Health Policy Advisory Committee on Technology

Technology Brief

Ablative Techniques for the Treatment of Localised Prostate Cancer

November 2014
Ablative techniques for localised prostate cancer: November 2014

**Description of the technology**

Prostate cancer is common and is increasingly detected in its early stages through prostate-specific antigen (PSA) screening. The traditional approach to localised prostate cancer involves removal of the whole prostate gland. While this is designed to maximise the likelihood of a cure, it is also associated with a range of adverse effects in the adjacent genitourinary and gastrointestinal systems.

Presented in this report are four emerging technologies that aim to treat localised prostate cancer by focal tissue ablation using various forms of energy, rather than by removal of the whole prostate gland. The four technologies and the forms of energy they use are:

1. **Cryosurgery / cryotherapy / cryoablation** (via extreme cold);
2. **Radiofrequency ablation** (RFA) (via heat);
3. **Irreversible electroporation** (IRE) (via electric current);
4. **Magnetic resonance** (MR)-guided focal laser ablation (via heat).

All techniques employ similar overall approaches. With the patient in the operating room under general (or in some cases, spinal) anaesthesia, several needle electrodes are passed through the perineal skin into the targeted prostate tissue using imaging guidance. The type of imaging guidance varies by technique, and may include transrectal ultrasound [TRUS], magnetic resonance [MR] imaging, or MR-TRUS fusion.

**Cryosurgery**: gas at temperatures colder than -40°C is passed through needle electrodes, creating ice balls that destroy the targeted tissue in several freeze-thaw cycles. Cryoablation of the prostate was first introduced in the 1960s; however, it was abandoned due to an unacceptably high complication rate. It was reintroduced in the 1990s as a result of improvements in percutaneous and cryogenic instrumentation, and the development of TRUS, which allowed monitoring of the freezing process.

**RFA**: thermal energy, at a temperature of about 100°C, is generated from high frequency alternating current by a radiofrequency generator. The thermal energy is delivered to the prostate tumour(s) through monopolar or bipolar needle electrodes and the targeted tissue is irreversibly destroyed by coagulative necrosis.

**IRE**: low voltage direct electric current delivered via multiple electrodes. This creates a strong electrical field that permanently damages cell membranes, leading to cell death, without a thermal effect.
**MR-guided focal laser ablation:** thermal energy is used for tissue destruction, leading to homogeneous tissue necrosis. MR imaging can be used during the treatment to provide real-time temperature monitoring and visualisation of the treatment zone.6

**Company or developer**

There are a number of cryotherapy and RFA devices available for use in Australia. A non-exhaustive list of devices that appear on the ARTG is provided in Table 1. These devices are for use in ablative surgical procedures, and it is unclear whether they are specifically applicable to treatment of localised prostate cancer.

One of the included studies in this technology brief used the NanoKnife® System (AngioDynamics, USA) in the provision of IRE.1, 7 This device does not appear on the ARTG.

One of the studies focussing on MR-guided focal laser ablation used a US Food and Drug Administration approved MR-guided laser system promoted for use in minimally invasive neurosurgery.6 Originally marketed by Visualase, Inc. (Houston, Texas, USA) the company was acquired by Medtronic, Inc. (Minneapolis, Minnesota, USA) in late July 2014.8

**Reason for assessment**

Prostate cancer is common and is increasingly being detected in its early stages. There is growing interest in focal treatment for localised cancers because it preserves some of the prostate gland. This may help prevent complications associated with treating the entire prostate, including urinary incontinence or retention, erectile dysfunction and diarrhoea. Focal treatment of localised prostate cancer could have major health and cost benefits.

**Stage of development in Australia**

- Yet to emerge (RFA, IRE, and MR Guided focal laser ablation)
- Experimental (cryosurgery)
- Investigational
- Nearly established
- Established
- Established but changed indication or modification of technique
- Should be taken out of use

**Licensing, reimbursement and other approval**

There are a number of devices available to perform cryotherapy and RFA. Table 1 provides a non-exhaustive list of the devices which have received Therapeutic Goods Administration (TGA) approval. The public summary documents do not provide the specific use for which each device is indicated.
### Table 1  Non-exhaustive list of TGA approved local ablative devices

