	n/a	n/a	n/a	$173 (MBS item 51303)
Hospital facility services[g]	$1 271[h]	$1 271[h]	$3 891[i]	$1 271[h]	$1 271[h]
Total cost	**$14 790**	**$12 036**	**$5 732**	**$10 473**	**$10 290**

Sources: Medicare Australia 2008b; Australian Health Insurance Association 2008; Department of Health and Ageing 2005

[a] Equipment cost when the an nual volume of cryotherapy procedures per instrument is 20; [b] Equipment cost when the annual volume of cryotherapy procedures per instrument is 500; [c] EDAP TMS SA develops and markets the Ablatherm® FIHU system; [d] The cost of brachytherapy seeds listed on the Prostheses List ranges from $6800 to $7150. $7000 is used as an approximate average; [e] It is indicated that the procedural time for cryotherapy is about 180 minutes, which is equal to the operation time for radical prostatectomy; therefore, it would be reasonable to use the fee for radical prostatectomy. While the surgical time for HIFU is around two-thirds of that for radical prostatectomy; so the professional fee is calculated as multiplying the fee for radical prostatectomy by 2/3; [f] The average times for cryotherapy, radical prostatectomy, HIFU and brachytherapy are 180 minutes, 180 minutes, 120 minutes and 90 minutes, respectively; [g] Items not covered by Medicare; [h] Total average charge per AR-DRG V5.1 Private Hospital Data Bureau; L08B – URETHRAL PROCEDURES-CC; average length of hospital stay: 1.22 days; [i] Total average charge per AR-DRG V5.1 Private Hospital Data Bureau; L07A – TRANSURETHRAL PROCS+CSCC; average length of hospital stay: 5.47 days.

n/a: not applicable; TRUS: transrectal ultrasound

Table 22 Unit costs of salvage cryotherapy, hormone therapy and watchful waiting in a private healthcare setting

Year	Item	Cryotherapy [a]	Cryotherapy [b]	Hormone therapy		Watchful waiting	Source
				Goserelin	Leuprorelin		
1st year	Pre-treatment work-up	$1 519	$1 519	$1 397	$1 397	$1 397	Table 18
	Procedure	$14 790[a]	$12 036[b]	n/a	n/a	n/a	Table 21
	Neoadjuvant hormone therapy[c]	$113	$113	n/a	n/a	n/a	Table 19
	Ongoing hormone therapy	n/a	n/a	$4 316	$5 040	n/a	Table 19
	Follow-up visits[d]	$40x5	$40x5	$40x4	$40x4	$40x4	MBS item 105
	Follow-up PSA tests[d]	$21x5	$21x5	$21x4	$21x4	$21x4	MBS item 66656
	Other blood tests[e]	n/a	n/a	$35	$35	n/a	MBS item 65070 and 66512
	Total	**$16 727**	**$13 973**	**$5 992**	**$6 716**	**$1 641**	
2nd year	Ongoing hormone therapy	n/a	n/a	$4 110	$4 800	n/a	Table 19
	Follow-up visit(s)[f]	$38x1	$38x1	$38x2	$38x2	$38x2	MBS item 105
	Follow-up PSA test(s)[f]	$20x1	$20x1	$20x2	$20x2	$20x2	MBS item 66656
	Other blood tests[e]	n/a	n/a	$33	$33	n/a	MBS item 65070 and 66512
	Total	**$16 785**	**$14 031**	**$10 252**	**$11 666**	**$1 757**	
3rd year	Ongoing hormone therapy	n/a	n/a	$3 915	$4 571	n/a	
	Follow-up visit(s) and blood tests	$55	$55	$143	$143	$111	
	Total	**$16 840**	**$14 086**	**$14 309**	**$16 379**	**$1 868**	
4th year	Ongoing hormone therapy	n/a	n/a	$3 728	$4 354	n/a	
	Follow-up visit(s) and blood tests	$53	$53	$135	$135	$105	
	Total	**$16 893**	**$14 139**	**$18 173**	**$20 869**	**$1 973**	
5th year	Ongoing hormone therapy	n/a	n/a	$3 551	$4 146	n/a	
	Follow-up visit(s) and blood tests	$50	$50	$130	$130	$101	
	Total	**$16 943**	**$14 189**	**$21 853**	**$25 144**	**$2 074**	
10th year	**Total**	**$17 160**	**$14 406**	**$37 785**	**$43 999**	**$2 508**	

Source: Medicare Australia 2008b)

[a] Procedure cost when the annual volume of cryotherapy procedures is 20 per instrument; [b] Procedure cost when the annual volume of cryotherapy procedures is 500 per instrument; [c] 113 = 996 x 0.05 + 1260 x 0.05. The costs of NHT are not covered by MBS for this indication, thus borne by the patient; [d] In the first year the numbers of follow-up visits / PSA tests after cryotherapy and during ongoing hormone therapy or watchful waiting are 5 and 4, respectively; [e] Other blood tests include full blood count, liver function tests and kidney function tests. They are required only for hormone therapy, with a frequency of once a year; [f] In the second year and thereafter, the frequencies of follow-up visits / PSA tests for cryotherapy and hormone therapy or watchful waiting are every 12 months and 6 months, respectively.

n/a: not applicable; PSA: prostate-specific antigen

Cost to the Australian Government

The Australian Government is responsible for payment of the rebate on items from the MBS. As salvage cryotherapy for recurrent or persistent prostate cancer will be performed in a hospital facility, the rebate would be 75 per cent of the schedule fee for a private hospital facility. For pharmaceutical benefit items, the maximum cost is $32.90 for general patients, $5.30 for concessional patients or those who reach the Safety Net threshold and $0 for concessional patients who reach the Safety Net threshold. The difference between these figures and the dispensed price of a pharmaceutical benefit item is borne by the government. The unit costs of cryotherapy, hormone therapy and watchful waiting to the government are presented in Table 23.

Table 23 Unit costs to the Australian Government

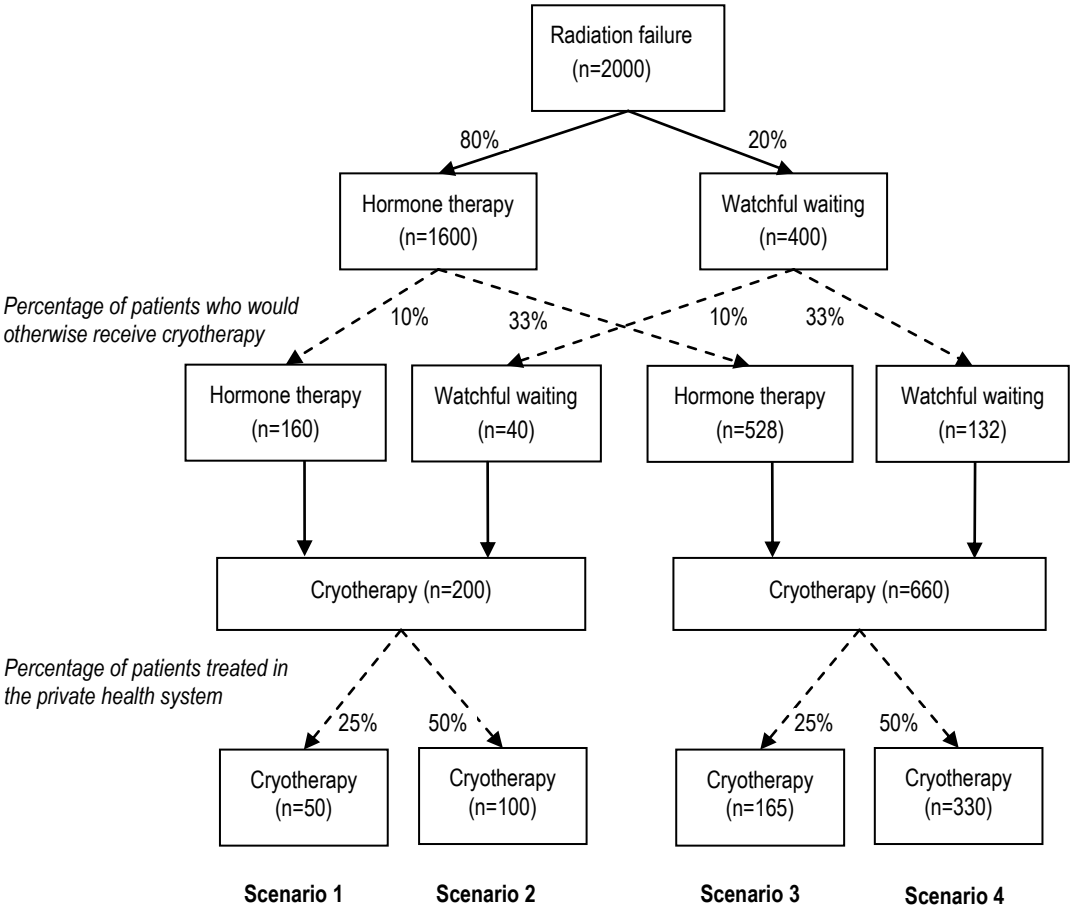
Year	Item	Cryotherapy	Goserelin	Leuprorelin	Watchful waiting	Source
1st year	Pre-treatment work-up	$1 139	$1 048	$1048	$1 048	Table 18
	Procedure[a]	$1 463	n/a	n/a	n/a	Table 21
	Ongoing hormone therapy	n/a	$4 090[b]	$4 927[c]	n/a	Table 19
	Follow-up visits	$30x5	$30x4	$30x4	$30x4	Table 22
	Follow-up PSA tests	$16x5	$16x4	$16x4	$16x4	Table 22
	Other blood tests	n/a	$26	$26	n/a	Table 22
	Total	**$2 831**	**$5 347**	**$6 184**	**$1 231**	
2nd year	Ongoing hormone therapy	n/a	$3 895	$4 692	n/a	
	Follow-up visit(s)	$29x1	$29x2	$29x2	$29x2	Table 22
	Follow-up PSA test(s)	$15x1	$15x2	$15x2	$15x2	Table 22
	Other blood tests	n/a	$25	$25	n/a	Table 22
	Total	**$2 874**	**$9 354**	**$10 988**	**$1 318**	
5th year	**Total**	**$2 993**	**$20 267**	**$24 070**	**$1 555**	
10th year	**Total**	**$3 156**	**$35 253**	**$42 038**	**$1 881**	

[a] Procedural costs include professional, anaesthesia and TRUS monitoring fee; other cost items for cryotherapy listed in Table 21, such as equipment fee and hospital facility services fee, are not covered by Medicare; [b] According to Pharmaceutical Benefits Schedule Item Reports (Medicare Australia 2008d), the patient breakdown for Goserelin is 0.46 for general patients, 0.44 for concessional patients or those who reach the Safety Net threshold, and 0.10 for concessional patients who reach the Safety Net threshold. Therefore, the annual cost of Goserelin borne by the government should be calculated as (332 - 0.46 x 32.9 - 0.44 x 5.3) x 13; [c] According to Pharmaceutical Benefits Schedule Item Reports (Medicare Australia 2008d), the patient breakdown for Leuprorelin is 0.19 for general patients, 0.60 for concessional patients or those who reach the Safety Net threshold, and 0.21 for concessional patients who reach the Safety Net threshold. Therefore, the annual cost of Leuprorelin borne by the government should be calculated as (420 - 0.19 x 32.9 - 0.60 x 5.3) x 12.

n/a: not applicable; PSA: prostate-specific antigen; TRUS: transrectal ultrasound

The calculation of the total costs of cryotherapy to the Australian Government, shown in Table 24, was based on the following assumptions: 1) 80 per cent and 20 per cent of the patients experiencing radiation failure receive hormone therapy and watchful waiting, respectively; 2) Goserelin and Leuprorelin are used by equal numbers of patients; 3) both hormone therapy and watchful waiting take place in the private health sector. The base case assumes that 2000 patients have recurrent or persistent prostate cancer after radiotherapy per year in Australia (in the range 588–3374) (page 16, Appendix G). Four scenarios were costed, including two where different proportions of patients (10% and 33%) with radiation failure undergo salvage cryotherapy, and two with different public to private patient splits for cryotherapy (75:25 and 50:50) (Figure 7).

Figure 7 Patient breakdown in estimating total costs to the Australian Government (base case)



Scenario 1: 10% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 2: 10% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
Scenario 3: 33% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 4: 33% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.

To calculate the financial implications to the Australian Government of subsidising salvage cryotherapy for the treatment of recurrent or persistent prostate cancer following radiotherapy, the estimated cost per procedure was multiplied by the expected uptake of the procedure in private hospitals. As 50–330 procedures are expected to be performed annually in the private sector, a *saving* of between $688 608 and $2 739 439 for salvage cryotherapy would be incurred by the government in the first year relative to the currently available treatments, namely hormone therapy and watchful waiting. This cost saving would nearly double in the first 2 years. If patients have a longer disease-specific survival, salvage cryotherapy would be a more cost-saving procedure compared to hormone therapy and watchful waiting.

Table 24 Total costs to the Australian Government (base case)

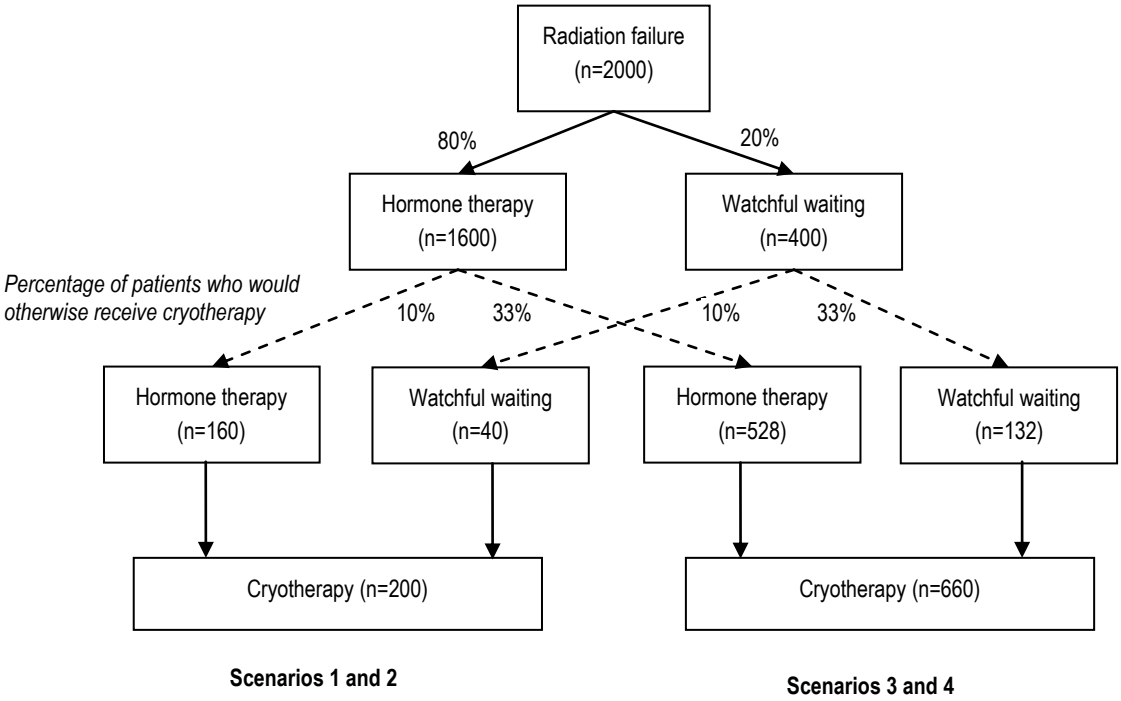
	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	50	160	40	
1 year	$141 525	$922 428	$49 230	–$830 133
2 years	$143 704	$1 627 331	$52 716	–$1 536 343
5 years	$149 636	$3 546 956	$62 208	–$3 459 528
Scenario 2				
Number of patients	100	160	40	
1 year	$283 050	$922 428	$49 230	–$688 608
2 years	$287 407	$1 627 331	$52 716	–$1 392 639
5 years	$299 273	$3 546 956	$62 208	–$3 309 892
Scenario 3				
Number of patients	165	528	132	
1 year	$467 033	$3 044 012	$162 459	–$2 739 439
2 years	$474 222	$5 370 192	$173 962	–$5 069 932
5 years	$493 800	$11 704 955	$205 287	–$11 416 442
Scenario 4				
Number of patients	330	528	132	
1 year	$934 065	$3 044 012	$162 459	–$2 272 406
2 years	$948 444	$5 370 192	$173 962	–$4 595 710
5 years	$987 600	$11 704 955	$205 287	–$10 922 642

Scenario 1: 10% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 2: 10% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
Scenario 3: 33% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 4: 33% of patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
[a] A negative difference is a cost saving resulting from cryotherapy compared to hormone therapy and watchful waiting.

Total cost to the Australian healthcare system overall

The total cost of salvage cryotherapy to the Australian healthcare system would include co-payments, costs of disposables, hospital services and capital equipment as well as medical services. Calculation of the total cost relied on the same assumptions described in the 'Cost to the Australian Government' section (page 58). As presented in Figure 8, the costs were calculated in four scenarios with different proportions of patients with radiation failure receiving salvage cryotherapy (10% and 33%) and two different annual volumes of cryotherapy procedures achieved per machine (20 and 500). Table 25 includes costs for the base case (2000 patients with persistent or recurrent prostate cancer); the lower and the upper estimates (588, 3374) are costed in Appendix G.

Figure 8 Patient breakdown for estimating total costs to the Australian healthcare system overall (base case)



Scenario 1:10% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 2: 10% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.
Scenario 3: 33% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 4: 33% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.

In scenarios 1 and 2, 10 per cent of patients who have recurrent or persistent prostate cancer after radiotherapy are treated by salvage cryotherapy, incurring an *additional* cost of $1 712 230–$2 263 040 to the Australian healthcare system in the first year. The range reflects the different scenarios where one site uses its cryotherapy equipment for only 20 procedures per year (scenario 1) and where the equipment is used at maximum efficiency (500 procedures per year, scenario 2). Cryotherapy would result in higher expenditures relative to hormone therapy and watchful waiting if the procedure is carried out in 33 per cent of those experiencing recurrent or persistent prostate cancer after radiotherapy, with an *additional* cost of $5 650 360–$7 468 032. The total expenditures required for ongoing hormone therapy and watchful waiting are substantially less than those for cryotherapy in the first year, largely due to the expensive disposable Cryokit and gases required for the cryotherapy procedure ($8 700 per patient). In the first 2 years salvage cryotherapy would still incur an *additional* cost, but with a narrower cost difference compared to stand-alone hormone therapy and watchful waiting. If all the patients who are treated by salvage cryotherapy live longer than 5 years without treatment failure, cryotherapy would result in a cost *saving* of between $454 151 and $3 316 370.

Table 25 Total costs to the Australian healthcare system overall (base case)

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	200	160	40	
1 year	$3 345 320	$1 016 640	$65 640	$2 263 040
2 years	$3 356 939	$1 753 402	$70 288	$1 533 250
5 years	$3 388 581	$3 759 787	$82 944	–$454 151
Scenario 2				
Number of patients	200	160	40	
1 year	$2 794 510	$1 016 640	$65 640	$1 712 230
2 years	$2 806 129	$1 753 402	$70 288	$982 440
5 years	$2 837 771	$3 759 787	$82 944	–$1 004 961
Scenario 3				
Number of patients	660	528	132	
1 year	$11 039 556	$3 354 912	$216 612	$7 468 032
2 years	$11 077 899	$5 786 226	$231 949	$5 059 723
5 years	$11 182 316	$12 407 298	$273 716	–$1 498 698
Scenario 4				
Number of patients	660	528	132	
1 year	$9 221 884	$3 354 912	$216 612	$5 650 360
2 years	$9 260 227	$5 786 226	$231 949	$3 242 052
5 years	$9 364 644	$12 407 298	$273 716	–$3 316 370

Scenario 1:10% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.

Scenario 2: 10% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.

Scenario 3: 33% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.

Scenario 4: 33% of patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.

[a] A positive difference and a negative difference represent an additional cost and a cost saving, respectively, resulting from cryotherapy compared to hormone therapy and watchful waiting.

Discussion

Is it safe?

A total of 18 case series (level IV intervention evidence) assessed the safety of salvage cryotherapy (±NHT) for the treatment of recurrent or persistent prostate cancer after radiotherapy. The available evidence does not provide information on the relative safety of this procedure compared to its comparators: salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT).

The most significant complication identified as resulting from the salvage cryotherapy procedure following radiation failure is a recto-urethral fistula, with incidence rates ranging between 0 and 7.1 per cent over follow-up periods of 8.3–72.5 months. The size of the cryoprobes used in an argon-based cryotherapy system did not influence the frequency of occurrence of fistula following the procedure. However, it is noted that patients undergoing brachytherapy before cryotherapy were more likely to develop recto-urethral fistula than those having EBRT as their primary treatment.

Impotence was the most common complication following salvage cryotherapy. The high (up to 100%) impotence rate after cryotherapy was due to the accumulative influence of primary radiotherapy and salvage treatment. Between 60 and 100 per cent of patients with potency before cryotherapy would develop impotence after the procedure. Data were not available to compare any change in potency before/after the procedure between second-generation cryotherapy (using thicker needles) and third-generation cryotherapy (using thinner needles).

Urinary incontinence occurred in 0 to 33.3 per cent of patients post-procedurally. There was no significant difference between the incidence of incontinence after third- or second-generation cryotherapy. Other urethral complications, such as urethral sloughing, urethral stricture, bladder neck obstruction and urethral ulcer, had relatively lower incidence rates of no more than 11.1 per cent during various follow-up periods. It was suggested that the reduction in the occurrence of urethral damage from cryotherapy procedures, compared to previous generations of cryotherapy, is attributable to the use of urethral warming in second- or third-generation cryotherapy systems, rather than the technological development of the cryotherapy machine (expert opinion of the Advisory Panel).

Minor complications following salvage cryotherapy for radiation failure included pelvic and/or perineal and/or rectal pain, UTI, transient haematuria, scrotal swelling, penile tingling and/or numbness, and proctitis, with rates of no more than 34 per cent. These complications required only conservative treatment.

There were a small number of studies that included a few patients who underwent liquid nitrogen-based cryotherapy procedures. The clinical outcomes of cryotherapy systems using different freezing agents were not analysed separately due to the lack of data.

Discrepancies in safety outcomes, for example incontinence and impotence, as well as in effectiveness outcomes, such as duration of PSA control, are noteworthy in this assessment report. Some of the differences may have resulted from the following factors: 1) lack of consensus on patient selection—patients with known adverse prognostic

features such as high PSA level, high Gleason score, and extra-capsular tumour extension or metastatic diseases were included in some studies but not in others; 2) a variety of cryotherapy generations—both thinner and thicker needle-sized cryotherapy systems using argon gas as their freezing agent were assessed in this report, and several articles involving a few liquid nitrogen-based cryotherapy procedures were also included in the systematic review; 3) variations in the definitions of biochemical failure, impotence, incontinence, obstruction and so on; 4) differences in self-reporting of outcomes (eg incontinence and impotence) among individual patients and various case series; 5) surgeons with different levels of experience at performing the cryotherapy procedure; 6) relatively small samples in the case series included in this assessment (of the total of 20 case series identified from the literature, 15 studies involved fewer than 50 salvage cryotherapy procedures; and 7) varying periods of follow-up—the longer the follow-up period, the more likely it is to find an adverse event.

Is it effective?

Twenty-one case series (level IV intervention evidence) assessed the effectiveness of salvage argon-based cryotherapy (±NHT) for recurrent or persistent prostate cancer after radiotherapy. No evidence was identified that considered the effectiveness of salvage cryotherapy (±NHT) in relation to its comparators: salvage prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT).

Studies included in this assessment report varied in their follow-up periods, with the mean ranging from 8.3 to 72.5 months after salvage argon-based cryotherapy. Within the follow-up periods in all case series, only two patients died from prostate cancer, resulting in disease-specific survival rates between 95 and 100 per cent. The 5-year and 8-year overall survival rates, as reported by one included study, were 97 per cent and 92 per cent, respectively, in those patients who were followed up 5 years and 8 years after cryotherapy.

There was no consensus on whether or not routine post-cryotherapy biopsy examination should be performed. Some of the clinical institutes carried out biopsies on all patients who underwent salvage cryotherapy or whenever they were logistically feasible, while others biopsied those patients with abnormal results in PSA testing. Overall, 50 per cent or more of the patients who were prescribed biopsy after cryotherapy procedure were histologically confirmed as disease free.

There were large variations in 1-year and 2-year BRFS rates, which were 44 to 89 per cent and 38 to 79 per cent, respectively, across different case series included for assessment. The wide range in duration of PSA control among distinct studies was partly attributable to: various PSA cut-off values used for the definition of biochemical recurrence, differences in the length of follow-up periods and different inclusion criteria during patient selection. Ismail et al (2007) discovered that patients with a PSA level of 10 ng/mL or less, a Gleason score of 6 or lower and a clinical stage of 2b or below before the primary radiotherapy had a higher rate of BRFS compared to those patients who did not fulfil these criteria.

Only a small percentage of patients who underwent salvage cryotherapy following radiation failure developed local or distant metastatic disease (0–15.8%).

Urinary and sexual symptoms were not controlled after salvage cryotherapy; on the contrary, urinary and sexual dysfunction or discomfort was more serious after the

cryotherapy procedure than before. However, in general, patients had a healthy level of functioning and were in a good state of health and QoL after salvage cryotherapy.

The majority of the studies reporting clinical outcomes of salvage argon-based cryotherapy had follow-up periods ranging from 1 to 2 years. Only one case series identified in the literature followed up patients for more than 5 years after the procedure. Therefore, no conclusions can be reached regarding the long-term treatment effectiveness of argon-based cryotherapy following radiotherapy failure. The insufficient post-treatment follow-up is especially noteworthy in the assessment of a treatment for prostate cancer, since this disease has a slow development and progression course. Further clinical studies with long follow-up periods are indicated for a comprehensive evaluation of the argon-based cryotherapy procedure.

The body of evidence included in this assessment was appraised according to the NHMRC's guidance on clinical practice guideline development (NHMRC 2008). Table 26 presents the results of the appraisal of the evidence considered in this assessment. The populations of the studies examined were generalisable to the target population of patients with localised recurrent or persistent prostate cancer after radiotherapy within Australia. With all studies being conducted in developed countries with similar standards of practice in the treatment of radiation failure, the results of the studies are applicable to the Australian healthcare context, except that the length of hospital stay after cryotherapy in the United States healthcare setting (usually a same-day procedure) would be shorter than that (an overnight stay) in clinical practice in Australia (expert opinion of the Advisory Panel).

Table 26 Assessment of body of evidence for effectiveness of salvage cryotherapy[a]

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence-base				Level IV studies, or level I to III studies with high risk of bias
Consistency		Most studies are consistent and inconsistency may be explained		
Clinical impact			Moderate	
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 25

What are the economic considerations?

A financial incidence analysis of salvage cryotherapy relative to hormone therapy and watchful waiting was conducted to estimate the expenditures involved with each management strategy from both an Australian Government perspective and a healthcare system perspective. Although salvage radical prostatectomy, salvage HIFU and salvage

brachytherapy were regarded as appropriate comparators in assessing the safety and the effectiveness of cryotherapy, they are seldom performed in clinical practice in Australia. The costs of these curative treatments were therefore not considered when estimating the potential financial impact of cryotherapy if it was to be listed on the MBS.

The estimate of the financial implications of salvage cryotherapy to the Australian Government and the Australian healthcare system overall relied on three assumptions: 1) that patients experiencing recurrent or persistent prostate cancer after radiotherapy currently undergo either stand-alone hormone therapy or watchful waiting, with a ratio of 80:20; 2) that all patients receive stand-alone hormone therapy and watchful waiting in the private health sector; and 3) that half of the patients receiving hormone therapy are treated by Goserelin and the other half by Leuprorelin. On these assumptions, several scenarios were costed in the financial analysis, including the impact of different proportions of patients receiving salvage cryotherapy, the costs associated with cryotherapy equipment used for this indication alone versus at maximum feasible efficiency, and with two different public to private patient splits. It is acknowledged that a percentage of patients who undergo salvage cryotherapy are likely to have further disease recurrence. However, the additional costs of further treatment have not been included in the financial analysis due to the absence of long-term follow-up data on cryotherapy.

It was highlighted that the total costs to the government and the whole society varied over different time spans. Cryotherapy would result in a cost *saving* of between $688 608 and $2 739 439 to the Australian Government in the first year. The longer the disease-free survival, the more money would be saved by salvage cryotherapy. Ongoing hormone therapy would incur substantial costs for androgen deprivation drugs for each additional year, whereas the annual expenditures on follow-up visits and PSA tests after cryotherapy are considerably lower. In terms of total costs to the Australian healthcare system overall, cryotherapy would incur an *additional* cost of $1 712 230–$7 468 032 in the first year. However, between the third year and the fourth year, the overall financial burden of salvage cryotherapy to the Australian healthcare system would be *exceeded* by that of hormone therapy and watchful waiting. If the disease-specific survival is more than 5 years after salvage cryotherapy for all patients, the cost *saving* of cryotherapy would range between $454 151 and $3 316 370.

Other relevant considerations

This section provides information that does not fit with the evidence-based assessment of the safety, effectiveness and cost-effectiveness of salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy, but nevertheless impacts on this assessment.

Safety and effectiveness of the comparators

Evidence relating to the safety and effectiveness of the comparators has not been included in the systematic review as no comparative data for salvage cryotherapy and radical prostatectomy, HIFU or brachytherapy are available. Therefore, it is not possible to make definitive statements regarding relative safety and effectiveness between salvage cryotherapy and its comparators without a prospective head-to-head clinical trial. Despite this, the safety and effectiveness of the comparators should be noted, as the clinical outcomes of radical prostatectomy, HIFU and brachytherapy for the treatment of

persistent or recurrent prostate cancer may have an impact on the decision for or against argon-based cryotherapy being listed on the MBS.

Radical prostatectomy (following primary radiotherapy), like salvage cryotherapy, is complicated by radiation-induced tissue fibrosis and dense tissue adhesions. The rate of complications from salvage radical prostatectomy appears to have decreased over time, which suggests the existence of a physician learning curve or modification of surgical techniques. Stephenson et al (2004) compared patients who underwent radical prostatectomy after radiotherapy before 1993 with those who were treated after that time. The authors discovered that, since 1993, the rate of rectal injury is significantly less (2% vs 15%, p=0.01). The overall rate of major complications declined from 33 per cent of patients treated before 1993 to 13 per cent after 1993 (p=0.02). No difference in the frequency of incontinence or bladder neck strictures was observed over time. Several recent non-systematic reviews reported that post-salvage prostatectomy incidence rates of rectal injury, urinary incontinence and bladder neck stricture were 0 to 10 per cent, 0 to 67 per cent, and 7 to 30 per cent, respectively. The majority of case series investigating salvage radical prostatectomy after radiation failure do not document impotence rates, with the exception of one study identified, in which 100 per cent of patients lost their potency after a salvage prostatectomy procedure (Ahmed et al 2005; Dudderidge et al 2007; Nguyen et al 2007). As to the reported effectiveness outcomes, 5-year PSA control was achieved in 31 to 83 per cent of patients who had radical prostatectomy for the treatment of recurrent or persistent prostate cancer, using a PSA level of 0.2 ng/mL as the cut-off value for biochemical recurrence (Nguyen et al 2007). Using the same criteria, Amling et al (1999) reported a 10-year BRFS rate of 43 per cent in a case series involving 108 salvage radical prostatectomy procedures.

The clinical outcomes of salvage HIFU were reported in several case series and were summarised by Chalasani et al (2008). In this review the impotence rates after salvage HIFU were quite high, ranging from 66 to 100 per cent. The incidence rates of rectal fistula were between 0 and 16 per cent. Between 10 and 50 per cent of the patients who underwent salvage HIFU developed incontinence after the procedure. BRFS was achieved in 17 to 57 per cent of patients in various series using different definitions of biochemical failure and with varied lengths of follow-up periods. Five-year PSA control was achieved in 17 to 44 per cent of patients who received HIFU following radiation failure, when biochemical failure was defined as a PSA level >2.0 ng/mL above the nadir.

Salvage brachytherapy is the other investigational treatment option for persistent or recurrent prostate cancer after radiotherapy. Two non-systematic reviews have summarised 13 case series investigating salvage brachytherapy following radiation failure (Bong & Keane 2007; Nguyen et al 2007). Reported complications following the salvage brachytherapy procedure included rectal injury (0–15%), urinary incontinence (0–31%) and urethral strictures (3%). The 5-year BRFS rates ranged from 20 to 89 per cent across case series, with various follow-up periods and using different PSA cut-off values for the definition of biochemical failure. Among all the studies included in the above two reviews, the largest series involved a total of 49 salvage brachytherapy procedures with a mean follow-up period of 64 months (Grando et al 1999). In this case series 3-year and 5-year PSA control were achieved in 48 per cent and 34 per cent, respectively, of patients who underwent salvage brachytherapy. The actual disease-specific survival rates at 3 and 5 years were 89 per cent and 79 per cent, respectively.

The Advisory Panel expressed the opinion that there have been concerns among clinicians over the safety of the potentially curative treatments that salvage cryotherapy has been compared against (salvage radical prostatectomy, salvage HIFU and salvage brachytherapy). Furthermore, the long-term effectiveness of salvage HIFU and salvage brachytherapy is unproven by clinical studies. The Advisory Panel therefore suggested that salvage cryotherapy would be the preferred treatment option for patients who meet the selection criteria. However, this expert opinion was given with the acknowledgement that it was potentially biased, due to cryotherapy being the only local salvage treatment option offered within the specific Advisory Panel member's clinical practice.

Based on the current available evidence in the literature and the expert opinion of the Advisory Panel, the safety and effectiveness of salvage cryotherapy do not appear to be worse than those of its comparators. However, it should be noted that any conclusions on the comparative safety or effectiveness of salvage cryotherapy are highly speculative, as there are no direct comparative studies identified in the literature investigating the safety and effectiveness of salvage cryotherapy for the treatment of recurrent or persistent prostate cancer after radiotherapy relative to salvage radical prostatectomy, salvage HIFU and salvage brachytherapy. Heterogeneity in cryotherapy generations, differences in subject selection, discrepancies in the definitions of some safety or effectiveness outcomes, and variations in surgeon skills are noteworthy among various studies. Furthermore, an indirect comparison between salvage cryotherapy and its comparators would be vulnerable to bias because of the relatively small sample sizes and insufficient follow-up data in clinical studies examining salvage treatments of prostate cancer following radiation failure.

Accessibility of curative treatments and implications for patients

The accessibility of salvage cryotherapy and its comparators (salvage radical prostatectomy, salvage HIFU and salvage brachytherapy) by those patients who could potentially benefit is an important issue when assessing the cryotherapy procedure following radiation failure.

Due to its high price, limited indications and the specialised equipment and skills required to perform the procedure, cryotherapy is expected to only be available in a few centres in Australia. Salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy is currently performed in only one clinic in Australia (expert opinion of the Advisory Panel). Even with a limited quantity of cryotherapy units, they may well be under-utilised due to the small clinical need for the salvage cryotherapy procedure. However, since recurrent or persistent prostate cancer is not the only indication for which cryotherapy may be carried out, an argon-based cryotherapy system has the potential for efficient throughput if also used for other therapeutic applications.

As a common major urological procedure, radical prostatectomy is now performed in many clinics in Australia. However, salvage radical prostatectomy for the treatment of recurrent or persistent prostate cancer following radiotherapy is not widely performed for two reasons: 1) the complicated anatomic peri-prostate tissue damage induced by primary radiotherapy requires further surgical training for the salvage radical prostatectomy procedure following radiation failure; and 2) the disappointing safety outcomes reported by earlier studies have resulted in poor acceptance of salvage radical prostatectomy by both health professionals and patients. Salvage radical prostatectomy following radiation failure might be expected to be carried out in additional specialised

hospitals in the future, following the accumulation of clinical experience in performing this procedure and likely further modification of surgical techniques.

Salvage HIFU is a relatively new potential treatment option for patients who fail primary radiotherapy. This technology has been increasingly used and studied in recent years (Chalasani et al 2008). None of the HIFU systems can be located on the ARTG website, although HIFU Sonablate 500® was announced to have received TGA full marketing approval by its distributor, THS International Inc, in August 2005 (Medical News Today 2005). HIFU for the treatment of localised prostate cancer is not reimbursed by Medicare. In current clinical practice the salvage HIFU procedure following radiotherapy is still in the investigational stage, and is performed in a very limited number of clinical centres in Australia. It is also expected that the high cost of the required equipment, as well as the specialised surgical skills required for the procedure, would obstruct the diffusion of HIFU as a treatment for recurrent or persistent prostate cancer after radiation failure in the Australia healthcare system in the near future.

Although primary brachytherapy in the treatment of localised prostate cancer has been well established, the performance of salvage brachytherapy in patients with radiation failure is still under study. Re-irradiation is only occasionally performed in a few institutions in Australia.

Patients experiencing radiation failure who are suitable for salvage treatment and fit for surgery would be candidates for all salvage treatment options: cryotherapy, radical prostatectomy, HIFU and brachytherapy. As for those patients who are not fit for major surgery (eg older men with significant comorbidities), salvage cryotherapy, salvage HIFU and salvage brachytherapy are potential treatment options. However, for the reasons outlined above, there are many patients who may be suitable for, but currently do not undergo, curative treatments. In these cases, hormone therapy (as a stand-alone treatment) and watchful waiting are prescribed, not with curative intent but to reduce the tumour size rather than eliminate it or run the risk of metastases (Lam & Belldegrun 2004; Izawa et al 2002). It is possible that, if salvage cryotherapy is reimbursed and more hospitals invest in cryotherapy units, the availability of the cryotherapy option would provide access to curative treatments for patients who otherwise would not receive any. This is particularly the case for patients who are not suitable for surgery (older men or men with comorbidities) but who could tolerate a less invasive procedure.

Skills required for performing cryotherapy

The argon-based cryotherapy system for prostate cancer uses a template that is very similar to brachytherapy, allowing urologists and radiation oncologists currently performing brachytherapy to be easily trained in cryotherapy techniques (Scanmedics Pty Ltd 2007). However, it is noteworthy that the placement of cryoneedles and thermoprobes during a salvage cryotherapy procedure can be more challenging than during a primary cryotherapy procedure because of the peri-prostate anatomic planes damage incurred by previous radiotherapy. This radiation-induced tissue damage is particularly serious following brachytherapy, after which the radiation seeds within the prostate gland scatter the ultrasound waves and mimic the cryoprobe ultrasonically, resulting in distorted TRUS images during treatment planning and real-time monitoring (Gowardhan et al 2007). Performing salvage cryotherapy after radiotherapy requires extensive training, and the learning curve associated with the procedure is considerable. It is reasonable to expect fewer complications to occur as experience with this procedure increases.

Equity between different population groups

The MSAC should consider topics such as access and equity when determining whether a health technology should be recommended for reimbursement. There is currently an increasing (age-standardised) mortality excess for prostate cancer patients in rural and regional areas, as compared to men who live in capital cities (Coory & Baade 2005). There are many potential reasons for this, but the evidence has suggested that access to urologists and the management options available to men depend on where they live.

In 2000–02, rates of radical prostatectomy were 29 per cent lower in men from rural areas of Australia (Coory & Baade 2005). The applicant suggested that the shorter hospitalisation and recovery time associated with cryotherapy (compared to salvage prostatectomy) would make it more accessible for patients in rural and remote areas, potentially improving equity. However, as all cryotherapy procedures would need to be done in one of the few tertiary centres with the highly specialised equipment and personnel, patients from rural and remote areas would still need to travel for the procedure. Furthermore, patients from rural areas are also less likely to have had radiotherapy as the primary treatment for their prostate cancer, as radiotherapy options are more limited in rural hospitals (Hall et al 2005). Fewer men in rural areas would therefore be indicated for cryotherapy for persistence or recurrence after primary radiation. It is therefore unlikely that the option of salvage cryotherapy would increase equity of access to curative treatments between metropolitan and rural populations.

Patient journey

By the time men have persistence or recurrence of prostate cancer after radiation failure, they have already journeyed a considerable way with the disease—from the initial symptoms to referral, investigation, diagnosis, treatment and follow-up. These men are likely to have become well educated on their prostate cancer, and already made some difficult decisions about the trade-off between QoL and eradicating the cancer. Unfortunately, quite a proportion of men who undergo primary radiation therapy will have suffered adverse events, such as impotence, as a result of the treatment for their cancer, and this can have a large psychosocial impact on men. Impotence can be accompanied by concerns over masculinity, can impact on the ability to participate in an enjoyable activity, and may cause strain on intimate relationships (Broom 2007). Any additional treatment given to these men is likely to further impact on their functioning. Decisions regarding management of the recurrent or persistent prostate cancer therefore need to be made with great care.

