



**Australian Government**

**Department of Health**

# **RATIFIED PICO**

**Application 1597:**

**Cryoablation for small renal mass**

Summary of PICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	<p>Patients:</p> <ul style="list-style-type: none"> <li>• with localised primary malignant renal cell carcinoma (stage T1aN0M0), ≤4 cm in greatest dimension, with malignancy confirmed by pre-ablation biopsy; and</li> <li>• indicated for intervention after diagnosis but not suitable for partial nephrectomy; patients with one or more of the following characteristics are the focus of interest for this application: <ul style="list-style-type: none"> <li>○ Elderly and/or frailty;</li> <li>○ High surgical risk;</li> <li>○ Poor renal function;</li> <li>○ Solitary kidney;</li> <li>○ Bilateral kidney tumours;</li> <li>○ Hereditary/multiple renal cell carcinomas.</li> </ul> </li> </ul>
Intervention	Cryoablation (percutaneous, laparoscopic or open surgical approach)
Comparator(s)	<ul style="list-style-type: none"> <li>• Main comparators: laparoscopic radical nephrectomy; active surveillance/delayed therapy;</li> <li>• Supplementary: partial nephrectomy; thermal ablation (radiofrequency ablation, microwave ablation)</li> </ul> <p><i>Please note: The safety and effectiveness of the supplementary comparators should be compared to the proposed intervention, both directly and indirectly, via comparison of the supplementary comparators against the main comparators</i></p>
Outcomes	<ul style="list-style-type: none"> <li>• Safety: peri- and post-procedure outcomes, adverse events and complications.</li> <li>• Clinical effectiveness: <ul style="list-style-type: none"> <li>○ Tumour growth rate (especially for patients on active surveillance);</li> <li>○ Salvage or repeat procedure rates;</li> <li>○ Oncologic outcomes (local recurrence rates, metastatic rates);</li> <li>○ Survival (local recurrence-free, disease-free, progression-free, cancer-specific, overall), mortality;</li> <li>○ Functional outcomes (physical, renal);</li> <li>○ Patient-relevant outcomes (e.g. pain control, satisfaction, quality of life).</li> </ul> </li> <li>• Cost-effectiveness: <ul style="list-style-type: none"> <li>○ Costs associated with the performance of the proposed and comparator procedures (e.g. anaesthesia, pre- and post-treatment imaging, biopsy, professional attendance, specialist fees, medication use peri-procedure, hospital length of stay, equipment, etc.);</li> <li>○ Costs associated with the monitoring or surveillance of the proposed and comparator procedures (e.g. blood tests, professional attendances, imaging);</li> <li>○ Costs associated with the management of adverse events or complications peri- and post-procedure</li> </ul> </li> <li>• Other healthcare resource use – e.g. equipment, consumables</li> <li>• Total Australian Government healthcare costs</li> </ul>

## POPULATION

PASC confirmed the proposed population, but highlighted that malignancy needs to be histologically proven prior to the procedure. PASC noted that core biopsy would be the only likely option for the patient, which would have implications for completeness of staging. The applicant agreed with this, noting the available evidence contains a mixture of studies conducted in patients with small renal mass (where RCC has not been confirmed) and patients with biopsy-confirmed RCC. Both will be included in the applicant's assessment report, with most weight given to studies in patients with biopsy-confirmed RCC.

PASC advised that the base-case population should include tumours  $\leq 4$  cm in greatest dimension, but an alternative population investigated in the sensitivity analysis should include tumours  $\leq 3$  cm in greatest dimension, due to variation of this threshold in clinical guidelines. The applicant agreed, adding that tumours  $\leq 3$  cm will be included, where evidence is available.