<table>
<thead>
<tr>
<th>Technology</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryotherapy</strong></td>
<td>Atricure Inc., United States, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Brymill Cryogenic Systems, United States, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Galil Medical Inc. Israel, cryotherapy system for minimally-invasive systems</td>
</tr>
<tr>
<td></td>
<td>MedGyn Products Inc., United States, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Medtronic CryoCath LP, Canada, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>MyoScience Inc., United States, percutaneous cryotherapy applications</td>
</tr>
<tr>
<td></td>
<td>New Medical Technologies GmbH, Switzerland, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Wallach Surgical Devices Inc., United States, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Walmay Holdings P/L, Australia, cryosurgical unit, general purpose</td>
</tr>
<tr>
<td><strong>RFA</strong></td>
<td>AD Elektronik GmbH, Germany, radiofrequency ablation unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Atricure Inc., United States, radiofrequency ablation unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Biosense Webster Inc., United States, radiofrequency ablation unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Irvine Biomedical Inc., United States, radiofrequency ablation unit, general purpose</td>
</tr>
<tr>
<td></td>
<td>Kimberley Clarke, United States, radiofrequency ablation unit, general purpose</td>
</tr>
<tr>
<td><strong>IRE</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>MR-guided focal laser</strong></td>
<td>NA</td>
</tr>
</tbody>
</table>

**Australian Therapeutic Goods Administration approval**

- [x] Yes  
- [ ] No  
- [ ] Not applicable

**Technology type**  
- Procedure / Device

**Technology use**  
- Therapeutic
**Patient Indication and Setting**

**Disease description and associated mortality and morbidity**

The prostate is part of the male reproductive system, located immediately below the bladder and just in front of the bowel. Doughnut-shaped, it surrounds the beginning of the urethra and the nerves that control penile erections are nearby. The prostate’s main function is to produce fluid that protects and enriches sperm. Prostate cancer occurs when some of the cells of the prostate reproduce more rapidly than in a normal prostate, causing a tumour to develop. When the tumour is confined to the prostate gland it is considered to be localised. However, the cancer can metastasise to other parts of the body, particularly the bones and lymph nodes. One of the symptoms of localised prostate cancer is difficulty passing urine, although the condition is often diagnosed at an asymptomatic stage, particularly when serum PSA levels are monitored.

**Number of patients**

According to the Australian Institute of Health and Welfare (AIHW), prostate cancer is the most commonly diagnosed non-cutaneous cancer in the country, with 21,808 new cases being diagnosed in 2009. The age-standardised incidence is increasing, from 79 new cases per 100,000 males in 1982, to 194 new cases per 100,000 males in 2009. The increase is expected to continue owing to more testing, changes in diagnostic practices and population ageing. Prostate cancer was the fourth leading cause of death among Australian males in 2011 (3294 deaths), although the age-standardised mortality rate has been decreasing and this trend is expected to continue. Recent 5-year survival rates are relatively high, for example the rate was 90 per cent in 2007.

Aboriginal or Torres Strait Islander men are less likely to be diagnosed with, but equally likely to die, from prostate cancer. This may be due to variations in the number of men undergoing screening, population risk profiles and population age profiles. International data from 2008 show that the incidence of prostate cancer was higher in Australia than in other country groups studied. The mortality rate in Australia was similar to those in Northern Europe and New Zealand, and higher than those in North America and Asia. AIHW data do not report on prostate cancer by grade or stage, so the proportion of localised to all prostate cancers was not available.

New Zealand Ministry of Health data from 2010 reveal similar rates and trends. Prostate cancer was the most common cancer in men, accounting for 27 per cent of all male cancer registrations. It accounted for 13 per cent of all male deaths from cancer, making it the third most common cause of cancer death in New Zealand men. The incidence of prostate cancer among Māori men is lower than in non-Māori men; in 2010 the incidence was 86 per 100,000 versus 100 per 100,000 respectively. However, the mortality rate is 72 per cent.
higher among Māori men. From 2000 to 2010, the mortality rate declined by 32 per cent for non-Māori men but only by six per cent for Māori men.

**Speciality**
Men’s health and sexual health

**Technology setting**
Specialist hospital / general hospital / outpatient service

**Impact**

**Alternative and/or complementary technology**

The four ablative technologies described are considered direct substitutes for the current approach to treating focal prostate cancer. The current technique involves removing or obliterating the whole prostate gland through procedures such as radical prostatectomy, external-beam radiotherapy (EBRT) and brachytherapy. The complications associated with current treatments are an important factor. An estimated 27 to 56 per cent of men who receive treatment for prostate cancer do so for cancers that would not have become clinically evident during their lifetime. New evidence suggests that the natural history of prostate cancer is driven by the largest lesion with the highest grade, known as the index lesion. Focal therapy, which involves targeting the index lesion while sparing the rest of the gland, is of increasing interest for men with low- and intermediate-volume prostate cancer. Such tissue-preserving strategies offer a compromise between the benefits of cancer treatment and the adverse effects associated with such treatment.