There is currently no 'gold standard' treatment for recurrent or persistent prostate cancer after radiation failure, due to the lack of high-quality evidence. The scientific literature has not reported any particular salvage treatment to be effective for all men with recurrence or persistence of prostate cancer. Therefore, the best option for individual patients is to be fully informed on the possible harms and benefits that may result from the different treatments. This allows men to consider their treatment preferences, and to give true informed consent to whichever treatment they choose based on their personal values. A shared decision-making process between the patient and physician is important, as the literature suggests that what is viewed to be most important by physicians may not be in keeping with patient values. A systematic review by Zeliadt et al (2006) reported that cancer eradication is nearly every patient's primary concern when initially diagnosed. However, after investigating treatment options, other issues emerge. In a study of 1000 men with prostate cancer, 45 per cent defined an effective treatment as one that preserves QoL, compared to approximately 42 per cent who defined an effective

treatment as one that extends expected survival or delays disease progression. In contrast, physicians were much more likely (90%) to define treatment effectiveness by survival.

Patients' attitudes towards adverse events following various treatment options greatly influence the decision-making process in clinical practice (Bloch et al 2007). It was reported by Volk et al (2004) that males would commonly choose to trade off some years of life expectancy in order to avoid impotence and mild-to-moderate incontinence as adverse consequences of prostate cancer treatments. This result is consistent with Singer et al's study (1991), in which subjects expressed their willingness to choose treatments with shorter survival prospects if their chances of maintaining potency were greater. However, Fosså et al (1997) argued that prostate cancer patients seemed to accept complications, such as impotence and incontinence, as the price for a treatment that might cure the disease. O'Rourke (1999) supported Fosså et al's conclusion by demonstrating that patients' choice of a prostate cancer treatment would not be deterred by their concerns about potential complications, although patients were less willing to undergo a treatment at any cost than were their wives. These results should emphasise that there is large interpersonal variability in how side effects of treatments are viewed by patients.

No studies on patient preferences regarding salvage treatments for recurrent or persistent prostate cancer following radiotherapy have been identified. Articles identified by this assessment indicated that patients generally had a good QoL and health status after salvage cryotherapy for recurrent or persistent prostate cancer following radiotherapy, although patients' sexual and/or urinary function deterioriated after the procedure. However, there was a scarcity of evidence on the QoL in patients who were treated by salvage radical prostatectomy or other treatments following radiation failure (Sanderson et al 2006). Therefore, it is difficult to predict what patient preferences may be regarding salvage cryotherapy, due to the lack of comparative evidence on how it impacts on either QoL or survival. It is reasonable to assume that, if salvage cryotherapy could provide an acceptable level of safety and effectiveness, and was the only available curative treatment option, patient preference (and that of the clinician) would frequently be for salvage cryotherapy instead of hormone therapy or watchful waiting. When salvage cryotherapy and salvage radical prostatectomy are compared, it is assumed that patients might prefer to receive cryotherapy due to its minimally invasive nature. It is also hypothesised, in comparison to salvage brachytherapy, that cryotherapy might be preferred because of the absence of further radiation. While cryotherapy is likely to be a more expensive treatment option upfront than those currently available, due to the high cost of associated disposables, cost is rarely cited as an important factor in the decision-making process by patients (Zeliadt et al 2006). What is clear from the literature is that patient preferences vary to a large degree and, in the absence of evidence on the clear benefit of one treatment over another, are core to treatment decisions.

Conclusions

Safety

The small volume of evidence that assessed the safety outcomes of salvage argon-based cryotherapy (±NHT) for recurrent or persistent prostate cancer after radiotherapy was of a low level (level IV intervention evidence) and provided no comparative data in relation to salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT).

No deaths or life-threatening events were observed as a direct result of cryotherapy. A considerable number of patients reported impotence (60–100%) and urinary incontinence (0–33.3%). Fistula was the most serious complication, although it was not common (0–7.1%). Urethral sloughing, bladder neck obstruction, urethral stricture and urethral ulcer were also reported as major complications following a cryotherapy procedure.

Pelvic and/or perineal and/or rectal pain was the most common minor complication (in 0–39.6% of men who underwent salvage cryotherapy). Other minor adverse events reported after salvage cryotherapy include UTI, scrotal swelling, transient haematuria, penile tingling and/or numbness, and proctitis. All of the minor complications were self-limiting and did not need any medication.

In general, the evidence reported inconsistent findings with respect to the safety of salvage cryotherapy (±NHT) for recurrent or persistent prostate cancer after radiotherapy. Variations in the incidence rates for each complication across case series occurred for a number of reasons, including small sample sizes in the included case series, subjectivity in the reporting of some of the complications, and different skill and expertise levels of the surgical teams.

There was no evidence that the 17-G cryotherapy system, compared to the argon-based cryotherapy system using larger cryoprobes, would improve the safety outcomes.

Overall, apart from the risk of impotence and incontinence, salvage cryotherapy appears to be a reasonably safe procedure. Based on naïve comparisons using evidence from a non-systematic search of the literature regarding the safety of the comparators, as well as the expert opinion of the Advisory Panel, the safety of salvage cryotherapy (±NHT) is expected be no worse than salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) or salvage brachytherapy (±NHT). However, due to the lack of direct comparative evidence, the relative safety of salvage cryotherapy (±NHT) is unknown.

Effectiveness

The volume of evidence used to assess the effectiveness of salvage argon-based cryotherapy (±NHT) consisted solely of low-level uncontrolled case series (level IV intervention evidence) and is therefore considered to be of poor methodological value. However, the populations included in the studies examined were generalisable to the target population within Australia, ie patients with locally recurrent or persistent prostate cancer after radiotherapy who are suitable for salvage treatment. The results of the studies are applicable to the Australian healthcare context, with all studies being

conducted in developed countries with similar standards of practice in the treatment of recurrent or persistent prostate cancer after radiotherapy.

In general, case series identified in the literature did not have sufficient follow-up, with only one study following up their patients more than 5 years (mean follow-up period of 72.5 months). Within the short follow-up periods of included case series, both overall survival rates (92–100%) and disease-specific survival rates (95–100%) were high among the patient populations.

Two-year PSA control was achieved in 38 to 79 per cent of patients across case series, using different PSA cut-off values for the definition of biochemical recurrence. The 7-year BRFS was reported as 59 per cent if biochemical failure was defined as PSA level equal to or more than 0.5 ng/mL. Patients with lower PSA levels, lower Gleason scores and earlier clinical stages before primary radiotherapy were more likely to have longer duration of PSA control.

At least 50 per cent of patients had disease-free survival confirmed by biopsy, regardless of whether they were carried out routinely or selectively. Metastatic diseases were uncommon for patients undergoing salvage cryotherapy (0–15.8%). In general, patients had a good health status and QoL after the procedure, although their sexual and urinary symptoms were exaggerated by cryotherapy.

In conclusion, on the basis of low-level evidence, salvage argon-based cryotherapy procedure (±NHT) appears to be an effective procedure for the treatment of recurrent or persistent prostate cancer after radiotherapy within a relative short follow-up period. However, the complete absence of evidence comparing the procedure against salvage radical prostatectomy (±NHT), salvage HIFU (±NHT) and salvage brachytherapy (±NHT) does not allow any conclusions to be drawn in regard to the effectiveness of the salvage cryotherapy procedure (±NHT) against its comparators. However, as it is a potentially curative treatment, cryotherapy is likely to be more effective than hormone therapy or watchful waiting, which are currently the most common management options chosen due to lack of access to other salvage procedures.

Economic considerations

A cost-effectiveness analysis could not be performed due to the lack of any comparative evidence assessing salvage cryotherapy for the treatment of recurrent or persistent prostate cancer after radiation failure.

The financial impact of the cryotherapy procedure being listed on the MBS was estimated compared against the two most common management strategies after radiation failure: stand-alone hormone therapy and watchful waiting. The financial incidence analysis estimated that salvage cryotherapy would *save* the Australian Government $688 608 to $2 739 439 in the first year if 50–330 salvage procedures were performed in the private sector annually under different scenarios. This cost saving would rise dramatically with the increment of disease-free survival periods, due to the relatively high costs of ongoing hormone therapy drugs per year. If all patients who are treated by salvage cryotherapy live at least 5 years post-procedurally without experiencing cancer recurrence or metastases (ie without downstream costs associated with treatment failure), there would be an overall cost *saving* of between $3 309 892 and $11 416 442 to the Australian Government.

This does not reflect the total cost to the Australian healthcare system overall, which would also include patient co-payments, costs of disposables, hospital accommodation and capital costs. In the first year the total cost to the Australian healthcare system for salvage cryotherapy is estimated to range from $2 794 510 to $11 039 556 under different scenarios, where different proportions of patients with radiation failure undergo salvage cryotherapy and various numbers of cryotherapy procedures are performed per cryotherapy instrument annually. An *additional* cost of between $1 712 230 and $7 468 032 for cryotherapy would be borne by the healthcare system relative to stand-alone hormone therapy and watchful waiting in the first year. The extremely high cost of cryotherapy is mainly caused by the expensive disposable Cryokit and gases. The additional cost of cryotherapy in the first year would be offset by the high ongoing expenditure required for androgen deprivation drugs each additional year. If 5-year disease-free survival is achieved in all patients receiving cryotherapy, the cost implications of cryotherapy to the healthcare system would be a *saving* of $454 151 to $3 316 370 relative to ongoing hormone therapy and watchful waiting.

Appendix A Advisory Panel and Evaluators

Advisory Panel – Application 1124 – Cryotherapy for recurrent prostate cancer and renal cancer

Part A: Salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Member	Expertise
Dr Kwun Fong (Chair)	Thoracic Medicine
Prof Dick Fox (Deputy Chair)	Oncology
Dr William John Lynch	Urology
Dr Stuart McAlister Lyon	Radiology
Dr Bronwyn Matheson	Radiation Oncology
Mr Alan Moran	Consumer Health

Evaluators

Name	Organisation
Ms Zhaohui Liufu	Research Officer, Adelaide Health Technology Assessment
Ms Skye Newton	Senior Research Officer, Adelaide Health Technology Assessment
Prof. Janet Hiller	Director, Adelaide Health Technology Assessment

Appendix B Search strategies

Table 27 Search terms used

Element of clinical question	Search terms
Population	prostat* OR prostate[MeSH]
Intervention/test	cryotherap* OR cryotherapy[MeSH] OR cryosurg* OR cryosurgery[MeSH] OR cryoablat* OR minimally invasive therap*
Comparator (if applicable)	n/a
Outcomes (if applicable)	n/a
Limits	1995 – 2008 NOT (Limits: Animals NOT Limits: Human)

MeSH: Medical subject heading, based on a Medline/PubMed platform; n/a: not applicable

Table 28 Bibliographic databases

Electronic database	Time period
CINAHL	1995–11/2008
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1995–11/2008
Current Contents	1995–11/2008
Embase.com (including Embase and Medline)	1995–11/2008
Pre-Medline	1995–11/2008
ProceedingsFirst	1995–11/2008
Web of Science – Science Citation Index Expanded	1995–11/2008
EconLit	1995–11/2008

Table 29 Other sources of evidence (1995-11/2008)

Source	Location
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au
Australian Department of Health and Ageing	http://www.health.gov.au
NHMRC- National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Health Technology Assessment International (HTAi)	http://www.htai.org/
International Network for Agencies for Health Technology Assessment	http://inahta.org/
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	https://portal.nihr.ac.uk/Pages/NRRArchive.aspx
Google Scholar	http://scholar.google.com/
Websites of Health Technology Agencies	See Table 30
Websites of Specialty Organisations	See Table 31
Hand searching (journals from 2007–08)	
AJR. American Journal of Roentgenology	Library or electronic access
BJU International	Library or electronic access
Cardiovascular and Interventional Radiology	Library or electronic access
European Urology	Library or electronic access
International Journal of Urology	Library or electronic access
The Journal of Urology	Library or electronic access
Journal of Vascular and Interventional Radiology	Library or electronic access
Radiology	Library or electronic access
Urology	Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	MSAC Advisory Panel
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

Table 30 Websites of Health Technology Assessment Agency

Health Technology Assessment Agency	Website
AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/evidence/
Centre for Health Economics, Monash University	http://chpe.buseco.monash.edu.au
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/english/home.html
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications/
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Association for Health Services and Policy Research (CAHSPR)	http://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/engelsk.html
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gr.nl/index.php
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Centre for Health Technology Assessment (SMM)	http://www.kunnskapssenteret.no/
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"I/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/english?l=en
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
Health Technology Board for Scotland	http://www.htbs.org.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry	https://research.tufts-nemc.org/cear/default.aspx
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Office of Health Technology Assessment Archive (US)	http://fas.org/ota/
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/consumertec/index.html
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Table 31 Websites of specialty organisations

Consumer websites	
Andrology Australia	http://www.andrologyaustralia.org/
Lions Australia Prostate Cancer Website	http://www.prostatehealth.org.au/
Prostate Cancer Foundation of Australia	http://www.prostate.org.au/
Professional societies	
American Urological Association	http://www.auanet.org/
Urological Society of Australia and New Zealand	http://www.urosoc.org.au/
International Society of Cryosurgery	http://www.societyofcryosurgery.org/

Appendix C Studies included in the review

Table 32 Studies included in the review of cryotherapy for recurrent or persistent prostate cancer after radiotherapy

Study	Location	Level of evidence (interventional) Quality Study design	Inclusion/exclusion criteria	Study population	Intervention	Outcomes	Follow-up period
3rd generation							
(Clarke et al 2007)	Medical University of South Carolina, Charleston, the United States	Level IV Quality: 4.5/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed recurrent, clinically organ-confined prostate cancer after radiotherapy *Exclusion* Patients with positive results in capromab pendetide scan	Number of patients: 47 25 patients between the age of 60 and 69 years; 22 patients older than 70 years Pre-cryotherapy PSA level: 36 patients ≤10 ng/mL; 11 patients >10 ng/mL Pre-cryotherapy Gleason score: 39 patients between 6 and 7; 8 patients between 8 and 10	Galil 17-G argon-based cryotherapy system Cryoprobe size: 17-G Cryoprobe number: 8 2 FTC None of the patients underwent NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Secondary: Duration of PSA control, length of hospital stay	Mean: 25 months (range: 7–53 months)
(Cresswell et al 2006)[a]	Sunderland Royal Hospital, Sunderland, the United Kingdom	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed prostate cancer after radiotherapy failure *Exclusion* Patients with positive results in MRI or bone scan	Number of patients: 20 Age: mean: 66 years (range: 56–79 years) Pre-cryotherapy prostate volume: media: 23.3 mL (range: 6.0–50.6 mL) Pre-cryotherapy PSA level: median: 7 ng/mL (range: 2.5–21.1 ng/mL) Pre-cryotherapy IPSS: median: 6 (range: 1–20) Pre-cryotherapy QoL score: median: 1 (range: 0–5)	17-G argon-based cryotherapy system Cryoprobe size: 17-G Cryoprobe number: 12–16 2 FTC Patients with prostate glands significantly >50 cm^3 underwent NHT for 3 months	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Primary: Overall survival, disease-specific survival Secondary: Biopsy-confirmed disease-free survival, duration of PSA control, local lymph node involvement or distant metastases; QoL; symptom control, length of hospital stay	Mean: 9 months (range: 6 weeks – 18 months)

(Cytron et al 2003)	Barzilai Medical Center, Ashkelon, Israel	Level IV Quality: 3.5/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed organ-confined prostate cancer after radiotherapy failure *Exclusion* Not stated	Number of patients: 5 1 patient underwent primary EBRT as primary treatment; 4 patients had primary brachytherapy Pre-cryotherapy prostate volume: mean: 37.9 mL (range: 28.7–48 mL) Pre-cryotherapy PSA level: mean: 6.44 ng/mL (range: 4.7–8.4 ng/mL) Pre-cryotherapy Gleason score: mean: 5.5 (range: 5–6) Pre-cryotherapy clinical stage: T1–T2	SeedNet 17-G argon-based cryotherapy system Cryoprobe size: 17-G Cryoprobe number: ≥2 ≥2 FTC None of the patients underwent NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Secondary: Duration of PSA control	Mean: 13.2 months (range: 9– 18 months)
(Eisenberg & Shinohara 2008)	University of California, San Francisco, the United States	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-proven prostate cancer after radiotherapy failure, and with a unilateral focus of disease *Exclusion* Patients with evidence of seminal vesicles involvement, prostate glands >50 cm^3, positive results in bone scan or CT scan of the abdomen and pelvis which indicated metastatic disease, or history of transurethral resection of the prostate	Number of patients: 19 Age: mean: 71 years 11 patients underwent primary EBRT; 8 patients had primary EBRT + brachytherapy Pre-radiotherapy prostate volume: mean: 17 ml (range: 6–29 mL) Pre-radiotherapy Gleason score: 12 patients <7; 7 patients ≥8 Pre-cryotherapy PSA level: mean: 3.3 ng/ml (range: 0.28–8.96 ng/mL)	SeedNet 17-G argon-based cryotherapy system Cryoprobe number: 2–4 2–4 FTC None or the patients underwent NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Primary: Disease-specific survival Secondary: Biopsy-confirmed disease-free survival, duration of PSA control, length of hospital stay	Median: 18 months (range: 6– 33 months)
(Gowardhan et al 2007)[a]	Sunderland Royal Hospital, Sunderland, the United Kingdom	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed prostate cancer after radiotherapy failure *Exclusion* Positive MRI, or bone scan	Number of patients: 42 Mean age 60.48 years (range: 48–72 years) 32 patients underwent primary EBRT; 10 patients had primary brachytherapy Pre-cryotherapy PSA level: EBRT group: mean: 31.55 ng/mL	SeedNet 17-G argon-based cryotherapy system Cryoprobe size: 17-G 2 FTC Patients with prostate glands >50 cm^3 underwent NHT for	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Duration of PSA control	Mean 19.16 months (range: 6 weeks – 36 months)

				(range: 2.2–85 ng/mL) Brachytherapy group: mean: 13.5 ng/mL (range: 4.8–32.2 ng/mL)	3 months		
(Han et al 2003)[b]	Eight institutions, the United States	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed prostate cancer after radiotherapy failure *Exclusion* Not stated	Number of patients: 18/122 For a total 122 patients Age: mean: 69.7 years (range: 53–85 years) Pre-cryotherapy PSA level: 92 patients ≤10 ng/mL; 31 patients >10 ng/mL	Galil 17-G argon-based cryotherapy system Cryoprobe size: 17-G Cryoprobe number: 12–15 2–4 FTC Some patients with large prostate glands, high Gleason scores, and/or PSA level >10 ng/mL underwent NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Duration of PSA control, length of hospital stay	For a total 122 patients: up to 12 months
(Han et al 2004)[b]	Several institutions, the United States	Level IV Quality: 3/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed prostate cancer after radiotherapy failure *Exclusion* Not stated	Number of patients: 29	SeedNet 17-G argon-based cryotherapy system Cryoprobe size: 17-G 2–3 FTC	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Duration of PSA control	Not stated
(Mouraviev et al 2006)	Duke University Medical Center, Durham, the United States	Case report	*Inclusion* Patients with biopsy-confirmed prostate cancer after brachytherapy failure, with negative results in ProstaScint scan and bone scan *Exclusion* Not stated	Age: 75 years Pre-cryotherapy PSA level: 4.8 ng/mL Pre-cryotherapy prostate volume: 12.3 mL	17-G argon-based cryotherapy system Cryoprobe size: 17-G 2 FTC	*Safety* Adverse events post-operatively and during follow-up	12 months
(Zisman et al 2001)	University of California, Los Angeles; Allegheny General Hospital, Pittsburgh, the	Level IV Quality: 4.5/6 Retrospective	*Inclusion* Patients with biopsy-confirmed recurrent, clinically organ-confined prostate cancer after radiotherapy failure	Number of patients: 17 14 patients underwent primary EBRT; 3 patients had primary brachytherapy Pre-cryotherapy PSA level: ≤15 ng/mL	SeedNet 17-G argon-based cryotherapy system Cryoprobe size: 17-G Cryoprobe number: 10–	*Safety* Adverse events post-operatively and during follow-up	Not stated

	United States	case series	*Exclusion* Patients with prostate glands >40 mL, PSA levels >15 mL, positive results in laparoscope pelvic lymph node dissection, or positive work-up indicating metastatic disease		15 2 FTC Some patients underwent NHT	*Effectiveness* length of hospital stay	
3rd generation or 2nd generation							
(Bahn et al 2003)	Community Memorial Hospital, Ventura; Huron-Valley Sinai Hospital, Commerce Township; Crittenton Hospital, Rochester; University of Calgary, Irvine, the United States	Level IV Quality: 4.5/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed recurrent prostate cancer after radiotherapy failure *Exclusion* Patients with evidence of metastatic diseases	Number of patients: 59 Age: mean: 67.5 years Patients underwent EBRT or brachytherapy at least 24 months before cryotherapy Pre-cryotherapy PSA level: media: 5.6 ng/mL (range: 0.01–57 ng/mL) Pre-cryotherapy Gleason score: median: 7 (range: 5–9)	Argon-based cryotherapy system Cryoprobe number: 4–6 2 TFC Patients with prostate gland >40 mL, Gleason score ≥7 or stage ≥T2b underwent 3 months of NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Biopsy-confirmed disease-free survival, duration of PSA control, length of hospital stay	Mean: 72.5 months
(Donnelly et al 2005)[c]	University of Calgary, Calgary; Tom Baker Cancer Centre, Calgary; University of Toronto, Toronto, Canada	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed recurrent prostate and/or seminal vesicle cancer after EBRT failure *Exclusion* Patients with prostate glands ≥60 mL, PSA level >20 ng/mL or positive results in chest X-ray or bone scan)	Number of patients: 46 Age: mean: 68.9 years (range: 56–78 years) Pre-cryotherapy PSA level: media: 5.6 ng/mL (range: 0.1–16.1 ng/mL) Pre-cryotherapy Gleason score: 27 patients between 5–7; 19 patients ≥8	SeedNet 17-G argon-based cryotherapy system (6 patients) or CryoCare argon-based cryotherapy system (40 patients) 2 FTC 7 patients with prostate glands between 30 and 60 g underwent NHT for 3 months	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Biopsy-confirmed disease-free survival, duration of PSA control, length of hospital stay	Median: 20 months (range: 2–50 months)
(Ismail et al 2007)	The Royal Surrey county Hospital and St Luke's Cancer Centre, Guildford, the United Kingdom	Level IV Quality: 4.5/6 Prospective case	*Inclusion* Patients with biopsy-confirmed recurrent prostate cancer after radiotherapy failure	Number of patients: 100 Age: mean: 66.8 years (range 54–78 years) 45 underwent 2nd-generation cryotherapy, 22 underwent 3rd-	SeedNet 17-G argon-based cryotherapy system (55 patients) or CryoCare argon-based cryotherapy system (45 patients)	*Safety* Adverse events post-operatively and during follow-up	Mean: 33.5 months (range: 12–79 months)

		series	*Exclusion* Patients with evidence of pelvic lymph node involvement or metastatic diseases	generation cryotherapy Pre-cryotherapy PSA level: median: 5.4 ng/mL Patents divided into 3 groups according to their pre-radiotherapy PSA levels, Gleason scores and clinical stages: Low-risk group: PSA level ≤10 ng/mL, Gleason score ≤6 and clinical state ≤T2b; Intermediate-risk group: PSA level >10 ng/mL, Gleason score >6 or clinical state >T2b; High-risk group: patients had ≥2 unfavourable risk factors	2 FTC 46 patients with prostate glands ≥50 cm^3 underwent NHT for 3 months	*Effectiveness* Duration of PSA control, symptom control, QoL, length of hospital stay	
(Robinson et al 2006)[c]	Tom Baker Cancer Centre, Calgary; University of Calgary, Calgary; Nanaimo Regional Hospital, Nanaimo, Canada	Level IV Quality: 3.5/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed recurrent prostate cancer or seminal vesicle cancer after radiotherapy failure *Exclusion* Patients with PSA level >20 ng/mL, or with positive results in chest X-ray or bone scan	Number of patients: 46 Age: mean: 70 years (range: 57–79 years) Pre-cryotherapy PSA level: 40 patients ≤10 ng/mL; 6 patients >10 ng/mL Pre-cryotherapy Gleason score: 26 patients between 5–7; 19 patients ≥8	SeedNet 17-G argon-based cryotherapy system (6 patients) or CryoCare argon-based cryotherapy system (40 patients) 2 FTC 12 patients underwent NHT for 3 months	*Effectiveness* Overall survival, disease-specific survival, duration of PSA control, symptom control, QoL, length of hospital stay	Not stated
2nd generation							
(Anastasiadis et al 2003)[d]	College of Physicians and Surgeons of Columbia University, New York, the United States	Level IV Quality: 3.5/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed recurrent prostate cancer after radiotherapy *Exclusion* Patients with evidence of pelvic lymph node involvement, seminal vesicle invasion or positive results in bone scan	Number of patients: 42 Age: mean: 72.8 years	CryoCare argon-based cryotherapy system Cryoprobe number: 6 2 FTC All patients received NHT for 3 months	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* QoL, length of hospital stay	Mean: 11.4 months

(Chin et al 1998)[e]	London Health Sciences Centre, University of Western Ontario, London, Canada	Level IV Quality: 4/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed persistent prostate cancer after radiotherapy *Exclusion* Patients with positive results in bone scan, abdomen and pelvis CT scan or lymphadenectomy	Number of patients: 45/52 44 patients underwent primary EBRT; 1 patients had primary brachytherapy For a total 52 patients: Age: mean: 62 years Pre-cryotherapy PSA level: range: 0.2–77 ng/mL	CryoCare argon-based cryotherapy system (34 patients); Candela liquid-nitrogen cryotherapy system (11 patients) Cryoprobe number: ≤8 2 FTC Some patients received NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Biopsy-confirmed disease-free survival, duration of PSA control	For a total 52 patients Range: 1–30 months
(Chin et al 2001)[e]	London Health Sciences Centre, University of Western London, Canada	Level IV Quality: 4/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed or clinical evidence of recurrent prostate cancer after radiotherapy *Exclusion* Patients with positive results in bone scan, abdomen and pelvis CT or lymphadenectomy	Number of patients: 118 Age: median: 68 years Pre-cryotherapy PSA level: 60 patients <5 ng/mL; 58 patients ≥5 ng/mL Pre-cryotherapy Gleason score: 68 patients <8; 50 patients ≥8	CryoCare argon-based cryotherapy system (107 patients); Candela liquid-nitrogen cryotherapy system (11 patients) Cryoprobe number: 5–6 2 FTC 71 patients underwent NHT	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Biopsy-confirmed disease-free survival, duration of PSA control	Median: 18.6 months (range: 3–54 months)
(Chin et al 2003)[e]	London Health Sciences Centre, University of Western Ontario, London, Canada	Level IV Quality: 4.5/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed recurrent or residual prostate cancer *Exclusion* Patients with positive results in CT scan, bone scan or lymphadenectomy (with few exceptions pre-cryotherapy PSA level <10 ng/mL)	Number of patients: 106 Age: median 68.7 years (range: 53.7–81.8 years) 104 patients underwent primary EBRT; 2 patients had primary EBRT + brachytherapy	CryoCare argon-based cryotherapy system (95 patients); Candela liquid-nitrogen cryotherapy system (11 patients) Cryoprobe number: ≤8 2 FTC 58 patients underwent NHT	*Effectiveness* Biopsy-confirmed disease-free survival	≤43 months
(de la Taille et al 2000a)[d]	College of Physicians and Surgeons, Columbia University, New York, the United States	Level IV Quality: 3.5/6 Prospective	*Inclusion* Patients with biopsy-confirmed local recurrent prostate cancer after radiotherapy	Number of patients: 19 Pre-cryotherapy PSA level: mean: 5.9 ng/mL (range: 0.6–25 ng/mL) Pre-cryotherapy Gleason score: mean:	CryoCare argon-based cryotherapy system 2 FTC All patients received	*Safety* Adverse events post-operatively and during follow-up	Mean: 8.3 months

		case series	*Exclusion* Patients with evidence of pelvic lymph node involvement, seminal vesicle invasion or positive results in bone scan	7.2 (range: 6–9)	NHT for 3 months	*Effectiveness* Overall survival, disease-specific survival, local lymph node involvement or distant metastases, duration of PSA control, length of hospital stay	
(de la Taille et al 2000b)[d]	College of Physicians and Surgeons, Columbia University, New York, the United States	Level IV Quality: 4/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed local recurrent prostate cancer after radiotherapy *Exclusion* Patients with evidence of pelvic lymph node involvement, seminal vesicle invasion or positive results in bone scan	Number of patients: 18/43 For a total 43 patients: Age: mean: 69.4 years (range: 48.1–83.6 years) Pre-cryotherapy PSA level: mean: 7.07 ng/mL (range: 0.6–50 ng/mL) Pre-cryotherapy Gleason score: mean 7.3 (range: 4–9)	CryoCare argon-based cryotherapy system 2 FTC All patients received NHT for 3 months	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Duration of PSA control, length of hospital stay	For a total 43 patients Mean: 21.9 months (range: 1.2–54 months)
(Ghafar et al 2001)[d]	College of Physicians and Surgeons, Columbia University, New York, the United States	Level IV Quality: 4/6 Prospective case series	*Inclusion* Patients with biopsy-confirmed recurrent prostate cancer after radiotherapy *Exclusion* Patients with evidence of pelvic lymph node involvement, seminal vesicle invasion or positive results in bone scan	Number of patients: 38 Age: mean: 71.9 years (range: 54.1–81.7 years Comorbidity: 14 patients with hypertension; 6 patients with coronary artery disease; 8 patients with diabetes Pre-cryotherapy PSA level: mean: 7.5 ng/mL (range: 0.4–28 ng/mL) Pre-cryotherapy Gleason score: mean: 7.0 (range: 6–10) Pre-cryotherapy clinical stage: T1–T3	CryoCare argon-based cryotherapy system Cryoprobe number: 6 2 FTC All patients received NHT for 3 months	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Duration of PSA control, length of hospital stay	Mean: 20.7 months (range: 3–37 months)
(Ng et al 2007)[e]	London Health Sciences Centre, University of Western Ontario, London, Canada	Level IV Quality: 4.5/6 Retrospective case series	*Inclusion* Patients with biopsy-confirmed or clinical evidence of recurrent prostate cancer after radiotherapy	Number of patients: 187 Age: mean: 70.9 years (range: 53.6–81.7 years) 183 patients underwent primary EBRT; 3 patients had primary brachytherapy; 1 patients received primary EBRT+	CryoCare argon-based cryotherapy system (176 patients); Candela liquid-nitrogen cryotherapy system (11 patients) Cryoprobe number: 2–8 2 FTC	*Safety* Adverse events post-operatively and during follow-up *Effectiveness* Overall survival, local lymph	Mean: 39 months

			Exclusion Patients with positive results in CT scan or bone scan	brachytherapy Pre-cryotherapy PSA level: median: 4.9 ng/mL (range: 0–36.4 ng/mL) Pre-cryotherapy Gleason score: 93/154 patients <8, 61/154 patients ≥8	133 patients had NHT for 3–6 months	node involvement or distant metastases, Biopsy-confirmed disease-free survival, duration of PSA control, length of hospital stay	

[a] May be overlap between patient series; [b] May be overlap between patient series; [c] May be overlap between patient series; [d] May be overlap between patient series; [e] May be overlap between patient series

FTC: freeze/thaw cycle; NHT: neoadjuvant hormone therapy; QoL: quality of life; MRI: magnetic resonance imaging; EBRT: external beam radiotherapy; PSA: prostate-specific antigen; TRUS: transrectal ultrasound; CT: computed tomography

Appendix D Excluded studies

Not a study, a systematic review, or a meta-analysis (110)

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Not a higher level of evidence than available in English (20)

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Appendix E Critical appraisal checklist

Checklist for the critical appraisal of case series

Title of review:

Title of study:

Author(s)

Year:

Comparators:

Score: /6

1. Is the study based on a representative sample selected from a relevant population? /1

2. Are the criteria for inclusion explicit? /1

3. Did all individuals enter the survey at a similar point in their disease progression? /1

4. Was follow-up long enough for important events to occur? /1

5. Were outcomes assessed using objective criteria or was blinding used? /1

6. If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors? /1

Source: Khan et al 2001

Appendix F Questionnaires

Table 33 IPSS questionnaire

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	**1 time**	**2 times**	**3 times**	**4 times**	**5 times or more**	
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							
Quality of life due to urinary symptoms	**Delighted**	**Pleased**	**Mostly satisfied**	**Mixed - about equally satisfied and dissatisfied**	**Mostly dissatisfied**	**Unhappy**	**Terrible**
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Source: Canadian Prostate Cancer Network 2008

Table 34 EORTC-QLQ-C30 questionnaire

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair for most of the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
DURING THE PAST WEEK:				
6. Were you limited in doing your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
DURING THE PAST WEEK:				
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1		3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhoea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4
FOR THE FOLLOWING QUESTIONS, PLEASE CIRCLE THE NUMBER BETWEEN 1 & 7 THAT BEST APPLIES TO YOU				
29. How would you rate your overall health during the past week? 1 2 3 4 5 6 7 Very poor Excellent				
30. How would you rate your overall quality of life during the past week? 1 2 3 4 5 6 7 Very Poor Excellent				

Source: Robinson et al 2006

Table 35 PCI questionnaire

URINARY FUNCTION	
1. Over the past 4 weeks, how often have you leaked urine?	
Every day	1
About once a week	2
Less than once a week	3
Not at all	4
2. Which of the following best describes your urinary control during the last 4 weeks?	
No control whatsoever	1
Frequent dribbling	2
Occasional dribbling	3
Total control	4
3. How many pads or adult diapers per day did you usually use to control leakage during the last 4 weeks?	
3 or more pads per day	1
1–2 pads per day	2
No pads	3
How big a problem, if any, has each of the following been for you during the last 4 weeks?	
4. Dripping urine or wetting your pants	
No problem	0
Very small problem	1
Small problem	2
Moderate problem	3
Big problem	4
5. Urine leakage interfering with your sexual activity	
No problem	0
Very small problem	1
Small problem	2
Moderate problem	3
Big problem	4
URINARY BOTHER	
6. Overall, how big a problem has your urinary function been for you during the last 4 weeks?	
No problem	1
Very small problem	2
Small problem	3
Moderate problem	4
Big problem	5
BOWEL FUNCTION	
7. How often have you had rectal urgency (felt like I had to pass stool, but did not) during the last 4 weeks?	
More than once a day	1
About once a day	2
More than once a week	3
About once a week	4
Rarely or never	5
8. How often have you had stools (bowel movements) that were loose or liquid (no form, watery, mushy) during the last 4 weeks?	
Never	1
Rarely	2
About half the time	3
Usually	4
Always	5
9. How much distress have your bowel movements caused you during the last 4 weeks?	
Severe distress	1
Moderate distress	2

Little distress	3
No distress	4

10. How often had you had crampy pain in your abdomen or pelvis during the last 4 weeks?

Several times a day	1
About once a day	2
Several times a week	3
About once a week	4
About once this month	5
Rarely or never	6

BOWEL BOTHER

11. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

Big problem	1
Moderate problem	2
Small problem	3
Very small problem	4
No problem	5

SEXUAL FUNCTION

How would you rate each of the following during the last 4 weeks?

12. Your level of sexual desire

Very poor	1
Poor	2
Fair	3
Good	4
Very good	5

13. Your ability to have an erection?

Very poor	1
Poor	2
Fair	3
Good	4
Very good	5

14. Your ability to reach orgasm (climax)?

Very poor	1
Poor	2
Fair	3
Good	4
Very good	5

15. How would you describe the usual QUALITY of your erections?

Not at all	1
Not firm enough for sexual activity	2
Firm enough for masturbation and foreplay only	3
Firm enough for intercourse	4

16. How would you describe the FREQUENCY of your erections?

I NEVER had an erection when I wanted one	1
I had an erection LESS THAN HALF the time I wanted one	2
I had an erection ABOUT HALF the time I wanted one	3
I had an erection MORE THAN HALF the time I wanted one	4
I had an erection WHENEVER I wanted one	5

17. How often had you awakened in the morning or night with an erection?

Never	1
Seldom (less than 25% of the time)	2
Not often (less than half the time)	3
Often (more than half the time)	4
Very often (more than 75% of the time)	5

18. During the past 4 weeks, did you have vaginal or anal intercourse?

No	1
Yes, once	2
Yes, more than once	3
19. Overall, how would you rate your ability to function sexually during the last 4 weeks?	
Very poor	1
Poor	2
Fair	3
Good	4
Very good	5
SEXUAL BOTHER	
20. Overall, how big a problem has your sexual function been for you during the last 4 weeks?	
No problem	1
Very small problem	2
Small problem	3
Moderate problem	4
Big problem	5

Source: Litwin et al 1998

Appendix G Further scenarios for financial analysis

In order to simplify the financial analysis, a base case scenario was chosen assuming that 2000 patients have recurrent or persistent prostate cancer after radiotherapy per year in Australia. Two further scenarios are presented below, outlining the minimum and maximum cost implications when radiation failure is discovered in 588 patients and 3374 patients, respectively (see the 'Clinical need' section on page 16).

1. Cost implications (minimum estimate) when 588 patients have recurrent or persistent prostate cancer after radiotherapy per year in Australia

Figure 9 Patient breakdown in estimating the clinical need for cryotherapy (minimum)

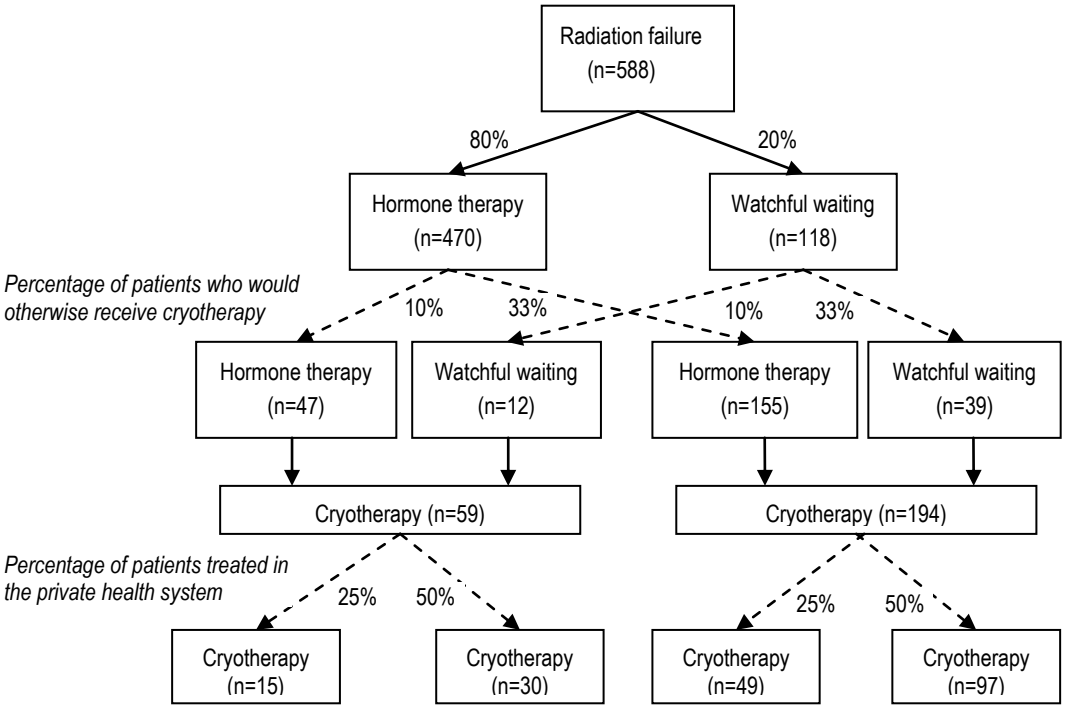

Table 36 Total costs to the Australian Government (minimum)

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	15	47	12	
1 year	$42 458	$270 963	$14 769	–$243 275
2 years	$43 111	$478 028	$15 815	–$450 732
5 years	$44 891	$1 041 918	$18 662	–$1 015 690
Scenario 2				
Number of patients	30	47	12	
1 year	$84 915	$270 963	$14 769	–$200 817
2 years	$86 222	$478 028	$15 815	–$407 621
5 years	$89 782	$1 041 918	$18 662	–$970 799

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 3				
Number of patients	49	155	39	
1 year	$138 695	$893 602	$47 999	–$802 907
2 years	$140 830	$1 576 477	$51 398	–$1 487 045
5 years	$146 644	$3 436 114	$60 653	–$3 350 123
Scenario 4				
Number of patients	97	155	39	
1 year	$274 559	$893 602	$47 999	–$667 043
2 years	$278 785	$1 576 477	$51 398	–$1 349 090
5 years	$290 295	$3 436 114	$60 653	–$3 206 472

Scenario 1: 10% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 2: 10% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
Scenario 3: 33% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 4: 33% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
[a] A negative difference is a cost saving resulting from cryotherapy compared to hormone therapy and watchful waiting.

