Medical Services Advisory Committee

Public Summary Document

Application No. 1124
Cryotherapy for Recurrent Prostate Cancer and Renal Cancer

Applicant: **Scanmedics Pty Ltd**
Date of MSAC consideration: **46th MSAC meeting, 11 September 2009, Melbourne**

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

1. Purpose of Application

Scanmedics Pty Ltd submitted an application to MSAC for public funding of cryotherapy for recurrent or persistent prostate cancer after radiotherapy. The application refers to the use of third-generation cryotherapy as a treatment for persistent or recurrent prostate cancer after radiotherapy. It is also known as salvage cryotherapy or salvage cryosurgery. The indications were locally recurrent prostate cancer in a patient previously treated by radiation, with no distant metastases, and significant life expectancy.

2. Background

The applicant requested the procedure be listed on the Medicare Benefits Schedule (MBS) at $922.70 – a fee equal to the fee for the urological component of implantation of brachytherapy seeds for treatment of early prostate cancer. The MBS fees for the comparator are $1,408.00 item 37210 and $1,710.05 item 37211. The applicant noted that urologists or radiation oncologists will provide the service, after additional specific training in cryotherapy. As cryotherapy is delivered using a template based system that is very similar to the template used by urologists and radiation oncologists who perform brachytherapy for early prostate cancer, a short learning curve and similar skill requirement and duration of procedure would apply. The applicant further noted that this procedure does not require the combined effort and costs of a urologist and radiation oncologist.

Cryotherapy is a procedure that can be used for recurrent or persistent prostate cancer after radiotherapy. In the past 20 years there have been advances in cryoablative technology to reduce the occurrence of post-procedural adverse events, including the use of transrectal ultrasound guidance and urethral warming, as well as the transition from liquid nitrogen-driven to argon gas-based systems. Both second- and third-generation cryotherapy take advantage of these technologies, the only difference between them being the reduction in 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 during the procedure 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.

3. Clinical need

The clinical need for salvage cryotherapy varies according to the characteristics of patients who meet the proposed eligibility criteria (ie patients with biopsy-confirmed recurrent or persistent prostate cancer after radiotherapy who have no evidence of distant disease). MSAC noted that this eligible patient population is likely to include a large number of older individuals (>70 years of age) who are unsuitable for surgery (either as primary or salvage treatment) or any other ablative procedure in this salvage setting.

However, MSAC also recognised that a small group of younger patients elect to receive radiotherapy as a primary treatment option rather than surgery. This group of patients may derive a significant benefit if salvage cryotherapy was proven to be curative. This small subgroup might form the basis of a small niche role for cryotherapy within the overall eligible population.

MSAC noted that the lack of evidence comparing the outcomes of alternative treatment options for prostate cancer means that patient choice based on treatment complications may be a key driver of treatment choice. As complication rates with the more ablative procedures are considered to be decreasing with technological advances, there is renewed interest in these procedures, with brachytherapy an increasing choice (particularly in younger patients). As prior radiotherapy may potentiate complications in most patients requiring further treatment following radiotherapy failure, there are still concerns regarding the appropriate use of ablative salvage procedures, for both the older and the younger patient.

Like the other ablative procedures (as alternatives to watchful waiting with hormonal therapy as needed), a clinical need for cryotherapy is only likely to be identified for subsets of patients, so the first question for any funding decision is how to target the group that would most benefit from any type of ablative procedure. However, defining the precise characteristics of this small subgroup would neither be simple nor practical. In addition, the natural history of the disease is still unclear, and many patients with prostate cancer, including younger patients, do not die from the disease. Limiting funding to younger patients might therefore reinforce more inappropriate screening and treatment behaviours.

4. Comparator

Salvage cryotherapy is proposed as an alternative to salvage radical prostatectomy, salvage high-intensity focused ultrasound (HIFU) and salvage brachytherapy. Public reimbursement for salvage brachytherapy and HIFU is not available through the MBS and all salvage procedures are rarely performed. A more common (but non-curative) alternative treatment option in this patient group is watchful waiting with hormonal therapy as needed.

MSAC also noted the difficulty in determining the appropriate comparator in the absence of any evidence that any of the salvage comparators used (radical prostatectomy, HIFU and brachytherapy) is curative, as well as the fact that these comparators are still in a process of being clinically evaluated. Watchful waiting with hormonal therapy as needed is not intended to be curative and so was not included as a clinical comparator in the assessment report on this basis.