**Current technology**

The approach to treating prostate cancer depends on a number of factors including cancer stage (localised or metastasised); Gleason score (reflects the degree of cellular differentiation); PSA level and trend; patient age and general health; potential treatment side-effects and patient preference. The most common approaches to treatment of localised prostate cancer are radical prostatectomy, EBRT and brachytherapy. Radical prostate surgery is generally reserved for men with localised prostate cancer, at least a 10-year life expectancy and who are good surgical candidates. EBRT and brachytherapy also require men to have localised cancer and at least a 10-year life expectancy. Watchful waiting and active surveillance with regular PSA testing and digital rectal exams are also possible strategies, particularly for men older than 75 years and for those with significant comorbidities. Hormone therapy may be used as a neoadjuvant therapy (a treatment given prior to the primary therapy) for up to six months before radiotherapy. This aims to shrink the tumour before treatment, particularly for men with medium- or high-risk, or locally advanced prostate cancer. It may also be given for a period of time after radiotherapy as an adjuvant therapy.
Diffusion of technology in Australia

According to web-based advertising there is one urologist in Australia offering cryosurgery for focal prostate cancer.\(^\text{16}\) Additional focal therapies for prostate cancer currently available in Australia include: IRE, High intensity focused ultrasound, Photo Dynamic Therapy, and focal interstitial low dose rate brachytherapy. The availability of these techniques; however, is limited to one urologist in each instance (personal correspondence, University of South Australia). No evidence was located to suggest that RFA, or MR-guided focal laser ablation therapies are being used to treat localised prostate cancer in Australia or New Zealand.

International utilisation

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
<tr>
<td>Australia</td>
<td>✓ (IRE)</td>
</tr>
<tr>
<td>Belgium</td>
<td>✓ (RFA)</td>
</tr>
<tr>
<td>Canada</td>
<td>✓ (cryosurgery, MR-guided focal laser ablation)</td>
</tr>
<tr>
<td>England</td>
<td>✓ (IRE)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>✓ (focal laser ablation)</td>
</tr>
<tr>
<td>United States</td>
<td>✓ (cryosurgery, IRE, MR-guided focal laser ablation)</td>
</tr>
</tbody>
</table>

Table notes: IRE = irreversible electroporation; MR = magnetic resonance; RFA = radiofrequency ablation

Cost infrastructure and economic consequences

Australian health care expenditure on prostate cancer was estimated to be $349 million in 2008-09. This was an increase of 23 per cent over 2004-05 and is attributed to an increase in new diagnoses. Just over half of the total cost (56%) was due to inpatient services, followed by prescription drugs (36%) and out-of-hospital medical expenses (9%).\(^\text{11}\) Men aged 75 to 84 years are the peak age group affected. Data on the proportion of prostate cancer cases that are considered localised was not available. However, changes in practice patterns to reduce the aggressiveness of treatment (assuming outcomes are at least as favourable) would provide cost savings.

Ethical, cultural or religious considerations

No ethical, cultural or religious implications were identified in the included literature.

Evidence and Policy

Safety and effectiveness

Four technologies are reviewed. Table 2 shows the number of studies and types of evidence included for each technology.
As a greater amount of higher lever evidence is available for cryotherapy, as opposed to the other techniques included in this technology brief, essential details of the identified comparative literature are reported in Table 4 below.
therapy recurrence was for men with recurrent localised prostate cancer. Inclusion criteria were identified that no studies on prostate cancer were identified that met the (unspecified) inclusion criteria. The study primarily focussed on safety and feasibility, with some 12-month efficacy data available. A German-language SR of RFA to treat several diseases, including prostate cancer, was also located. However, the English executive summary stated that no studies on prostate cancer were identified that met the (unspecified) inclusion criteria.\textsuperscript{18}

**Radiofrequency ablation**

One publication describing the use of RFA to treat prostate cancer was located.\textsuperscript{5} The study primarily focussed on safety and feasibility, with some 12-month efficacy data available. A German-language SR of RFA to treat several diseases, including prostate cancer, was also located. However, the English executive summary stated that no studies on prostate cancer were identified that met the (unspecified) inclusion criteria.\textsuperscript{18}

**Shariat et al 2005**\textsuperscript{5}

In a small, prospective, phase I/II case series study (level IV interventional evidence) in Texas, researchers assessed the feasibility, safety, morbidity and preliminary efficacy of RFA for men with recurrent localised prostate cancer who were hormone-naïve. Diagnosis of recurrence was based on rising serum PSA levels on at least three separate occasions at least two weeks apart. Of the 11 participants in the study, eight had failed prior radiation therapy with curative intent and three had been followed via watchful waiting, as they were