Table 37 Total costs to the Australian healthcare system overall (minimum)

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	59	47	12	
1 year	$986 869	$298 638	$19 692	$668 539
2 years	$990 297	$515 062	$21 086	$454 149
5 years	$999 631	$1 104 438	$24 883	–$129 690
Scenario 2				
Number of patients	59	47	12	
1 year	$824 381	$298 638	$19 692	$506 051
2 years	$827 808	$515 062	$21 086	$291 660
5 years	$837 142	$1 104 438	$24 883	–$292 178
Scenario 3				
Number of patients	194	155	39	
1 year	$3 244 960	$984 870	$63 999	$2 196 091
2 years	$3 256 231	$1 698 608	$68 530	$1 489 092
5 years	$3 286 923	$3 642 294	$80 871	–$436 241
Scenario 4				
Number of patients	194	155	39	
1 year	$2 710 675	$984 870	$63 999	$1 661 806
2 years	$2 721 946	$1 698 608	$68 530	$954 807
5 years	$2 752 638	$3 642 294	$80 871	–$970 527

Scenario 1:10% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 2: 10% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.
Scenario 3: 33% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 4: 33% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.
[a] A positive difference and a negative difference represent an additional cost and a cost saving, respectively, resulting from cryotherapy compared to hormone therapy and watchful waiting.

2. Cost implications (maximum estimate) when 3374 patients have recurrent or persistent prostate cancer after radiotherapy per year in Australia

Figure 10 Patient breakdown in estimating the clinical need for cryotherapy (maximum)

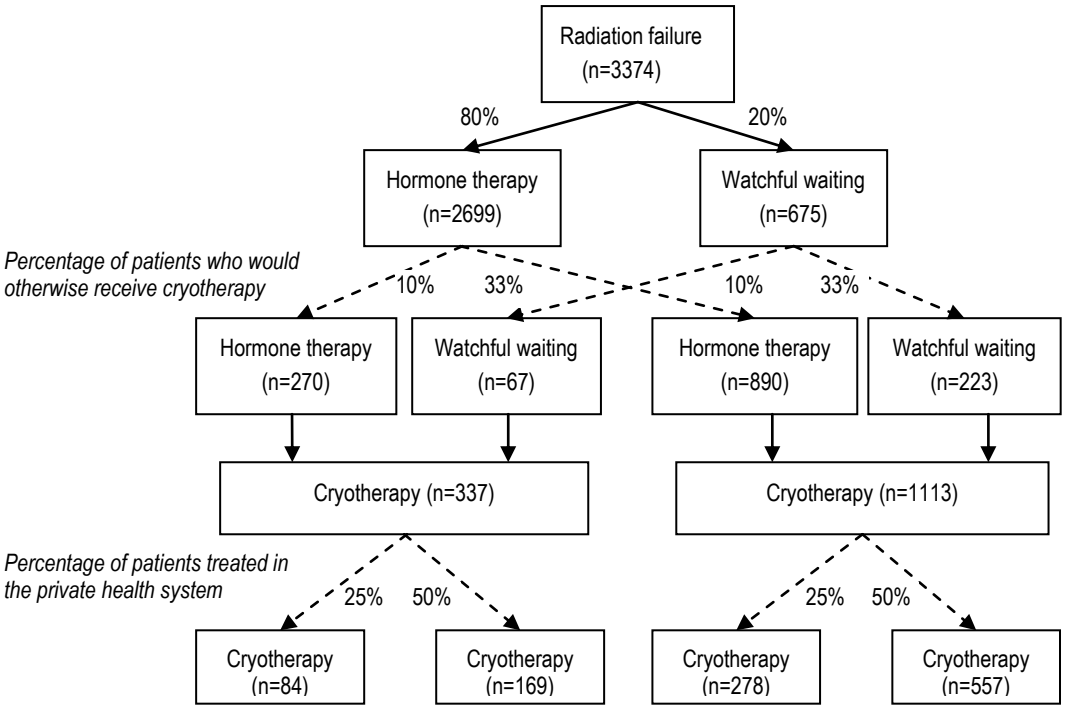

Table 38 Total costs to the Australian Government (maximum)

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	84	270	67	
1 year	$237 762	$1 554 291	$82 953	–$1 399 482
2 years	$241 422	$2 742 052	$88 826	–$2 589 456
5 years	$251 389	$5 976 621	$104 821	–$5 830 053
Scenario 2				
Number of patients	169	270	67	
1 year	$478 355	$1 554 291	$82 953	–$1 158 889
2 years	$485 718	$2 742 052	$88 826	–$2 345 160
5 years	$505 771	$5 976 621	$104 821	–$5 575 671
Scenario 3				
Number of patients	278	890	223	
1 year	$786 879	$5 131 006	$274 457	–$4 618 584
2 years	$798 992	$9 052 028	$293 890	–$8 546 926
5 years	$831 978	$19 729 944	$346 811	–$19 244 776
Scenario 4				
Number of patients	557	890	223	
1 year	$1 576 589	$5 131 006	$274 457	–$3 828 874
2 years	$1 600 858	$9 052 028	$293 890	–$7 745 060
5 years	$1 666 949	$19 729 944	$346 811	–$18 409 805

Scenario 1: 10% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.

Scenario 2: 10% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
Scenario 3: 33% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 75:25.
Scenario 4: 33% of the patients with radiation failure receive salvage cryotherapy; the public to private patient split for cryotherapy is 50:50.
[a] A negative difference is a cost saving resulting from cryotherapy compared to hormone therapy and watchful waiting.

Table 39 Total costs to the Australian healthcare system overall (maximum)

	Cryotherapy	Hormone therapy	Watchful waiting	Difference[a]
Scenario 1				
Number of patients	337	270	67	
1 year	$5 636 864	$1 713 038	$110 603	$3 813 222
2 years	$5 656 442	$2 954 482	$118 435	$2 583 525
5 years	$5 709 758	$6 335 242	$139 761	–$765 244
Scenario 2				
Number of patients	337	270	67	
1 year	$4 708 750	$1 713 038	110 603	$2 885 108
2 years	$4 728 328	$2 954 482	$118 435	$1 655 411
5 years	$5 709 758	$6 335 242	$139 761	–$765 244
Scenario 3				
Number of patients	1113	890	223	
1 year	$18 616 706	$5 655 060	$365 943	$12 595 703
2 years	$18 681 366	$9 753 298	$391 853	$8 536 214
5 years	$18 857 451	$20 913 817	$462 414	–$2 518 780
Scenario 4				
Number of patients	1113	890	223	
1 year	$15 551 450	$5 655 060	$365 943	$9 530 447
2 years	$15 616 110	$9 753 298	$391 853	$5 470 959
5 years	$15 792 196	$20 913 817	$462 414	–$5 584 035

Scenario 1:10% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 2: 10% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.
Scenario 3: 33% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 20.
Scenario 4: 33% of the patients with radiation failure receive salvage cryotherapy; the annual volume of cryotherapy procedures is 500.
[a] A positive difference and a negative difference represent an additional cost and a cost saving, respectively, resulting from cryotherapy compared to hormone therapy and watchful waiting.

Glossary and abbreviations

AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASTRO	American Society for Therapeutic Radiology and Oncology
BRFS	Biochemical recurrence-free survival
CT	Computed tomography
DRE	Digital rectal examination
EBRT	External beam radiotherapy
EORTC	European Organization for Research and Treatment of Cancer
EORTC-QLQ-C30	A self-administered standardised multiscale questionnaire measuring health-related QoL that is relevant to the experience of cancer
FTC	Freeze/thaw cycle
Gleason score	A sum of the differentiation grade scores of cancer cells from two sections of a prostate cancer. The scale goes from 2 (well-differentiated, least aggressive) to 10 (undifferentiated, most aggressive)
HIFU	High-intensity focused ultrasound
HTA	Health Technology Assessment
IPSS	International Prostate Symptom Score
LHRH	Luteinizing hormone-releasing hormone
MBS	Medicare Benefits Schedule
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service (United Kingdom)
NHT	Neoadjuvant hormone therapy
PBS	Pharmaceutical Benefits Scheme
PCI	Prostate Cancer Index
PSA	Prostate-specific antigen
QoL	Quality of life
RTOG	Radiation Therapy Oncology Group
TRUS	Transrectal ultrasound
Urethral sloughing	Necrotic tissue from the prostate entering the urinary tract
UTI	Urinary tract infection

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Part B – Cryotherapy for renal cancer

September 2009

MSAC application 1124

Assessment report

Executive summary

The procedure

Cryotherapy is a procedure that can be used for renal cancer. It kills the cancer cells through a process of repeated freezing and thawing. The newer generations of cryotherapy use argon gas during the rapid freezing phase to form an ice ball around the top of the cryoprobe through the Joule-Thomson effect. Helium gas is then delivered to produce active thawing. Intra-operative ultrasound is required to monitor the cryoablative process. Multiple renal tumours may be treated in one cryotherapy procedure. Although renal cryotherapy can be performed using an open surgical approach, laparoscopic cryotherapy and percutaneous cryotherapy are more commonly used in current clinical practice.

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from Adelaide Health Technology Assessment, in the Discipline of Public Health, School of Population Health and Clinical Practice within the University of Adelaide, was engaged to conduct a systematic review of literature on cryotherapy for renal cancer. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC on the safety, effectiveness and cost-effectiveness of cryotherapy for renal cancer..

MSAC's assessment of cryotherapy

Clinical need

Cryotherapy is indicated for small (<4 cm) renal tumours *presumed* to be cancers. Patients are potential candidates for renal cryotherapy if they have a single functioning kidney, bilateral tumours or pre-existing renal disease, or are not fit for radical nephrectomy.

In 2003 a total of 2019 new renal malignant tumours were discovered in Australia, giving an incidence rate of 13.2 per 100 000 men and 7.2 per 100 000 women. Of these 2019 cancers, it is assumed that approximately one-third would have metastasised by the time of diagnosis. Of the remaining 1346 renal cancers, 39 per cent were small enough (≤4 cm) to be treated by cryotherapy. Between one-third and one-fifth of small renal lesions are benign or with low malignant potential; therefore, the number of small renal tumours diagnosed annually in Australia that would potentially benefit from cryotherapy ranges between 656 and 788.

The AIHW data indicated that 429 partial nephrectomy surgeries were performed in the year 2004–05. Given the assumption that 20 per cent of these patients would choose

cryotherapy if funded, 86 partial nephrectomy procedures would be substituted by renal cryotherapy procedures. In addition, the Advisory Panel suggested that between 0 and 100 patients who undergo radiofrequency ablation (RFA) would otherwise receive cryotherapy, and that 10 cryotherapy procedures are currently carried out per year across Australia. Therefore, it is estimated that the clinical need for cryotherapy would range between 96 and 196 procedures per year.

However, the expert opinion of the Advisory Panel indicated that cryotherapy procedures would likely be offered to many more patients in the future if the use of imaging studies rises (as more small renal lesions would be detected) and patients take a more active part in the treatment decision-making process in clinical practice.

Safety

The safety of cryotherapy for *presumed* renal cancer was reported by 35 studies: three of these were controlled studies that compared cryotherapy against partial nephrectomy or RFA; 16 were case series; and the remaining 16 were case reports.

Limited evidence on the comparative safety of cryotherapy versus partial nephrectomy indicated that the safety of laparoscopic cryotherapy was no worse than that of laparoscopic partial nephrectomy, as the post-operative complication rates and the pre/post-procedural serum creatinine levels were not significantly different between these two treatments. Furthermore, laparoscopic cryotherapy resulted in less blood loss than laparoscopic partial nephrectomy.

It would also appear that laparoscopic or percutaneous cryotherapy is likely to be as safe as RFA in terms of post-operative adverse event rates and blood loss. However, laparoscopic cryotherapy resulted in longer anaesthesia time than RFA; but fewer pain control drugs were required for percutaneous cryotherapy than for RFA.

Although no data were identified comparing renal cryotherapy with surveillance, cryotherapy is not expected to be safer than conservative treatment.

One procedure-related death was reported in a case report. The patient was an elderly woman with multiple cardiovascular and respiratory comorbidities. Three days after the renal cryotherapy procedure, she stopped the anticoagulation therapy for atrial fibrillation due to the occurrence of pleural effusion. The patient died of a pulmonary embolism involving her right main pulmonary artery on day 20 post-procedurally.

Intra-operative complications, such as bowel injury, urine leak, bleeding, haematoma and severe respiratory distress, were not uncommon, with rates ranging from 0 to 28.6 per cent. Between 0 and 21.4 per cent of patients experienced major post-operative adverse events, most of which were heart or pulmonary complications. This may reflect the patient selection criteria, as cryotherapy is usually indicated for patients who are not fit for radical nephrectomy. These patients are usually older and with comorbidities, and may already have cardiovascular or respiratory disease before undergoing renal cryotherapy.

Peri-procedural blood loss during cryotherapy was not significant, estimated to be between 10 and 103 mL in all except one patient, who lost 1000 mL of blood during a cryotherapy procedure. Minor complications resulting from cryotherapy included small

haematoma, transient urine leak, neuropraxia and pain. The finding that no significant difference existed between pre- and post-operative serum creatinine levels indicated that kidney function did not deteriorate after cryotherapy.

No studies directly compared the safety between second-generation and third-generation cryotherapy. However, an indirect comparison of the results from the identified studies indicated that smaller cryoprobe size did not improve the safety outcomes of the procedure.

No significant differences in major complication rates were discovered between laparoscopic and percutaneous cryotherapy, although laparoscopic cryotherapy resulted in fewer minor adverse events than percutaneous cryotherapy.

Effectiveness

Twenty-five studies reported on the short-term effectiveness of cryotherapy for *presumed* renal cancer. None of these studies followed up their patients for longer than 5 years.

Four studies compared cryotherapy against partial nephrectomy or RFA. There was insufficient evidence on which to determine the effectiveness of cryotherapy relative to partial nephrectomy. Although local tumour progression rates after laparoscopic cryotherapy were not significantly different from those following laparoscopic partial nephrectomy during follow-up periods of less than 1 year, other important oncological outcomes, such as overall survival, disease-specific survival, tumour persistence and metastases, were not compared between cryotherapy and partial nephrectomy. No significant difference in tumour progression or local tumour persistence was observed between cryotherapy (laparoscopic and percutaneous) and RFA within 2 years post-operatively.

The length of hospital stay was shorter for percutaneous cryotherapy than for open partial nephrectomy, laparoscopic partial nephrectomy and RFA. Laparoscopic cryotherapy was associated with longer hospital stay relative to RFA. However, laparoscopic cryotherapy required less surgical time and shorter hospital stays than open and laparoscopic partial nephrectomy.

No evidence was identified that compared the effectiveness of renal cryotherapy against surveillance.

The overall survival rates and disease-specific survival rates following cryotherapy for small renal tumours were 87.5 to 100 per cent and 100 per cent, respectively, during follow-up periods of up to 22 months. Patient deaths were attributable to either cardiovascular diseases or other cancers.

Technical success was achieved in more than 90 per cent the cryotherapy procedures. Between 0 and 13.6 per cent of target tumours were not adequately treated. Risk factors for tumour persistence included endophytic renal lesions, technical failure and difficulties in cryoprobe placement. Local tumour progression was observed in between 0 and 25.0 per cent of treated renal lesions during follow-up periods of 5 to 47 months. Only one case (10.0%) of retroperitoneal lymph node metastasis after renal cryotherapy was reported across studies within periods of up to 28 months.

In general, cryotherapy for presumed renal cancer appears to have promising short-term effectiveness. However, the long-term follow-up effectiveness data are still not available. In addition, it should be highlighted that these tumour outcomes, except metastases, were reported in patients with both benign and malignant renal tumours, which may make cryotherapy appear more effective than when it is used only for the treatment of renal cancer.

Economic considerations

Due to the lack of evidence indicating the effectiveness of renal cryotherapy relative to partial nephrectomy, a financial incidence analysis, rather than a cost-effectiveness analysis, was performed to estimate the cost implications of cryotherapy should it receive public funding.

The estimated unit costs for laparoscopic cryotherapy and percutaneous cryotherapy are $13 005 and $11 976, respectively, when 100 cryotherapy procedures are performed annually per instrument, and $12 546 and $11 517, respectively, if an efficient throughput is achieved (500 procedures per year per cryotherapy machine). In comparison, the unit costs for open partial nephrectomy, laparoscopic partial nephrectomy and RFA are $8968, $6708 and $5071, respectively. The relatively higher expenditure associated with cryotherapy is primarily due to the cost of the disposable Cryokit and gases.

The financial implications to the Australian Government for each laparoscopic cryotherapy procedure and percutaneous cryotherapy procedure would be $1506 and $1365, respectively, resulting in an *additional* cost of up to $463 relative to open partial nephrectomy, laparoscopic partial nephrectomy and RFA.

Overall, the total cost of cryotherapy to the Australian healthcare system would range between $1 779 228 and $1 846 243 in the base case where 95 laparoscopic cryotherapy procedures and 51 percutaneous cryotherapy procedures are performed annually in Australia. An *additional* cost to the healthcare system of $729 238 to $791 664 would be incurred by cryotherapy relative to partial nephrectomy, RFA and the current usage of cryotherapy. The cost impact of cryotherapy on the Australian Government is not significant, being an *additional* $9568 or $18 715, when an estimated 37 or 74 cryotherapy procedures, respectively, are performed in the private health sector.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of cryotherapy, which is a therapeutic intervention for renal cancer. The MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. The MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for cryotherapy for renal cancer.

Rationale for assessment

Scanmedics Pty Ltd has submitted an application to the MSAC to have an assessment undertaken of the safety, effectiveness and cost-effectiveness of cryotherapy for renal cancer.

Background

The procedure

Cryotherapy for renal cancer kills neoplastic cells by targeted freezing and thawing of kidney tissue. Early forms of cryotherapy used liquid nitrogen as the freezing agent, but both second- and third-generation cryotherapy are argon-based systems, the only difference between them being the diameter of the cryoprobes. During a cryotherapy procedure, probes are placed into the target renal tumour. Argon gas expanding in the chamber at the end of the probe results in a reduction of temperature to produce an ice ball around the cryoprobe through the Joule-Thomson process. Helium gas is then used to induce active thawing, and the process is repeated. Cancer cells are ruptured and killed through the freeze/thaw cycle (FTC).

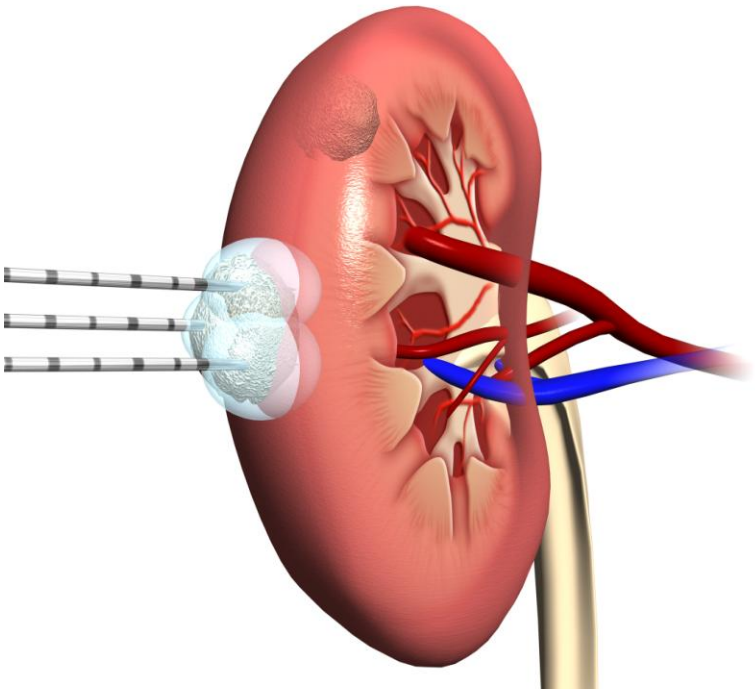
There are a range of different methods for performing renal cryotherapy, depending on the general health of the patient, and the size and location of the tumour. Cryosurgery may be performed using an open surgical approach but this technique is not often used (Galil Medical 2007). It may also be performed using laparoscopic guidance. With this approach, one to four surgical incisions are made, allowing laparoscopic ultrasound monitoring of needle placement, and percutaneous placement of thermal sensors. Ultrasound is also used to monitor the freeze/thaw process. Alternatively, renal cryotherapy may be performed percutaneously without any surgical incisions. The patient is placed inside a magnetic resonance imaging (MRI) or computed tomography (CT) machine, and the cryotherapy occurs without invasive imaging. While all three techniques can be done under general anaesthesia, percutaneous cryotherapy may be done under local anaesthetic and light sedation (Galil Medical 2007). The percutaneous route is only suitable for posterior or posteriolateral tumours (Scanmedics Pty Ltd 2007). Regardless of the form of cryotherapy, two FTCs occur, and then the needles are withdrawn and the patient monitored.

Intended purpose

Cryotherapy is proposed as a method of treating small renal cancers (<4 cm), where minimally invasive or nephron-sparing treatment is indicated. For example, older patients or those with comorbidities such as diabetes may benefit from minimally invasive treatment. This treatment, which retains the functional units of the kidney (nephron-sparing), is important for patients with pre-existing renal disease or multiple tumours, and is vital for patients with a single functioning kidney or bilateral tumours (Aron & Gill 2005; Gill 2005; Scanmedics Pty Ltd 2007).

Relative contraindications are cancer of the hilum (or hilus) or tumour invasion into the Bellini duct (or collecting duct) system of the kidney (which connects the nephrons to the ureter) (Scanmedics Pty Ltd 2007).

Figure 11 Renal cryotherapy



Source: Galil Medical Inc 2007; used with permission

Existing treatments

The clinical decision-making process concerned with the use of cryotherapy in the treatment of renal cancer is presented in Figure 12 (page 129).

Cryotherapy is proposed as an alternative to partial nephrectomy, where the tumour and some of the surrounding kidney are removed surgically while sparing some of the functional units of the kidneys (nephrons) (Atkins & Richie 2007). Partial nephrectomy is currently the 'gold standard' in the treatment of small renal tumours, and can be performed through either an open or laparoscopic surgical approach (Cozar & Tallada 2008; Russo 2007).

Radiofrequency ablation (RFA) is another nephron-sparing treatment that may be an alternative to cryotherapy and partial nephrectomy. Under ultrasound and CT guidance, a probe is inserted into the tumour. It uses a high-frequency alternating current to heat the tip of the probe, killing the surrounding cells (Krehbiel et al 2008).

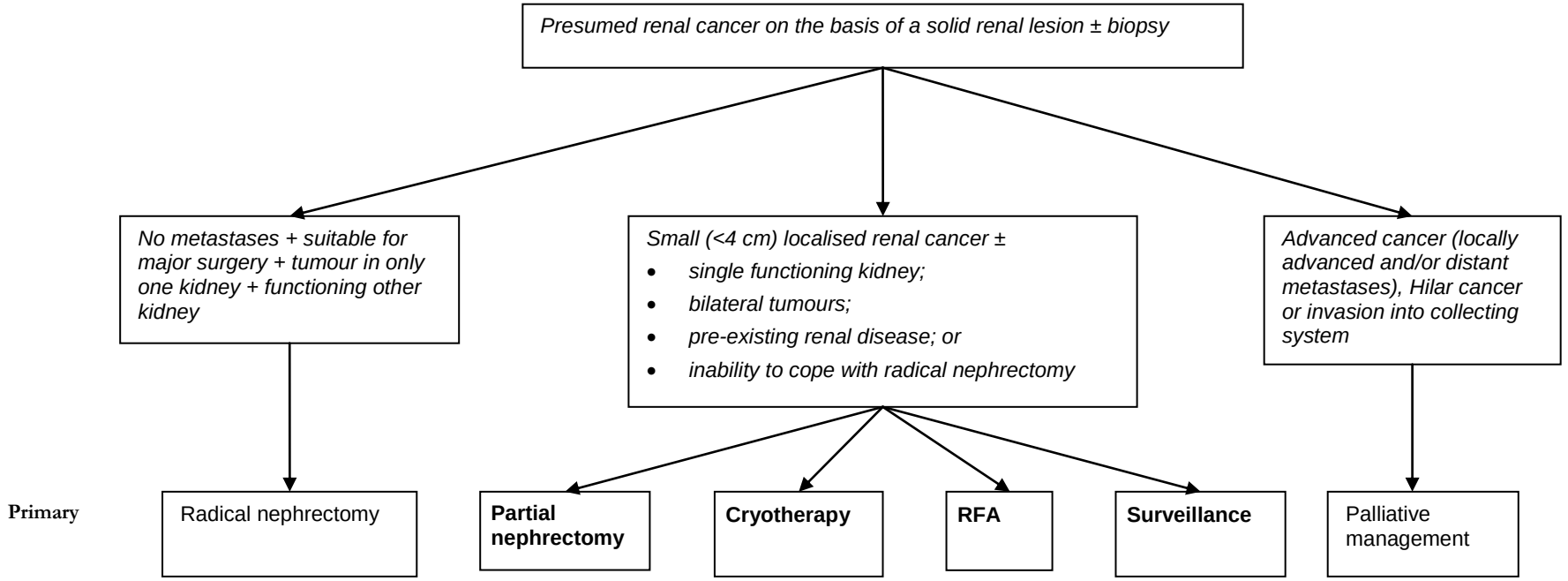
Conservative treatment by means of surveillance has been advocated by a proportion of clinicians, since it is reported that a majority of small renal tumours grow at a slow rate (0.26–0.70 cm/year) or not at all, and from one-fifth to one-third of small renal masses turn out to be benign lesions or with low malignant potential on final histology. Patients who choose surveillance receive follow-up imaging; when there are hints of malignancy (eg rapid tumour growth rate), the renal tumours would be extirpated or ablated by invasive procedures (Abouassaly et al 2008; Bosniak et al 1995; Gill 2005; Kouba et al 2007; Marshall 2005).

Other procedures, such as high-intensity focused ultrasound (HIFU), laser interstitial thermal therapy and microwave ablation, are currently being investigated for the treatment of small renal cancer (Klingler et al 2008). They will not be considered comparators to cryotherapy for this systematic review as these treatments are novel ablative techniques for renal cancer and still under development (Lane & Novick 2007; Wen & Nakada 2006; Zisman & Zerifin 2008).

Comparators

The aim of this report is to evaluate the evidence of the safety, effectiveness and cost-effectiveness of argon-based cryotherapy in the management of renal cancer compared with partial nephrectomy, RFA and surveillance.

Figure 12 Clinical decision tree for renal cancer



RFA: radiofrequency ablation

Clinical need / burden of disease

Renal cancer covers a variable group of tumours that have distinct features. Approximately 60 per cent of cases are clear cell carcinomas, 5–15 per cent are papillary, 5–10 per cent are chromophobic tumours, 5–10 per cent are oncocytomas, and a small percentage (<1%) are collecting or Bellini duct tumours (Braunwald et al 2001). Low-stage renal cancer may be detected during investigations for other medical conditions. Higher stage or grade tumours may produce symptoms including blood in the urine (haematuria), pain or mass in the flank or loin, anaemia, weight loss, fever and hypertension.

In 2003 there were 2019 new renal cancers identified in Australia, which corresponds to an annual incidence rate of 13.2 cases per 100 000 men and 7.2 cases per 100 000 women (AIHW 2007). The lifetime risk of having or developing renal cancer is 1 in 50 for males, and 1 in 103 for females (AIHW 2007). Renal cancer may be diagnosed at any age, but incidence peaks between 50 and 70 years (Braunwald et al 2001). In 2005 there were 847 deaths due to renal cancer (AIHW 2007).

Approximately one-third of renal cancer patients have metastases at the time of diagnosis (Planz et al 2003), so would therefore not be suitable for surgery. Using the total incidence data above, this would suggest that there are 1 346 new patients every year without metastases in Australia. Data from the United States in 2002 indicate that 39 per cent of renal cancers are 4 cm or smaller (an increase of 9% from 1988) (Nguyen et al 2006). Therefore, the estimated number of patients in Australia with small renal cancer who are suitable for minimally invasive surgery would be 525 (39% of 1346). Since, from the literature, it was indicated that malignant renal tumours account for between two-thirds and four-fifths of small renal lesions, there would be 656–788 patients with small renal lesions (Abouassaly et al 2008; Bosniak et al 1995; Gill 2005; Kouba et al 2007; Marshall 2005).

In 2004–05 there were 429 partial nephrectomies performed in Australia (AIHW 2006). Scanmedics Pty Ltd suggested that approximately 20 per cent of patients who receive minimally invasive treatment would be suitable for cryotherapy. This would result in 86 patients receiving cryotherapy per annum from those patients who are now treated by partial nephrectomy. The expert opinion from the Advisory Panel suggested that around 100 renal RFA procedures are performed in Australia per year, and from 0 to 100 per cent of these patients would undergo cryotherapy instead if it were funded. Therefore, another 0 to 100 cryotherapy procedures would be expected annually. In addition, the applicant also indicated that approximately 10 cryotherapy procedures are currently carried out annually in Australia. None of the patients who receive surveillance would be expected to otherwise choose cryotherapy, since the 'gold standard' treatment, partial nephrectomy, is widely accessible in current clinical practice; therefore, these patients undergo surveillance because they either refuse or are not suitable for invasive procedures (including cryotherapy). In total, the clinical need for renal cryotherapy would be between 96 and 196 procedures per annum.

This figure might double or triple in the following two circumstances: 1) where the use of imaging increases, and more small renal tumours would therefore be discovered; and 2) where patients are more involved in the decision-making process—surveillance might be the suggested option that clinicians think best, whereas patients would prefer to be actively treated (expert opinion of the Advisory Panel).

Marketing status of the technology

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). The third-generation cryosurgical unit (manufactured by Gilil Medical, Yokneam, Israel) is registered on the ARTG under the following item:

ARTG no.	Product no.	Product description	Sponsor
144069	**231903**	**Cryosurgical unit, general-purpose**	**Scanmedics Pty Ltd**

Source: Therapeutic Goods Administration 2008

Current reimbursement arrangement

Currently, there are no listings on the Medicare Benefits Schedule (MBS) for cryotherapy or RFA for renal cancer. The MBS items listed for partial nephrectomy are shown in Table 40.

Table 40 Relevant MBS items for renal cancer

MBS item	Descriptor	Fee	Benefit
36522	NEPHRECTOMY, partial (Anaes.) (Assist.)	$1 023.60	$767.70
36525	NEPHRECTOMY, partial, complicated by previous surgery on the same kidney (Anaes.) (Assist.)	$1 454.55	$1 090.95

Source: Medicare Australia 2008

Approach to assessment

Objectives

To determine whether there is sufficient evidence, in relation to safety, effectiveness and cost-effectiveness, to have argon-based cryotherapy for the treatment of small renal cancer listed on the Medicare Benefits Schedule.

Research questions

1. What is the safety of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?

2. What is the effectiveness of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?

3. What is the cost-effectiveness of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?

Expert advice

An advisory panel with expertise in urology, radiology, medicine oncology and consumer issues was established to evaluate the evidence and provide advice to the MSAC from a clinical perspective. In selecting members for advisory panels, the MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations, and consumer bodies for nominees. Membership of the Advisory Panel associated with this application is provided at Appendix H.

Review of literature

Literature sources and search strategies

The medical literature was searched to identify relevant studies and reviews for the period between 1995 (or, if inception of the database was later, from that date) to November 2008, as cryotherapy using the argon–helium system was first used in clinical practice in the middle of the 1990s (Ahmed et al 2005). Appendix I describes the electronic databases that were used for this search and other sources of evidence that were investigated. Grey literature[9] was included in the search strategy. Unpublished literature, however, was not canvassed as it is difficult to search for this literature exhaustively and systematically; and trials that are difficult to locate are often smaller and of lower methodological quality (Egger et al 2003). It is, however, possible that these unpublished data could impact on the results of this assessment.

[9] Literature that is difficult to find including published government reports, theses, technical reports, non-peer-reviewed papers etc.

The search terms used to identify literature in electronic bibliographic databases on the safety, effectiveness and cost-effectiveness of using cryotherapy for small renal cancer are also presented in Appendix I.

Inclusion/exclusion criteria

In general, studies were excluded if they:

- did not address the research question;
- assessed cryotherapy for renal tumours larger than 4 cm;
- used liquid nitrogen-based cryotherapy;
- did not report what generation of cryotherapy was used;
- did not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes (in some instances a study was included to assess one or more outcomes but had to be excluded for other outcomes due to data inadequacies);
- were in other languages and were of a lower level of evidence than that available in English; or
- did not have the appropriate study design.

If the same data were duplicated in multiple articles, results from the most comprehensive or most recent article only were included.

The inclusion criteria relevant to each of the research questions posed in this assessment are provided in Box 4, Box 5 and Box 6 in the 'Results' section of this report.

Search results

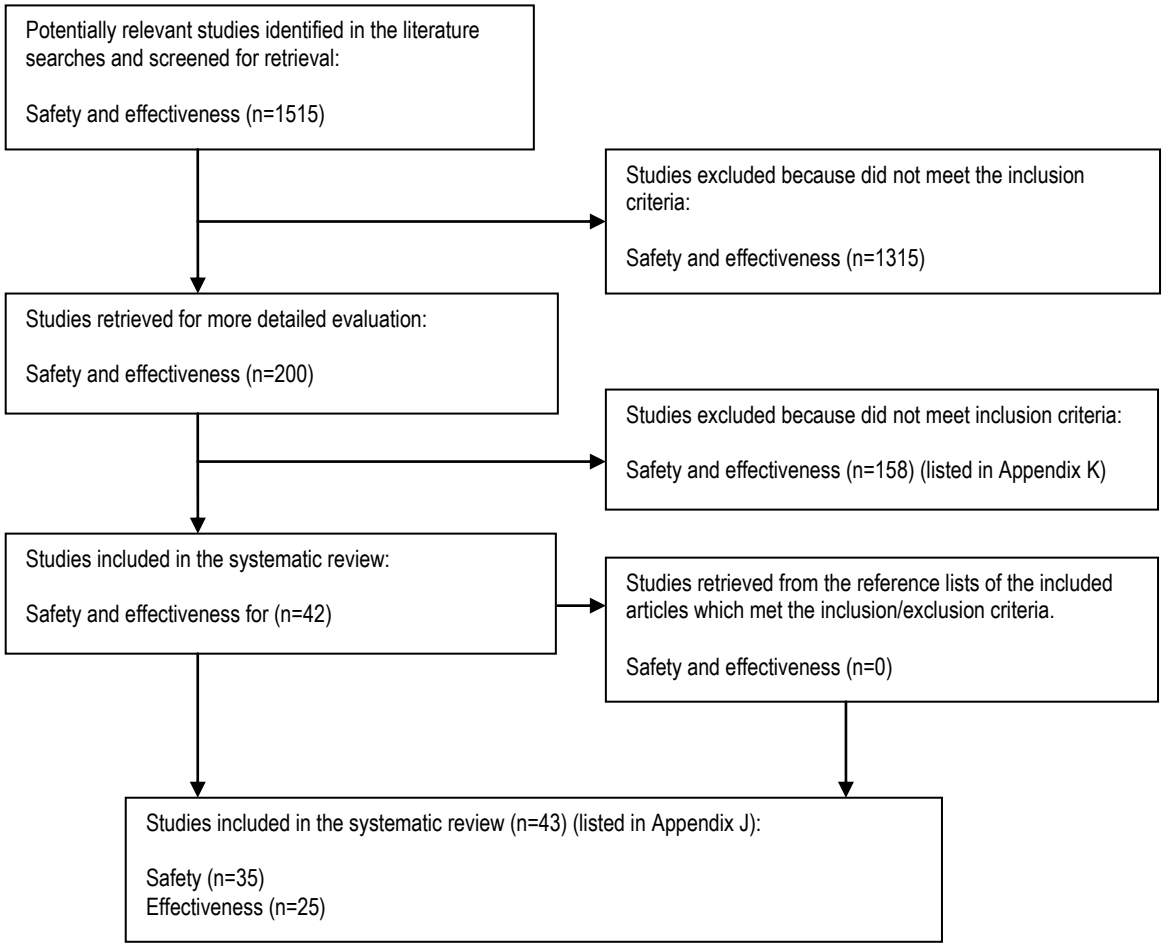
The process of study selection for this report went through six phases:

7. All reference citations from all literature sources were collated into an Endnote 8.0.2 database.
8. Duplicate references were removed.
9. Studies were excluded, on the basis of the citation information, if it was obvious that they did not meet the pre-specified inclusion criteria. All other studies were retrieved for full-text assessment.
10. Studies were included to address the research questions if they met the pre-specified criteria applied by the reviewer on the full-text articles. Those articles meeting the criteria formed part of the evidence-base. The remainder provided background information.
11. The reference lists of the included articles were pearled for additional relevant studies. These were retrieved and assessed according to phase 4.

12. The evidence-base consisted of articles from phases 4 and 5 that met the inclusion criteria.

Any doubt concerning inclusions at phase 4 was resolved by consensus between the two reviewers, with a third reviewer available (although not required) for adjudication. The results of the process of study selection are provided in Figure 13.

Figure 13 Summary of the process used to identify and select studies for the assessment of cryotherapy for renal cancer



Source: Adapted from Moher et al 1998

Data extraction and analysis

A profile of key characteristics was developed for each included study (Appendix J). These study profiles described the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention, comparator intervention (where relevant), inclusion/exclusion criteria, outcomes assessed and follow-up period for each included study.

Studies that were unable to be retrieved or that met the inclusion criteria but contained insufficient or inadequate data for inclusion are provided in Appendix K.

Definitions of all technical terms and abbreviations are provided in the Glossary. Descriptive statistics were extracted or calculated for all safety and effectiveness outcomes in the individual studies.

Validity assessment of individual studies

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 41) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

Table 41 Evidence dimensions

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design [a]
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

[a] See Table 42

Strength of the evidence

The three subdomains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 42.

Level

A study comparing percutaneous cryotherapy with laparoscopic cryotherapy was ranked level IV interventional evidence because the comparator used in the study was not partial nephrectomy, radiofrequency ablation or surveillance.

Table 42 Designations of levels of interventional evidence

Level	Intervention[a]
I[b]	A systematic review of level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (ie alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial[c] Cohort study Case-control study Interrupted time series with a control group
III-3	A comparative study without concurrent controls: Historical control study Two or more single-arm studies[d] Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: NHMRC 2005

[a] Definitions of these study designs are provided in NHMRC 2000, pp 7–8; [b] A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence; [c] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (ie utilising A vs B and B vs C to determine A vs C); [d] Comparing single-arm studies (ie case series from two studies).

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question, eg level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Quality

Study quality was assessed using the critical appraisal checklists provided in Table 43. The appraisal of intervention studies pertaining to treatment safety and effectiveness was undertaken using a checklist developed by the NHMRC (2000). This checklist was used for systematic reviews / health technology assessment (HTA reports), randomised controlled trials, cohort studies and case-control studies. Uncontrolled before-and-after case series are a poorer level of evidence with which to assess effectiveness. The quality of this type of study design was assessed according to a checklist developed by the UK National Health Service (NHS) Centre for Reviews and Dissemination (Khan et al 2001).

Table 43 Quality checklists

Study type	Checklists
Systematic reviews / HTA reports	NHMRC Checklist Table 1.4 (NHMRC 2000)
Randomised controlled trials	NHMRC Checklist Table 1.4 (NHMRC 2000)
Cohort study	NHMRC Checklist Table 1.4 (NHMRC 2000)
Case-control	NHMRC Checklist Table 1.4 (NHMRC 2000)
Intervention case series	NHS CRD Quality Assessment Scale (Khan et al 2001)

Statistical precision

Statistical precision was determined using standard statistical principles. Small confidence intervals and p-values give an indication as to the probability that the reported effect is real (NHMRC 2000).

Size of effect in individual studies

For intervention studies on cryotherapy it was important to assess whether statistically significant differences are also clinically important. The size of the effect needed to be determined, as well as whether the 95 per cent confidence interval includes only clinically important effects. Rank scoring methods were used to determine the clinically important benefit of the size of the effect in studies, as well as the clinical relevance of the evidence in controlled studies (NHMRC 2000).

Relevance of evidence in individual studies

Similarly, the outcome being measured in the studies should be appropriate and clinically relevant. Inadequately validated (predictive) surrogate measures of a clinically relevant outcome should be avoided (NHMRC 2000). When assessing the safety and effectiveness of cryotherapy, rank scoring methods were used to determine the clinical relevance of the outcome being assessed in any controlled studies (NHMRC 2000).