### Kidney cancer

Kidney cancer is the ninth most commonly diagnosed cancer in Australia in 2019. The estimated incidence for 2019 is 3,814 new cases and accounts for 2.6% of all new cases of cancer diagnosed in the year.<sup>1</sup> Comparing the cancer incidence rates between 1982 and 2019, kidney cancer ranks third in having the greatest percentage increase of 108% from an age-standardised rate (ASR) of 6.2/100,000 in 1982 to 12.9/100,000 in 2019, after thyroid (396%) and liver (378%) cancers.<sup>2</sup> Among the newly diagnosed, two-thirds (66.6%) are men and one in two (53.0%) are aged  $\geq 65$  years (28.8% aged 65-74 years, 24.2% aged  $\geq 75$  years).<sup>3</sup> The median age at diagnosis is 65 years.<sup>4</sup>

Kidney cancer is also ranked as the 18<sup>th</sup> (2019) most common causes of death from cancers in Australia and is estimated to be responsible for 1,034 deaths in 2019 (ASR 3.3/100,000), accounting for 2.1% of all deaths from cancers in the year.<sup>5</sup> Comparing the cancer mortality rates between 1982 and 2019, the ASR for kidney cancer decreased from 3.9/100,000 in 1982 to 3.3/100,000 in 2019, a decrease of 15.4%.<sup>6</sup> Among those who died of kidney cancer, two-thirds (66.0%) are men and three out of four (75.5%) are aged  $\geq 65$  years (24.2% aged 65-74 years, 51.3% aged  $\geq 75$  years).<sup>7</sup> The median age at death is 74.0 years.<sup>8</sup>

Compared with the general population, the 5-year relative survival<sup>9</sup> (2011-2015) for kidney cancer is 77.4% (50.7% in 1986-1990).<sup>10</sup> As at the end of 2014, the 1- and 5-year prevalence<sup>11</sup> is 3,099 and 12,364 persons respectively (10-year prevalence: 19,928 persons; 33-year prevalence: 29,264 persons).

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for 80%<sup>12</sup>-90%<sup>13</sup> of all kidney malignancies. Clear cell RCC is the most common subtype of RCC (80-90%). The other two main subtypes are papillary RCC (10-15%) and chromophobe RCC (4-5%).<sup>14</sup> Different subtypes are known to have different tumour stage, grade and cancer-specific survival. Known risk factors for kidney cancer include smoking, obesity, hypertension and familial history.<sup>15</sup> Symptoms for kidney cancer may include haematuria, flank pain, abdominal mass, fatigue, unexplained weight loss or fever (not caused by a cold or flu)<sup>16</sup> and when present often correlates with locally advanced or metastatic RCC<sup>17</sup> with poorer prognosis.<sup>18</sup>

### *Small renal masses or renal tumours*

Small renal masses (SRMs) or renal tumours, the focus of this Application, are renal lesions not more than 4 cm in greatest dimension. The definition of SRMs has changed over time. The term 'small' renal mass was first used in the Tumour Nodes Metastasis (TNM) staging system in 1974 to describe renal tumour in the absence of kidney enlargement. SRM (stage T1) was defined as renal lesions <2.5 cm in diameter in the TNM 1987 version but the upper limit for SRM (stage T1) was increased to 7 cm in diameter in the 1997 version. From the 2002 version onwards, T1 tumours are further divided into two sub-categories using 4 cm as the cut-off: T1a ( $\leq 4$  cm) and T1b ( $>4$  but  $\leq 7$  cm).<sup>19</sup> International guidelines and peak professional bodies these days commonly define SRMs as contrast-enhanced renal tumours  $\leq 4$  cm in diameter, with image characteristics usually consistent with stage T1aN0M0 RCC<sup>20</sup> (see

## Appendix 1<sup>21</sup>).

Owing to the increasing use of diagnostic imaging (ultrasound, computer tomography [CT]) to investigate abdominal symptoms not related to the kidney, SRMs are increasingly detected at early asymptomatic stage,<sup>22</sup> which in turn is considered to contribute to the increasing incidence of RCC.<sup>23</sup> It was reported that over 60% of RCC are detected incidentally during abdominal ultrasound or CT performed for other purposes.<sup>24</sup> Majority of the patients with incidentally-detected SRMs are asymptomatic.<sup>25</sup> Majority of the SRMs are asymptomatic and non-aggressive at diagnosis.<sup>26</sup>