MSAC also noted that the comparators in the clinical assessment were not used in the financial analysis of the assessment report, which instead used watchful waiting with hormonal therapy as needed. Hormonal therapy is used by a large proportion of the eligible population group, despite the lack of evidence for its effectiveness and the fact that some patients are hormone resistant.

MSAC accepted that assessment against all identified comparators was relevant, even in the absence of MBS reimbursement. Other potentially curative alternatives in the salvage setting (radical prostatectomy, HIFU and brachytherapy) are appropriate comparators for the small number of young men who have elected to have initial radiotherapy and have then recurred. These patients may still have a chance of cure and so who might benefit from salvage cryotherapy or another ablative procedure. If such a small subgroup could be identified, the question would be whether cryotherapy warrants funding ahead of the other treatment options.

However MSAC noted that, like surgery, cryotherapy is unlikely to be suitable for radiotherapy failures in older patients due to the increased risk of complications. Watchful waiting with hormonal therapy as needed is the appropriate comparator if some of this larger group of patients would be offered salvage cryotherapy.

5. Safety

The current evidence for safety suggests that this treatment is acceptable, noting that this evidence is limited by a lack of comparative studies. Morbidity is due mainly to fistulae and other complications. MSAC was concerned at a reported complication rate of 7% for cryotherapy where the mean for other treatment modalities is 1% or 2%. The technique of salvage cryotherapy (with or without neoadjuvant hormonal therapy) has become safer as a result of improved technology. The morbidity of surgery was also noted to be reducing. Overall, MSAC concluded that, as an invasive procedure, salvage cryotherapy causes more morbidity than watchful waiting with hormonal therapy as needed, and that there is no convincing basis to determine that salvage cryotherapy is any safer than salvage radical prostatectomy, salvage HIFU or salvage brachytherapy.

6. Clinical effectiveness

MSAC noted the difficulty in obtaining any clear evidence of benefit for cryotherapy in the target group. The strength of evidence for clinical effectiveness is limited by the quality of the few case series studies available, which were of insufficient duration and lacked a standardised way of assessing cancer recurrence – the studies used a range of biochemical definitions, clinical assessments and biopsies. An evaluation of effectiveness of an intervention in this clinical setting needs long-term follow-up data, ideally over 10 years. Based on the available clinical evidence, MSAC concluded that, while salvage cryotherapy appears to be effective in the short term for the treatment of recurrent or persistent prostate cancer after radiotherapy, findings were inconsistent on its long-term effectiveness.

As a potentially curative treatment, salvage cryotherapy may be expected to be more effective than conservative watchful waiting with hormonal therapy as needed. However, the evidence on quality of life outcomes achieved over time from watchful waiting with hormonal therapy as needed, or from any other procedure assessed, was inconclusive. As no studies directly compared salvage cryotherapy with the other potentially curative procedures of salvage radical prostatectomy, salvage HIFU and salvage brachytherapy, MSAC concluded that it was impossible to draw any conclusions as to the comparative effectiveness of these procedures.

7. Cost-effectiveness

MSAC noted that if salvage cryotherapy for recurrent or persistent prostate cancer proves to be as effective and as safe in the long term as currently used treatments, then the financial incidence analysis in the assessment report suggests that it would be more costly to the Australian Government from the first year but could be cost-saving to the Australian health care system over five years. The cost to the Australian health care system is substantially higher in the first year of treatment, but the increment would become less in the second and third years. After that, cryotherapy is estimated to result in net cost savings.

However, the following caveats however were noted in relation to this conclusion:

- the comparators in the clinical assessment (other ablative therapies) were not used in financial analysis, which instead used watchful waiting with hormonal therapy as needed;
- a series of five assumptions was required and four different scenarios were used, each with varied throughputs;
- there were concerns around the quality of the evidence;
- there was no inclusion of the potential for a subsequent cryotherapy procedure (which is not to be confused with having a second cycle of cryotherapy within the initial procedure) as the technology is not of sufficient maturity for any data to be available regarding this potential; and

- the data were insufficient to undertake more detailed analysis, and the analysis presented concluded that there would be potential cost savings over watchful waiting with hormonal therapy as needed if all assumptions are true. In contrast, cryotherapy is more expensive than any of the three alternative treatments considered in the clinical assessment.