Assessment of the body of evidence

Appraisal of the body of evidence was conducted along the lines suggested by the NHMRC in their guidance on clinical practice guideline development (NHMRC 2005). Five components are considered essential by the NHMRC when judging the body of evidence:

- the volume of evidence – which includes the number of studies sorted by their methodological quality and relevance to patients
- the consistency of the study results – whether the better quality studies had results of a similar magnitude and in the same direction, ie homogenous or heterogenous findings
- the potential clinical impact – appraisal of the precision, size and clinical importance or relevance of the primary outcomes used to determine the safety and effectiveness of the test
- the generalisability of the evidence to the target population
- the applicability of the evidence – integration of the evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice.

A matrix for assessing the body of evidence for each research question, according to the components above, was used for this assessment (Table 44) (NHMRC 2008). Once the results of the studies had been synthesised, the overall conclusion as derived from the body of evidence was presented to answer each clinical question – see 'Discussion' section (page 194).

Table 44 Body of evidence assessment matrix

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several level I or II studies with low risk of bias	One or two level II studies with low risk of bias or a systematic review / multiple level III studies with low risk of bias	Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	Level IV studies, or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population(s) studied in body of evidence are the same as the target population	Population(s) studied in body of evidence are similar to the target population	Population(s) studied in body of evidence differ to target population but it is clinically sensible to apply this evidence to target population	Population(s) studied in body of evidence are different to target population and it is hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC 2008

Results of assessment

Is it safe?

Argon-based cryotherapy for treatment of renal cancer was assessed in terms of possible patient harms that may result from the procedure. Box 4 outlines the inclusion criteria determined a priori for the assessment of the safety of using cryotherapy.

Box 4 Inclusion criteria for studies assessing the safety of cryotherapy for renal cancer

Research question	
What is the safety of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?	
Characteristics	**Criteria**
Population	Patients with presumed small (<4 cm) localised renal cancer
Intervention	Cryotherapy (argon-based)
Comparators	Partial nephrectomy, RFA or surveillance
Outcome	Primary – major treatment-induced complications, eg fatality, haemorrhage, renal injuries, renal dialysis, ureteric injuries, renal vessel injuries, renal pelvis injuries, small bowel injuries, injury to other adjacent structures, pneumonia, fistula, renal failure or serious infection Secondary – minor treatment-induced complications, eg probe site pain, bleeding not requiring transfusion, transient urinary leakage or minor infection
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials; animal, in-vitro and laboratory studies were excluded
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.

In most cases biopsy of renal tumours is not carried out before treatment. The population treated by cryotherapy, partial nephrectomy or RFA are usually those with *presumed* small (<4 cm) renal cancers, which usually include a heterogeneous mixture of malignancies and benign lesions (as determined by post-operative histology).

There was an attempt to exclude those studies where an overlap of results was evident, but there may still be some overlap left in study populations in studies from the same co-authors or institutions.

For the purpose of this assessment, the outcomes considered have been prioritised into primary or secondary safety outcomes based on the severity of the adverse events (Box 4).

Primary safety outcomes

Major complications

Major complications as a result of argon-based cryotherapy for presumed renal cancer were reported by a total of 34 studies. Of these, two were comparative studies with concurrent controls (level III-2 intervention evidence): one examined the safety of laparoscopic cryotherapy relative to laparoscopic partial nephrectomy (O'Malley et al 2007), and the other compared the rates of intra-operative and post-operative complications among patients undergoing laparoscopic cryotherapy, percutaneous

cryotherapy or percutaneous RFA (Bandi et al 2008). Also included in this assessment of safety were 16 uncontrolled case series (level IV intervention evidence): six investigated third-generation cryotherapy, and the other ten case series used second-generation cryotherapy as their intervention. In addition, 16 case reports that provided data on safety outcomes were also identified. The study profiles for all included studies are listed in Appendix J. Data from the included studies have been extracted into Table 45, Table 46 and Table 47, and ordered in a hierarchical manner according to each study's level of evidence, cryotherapy generation, quality assessment and sample size.

One procedure-related death was reported in a case report by Romero et al (2007). This patient was an 87-year-old woman with multiple comorbidities, including obstructive pulmonary disease, hypertension, congestive heart failure and atrial fibrillation. She was treated with anticoagulants, and had received a pacemaker implant and a laparotomy for peritonitis. A CT scan revealed a 1.7 cm x 2.7 cm exophytic renal mass on her left kidney. The patient underwent second-generation cryotherapy to ablate the tumour and tolerated the procedure well. Post-operative histology showed papillary renal cell carcinoma. The anticoagulation therapy for atrial fibrillation resumed 1 day after cryotherapy. On the third day the patient experienced shortness of breath and pain in the left side of the chest due to pleural effusion, which was drained by a chest tube. She stopped anticoagulation therapy and received fresh frozen plasma and additional blood products. The patient died of a pulmonary embolism involving the right main pulmonary artery 20 days after the cryotherapy procedure. No other studies identified in the literature reported intra-operative or post-operative death related to cryotherapy for renal tumours.

The moderate-quality study by O'Malley et al (2007) compared the rates of post-operative complications between laparoscopic cryotherapy using thin cryoneedles (17-G) and laparoscopic partial nephrectomy. Patients in the two groups were matched for gender, number of comorbidities, American Society of Anesthesiologists (ASA)[10] physical status score, body mass index (BMI), location and size of tumours, and baseline renal function. The authors observed no significant difference in the incidence rates of major complications between the laparoscopic cryotherapy group and the laparoscopic partial nephrectomy group (p=1.000). Two out of 15 patients (13.3%) who underwent cryotherapy for renal tumours developed major complications during follow-up; one had pneumonia, and the other experienced a myocardial infarction post-operatively. Of the patients in the partial nephrectomy group, 20 per cent had major adverse events, including a myocardial infarction, a case of deep venous thrombosis and a large perirenal haematoma.

Bandi et al (2008), in a poor-quality controlled study, reported safety outcomes following argon-based cryotherapy (laparoscopic and percutaneous) relative to percutaneous RFA. Patients in the three groups were well matched for age, gender, BMI, ASA score and number of tumours. However, the mean tumour size in the laparoscopic cryotherapy group (2.6 cm) was significantly larger than that in the percutaneous cryotherapy group (2.2 cm, $p<0.05$) and that in the percutaneous RFA group (2.2 cm, $p<0.05$). The rates of

[10] American Society of Anesthesiologists (ASA) physical status score is a measurement of physical status, comorbidities and physiological stability. ASA score 1: a healthy patient; 2: a patient with mild systemic disease; 3: a patient with severe systemic disease that limits activity but is not incapacitating; 4: a patient with an incapacitating systemic disease that is a constant threat to life; 5: a moribund patient not expected to survive without operation (American Society of Anesthesiologists 1963)

major intra-operative complications for laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA were 3.4 per cent, 10.0 per cent and 6.7 per cent, respectively, with no significant difference among the three groups (p=0.25). One case of significant bleeding (treated with haemostatic agents; data on volume of blood loss not available from the report) and one case of bowel injury (requiring laparoscopic repair) occurred intra-operatively in a total of 58 laparoscopic cryotherapy procedures. Of the 20 patients who underwent percutaneous cryotherapy, one presented with a urine leak, while another had a haematoma identified during the procedure. A haematoma also developed intra-operatively in one patient in the percutaneous RFA group of 15 patients. Furthermore, the authors discovered no significant difference in the rates of major post-operative complications among the three intervention groups (p=0.56). Five out of 58 patients (8.6%) receiving laparoscopic cryotherapy developed major complications, including atrial fibrillation (1.7%), respiratory failure (1.7%), narcotic overdose (1.7%) and symptomatic perirenal haematoma (3.4%). Two patients in the percutaneous cryotherapy group (10.0%) and two in the percutaneous RFA group (13.3%) experienced significant prolonged neuropraxia post-operatively. In addition, one case (6.7%) of large retroperitoneal haematoma that required blood transfusion was also reported following a percutaneous procedure.

Table 45 Major complications from cryotherapy for presumed renal cancer (controlled studies)

Study	Evidence level and quality[a]	Number of procedures	Major complications (per procedure)		Risk difference[b] (95% CI)	Relative risk[c] (95% CI)	p-value[d]
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 4/4 R: 1/5	30	**LCT (n=15)**	**LPN (n=15)**	–0.07 (–0.25, 0.17)	0.67 (0.14, 3.04)	1.000
			Post-operative complications				
			2/15 (13.3%) Pneumonia: 1/15 (6.7%) Myocardial infarction: 1/15 (6.7%)	3/15 (20.0%) Myocardial infarction: 1/15 (6.7%) Deep venous thrombosis: 1/15 (6.7%) Large perirenal haematoma: 1/15 (6.7%)			
2nd or 3rd generation							
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retro-spective cohort study Clin I: 2/4 R: 1/5	73	**LCT (n=58)**	**RFA (n=15)**	–0.03 (–0.15, 0.04)	0.52 (0.07, 3.90)	0.504
			Intra-operative complications				
			2/58 (3.4%) Significant bleeding: 1/58 (1.7%) Bowel injury: 1/58 (1.7%)	1/15 (6.7%) Haematoma: 1/15 (6.7%)			

	Clin I: 2/4 R: 1/5		*Post-operative complications*		–0.11 (–0.31, 0.04)	0.43 (0.13, 1.55)	0.348
			5/58 (8.6%) Narcotic overdose: 1/58 (1.7%) Atrial fibrillation: 1/58 (1.7%) Respiratory failure: 1/58 (1.7%) Symptomatic haematoma: 2/58 (3.4%)	3/15 (20%) Large retroperitoneal haematoma: 1/15 (6.7%) Significant prolonged neuropraxia: 2/15 (13.3%)			
	Clin I: 4/4 R: 1/5	35	**PCT (n=20)**	**RFA (n=15)**	0.03 (–0.12, 0.13)	1.50 (0.21, 11.26)	1.000
			Intra-operative complications				
			2 (10.0%) Urine leak: 1/20 (5.0%) Haematoma: 1/20 (5.0%)	1/15 (6.7%) Haematoma: 1/15 (6.7%)			
	Clin I: 4/4 R: 1/5		*Post-operative complications*		–0.10 (–0.26, 0.11)	0.50 (0.11, 2.32)	0.631
			2/20 (10.0%) Significant prolonged neuropraxia: 2/20 (10.0%)	3 (20%) Large retroperitoneal haematoma: 1/15 (6.7%) Significant prolonged neuropraxia: 2/15 (13.3%)			

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Relative risk of all major intra-operative or post-operative complications. Relative risk is calculated as the risk in one group divided by the risk in the other group; [c] Risk difference of all major intra-operative or post-operative complications. Risk difference is calculated as the risk in one group minus the risk in the other group; [d] Statistical significance of differences calculated by two-tailed Fisher's exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Six case series provided data on major complications resulting from the use of third-generation cryotherapy for renal tumours. Three good-quality studies did not report any major intra-operative or post-operative complications in their patient groups (Caviezel et al 2008; Polascik et al 2007; Wright et al 2007). However, in Wyler et al's (2007) moderate-quality study, four out of 14 patients (28.6%) had intra-operative bleeding (mean = 166 mL), which required one intra-corporeal stitch in each patient. Significant secretion (200–250 mL) was observed in three patients (21.4%) within the first 12 hours after the cryotherapy procedure, when a drain was inserted.

Six out of ten case series that investigated second-generation cryotherapy for small renal tumours reported no major peri-operative or post-operative adverse events. In the remaining four studies the one with the highest quality was by Weld et al (2007). In this case series of 31 laparoscopic cryotherapy procedures, one case (3.2%) of significant blood loss (1000 mL) occurred intra-operatively. This patient required post-operative blood transfusions and developed an ileus and gross haematuria after cryotherapy. CT showed a small perirenal urinoma, hydronephrosis and blood clot within the collective system of the kidney. This patient responded well to ureteric stenting. Atrial fibrillation (3.2%) and heart failure (3.2%) were also reported by Weld and colleagues as major

adverse consequences of the cryotherapy procedure. Goel et al (2008) reported their initial experience of performing Single Port Access Laparoscopic System cryotherapy procedure in six patients, and described the requirement for post-operative blood transfusions in one patient (16.7%) with a medical history of anaemia and pulmonary disease. Hinshaw et al (2008) carried out a moderate-quality study comparing clinical outcomes between percutaneous cryotherapy and laparoscopic cryotherapy. No significant difference in either intra-operative or post-operative complication rates was reported between the two groups ($p>0.05$), although two out of 60 patients (3.3%) who received laparoscopic cryotherapy had major intra-operative complications, one with bowel injury and the other with severe respiratory distress; and one patient experienced atrial fibrillation post-operatively. Pneumonia resulting from the cryotherapy procedure was reported by Moon et al (2004) as a major adverse event, with a rate of 6.3 per cent (1 out of 16 patients).

Table 46 Major complications from cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of procedures	Intervention	Major complications (per procedure)
3rd generation				
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	32 (35 tumours)	Laparoscopic cryotherapy	Intra-operative complications: 0/32 Post-operative complications: 0/32
(Polascik et al 2007)[a]	Level IV Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	Intra-operative complications: 0/32 Post-operative complications: 0/32
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	Intra-operative complications: 0/32 Post-operative complications: 0/32
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneo-scopy-assisted cryotherapy: 13 Open cryotherapy: 1	Intra-operative complications: 4/14 (28.6%) Bleeding (166±115 mL): 4/14 (28.6%) Post-operative complications: 3/14 (21.4%) Significant secretion (200–250 mL): 3/14 (21.4%)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	23 (30 tumours)	Laparoscopic cryotherapy	Intra-operative complications: 0/23 Post-operative complications: 0/23
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 (tumours)	Laparoscopy-assisted percutaneous cryotherapy	Intra-operative complications: 0/23 Post-operative complications: 0/23
2nd generation				
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	31 (36 tumours)	Laparoscopic cryotherapy	Intra-operative complications: 1/31 (3.2%) Significant blood loss: 1/31 (3.2%) Post-operative complications: 3/31 (9.7%) Gross haematuria: 1/31 (3.2%) Atrial fibrillation: 1/31 (3.2%) Heart failure: 1/31 (3.2%)
(Shingleton & Sewell 2003)[c]	Level IV Quality: 4.5/6 Retrospective case series	10	Percutaneous cryotherapy	Intra-operative complications: 0/10 Post-operative complications: 0/10

(Shingleton & Sewell 2002a)[c]	Level IV Quality: 4.5/6 Case series	3 (4 tumours)	Percutaneous cryotherapy	Intra-operative complications: 0/3 Post-operative complications: 0/3
(Georgiades et al 2008)	Level IV Quality: 4/6 Case series	45	Percutaneous cryotherapy	Intra-operative complications: n/a Colon or pancreas injury: 0/45 Pneumothorax: 0/45 Post-operative complications: n/a Renal failure: 0/45 Ureteric injury: 0/45
(Permpongkosol et al 2006)[d]	Level IV Quality: 4/6 Retrospective case series	20 (22 tumours)	Percutaneous cryotherapy	Intra-operative complications: 0/20 Post-operative complications: 0/20
(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	Intra-operative complications: 0/6 Post-operative complications: 1/6 (16.7%) Anaemia: 1/6 (16.7%)
(Gupta et al 2006)[d]	Level IV Quality: 3.5/6 Retrospective case series	10 (14 tumours)	Percutaneous cryotherapy	Intra-operative complications: 0/10 Post-operative complications: 0/10
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	Intra-operative complications: 0/8 Post-operative complications: 0/8
(Hinshaw et al 2008)[e]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	Intra-operative complications: 0/30 Post-operative complications: 0/30
		60	Laparoscopic cryotherapy	Intra-operative complications: 2/60 (3.3%) (PCT vs LCT: p>0.05) Bowel injury: 1/60 (1.7%) Severe respiratory distress: 1/60 (1.7%) Post-operative complications: 1/60 (1.7%) (PCT vs LCT: p>0.05) Atrial fibrillation: 1/60 (1.7%)
(Moon et al 2004)[e]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Intra-operative complications: 0/16 Post-operative complications: 1/16 (6.3%) Pneumonia: 1/16 (6.3%)

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura, [c] May be overlap between patient series; [d] May be overlap between patient series; [e] May be overlap between patient series.

LCT: laparoscopic cryotherapy; n/a: not available; PCT: percutaneous cryotherapy

Case reports may be useful for describing rare complications. In general, they provide less information than case series since it is impossible to determine the denominator, ie how many patients received cryotherapy for renal tumours and were at risk of harm but did not necessarily have any adverse events. Of the 16 case reports identified in the literature, five reported significant post-operative complications resulting from cryotherapy. These included a perirenal haematoma and pleural effusion (requiring blood transfusion and removal of sanguineous fluid in the chest), a massive pulmonary thromboembolism (treated successfully with anticoagulation therapy), a urinary fistula (managed with nephrectomy after drainage failure), a colorenal fistula (necessitating a stent), and a filling defect and partial urothelial slough in the renal pelvis (resolved by

ureteroscopic slough removal and a temporary stent) (Brown & Bhayani 2007; Chen et al 2008; Mitre et al 2008; Romero et al 2007; Vanderbrink et al 2007)

Table 47 Major complications from cryotherapy for presumed renal cancer (case reports)

Study	Number of procedures	Intervention	Major complications
3rd generation			
(Bassignani et al 2004)	2	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Chen et al 2008)[a]	1	Laparoscopic cryotherapy	Intra-operative complications: 0 Post-operative complications: 1 Filling defect and partial urothelial slough: 1
(Hruby et al 2006)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Kodama et al 2005)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(McClung et al 2007)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Pantuck et al 2002)[b]	1	Cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Polcari et al 2007)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Zhu et al 2005)	2	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
2nd generation			
(Blaschko et al 2007)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Brown & Bhayani 2007)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 1 Urinary fistula: 1
(Leflore et al 2007)	1	Cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Mitre et al 2008)	1	Laparoscopic cryotherapy	Intra-operative complications: 0 Post-operative complications: 1 Massive pulmonary thromboembolism: 1
(Romero et al 2007)	2	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 2 Procedure-related death: 1 Perirenal haematoma and pleural effusion: 1
(Sewell et al 2003)	2	Cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Shingleton & Sewell 2002b)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 0
(Vanderbrink et al 2007)	1	Percutaneous cryotherapy	Intra-operative complications: 0 Post-operative complications: 1 Colorenal fistula: 1

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] All authors are consultants for Galil Medical.

Secondary safety outcomes

Minor complications

Minor complications following argon-based cryotherapy for presumed renal cancer were reported by a total of 32 observational studies, including one controlled study (level III-2 intervention evidence), 15 case series (level IV intervention evidence) and 16 case reports (Table 48, Table 49 and Table 50). The study profiles for all the included studies are shown in Appendix J.

In a matched-pairs cohort study of moderate quality, O'Malley et al (2007) compared third-generation laparoscopic cryotherapy with laparoscopic partial nephrectomy. In the cryotherapy group of 15 procedures, one patient experienced a gout attack, and another had hyponatraemia during the follow-up period. While none of the patients receiving partial nephrectomy developed minor complications post-operatively, the zero incidence rate of minor complications was not statistically different from the rate of 13.3 per cent in the cryotherapy group (p=0.483) due to the small sample size.

Table 48 Minor complications from cryotherapy for presumed renal cancer (controlled study)

Study	Evidence level and quality[a]	Number of procedures	Minor complications (per procedures)		Risk difference (95% CI)	Relative risk (95% CI)	p-value[b]
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 4/4 R: 1/5	30	**LCT (n=15)** 2/15 (13.3%) Gout attack: 1/15 (6.7%) Hyponatraemia: 1/15 (6.7%)	**LPN (n=15)** 0/15	0.13 (–0.04, 0.13)	Infinity (0.56, infinity)	0.483

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy

Of the six case series that reported on the frequency of minor complications following third-generation cryotherapy, the largest good-quality study was by Wright et al (2007). The authors did not observe any minor complications after 32 laparoscopic cryotherapy procedures in this study. Another good-quality case series by Polascik et al (2007) reported one case (3.8%) of transient ileus in a total 26 patients. Superficial skin frostbite and asymptomatic haematoma were also reported as minor complications from cryotherapy, with rates of 14.3 per cent and 25.0 per cent, respectively (Gore et al 2005; Wyler et al 2007).

Nine uncontrolled studies reported minor complications from second-generation cryotherapy. Weld et al (2007), in their case series of 31 laparoscopic cryotherapy procedures, discovered one case of transient urine leak (3.2%) during the follow-up period. One out of three patients developed ileus post-operatively in Shingleton and Sewell's (2003) high-quality study. This adverse event was considered secondary to narcotic analgesics and was resolved without intervention. In Permpongkosol et al's (2006) moderate-quality study, a total of 23 renal malignancies were ablated by 21 cryotherapy procedures, five (23.8%) of which caused minor post-operative adverse events, including small pneumothorax in one patient, insignificant haemorrhage in two patients, transient pain in one patient and flank muscle laxity in one patient. However, it

is also noted that one patient in this case series had a renal tumour larger than 4 cm. Since complications in this patient were not reported separately, the actual minor complication rate for cryotherapy in the treatment of renal tumours less than 4 cm was not available from this study. Hinshaw et al (2008) observed a higher rate of minor complications for percutaneous cryotherapy than for laparoscopic cryotherapy (13.3% vs 1.7%, p=0.04). A total of five patients, four in the percutaneous group and one in the laparoscopic group, developed minor complications, including an asymptomatic and self-limited urine leak, an asymptomatic perirenal haematoma, an intercostal neuropraxia and a self-limited flank paresthesia.

Table 49 Minor complications from cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of procedures	Intervention	Minor complications (per procedure)
3rd generation				
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	32 (35 tumours)	Laparoscopic cryotherapy	Minor complications: 0/32
(Polascik et al 2007)[a]	Level IV Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	Minor complications: 1/26 (3.8%) Transient ileus: 1/26 (3.8%)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	Minor complication: 0/7
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneo-scopy-assisted cryotherapy: 13 Open cryotherapy: 1	Minor complications: 2/14 (14.3%) Superficial skin frostbite: 2/14 (14.3%)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	23 (30 tumours)	Laparoscopic cryotherapy	Minor complications: 0/23
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 tumours)	Laparoscopy-assisted percutaneous cryotherapy	Minor complications: 1/4 (25.0%) Asymptomatic haematoma: 1/4 (25.0%)
2nd generation				
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	31 (36 tumours)	Laparoscopic cryotherapy	Minor complications: 1/31 (3.2%) Transient urine leak: 1/31 (3.2%)
(Shingleton & Sewell 2003)[c]	Level IV Quality: 4.5/6 Retrospective case series	10	Percutaneous cryotherapy	Minor complications: 0/10
(Shingleton & Sewell 2002a)[c]	Level IV Quality: 4.5/6 Case series	3 (4 tumours)	Percutaneous cryotherapy	Minor complications: 1/3 (33.3%) Transient ileus: 1/3 (33.3%)
(Georgiades et al 2008)	Level IV Quality: 4/6 Case series	45	Percutaneous cryotherapy	Minor complications: n/a Ablation-related infection: 0/45

(Permpongkosol et al 2006)	Level IV Quality: 4/6 Retrospective case series	21 (23 tumours[d])	Percutaneous cryotherapy	Minor complications: 5/21 (23.8%) Small pneumothorax: 1/21 (4.8%) Haemorrhage: 2/21 (9.5%) (did not require blood transfusion) Transient pain: 1/21 (4.8%) Flank muscle laxity: 1/21 (4.8%)
(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	Minor complications: 1/6 (16.7%) Small perirenal haematoma: 1/6 (16.7%)
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	Minor complications: 0/8
(Hinshaw et al 2008)[e]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	Minor complications: 4/30 (13.3%) Asymptomatic perirenal haematoma: 1/30 (3.3%) Asymptomatic and self-limited urine leak: 1/30 (3.3%) Self-limited flank paresthesia and neuralgia: 1/30 (3.3%) Intercostal neurapraxia: 1/30 (3.3%)
		60	Laparoscopic cryotherapy	Minor complications: 1/60 (1.7%) (PCT vs LCT: p=0.04) Asymptomatic perirenal haematoma, asymptomatic and self-limited urine leak, self-limited flank paresthesia and neuralgia, or intercostal neuropraxia (one of the above complications, not specified in the article): 1/60 (1.7%)
(Moon et al 2004)[e]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Minor complications: 0/16

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura; [c] May be overlap between patient series; [d] One patient with a tumour >4 cm; [e] May be overlap between patient series
n/a: not available; LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy

Fourteen out of 16 case reports identified by this assessment mentioned no minor complications. Transient haematuria and mild fever resulting from argon-based cryotherapy were reported by Leflore et al (2007) and Kodama et al (2005), respectively.

Table 50 Minor complications from cryotherapy for presumed renal cancer (case reports)

Study	Number of procedures	Intervention	Minor complications
3rd generation			
(Bassignani et al 2004)	2	Percutaneous cryotherapy	Minor complications: 0
(Chen et al 2008)[a]	1	Laparoscopic cryotherapy	Minor complications: 0
(Hruby et al 2006)	1	Percutaneous cryotherapy	Minor complications: 0
(Kodama et al 2005)	1	Percutaneous cryotherapy	Minor complications: 1 Mild fever: 1
(McClung et al 2007)	1	Percutaneous cryotherapy	Minor complications: 0
(Pantuck et al 2002)[b]	1	Cryotherapy	Minor complications: 0
(Polcari et al 2007)	1	Percutaneous cryotherapy	Minor complications: 0
(Zhu et al 2005)	2	Percutaneous cryotherapy	Minor complications: 0

2nd generation			
(Blaschko et al 2007)	1	Percutaneous cryotherapy	Minor complications: 0
(Brown & Bhayani 2007)	1	Percutaneous cryotherapy	Minor complications: 0
(Leflore et al 2007)	1	Cryotherapy	Minor complications: 1 Transient haematuria: 1
(Mitre et al 2008)	1	Laparoscopic cryotherapy	Minor complications: 0
(Romero et al 2007)	2	Percutaneous cryotherapy	Minor complications: 0
(Sewell et al 2003)	2	Cryotherapy	Minor complications: 0
(Shingleton & Sewell 2002b)	1	Percutaneous cryotherapy	Minor complications: 0
(Vanderbrink et al 2007)	1	Percutaneous cryotherapy	Minor complications: 0

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] All authors are consultants for Galil Medical.

Blood loss

Estimated volume of blood loss

Data on estimated volume of blood loss from argon-based cryotherapy were provided by two controlled studies (level III-2 intervention evidence) and nine case series (level IV intervention evidence) (Table 51 and Table 52).

In a matched-pairs cohort study of moderate quality, O'Malley et al (2007) estimated that the mean blood loss from laparoscopic cryotherapy was 58.7 mL (standard deviation (SD) = 28.5 mL), which was both statistically (p=0.002) and clinically significantly less than that from laparoscopic partial nephrectomy (mean = 221.7 mL, SD = 182.5 mL). In the other, a poor-quality controlled study, mean blood loss of 64 mL was estimated in 58 patients who were treated by laparoscopic cryotherapy; and one haematoma was discovered in each of the two (cryotherapy and RFA) percutaneous ablation groups. No significant difference in estimated blood loss was observed among the three intervention groups (Bandi et al 2008).

Table 51 Estimated volume of blood loss from cryotherapy for presumed renal cancer (controlled studies)

Study	Evidence level and quality[a]	Number of patients	Mean estimated volume of blood loss		Mean difference (95% CI)	Mean quotient (95% CI)	p-value
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 1/4 R: 1/5	30	**LCT (n=15)** 58.7±28.5 mL	**LPN (n=15)** 221.7±182.5 mL	–163 mL (–261 mL, –65 mL)	0.26 (0.17, 0.49)	0.002
2nd or 3rd generation							
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 4/4 R: 1/5	73	**LCT (n=58)** 64 mL	**RFA (n=15)** 1 haematoma	n/a	n/a	>0.05

	Clin I: 4/4 R: 1/5	35	**PCT (n=20)** 1 haematoma	**RFA (n=15)** 1 haematoma	n/a	n/a	>0.05

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome)

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; n/a: not available; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Mean/median blood loss of between 10 mL and 78 mL was reported by three case series that investigated laparoscopic cryotherapy using third-generation cryotherapy systems. In a high-quality study by Wright et al (2007), blood loss of 5–160 mL (mean = 32 mL) was observed in 32 patients, none of which required blood transfusions. One patient in Polascik et al's (2007) case series received blood transfusions post-procedurally due to pre-existing anaemia rather than significant peri-operative blood loss. The study, which examined retroperitoneoscopy-assisted cryotherapy and open cryotherapy for renal cancer, reported a relatively higher mean blood loss of 93 mL (range: 0–300 mL) (Wyler et al 2007). However, no further data were available to determine whether a different surgical approach would have impacted on the volume of blood loss from laparoscopic cryotherapy.

The estimated blood loss from second-generation cryotherapy procedures ranged from 40 to 103 mL. Weld et al (2007), in a good-quality study involving 31 procedures, reported a mean estimated blood loss of 97 mL, with an extreme of 1000 mL, during a laparoscopic cryotherapy procedure (Weld et al 2007). The patient developed gross haematuria and ileus post-operatively and required blood transfusions. No other patients undergoing second-generation cryotherapy necessitated blood transfusions after the procedure, including one patient who lost 400 mL in Colon et al's (2003) case series and another with an estimated blood loss of 250 mL in Moon et al's (2004) study.

Table 52 Estimated volume of blood loss from cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of procedures	Intervention	Estimated blood loss
3rd generation				
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	32 (35 tumours)	Laparoscopic cryotherapy	Mean: 32 mL (range: 5–160 mL)
(Polascik et al 2007)[a]	Level IV case series Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	Median: 10 mL (range: 0–200 mL)
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	Mean: 93 mL (range: 0–300 mL)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	23 (30 tumours)	Laparoscopic cryotherapy	Mean: 78 mL
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 tumours)	Laparoscopy-assisted percutaneous cryotherapy	Mean: 29 mL (range: 5–100 mL)
2nd generation				
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	31 (36 tumours)	Laparoscopic cryotherapy	Mean: 97 mL (range: 10–1000 mL)

(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	Mean: 83±26 mL
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	Mean: 103 mL (range: 50–400 mL)
(Moon et al 2004)	Level IV case series Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Mean: 40 mL (range: 0–250 mL)

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura.

Serum haematocrit and haemoglobin

Significant blood loss can be implied by a reduction in serum haematocrit level or serum haemoglobin level. Each of the two surrogate measures of blood loss was reported by one study (Table 53). O'Malley et al (2007) compared post-operative serum haematocrit levels between laparoscopic cryotherapy and laparoscopic partial nephrectomy in patients with matched characteristics, including baseline haematocrit level (38.4% vs 40.7%, p=0.681). The authors observed no significant difference in post-operative haematocrit levels between the two intervention groups (p=0.776). Patients in both groups had lower mean haematocrit levels after treatments than their baseline levels, with a mean reduction in the partial nephrectomy group nearly doubling that reported in the cryotherapy group (6.1% vs 3.3%). However, the statistical as well as clinical difference of the mean changes in serum haematocrit level between the two groups was undetermined due to a lack of primary data. A comparison between the pre-treatment and post-treatment haemoglobin levels was performed by Caviezel et al (2008) in a case series of seven patients who received percutaneous cryotherapy for renal tumours. The authors reported a decrease of 0.3 g/dL (from 13.9 g/dL to 13.6 g/dL) in mean serum haemoglobin level after cryotherapy, and observed no statistically significant mean change (p>0.05).

Table 53 Serum haematocrit level and haemoglobin level before and after cryotherapy for presumed renal cancer

Study	Evidence level and quality[a]	Number of patients	Intervention	Mean level		
				Pre-treatment	Post-treatment	Mean change
Serum haematocrit level						
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 3/4 R: 2/5	15	Laparoscopic cryotherapy	38.4±3.2%	35.1±3.9%	–3.3 %
		15	Laparoscopic partial nephrectomy	40.7±3.5%	34.6±4.1%	–6.1%
		Mean difference (95% CI)		–2.3% (–4.81%, 0.21%)	0.5% (–2.49%, 3.49%)	2.9%
		Mean quotient (95% CI)		0.94 (0.89, 1.01)	1.01 (0.93, 1.11)	0.54
		p-value		0.681	0.766	n/a
Serum haemoglobin level						
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	13.9 g/dL (range: 12.1–16.0 g/dL)	13.6 g/dL (range: 12.0–14 g/dL)	–0.3 g/dL (*p* >0.05)

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 ranked as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome)

CI: confidence interval n/a: not available

Serum creatinine level

Measurement of serum creatinine level, as an estimate of glomerular filtration rate, has been widely used as an indirect measure of renal function in clinical practice: an abnormal rise in serum creatine level indicates a loss of kidney function (Perrone et al 1992). Serum creatinine levels, before and after argon-based cryotherapy, were reported by one controlled study (level III-2 intervention evidence) and nine case series (level IV intervention evidence) (Table 54 and Table 55). Levels after cryotherapy were between 0.05 mg/dL less and 0.23 mg/dL more than their baseline values. These changes were not statistically significant.

In O'Malley et al's (2007) moderate-quality study, patients in the laparoscopic cryotherapy group and those in the laparoscopic partial nephrectomy group were well matched for each patient characteristic, including their pre-procedural serum creatinine levels (1.17 mg/dL vs 1.21 mg/dL, p=0.681). After treatment the mean post-procedural creatinine levels increased by 0.02 mg/dL in patients who underwent laparoscopic cryotherapy, and decreased by 0.03 mg/dL in the laparoscopic partial nephrectomy group. However, no significant difference in post-treatment serum creatinine levels was observed between the two intervention groups (p=0.891).

Table 54 Serum creatinine levels before and after cryotherapy for presumed renal cancer (controlled study)

Study	Evidence level and quality[a]	Number of patients	Intervention	Serum creatinine level		
				Pre-treatment	Post-treatment	Mean change
3rd generation						
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 3/4 R: 2/5	15	Laparoscopic cryotherapy	Mean: 1.17±0.33 mg/dL	Mean: 1.19±0.29 mg/dL	0.02 mg/dL
		15	Laparoscopic partial nephrectomy	Mean: 1.21±0.16 mg/dL	Mean: 1.18±0.24 mg/dL	–0.03 mg/dL
		Mean difference (95% CI)		–0.040 mg/dL (–0.234 mg/dL, –0.154 mg/dL)	0.010 mg/dL (–0.189 mg/dL, 0.209 mg/dL)	0.05 mg
		Mean quotient (95% CI)		0.967 (0.812, 1.131)	1.008 (0.850, 1.191)	–0.667
		p-value		p=0.681	p=0.891	n/a

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome)

CI: confidence interval; n/a: not available

Of the nine descriptive studies, the good-quality study with the largest sample size was by Wright et al (2007). In a total of 32 patients with 35 renal tumours, the mean creatinine level rose slightly from 1.17 mg/dL (SD = 0.33 mg/dL) at baseline to 1.19 mg/dL (SD = 0.29 mg/dL) post-procedurally (p=0.38). The greatest serum creatinine level change was reported by Wyler et al (2007). In this moderate-quality case series of 14 patients, an increase of 0.23 mg/dL in mean serum creatinine level from the baseline 1.22 mg/dL was observed 1 day after cryotherapy; afterwards the mean creatinine level dropped from

1.45 mg/dL on the first day to 1.24 mg/dL on day 3 post-operatively. The authors reported a serum creatinine level of 1.37 mg/dL 1 year after cryotherapy and observed no significant mean changes in serum creatinine levels during the first-year follow-up period (p=0.69). The only study that reported a reduction in mean serum creatinine level after cryotherapy was by Permpongkosol et al (2006). In this case series 23 renal malignancies were treated by 21 percutaneous cryotherapy procedures. The mean creatinine level decreased from 1.49 mg/dL pre-procedurally to 1.44 mg/dL after cryotherapy; statistical analysis was not performed due to the lack of original data. Furthermore, the actual change in serum creatinine levels in patients with small (<4 cm) renal cancer was not available from this study, since one patient with a renal tumour larger than 4 cm was also included in the mean creatinine level calculation.

Table 55 Serum creatinine levels before and after cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of patients	Intervention	Mean serum creatinine level		
				Pre-treatment	Post-treatment	Mean change
3rd generation						
(Wright et al 2007)	Level IV Quality: 4.5/6 Case series	32 (35 tumours)	Laparoscopic cryotherapy	1.3 mg/dL (range: 0.9–2.3 mg/dL)	1.5 mg/dL (range: 1.1–2.3 mg/dL)	0.2 mg/dL (p=0.38)
(Polascik et al 2007)[a]	Level IV Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	n/a	n/a	Median change: 0.1 mg/dL (range: 0.4–1.8 mg/mL)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	1.4 mg/dL (range: 0.7–2.0 mg/dL)	1 day: 1.5 mg/dL (range: 0.8–2.0 mg/dL)	0.1 mg/dL (p>0.05)
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	1.22±0.72 mg/dL	1 day: 1.45±0.74 mg/dL	0.23 mg/dL
					3 days: 1.24±0.62 mg/dL	0.02 mg/dL
					1 year: 1.37±0.67 mg/dL	0.15 mg/dL (p=0.69)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	23 (30 tumours)	Laparoscopic cryotherapy	1.15 mg/dl	1 day: 1.17 mg/dL	0.02 mg/dL (p=0.462)
					11 months: 1.18 mg/dL	0.03 mg/dL
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 tumours)	Laparoscopy-assisted percutaneous cryotherapy	1.0 mg/dL (range: 0.7–1.2 mg/dL)	n/a	n/a (p=0.25)
2nd generation						
(Shingleton & Sewell 2003)	Level IV Quality: 4.5/6 Case series	10	Percutaneous cryotherapy	0.21±0.09 mg/dL (range: 0.05–0.41 mg/dL)	0.23±0.13 mg/dL (range: 0.06–0.54 mg/dL)	0.02 (p=0.644)[b]

(Permpongkosol et al 2006)	Level IV Quality: 4/6 Retrospective case series	21 (23 tumours)[c]	Percutaneous cryotherapy	1.49 mg/dL (range: 0.5–3.8 mg/dL)	1.44 mg/dL (range: 0.6–3.7 mg/dL)	–0.05 mg/dL
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Case series Prospective case series	8	Laparoscopic cryotherapy	1.3±0.6 mg/dL (range: (0.5–2.3 mg/dL)	5–16 months: 1.3±0.7 mg/dL (range: 0.6–2.6 mg/dL)	0.1±0.3 mg/dL (range: 0.5–0.2 mg/dL)

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] Statistical significance of differences calculated by two-tailed paired t-test; [c] One patient with a tumour >4 cm

n/a: not available

Pain control requirements

Two controlled studies compared pain control requirements between cryotherapy and RFA, with data on intra-operative anaesthesia provided by both studies, while post-operative analgesia usage was investigated in one of them (Table 56).

In a good-quality study by Allaf et al (2005), patients in the percutaneous cryotherapy group (n=10) and those in the percutaneous RFA group (n=14) were matched for demographic characteristics, tumour size and tumour location. For both cryotherapy and RFA, fentanyl and midazolam were used intravenously to induce conscious sedation. The requirements of fentanyl and midazolam for percutaneous cryotherapy were 75 μg and 1.6 mg, respectively, which were significantly less than their use for percutaneous RFA (fentanyl: 165 μg, $p<0.001$; midazolam: 2.6 mg, $p=0.026$). In the RFA group, one patient required general anaesthesia, another needed additional sedative and analgesic drugs, and a percutaneous RFA procedure for a third patient was terminated prematurely due to excessive pain and bradycardia; whereas none of the patients in the cryotherapy group required any alternate or supplemental anaesthetics. The authors concluded that percutaneous cryotherapy was associated with reduced requirements for pain control when compared to percutaneous RFA.

Bandi et al (2008) examined intra-operative as well as post-operative pain control requirements among laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA. Patients in the three intervention groups were matched for demographic parameters but not for tumour size: renal lesions ablated by laparoscopic cryotherapy were larger than those treated with percutaneous ablation (2.6 cm vs 2.2 cm, $p<0.05$). In this study the mean anaesthesia time for laparoscopic cryotherapy (247 minutes) was significantly longer than that for either of the two percutaneous ablation procedures (percutaneous cryotherapy: 148 minutes, $p<0.001$; percutaneous RFA: 158 minutes, $p<0.001$). However, whether the statistically significant difference in anaesthesia time was attributable to various surgical approaches was indeterminable owing to the heterogeneity in pre-treatment tumour sizes among intervention groups. It was also reported that opioid analgesic requirements were not significantly different among laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA ($p>0.05$), although there was a trend for less opioid use in the two percutaneous ablation groups.