It was reported that as many as 25% of SRMs are benign and another 25% are indolent with limited metastatic potential.<sup>27</sup> Others reported that 20-46% of SRMs are histologically benign.<sup>28</sup> Not more than 6% of patients had metastases in a retrospective study of almost 2,000 patients with SRMs ≤4 cm (T1a RCC) and who received either partial or radical nephrectomy in 2009-2013.<sup>29</sup> Most malignant SRMs also grow slowly<sup>30</sup> (2-3 mm/year).<sup>31</sup> To avoid over-treatment of SRMs, accurate prediction of benign versus malignant SRMs is important but has remained challenging in clinical practice as there is currently no validated non-invasive prognostic tool available.<sup>32</sup> The male gender and tumour size are the two factors that have been shown to be statistically significantly associated with malignancy.<sup>33</sup>

### *Diagnostic evaluation and treatment options*

To detect and diagnose renal masses, imaging modalities like CT, ultrasound or magnetic resonance imaging (MRI) are used. Based on the imaging findings, renal masses are classified as solid or cystic masses. For solid masses, the presence of contrast enhancement or restriction is the most important criterion for malignancy.<sup>34</sup> To detect metastases in the lungs or mediastinal lymph nodes, chest CT is the most accurate diagnostic tool. Bone and brain imaging may also be indicated when bone or brain metastases are suspected. For cystic masses, classification based on CT presentation into Bosniak categories<sup>35</sup> may help predict the risk of malignancy and therefore guide treatment planning.<sup>36</sup> Evaluation of tumour type size, type and stage is important because together with patient-related factors would contribute significantly to what treatment options available and are recommended. International guidelines<sup>37</sup> on the management of RCC broadly categorise their recommendations according to whether the disease is local, loco-regional or metastatic. For localised primary RCC, surgery is the only curative treatment<sup>38</sup> whereas for metastatic RCC, systemic therapy may be required.<sup>39</sup>

Treatment recommendations for SRMs have evolved over time, from the more aggressive open radical nephrectomy (RN) in the past, to less invasive laparoscopic (or robot-assist laparoscopic) partial nephrectomy (PN), to minimally invasive percutaneous thermal ablative (TA) techniques like radiofrequency ablation (RFA), cryoablation (CA) or microwave ablation (MWA), and to active surveillance (AS).<sup>40</sup> AS was used to be reserved for elderly and frail, with short life expectancy or with significant comorbidities and high surgical risk, etc. while the surgical treatment options were for those who are younger. However, with the increasing knowledge of the natural history of SRMs (e.g. that many SRMs are indolent, with slow growth rate of 2-3 mm/year and low metastatic potential) and recognition of the importance of renal function preservation especially in those with solitary kidney or with compromised kidney function at baseline, it is now widely acknowledged that nephron-sparing treatment approach (e.g. PN, image-guided ablation) for SRMs are preferred over open radical approach and that unnecessary treatment for SRMs should also be avoided if possible, especially e.g. in patients with short life expectancy.<sup>41</sup>

Appendix 2 presents a summary of treatment options available for SRMs as recommended in international guidelines. In general, for localised primary RCC (stage T1a), the recommended treatment options are as follows:

- Partial nephrectomy (PN) is the preferred option<sup>42</sup> and is recommended to be offered to all for whom intervention is indicated<sup>43</sup> and whose tumour is amenable to the approach.<sup>44</sup> PN can be carried out via open, laparoscopic or robot-assisted laparoscopic approaches.<sup>45</sup>
- Laparoscopic radical nephrectomy (RN) is recommended if PN is not technically feasible<sup>46</sup> or if tumour is of significant complexity not amenable to PN.<sup>47</sup>
- Cryoablation (CA), radiofrequency ablation (RFA) and microwave ablation (MWA) are options in patients with small cortical tumours  $\leq 3$  cm,<sup>48</sup> elderly, comorbid and are not fit for surgery.<sup>49</sup> Percutaneous thermal ablation (TA) (CA, RFA, MWA) is considered an option in patients whose tumours are such that complete ablation is achievable.<sup>50</sup>
- Active surveillance (AS) with delayed therapy (DT) – recommended as initial management for patients not indicated for intervention at diagnosis<sup>51</sup> or, for patients indicated for intervention but not fit for PN or laparoscopic RN. It is also an option in elderly patients with significant comorbidities or patients with a short life expectancy (e.g.  $< 5$  years) and competing mortality risks.<sup>52</sup>

### **Proposed patient population**

The proposed patient population (for whom public subsidy of the medical service is sought) is characterised as follows:

Patients:

- with localised primary malignant renal cell carcinoma (stage T1aN0M0),  $\leq 4$  cm in greatest dimension, with malignancy confirmed by pre-ablation biopsy; and
- indicated for intervention after diagnosis but not suitable for partial nephrectomy; patients with one or more of the following characteristics are the focus of interest for this Application:
  - Elderly and/or frailty;
  - High surgical risk;
  - Poor renal function;
  - Solitary kidney;
  - Bilateral kidney tumours;
  - Hereditary/multiple renal cell carcinomas.

This is broadly similar to that proposed in the Application Form<sup>53</sup> with slight differences. Firstly, confirmation of malignancy by biopsy is added as one of the eligibility criteria, as recommended by the Urology Society of Australia and New Zealand.<sup>54</sup> Secondly, the applicant proposed that cryoablation be indicated in cases where it is technically difficult to perform PN.<sup>55</sup> However, this indication is not included in any of the international guidelines presented in Appendix 2. As mentioned in the previous paragraphs, laparoscopic RN is recommended if PN is not technically feasible<sup>56</sup> or if tumour is of significant complexity not amenable to PN.<sup>57</sup> It is not clear at the PICO development stage regarding the availability of any evidence of the specific use of CA in cases where PN is not technically feasible. It is therefore not included as an eligibility criterion at this stage. Subject to results of evidence developed in the Applicant Developed Assessment Report, MSAC may revise the eligibility criteria. Table 1 below presents a summary of the proposed eligibility criteria and associated rationale.

**Table 1 Summary of the eligibility criteria for the proposed patient population**

Proposed eligibility criteria	Rationale
<b>Tumour-related factors:</b>	
Localised primary malignant RCC (T1aNOM0), ≤4 cm in greatest dimension	<ul style="list-style-type: none"> <li>As per international guidelines in general (Appendix 2) although some guidelines recommend the use of CA in ≤3 cm (see potential alternative eligibility criteria below).<sup>58</sup></li> <li>Cryoablation (CA) is indicated for SRM ≤4 cm in diameter. The cut-off of 4 cm is by consensus.</li> <li>Large-volume CA (&gt;5 cm) increases the risk of complications (e.g. bleeding, cryoshock, acute renal failure from cryoglobulinaemia).<sup>59</sup></li> </ul>
Malignancy and subtype confirmed by biopsy	<ul style="list-style-type: none"> <li>To avoid over treatment or unnecessary surgery in the event of benign or indolent lesions.<sup>60</sup></li> <li>To collect pathology information about the tumour prior to ablation after which is not feasible. Histopathological information may affect downstream management in the future.</li> <li>As recommended in the literature<sup>61</sup>, ESMO Clinical Practice Guidelines (see Appendix 2) and the Urologist Society of Australia and New Zealand (targeted consultation form for the Application Form).</li> </ul>
<b>Patient-related factors:</b>	
Indicated for intervention after diagnosis	Not all patients with localised primary RCC ≤4 cm are indicated for interventions. For example, if patients have limited life-expectancy (<5 years) because of old age or other significant comorbidities with competing mortality risks, AS may be a better option in this setting.
Patient characteristics	<ul style="list-style-type: none"> <li>Elderly and/or frailty;</li> <li>High surgical risk;</li> <li>Poor renal function;</li> <li>Solitary kidney;</li> <li>Bilateral kidney tumours;</li> <li>Hereditary/multiple renal cell carcinomas.</li> </ul> <p>This is broadly similar to that proposed in the Application Form<sup>62</sup>, in the Targeted Consultation Survey feedback by RANZCR and international guidelines (Appendix 2).</p> <p>Patients with these characteristics may not be suitable candidates for PN in general.</p>