The financial incidence analysis did not address potential costs associated with morbidity related to the procedure or to the possibility of a repeat procedure. In addition, MSAC noted that the cost implications of cryotherapy for recurrent or persistent prostate cancer assume 100 per cent of cryotherapy patients would be free of disease during follow-up periods, otherwise additional costs would be incurred to both the Australian Government and the health care system overall for the treatment of recurrence after salvage cryotherapy.

MSAC was also concerned with the assumptions used in estimating the cost of hormone therapy over time, especially the assumption that no hormone therapy would be used following cryotherapy (MSAC considered it likely that some of these patients would ultimately go back on hormone therapy). MSAC noted the current use of hormonal therapy by a large proportion of the eligible population group, despite the lack of evidence for its effectiveness and the fact that some patients are hormone resistant. Patients may choose to resume hormonal therapy if their prostate specific antigen (PSA) rises slightly, which may not be infrequent if a low PSA threshold is used as the basis for re-commencing hormonal therapy. It was also pointed out that the financial incidence analysis assumed that the costs of hormonal therapy did not fall over this time, whereas it is known that patents for several of the agents used are about to expire, and prices of these drugs are therefore likely to fall. Overall, MSAC concluded that this analysis is more of a 'best case' analysis than a 'base case' analysis for the public funding of cryotherapy and was therefore not persuaded by the economic case for public funding.

8. Possibility of Interim Funding

Given the lack of high level evidence for clinical effectiveness and cost-effectiveness, MSAC discussed the possibility of interim listing on the MBS and requiring prospective follow-up audit limited to patients who have biopsy-proven, locally recurrent prostate cancer in the absence of metastatic disease, following primary radiation, with or without NHT. However, following discussion of this option, MSAC agreed that the criteria for listing with interim funding that are described in MSAC Guidelines are not met by this procedure.

Even if interim funding were to be considered, it would still not be possible to generate the evidence needed in two or three years to provide guidance over whether funding should continue – even using biopsy recurrence as the most convincing surrogate outcome would be problematic given that 30-40% of men over 50 have prostate cancer on biopsy, resulting in a high false positive rate for clinically meaningful disease progression. Data on prostate-specific mortality across different subgroups of the eligible population are not available, and a time frame of up to 30 years to collect data for younger patients is an unrealistically long time to conduct an evaluation for interim funding.

9. Summary of Consideration and Rationale for MSAC's Advice

There is uncertainty over the comparative effectiveness of any option in this patient setting due to the low strength of evidence and the underlying uncertainty over the natural history of the disease. Cryotherapy causes more morbidity than watchful waiting and hormonal therapy and is unlikely to be any more effective than radical prostatectomy or brachytherapy. The conclusion from the economic analysis of cost saving (compared to watchful waiting with hormonal therapy as needed) relies on an unconvincing assumption that no hormonal therapy would be used following cryotherapy, and relaxing this assumption to allow some post-cryotherapy use of hormonal therapy would at least reduce the estimate of cost saving and might even make cryotherapy more expensive overall (especially as the costs of hormonal therapy will fall as these drugs come off patent). There may be a small number of young men within the eligibility criteria who might benefit from cryotherapy, but this number is likely to be too small to enable clinical trial data to be generated. If

funded, it would be difficult to avoid an increase in use of cryotherapy for older men for whom the harms may be more likely to outweigh the benefits.

10. MSAC's Advice to the Minister

MSAC advises that cryotherapy should not be listed on the MBS without any limitations.

MSAC advises that cryotherapy should not be listed on the MBS on an interim funding basis, as the criteria for listing with interim funding that are described in MSAC Guidelines are not met by this procedure, and noting that further data would still not be likely to be available during the interim funding period.

Although members considered that it is possible that a small cohort of younger, fitter men may benefit from the procedure in certain circumstances, MSAC's advice is based primarily on the level of uncertainty in the clinical and economic assessments, and on the potential increase in inappropriate utilisation if public funding were provided.

Members agreed that the treatment of prostate cancer was a very important health issue, but that the field lacked data, not only in relation to the natural history of the disease, but also in relation to comparative safety, effectiveness and cost-effectiveness of available treatment modalities.

11. Context for Decision

This advice was made under the MSAC Terms of Reference:

- Advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported.
- Advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness.
- Advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures.
- Undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to the AHMAC.

12. Linkages to Other Documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.

The MSAC Assessment Report is available at http://www.msac.gov.au/internet/msac/publishing.nsf/Content/MSACCompletedAssessments1120-1140