Table 56 Pain control requirements for cryotherapy for presumed renal cancer

Study	Evidence level and quality[a]	Number of patients	Pain control requirements		Mean/risk difference	p-value
2nd or 3rd generation						
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 4/4 R: 2/5	73	**LCT (n=58)**	**RFA (n=15)**	89 minutes	<0.001
			Anaesthesia time			
			Mean: 247 minutes	Mean: 158 minutes		
	Clin I: 4/4 R: 2/5		*Opioid use (morphine equivalents)*		15 mg	>0.05
			Median: 19 mg	Median: 4 mg		
	Clin I: 3/4 R: 2/5	35	**PCT (n=20)**	**RFA (n=15)**	–10 minutes	>0.05
			Anaesthesia time			
			Mean: 148 minutes	Mean: 158 minutes		
	Clin I: 3/4 R: 2/5		*Opioid use (morphine equivalents)*		1 mg	>0.05
			Median: 5 mg	Median: 4 mg		
2nd generation						
(Allaf et al 2005)	Level III-2 Quality: 4.5/6 Matched-pairs retrospective cohort study Clin I: 2/4 R: 2/5	24	**PCT (n=10)**	**RFA (n=14)**	–90 µg	<0.001
			Fentanyl use			
			Mean: 75 µg (range: 50–150 µg)	Mean: 165 µg (range: 125–300 µg)		
	Clin I: 2/4 R: 2/5		*Midazolam use*		–1.3 mg	0.026
			Mean: 1.6 mg (range: 1.0–5.0 mg)	Mean: 2.9 mg (range: 1.0–6.0 mg)		
	Clin I: 4/4 R: 2/5		*General anaesthetics needed*		–0.07 (–0.07, 0.06)	1.000[b]
			0/10	1/14 (1.7%)		
	Clin I: 4/4 R: 2/5		*Supplemental sedation and analgesia needed*		–0.07 (–0.07, 0.06)	1.000[b]
			0/10	1/14 (1.7%)		
	Clin I: 4/4 R: 2/5		*Premature termination of procedure*		–0.071 (–0.07, 0.06)	1.000[b]
			0/10	1/14 (1.7%)		

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Summary – What is the safety of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?

Since, in most cases, renal biopsy is not carried out before treatment, cryotherapy was assessed in a population of patients with *presumed* small localised renal cancer.

Thirty-five studies were identified that reported on the safety of argon-based cryotherapy for renal tumours. Of these, three controlled studies compared cryotherapy (laparoscopic or percutaneous) with partial nephrectomy or RFA (level III-2 intervention evidence). The remaining studies were 16 case series (level IV intervention evidence) and 16 case reports. In general, studies assessing the safety of cryotherapy were relatively small, with the largest study reporting on 58 cryotherapy procedures (Bandi et al 2008).

One procedure-related death was reported by Romero et al (2007) in a case report. The patient was an 87-year-old female with multiple respiratory and cardiovascular diseases. She underwent second-generation cryotherapy and developed pleural effusion on day 3. This caused the patient to halt her anticoagulation therapy for atrial fibrillation. She received fresh frozen plasma and additional blood products. The woman died of pulmonary embolism involving the right main pulmonary artery 20 days after cryotherapy.

O'Malley et al (2007), in a moderate-quality matched-pairs cohort study, compared adverse events between laparoscopic cryotherapy and laparoscopic partial nephrectomy, and reported no significant difference in either major post-operative complication rate or minor complication rate between the two groups. The safety of cryotherapy relative to RFA was investigated by Bandi et al (2008) in a poor-quality controlled study. The authors discovered no difference in major intra-operative or post-operative complication rates among laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA.

Between 0 and 28.6 per cent of patients had intra-operative complications, including bowel injury, urine leak, bleeding, haematoma and severe respiratory distress. The highest rate was reported by Wyler et al (2007). In this study four out of 14 (28.6%) patients experienced bleeding during cryotherapy procedures, whereas the other studies reported that major intra-operative complications occurred in no more than 3.4 per cent of the cryotherapy procedures.

Major post-operative complications developed in 0 to 21.4 per cent of patients. Most of the significant complications were cardiovascular or respiratory diseases such as myocardial infarction, atrial fibrillation, heart failure, pneumonia and respiratory failure. This might correspond to the patient selection criteria for cryotherapy in clinical practice, where the procedure is usually reserved for patients of advanced age, and with comorbidities, who have already had heart or lung diseases or are subject to these diseases after surgical treatments.

The majority of reported minor complications, which included small perirenal haematoma, transient urine leak, neuropraxia, flank muscle laxity and so on, were self-limiting and did not require medical intervention. O'Malley et al (2007) discovered significantly less estimated blood loss for laparoscopic cryotherapy than for laparoscopic partial nephrectomy (mean difference: –163 mL; 95% CI: –261 mL, –65 mL). However, the volume of blood loss between cryotherapy (laparoscopic or percutaneous) and percutaneous RFA was not significantly different (Bandi et al 2008). The mean estimated blood loss from

cryotherapy ranged between 10 mL and 103 mL, with an extreme of 1000 mL in one case. There was a trend towards less blood loss for third-generation cryotherapy than second-generation cryotherapy. Reductions in serum haematocrit level and serum haemoglobin level were discovered after cryotherapy, but with no significant mean changes. After cryotherapy there were minor changes in serum creatinine levels relative to their baseline values, with no statistical significance.

Allaf et al (2005), in a good-quality study, reported reduced requirement for analgesia in the percutaneous cryotherapy group compared to the RFA group. However, in the other poor-quality comparative study, Bandi et al (2008) did not find any significant difference in opioid use among laparoscopic cryotherapy, percutaneous cryotherapy and RFA.

Is it effective?

Studies were included in this assessment of the effectiveness of cryotherapy for renal cancer according to the criteria outlined in Box 5.

Box 5 Inclusion criteria for studies assessing the effectiveness of cryotherapy for renal cancer

Research question	
What is the effectiveness of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?	
Characteristics	**Criteria**
Population	Patients with presumed small (<4 cm) localised renal cancer
Intervention	Cryotherapy (argon-based)
Comparators	Partial nephrectomy, RFA or surveillance
Outcome	Primary – overall survival or mortality rate, disease-specific survival Secondary – disease-free survival (determined by imaging or biopsy), local recurrence, progression-free survival, quality of life, symptom control (eg haematuria), cryolesion size, length of hospital stay, operative time
Study design	Randomised or non-randomised controlled trials, cohort studies, registers, case series, case reports or systematic reviews of these study designs. Non-systematic reviews, abstracts, editorials; animal, in-vitro and laboratory studies were excluded.
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.

The patient inclusion criterion for evaluating the effectiveness of cryotherapy was revised to be consistent with assessment of the safety of cryotherapy. Articles that investigated cryotherapy for the treatment of *presumed* small (<4 cm) localised renal cancer (not only those with confirmed malignancies) were included for assessment.

There was an attempt to exclude those studies where an overlap of results was evident, but there may still be some overlap left in study populations in studies from the same co-authors or institutions.

Primary effectiveness outcomes

Overall survival and disease-specific survival

Data on overall survival rates and disease-specific survival rates were provided by one controlled study (level III-2 intervention evidence) and five case series (level IV intervention evidence). Within these studies the overall survival rates were between 87.5 and 100 per cent during follow-up periods of 9.6 to 22 months. Since all identified deaths were caused by reasons other than renal tumours, a disease-specific survival rate of 100 per cent was achieved across all studies (Table 57 and Table 58).

In Bandi et al's (2008) controlled study, patients who were treated with laparoscopic cryotherapy had larger tumours (2.6 cm vs 2.2 cm, $p<0.05$) and longer follow-up periods (22 months vs 13 months) than those receiving percutaneous ablation procedures (cryotherapy or RFA) for renal tumours. No significant difference in overall survival rates was observed between the two surgical approach groups ($p=0.738$). During the follow-up periods, seven patients in the laparoscopic cryotherapy group and three in the

percutaneous ablation group died from unrelated causes, resulting in a 100 per cent disease-specific survival rate in both groups. However, a comparison of overall survival rates between cryotherapy (laparoscopic or percutaneous) and RFA was not available from this study, as survival data for patients receiving percutaneous cryotherapy and those undergoing percutaneous RFA were not provided separately.

Table 57 Overall survival and disease-specific survival after cryotherapy for presumed renal cancer (controlled study)

Study	Evidence level and quality[a]	Number of patients	Follow-up period: overall survival and disease-specific survival (per patient)		Risk difference (95% CI)	Relative risk (95% CI)	p-value[b]
2nd or 3rd generation							
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 3/4 R: 1/5	93	**LCT (n=58)**	**PA (n=35)**	0.04 (–0.10, 0.12)	1.41 (0.42, 4.86)	0.738
			Overall survival				
			22 months (mean): 51/58 (87.9%)	13 months (mean): 32/35 (91.4%)			
	Clin I: 3/4 R: 1/5		*Disease-specific survival*		0.00 (0.00, 0.00)	1.00 (1.00, 1.00)	1.000
			22 months (mean): 58/58 (100%)	13 months (mean): 35/35 (100%)			

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; PA: percutaneous ablation = percutaneous cryotherapy + percutaneous radiofrequency

Two case series reported overall survival after third-generation cryotherapy for renal tumours. Polascik et al (2007), in a good-quality case series of 26 laparoscopic cryotherapy procedures for 28 renal tumours, did not report any deaths during a follow-up period of 21 months. In the other case series with the same length of follow-up as that in Polascik et al's study, two out of 14 patients (87.5%) died from unrelated causes, which were myocardial infarction at 2 months and cerebrovascular incident at 13 months post-operatively (Wyler et al 2007).

Of the three case series investigating second-generation cryotherapy, one with the highest quality but the smallest sample size (n=10) reported an overall survival rate of 100 per cent during its 19.3-month follow-up period (Shingleton & Sewell 2003). Survival following percutaneous cryotherapy and laparoscopic cryotherapy was compared by Hinshaw et al (2008) in a moderate-quality study involving 90 patients. Within a mean follow-up period of 14 months, no patient died in the percutaneous cryotherapy group, whereas six patients receiving laparoscopic cryotherapy for renal tumours died from unrelated causes—one after a myocardial infarction and five after other malignancies, including lung cancer, hepatic adenocarcinoma, oesophageal cancer, pancreatic cancer and squamous cell cancer. However, no significant difference in overall survival rates was observed between the two cryotherapy approaches (p=0.173). In the other case series by Moon et al (2004), 14 out of 16 patients (87.5%) survived during a mean follow-up period of 9.6 months, with two patients dying from vascular diseases.

Table 58 Overall survival and disease-specific survival after cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of patients	Intervention	Follow-up period: overall survival and disease-specific survival (per patient)
3rd generation				
(Polascik et al 2007)[a]	Level IV Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	Overall survival 20.9 months (median): 26/26 (100%) Disease-specific survival 20.9 months (median): 26/26 (100%)
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy -assisted cryotherapy: 13 Open cryotherapy: 1	Overall survival 21 months (mean): 12/14 (87.5%) Death from unrelated causes: 2 Myocardial infarction: 1 Cerebrovascular incident: 1 Disease-specific survival 21 months (mean): 14/14 (100%)
2nd generation				
(Shingleton & Sewell 2003)	Level IV Quality: 4.5/6 Retrospective case series	10	Percutaneous cryotherapy	Overall survival 19.3 months (mean): 10/10 (100%) Disease-specific survival 19.3 months (mean): 10/10 (100%)
(Hinshaw et al 2008)[b]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	Overall survival 14.5 months (mean): 30/30 (100%) Disease-specific survival 14.5 months (mean): 30/30 (100%)
		60	Laparoscopic cryotherapy	Overall survival 14.6 months (mean): 54/60 (90.0%) (LCT vs PCT: p=0.173)[c] Death from unrelated causes: 6 Myocardial infarction: 1 Lung cancer: 1 Hepatic adenocarcinoma: 1 Oesophageal cancer: 1 Pancreatic cancer: 1 Squamous cell cancer: 1 Disease-specific survival 14.6 months (mean): 60/60 (100%)
(Moon et al 2004)[b]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Overall survival 9.6 months (mean): 14/16 (87.5%) Death from unrelated causes: 2 Vascular disease: 2 Disease-specific survival 9.6 months (mean): 16/16 (100%)

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] May be overlap between patient series; [c] Statistical significance of differences calculated by two-tailed Fisher's exact test

LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy

Secondary effectiveness outcomes

Box 5 outlines the secondary measures of effectiveness that were sought for in the literature on cryotherapy for presumed renal cancer. No studies reported on the impact of cryotherapy on quality of life.

Tumour persistence

The detection of disease persistence following surgical ablation of renal tumours mainly relies on follow-up imaging. According to the definition from the International Working Group on Image-Guided Tumour Ablation, tumour persistence refers to persistent enhancing lesions revealed by post-operative imaging examinations, usually contrast-enhanced CT or MRI (Goldberg et al 2003).

Data on tumour persistence rates after cryotherapy for presumed renal cancer were provided by 15 studies, including one controlled study (level III-2 intervention evidence) and 14 case series (level IV intervention evidence) (Table 59 and Table 60). As reported by these studies, between 0 and 13.6 per cent of renal tumours were inadequately treated by cryotherapy, as determined by follow-up image examinations.

In Bandi et al's (2008) poor-quality controlled study, patients in the laparoscopic cryotherapy group, percutaneous cryotherapy group and percutaneous RFA group were matched for patient characteristics, except that there were slightly larger tumours in the laparoscopic cryotherapy group than in the other two percutaneous ablation groups (2.6 cm vs 2.2 cm, $p<0.05$). The authors reported tumour persistence rates of 3.4 per cent, 10.0 per cent and 0 per cent for laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA, respectively, with no significant difference among the three groups (laparoscopic cryotherapy vs percutaneous RFA: $p=1.000$; percutaneous cryotherapy vs percutaneous RFA: $p=0.496$).

Table 59 Tumour persistence after cryotherapy for presumed renal cancer (controlled study)

Study	Evidence level and quality[a]	Number of tumours	Follow up: tumour persistence (per tumour)		Risk difference (95% CI)	Relative risk (95% CI)	p-value[b]
2nd or 3rd generation							
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 4/4 R: 2/5	73	**LCT (n=58)** Early follow-up: 2/58 (3.4%)	**RFA (n=15)** Early follow-up: 0/15	0.03 (–0.07, 0.03)	Infinity (0.14, infinity)	1.000
	Clin I: 4/4 R: 2/5	35	**PCT (n=20)** Early follow-up: 2/20 (10.0%)	**RFA (n=15)** Early follow-up: 0/15	0.10 (–0.05, 0.10)	Infinity (0.41, infinity)	0.496

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Of the five case series that reported tumour persistence following third-generation cryotherapy for renal tumours, the good-quality study with the largest sample size was by Wright et al (2007). In this case series of 35 renal tumours treated with 32 laparoscopic cryotherapy procedures, two continued enhancing lesions were revealed by contrast-enhanced CT 3 months after the procedure, resulting in a tumour persistence rate of 5.7 per cent. In addition, the authors found that the endophytic status of a tumour predicted disease persistence (multivariate analysis, $p<0.05$). Two of the three patients with endophytic lesions had persistent tumours, whereas none of the 32 exophytic tumours persisted. The high rate of tumour persistence in endophytic tumours was attributable to difficulties in targeting these lesions entirely on intra-procedural

ultrasound without any visual clues. Tumour persistence was also reported by Beemster et al (2008) in a moderate-quality case series of 26 laparoscopic cryotherapy procedures. Follow-up CT revealed one (3.8%) residual enhancing lesion at the location of the original tumour within the first 3 months. The persistent tumour was managed with nephrectomy, and thereafter histologically diagnosed as renal cancer. Authors of the other three case series did not discover tumour persistence in their moderate- to good-quality studies (Caviezel et al 2008; Gore et al 2005; Lehman et al 2008).

Tumour persistence rates in patients who underwent second-generation cryotherapy were reported by nine studies. In a good-quality case series of 31 laparoscopic cryotherapy procedures for 36 renal tumours, no enhancement of the ablated tumours was detected by radiographic imaging of the kidney within 36 months post-procedure (Weld et al 2007). The other high-quality study by Shingleton and Sewell (2003) reported that, during a mean follow-up period of 9.3 months, one out of ten tumours showed persistent enhancement on CT or MRI, giving a tumour persistence rate of 10.0 per cent. The renal lesion that persisted after cryotherapy was originally treated with only a single cryoprobe, which possibly accounted for the incomplete percutaneous-approached ablation. The highest tumour persistence rate (13.6%) was reported by Permpongkosol et al (2006) in a moderate-quality case series of 20 percutaneous cryotherapy procedures for 22 malignant renal tumours. A total of three tumours were not completely treated—two were technical failures as described later in the 'Technical success' section (page 168), and the third renal lesion was located at the tip of the lower pole. It was difficult to place the cryoprobes in this tumour, as the kidney dodged from the needles with each attempted cryoprobe insertion.

Tumour persistence rates were compared between the two cryotherapy approaches (percutaneous and laparoscopic) in a moderate-quality study by Hinshaw et al (2008). Despite the larger tumour size in the laparoscopic cryotherapy group (2.5 cm vs 2.1 cm, p=0.04), the authors discovered no significant difference in tumour persistence rates between the two cryotherapy groups (p=0.68), although there was a trend towards a lower persistence rate among patients who underwent laparoscopic cryotherapy (6.7% vs 10.0%). All three residual renal tumours in the percutaneous cryotherapy group and two of the four persistent renal lesions in the laparoscopic cryotherapy group were treated successfully with a second percutaneous cryotherapy procedure. The remaining two patients did not undergo re-treatment: one died from unrelated causes before a second treatment could be given, and the other was followed up with further renal imaging due to inconclusive findings on the initial imaging.

Table 60 Tumour persistence after cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of tumours	Intervention	Follow-up imaging study	Follow-up period: tumour persistence (per tumour)
3rd generation					
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	35 (in 32 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT	3 months: 2/35 (5.7%)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	28 months (mean): 0/7

(Beemster et al 2008)	Level IV Quality: 3.5/6 Case series	26	Laparoscopic cryotherapy	Contrast-enhanced CT	3 months: 1/26 (3.8%)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	30 (in 23 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	3 months: 0/30
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	5 (in 4 patients)	Laparoscopy-assisted percutaneous cryotherapy	Contrast-enhanced CT	6 months: 0/5
2nd generation					
(Weld et al 2007)[a]	Level IV Quality: 5.5/6 Prospective case series	36 (in 31 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	36 months: 0/36
(Shingleton & Sewell 2003)	Level IV Quality: 4.5/6 Retrospective case series	10	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	19.3 (mean): 1/10 (10.0%)
(Georgiades et al 2008)	Level IV Quality: 4/6 Case series	45	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	0/45[b]
(Permpongkosol et al 2006)[c]	Level IV Quality: 4/6 Retrospective case series	22 (in 20 patients)	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	1.8–3.6 months: 3/22 (13.6%)
(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	Contrast-enhanced CT	3 months: 0/3
(Gupta et al 2006)[c]	Level IV Quality: 3.5/6 Retrospective case series	14 (in 10 patients)	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	8.3 months (mean): 0/14
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	Contrast-enhanced CT	5–16 months: 0/8
(Hinshaw et al 2008)[d]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	n/a	6 months: 3/30 (10.0%)
		60	Laparoscopic cryotherapy	n/a	6 months: 4/60 (6.7%) (LCT vs PCT: p=0.68)
(Moon et al 2004)[d]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	9.6 months (mean): 0/16

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] Follow-up period was not available; [c] May be overlap between patient series; [d] May be overlap between patient series

CT: computed tomography; MRI: magnetic resonance imaging; LCT: laparoscopic cryotherapy; n/a: not available; PCT: percutaneous cryotherapy

Local tumour progression

Local tumour progression, as defined by the International Working Group on Image-Guided Tumour Ablation, is a growth of tumour size or new enhancement at the site of the previous ablated tumour on follow-up imaging studies (Goldberg et al 2003). The rates of local tumour progression following cryotherapy were between 0 and 25.0 per cent, as reported by 17 studies described in Table 61 and Table 62.

In a moderate-quality controlled study, O'Malley et al (2007) compared local tumour progression between a laparoscopic cryotherapy group and a laparoscopic partial nephrectomy group, where patients were well matched for demographic characteristics as well as tumour location and size. The authors observed no local tumour progression in either of the two groups during a follow-up period of less than 12 months. In the other controlled study, which involved 58 laparoscopic cryotherapy procedures, 20 percutaneous cryotherapy procedures and 15 percutaneous RFA procedures, the patients in the laparoscopic cryotherapy group had larger renal tumours than those in the other two percutaneous ablation groups (2.6 cm vs 2.2 cm, $p<0.05$). No significant difference in local tumour progression rates was observed among the three intervention groups ($p=1.000$); however, during follow-up (ranging from 12 to 22 months), one case of local tumour progression (1.7%) was discovered in the laparoscopic cryotherapy group, whereas no patients in the other two groups had local tumour progression (Bandi et al 2008).

Table 61 Local tumour progression after cryotherapy for presumed renal cancer (controlled studies)

Study	Evidence level and quality[a]	Number of tumours	Follow-up period: local tumour progression (per tumour)		Risk difference (95% CI)	Relative risk (95% CI)	p-value[b]
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 3/4 R: 2/5	30	**LCT (n=15)** 11.9 months (mean): 0/15	**LPN (n=15)** 9.8 months (mean): 0/15	0.00 (0.00, 0.00)	Not calculable	1.000
2nd or 3rd generation							
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 4/4 R: 2/5	73	**LCT (n=58)** 22 months (mean): 1/58 (1.7%)	**RFA (n=15)** 15 months (mean): 0/15	0.02 (–0.05, 0.02)	Infinity (0.07, infinity)	1.000
	Clin I: 3/4 R: 2/5	35	**PCT (n=20)** 12 months (mean): 0/20	**RFA (n=15)** 15 months (mean): 0/15	0.00 (0.00, 0.00)	Not calculable	1.000

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Six case series reported local tumour progression after third-generation cryotherapy for renal tumours. In a good-quality case series of 35 renal tumours in 32 patients, two new enhancing lesions, ipsilateral to previous ablated tumours, were detected on contrast-

enhanced CT in two patients, one at 9 months and the other at 12 months post-procedurally, resulting in a local tumour progression rate of 6.3 per cent during an 18-month follow-up period (Wright et al 2007). Authors of the other two good-quality case series did not discover any local tumour progression within their follow-up periods of 21 to 28 months (Caviezel et al 2008; Polascik et al 2007). A moderate-quality study by Gore et al (2005) reported that none of the five renal tumours ablated in four laparoscopy-assisted percutaneous cryotherapy procedures showed enhancement on contrast-enhanced CT at 3 months post-operatively. However, one 0.7 cm enhancing lesion was detected on repeat CT 6 months after cryotherapy. The progressing renal lesion was managed with percutaneous RFA, and there was no evidence of tumour persistence or local tumour progression within 6 months after the salvage treatment.

A total of nine cases of local tumour progression following second-generation cryotherapy were reported by six case series. In a good-quality study with the longest follow-up period (46 months), one new enhancing lesion with a diameter of 2 cm was revealed by contrast-enhanced CT 36 months after cryotherapy, resulting in a tumour progression rate of 2.8 per cent in a total of 36 renal tumours. The patient who had local tumour progression opted for active surveillance with imaging follow-up due to the worsening of comorbidities (Weld et al 2007). The other high-quality study by Shingleton and Sewell (2003) reported that two out of 10 patients had renal tumour progression during a 19-month follow-up period. In one patient a 0.5-cm enhancing lesion was detected by imaging of the kidney at 22 months post-operatively. The other patient developed two large renal tumours (both >4.5 cm), ipsilateral to the previous ablated tumour, after cryotherapy. Shingleton and Sewell (2002a), in a good-quality case series of four renal tumours treated with three percutaneous cryotherapy procedures, discovered one enhancing renal lesion on a 6-month CT scan, resulting in a local tumour progression rate of 25.0 per cent in this small-sample case series. Two cases of local tumour progression were reported by Permpongkosol et al (2006) in a moderate-quality case series of 22 malignant renal tumours in 20 patients during a 12-month follow-up period. Both patients had relatively larger tumour size (3.9 cm) before cryotherapy and elected for active surveillance of the progressing renal tumours with kidney imaging because of their advanced age. Hinshaw et al (2008) observed no significant difference in local tumour progression rates between laparoscopic cryotherapy and percutaneous cryotherapy ($p=1.0$). The only case of tumour progression was discovered at 14 months after a laparoscopic cryotherapy procedure, and was treated with an open partial nephrectomy. Post-operative histology showed renal cell carcinoma. Ten months after the salvage surgery, this patient developed another locally progressing lesion and was subsequently managed with percutaneous cryotherapy. The patient also received systemic treatment and was still alive 66 months after the original cryotherapy. The other two cases of local tumour progression were reported by Bolte et al (2006) in a moderate-quality case series of 18 laparoscopic cryotherapy procedures. One renal lesion was diagnosed as renal cancer by percutaneous biopsy and was removed by an open partial nephrectomy; the other renal tumour was followed up by imaging examinations owing to the patient's serious comorbidities.

Table 62 Local tumour progression after cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of tumours	Intervention	Follow-up imaging study	Follow-up period: local tumour progress (per tumour)
3rd generation					
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	35 (32 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT	18 months (median): 2/35 (6.3%)
(Polascik et al 2007)[a]	Level IV Quality: 4.5/6 Case series	28 (26 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	20.9 months (median): 0/28
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	28 months (mean): 0/7
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	Contrast-enhanced CT	21 months (mean): 0/13
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	30 (23 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	>12 months: 0/8
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	5 (4 patients)	Laparoscopy-assisted percutaneous cryotherapy	Contrast-enhanced CT	8–17 months: 1/5 (20.0%)
2nd generation					
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	36 (31 patients)	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	45.7 months (mean): 1/36 (2.8%)
(Shingleton & Sewell 2003)[c]	Level IV Quality: 4.5/6 Retrospective case series	10	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	19.3 (mean): 2/10 (20.0%)
(Shingleton & Sewell 2002a)[c]	Level IV Quality: 4.5/6 Case series	3 (4 tumours)	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	13 months (mean): 1/3 (25.0%)
(Permpongkosol et al 2006)	Level IV Quality: 4/6 Retrospective case series	22 (21 patients)	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	12.3 months (mean): 2/22 (9.1%)
(Atwell et al 2008)	Level IV Quality: 3.5/6 Retrospective case series	86	Percutaneous cryotherapy	Contrast-enhanced CT or MRI	3–39 months: 0/86
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	Contrast-enhanced CT	5–16 months: 0/8

(Hinshaw et al 2008)[d]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	n/a	14.5 months (mean): 0/30
		60	Laparoscopic cryotherapy	n/a	14.6 months (mean): 1/60 (1.7%) (PCT vs LCT: p=1.0)
(Bolte et al 2006)	Level IV Quality: 3/6 Retrospective case series	18	Laparoscopic cryotherapy	Contrast-enhanced MRI	6–48 months: 2/18 (11.1%)
(Moon et al 2004)[d]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	Contrast-enhanced CT or MRI	9.6 months (mean): 0/16

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura; [c] May be overlap between patient series [d] May be overlap between patient series

CT: computed tomography; MRI: magnetic resonance imaging; LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy; n/a: not available

Metastases

Data on disease metastases following argon-based cryotherapy for presumed renal cancer were provided by four studies as described in Table 63, all of which were case series of moderate to good quality (level IV intervention evidence).

In a good-quality study by Caviezel et al (2008), five renal malignancies and two angiomyolipomas were treated with percutaneous cryotherapy using a third-generation cryotherapy system. The authors discovered no metastasis within a mean follow-up period of 28 months. The study by Wyler et al (2007) was a moderate-quality case series of 14 renal tumours, including ten renal cell carcinomas, two angiomyolipomas and two tumours without definite histological diagnosis (one with inconclusive histology result and one with no histology). During a follow-up period of 21 months, one out of 14 patients had evidence of metastases. This patient had a surgical history of nephrectomy for multifocal renal malignancies and underwent cryotherapy for a contralateral renal malignancy. Retroperitoneal lymph node metastasis was revealed by imaging at 9 months after cryotherapy. Second-generation cryotherapy was used for 10 renal tumours in Shingleton and Sewell's (2003) study and 22 renal malignancies in Permpongkosol et al's (2006) case series. No case of metastasis was discovered in these two studies during follow-up periods ranging from 12 to 19 months.

Table 63 Metastases after cryotherapy for presumed renal cancer

Study	Evidence level and quality	Number of malignancies (total renal tumours)	Intervention	Follow-up period: metastases (per malignancy)
3rd generation				
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	5 (7)	Percutaneous cryotherapy	28 months (mean): 0/5
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	10 (14)	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	21 months (mean): 1/10 (10.0%)

2nd generation				
(Shingleton & Sewell 2003)	Level IV Quality: 4.5/6 Retrospective case series	n/a (10)	Percutaneous cryotherapy	19.3 months (mean): 0
(Permpongkosol et al 2006)	Level IV Quality: 4/6 Retrospective case series	22 (22)	Percutaneous cryotherapy	12.3 months (mean): 0/22

n/a: not available

Technical success

According to the standardised terminology and reported criteria adopted by the International Working Group on Image-Guided Tumour Ablation, a cryotherapy procedure for the treatment of a renal tumour is defined as having technical success if the tumour is treated according to protocol and completely covered by the ice ball, with a margin of at least 1 cm beyond the tumour, as determined by intra-procedural imaging examinations (Goldberg et al 2003).

The seven case series (level IV intervention evidence) that reported on the technical success of cryotherapy showed that between 91 and 100 per cent of cryotherapy procedures were technically successful (Table 64). No higher level of evidence was identified in the literature that compared technical success between cryotherapy and partial nephrectomy or RFA for the treatment of renal tumours.

Of the two good-quality case series investigating third-generation cryotherapy, one study by Wright et al (2007) reported a case of technical failure in a total of 35 renal tumours that were ablated in 32 laparoscopic cryotherapy procedures, resulting in a technical success rate of 97.1 per cent. In the other good-quality study, all of the seven percutaneous cryotherapy procedures were technically successfully performed (Caviezel et al 2008).

Technical success rates of second-generation cryotherapy were reported by five studies. In a moderate-quality case series by Permpongkosol et al (2006), 90.9 per cent of the 22 renal malignancies were technically successfully ablated by percutaneous cryotherapy procedures. Intra-operative CT revealed two tumours not being covered by ice balls 1 cm greater than tumour sizes. One of the technical failures was caused by the cryoprobes, which were too thin (2.2 mm) for a complete ablation. The other failure was attributed to the central location of the tumour, which made it impossible to be treated with a larger ice ball. Atwell et al (2008) also reported one case (out of 86) of technical failure due to a tumour located adjacent to the central structure of the kidney, resulting in a technical success rate of 98.8 per cent. Hinshaw et al (2008) compared technical success rates between percutaneous cryotherapy and laparoscopic cryotherapy in 90 patients. Renal tumours treated with laparoscopic cryotherapy were slightly larger than those ablated by percutaneous cryotherapy (2.5 cm vs 2.1 cm, p=0.04). In this study technical success rates were reported as 100 per cent and 98.3 per cent for percutaneous cryotherapy and laparoscopic cryotherapy, respectively, with no significant difference between the two groups (p=1.000). The technical failure discovered during a laparoscopic procedure was due to the location of the target tumour being too close to a large renal vein to be treated with a larger ice ball.

Table 64 Technical success for cryotherapy for presumed renal cancer

Study	Evidence level and quality	Number of tumours	Intervention	Technical success (per tumour)
3rd generation				
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	35 (32 procedures)	Laparoscopic cryotherapy	34/35 (97.1%)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	7/7 (100%)
2nd generation				
(Permpongkosol et al 2006)[a]	Level IV Quality: 4/6 Retrospective case series	22 (20 procedures)	Percutaneous cryotherapy	20/22 (90.9%)
(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	6/6 (100%)
(Atwell et al 2008)	Level IV Quality: 3.5/6 Retrospective case series	86	Percutaneous cryotherapy	85/86 (98.8%)
(Gupta et al 2006)[a]	Level IV Quality: 3.5/6 Retrospective case series	14 (10 procedures)	Percutaneous cryotherapy	14/14 (100%)
(Hinshaw et al 2008)	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	30/30 (100%)
		60	Laparoscopic cryotherapy	59/60 (98.3%) (PCT vs LCT: p=1.000)[b]

[a] May be overlap between patient series; [b] Statistical significance of differences calculated by two-tailed Fisher's exact test

LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy

Operative time

Operative time was reported by a total of 10 studies as described in Table 65 and Table 66, including two cohort studies (level III-2 intervention evidence) and eight case series (level IV intervention evidence). Within these studies the mean operative time for argon-based cryotherapy for presumed renal cancer ranged between 77 and 240 minutes.

Both of the moderate-quality controlled studies compared operative time between cryotherapy and partial nephrectomy. Patients in O'Malley et al's (2007) study were well matched for demographic parameters as well as clinical features between the two intervention groups. Tumours treated by laparoscopic cryotherapy and laparoscopic partial nephrectomy were all located on the peripheral of the kidney, with no difference in tumour size between the two intervention groups (p=0.524). The authors observed significantly less operative time for laparoscopic cryotherapy than for laparoscopic partial nephrectomy (152 minutes vs 248 minutes, p<0.001).

In the other controlled study by Link et al (2006), the tumour size in patients who underwent open partial nephrectomy was significantly larger than that in the laparoscopic cryotherapy group (3.3 cm vs 2.4 cm, p=0.002). A significant difference in operative time was reported between laparoscopic cryotherapy and open partial nephrectomy, with less time required for cryotherapy procedures (154 minutes vs 264 minutes, p<0.001). However, the authors observed no significant difference either in tumour size (p=0.431)

or in operative time (p=0.095) between the laparoscopic cryotherapy group and the laparoscopic partial nephrectomy group.

Table 65 Operative time for cryotherapy for presumed renal cancer (controlled studies)

Study	Evidence level and quality[a]	Number of procedures	Mean operative time		Mean difference (95% CI)	Mean quotient (95% CI)	p-value
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 1/4 R: 3/5	30	**LCT (n=15)** 152±37 minutes	**LPN (n=15)** 248±60 minutes	–96 minutes (–127 minutes, –65 minutes)	0.61 (0.51, 0.74)	<0.001
2nd or 3rd generation							
(Link et al 2006)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 2/4 R: 3/5	245	**LCT (n=28)** 154±41 minutes	**LPN (n=217)** 186±63 minutes	–32 minutes (–56 minutes, –8 minutes)	0.83 (0.74, 0.92)	0.010[b]
	Clin I: 1/4 R: 3/5	78	**LCT (n=28)** 154±41 minutes	**OPN (n=50)** 264±80 minutes	–110 minutes (–142 minutes, –78 minutes)	0.58 (0.51, 0.66)	<0.001[b]

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] Statistical significance of differences calculated by two-tailed unpaired *t* exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; OPN: open partial nephrectomy;

Of the eight case series that reported operative time for argon-based cryotherapy for renal tumours, the study by Wright et al (2007) had the largest sample of 32 laparoscopic cryotherapy procedures. In this high-quality case series the mean operative time was 115 minutes for third-generation cryotherapy for the treatment of 35 peripheral renal tumours with a mean diameter of 1.9 cm. The longest operative time was reported by Caviezel et al (2008). In this high-quality study a mean operative time of 240 minutes was required for percutaneous cryotherapy for small (mean of 2.1 cm) peripheral renal tumours. In Permpongkosol et al's (2006) case series a total of 22 malignant renal tumours were treated with second-generation cryotherapy. Although the mean tumour size in this study was the same as that in Caviezel et al's case series, the operative time was only one-third (77 minutes) of that reported by Caviezel et al.

Table 66 Operative time for cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of procedures	Intervention	Tumour location	Mean tumour size	Mean operative time
3rd generation						
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	32 (35 tumours)	Laparoscopic cryotherapy	Peripheral	1.9 cm	115 minutes (range: 60–210 minutes)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	Peripheral	2.1 cm	240 minutes (range: 160–280 minutes)
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperiton-eoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	Peripheral	2.8 cm	167 minutes (range: 120–200 minutes)
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 tumours)	Laparoscopic-assisted percutaneous cryotherapy	Peripheral	2.0 cm	125 minutes (range: 86–169 minutes)
2nd generation						
(Permpongkosol et al 2006) [a]	Level IV Quality: 4/6 Retrospective case series	20 (22 tumours)	Percutaneous cryotherapy	n/a	2.1 cm	77 minutes (range: 45–125 minutes)
(Goel & Kaouk 2008)	Level IV Quality: 4/6 Prospective case series	6	Laparoscopic cryotherapy	n/a	2.6 cm	170 minutes
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	n/a	2.6 cm	120 minutes (range: 90–180 minutes)
(Moon et al 2004)	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	n/a	2.6 cm	188 minutes (range: 131–440 minutes)

n/a: not available

Cryolesion size

Data on changes in cryoablated masses (cryolesions) following argon-based cryotherapy for presumed renal cancer were provided by six case series (level IV intervention evidence) (Table 67). Across these studies the cryolesion sizes at 3 months, instead of 1 day, after the procedure were used as the reference lesions, since the immediate post-procedural reactive inflammation and haemorrhage in the ablated lesion might influence the measurement of cryolesion size during early follow-up (Beemster et al 2008).

In Wyler et al's (2007) moderate-quality study involving 13 retroperitoneoscopy-assisted cryotherapy procedures and one open cryotherapy procedure, a continuous reduction in cryolesion size was observed during the first 36 months following third-generation

cryotherapy procedures. The mean diameter of cryolesions decreased by 24.1 per cent (from 2.9 cm to 2.2 cm), 34.5 per cent (from 2.9 cm to 1.9 cm) and 37.9 per cent (from 2.9 cm to 1.8 cm) in 12 months, 24 months and 36 months, respectively. Cryolesions also diminished in Beemster et al's (2008) case series of 26 renal tumours, from 2.7 cm at 3 months to 1.2 cm at 24 months post-operatively. In addition, the authors discovered that the reduction in cryolesion size was independent of histological diagnosis of renal tumours, with a mean decrease of 46 per cent for malignancies and 52 per cent for benign lesions 12 months after cryotherapy (statistical analysis was not performed due to the small sample size). Of the three studies investigating second-generation cryotherapy, the high-quality study with the largest sample size was by Weld et al (2007). In this study of 36 renal tumours, cryolesions decreased from 2.4 cm at 3 months to 1.2 cm at 24 months (50%) and to 0.6 cm at 36 months (75%).

Table 67 Cryolesion size after cryotherapy for presumed renal cancer

Study	Evidence level and quality	Number of tumours	Intervention	Mean pre-treatment tumour size	Follow-up period: mean cryolesion size	Mean change[a]
3rd generation						
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	2.8 cm (range: 2.0–4.0 cm)	3 months: 2.9±0.74 cm	
					6 months: 2.4±0.39 cm	–0.5 cm (–17.2%)
					12 months: 2.2±0.26 cm	–0.7 cm (–24.1%)
					24 months: 1.9±0.19 cm	–1.0 cm (–34.5%)
					36 months: 1.8±0.36 cm	–1.1 cm (–37.9%)
(Beemster et al 2008)	Level IV Quality: 3.5/6 Case series	26	Laparoscopic cryotherapy	2.4 cm (range: 1.3–3.8 cm)	3 months (n=26): 2.7 cm (range: 1.7–4.2 cm)	
					6 months (n=25): 1.9 cm (range: 0–2.7 cm)	–0.8 cm (–29.6%) RCC: n/a (32%) Benign: n/a (24%)
					12 months (n=14): 1.5 cm (range: 0–2.2 cm)	–1.2 cm (–44.4%) RCC: n/a (46%) Benign: n/a (52%)
					24 months (n=5): 1.2 cm (range: 0–1.6 cm)	–1.5 cm (–55.6%)
					36 months (n=1): 1.4 cm	–1.3 cm (–48.1%)
(Wink et al 2007)	Level IV Quality: 3/6 Retrospective case series	8 (7 procedures)	Laparoscopic cryotherapy	2.2 cm (range: 1.1–3.2 cm)	3.2–16.2 months: 2.5 cm (range: 2.0–3.1 cm)	n/a

Study	Evidence level and quality	Number of tumours	Intervention	Mean pre-treatment tumour size	Follow-up period: mean cryolesion size	Mean change[a]
2nd generation						
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	36 (31 procedures)	Laparoscopic cryotherapy	2.1 cm (range: 0.5–4.0 cm)	3 months: 2.4 cm (range: 1–4.2 cm)	
					6 months: 2.1 cm (range: 0.8–4 cm)	–0.3 cm (–12.5%)
					12 months: 1.7 cm (range: 0–4 cm)	–0.7 cm (–29.2%)
					24 months: 1.2 cm (range: 0–3.2 cm)	–1.2 cm (–50.0%)
					36 months: 0.6 cm (range: 0–2.4 cm)	–1.8 cm (–75.0%)
(Gupta et al 2006)	Level IV Quality: 3.5/6 Retrospective case series	14 (10 procedures)	Percutaneous cryotherapy	2.2±0.9 cm (range: 1.1–4.0 cm)	1.2–10.3 months: 1.9±0.9 cm (range: 0.7–3.7 cm)	n/a
(Moon et al 2004)	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	2.6±1.0 cm (range: 1.5–5.5 cm)	1–4 months (n=16): 2.5±0.9 cm (range: 0.8–4.3 cm)	
					5–28 months (n=12): 1.6±0.8 cm (range: 0.8–3.4 cm)	–0.9 cm[c] (–36.0%)

[a] Cryolesions at 3 months were used as the reference lesions; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura; [c] Cryolesions at 1–4 months were used as the reference lesions

n/a: not available; RCC: renal cell carcinoma

Length of hospital stay

Length of hospital stay after argon-based cryotherapy relative to partial nephrectomy was reported by three controlled studies (level III-2 intervention evidence). Another study compared length of hospital stay between cryotherapy and RFA (level III-2 intervention evidence). An additional 12 case series were identified in the literature that also provided data on length of hospital stay after cryotherapy (level IV intervention evidence) (Table 68 and Table 69). Within these studies patients stayed in hospital for an average of 1.9 to 3.3 days after laparoscopic cryotherapy; while percutaneous cryotherapy required a relatively shorter mean hospital stay of 0.1–2.4 days.