Abbreviations: CA, cryoablation; PN, partial nephrectomy; RANZCR, Royal Australia and New Zealand College of Radiologists; RCC, renal cell carcinoma

## Potential alternative eligibility criteria and rationale

Table 2 presents an alternative eligibility criterion and rationale behind it.

**Table 2 Alternative eligibility criterion**

Alternative eligibility criterion	Rationale
Tumour size ≤3 cm	TA (CA, RFA, MWA) is recommended as an alternate approach for the management of SRM (T1a) <3 cm <sup>63</sup> or ≤3 cm <sup>64</sup> because efficacy is strongest for tumours <3 cm <sup>65</sup> and success rate decrease in tumours >3 cm. <sup>66</sup> Ablation in masses >3 cm is associated with higher rates of local recurrence/persistence and complications. <sup>67</sup>

Abbreviations: CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation; SRM, small renal mass; TA, thermal ablation

## Investigations and referral in the lead up to being considered eligible for the proposed medical service

In general, patients with SRMs suspicious of RCC are evaluated by laboratory tests (e.g. serum creatinine, haemoglobin, leukocyte, etc.) and imaging examinations (e.g. ultrasound, and/or CT, and/or MRI) as required.<sup>68</sup> The ESMO Clinical Practice Guidelines for RCC considers the use of contrast-enhanced chest, abdominal and pelvic CT as mandatory for accurate staging of RCC but routine use of bone scan or brain CT or MRI is not recommended.<sup>69</sup> CT is the primary imaging modality for characterisation of SRMs and can classify most cases into surgical or non-surgical lesions.<sup>70</sup> Renal tumour biopsy (percutaneous) is performed to select patients for surveillance,<sup>71</sup> to obtain histology prior to ablative treatment, to provide pathologic diagnosis and to guide subsequent surveillance.<sup>72</sup> Renal tumour biopsy is recommended before the performance of any ablative therapy and may require general anaesthesia.<sup>73</sup> Core biopsy is preferred to fine needle biopsy.<sup>74</sup>

In summary, it is anticipated that for a patient to be considered eligible for the proposed medical service, cryoablation, the following investigations would have to be performed:

- Blood tests; renal function tests;
- Ultrasound imaging;
- Contrast-enhanced CT imaging;
- Renal tumour biopsy and pathology services;
- Professional attendances – e.g. general practitioner, multidisciplinary team assessment with urologist, interventional radiologist, anaesthetist, etc. to decide on the suitability of the patient for PN and to counsel the patient on treatment options available including risks of potential harms/complications.<sup>75</sup>

## Previous 2009 MSAC Application

An application for the listing of cryoablation for small renal mass (SRM) on the Medicare Benefits Schedule (MBS) was received by the Department of Health in September 2019.

A similar application, Application 1124 (Cryotherapy for recurrent prostate cancer and renal cancer), was considered by the Medical Services Advisory Committee (MSAC) in September 2009. MSAC did not support public funding for cryotherapy for renal cancer because of lack of evidence that cryotherapy was as safe and effective as the treatment available at the time. The financial analysis also indicated public funding for this procedure would incur additional costs for the Australian Government and healthcare system (para 10, Part B of Public Summary Document 1124, September 2009 MSAC Meeting).