<table>
<thead>
<tr>
<th>Study/ location, level of evidence</th>
<th>Comparison; follow up</th>
<th>Patients</th>
<th>Safety</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chin 2008/ Canada Randomised trial (level I interventional evidence)</td>
<td>CRYO vs EBRT; all patients received 6 mos. AA therapy; mean follow-up 37 months</td>
<td>Clinically locally advanced prostate CA (T2C-T3B) (salvage for patients who failed RT); n=64 (CRYO=33, EBRT=31); mean age 70 years; median PSA=9.9 ng/mL</td>
<td>SAEs: CRYO= One each of acute urinary retention, CVA &amp; severe constipation; EBRT= One each of bloody diarrhoea &amp; perforated cecum.</td>
<td>4-yr DSS &amp; OS NSD between groups. Mean bDFS = CRYO 28 mos. vs EBRT 41 mos. 4-year bDFS = CRYO 13% vs EBRT 47%.</td>
</tr>
<tr>
<td>Donnelly 2010/ Canada Randomised trial (level I interventional evidence)</td>
<td>CRYO vs EBRT; all patients received six mos. AA therapy; median follow-up 100 months</td>
<td>Clinically localised prostate CA; n=244 (122 in each arm); mean age 69 years; median PSA=8.6 ng/mL</td>
<td>Deaths: Five in each study arm. Grade 3 of 4 toxicity (no grade 4): GI: CRYO= 3 vs EBRT=8 pts (mainly proctitis in EBRT arm); GU: CRYO=10 vs EBRT=7 pts (mainly urinary retention). Sexual intercourse at 36 mos. for those active preRx: 14 in each grp: CRYO= Four unassisted (not defined); EBRT=12 unassisted.</td>
<td>5-yr DSS &amp; OS NSD between groups. Failure at 36 mos. (defined as biochemical failure, radiologic disease, or further prostate CA Rx): CRYO=23.9% vs EBRT=23.7%; NSD. CA-positive Bx at 36 mos.: CRYO=8% vs EBRT=29%.</td>
</tr>
<tr>
<td>Williams 2012/ USA Data from a USA Medicare-linked database</td>
<td>CRYO vs brachytherapy; follow-up&gt;2 years</td>
<td>n=10,928 with localised prostate CA: primary CRYO= 943; brachytherapy=9985</td>
<td>CRYO was associated with more urinary AEs (41% vs 22%, p&lt;0.001) &amp; ED (35% vs 21%, p&lt;0.001) but brachytherapy was associated with more bowel complications (19% vs 12%, p&lt;0.001).</td>
<td>CRYO was associated with greater use of salvage AA therapy (1.4 vs 0.5 per 100 person-years, p&lt;0.001), suggesting poorer CA control.</td>
</tr>
</tbody>
</table>

**Table 4 Comparative studies of cryosurgery for prostate cancer treatment**

Table notes: AA = antiandrogen; AE = adverse event; bDFS = biochemical disease-free survival; Bx = biopsy; CA = cancer; CRYO = cryosurgery; DSS = disease-specific survival; EBRT = external beam radiotherapy; ED = erectile dysfunction; GI = gastrointestinal; GU = genitourinary; NSD = not significantly different; OS = overall survival; PSA = prostate specific antigen; RT = radiation therapy; Rx = treatment; SAE = serious adverse event; USA = United States of America.
not candidates for curative primary therapy. It was not reported whether the patients were enrolled consecutively.

The median patient age was 77 years (range, 60 to 82 years), median baseline PSA level was 5.7 ng/mL (range, 0.66 to 10.8 ng/mL) and median pre-radiofrequency interstitial tumour ablation (pre-RITA) Gleason score was 7 (range, 6 to 8). Treatment was delivered in an outpatient setting in a cystoscopy suite under intravenous sedation. RFA energy was applied via needles placed transperineally under TRUS guidance and only areas of biopsy-proven cancer were ablated. Median follow-up was 20 months (range, 3 to 38 months).

Safety

Early complications (immediately after treatment) were transient macrohæmaturia (blood in the urine) in two patients (19%), bladder spasm in one patient (9%) and dysuria (painful urination) in one patient (9%). The only late complication (not defined) was moderate constipation in one patient (9%).

Efficacy

PSA levels decreased after RFA by more than 50 per cent in 10 patients, eight of these patients decreased more than 70 per, and seven of these eight decreased more than 80 per cent. The mean PSA doubling time (PSADT) after RFA was slower (37 months, standard deviation [SD] 22) than it was before RFA (14 months, SD 13; \( p=0.008 \)). In the group of eight patients for whom radiation therapy had failed, PSADT after RFA was 127 per cent longer than it had been before RFA. In the watchful-waiting group, PSADT after RFA was 285 per cent longer.