As reported by O'Malley et al (2006), Mouraviev et al (2007) and Link et al (2006), argon-based laparoscopic cryotherapy resulted in shorter mean length of hospital stay than laparoscopic partial nephrectomy, although this difference was not always statistically significant. Open partial nephrectomy necessitated a mean hospital stay of at least 4.0 days, which was longer than the minimally invasive option of laparoscopic cryotherapy ($p<0.001$) (Link et al 2006; Mouraviev et al 2007). No significant difference in length of hospital stay was noticed between laparoscopic cryotherapy and percutaneous RFA ($p>0.05$), although there was a trend towards a longer hospital stay following laparoscopic cryotherapy (Badwan et al 2008). Length of hospital stay after percutaneous cryotherapy was shorter than any other procedures for renal tumours, including laparoscopic cryotherapy (Badwan et al 2008; Bandi et al 2008; Link et al 2006).

Table 68 Length of hospital stay after cryotherapy for presumed renal cancer (controlled studies)

Study	Evidence level and quality[a]	Number of patients	Mean length of hospital stay		Mean difference (95% CI)	Mean quotient (95% CI)	p-value
3rd generation							
(O'Malley et al 2007)	Level III-2 Quality: 4/6 Matched-pairs cohort study Clin I: 4/4 R: 3/5	30	**LCT (n=15)** 3.3±3.3 days	**LPN (n=15)** 4.4±3.9 days	–1.10 days (–3.80 days, 1.60 days)	0.75 (0.33, 1.60)	0.412
2nd or 3rd generation							
(Mouraviev et al 2007)[b]	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 2/4 R: 3/5	40	**LCT (n=20)** 2.0±1.2 days	**LPN (n=20)** 3.8±1.9 days	–1.8 days (–2.82 days, –0.78 day)	0.53 (0.36, 0.75)	0.001[c]
	Clin I: 1/4 R: 3/5	91	**LCT (n=20)** 2.0±1.2 days	**OPN (n=71)** 4.0±1.5 days	–2.00 days (–2.72 days, –1.28 days)	0.50 (0.36, 0.64)	<0.001[c]
(Link et al 2006)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 3/4 R: 3/5	245	**LCT (n=28)** 2.9±2.4 days	**LPN (n=217)** 3.1±1.6 days	–0.20 days (–0.88 day, 0.48 day)	0.94 (0.64, 1.24)	0.560[c]
	Clin I: 1/4 R: 3/5	78	**LCT (n=28)** 2.9±2.4 days	**OPN (n=50)** 4.5±1.4 days	–1.60 days (–2.46 days, –0.74 day)	0.64 (0.44, 0.86)	<0.001[c]
	Clin I: 1/4 R: 3/5	239	**PCT (n=22)** 0.1±0 day	**LPN (n=217)** 3.1±1.6 days	–3.00 days (–3.67 days, –2.33 days)	0.03 (0.03, 0.03)	<0.001[c]
	Clin I: 1/4 R: 3/5	72	**PCT (n=22)** 0.1±0 day	**OPN (n=50)** 4.5±1.4 days	–4.40 days (–5.00 days, –3.80 days)	0.02 (0.02, 0.02)	<0.001[c]
(Bandi et al 2008)	Level III-2 Quality: 2/6 Retrospective cohort study Clin I: 3/4 R: 3/5	73	**LCT (n=58)** 2.5 days	**RFA (n=15)** 2 days	0.50 day (n/a)	1.25 (n/a)	n/a
	Clin I: 4/4 R: 3/5	35	**PCT (n=20)** 1.1 days	**RFA (n=15)** 2 days	–0.90 day	0.55	>0.05

[a] See Appendix L: Rank scores for assessing the Clinical Importance (Clin I) of the benefit/harm (with 1 ranked as highly clinically important and 4 as indeterminate clinical importance), and rank scores for the Relevance (R) of the evidence (with 1 ranked as a highly relevant outcome and 5 as an unproven surrogate outcome); [b] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [c] Statistical significance of differences calculated by two-tailed unpaired *t* exact test

CI: confidence interval; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; n/a: not available; OPN: open partial nephrectomy; RFA: radiofrequency ablation

Table 69 Length of hospital stay after cryotherapy for presumed renal cancer (uncontrolled studies)

Study	Evidence level and quality	Number of patients	Intervention	Mean length of hospital stay
3rd generation				
(Wright et al 2007)	Level IV Quality: 4.5/6 Retrospective case series	32 (35 tumours)	Laparoscopic cryotherapy	2.3 days (range: 1–4 days)
(Polascik et al 2007) [a]	Level IV Quality: 4.5/6 Case series	26 (28 tumours)	Laparoscopic cryotherapy	Median: 2 days (range: 0–9 days)
(Caviezel et al 2008)	Level IV Quality: 4.5/6 Retrospective case series	7	Percutaneous cryotherapy	2.4 days (range: 2–5 days)
(Wyler et al 2007)	Level IV Quality: 4/6 Prospective case series	14	Retroperitoneoscopy-assisted cryotherapy: 13 Open cryotherapy: 1	5 days (range: 3–7 days)
(Lehman et al 2008)	Level IV Quality: 3.5/6 Prospective case series	23 (30 tumours)	Laparoscopic cryotherapy	1.65 days (range: 1–4 days)
(Gore et al 2005)	Level IV Quality: 3.5/6 Retrospective case series	4 (5 tumours)	Laparoscopy-assisted percutaneous cryotherapy	1.8 days (range: 1.4–2.2 days)
3rd or 2nd generation				
(Badwan et al 2008)	Level IV Quality: 3.5/6 Retrospective case series	23	Laparoscopic cryotherapy	3.3 days
		13	Percutaneous cryotherapy	0.3 day
2nd generation				
(Weld et al 2007)[b]	Level IV Quality: 5.5/6 Prospective case series	31 (36 tumours)	Laparoscopic cryotherapy	3 days (range: 1–9 days)
(Goel & Kaouk 2008)	Level IV Quality: 3.5/6 Prospective case series	6	Laparoscopic cryotherapy	2.3 days (range: 1–8 days)
(Colon & Fuchs 2003)	Level IV Quality: 3.5/6 Prospective case series	8	Laparoscopic cryotherapy	2.9 days (range: 1–5 days)
(Hinshaw et al 2008)[c]	Level IV Quality: 3/6 Retrospective case series	30	Percutaneous cryotherapy	1.1 days (range: 1–2 days)
		60	Laparoscopic cryotherapy	2.4 days (range: 1–15 days) (PCT vs LCT: p<0.0001)
(Moon et al 2004)[c]	Level IV Quality: 3/6 Retrospective case series	16	Laparoscopic cryotherapy	1.9 days (range: 1–8 days)

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] One of the authors, Landman, J., is a study investigator and consultant to Oncura; [c] May be overlap between patient series

LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy

Convalescence and patient satisfaction

A comparison of post-procedural convalescence and patient satisfaction was made between laparoscopic cryotherapy, percutaneous cryotherapy and percutaneous RFA in Bandi et al's (2008) retrospective cohort study. Patients in the three groups were matched for age, gender, BMI and ASA score. However, renal tumours that were treated with laparoscopic cryotherapy were significant larger than those ablated by percutaneous ablation procedures (percutaneous cryotherapy and percutaneous RFA) (2.6 cm vs 2.2 cm, $p<0.05$). Patients' convalescence after treatment was measured by the number of days patients needed to return to non-strenuous activity, strenuous activity, work and complete recovery, respectively. Patients' satisfaction was assessed on a 0 to 5 scale and whether they would recommend the procedure to others.

It was discovered that patients receiving laparoscopic cryotherapy required more time to return to non-strenuous activity (8.1 days vs 2.9 days, $p=0.009$) and strenuous activity (22.1 days vs 10.5 days, $p=0.007$) than those treated with percutaneous RFA. Laparoscopic cryotherapy was also associated with a delayed return to non-strenuous activity when compared with percutaneous cryotherapy, (8.1 days vs 3.1 days, $p=0.007$). No significant difference was discovered in patient satisfaction measured on a 0 to 5 scale among the three groups. All but one patient, who underwent percutaneous cryotherapy, stated that they would recommend the procedures to others.

Table 70 Convalescence and patient satisfaction after cryotherapy for presumed renal cancer

	Laparoscopic cryotherapy (n=58)	Percutaneous cryotherapy (n=20)	Percutaneous RFA (n=15)
Return to non-strenuous activity	8.1 days	3.1 days (LCT vs PCT: p=0.007)	2.9 days (LCT vs RFA: p=0.009)
Return to strenuous activity	22.1 days	16.2 days (LCT vs PCT: p>0.05)	10.5 days (LCT vs RFA: p=0.007)
Return to work	17.5 days	6.2 days (LCT vs PCT: p>0.05)	4.0 days (LCT vs RFA: p=0.05)
Return to complete recovery	27.5 days	13.5 days (LCT vs PCT: p=0.05)	18.0 days (LCT vs RFA: p>0.05)
Patient satisfaction	4.9	4.8 (LCT vs PCT: p>0.05	4.8 (LCT vs RFA: p>0.05)
Would recommend procedure to others	100%	95% (LCT vs PCT: p>0.05)	100% (LCT vs RFA: p>0.05)

Source: Bandi et al 2008

LCT: laparoscopic cryotherapy; PCT: percutaneous cryotherapy; RFA: radiofrequency ablation

Summary – What is the effectiveness of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?

Twenty-five studies were identified in the literature that met the inclusion criteria for this review (with the study population revised to patients with *presumed* small (<4 cm) localised renal cancer), reporting effectiveness outcomes as a result of argon-based cryotherapy for renal tumours. There were three controlled studies that compared cryotherapy (laparoscopic or percutaneous) against partial nephrectomy (open or laparoscopic); and one study that examined the effectiveness of cryotherapy relative to RFA (level III-2 intervention evidence). Also included in this assessment of effectiveness were 21 uncontrolled case series (level IV intervention evidence).

Between 87.5 and 100 per cent of patients survived during follow-up periods of less than 2 years after cryotherapy. Deaths were caused by either cardiovascular diseases or other malignancies; therefore, a disease-specific survival rate of 100 per cent was achieved. Bandi et al (2008), in a controlled study of poor quality, discovered no significant difference in overall survival rates between laparoscopic cryotherapy and percutaneous ablation procedures (percutaneous cryotherapy and percutaneous RFA). Note: overall survival was not compared between cryotherapy (laparoscopic or percutaneous) and RFA, as data on survival in patients who underwent percutaneous cryotherapy and those receiving percutaneous RFA were not provided separately.

More than 90 per cent of cryotherapy procedures were technically successful, with no difference between laparoscopic cryotherapy and percutaneous cryotherapy. The main reasons for technical failure were using cryoprobes that were too small, and having a tumour located adjacent to a large renal vein or in a central location.

Between 0 and 13.6 per cent of renal tumours were not adequately treated by cryotherapy, as detected by follow-up imaging. No difference in tumour persistence rates was observed between laparoscopy cryotherapy, percutaneous cryotherapy and percutaneous RFA, although the tumours treated with laparoscopic cryotherapy were slightly larger than those ablated by the two percutaneous ablation procedures. Potential predictors of tumour persistence include: endophytic status of the lesion, technical failure and difficulties in cryoprobe placement.

As reported by two controlled studies (Bandi et al 2008; O'Malley et al 2007), the rate of local tumour progression following cryotherapy was very similar to that after laparoscopic partial nephrectomy or RFA. During follow-up periods of 5 to 47 months, local tumour progression rates ranged between 0 and 25.0 per cent across studies. In Permpongkosol et al's (2006) study, 9.1 per cent of 22 renal malignancies were locally progressed within 12 months after percutaneous cryotherapy.

One case of metastasis was discovered in Wyler et al's (2007) case series of 10 renal cell carcinomas. Before cryotherapy, this patient had undergone nephrectomy for contralateral multifocal renal cancer. Follow-up imaging revealed retroperitoneal lymph node metastases 9 months after the cryotherapy procedure.

Although the size of cryolesions decreased continuously after cryotherapy across the studies, the differences were not statistically analysed due to the lack of primary data.

Laparoscopic cryotherapy required less operative time and a shorter hospital stay than laparoscopic partial nephrectomy, although these differences were not always statistically significant. Open partial nephrectomy was associated with both more operative time and a longer hospital stay when compared to laparoscopic cryotherapy. There was a trend towards a longer hospital stay after laparoscopic cryotherapy than following percutaneous RFA, although this difference was not significant. The mean length of hospital stay required for percutaneous cryotherapy was consistently shorter than that required for partial nephrectomy (open or laparoscopic), percutaneous RFA or laparoscopic cryotherapy (Bandi et al 2008; Link et al 2006; Mouraviev et al 2007; O'Malley et al 2007).

What are the economic considerations?

Background

In its assessment of a new service, the MSAC is required to consider not only the comparative effectiveness and safety of the service but also the comparative cost and cost-effectiveness of the service. The purpose of the economic evaluation is to inform the decision made by the MSAC on the additional costs and additional gains (health or other socially relevant outcomes) of the proposed service over the comparator when used in the Australian healthcare system. This is to ensure that society's ultimately scarce resources are allocated to those activities from which it will get the most value. That is, it seeks to enhance economic efficiency.

The costing exercise conducted is not intended for fee scheduling purposes, and is not a recommendation for funding at these levels.

Existing literature

The inclusion criteria determined a priori for assessing economic analysis of cryotherapy for renal cancer are outlined in Box 6.

Box 6 Inclusion criteria for studies assessing the cost-effectiveness of cryotherapy for renal cancer

Research question	
What is the cost-effectiveness of cryotherapy, compared to partial nephrectomy, RFA or surveillance, in patients with small localised renal cancer?	
Characteristics	**Criteria**
Population	Patients with presumed small (<4 cm) localised renal cancer
Intervention	Cryotherapy (argon-based)
Comparators	Partial nephrectomy, RFA or surveillance
Outcome	Cost, cost per event avoided, cost per life year gained, cost per quality adjusted life year or disability adjusted life year, incremental cost-effectiveness ratio
Study design	Economic studies, decision analytic modelling studies, economic analyses
Search period	1995–11/2008
Language	Non-English language articles were excluded unless they appeared to provide a higher level of evidence than the English language articles identified.

As with the inclusion criteria for assessing safety and effectiveness, the study population in which an economic analysis was performed was revised to include patients with *presumed* small (<4 cm) localised renal cancer to ensure that there were more studies for assessment.

No literature was identified that compared the cost-effectiveness of cryotherapy against partial nephrectomy or RFA. Two studies from the United States were available that performed cost comparisons between cryotherapy and partial nephrectomy based on retrospective cohorts of patients (level III-2 intervention evidence) (Link et al 2006; Mouraviev et al 2007) (Table 71). Both of these studies were subject to selection bias, as patients with larger, more complex tumours were significantly more likely to receive open partial nephrectomy (Link et al 2006; Mouraviev et al 2007). An additional two studies

compared the costs between laparoscopic cryotherapy and percutaneous cryotherapy in hospitals in the United States (level IV intervention evidence) (Badwan et al 2008; Hinshaw et al 2008). It is unknown how applicable the costs provided would be to the Australian healthcare setting.

Mouraviev et al (2007) included all costs from hospital admission until discharge, and reported that argon-based laparoscopic cryotherapy was less costly than laparoscopic partial nephrectomy ($10 105 vs $15 458, p=0.015) or open partial nephrectomy ($10 105 vs $13 299, p=0.008). The predominant cost saving of cryotherapy resulted from the reduced length of hospital stay.

Link et al (2006) excluded the surgeon's fee from the analysis, as there is no consensus on the appropriate professional fee for percutaneous cryotherapy. Capital equipment depreciation was also excluded, as none of the equipment is used solely for renal cancer (no estimate was provided for the proportion of use that would be for renal cancer). Based on the remaining costs between admission and discharge, percutaneous cryotherapy was the least costly procedure, resulting in a cost saving of US$3625 per case compared to laparoscopic partial nephrectomy and US$5155 per case compared to open partial nephrectomy. Despite a shorter operative time, second-generation laparoscopic cryotherapy did not have a cost advantage over laparoscopic partial nephrectomy, primarily due to the cost of the disposable cryoprobes (Link et al 2006). Laparoscopic cryotherapy was only cheaper than laparoscopic partial nephrectomy if one or two cryoprobes were used. Percutaneous cryotherapy retained its cost advantage over laparoscopic partial nephrectomy unless over seven cryoprobes were used.

Badwan et al (2008) reported higher hospital costs in patients who underwent laparoscopic cryotherapy than in those receiving percutaneous cryotherapy, and attributed the cost difference to the relatively expensive operating room charges, laparoscopic surgical fees, anaesthesia charges and hospital fees for laparoscopic cryotherapy. Hinshaw et al (2008) also observed that percutaneous cryotherapy was less costly than laparoscopic cryotherapy but did not suggest an explanation for the cost saving.

Table 71 Costs of cryotherapy

Study	Evidence level and quality	Number of patients	Cost items	Total cost per person (US$)			
				Laparoscopic cryotherapy	Percutaneous cryotherapy	Laparoscopic partial nephrectomy	Open partial nephrectomy
(Mouraviev et al 2007)	Level III-2 Quality: 3.5/6 Retrospective cohort study	111		(n = 20)		(n = 20)	(n = 71)
			Surgery [a]	5 080		4 760	3 370
			Nursing services	688		1 668	1 729
			Pharmacy	547		606	862
			Cardiac service	49		9	28
			Diagnostics and therapy	0		15	5
			Respiratory	42		198	126
			Radiology	72		223	167
			Laboratory	204		332	390
			Blood transfusion	41		123	227
			Total non-surgical costs	1 659		3 328	3 584
			Total direct costs	6 740		7 800	6 953
			Total	10 105		15 458	13 299
(Link et al 2006)	Level III-2 Quality: 2/6 Retrospective cohort study	317		(n = 28)	(n = 22)	(n = 217)	(n = 50)
			OR time	2 640	0	3 120	4 320
			OR consumables	619	0	619	170
			CT costs	0	406	0	0
			Percutaneous biopsy costs	0	382	0	0
			Cryoprobe costs	1 200	2 200	0	0
			Anaesthesia fee	289	0	327	420
			Hospital room	1 975	74	2 595	3 215
			Blood transfusion	19	47	72	139
			Total	6 743	3 109	6 734	8 264

Study	Evidence level and quality	Number of patients	Cost items	Total cost per person (US$)			
				Laparoscopic cryotherapy	Percutaneous cryotherapy	Laparoscopic partial nephrectomy	Open partial nephrectomy
(Badwan et al 2008)	Level IV Quality: 3.5/6 Retrospective case series	36		(n=23)	(n=13)		
			Laparoscopic surgical fees	3 415	n/a		
			Anaesthesia fee	2 790	n/a		
			OR charge	12 047	n/a		
			Ultrasound operator fee	317	n/a		
			Pathology laboratory fee	286	n/a		
			Radiology fee	n/a	527		
			Hospital fee	26 085	6 838		
			Total	32 900	9 240		
(Hinshaw et al 2008)	Level IV Quality: 3/6 Retrospective case series	90		(n=30)	(n=60)		
			Total [b]	14 175	23 618 (p<0.00001)		

[a] Including operating room surgical supplies, anaesthesia and post-anaesthesia care unit costs; [b] Including all professional fees associated with the procedure, charges for cryoprobes, operating room fees, technical charges related to the procedure, anaesthesia-related charges, charges associated with any imaging performed, nursing and medication chares, and hospital room charges

CT: computed tomography; n/a: not applicable; OR: operating room

Evidence about effectiveness of the intervention from this review

When undertaking economic analyses, initially a systematic review (and/or meta-analysis) is produced to determine whether there is evidence that the intervention is comparatively effective (see 'Effectiveness' section page 158). For the purposes of this economic evaluation, the proposed comparator is partial nephrectomy, as this is the current procedure most likely to be replaced by cryotherapy in the event that it receives public funding. The type of economic analysis conducted is conditional on the results of the systematic review on the safety and effectiveness of cryotherapy.

Limited evidence indicated that the safety of cryotherapy was no worse than partial nephrectomy in that no significant differences in the incidence rates of complications were reported between these two treatments, and cryotherapy resulted in less blood loss than partial nephrectomy (Table 51). One comparative study (O'Malley et al 2007) of moderate quality, with a small sample of 30 patients, demonstrated that the incidence of local tumour progression following laparoscopic cryotherapy was not significantly different from that after laparoscopic partial nephrectomy during a follow-up period of less than 12 months. However, other important measures of effectiveness, such as overall survival, disease-specific survival, tumour persistence and metastases, as well as local tumour progression in the long term, were not compared between cryotherapy and partial nephrectomy. Therefore, the Advisory Panel agreed that an economic evaluation was not warranted based on the current available evidence, since there was insufficient evidence to determine the effectiveness of cryotherapy relative to partial nephrectomy.

Although there was a lack of evidence to perform an economic evaluation, a financial analysis of the expenditures associated with cryotherapy for presumed renal cancer relative to current available treatments was conducted.

The cost data covered all non-trivial health system resources. Indirect costs, also known as productivity costs, were not considered. All cost data were expressed in Australian dollars. Where a time horizon beyond 12 months was adopted, a discount rate of 5 per cent was used.

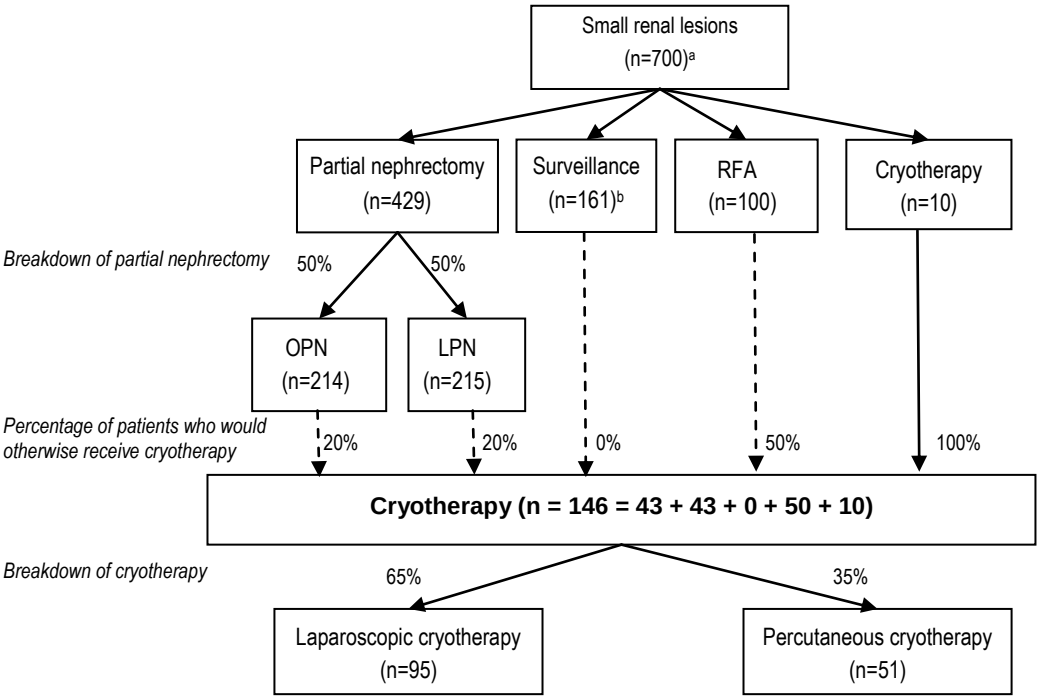
Financial incidence analysis

Likely number of procedures in a typical year

It is anticipated that the number of renal cryotherapy procedures that would be performed annually across Australia would range between 96 and 196. As previously described in the section addressing clinical need/burden (page 130), this estimate is based on data from AIHW, expert opinion of the Advisory Panel and advice from the applicant.

In order to simplify the financial analysis, a base case was chosen with the following assumptions: 1) three-quarters of small renal lesions are malignant tumours; and 2) 50 per cent of those patients currently receiving RFA would otherwise receive cryotherapy. As presented in Figure 14, the estimated number of cryotherapy procedures carried out in Australia would be 146. The Advisory Panel suggested a ratio of 65:35 between laparoscopic cryotherapy and percutaneous cryotherapy; therefore, it is estimated that 95 laparoscopic cryotherapy procedures and 51 percutaneous cryotherapy procedures would be performed per year across Australia. The financial implications of cryotherapy in scenarios other than the base case are presented in Appendix M.

Figure 14 Flowchart estimating the clinical need for cryotherapy (base case)



[a] Based on data from AIHW and the United States, it is estimated that, in Australia, a total of 538 small renal malignancies would be diagnosed each year. 700 = 525 ÷ 3/4; [b] 161 = 700 – 429 – 100 – 10.

LPN: laparoscopic partial nephrectomy; OPN: open partial nephrectomy; RFA: radiofrequency ablation

Unit costs

The work-up for cryotherapy, partial nephrectomy and RFA is the same (Table 72). Coagulation studies, chest X-ray, and abdomen and pelvic CT are required pre-procedurally to rule out patients who are considered not suitable for invasive local treatments: the first investigation detects those with bleeding problems and the latter two are used to identify tumour extension or cases of distant metastases. The pre-treatment work-up for surveillance is similar to that for cryotherapy, except that a pre-anaesthetic consult and coagulation studies are not needed for surveillance.

In the first year two follow-up visits and CT examinations, usually at 6 and 12 months, take place after partial nephrectomy; whereas cryotherapy and RFA, as ablative procedures, would need one extra visit and CT scan (at 3 months post-procedurally) than partial nephrectomy. Patients would be followed up every 3 months in the first year of surveillance (Table 72).

Table 72 Unit costs of work-up and follow-up for cryotherapy, partial nephrectomy, RFA and surveillance

Item	Cryotherapy[a]	Partial nephrectomy	Radiofrequency ablation	Surveillance	Source of estimate
Work-up					
Specialist consult	$79	$79	$79	$79	MBS item 104
Pre-anaesthetic consult	$79	$79	$79	n/a	MBS item 17615
Coagulation studies	$43	$43	$43	n/a	MBS item 65129 and 65070
Chest X-ray	$47	$47	$47	$47	MBS item 58503
Abdomen and pelvic CT	$480	$480	$480	$480	MBS item 56507
Follow-up					
Follow-up visits[c]	$40x3	$40x2	$40x3	$40x4	MBS item 105
Follow-up CTs[c]	$480x3	$480x2	$480x3	$480x4	MBS item 56507
Total	**$2 288**	**$1 768**	**$2 288**	**$2 686**	

Source: Medicare Australia 2008

[a] Cryotherapy includes percutaneous cryotherapy and laparoscopic cryotherapy; [b] Partial nephrectomy includes open partial nephrectomy and laparoscopic partial nephrectomy; [c] In the first year the numbers of follow-up consultations for cryotherapy, partial nephrectomy, RFA and surveillance are 3, 2, 3 and 4, respectively.

CT: computed tomography; n/a: not applicable

The costs associated with the additional capital equipment required for cryotherapy and RFA are presented in Table 73. The equivalent annual cost of the equipment would be $32 376 for cryotherapy and $5180 for RFA. The annual maintenance cost would be $25 000 and $0 for cryotherapy and RFA, respectively. The equipment cost per cryotherapy procedure is estimated at $574 or $115, when the annual throughput for cryotherapy machines is 100 or 500, respectively. The unit cost of RFA would be $69, with a procedure volume of 75 per cent per instrument.

Table 73 Cost per unit of additional capital equipment and maintenance for cryotherapy and RFA

Item	Cryotherapy	Cryotherapy	Radiofrequency ablation
Equipment price	$250 000 (Scanmedics Pty Ltd)	$250 000 (Scanmedics Pty Ltd)	$40 000 (Boston Scientific)
Estimated life of equipment	10 years (Scanmedics Pty Ltd)	10 years (Scanmedics Pty Ltd)	10 years (Boston Scientific)
Annual equivalent cost of equipment [a]	$32 376	$32 376	$5 180
Annual maintenance costs	$25 000 (Scanmedics Pty Ltd)	$25 000 (Scanmedics Pty Ltd)	$0 (Boston Scientific)
Total major capital equipment cost per annum	$57 376	$57 376	$5 180
Estimated annual volume of procedures[b]	100	500	75
Estimated cost per procedure	**$574**	**$115**	**$69**

[a] Annual equivalent cost of equipment for RFA was calculated using annuity at 5% p.a. for 10 years; [b] Expert opinion from the Advisory Panel

The unit costs of cryotherapy relative to its comparators are presented in Table 74, including all relevant costs regardless of the agency that bears them. Surveillance is not included, since no patients would be expected to convert from surveillance to cryotherapy. These patients would, therefore, not incur any additional costs or savings to

the government or to the society. Only one follow-up visit and CT examination are costed for cryotherapy and RFA, as the other two follow-up schedules are the same among cryotherapy, partial nephrectomy and RFA.

In scenarios using different throughputs for a cryotherapy machine (100 and 500 per year), laparoscopic cryotherapy is estimated to cost between $12 546 and $13 005 per procedure, while percutaneous cryotherapy costs between $11 517 and $11 976 per procedure. These estimates are for a private facility. The costs per open partial nephrectomy, laparoscopic partial nephrectomy and RFA are estimated at $8968, $6708 and $5071, respectively. Therefore, a cryotherapy procedure would be approximately $2550 to $6300 more expensive than a partial nephrectomy procedure, and the unit cost of cryotherapy would be double that of RFA. The high expenditure of a cryotherapy procedure is attributable to the expensive disposable Cryokit and gases ($6700).

Table 74 Unit cost of cryotherapy, partial nephrectomy and RFA in a private hospital facility

Item	Laparoscopic cryotherapy	Laparoscopic cryotherapy	Percutaneous cryotherapy	Percutaneous cryotherapy	Open partial nephrectomy	Laparoscopic partial nephrectomy	Radiofrequency ablation	Source of estimate
Equipment cost: capital and maintenance per procedure	$574[a]	$115[b]	$574[a]	$115[b]	n/a	n/a	$69	Table 73
Professional fee–surgeon[c]	$853	$853	$341	$341	$1 024	$1 024	$341	MBS item 36522
Anaesthesia initiation	$146	$146	$110	$110	$146	$146	$110	MBS item 20790 (laparoscopic cryotherapy and partial nephrectomy) and 20799 (percutaneous cryotherapy and radiofrequency ablation)
Anaesthesia time units[d]	$220	$220	$110	$110	$220	$220	$110	MBS item 23063
Renal biopsy	$159	$159	$159	$159	n/a	n/a	$159	MBS item 36561
Intra-operative CT	n/a	n/a	$470	$470	n/a	n/a	$470	MBS item 57341
Intra-operative ultrasound	$109	$109	$109	$109	n/a	$109	$109	MBS item 55054
Associated disposables[e]	$8 200	$8 200	$8 200	$8 200	n/a	$1 500	$1 800	Scanmedics Pty Ltd and Boston Scientific
Hospital facility services[f]	$2 224[g]	$2 224[g]	$1 383[h]	$1 383[h]	$7 578[i]	$3 709[j]	$1 383[h]	AR-DRG version 5.1 Private Hospital Data Bureau
Follow-up visit and CT	$520	$520	$520	$520	n/a	n/a	$520	MBS item 56507 and 105
Total	**$13 005**	**$12 546**	**$11 976**	**$11 517**	**$8 968**	**$6 708**	**$5 071**	

Sources: Department of Health and Ageing 2005, 2006; Medicare Australia 2008

[a] Equipment cost when the annual volume of cryotherapy procedures per instrument is 100; [b] Equipment cost when the annual volume of cryotherapy procedures per instrument is 500; [c] The professional fee for partial nephrectomy is $1024; and it is indicated that the surgical time for laparoscopic cryotherapy, percutaneous cryotherapy, open partial nephrectomy, laparoscopic partial nephrectomy, and RFA is 150 minutes, 60 minutes, 180 minutes, 180 minutes, and 60 minutes, respectively. The professional fee for laparoscopic cryotherapy, percutaneous cryotherapy and RFA was calculated as $1024 x 5 ÷ 6, $1024 ÷ 3 and $1024 ÷ 3, respectively; [d] The surgical time for laparoscopic cryotherapy, percutaneous cryotherapy, open partial nephrectomy, laparoscopic partial nephrectomy and RFA is 150 minutes, 60 minutes, 180 minutes, 180 minutes and 60 minutes, respectively; [e] Costs of renal Cryokit, gases and disposables for laparoscopic surgery are $6500, $200 and $1500, respectively; [f] Items not covered by Medicare; [g] Total average charge per AR-DRG version 5.1 Private Hospital Data Bureau; L62B – KDNY & UNRY TRCT NEOPLASMS-CSCC; average length of hospital stay: 2.82 days; [h] Total average charge per AR-DRG version 4.2 Private Hospital Data Bureau; L04B – KDY, URT & MJR BLDR PR N-NPM-CSCC; average length of hospital stay: 0.22 days. Consumer Price Index (CPI) adjusted fee: $1323 x 213.5 ÷ 204.3 (the Index for Health in 2004–05 was 204.3, in 2005–06 was 213.5); [i] Total average charge per AR-DRG version 5.1 Private Hospital Data Bureau; L03B – KDNY, URT & MJR BLDR PR NPSM-CSCC; average length of hospital stay: 6.46 days; [j] Total average charge per AR-DRG version 5.1 Private Hospital Data Bureau; L04C – KDNY, URT & MJR BLDR PR N-NPSM-CC; average length of hospital stay: 2.62 days.

CT: computed tomography; n/a: not applicable

Cost to the Australian Government

The Australian Government is responsible for payment of the rebate on items from the MBS. On the assumption that cryotherapy for presumed renal cancer will be performed in a private hospital facility, the rebate would be 75 per cent of the schedule fee. As presented in Table 75, the unit costs of laparoscopic cryotherapy and percutaneous cryotherapy to the government would be $1506 and $1365, respectively. The financial implications of cryotherapy to the government would range between $0 and an *additional* cost, per procedure, of $463 relative to open partial nephrectomy, laparoscopic partial nephrectomy and RFA.

Table 75 Unit costs to the Australian Government

Item	Laparoscopic cryotherapy	Percutaneous cryotherapy	Open partial nephrectomy	Laparoscopic partial nephrectomy	Radiofrequency ablation
Professional fee–surgeon	$640	$256	$768	$768	$256
Anaesthesia initiation	$110	$83	$110	$110	$83
Anaesthesia time units	$165	$83	$165	$165	$83
Renal biopsy	$119	$119	n/a	n/a	$119
Intra-operative CT	n/a	$353	n/a	n/a	$353
Intra-operative ultrasound	$82	$82	n/a	$82	$82
Follow-up visit and CT	$390	$390	n/a	n/a	$390
Total	**$1 506**	**$1 365**	**$1 043**	**$1 124**	**$1 365**

CT: computed tomography; n/a: not applicable

The total costs of cryotherapy to the Australian Government, as shown in Table 76, were estimated in two scenarios, where the public to private patient splits for cryotherapy are 75:25 and 50:50, respectively. As it is anticipated that there would be 146 cryotherapy procedures being performed annually, around 37 and 74 of these procedures would be eligible for MBS reimbursement if the proportions of cryotherapy procedures performed in the private health setting were 25 per cent and 50 per cent, respectively.

To calculate the financial implications to the Australian Government of subsidising cryotherapy for renal cancer, the estimated cost per procedure was multiplied by the expected uptake of the procedure in private hospitals. In the scenario where 24 laparoscopic cryotherapy procedures and 13 percutaneous cryotherapy procedures are expected to be performed annually in the private sector, an *additional* cost of $9568 for cryotherapy would be incurred by the government relative to the currently available treatments. When 50 per cent of cryotherapy procedures are performed in the private health setting, the Australian Government would bear an *additional* $18 715 in costs per year.

If *none* of the patients who currently undergo RFA would otherwise choose cryotherapy, the overall *additional* costs to the government would be $8440 and $16 459 in scenarios where the public to private patient splits were 75:25 and 50:50, respectively. In the event that *100 per cent* of the RFA procedures would be replaced by cryotherapy procedures, the government would pay an *additional* $10 837 or $20 971 when different proportions (25% and 50%, respectively) of cryotherapy procedures were carried out in the private healthcare setting (Appendix M).

Table 76 Total costs to the Australian Government (base case)

	Procedure	Number of patients[a]	Unit costs	Total cost
Scenario 1 (public to private patient split: 75:25)				
Currently	Open partial nephrectomy	11	$1 043	$11 468
	Laparoscopic partial nephrectomy	11	$1 124	$12 086
	Radiofrequency ablation	12	$1 365	$16 374
	Laparoscopic cryotherapy	2	$1 506	$3 011
	Percutaneous cryotherapy	1	$1 365	$1 365
In the future	Laparoscopic cryotherapy	24	$1 506	$36 132
	Percutaneous cryotherapy	13	$1 365	$17 739
	Difference[b]			**$9 568**
Scenario 2 (public to private patient split: 50:50)				
Currently	Open partial nephrectomy	22	$1 043	$22 935
	Laparoscopic partial nephrectomy	22	$1 124	$24 734
	Radiofrequency ablation	25	$1 365	$34 113
	Laparoscopic cryotherapy	3	$1 506	$4 517
	Percutaneous cryotherapy	2	$1 365	$2 729
In the future	Laparoscopic cryotherapy	48	$1 506	$72 264
	Percutaneous cryotherapy	26	$1 365	$35 477
	Difference[b]			**$18 715**

[a] From the flowchart in Figure 14, the equation 95 + 51 = 43 + 43 + 0 + 50 + 10 was derived. The numbers of patients in this table are calculated by the corresponding numbers of patients in the equation divided by 2 in scenario 1 or by 4 in scenario 2; [b] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency ablation and currently performed cryotherapy.

Total cost to the Australian healthcare system overall

The total cost to the Australian healthcare system would include co-payments, cost of disposables, hospital services and capital equipment as well as medical services. The costs were calculated in two scenarios with annual volumes of cryotherapy procedures of 100 and 500 achieved per machine (Table 77).

For 95 laparoscopic and 51 percutaneous cryotherapy procedures performed annually in the healthcare system, the total cost is estimated to be $1 846 243 and $1 779 228 for annual throughputs for a cryotherapy machine of 100 or 500, respectively. The total costs to the society for partial nephrectomy, RFA and currently performed cryotherapy are $674 068, $253 549 and $126 963 or $122 373 (for annual throughputs of 100 or 500), respectively. Therefore, the cost implications of cryotherapy to the Australian healthcare system overall would be an *additional* $791 664–$729 238, which is largely due to the disposable Cryokit and gases required for the cryotherapy procedure.

Given that 0 to 100 per cent of patients who are now treated with RFA would otherwise choose cryotherapy, the *additional* costs for cryotherapy to the healthcare system would range between $372 938 and $1 169 840 relative to currently available treatments (Appendix M).

Table 77 Total costs to the Australian healthcare system overall (base case)

	Procedures	Number of patients	Unit costs	Total costs
Scenario 1 (estimated annual volume of cryotherapy procedures: 100)				
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	50	$5 071	$253 549
	Laparoscopic cryotherapy	7	$13 005	$91 036
	Percutaneous cryotherapy	3	$11 976	$35 927
In the future	Laparoscopic cryotherapy	95	$13 005	$1 235 484
	Percutaneous cryotherapy	51	$11 976	$610 759
	Difference[a]			**$791 664**
Scenario 2 (estimated annual volume of cryotherapy procedures: 500)				
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	50	$5 071	$253 549
	Laparoscopic cryotherapy	7	$12 546	$87 823
	Percutaneous cryotherapy	3	$11 517	$34 550
In the future	Laparoscopic cryotherapy	95	$12 546	$1 191 878
	Percutaneous cryotherapy	51	$11 517	$587 350
	Difference			**$729 238**

[a] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency and currently performed cryotherapy.

Discussion

Is it safe?