Appendix 3 (at the end of this document) presents a comparison of selected characteristics between current Application 1597 and relevant sections of previous Application 1124, using information in the Application Form for current Application 1597, and Public Summary Document and Assessment Report for previous Application 1124.

#### *Utilisation estimates from the applicant*

The applicant estimates that, in 2019, 4,034 patients were diagnosed with kidney cancer:

- 28.2% are with SRMs (N=1,137),<sup>76</sup> and
- 5.9% (N=238) receive cryotherapy procedures.<sup>77</sup>

The applicant reported that these estimates are based on the method and assumptions used in the Assessment Report for Application 1124, assuming these are still valid. The applicant reported that these estimates will be revised in their Applicant Developed Assessment Report for 1597.<sup>78</sup>

## **INTERVENTION**

*PASC confirmed the proposed intervention, highlighting that the three approaches (percutaneous, laparoscopic and open surgery) would likely have different outcomes, so should be investigated and reported separately in the assessment report.*

*The applicant agreed with this, confirming its ADAR will include all available evidence on cryoablation, comparing it with the main and supplementary comparators, and presenting each of the approaches/modes of delivery separately (where possible) – being percutaneous, laparoscopic and open surgery. This will include the impact of the different approaches. By specifying the modes of delivery used in each study, MSAC can then make an informed decision, based on totality of the evidence.*

### ***Cryoablation***

The use of extreme cold to destroy tissues is not new. Cryoablation (or cryotherapy or cryosurgery) is one of the oldest ablative techniques and its clinical application dates back to the 1800s, from the use of dry ice (solid CO<sub>2</sub>, -78.5°C) as cryogen at the start of the 20<sup>th</sup> century to the widespread use of liquid nitrogen (up to -196°C) in modern days.<sup>79</sup> Cryotherapy has been used in various organs or regions of the body from head to foot.<sup>80</sup> Development of modern image-guided puncture techniques and miniaturisation of deep-reaching applicators have made it possible for percutaneous cryoablation to be used as a treatment option in the local ablation of tumours.<sup>81</sup>

There are many ablative tools available, from thermal based tools (e.g. focused ultrasound, laser, cryotherapy, radiofrequency) to microwave, irreversible electroporation and radiosurgery.<sup>82</sup> Only radiofrequency ablation (RFA) is relevant to the current Application (see next section Comparator).

A key feature of renal cryoablation is that it causes tumour necrosis by freezing,<sup>83</sup> in contrast to other thermal ablative techniques (e.g. RFA) which cause tissue destruction by heating.<sup>84</sup> In cryoablation, tissue necrosis is brought about by a two-step deep freeze-thaw cycle. To freeze the tumour, special ultra-thin hollow probes, cryoablation or cryoprobe needles, are inserted percutaneously into the target site under image guidance. During the freeze cycle, highly pressurised argon gas is delivered via the needles into a small chamber inside the tip of the needle where it quickly expands and cools<sup>85</sup> to cytotoxic temperature, resulting in rapid freezing of the target tissue. Intra- and extra-cellular ice crystals are formed, visualised as 'ice-ball' when monitored on computer tomography (CT) or magnetic resonance imaging (MRI).<sup>86</sup> Further tissue damage (cell membrane rupture) is achieved during the thaw cycle (by the circulation of helium gas<sup>87</sup>). The freeze-thaw cycle is repeated at least twice to ensure adequate freezing and destruction of cells at the centre (-140°C) and margin (-20°C) of the target site.<sup>88</sup> Up to 10 cryoprobes can be inserted into a target lesion and

the individual ice-balls formed from each cryoprobe may coalesce into a bigger ice-ball,<sup>89</sup> making it possible to produce complex ablation results by multiple overlapping cryoprobes.<sup>90</sup> Cryoablation times depend on the size and location of the lesion. A typical cryoablation session may include 6-10 minutes of freeze cycle and 5-10 minutes of thaw cycle, with the whole cycle repeated twice.<sup>91</sup> The applicant reported that cryoablation typically takes 1-2 hours to perform.<sup>92</sup>