At 12 months, three of the six patients (50%) in the radiation-failure group of eight patients with sufficient follow-up had no residual cancer on repeat systematic 12-core biopsy cores. In the watchful waiting group of three patients, two (66%) were free of cancer in biopsy cores sampled from the areas treated. Two of the four patients who had persistent cancer cells in the treated areas had received incomplete treatment due to high rising temperature in the rectal probe during the procedure. The researchers concluded that RFA is feasible and safe in patients with prostate cancer who have failed local radiation therapy, or who are not candidates for primary curative therapy.

Irreversible electroporation

No studies were located that included results. One study was described in a publication but results were not provided. ¹

MR-guided focal laser ablation

Two studies were located.⁶,¹⁹ One was reported only in a conference abstract but was included here due to the lack of available evidence.¹⁹
Lindner et al 2012\textsuperscript{19}

Authors from Canada reported their experience using MR-guided focal laser ablation as an outpatient treatment for 23 men with low-intermediate-risk prostate cancer (level IV intervention evidence).\textsuperscript{19} It was not reported whether the study was prospective and whether patients were enrolled consecutively. Under MR guidance, a 1.5 Tesla device, laser fibres were inserted into the prostate using locally developed surgical planning and guidance software. Thermal ablation was monitored using MR thermal mapping. Real-time ablation size was calculated using a Visulase Inc. workstation.

\textit{Safety}

There were no perioperative complications. All patients who were sexually potent before the procedure maintained potency, and urinary continence was not compromised.

\textit{Efficacy}

The treatment created an identifiable hypovascular defect on MR immediately after treatment that coincided with the targeted prostatic lesion. Mean targeted volume was 0.77 cc and mean ablated volume was 5.5 cc. Oncological results were not reported. This group is running trial NCT01094665, which is outlined in the section on ongoing research.

Oto et al 2013\textsuperscript{6}

A phase I study in the USA (level IV intervention evidence) focusing on feasibility and safety prospectively enrolled nine men with low-risk prostate cancer. It was not indicated whether enrolment was consecutive. Median patient age was 61 years (range, 52 to 77 years) and mean PSA level was 5.5 ng/mL (SD 2.6). Eight patients (89\%) had Gleason grade 6 cancer and one patient (11\%) had grade 7 cancer. Transperineal MR-guided focal laser ablation was undertaken with patients under conscious sedation. Patients were released home the day of treatment. The mean duration of the overall MR procedure was 2.5 to 4 hours and the duration of laser treatment to the prostate was 4.3 minutes (range, 1.5 to 7.5 minutes). Most of the procedure time was spent on localising and targeting the lesion. Follow-up examinations occurred at one, three and six months post-treatment (plus or minus two weeks), with follow-up biopsies at six months. All patients completed the six month follow-up.

\textit{Safety}

All nine patients tolerated the procedure well. There were no major complications or serious adverse events. Of particular interest was the lack of adverse effects in the urinary system (incontinence or urinary retention requiring surgical intervention) or new-onset erectile dysfunction not responsive to medication. No patients experienced these adverse effects. One patient developed an abrasion on the perineum that resolved with conservative measures, while another patient developed transient paresthesia (numbness, tingling or
burning sensation) involving one quarter of the glans penis, which resolved within three weeks.

Efficacy

The primary outcomes measured were changes in urinary function (incontinence or retention), as assessed by the International Prostate Symptom Score (IPSS), and new onset erectile dysfunction, assessed by the Sexual Health Inventory for Men (SHIM) score. Results showed no significant changes in these two areas. With respect to PSA levels, results showed no significant changes. Prior to surgery the PSA levels were 5.5 ng/mL (SD 2.6); at one month: 5.7 ng/mL (SD 4.4); three months: 4.7 ng/mL (SD 3.6); and at six months: 5.5 ng/mL (SD 4.0) ($p=0.8$). MR imaging-guided biopsy of the ablation zone at six months revealed benign prostatic tissue in seven of nine patients (78%) and Gleason grade 6 cancer in the remaining two (22%). In the latter two, review by the researchers suggested that the initial malignant tissue was not completely covered by the ablation zone.