Potential candidates for cryotherapy are usually selected on the basis of imaging suggestive of malignant renal tumours, as pre-procedural biopsy is seldom performed. Therefore, in most of the studies involving cryotherapy, only a proportion of patients in each study had renal malignancies that were pathologically confirmed after cryotherapy. Due to the paucity of evidence on cryotherapy specifically for renal cancer, the selection criteria were amended to include 'patients with *presumed* small localised renal cancer'. Therefore, cryotherapy was assessed in a group of patients with both malignant and benign renal tumours. The rationality of this amendment was supported by the search results of this assessment. Of the 26 controlled or uncontrolled studies identified in the literature (16 case reports not included), only one retrospective case series investigated cryotherapy in a group of patients with renal cell carcinomas that were histologically confirmed after cryotherapy (Permpongkosol et al 2006). In the remaining studies both patients with renal malignancies and those with benign tumours were included.

The relative safety of argon-based cryotherapy in comparison to partial nephrectomy was assessed by O'Malley et al (2007). In this moderate-quality study, patients in both the laparoscopic cryotherapy group and the laparoscopic partial nephrectomy group were well matched for demographic characteristics, number of comorbidities, ASA score, BMI, pre-treatment renal function, and tumour size and location. The authors reported no significant difference in complication rates between the two procedures ($p>0.05$). Compared to laparoscopic partial nephrectomy, laparoscopic cryotherapy resulted in less peri-procedural blood loss (58.7 mL vs 221 mL), which was both statistically ($p=0.002$) and clinically significant.

Safety outcomes following cryotherapy (laparoscopic and percutaneous) and RFA were compared by two studies (Allaf et al 2005; Bandi et al 2008). It was discovered that the major complication (intra-operative or post-operative) rates and estimated blood loss were not significantly different either between laparoscopic cryotherapy and RFA or between percutaneous cryotherapy and RFA ($p>0.05$). When compared with RFA, laparoscopic cryotherapy was associated with more anaesthesia time (247 minutes vs 158 minutes), whereas percutaneous cryotherapy had less requirement for sedative drugs (fentanyl: 75 μg vs 165 μg, $p<0.001$; midazolam: 1.6 mg vs 2.6 mg, $p=0.026$).

One procedure-related death was reported in a case report. This highlights the usefulness of case reports for describing rare safety outcomes. Although a higher level of evidence for each outcome is used to draw conclusions on the safety of cryotherapy relative to partial nephrectomy or RFA, rare complications following cryotherapy are unlikely to be reported by controlled studies or case series. Studies that reported the safety outcomes of cryotherapy were so small, with the largest involving 58 cryotherapy procedures (Bandi et al 2008), that rare adverse events were unlikely to occur in their patient populations. Therefore, case reports play an essential role in identifying more complications from cryotherapy, but caution should be exercised while commenting on rare complications based on case reports that have been presented for cryotherapy and not its comparators.

Large heterogeneity in major intra-operative complication rates was observed between case series, with a rate of 28.6 per cent reported by Wyler et al (2007) and rates of less

than 4 per cent in the remaining series. This emphasises one of the difficulties in comparing clinical outcomes between uncontrolled case series in which there is no reference group. Results may be biased owing to different methods of reporting adverse events, variation in surgeons' experience in performing the cryotherapy procedure, and the relatively small sample sizes within the studies included in this assessment.

Major complications following cryotherapy were not uncommon, with incidence rates ranging from 0 to 21.4 per cent of procedures. The majority of significant post-operative adverse events were heart or pulmonary diseases. These findings were deemed to be attributable to the clinical indications for cryotherapy, that is for patients who are unfit for major surgery (usually older patients or those with multiple comorbidities). This patient selection criterion results in cryotherapy procedures being carried out in a group of patients either with pre-existing cardiovascular or respiratory diseases or who are vulnerable to developing these diseases after cryotherapy.

One study by Hinshaw et al (2008) compared safety outcomes between different cryotherapy approaches. The authors discovered a higher incidence rate of minor complications in patients who underwent percutaneous cryotherapy than in those receiving laparoscopic cryotherapy (13.3% vs 1.7%, p=0.04). They attributed the difference to less experience in performing percutaneous cryotherapy and to a lack of direct visual cues for cryoprobe placement during the percutaneous cryotherapy procedure.

There was no evidence that the 17-G cryotherapy system, compared to the argon-based cryotherapy system using thicker cryoprobes, resulted in lower complication rates or less blood loss, although the use of thinner cryoprobes was assumed to improve the safety of cryotherapy.

Is it effective?

The effectiveness of argon-based cryotherapy for presumed renal cancer was assessed in four non-randomised controlled studies and 21 case series.

During follow-up periods of 9.6–22 months, none of the patients in the identified studies died from renal tumours, resulting in a disease-specific survival rate of 100 per cent. Between 0 and 12.5 per cent of patients died from cardiovascular diseases or other malignancies, which might, like the occurrence of major post-operative complications, be related to the patient selection criteria for cryotherapy in clinical practice. No comparative data on overall survival were available between cryotherapy and partial nephrectomy or RFA.

Other effectiveness outcomes of cryotherapy were compared to partial nephrectomy in three studies (Link et al 2006; Mouraviev et al 2007; O'Malley et al 2007). No difference in local tumour progression rates was reported between laparoscopic cryotherapy and laparoscopic partial nephrectomy. Compared to partial nephrectomy (laparoscopic or open), laparoscopic cryotherapy was associated with less operative time and a shorter hospital stay, although the differences between laparoscopic partial nephrectomy and laparoscopic cryotherapy were not always significant. Percutaneous cryotherapy required a hospital stay of less than 1 day, which was significantly shorter than the two partial nephrectomy procedures and laparoscopic cryotherapy ($p<0.001$).

Bandi et al (2008) assessed the effectiveness of cryotherapy (both laparoscopic and percutaneous) relative to percutaneous RFA, and reported no difference in tumour persistence rates, local tumour progression rates or length of hospital stay among the three procedures.

In general, data on the short-term effectiveness of cryotherapy for renal tumours indicated cryotherapy to be a promising minimally invasive treatment, with low rates of technical failure (0–10.0%), tumour persistence (0–13.6%), local tumour progression (0–25.0%) and metastases (0–10.0%). However, it is noteworthy that, of the 25 studies that reported effectiveness outcomes of cryotherapy, 24 involved both patients with malignancies and those with benign lesions; only the case series by Permpongkosol et al (2006) investigated cryotherapy specifically for renal cancer. Since patients with benign tumours would be likely to have more favourable effectiveness outcomes, especially in aspects of survival, tumour persistence, local tumour progression and metastases, pooling data from studies involving a heterogeneous group of renal tumours might make cryotherapy appear more effective than if the procedure was used only for renal caner (Gill et al 2000; Rukstalis et al 2001). In this assessment, an attempt was made to extract data on clinical outcomes of cryotherapy for renal cancer, but the effectiveness of cryotherapy was mainly assessed in a population of patients with malignancies and benign masses due to a lack of data in each subgroup.

Another consideration in reporting the effectiveness of cryotherapy is the length of the follow-up period. The slow nature of progression of small renal tumours suggests that 5-year or 10-year follow-up periods are essential in assessing oncologic outcomes after cryotherapy (Birnbaum et al 1990; expert opinion of the Advisory Panel). However, in general, studies identified in the literature that examined cryotherapy for renal tumours did not have sufficient follow-up, with the longest follow-up period being less than 4 years (45.7 months) (Weld et al 2007). It is apparent that studies with short follow-up periods were not able to report meaningfully on outcomes, such as survival, local tumour progression and metastases, related to cryotherapy in the treatment of renal tumours. Therefore, long-term follow-up data remain critically important for a complete assessment of cryotherapy for renal tumours.

Imaging examinations such as CT, MRI and ultrasound play multiple roles in the cryotherapy procedure: selecting appropriate candidates for cryotherapy by providing tumour parameters (eg number, size, shape, location); guiding cryoprobe placement; determining technical success; and documenting tumour outcomes. Although, in many cases, a good correlation between imaging and histological findings has been reported, there is a chance that imaging studies might overestimate or underestimate the true extent of a tumour (Goldberg et al 2000, 2003; Rendon et al 2002). Therefore, imaging results and histological findings should always be carefully differentiated when clinical outcomes of cryotherapy for renal tumours are reported.

No comparative data were available that reported the effectiveness outcomes following cryotherapy and those during surveillance. There were several studies investigating natural history and actual growth of small renal tumours with imaging features suggestive of cancer. In one case series by Abouassaly et al (2008), a total of 110 elderly patients (mean age: 81 years) with comorbidities were managed with surveillance. The mean tumour diameter was 2.5 cm (range: 0.9–11.2 cm) before surveillance. An average tumour growth rate of 0.26 cm per year was observed in 89 of these patients with follow-up imaging, although 38 (42.7%) of the 89 showed no tumour growth. Four out of the 110 (3.6%) patients with tumour progression underwent invasive treatments. Within a

24-month follow-up period, no patient died from renal tumours. The other three case series with smaller sample sizes also demonstrated that surveillance appeared to be a viable treatment option for patients with small renal tumours, with no obvious adverse impact on clinical outcomes. During follow-up periods of 32–44 months, no patient in these studies died from renal tumours, developed metastatic diseases or had disease upstaging secondary to delayed intervention (Birnbaum et al 1990; Kouba et al 2007; Wehle et al 2004).

The body of evidence included in this assessment was appraised according to the NHMRC guidance on clinical practice guideline development (NHMRC 2007). Table 78 presents the results of the appraisal of the evidence considered in this assessment. The populations of the studies examined were generalisable to the target population of patients with small localised renal tumours within Australia. The results of the studies are applicable to the Australian healthcare context, with all studies being conducted in developed countries with similar standards of practice in the treatment of small localised renal tumours.

Table 78 Assessment of body of evidence for effectiveness of cryotherapy[a]

Component	Excellent	Good	Satisfactory	Poor
Evidence-base			Level III studies with low risk of bias, or level I or II studies with moderate risk of bias	
Consistency		Most studies are consistent and inconsistency may be explained		
Clinical impact			Moderate	
Generalisability	Population(s) studied in body of evidence are the same as the target population			
Applicability		Applicable to Australian healthcare context with few caveats		

[a] For an explanation of this table refer to 'Assessment of the body of evidence' on page 138

What are the economic considerations?

Since there was insufficient evidence on which to base a cost-effectiveness analysis, a financial incidence analysis of cryotherapy relative to currently available treatments was carried out to indicate the expenditures involved with each procedure from an Australian Government perspective as well as from a society perspective.

The unit costs of laparoscopic cryotherapy and percutaneous cryotherapy are $13 005 and $11 976, respectively, when 100 procedures are performed annually on a cryotherapy machine, and $12 546 and $11 517, respectively, if the annual volume of cryotherapy procedures is 500 per instrument. Cryotherapy results in higher expenditures of around $2550–$7950 relative to partial nephrectomy and RFA. Given the scenario where 146 cryotherapy procedures are performed annually in Australia, with a ratio of 65:35 between laparoscopic cryotherapy and percutaneous cryotherapy, the total cost of

cryotherapy would range between $1 779 228 and $1 846 243. The financial implications of cryotherapy to the Australian healthcare system overall would be an *additional* cost of $729 238 –$791 664 per year relative to partial nephrectomy, RFA and the current level of cryotherapy use. The greater total expenditure on cryotherapy is largely a consequence of the expensive disposable Cryokit and gases.

The total costs to the Australian Government were estimated in two scenarios: if 37 cryotherapy procedures are performed in the private health sector (public to private patient split of 75:25), an *additional* cost of $9 568 would be borne by the Commonwealth; when 50 per cent of cryotherapy procedures are performed in the private healthcare setting, cryotherapy would result in an *additional* cost of $18 715 to the government relative to partial nephrectomy, RFA and currently performed cryotherapy.

It should be highlighted that the clinical need for renal cryotherapy procedures in Australia is expected to increase considerably, with more renal tumours being incidentally detected by imaging examinations and with patients playing an active role in the treatment decision-making process (preferring active treatments over surveillance). The cost estimates of the impact of cryotherapy to the society and the government are anticipated to double or triple in the future.

What are other considerations

This section provides information that does not fit with the evidence-based assessment of the safety, effectiveness and cost-effectiveness of cryotherapy for renal cancer, but nevertheless impacts on this assessment.

Technical considerations

Cryotherapy can be performed via laparoscopic or percutaneous access routes. It offers minimally invasive approaches to ablate suspicious renal malignancies in situ under the guidance of real-time monitoring with ultrasound, CT or MRI. Laparoscopic cryotherapy facilitates multifocal pathological sampling, direct visual monitoring of cryoprobe placement and cryolesion progression in relation to the target tumour. It visualises adjacent organs, such as bowl, spleen and liver, to avoid intra-procedural injuries, and establishes haemostasis when necessary (Gill 2005; Pattaras & Marshall 2005; Stein & Kaouk 2007).

Percutaneous cryotherapy is less invasive than laparoscopic cryotherapy and therefore results in shorter hospital stay and earlier convalescence. However, this procedure is more challenging than laparoscopic cryotherapy in that it is performed under guidance of imaging studies without any direct visual clues. Other disadvantages of the percutaneous cryotherapy procedure include difficulties in dodging vital structures during cryoprobe placement, and radiation exposure when intra-operative CT image guidance is used (Stein & Kaouk 2007).

Laparoscopic cryotherapy and percutaneous cryotherapy are considered to be more difficult and complex than open surgeries, and require substantial training. However, the learning curve for these two cryotherapy approaches is considerably shorter than that for laparoscopic partial nephrectomy, which requires that tumour extirpation, intra-corporeal suturing, collecting system repair and parenchymal defect reconstruction are completed within a limited period of warm renal ischemia (Aron et al 2007; Cestari et al 2007; Cozar & Tallada 2008). As cryotherapy for renal tumours is a relatively new procedure, most of

the studies identified in the literature have incorporated a learning curve. It is expected that better safety outcomes would be reported as experience and expertise in cryotherapy performance increase.

Cryotherapy is an in-situ ablative technology. The key difference from extirpative surgeries, such as open partial nephrectomy and laparoscopic partial nephrectomy, is that the surgical margin cannot be histologically examined after cryotherapy; hence, the pathological confirmation of complete tumour destruction is not available. Therefore, meticulous sequential follow-up imaging is essential for assessing treatment effectiveness and detecting tumour progression after cryotherapy (Gill et al 2000; Aron et al 2007).

Accessibility of cryotherapy and its comparators

The accessibility of cryotherapy and its comparators (partial nephrectomy, RFA and surveillance), by those patients who could potentially benefit, is an important issue when assessing cryotherapy for small renal cancer.

Patients with small renal cancer have multiple nephron-sparing treatment options. Open partial nephrectomy is one of the most commonly performed treatments of small renal tumours (Cozar & Tallada 2008; Russo 2007). It was once only reserved for patients with a single functioning kidney, bilateral renal tumours or renal insufficiency; now, open partial nephrectomy is considered a potential alternative to radical nephrectomy for patients with a normal contralateral kidney (Shuch et al 2006). As a well-established technology, open partial nephrectomy is performed in a large number of specialised hospitals (Cozar & Tallada 2008).

Minimally invasive procedures, presumably associated with fewer complications, shorter hospital stay and earlier recovery, are mostly beneficial for patients who are not suitable for surgery, usually older patients with comorbidities (Aron et al 2007; Dominguez-Escrig et al 2008). Current commonly used minimally invasive treatment options for small renal cancer include cryotherapy, laparoscopic partial nephrectomy and RFA. As mentioned in the 'Discussion' section of Part A – Salvage cryotherapy for recurrent or persistent prostate cancer after radiotherapy, the cryotherapy procedure would be expected to be performed in a limited number of clinics because of the costly cryotherapy system, specialised equipment and advanced procedural techniques required. However, in the future, cryotherapy might become more widespread in clinical practice in Australia when it has broader indications, and clinical experience in performing cryotherapy accumulates.

Laparoscopic partial nephrectomy is a rapidly emerging minimally invasive procedure that attempts to duplicate surgical principles of open partial nephrectomy, with clear advantages over the open approach, especially on wound-related morbidity. It is deemed as the 'gold standard' in the treatment of presumed small renal cancer. The primary obstacle for the wide use of laparoscopic partial nephrectomy is its steep learning curve. This challenging procedure can only be performed by experienced urologists in specialised centres (Dominguez-Escrig et al 2008; Gill et al 2002). It is anticipated that laparoscopic partial nephrectomy will be performed in more patients following an increase in surgical experience and technical training in this procedure.

RFA, like cryotherapy, is a newcomer in the treatment of small renal tumours. Although a variety of RFA generators have received TGA full marketing approval (Therapeutic Goods Administration 2008), RFA for the treatment of renal cancer is not reimbursed by Medicare. This technology is still under study and not widely used in clinical practice in

Australia. However, RFA may become widely accessible to patients with small renal cancers if it shows promising clinical outcomes when the technology is fully investigated.

Patients who choose surveillance should have access to regular follow-up imaging so that tumour progression can be monitored.

Equity between different population

The MSAC should consider topics such as equity when determining whether a health technology should be recommended for reimbursement. The applicant indicated that cryotherapy for renal cancer would be beneficial for patients living in rural or remote areas, as it is associated with less hospital stay and early convalescence when compared with open partial nephrectomy and laparoscopic partial nephrectomy. However, the highly specialised equipment and surgical skills required to perform the procedure will restrict cryotherapy to being available in only a small number of tertiary clinics. In addition, the ablative nature of cryotherapy makes serial post-operative imaging studies critical for tumour progression monitoring. Patients in rural or remote areas would still need to travel for the cryotherapy procedure and sequential radiological follow-up. Therefore, cryotherapy is unlikely to increase health equity between renal cancer patients in metropolitan areas and those in rural areas.

Patient journey

A patient's knowledge of their small renal cancer usually starts with incidental detection of a renal mass, since the majority of patients with small renal cancers have no symptoms. It is understandable that the diagnosis of renal tumour shocks asymptomatic patients more severely than those who have symptoms before diagnosis (Taylor 2002). Since renal cancer is a disease not often covered by media, public discussion or official reports, patients with small renal tumours are usually ignorant of the disease and its treatment at the time of diagnosis. It has been reported by some patients that they feel frustrated by the little chance they are given to discuss the disease and its treatment options with their clinicians (Taylor 2002).

The decision regarding treatment of small renal tumours is based on several uncertainties—in the growth rate of tumours, in the tumours' histology (malignancies or benign lesions) and in malignant potential and prognosis of renal cancer if it is pathologically confirmed (Birnbaum et al 1990; Gill 2005; Kouba et al 2007). Due to the above facts, a variety of treatment options are available for small renal tumours, with open partial nephrectomy at one extreme of invasiveness and surveillance at the other.

At present, laparoscopic partial nephrectomy is the 'gold standard' for the treatment of presumed small renal cancer, with reported 5-year overall and disease-specific survival rates of 86 per cent and 100 per cent, respectively (Lane & Gill 2007). Open partial nephrectomy also shows promising long-term oncologic outcomes, with 5-year and 10-year disease-specific survival rates of 88 per cent and 73 per cent, respectively (Fergany et al 2000). However, both of these extirpative treatments have limits. Open partial nephrectomy, as a surgery, is most beneficial for young patients with no significant comorbidities, whereas laparoscopic partial nephrectomy is constrained by the highly specialised skills required for performing this procedure (Aron et al 2007; Cestari et al 2007; Cozar & Tallada 2008; Russo 2007).

The ablative procedures potentially available to frail patients with comorbidities are cryotherapy and RFA. Neither of these procedures has sufficient follow-up to allow a

comprehensive assessment of their effectiveness. Patients can also select surveillance when they are not fit for or decline invasive treatments.

In general, each of the above mentioned treatments for small renal tumours has advantages and disadvantages. Therefore, a shared decision-making process between patients and clinicians, based on patients' full access to relevant evidence and information, is critical. No studies about patient preferences on treatments for small renal tumours have been identified. However, it is hypothesised that young patients without comorbidities might prefer to undergo open partial nephrectomy due to its proven long-term oncologic outcomes and wide accessibility. For older patients with comorbidities, patient preference would frequently be for laparoscopic partial nephrectomy if their treating clinicians have the specialised experience required for this procedure, because this procedure is the only minimally invasive choice with good long-term effectiveness. However, if cryotherapy proves itself to be a treatment with promising clinical outcomes over a sufficient follow-up period, patients might prefer cryotherapy over partial nephrectomy because of cryotherapy's minimally invasive nature, lower blood loss, shorter operative time and shorter hospital stay. It is difficult to predict what patient preferences may be between cryotherapy and RFA due to the lack of clinical evidence that one procedure is better than the other. Treatment decisions might therefore be based on the availability of these two treatments and surgeons' clinical experience. It is also hypothesised that, when compared with surveillance, cryotherapy would likely be the choice for those patients who can afford invasive procedures. Patients might feel 'safer' with the tumours being destroyed considering that a proportion of patients who undergo surveillance would eventually undergo invasive procedures after a period of expectant management (Abouassaly et al 2008; Birnbaum et al 1990; Kouba et al 2007; Wehle et al 2004).

Conclusions

Safety

Argon-based cryotherapy has been assessed in a population of patients with *presumed* small (<4 cm) localised renal cancer. Data on the safety of cryotherapy were provided by three controlled studies (level III-2 intervention evidence), 16 case series (level IV intervention evidence) and 16 case reports.

In general, laparoscopic cryotherapy was at least as safe as laparoscopic partial nephrectomy, as the estimated blood loss from cryotherapy was only one-quarter of that from partial nephrectomy and no significant differences in complication rates and pre/post-procedurally serum creatinine levels were observed between the two procedures.

Patients received fewer sedatives during percutaneous cryotherapy than percutaneous RFA, whereas laparoscopic cryotherapy required more anaesthesia time than both percutaneous procedures. Major complication rates and estimated blood loss were not significantly different among these three procedures.

No studies identified in the literature compared the safety of cryotherapy relative to surveillance. Since surveillance is a non-interventional therapy, cryotherapy is unlikely to be safer in the short term than surveillance in the treatment of small renal tumours.

In all studies identified in the literature, only one procedural-related death was reported: an elderly woman with multiple comorbidities died of a pulmonary embolism 20 days after cryotherapy. Cryotherapy for renal tumours frequently resulted in significant adverse events; however, this might be related to the patient selection criteria for cryotherapy in clinical practice, where cryotherapy is indicated for elderly patients with comorbidities. All minor complications from cryotherapy were self-limiting and did not require medical intervention. Peri-procedural blood loss was minor in all but one patient, who lost 1000 mL of blood during a cryotherapy procedure. The post-operative serum creatinine levels were not significantly different from their baseline values before cryotherapy.

Performing cryotherapy laparoscopically reduced the occurrence of minor complications when compared to percutaneous cryotherapy. No difference was found in the safety profiles between different generations of argon-based cryotherapy for renal tumours.

Effectiveness

Twenty-five observational studies were identified that reported on the effectiveness of cryotherapy for the treatment of *presumed* small renal cancer. Of these, four studies assessed the clinical outcomes of cryotherapy relative to partial nephrectomy or RFA (level III-2 intervention evidence), and the remaining 21 were case series (level IV intervention evidence). None of these studies had a follow-up period longer than 5 years.

There was insufficient evidence to determine the effectiveness of cryotherapy relative to partial nephrectomy, although no significant difference in local tumour progression rates was reported between the two procedures in a follow-up period of less than 12 months.

Cryotherapy, especially percutaneous cryotherapy, resulted in shorter hospital stay when compared to partial nephrectomy (laparoscopic or open). Less operative time was required for laparoscopic cryotherapy than for partial nephrectomy. No other effectiveness outcomes, such as overall survival, disease-specific survival, tumour persistence and metastases, were compared between cryotherapy and partial nephrectomy.

No significant difference in tumour persistence, local tumour progression or length of hospital stay was observed between cryotherapy (laparoscopic and percutaneous) and RFA.

Due to the lack of evidence comparing cryotherapy with surveillance, no conclusion can be drawn regarding the effectiveness of cryotherapy compared to surveillance.

In general, cryotherapy resulted in favourable short-term effectiveness outcomes in treatment of small renal tumours. Within follow-up periods of less than 2 years, overall survival rates and disease-specific survival rates after cryotherapy for small renal tumours were greater than 87 per cent and consistently 100 per cent, respectively. Relatively low rates in tumour persistence, local tumour progression, metastases and technical failure were also reported across studies.

However, long-term effectiveness of cryotherapy for presumed renal cancer has not been proved. In addition, assessing cryotherapy in patients with *presumed* renal cancer, which might include both benign and malignant renal tumours, is likely to overestimate the real effectiveness of cryotherapy in treatment of renal cancer.

Economic considerations

As there was not enough evidence indicating that cryotherapy is as effective as, or more effective than, partial nephrectomy, a cost-effectiveness analysis was not warranted. Instead, a financial incidence analysis was performed, employing a base case where 50 per cent of patients who are currently treated by RFA would otherwise choose cryotherapy.

It is estimated that cryotherapy would incur an *additional* annual cost of $9 568 or $18 715 to the Australian Government relative to partial nephrectomy, RFA and currently performed cryotherapy if 37 or 74, respectively, cryotherapy procedures are performed in the private health sector per year in Australia.

The total cost to the Australian healthcare system overall includes patient co-payments, costs of disposables, hospital services and capital equipment costs. The unit costs of laparoscopic cryotherapy and percutaneous cryotherapy are estimated to be $12 546–$13 005 and $11 517–$11 976, respectively, with different annual volumes of cryotherapy procedures per machine (100 and 500). In a scenario where 95 laparoscopic cryotherapy procedures and 51 percutaneous cryotherapy procedures are performed each year in Australia, the total cost to the healthcare system overall would range between $1 779 228 and $1 846 243. This is in contrast to the costs of partial nephrectomy, RFA and current levels of cryotherapy use, which require an expenditure of between $122 373 and $674 068. In total, if cryotherapy is funded on the MBS, it is expected to incur an *additional* cost of $729 238 to $791 664 to the Australian healthcare system overall relative to currently available treatments.

The *additional* cost of cryotherapy to the Australian society would range between $372 983 and $1 169 840 if 96 to 196 cryotherapy procedures are performed each year in Australia.

It is noteworthy that the cost implications of cryotherapy to the Australian Government and to the healthcare system overall would greatly exceed the above estimates if the number of cryotherapy procedures performed each year goes up. This is expected to occur in response to more small renal lesions being discovered by imaging studies and with patients being more involved in the clinical decision-making process, which increases the proportion of patients receiving active treatment (including cryotherapy) rather than surveillance.

Appendix H Advisory Panel and Evaluators

Advisory Panel – Application 1124 – Cryotherapy for recurrent prostate cancer and renal cancer

Part B: Cryotherapy for renal cancer

Member	Expertise
Dr Kwun Fong (Chair)	Thoracic Medicine
Prof Dick Fox (Deputy Chair)	Oncology
Dr William John Lynch	Urology
Dr Stuart McAlister Lyon	Radiology
Dr Bronwyn Matheson	Radiation Oncology
Mr Alan Moran	Consumer Health

Evaluators

Name	Organisation
Ms Zhaohui Liufu	Research Officer, Adelaide Health Technology Assessment
Ms Skye Newton	Senior Research Officer, Adelaide Health Technology Assessment
Prof. Janet Hiller	Director, Adelaide Health Technology Assessment

Appendix I Search strategies

Table 79 Search terms used

Element of clinical question	Search terms
Population	renal OR kidney* OR kidney[MeSH]
Intervention/test	cryotherap* OR cryotherapy[MeSH] OR cryosurg* OR cryosurgery[MeSH] OR cryoablat* OR focal ablat* OR minimally invasive therap*
Comparator (if applicable)	n/a
Outcomes (if applicable)	n/a
Limits	1995 – 2008 NOT (Limits: Animals NOT Limits: Human)

MeSH: Medical subject heading, based on a Medline/PubMed platform

n/a: not applicable

Table 80 Bibliographic databases

Electronic database	Time period
CINAHL	1995–11/2008
Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database	1995–11/2008
Current Contents	1995–11/2008
Embase.com (including Embase and Medline)	1995–11/2008
Pre-Medline	1995–11/2008
ProceedingsFirst	1995–11/2008
Web of Science – Science Citation Index Expanded	1995–11/2008
EconLit	1995–11/2008

Table 81 Other sources of evidence (1995–11/2008)

Source	Location
Internet	
Australian Clinical Trials Registry	http://www.actr.org.au
Australian Department of Health and Ageing	http://www.health.gov.au
NHMRC- National Health and Medical Research Council (Australia)	http://www.health.gov.au/nhmrc/
US Department of Health and Human Services (reports and publications)	http://www.os.dhhs.gov/
New York Academy of Medicine Grey Literature Report	http://www.nyam.org/library/greylit/index.shtml
Health Technology Assessment International (HTAi)	http://www.htai.org/
International Network for Agencies for Health Technology Assessment	http://inahta.org/
Trip database	http://www.tripdatabase.com
Current Controlled Trials metaRegister	http://controlled-trials.com/
National Library of Medicine Health Services/Technology Assessment Text	http://text.nlm.nih.gov/
U.K. National Research Register	https://portal.nihr.ac.uk/Pages/NRRArchive.aspx
Google Scholar	http://scholar.google.com/
Websites of Health Technology Agencies	See Table 82
Websites of Specialty Organisations	See Table 83
Hand searching (journals from 2007–08)	
American Journal of Nephrology	Library or electronic access
AJR. American Journal of Roentgenology	Library or electronic access
BJU International	Library or electronic access
Cardiovascular and Interventional Radiology	Library or electronic access
European Urology	Library or electronic access
International Urology Nephrology	Library or electronic access
International Journal of Urology	Library or electronic access
The Journal of Urology	Library or electronic access
Journal of Vascular and Interventional Radiology	Library or electronic access
Radiology	Library or electronic access
Urology	Library or electronic access
Expert clinicians	
Studies other than those found in regular searches	The MSAC Advisory Panel
Pearling	
All included articles will have their reference lists searched for additional relevant source material	

Table 82 Websites of Health Technology Assessment Agency

Health Technology Assessment Agency	Website
AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/Content/NavigationMenu/Research/ASERNIPS/default.htm
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/healthservices/cce/evidence/
Centre for Health Economics, Monash University	http://chpe.buseco.monash.edu.au
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/english/home.html
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Association for Health Services and Policy Research (CAHSPR)	http://www.cahspr.ca/
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUI)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Danish Institute for Health Services Research (DSI)	http://www.dsi.dk/engelsk.html
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://finohta.stakes.fi/EN/index.htm
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gr.nl/index.php
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://nzhta.chmeds.ac.nz/
NORWAY	
Norwegian Centre for Health Technology Assessment (SMM)	http://www.kunnskapssenteret.no/
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS)	http://www.isciii.es/htdocs/en/investigacion/Agencia_quees.jsp
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.aatm.es/cgi-bin/frame.pl/ang/pu.html

SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/english?l=en
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
Health Technology Board for Scotland	http://www.htbs.org.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health – Cost-Utility Analysis Registry	https://research.tufts-nemc.org/cear/default.aspx
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Office of Health Technology Assessment Archive (US)	http://fas.org/ota/
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/consumertec/index.html
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Table 83 Websites of specialty organisations

Consumer websites	
Kidney Health Australia	http://www.kidney.org.au/
Professional societies	
American Urological Association	http://www.auanet.org/
Australian and New Zealand Society of Nephrology	http://www.nephrology.edu.au/
Renal Society of Australasia	http://www.renalsociety.org/
Urological Society of Australia and New Zealand	http://www.urosoc.org.au/
International Society of Cryosurgery	http://www.societyofcryosurgery.org/

Appendix J Studies included in the review

Table 84 Studies included in the review of cryotherapy for renal cancer (controlled and uncontrolled studies)

Study	Location	Level of evidence (interventional) Quality Study design	Inclusion/exclusion criteria	Study population	Intervention Comparator	Outcomes	Follow-up period
3rd generation							
(Beemster et al 2008)	Academic Medical Center University of Amsterdam, the Netherlands	Level IV Quality: 3.5/6 (NHS CRD) Case series (unclear if retrospective or prospective)	*Inclusion* Patients with a suspicious small renal cancer (≤4 cm), with a follow-up period of ≥6 months after the cryotherapy procedure *Exclusion* Patients with metastatic disease, or followed up with MRI rather than CT	Number of patients: 26 Age: mean: 64 years (range: 51–79 years) 9 females, 17 males Tumour size: mean: 2.4 cm (range: 1.3–3.8 cm) Tumour histology: RCC: 11 (42%) Oncocytomas: 4 (15%) Angiomyolipoma: 1 (4%) Not diagnostic: 7 (27%) No biopsy: 3 (12%)	CryoNeedles or SeedNet argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 1.5 mm 2 FTC	*Effectiveness* Tumour persistence, cryolesion size	Mean: 17 months (range: 6–36 months)
(Caviezel et al 2008)	Geneva University Hospital, Geneva, Switzerland	Level IV Quality: 4.5/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with small (≤3 cm) solid renal tumours located on the peripheral of the kidney, with normal haemostatic parameters *Exclusion* Patients with contraindication to MRI, with evidence of involvement of the collecting system, or with evidence of lung metastasis	Number of patients: 7 Age: mean: 61.5 years (range: 34–84 years) 2 females, 5 males Tumour size: mean: 2.1 cm (1.1–3.0 cm) Tumour histology: RCC: 5 (71%) Angiomyolipoma: 1 (14%) Aspecific fibrovascular tissue: 1 (14%) Indications: Solitary kidney: 2 (29%) Chronic renal insufficiency: 4 (57%) Kidney graft: 1 (14%) Clinical stage: pT1aN0M0	Cryo-Hit argon-based cryotherapy system MRI-guided percutaneous cryotherapy Cryoprobe size: 2 mm 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Technical success, tumour persistence, local tumour progression, metastases, operative time, length of hospital	Mean: 28 months (range: 7–43 months)

				ASA score: mean: 2.5 (range: 2–3) Pre-cryotherapy serum creatinine level: mean: 124 umol/L (range: 173–166 umol/L) Pre-cryotherapy haemoglobin level: mean 13.9 g/dL (12.1–16.0 g/dL)		stay	
(Gore et al 2005)	University of California, Los Angeles, the United States Roswell Park Cancer Institute, New York, the United States	Level IV Quality: 3.5/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with tumours considered eligible for nephron-sparing surgery: with small (<4 cm) tumours at the periphery of the renal parenchyma *Exclusion* Not stated	Number of patients: 4 (5 tumours) Age: mean: 61.3 years (range: 22–79 years) Tumour size: mean: 2.0 cm (range: 1.5–2.0 cm) Indications: Small unilateral tumours: 2 (50%) Synchronous small contralateral tumour with a history of radical nephrectomy for a large RCC: 1 (25%) Small unilateral tumours with a history of tuberous sclerosis, with prior resection of multiple bilateral angiomyolipomas: 1 (25%) Pre-cryotherapy serum creatinine level: mean: 1.0 mg/dL (range: 0.7–1.2 mg/dL)	Galil argon-based cryotherapy system US-guided laparoscopy-assisted percutaneous cryotherapy Cryoprobe size: 17-G Cryoprobe number: 2-6 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Tumour persistence, local tumour progression, operative time, length of hospital stay	Range: 8–17 months
(Lehman et al 2008)	Columbia University, New York, the United State	Level IV Quality: 3.5/6 (NHS CRD) Prospective case series	*Inclusion* Patients with small (<3.0 cm) localised, enhancing renal mass on CT or MRI *Exclusion* Not stated	Number of patients: 23 (30 tumours) Age: mean: 70.2 years Tumour size: mean: 1.8 cm (range: 0.7–2.8 cm) Tumour histology: RCC: 14 (47%) Oncocytomas 6 (20%) Angiomyolipoma: 1 (3%) Myelolipoma: 1 (3%) Non-diagnostic or no biopsy: 8 (27%) ASA score: mean: 1.8 (range: 1–3) Pre-cryotherapy serum creatinine level: mean: 1.15 mg/dL	17-gauge argon-based cryotherapy system US-guided laparoscopic cryotherapy 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Tumour persistence, local tumour progression, length of hospital stay	Mean: 11 months (range: 3–20 months)

(O'Malley et al 2007)	New York University School of Medicine, New York, the United States	Level III-2 Quality: 4/6 (NHMRC) Matched-pairs cohort study	*Inclusion* Elderly patients with known comorbidities (poor surgical candidates), with small (<4 cm) peripheral tumours *Exclusion* Not stated	*Intervention* Number of patients: 15 Age: mean: 76.1±4.5 years 6 females, 9 males Tumour size: 2.7±1.3 cm Indications: Comorbidities (>1): 7 (47%) Solitary kidney: 2 (13%) ASA score: 3–4: 9 (60%) BMI: mean: 29.1±6.8 kg/m^2 Pre-cryotherapy creatinine level: mean: 1.17±0.33 mg/dL Pre-cryotherapy haematocrit level: mean: 48.4±3.2%	*Intervention* SeedNet argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 17-G 2 FTC	*Safety* Intro-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Local tumour progression, operative time, length of hospital stay	*Intervention* Mean: 11.9 months
				Comparator Number of patients: 15 Age: mean: 75.7±4.6 years 3 females, 12 males Tumour size: 2.5±1.0 cm) Indications: Comorbidities (>1): 7 (47%) Solitary kidney: 0 ASA score: 3–4: 8 (53%) BMI: mean: 27.1±3.9 kg/m^2 Pre-cryotherapy creatinine level: mean: 1.21±0.16 mg/dL Pre-cryotherapy haematocrit level: mean: 40.7±3.5% (p<0.005 in all patient characteristics)	*Comparator* US-guided laparoscopic partial nephrectomy		*Comparator* Mean: 9.83 months

(Polascik et al 2007)[a, b]	Duke University Medical Center, Durham, the United States	Level IV Quality: 4.5/6 (NHS CRD) Case series (unclear if retrospective or prospective)	*Inclusion* Patients with small (≤3.5 cm) renal mass(es) who were considered candidates for nephron-sparing surgery: absence of local and systematic spread on MRI or CT, and ability to tolerate general anaesthesia *Exclusion* Not stated	Number of patients: 26 (28 tumours) Age: median: 64 years (range: 44–79 years) 10 females, 16 males Tumour size: median: 2.0 cm (range: 1–3.5 cm) Tumour histology: Clear cell RCC: 19 (68%) Papillary RCC: 3 (11%) Oncocytoma: 4 (14%) Angiomyolipoma: 2 (7%)	Galil argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 17-G 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Overall survival, disease-specific survival, local tumour progression, length of hospital stay	Mean: 21 months
(Wink et al 2007)	University of Amsterdam, St Lucas Andreas Hospital, Amsterdam, the Netherlands Onze Lieve Vrouwen Gasthuis, Amsterdam, the Netherlands	Level IV Quality: 3/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with small solid renal tumours *Exclusion* Not stated	Number of patients: 7 (8 tumours) Age: mean: 64 years (range: 52–78 years) 1 female, 6 males Tumour size: median: 2.0 cm (range: 1.1–3.2 cm)	SeedNet argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 17-G 2 FTC	*Effectiveness* Cryolesion size	Range: 3.2–17.6 months
(Wright et al 2007)	Loyala University Medical Center, Maywood, the United States University of Maryland Medical Center, Baltimore, the United States	Level IV Quality: 4.5/6 (NHS CRD) Retrospective case series	*Inclusion* Small (<4 cm), localised, peripheral renal tumour *Exclusion* Not stated	Number of patients: 32 (35 tumours) Age: mean: 67 years (range: 41–85 years) 15 females, 17 males Tumour size: mean: 1.9 cm (range: 1–4 cm) Tumour histology: RCC: 18 (67%) Benign: 5 (18%) Not conclusive: 4 (15%) Indications: Solitary kidney: 5 (16%) Compromised contralateral kidney: 1 (3%) Normal contralateral kidney: 26 (81%)	Oncura argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 17-G Cryoprobe number: 1–6 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Technical success, tumour persistence, local tumour progression, operative time, length of hospital	Median: 18 months (minimum: 6 months)

						stay	
(Wyler et al 2007)	University Hospital Basel, Basel, Switzerland	Level IV Quality: 4/6 (NHS CRD) Prospective case series	*Inclusion* Patients with solitary small (<4 cm) peripheral renal tumours *Exclusion* Patients with tumours extending into the collecting system	Number of patients: 14 Age: mean: 68 years (range: 49–83 years) 4 females, 10 males Tumour size: mean: 2.8 cm (range: 2.0–4.0 cm) Tumour histology: RCC: 10 (71%) Angiomyolipoma: 2 (14%) Not conclusive: 1 (7%) No histology: 1 (7%) Indications: Solitary kidney: 2 (14%) ASA score: 3: 9 (64%); 2: 4 (29%); 1: 1 (7%)	SeedNet argon-based cryotherapy system US-guided retroperitoneoscopy-assisted cryotherapy (13 patients) US-guided open cryotherapy (1 patient) Cryoprobe size: 17-G Cryoprobe number: 6 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss *Effectiveness* Overall survival, disease-specific survival, local tumour progression, operative time, cryolesion size, length of hospital stay	Mean: 21 months (range: 2–42 months)
2nd or 3rd generation							
(Badwan et al 2008)	Washington University School of Medicine, St. Louis, the United States	Level IV Quality: 3.5/6 (NHS CRD) Retrospective uncontrolled post-test case series	*Inclusion* Laparoscopic cryotherapy: patients with small (<4 cm) renal tumours, amenable to surgical intervention Percutaneous cryotherapy: patients with renal tumours <3 cm), advanced age, presence of comorbid conditions precluding other procedures *Exclusion* Not stated	Number of patients: 36 Laparoscopic cryotherapy: 23 Percutaneous cryotherapy: 13	Laparoscopic cryotherapy Percutaneous cryotherapy	*Effectiveness* Length of hospital stay *Cost-effectiveness* Hospital costs	Until discharge