Apart from causing tumour death by 'freezing', another important feature of image-guided percutaneous renal cryoablation is that it is minimally invasive, nephron-sparing and renal function preserving.<sup>93</sup> Minimal invasiveness of interventions is desirable as the risk of peri- and post-procedural complications and/or morbidities is lower, recovery is quicker and patient tolerability better.<sup>94</sup> It is desirable to preserve as much renal function as possible as it is now recognised that decreased renal function and chronic kidney disease is a risk factor for cardiovascular morbidity and mortality.<sup>95</sup> It is therefore important especially for patients with compromised renal function at baseline, with solitary kidney, etc.<sup>96</sup>

Image guidance for renal cryoablation is important for the precise location of the target site, accurate placement of the cryoprobes and monitoring. While the ice-ball may be visualised and monitored with ultrasound, CT or MRI, 3-dimensional visualisation is only possible with CT or MRI.<sup>97</sup> Direct visualisation of the ice-ball and its margin in real-time on CT or MRI allows more precise monitoring of the ablation zone and is considered an advantage of CA.<sup>98</sup>

#### *Expected use of cryoablation*

If approved, cryoablation is expected to be offered as an alternative treatment option for patients with localised, primary malignant RCC (stage T1aN0M0) ( $\leq 4$  cm in diameter), with malignancy and subtype confirmed by pre-ablation biopsy but not suitable for PN (c.f. Table 1):

As mentioned before, CA may be performed via percutaneous, laparoscopic or open surgical approach. Percutaneous CA is the most commonly used approach. Image-guided percutaneous CA is performed mostly under conscious sedation<sup>99</sup> but may also be performed under local or general anaesthesia.<sup>100</sup> The Urology Society of Australia and New Zealand reported that most procedures of CA would require specialist anaesthetist attendance to provide heavy sedation or general anaesthesia.<sup>101</sup> Some procedures may be performed as day cases but most patients would stay overnight in the hospital for observation and have a follow-up scan the next day to confirm complete tumour ablation, check for any treatment-related complications<sup>102</sup>, etc.<sup>103</sup> Patients are followed up with serial contrast-enhanced CT at three, six months post-treatment and then annually up to five years.<sup>104</sup> The frequency of follow-up monitoring and imaging is dependent on the final pathological diagnosis as confirmed after.

Management of renal masses involves a multidisciplinary team. Urologists conduct initial assessment, confirm diagnosis and perform partial or radical nephrectomy if surgery is indicated.<sup>105</sup> Percutaneous CA is performed by interventional radiologists, specially trained for the procedure.<sup>106</sup> Percutaneous renal tumour biopsy, as recommended to be performed prior to CA to confirm malignancy and subtype,<sup>107</sup> involves interventional radiologist and a pathologist and may require general anaesthesia.<sup>108</sup> A radiologist and urologist may also be involved in the follow-up after treatment. Repeat CA may be required in some patients<sup>109</sup> in the event of incomplete ablation (residual tumour) or local recurrence.<sup>110</sup>

### *Different ways to provide cryoablation*

Apart from the most commonly performed percutaneous approach, renal cryoablation may also be performed by surgeons using a laparoscopic, or open surgical approach (rare today).<sup>111</sup> Selection of approach is dependent on local expertise and tumour characteristics.<sup>112</sup> RANZCR advised that laparoscopic CA should be reserved for patients unsuitable for percutaneous CA or standard surgical resection techniques.<sup>113</sup>