Economic evaluation

The only economic information located was in the USA Medicare clinical study of Williams et al\textsuperscript{15} that used registry data to compare cryosurgery and brachytherapy for the treatment of localised prostate cancer. This study reported expenditures in 2008 USD and they are presented here alongside a conversion to the 2008 Australian dollar\textsuperscript{1}. While median baseline health care expenditures in the six months before prostate cancer diagnosis were significantly higher for men who received cryotherapy versus those who underwent brachytherapy (US$1,941 vs US$1,799, $p<0.001$) ($2,913 vs 2,700), median health care costs six months after diagnosis were higher for the patients who underwent brachytherapy (US$15,146 vs US$19,398, $p<0.001$) ($22,734 vs 29,116). The authors determined that the costs attributable to cryotherapy compared with brachytherapy were US$12,629 vs US$16,887 respectively ($p<0.001$) ($18,956 vs 25,347). Williams et al found no other cost analyses aside from a 2003 assessment performed by Hummel et al\textsuperscript{20} from the UK, who included quality of life considerations. They found that cryotherapy was inferior to the other treatments available at the time with respect to cost-effectiveness owing to the greater likelihood of erectile dysfunction following the procedure.

\textsuperscript{1} Based on the calculator at https://eppi.ioe.ac.uk/costconversion/default.aspx.
Ongoing research

A search of ClinicalTrials.gov and the Australian and New Zealand Clinical Trials Register identified a large number of studies exploring the treatments outlined in this technology brief. Five studies were found for cryosurgery, one for RFA, four for IRE and five for MR-guided focal laser therapy. The studies are described briefly in Tables 4, 5 and 6.

Cryosurgery

At least five studies are underway, either ongoing or recruiting. Four are in different centres in the USA and one is in Taiwan (Table 4). The total enrolled patient group across the five studies is more than 1,200 men, with study end dates ranging from estimates of October 2014 to January 2019.

<table>
<thead>
<tr>
<th>Trial number* / location / note</th>
<th>Study design</th>
<th>Status</th>
<th>n=</th>
<th>Patients / indication</th>
<th>Outcomes / length of follow-up</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01398657/ Taiwan</td>
<td>Randomised open-label: CRYO alone, or CRYO with adjuvant ADT</td>
<td>Recruiting</td>
<td>182</td>
<td>High-risk localised prostate CA (PSA&gt;20 ng/mL, Gleason score ≥8, or clinical staging ≥T2c)</td>
<td>Safety &amp; efficacy. Treatment failure at 3 years (determined by PSA, Bx or initiation of hormone therapy) Follow-up: 36 months</td>
<td>Jun. 2016</td>
</tr>
<tr>
<td>NCT00774436/ USA</td>
<td>Cohort</td>
<td>Ongoing</td>
<td>50</td>
<td>Low-risk localised prostate cancer</td>
<td>Efficacy &amp; QOL Follow-up: 6 months</td>
<td>Oct. 2014</td>
</tr>
<tr>
<td>NCT00824928/ USA Manufacturer listed as collaborator</td>
<td>Cohort</td>
<td>Recruiting</td>
<td>800</td>
<td>Salvage CRYO for recurrent prostate CA</td>
<td>Development of a registry. Treatment failure (via PSA) at 2+ years</td>
<td>Dec. 2014</td>
</tr>
<tr>
<td>NCT00877682/ USA Manufacturers listed as collaborators</td>
<td>Cohort</td>
<td>Ongoing</td>
<td>100</td>
<td>Localised prostate CA – focal CRYO to be used to treat tumour only</td>
<td>Safety, efficacy &amp; QOL Follow-up: 6, 12 and 36 months</td>
<td>Apr. 2016</td>
</tr>
<tr>
<td>NCT01727284/ USA (MR-guided CRYO)</td>
<td>Cohort</td>
<td>Recruiting</td>
<td>100</td>
<td>Prostate bed recurrences &lt;5cm; not good candidates for surgery or RT, or RT can be postponed</td>
<td>Safety &amp; efficacy Follow-up: 36 months</td>
<td>Jan. 2019</td>
</tr>
</tbody>
</table>

* Information is from clinicaltrials.gov

Table notes: ADT = androgen deprivation therapy; Bx = biopsy; CA = cancer; CRYO = cryosurgery; MR = magnetic resonance; PSA = prostate specific antigen; QOL = quality of life; RT = radiotherapy; USA = United States of America.
Radiofrequency ablation

Study NCT01423006, a small pilot study in the USA, treated five patients with very low-risk prostate cancer with RFA using EN Cage™ technology (Trod Medical, Leuven, Belgium). Patient selection criteria were not reported. The primary outcome measure was negative prostate biopsy rate at six months. The study also aimed to measure adverse events and quality of life at six months. The study started in August 2011 and final data collection occurred in March 2013, although the results of the study are not yet available. The device manufacturer recently raised EUR 4.75m ($8.15m) to perform clinical studies in both Europe and the USA on the use of the technology for the focal treatment of prostate cancer.

Irreversible electroporation

Although there is little published information about this technology there are five studies ongoing or recruiting. There is one study each in Australia, England and the USA, and two in the Netherlands (Table 5). The status of the small Australian study is unclear as the information has not been updated for two years. Including the 200 men in the Dutch randomised controlled trial, the total enrolled population will be about 250 men.