(Bandi et al 2008)[c]	University of Wisconsin, Madison, the United States	Level III-2 Quality: 2/6 (NHMRC) Retrospective cohort study	*Inclusion* Patients with small (<4 cm) renal tumours *Exclusion* Not stated	*Interventions* Number of patients: 58 Age: mean: 66 years 33 males, 25 females Tumour size: mean: 2.6 cm BMI: mean: 30 kg/mm^2 ASA score: mean: 3	*Interventions* Argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe number: mean: 1.5 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, pain control requirements *Effectiveness* Overall survival, disease-specific survival, tumour persistence, local tumour progression, length of hospital stay, convalescence and patient satisfaction	*Interventions* Mean: 28 months
				Number of patients: 20 Age: mean: 69 years 16 males, 4 females Tumour size: mean: 2.2 cm (LCT vs PCT: p<0.005) BMI: mean: 31 kg/mm^2 ASA score: mean: 3	Percutaneous cryotherapy with mean 1.1 probes using argon gas 2 FTC Ultrasound or fluoroscopy guidance		Mean: 15 months
				Comparators Number of patients: 15 Age: mean: 63 years 11 males, 4 females Tumour size: mean: 2.2 cm (LCT vs RFA: p<0.005) BMI: mean: 28 kg/mm^2 ASA score: mean: 3	*Comparator* Percutaneous RFA Mean 1.6 probes		*Comparator* Mean: 20 months
(Link et al 2006)[d]	Johns Hopkins Medical Institutions, Baltimore, the United States	Level III-2 Quality: 2/6 (NHMRC) Retrospective cohort study	*Inclusion* Originally reserved for cases of renal insufficiency or the solitary kidney; now used for majority of patients with localised renal tumour *Exclusion* Not stated	*Interventions* Number of patients: 28 Tumour size: mean: 2.4±0.9 cm	*Interventions* Argon-based cryotherapy system Laparoscopic cryotherapy	*Effectiveness* Length of hospital stay *Cost-effectiveness* Hospital costs	Until discharge
				Number of patients: 22 Tumour size: mean: 2.3±1.1 cm	Argon-based cryotherapy system CT-guided percutaneous cryotherapy		
				Comparators Number of patients: 217 Tumour size: mean: 2.6±1.3 cm (LCT vs LPN: p=0.431) (PCT vs LPN: p=0.297)[e]	*Comparators* Laparoscopic partial nephrectomy		

				Number of patients: 50 Tumour size: mean: 3.5±1.7 cm (LCT vs OPN: p=0.002; PCT vs OPN: p=0.003)[e]	Open partial nephrectomy		
(Mouraviev et al 2007)[a, b]	Duke University Medical Center, Durham, the United States	Level III-2 Quality: 3.5/6 (NHMRC) Retrospective case series	*Inclusion* Patients with small (≤3.5 cm) solid tumour, absence of local and systematic spread, and the ability to tolerate general anaesthesia. Indications for nephron-sparing surgery include: (1) absolute indication: where radical nephrectomy would render the patient anephric (eg RCC involving a solitary functioning); (2) relative indication: unilateral RCC and functioning but compromised kidney by concomitant disease (eg hereditary form of RCC such as von Hippel-Lindau disease); and (3) elective indication: localised unilateral RCC and normal contralateral kidney with size criterion tumour ≤3.5 cm *Exclusion* Not stated	*Intervention* Number of patients: 20 Age: mean: 65 years ±9 years 13 females, 7 males Tumour size: mean: 2.0±0.7 cm Tumour histology: Malignant/benign (%): 84/16 ASA score: mean: 2.47±0.5	*Intervention* Argon-based cryotherapy system Laparoscopic cryotherapy	*Effectiveness* Length of hospital stay *Cost-effectiveness* Hospital costs	Until discharge
				Comparators Number of patients: 20 Age: mean: 62±13 years 12 females, 8 males Tumour size: mean: 2.0±0.6 cm Tumour histology: Malignant/benign (%): 78/22 ASA score: mean: 2.28±0.7	*Comparators* Laparoscopic partial nephrectomy		
				Number of patients: 71 Age: mean: 58±13 years 38 females, 33 males Tumour size: mean: 2.2±0.7 cm Tumour histology: Malignant/benign (%): 85/15 ASA score: mean: 2.47±0.6	Open partial nephrectomy		
2nd generation							

(Allaf et al 2005)[d]	Johns Hopkins Medical Institutions, Baltimore, the United States	Level III-2 Quality: 4.5/6 (NHMRC) Matched-pairs retrospective cohort study	*Inclusion* Patients with small (≤4 cm) renal masses *Exclusion* Not stated	*Intervention* Number of patients: 10 (11 tumours) Age: mean: 66.5 years (range: 36–84 years) 0 females, 10 males Tumour size: mean: 2.0 cm (range: 1.3–3.3 cm) ASA score: 3: 4 (40%); 4: 6 (60%) *Comparator* Number of patients: 14 (15 tumours) Age: mean: 68.1 years (range: 39–86 years) 3 females, 11 males Tumour size: mean: 2.3 cm (range: 1.0–4.0 cm) ASA score: 3: 4 (28%); 4: 10 (72%) (p>0.05 in all patient characteristics)	*Intervention* CryoCare argon-based cryotherapy system CT-guided percutaneous cryotherapy 2 FTC *Comparator* CT-guided percutaneous RFA	*Safety* Pain control requirements	Until discharge
(Atwell et al 2008)	Mayo Clinic, Rochester, the United States	Level IV Quality: 3.5/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with small (<4 cm) solid renal mass *Exclusion* Not stated	Number of patients: Not stated/110 (86/115 tumours) In the total 110 patients (115 tumours): 33 females, 77 males Age: mean: 72 years (range: 47–93 years) Tumour size: mean: 3.3 cm (range: 1.5–7.3 cm) Tumour histology: RCC: 52 (45%) Oncocytoma: 16 (14%) Oncocytic tumour: 8 (7%) Atypical or suspicious tumour: 2 (2%) Epithelial neoplasm favouring RCC: 1 (1%) Necrosis: 1 (1%) RCC history: 15 (13%) Solid and presumed to be malignancy: 10 (7%)	Perc-24 argon-based cryotherapy system CT-guided and US-guided percutaneous cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: mean: 2 (range: 1–8) 2 FTC	*Effectiveness* Technical success, local tumour progression	In the total 110 patients: Mean: 13.3 months (range: 3–39 months)
(Bolte et al 2006)[c]	University of Wisconsin Hospital and Clinics, Madison, the United States	Level IV Quality: 3/6 (NHS CRD) Retrospective	*Inclusion* Patients with small (<4 cm) non-cystic, exophytic renal masses who were followed up with MRI for at least 6 months	Number of patients: 18 Age: range: 54–88 years 4 females, 14 males	AccuProbe argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 2.4–4.8 mm	*Effectiveness* Local tumour progression	Range: 6–48 months

		case series	*Exclusion* Not stated		Cryoprobe number: 1–2 2 FTC		
(Colon & Fuchs 2003)	Cedars-Sinai Medical Center, Los Angeles, the United States	Level IV Quality: 3.5/6 (NHS CRD) Prospective case series	*Inclusion* Patients with small renal lesions and significant comorbidities *Exclusion* Not stated	Number of patients: 8 Age: mean: 75.6 years (range: 68–82 years) 5 females, 3 males Tumour size: mean: 2.6 cm (range: 1.4–3.8 cm) Indications: Solitary kidneys: 3 (38%) Comorbidities (>4): 7 (88%)	CryoProbe argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 3 mm 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss, serum creatinine level *Effectiveness* Tumour persistence, local tumour progression, operative time, length of hospital stay	Range: 5–16 months
(Georgiades et al 2008)	John Hopkins Hospital, Baltimore, the United States	Level IV Quality: 4/6 (NHS CRD) Case series (unclear if retrospective or prospective)	*Inclusion* Patients with Bosniak class III/IV [f] small (≤4 cm) renal lesions *Exclusion* Patients with uncorrectable bleeding diathesis, lack of percutaneous window, with disease extending into renal vein or invading adjacent organs, or with survival-limiting metastatic other diseases	Number of patients: not available / 46 (45/51 tumours) In the total of 46 patients (51 tumours): 15 females, 31 males Age: median: 67 years (range: 43–90 years) Tumour histology: RCC: 29 (63%) Oncocytoma: 3 (7%) Angiomyolipoma: 2 (4%) No further classified benign lesions: 2 (4%) RCC history: 5 (11%) No biopsy: 5 (11%) Pre-cryotherapy creatinine level: mean: 1.3±0.6 mg/dL	EndoCare argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 1.7–2.4 mm Cryoprobe number: mean: 2.5 2 FTC	*Safety* Intra-operative or post-operative complications *Effectiveness* Tumour persistence	Not available

(Goel & Kaouk 2008)	Glickman Urological and Kidney Institute Cleveland Clinic, Cleveland, the United States	Level IV Quality: 4/6 (NHS CRD) Prospective case series	*Inclusion* Patients with small (<3 cm) localised renal mass, with renal insufficiency or increased surgical risk for partial nephrectomy *Exclusion* Patients with multiple abdominal surgeries or solitary kidneys	Number of patients: 6 Age: mean: 73±9 years Tumour size: mean: 2.6±0.4 cm BMI: mean: 33±10 kg/m^2	EndoCare argon-based cryotherapy system US-guided laparoscopic cryotherapy (single port access) Cryoprobe size: 2.4–3.8 mm Cryoprobe number: mean: 1.5 (range: 1–2) 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss *Effectiveness* Tumour persistence, operative time, length of hospital stay	Not available
(Gupta et al 2006)[d]	Johns Hopkins Hospital, Baltimore, the United States	Level IV Quality: 3.5/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with small (<4 cm) renal masses, who were poor surgical candidates or otherwise warranted nephron-sparing treatment, and with imaging follow-up period of 1 month or more *Exclusion* Not stated	Number of patients: 10 (14 tumours) Age: mean: 70 years (range: 36–81 years) 0 females, 10 males Tumour size: mean: 2.2 cm (range: 1.0–3.9 cm) Tumour histology: RCC: 5 (50%) Hereditary tumours: 1 (10%) Metastatic sarcoma: 1 (10%) Not conclusive: 3 (30%)	CryoCare argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: 1–3 2 FTC	*Safety* Intra-operative or post-operative complications *Effectiveness* Technical success, tumour persistence, cryolesion size	Mean: 8.3 months (range: 1.8–10.3 months)
(Hinshaw et al 2008)[c]	University of Wisconsin, Madison, the United States	Level IV Quality: 3/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with solid renal masses *Exclusion* Patients had two tumours ablated at a single session, or underwent cryotherapy for the residual disease identified after previous treatment	Number of patients: 30 Age: mean: 67.0±10.8 years Tumour size: mean: 2.1±0.73 cm	CryoCare argon-based cryotherapy system US-guided or CT-guided percutaneous cryotherapy Cryoprobe size: 1.7–2.4 mm 2 FTC	*Safety* Intra-operative or post-operative complications *Effectiveness* Disease-specific survival, technical success, tumour persistence, local tumour progression, length of hospital stay *Cost-effectiveness* Hospital costs	Mean: 14.5 months
				Number of patients: 60 Age: mean: 67.4±11.0 years (LCT vs PCT: p=0.89) Tumour size: mean: 2.5±0.83 cm (LCT vs PCT: p=0.04	CryoCare argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 2.4–3.0 mm 2 FTC		Mean: 14.6 months (LCT vs PCT: p=1.0)

(Moon et al 2004)[c]	University of Wisconsin, Madison, the United States	Level IV Quality: 3/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with small (<4 cm) renal tumours *Exclusion* Not stated	Number of patients: 16 Age: mean: 67 years (range: 43–84 years) 5 females, 11 males Tumour size: mean: 2.6 cm (range: 1.5–3.5 cm) Tumour histology: RCC: 5 (31%) Oncocytoma: 2 (13%) Nephrosclerosis: 1 (6%) Fibrosis: 1 (6%) Inflammation: 1 (6%) Renal cortex: 1 (6%) Normal renal tissue: 1 (6%) No biopsy: 4 (25%) Indications: Elective: 10 (63%) Solitary kidney: 3 (19%) Renal failure: 2 (13%) von Hippel-Lindau disease: 1 (6%) BMI: mean: 30 kg/m^2 (range: 23–47 kg/m^2)	AccuProbe argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 2.4–5.0 mm 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss *Effectiveness* Overall survival, disease-specific survival, tumour persistence, local tumour progression, operative time, cryolesion size, length of hospital stay	Mean: 9.6 months (range: 1–28 months)
(Permpongkosol et al 2006)[d]	Johns Hopkins University School of Medicine, Baltimore, the United States	Level IV Quality: 4/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with biopsy-confirmed small (<4 cm) localised solid RCC *Exclusion* Patients with lymph node involvement or metastases, with the presence of a bleeding dyscrasia, or unable to stop anticoagulation therapy	Number of patients: 20/21 (22/23 tumours) In the total 21 patients: 5 females, 16 males Age: mean: 71.5 years Indications: Comorbid conditions: 12 (57.1%) Solitary kidney: 3 (14.3%) Contralat renal cancer: 2 (9.5%) End stage renal disease: 2 (9.5%) von Hippel-Lindau disease: 2 (9.5%) Tumour size: mean: 2.1 cm (range: 0.5–4.3 cm) Tumour histology: Clear cell RCC: 13 (61.9%) Papillary RCC: 6 (28.6%) Granular RCC: 1 (4.8%) Mix: 1 (4.8%) Tumour position:	EndoCare argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 2.2–2.4 mm Cryoprobe number: mean: 2 (range: 1–5)	*Safety* Intra-operative or post-operative complications, serum creatinine level *Effectiveness* Technical success, tumour persistence, local tumour progression, metastases, operative time	Mean: 12.3 months (range: 4.6–18.3 months)

				Anterior: 2 (9%) Lateral: 4 (17%) Posterior: 17 (74%) Tumour classification: Exophytic: 15 (65%) Endophytic: 8 (35%) Central: 6 (26%) Non-central: 17 (74%) ASA score: median: 3 (range: 2–4) Pre-cryotherapy serum creatinine level: mean: 1.49 mg/dL (range: 0.5–3.8 mg/dL)			
(Shingleton & Sewell 2002a)[g]	University of Mississippi Medical Center, Jackson, the United States	Level IV Quality: 4.5/6 (NHS CRD) Case series (unclear if retrospective or prospective)	*Inclusion* Patients with von Hippel-Lindau disease and radiographic determined small (≤4 cm) solid renal tumours, aged over 18 years, with ability to undergo MRI *Exclusion* Patients with pacemakers or metallic implants or bleeding diathesis	Number of patients: 3/4 (4/5 tumours) Age: mean: 44.7 years (range: 35–62 years) 2 females, 1 males Indication: Hippel-Lindau disease: 3 (100%) Solitary kidney: 2 (6.7%)	Argon-based cryotherapy system MRI-guided percutaneous cryotherapy Cryoprobe size: 2–3 mm 3 FTC	*Safety* Intra-operative or post-operative complications *Effectiveness* Local tumour progression	Mean: 13 months (range: 12–15 months)
(Shingleton & Sewell 2003)[g]	University of Mississippi Medical Center, Jackson, the United States	Level IV Quality: 4.5/6 (NHS CRD) Retrospective case series	*Inclusion* Patients with solitary kidneys and small (≤4 cm) solitary renal masses who underwent percutaneous cryotherapy *Exclusion* Patients who were lost to follow-up	Number of patients: 10/12 Age: mean: 58.9 years (range: 29–76 years) Tumour size: mean: 2.4 cm (range: 1.0–4.5 cm) Indications: Solitary kidney: 10 (100%)	Argon-based cryotherapy system MRI-guided percutaneous cryotherapy Cryoprobe size: 3 mm Cryoprobe number: 1–4 3 FTC	*Safety* Intra-operative or post-operative complications, serum creatinine level *Effectiveness* Overall survival, disease-specific survival, tumour persistence, local tumour progression	Mean: 19.3 months (range: 3–36 months)

(Weld et al 2007)[h]	Washington University School of Medicine, St. Louis, the United States University of California, Irvine, the United States Columbia University School of Medicine, New York, the United States	Level IV Quality: 5.5/6 (NHS CRD) Prospective case series	*Inclusion* Patients with small (≤4 cm) renal mass, with a minimal follow-up period of 36 months *Exclusion* Not stated	Number of patients: 31 (36 tumours) Age: mean: 65.3 years (range: 28–90 years) 15 females, 16 males Tumour size: mean: 2.1 cm (range: 0.5–4.0 cm) Tumour histology: Malignant: 22 (61%) Clear cell RCC: 17 (47%) Papillary RCC: 4 (11%) Chromophobe: 1 (3%) Benign: 14 (39%) Oncocytom: 6 (17%) Tumour location: Exophytic: 27 (75%) Endophytic: 5 (14%) Hilar: 4 (11%) Indications: Comorbidities (⩾3): 15 (48%) Hypertension: 20 (65%) Cardiovascular disease: 13 (42%) Diabetes: 9 (29%) von Hippel-Lindau: 2 (6%) Contralateral kidney: Surgically absent or non-functional: 4 (13%) Prior partial nephrectomy: 2 (7%)	EndoCare argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 3.4–5 mm Cryoprobe number: 1–3 2 FTC	*Safety* Intra-operative or post-operative complications, blood loss *Effectiveness* Tumour persistence, local tumour progression, length of hospital stay	Mean: 45.7 months (range: 36–63 months)

[a] May be overlap between patient series; [b] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [c] May be overlap between patient series; [d] May be overlap between patient series; [e] Statistical significance of differences calculated by two-tailed Fisher's exact test; [f] Bosniak classification of cystic renal masses on CT scans: class I: simple cystic renal mass; class II: probably benign cystic renal mass; class III: Indeterminate cystic renal mass; class IV: malignant cystic renal mass (Wolf 1998); [g] May be overlap between patient series; [h] One of the authors, Landman, J., is a study investigator and consultant to Oncura

ASA: American Society of Anesthesiologists physical status; BMI: body mass index; CT: computed tomography; FTC: freeze/thaw cycle; LCT: laparoscopic cryotherapy; LPN: laparoscopic partial nephrectomy; MRI: magnetic resonance imaging; OPN: open partial nephrectomy; PCT: percutaneous cryotherapy; RCC: renal cell carcinoma; RFA: radiofrequency ablation therapy; US: ultrasound

Table 85 Studies included in the review of cryotherapy for renal cancer (case reports)

Study	Setting	Patient characteristics	Intervention	Safety outcomes
3rd generation				
(Bassignani et al 2004)	University of Virginia Health Sciences Center, Charlottesville, the United States Galil Medical, New York, the United States	72-year-old male with surgical history of removal of a high-grade contralateral RCC 18 months previously, with a new mass (3.0 cm) in the normal kidney discovered by CT scan 6-months previously 81-year-old female with a small renal mass (3.0 cm), with no history or biopsy confirmation of RC	Argon-based cryotherapy system US-guided percutaneous cryotherapy Cryoprobe size: 17-G 2 FTC	No complications
(Chen et al 2008)[a]	Duke University Medical Center, Durham, the United States	63-year-old morbidly obese man with coronary artery disease who had undergone right radical nephrectomy for RCC, and had enlarging left renal mass	Argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 17-G Cryoprobes number: 6 2 FTC	At 3 months a filling defect and partial urethelial slough in the renal pelvis was identified. Ureteroscopic slough was removed and temporary stent put in. Patient remained clinically asymptomatic after treatment.
(Hruby et al 2006)	Columbia University Medical Center, New York, the United States	50-year-old man with a 3.2 cm mass in a renal allograft	Argon-based cryotherapy system US-guided percutaneous cryotherapy Cryoprobe size: 1.47 mm Cryoprobes number: 4 2 FTC	No complications
(Kodama et al 2005)	Hokkaido University Graduate School of Medicine, Sapporo, Japan	35-year-old woman with von Hippel-Lindau disease with bilateral multiple renal tumours (2 in left kidney, 3 in right)	CryoHit argon-based cryotherapy system MRI-guided percutaneous cryotherapy Cryoprobe size: 2–3 mm 2 FTC	Patient had mild fever for a few days, and was discharged uneventfully 2 days after procedure.
(McClung et al 2007)	Loyola University Medical Center, Maywood, the United States	73-year-old man with an enhancing right renal mass in lower pole with multiple bilateral complex cysts, who had undergone hand-assisted partial nephrectomy for renal mass	Argo-based cryotherapy system Percutaneous cryotherapy Cryoprobe size: 17-G	No complications
(Pantuck et al 2002)[b]	University of California, LA & Alleghany General Hospital, Pittsburgh, the United States	37-year-old woman with type IIB von Hippel-Lindau disease who had undergone right adrenalectomy for a pheochromocytoma	Galil argon-based cryotherapy system Cryoprobe size: 1.5 mm Cryoprobe number: 5 2 FTC Right kidney exposed using supra-11th, extrapleural, extraperitoneal excision	No complications
(Polcari et al 2007)	Loyola University Medical Center, Maywood, the	62-year-old woman with hypertension, multiple abdominal surgeries (including ventral hernia repair with	Argon-based cryotherapy system CT-guided percutaneous cryotherapy	No complications

	United States	mesh over anterior abdominal wall), with 1.5 cm exophytic mass in lower pole of left kidney	Cryoprobe size: 17-G Cryoprobe number: 3 2 FTC	
(Zhu et al 2005)	Hokkaido University Graduate School of Medicine, Sapporo, Japan	71-year-old man with a 3.4 cm peripheral RCC located in the lower pole of the right kidney 58-year-old women with a 3.6 cm RCC located in the upper pole of the left kidney	Cryo-Hit argon-based cryotherapy system US-guided percutaneous cryotherapy Cryoprobe size: 3 mm Cryoprobe number: 3 2 FTC	No complications
2nd generation				
(Blaschko et al 2007)	University of California, Irvine, the United States	73-year-old obese man (BMI = 34.9 kg/m^2) with an enhancing 2.8 cm renal mass on posterior aspect of upper pole of left kidney, with coronary artery disease and hypertension, and with surgical history of radical prostatectomy	EndoCare argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: 4 2 FTC	No complications
(Brown & Bhayani 2007)	Washington University School of Medicine, St Louis, the United States	65 year old African American woman with invasive vulvar cancer, treated with chemoradiation, which led to vesicovaginal fistula and ileal conduit. She had growing renal tumour (2.4 cm) and wished to avoid surgery	Argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 21-G Cryoprobe number: 5 2 FTC	Three months after cryotherapy, the patient had urinary fistula, and after two unsuccessful drainages underwent nephrectomy.
(Leflore et al 2007)	Southern Illinois University School of Medicine, Springfield, the United States	14-year-old girl with a 2 cm renal angiomyolipoma, which increased to 2.9 cm over 2 years	Argon-based cryotherapy system Cryoprobe size: 8 mm Cryoprobe number: 1 2 FTC	The patients had post-procedural transient haematuria treated expectantly and resolved by day 2.
(Mitre et al 2008)	Hospital Das Clínicas, Faculadade de Medicina da Universidade de Sao Paulo, Brazil	63-year-old white male with four bilateral peripherally located papillary RCCs (one 2 cm tumour, two 3 cm tumours, and one 4 cm tumour), with a family history of RCC and a surgical history of an open prostatectomy for treatment of benign prostatic hyperplasia	Argon-based cryotherapy system US-guided laparoscopic cryotherapy Cryoprobe size: 3 mm Cryoprobe number: 5	The patient had massive pulmonary thromboembolism, which was treated with heparin; pulmonary function was progressively restored in subsequent weeks.
(Romero et al 2007)	Johns Hopkins Medical Institutions, Baltimore, the United States	60-year-old woman with history of hypertension, transient ischemic attack, asthma and Cushing's syndrome, who had bilateral renal masses	Argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: 5 2 FTC	On the day of procedure, the patient presented nausea and vomiting. A repeat CT scan showed right perirenal haematoma and right-side pleural effusion, requiring blood transfusion and removal of sanguineous fluid in chest.

		87-year-old woman with history of chronic obstructive pulmonary disease, hypertension, congestive heart failure and atrial fibrillation, with exophytic mass (2.7 cm) on left kidney	Argon-based cryotherapy system CT-guided laparoscopic cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: 2 2 FTC	On the third day after cryotherapy, the patient developed shortness of breath and left-sided pain caused by pleural effusion, which was drained by a chest tube. She received fresh frozen plasma and additional blood products. The patient died of pulmonary embolism involving right main pulmonary artery on day 20 post-operatively.
(Sewell et al 2003)	University of Mississippi Medical Center, Jackson, the United States	50-year-old man with history of chronic renal failure, insulin-dependent diabetes mellitus, congestive heart failure, hypertension, pancreatitis and alcohol abuse, with 1.5 cm mass in kidney	Argon-based cryotherapy system MRI-guided cryotherapy Cryoprobe size: 3 mm 3 FTC	The patient tolerated procedure well but died after 25-month follow-up period of unrelated causes.
		77-year-old man with adenocarcinoma of the colon, previous left nephrectomy, previous right heminephrectomy, and third RCC found in right kidney		The patient tolerated procedure well.
(Shingleton & Sewell 2002b)	University of Mississippi, Jackson, the United States	66-year-old man who had received a transplanted kidney for end-stage renal disease secondary to hypertension 9 years prior, who had a 1.5 cm lesion in allograft, and a 3 cm mass in native kidney Native kidney removed by radical nephrectomy, allograft treated with cryotherapy	Argon-based cryotherapy system MRI-guided percutaneous cryotherapy Cryoprobe size: 3 mm 3 FTC	No complications
(Vanderbrink et al 2007)	Long Island Jewish Medical Center, New York, the United States	63-year-old man with 2.6x1.7 cm enhancing renal mass, who refused surgery	Argon-based cryotherapy system CT-guided percutaneous cryotherapy Cryoprobe size: 2.4 mm Cryoprobe number: 2	Two months after cryotherapy, the patient had a colorenal fistula, resulting in sudden onset of urinary frequency and dysuria. He was treated with a stent, which was removed after 2.5 months, and has done well since.

[a] One of the authors, Polascik, T. J., is a research consultant to Galil Medical; [b] All authors are consultants for Galil Medical

FTC: freeze/thaw cycle; MBI: body mass index; RCC: renal cell carcinoma; CT: computed tomography; MRI: magnetic resonance imaging; US: ultrasound

Appendix K Excluded studies

Not a study, a systematic review, or a meta-analysis (67)

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Appendix L Critical appraisal checklist

Checklist for the critical appraisal of cohort studies

Title of review:

Title of study:

Author(s)

Year:

Comparators:

Score: /6

1. How were subjects selected for the 'new intervention'? /1

2. How were subjects selected for the comparison or control group? /1

3. Does the study adequately control for demographic characteristics, clinical features and other potential confounding variables in the design or analysis? /1

4. Was the measurement of outcomes unbiased (ie blinded to treatment group and comparable across groups)? /1

5. Was follow-up long enough for outcomes to occur? /1

6. Was follow-up complete and were there exclusions from the analysis? /1

Source: NHMRC 2000

Checklist for the critical appraisal of case series

Title of review:

Title of study:

Author(s)

Year:

Comparators:

Score: /6

7. Is the study based on a representative sample selected from a relevant population? /1

8. Are the criteria for inclusion explicit? /1

9. Did all individuals enter the survey at a similar point in their disease progression? /1

10. Was follow-up long enough for important events to occur? /1

11. Were outcomes assessed using objective criteria or was blinding used? /1

12. If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors? /1

Source: Khan et al 2001

Checklist for appraising the clinical importance of benefit (harm)

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Clinically important effect:

Rank Score : **/4**

1 A clinically important benefit for the full range of plausible estimates. The confidence limit closest to the measure of no effect (the 'null') rules out a clinically unimportant effect of the intervention. /1

2 The point estimate of effect is clinically important BUT the confidence interval includes clinically unimportant effects. /1

3 The confidence interval does not include any clinically important effects. /1

4 The range of estimates defined by the confidence interval includes clinically important effects BUT the range of estimates defined by the confidence interval is also compatible with no effect, or a harmful effect. /1

Source: NHMRC 2000

Checklist for classifying the relevance of evidence

Title of review:

Title of study:

Author(s):

Year:

Comparators:

Rank Score : /4

1. Evidence of an effect on patient-relevant clinical outcomes, including benefits and harms, and quality of life and survival. /1

2. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention. /1

3. Evidence of an effect on a surrogate outcome that has been shown to be predictive of patient-relevant outcomes for the same intervention. /1

4. Evidence of an effect on proven surrogate outcomes but for a different intervention and population. /1

5. Evidence confined to unproven surrogate outcomes. /1

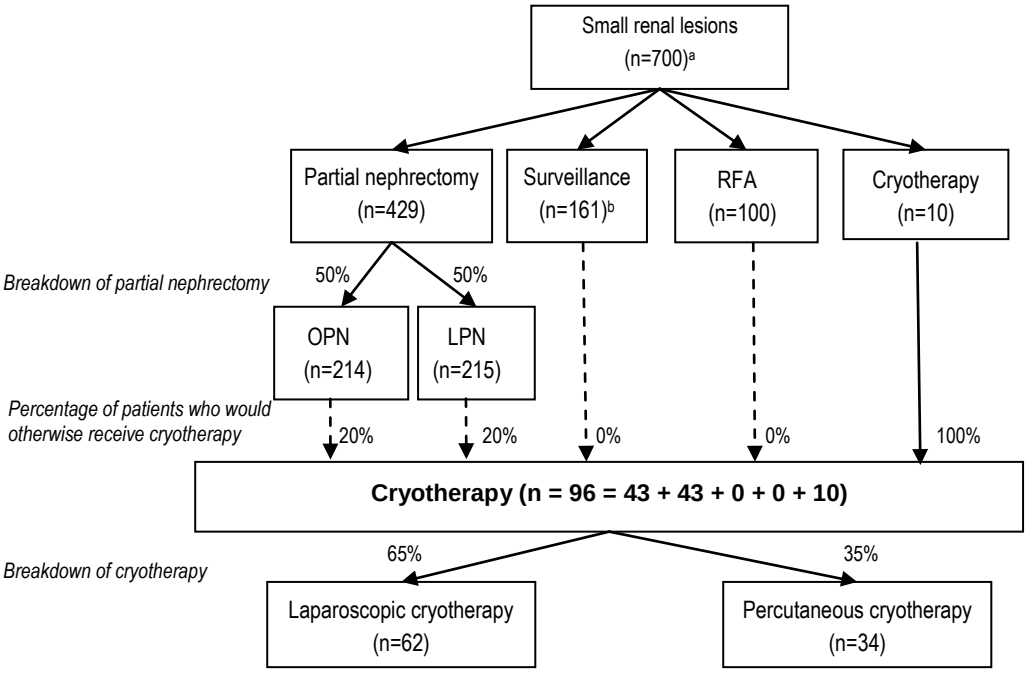
Source: NHMRC 2000

Appendix M Further scenarios for financial analysis

In order to simplify the financial analysis, a base case scenario was chosen assuming that 50 per cent of patients who currently receive RFA would choose cryotherapy if it were to become available. Two further scenarios are presented below, outlining the minimum and maximum cost implications when 0 and 100 per cent of RFA patients would prefer to receive cryotherapy.

1. Cost implications (minimum estimate) when 0 per cent of patients who are now treated with RFA would otherwise choose cryotherapy

Figure 15 Flowchart estimating the clinical need for cryotherapy (minimum)



[a] Based on data from AIHW and the United States, it is estimated that, in Australia, a total of 538 small renal malignancies were diagnosed each year. 700 = 525 ÷ 3/4; [b] 161 = 700 – 429 – 100 – 10.

LPN: laparoscopic partial nephrectomy; OPN: open partial nephrectomy; RFA: radiofrequency ablation

Table 86 Total costs to the Australian Government (minimum)

	Procedure	Number of patients	Unit costs	Total cost
	Scenario 1 (public to private patient split: 75:25)			
Current	Open partial nephrectomy	11	$1 043	$11 468
	Laparoscopic partial nephrectomy	11	$1 124	$12 086
	Radiofrequency ablation	0	$1 365	$0
	Laparoscopic cryotherapy	2	$1 506	$3 011
	Percutaneous cryotherapy	1	$1 365	$1 365
In the future	Laparoscopic cryotherapy	16	$1 506	$24 088
	Percutaneous cryotherapy	9	$1 365	$12 281
	Difference[a]			**$8 440**
	Scenario 2 (public to private patient split: 50:50)			
Currently	Open partial nephrectomy	22	$1 043	$22 935
	Laparoscopic partial nephrectomy	22	$1 124	$24 734
	Radiofrequency ablation	0	$1 365	$0
	Laparoscopic cryotherapy	3	$1 506	$4 517
	Percutaneous cryotherapy	2	$1 365	$2 729
In the future	Laparoscopic cryotherapy	32	$1 506	$48 176
	Percutaneous cryotherapy	17	$1 365	$23 197
	Difference[a]			**$16 459**

[a] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency ablation and currently performed cryotherapy.

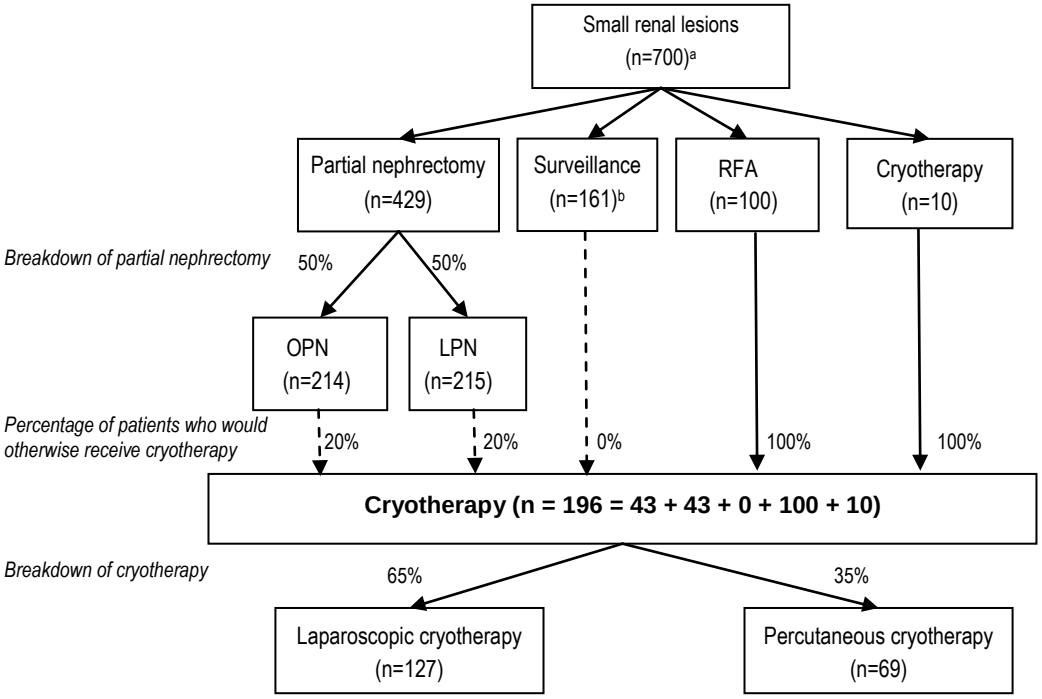
Table 87 Total costs to the Australian healthcare system overall (minimum)

	Procedures	Number of patients	Unit costs	Total costs
	Scenario 1 (estimated annual volume of cryotherapy procedures: 100)			
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	0	$5 071	$0
	Laparoscopic cryotherapy	7	$13 005	$91 036
	Percutaneous cryotherapy	3	$11 976	$35 927
In the future	Laparoscopic cryotherapy	62	$13 005	$806 316
	Percutaneous cryotherapy	34	$11 976	$407 173
	Difference[a]			**$412 458**
	Scenario 2 (estimated annual volume of cryotherapy procedures: 500)			
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	0	$5 071	$0
	Laparoscopic cryotherapy	7	$12 546	$87 823
	Percutaneous cryotherapy	3	$11 517	$34 550
In the future	Laparoscopic cryotherapy	62	$12 546	$777 857
	Percutaneous cryotherapy	34	$11 517	$391 567
	Difference[a]			**$372 983**

[a] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency ablation and currently performed cryotherapy.

2. Cost implications (maximum estimate) when 100 per cent of patients who are now treated with RFA would otherwise choose cryotherapy

Figure 16 Flowchart estimating the clinical need for cryotherapy (maximum)



[a] Based on the data form AIHW and the United States, it is estimated that, in Australia, a total of 538 small renal malignancies were diagnosed each year. 700 = 525 ÷ 3/4; [b] 161 = 700 – 429 – 100 – 10.

LPN: laparoscopic partial nephrectomy; OPN: open partial nephrectomy; RFA: radiofrequency ablation

Table 88 Total costs to the Australian Government (maximum)

	Procedure	Number of patients	Unit costs	Total cost
Scenario 1 (public to private patient split: 75:25)				
Current	Open partial nephrectomy	11	$1 043	$11 468
	Laparoscopic partial nephrectomy	11	$1 124	$12 086
	Radiofrequency ablation	25	$1 365	$34 113
	Laparoscopic cryotherapy	2	$1 506	$3 011
	Percutaneous cryotherapy	1	$1 365	$1 365
In the future	Laparoscopic cryotherapy	33	$1 506	$49 682
	Percutaneous cryotherapy	17	$1 365	$23 197
	Difference[a]			**$10 837**
Scenario 2 (public to private patient split: 50:50)				
Currently	Open partial nephrectomy	22	$1 043	$22 935
	Laparoscopic partial nephrectomy	22	$1 124	$24 734
	Radiofrequency ablation	50	$1 365	$68 225
	Laparoscopic cryotherapy	3	$1 506	$4 517
	Percutaneous cryotherapy	2	$1 365	$2 729
In the future	Laparoscopic cryotherapy	64	$1 506	$96 352
	Percutaneous cryotherapy	35	$1 365	$47 758
	Difference[a]			**$20 971**

[a] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency ablation and currently performed cryotherapy.

Table 89 Total costs to the Australian healthcare system overall (maximum)

	Procedures	Number of patients	Unit costs	Total costs
Scenario 1 (estimated annual volume of cryotherapy procedures: 100)				
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	100	$5 071	$507 098
	Laparoscopic cryotherapy	7	$13 005	$91 036
	Percutaneous cryotherapy	3	$11 976	$35 927
In the future	Laparoscopic cryotherapy	127	$13 005	$1 651 647
	Percutaneous cryotherapy	69	$11 976	$826 321
	Difference[a]			**$1 169 840**
Scenario 2 (estimated annual volume of cryotherapy procedures: 500)				
Currently	Open partial nephrectomy	43	$8 968	$385 624
	Laparoscopic partial nephrectomy	43	$6 708	$288 444
	Radiofrequency ablation	100	$5 071	$507 098
	Laparoscopic cryotherapy	7	$12 546	$87 823
	Percutaneous cryotherapy	3	$11 517	$34 550
In the future	Laparoscopic cryotherapy	127	$12 546	$1 593 353
	Percutaneous cryotherapy	69	$11 517	$794 650
	Difference[a]			**$1 084 464**

[a] A positive difference is an additional cost resulting from cryotherapy compared to partial nephrectomy, radiofrequency ablation and currently performed cryotherapy.

Glossary and abbreviations

AIHW	Australian Institute of Health and Welfare
ARTG	Australian Register of Therapeutic Goods
ASA	American Society of Anesthesiologists physical status: ASA is a measurement of physical status, comorbidities and physiological stability.
BMI	Body mass index
CI	Confidence interval
CT	Computed tomography
FTC	Freeze/thaw cycle
HIFU	High-intensity focused ultrasound
HTA	Health Technology Assessment
LCT	Laparoscopic cryotherapy
LPN	Laparoscopic partial nephrectomy
MBS	Medicare Benefits Schedule
MRI	Magnetic resonance imaging
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NHS	National Health Service (United Kingdom)
OPN	Open partial nephrectomy
PCT	Percutaneous cryotherapy
RCC	Renal cell carcinoma
RFA	Radiofrequency ablation
SD	Standard deviation

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