Table 5
Ongoing trials of IRE for localised prostate cancer

<table>
<thead>
<tr>
<th>Trial number* / location / note</th>
<th>Study design</th>
<th>Status</th>
<th>n=</th>
<th>Patients / indication</th>
<th>Outcomes / length of follow-up</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01835977/ Netherlands</td>
<td>Randomised single blind (patients): IRE to whole prostate or affected half</td>
<td>Not yet recruiting</td>
<td>200</td>
<td>High volume, low- or intermediate-risk prostate CA</td>
<td>Safety &amp; efficacy Follow-up: 36 months</td>
<td>Jan. 2018</td>
</tr>
<tr>
<td>NCT01790451/ Netherlands</td>
<td>Cohort</td>
<td>Enrolling by invitation</td>
<td>16</td>
<td>Low- or intermediate-risk prostate CA, scheduled for radical prostatectomy 30 days later</td>
<td>Safety, efficacy &amp; QOL Follow-up: 12 months</td>
<td>Sept. 2014</td>
</tr>
<tr>
<td>NCT01726894/ England</td>
<td>Cohort</td>
<td>Ongoing</td>
<td>20</td>
<td>Locally contained, MR-visible cancer of the anterior prostate</td>
<td>Safety &amp; efficacy Follow-up: 12 months</td>
<td>Aug. 2015</td>
</tr>
<tr>
<td>ACTRN12612000523808/ Australia</td>
<td>Cohort</td>
<td>Recruiting</td>
<td>6</td>
<td>Low- or intermediate-risk prostate CA, scheduled for radical prostatectomy 2 to 4 weeks later</td>
<td>Safety, efficacy, patient satisfaction &amp; cost-effectiveness Follow-up: 1 week post prostatectomy</td>
<td>Registered in 2012. Current status unclear</td>
</tr>
</tbody>
</table>

* Information is from clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry.
Table notes: CA=cancer; MR=magnetic resonance; QOL=quality of life; USA=United States of America.
**MR-guided focal laser ablation**

Five case series studies have enrolled or will enrol a total of about 130 men (Table 6). The trials are being conducted in the USA (three trials), Canada (one trial) and the Netherlands (one trial). Four of the five studies should be complete by mid-2015. The fifth study aims to track 3-year disease-free survival and will not be complete until mid-2019.

### Table 6  Ongoing trials of MR-guided focal laser ablation for localised prostate cancer

<table>
<thead>
<tr>
<th>Trial number* / location / note</th>
<th>Study design</th>
<th>Status</th>
<th>n=</th>
<th>Patients / indication</th>
<th>Outcomes / length of follow-up</th>
<th>Estimated completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 01192438/ USA</td>
<td>Cohort</td>
<td>Completed Sept. 2011 (no publications yet)</td>
<td>9</td>
<td>Low grade prostate CA</td>
<td>Safety Follow-up: 6 months</td>
<td>Sept. 2011</td>
</tr>
<tr>
<td>Collaborator is MR-guided laser company (Visualase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT 01094665/ Canada</td>
<td>Cohort</td>
<td>Recruiting (start date Nov 2009)</td>
<td>60</td>
<td>Early stage prostate CA, as yet untreated</td>
<td>Safety &amp; feasibility Follow-up: 4 months</td>
<td>Dec. 2013</td>
</tr>
<tr>
<td>Presumably the Lindner et al (2012) abstract, which forms part of this technology brief, reports on 23 men from this cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT 01792024/ USA</td>
<td>Cohort</td>
<td>Ongoing (start date Jan 2013)</td>
<td>27</td>
<td>Early stage prostate CA, as yet untreated</td>
<td>Safety, efficacy &amp; QOL Follow-up: 12 months</td>
<td>Feb. 2015</td>
</tr>
<tr>
<td>NCT 01377753/ USA</td>
<td>Cohort</td>
<td>Ongoing (start date May 2011)</td>
<td>15</td>
<td>Localized prostate CA visible on MR</td>
<td>Safety &amp; feasibility Follow-up: 3 years</td>
<td>Apr. 2015</td>
</tr>
<tr>
<td>NCT 02200809/ Netherlands</td>
<td>Cohort</td>
<td>Recruiting (start date July 2014)</td>
<td>20</td>
<td>Intermediate-risk prostate CA, as yet untreated</td>
<td>Efficacy (3-year disease-free survival) Follow-up: 3 years</td>
<td>Jul. 2019</td>
</tr>
</tbody>
</table>

* Information from clinicaltrials.gov

Table notes: CA = cancer; MR = magnetic resonance; NCI = National Cancer Institute; NR = not reported; QOL = quality of life; USA = United States of America.

**Other issues**

The Williams et al\(^ {15} \) Medicare database study from the USA noted several interesting socio-demographic differences between men who received cryosurgery and those who were treated with EBRT. Men who underwent cryotherapy were significantly:

- more likely to have a higher grade (36% versus 13%) and clinical stage of disease (T3/unknown 5% versus 2%); be older than 75 years (41% versus 31%); be African American (12% versus 6%); and live in urban areas (11% versus 9%);
- less likely to live in areas where at least 90 per cent of the population had graduated high school (32% versus 40%); and have median household income of more than USD 60,000 (13% versus 21%)
It is unclear whether these differences between the treatment populations would be seen in other countries.

There are also questions regarding appropriateness of focal therapy for prostate cancer as a viable technique because of safety and efficacy issues. The Urology Society of Australia and New Zealand (USANZ) position below summarises these concerns:

Due to the lack of long-term data on focal therapy regarding the ability to accurately target a lesion, on the long-term cancer control, on the side effects of treatment, and on the ability to provide safe salvage options should treatment failure occur – USANZ believe that focal therapy for prostate cancer remains an experimental technique.22

It is important to note, that focal therapy may require more frequent surveillance then whole gland therapy, which in turn may have an impact on cost considerations.

**Summary of findings**

Australian data shows a rising incidence in the diagnosis of prostate cancer, which is largely attributable to increased testing, changes in diagnostic practices and ageing of the population. In many cases the cancer is localised within the prostate gland, yet current treatments often target the entire gland and can result in significant complications in adjacent organ systems. In particular, current treatments can result in urinary incontinence or retention, bowel disturbances and erectile dysfunction. Focal treatment of only the cancerous tissue may lead to fewer adverse effects, and a number of avenues are being explored, including the ablation of tissue via extreme cold (cryosurgery), thermal energy (RFA and MR-guided focal laser) and electric current (IRE). The treatment can often be delivered in an outpatient setting and this may provide cost savings.

At present the evidence is sparse, particularly in terms of comparative studies although a number of studies are underway. Cryosurgery has been the most extensively explored, with the published literature including two randomised controlled trials and one comparative database study. These three studies had follow-up ranging from 24 to 100 months, although the two randomised studies were both small. The database study examined outcomes for 943 men undergoing cryosurgery compared with 9985 men undergoing brachytherapy. The evidence from the two randomised trials, looking at cryosurgery compared with EBRT, did not show a consistent benefit. Similarly, the database study of patients receiving cryosurgery, compared with brachytherapy, reported greater use of antiandrogen therapy in the cryotherapy group, suggesting poorer cancer control. However, cryosurgery techniques may be improving with attendant improvements in patient outcomes.

The remaining three focal ablation techniques are early in their development cycles; however, they do show promise. Although no studies for IRE were located, five are underway or planned with one being a randomised trial that aims to enrol 200 men. Similarly, only two small cohort studies for MR-guided focal laser therapy were located but
five cohort studies are underway. The evidence for RFA is scarce, with one very small cohort study located. Another small cohort study is underway, and there is a media report of recent funding for additional research in this area.

HealthPACT assessment

Despite a paucity of rigorous evidence describing the use of ablative therapies for localised prostate cancer, non-TGA approved technologies such as the Nanoknife® system are being marketed in Australia and New Zealand through 'free trials'. Studies included in this assessment are flawed as they did not use radical prostatectomy, which is a good treatment option especially for younger or high-risk patients, as the comparator. At this point in time focal therapy for prostate cancer should be considered experimental and should only be conducted under the auspices of a clinical trial. HealthPACT recommends that the evidence around this technology be updated and monitored for more information in 24-months and that other local ablation techniques should be included in any future technology update.

Number of studies included

All evidence included for assessment in this technology brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

- Total number of studies: 7 (including a level IV SR for cryosurgery)
- Total number of Level I studies: 2 (randomised trials for cryosurgery)
- Total number of Level III-2 studies: 1 (registry study for cryosurgery)
- Total number of Level IV studies: 4 (an SR of level IV studies for cryosurgery, two studies for MR-guided focal laser ablation, one study for RFA and no studies for IRE)

Search criteria to be used (MeSH terms)

cryotherapy OR cryosurgery OR cryoablation OR cryo-ablation OR radioablation OR radio-ablation OR radiofrequency ablation OR radio-frequency ablation OR focal laser ablation OR irreversible electroporation AND prostate AND cancer OR tumour OR tumor

Limits: English, Humans, Abstract available. (EMBASE limit 2005 to present)

References