Laparoscopic CA, under ultrasound guidance, involves exposure of the tumour and may involve extensive mobilisation of the kidney.<sup>114</sup> When compared with laparoscopic CA, percutaneous CA is associated with less pain, shorter hospitalisation, faster recovery and lower cost.<sup>115</sup> A systematic review of 11 retrospective comparative studies reported no significant difference in recurrence-free survival and overall survival between laparoscopic CA and percutaneous CA while the latter was associated with significantly shorter hospital stay and more favourable tumour recurrent rate.<sup>116</sup>

For the purpose of this PICO, it is proposed that CA (any approach) is the intervention of interest. However, subject to findings of the systematic review of comparative clinical effectiveness and safety in the applicant developed assessment report (ADAR), the Medical Services Advisory Committee (MSAC) may wish to consider restricting public subsidy to percutaneous CA only.

### *Current reimbursement status of cryoablation*

Renal cryoablation is not currently listing on the Medicare Benefits Schedule (MBS). However, cryoablation is currently funded for the destruction of malignant liver tumours (MBS item [30419](#)) and other skin or eye conditions (see [Appendix 4](#)).

### *Potential leakage of use of cryoablation*

The applicant did not expect any leakage of use beyond the proposed indications.<sup>117</sup>

Table 3 presents potential usage of CA outside the proposed indications and rationale.

**Table 3 Potential leakage of use of cryoablation**

<b>Potential leakage of use (not exhaustive)</b>	<b>Rationale</b>
CA being used in patients fit for PN	E.g. based on patient's preference for CA as a less invasive treatment over PN (as mentioned in the Application Form)
CA being offered as salvage treatment to patients after PN	E.g. Treatment failure or local recurrence after initial PN
CA being offered as salvage treatment to patients after ablative therapies (e.g. RFA, MWA)	E.g. Treatment failure or local recurrence after initial ablative therapies

Abbreviation: CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation

Figure 3 presents the clinical management algorithm after the proposed listing, taking into consideration potential leakage of use of cryoablation. Adding notes to proposed wording for restrictions on the proposed service may help to mitigate risk of leakage (see [Table 6](#)).

### *Device(s) associated with provision of the proposed medical service*

The applicant reported<sup>118</sup> that the proposed medical service relies on other devices to achieve its intended effect:

- Multi-use consumables: Visual-ICE<sup>®</sup> Cryoablation System (ARTG [221468](#));
- Single-use consumables: Galil Medical Cryoablation Needles (ARTG [224583](#)).

Both are available from the same manufacturer, Galil Medical, and are registered with the Therapeutic Goods Administration (TGA). In addition, the proposed medical service also requires the following items from other manufacturers: Argon gas cylinders (for freezing), Helium gas cylinders (for thawing) and sterile drape to cover the touch screen if the cryoablation system is operated by members of the sterile team.<sup>119</sup>

The applicant reported that the device associated with cryotherapy in the previous submission considered at the September 2009 MSAC Meeting is no longer registered with the TGA in Australia.<sup>120</sup>

There is, however, another similar device, being the ProSense Cryoablation system (IceCure Medical, Israel), registered in Australia (ARTG [308786](#)). The applicant reported that it was its understanding that the ProSense system is not used for this indication in Australia.<sup>121</sup> Rather than using argon gas as is the case with the Visual-ICE Cryoablation System, the ProSense Cryoablation System uses innovative liquid nitrogen-based cryogen to apply the cold to tissue. Its intended purpose as stated in the public ARTG summary describes ProSense as being typically used across clinical specialties (e.g. urology) to remove malignant or abnormal benign tissues (Appendix 5). An abstract<sup>122</sup> published at the 34 Annual European Association of Urology (EAU) Congress reported results of safety, feasibility and oncologic efficacy of the use of ProSense in percutaneous CA in 74 patients with SRMs  $\leq 4$  cm in Israel. It appears that the ProSense cryoablation system may also aim at achieving the same clinical positioning as Visual-ICE cryoablation system.

### **COMPARATOR/S**

*PASC queried the PICO's approach of using main comparators and supplementary comparators, and in particular, how partial nephrectomy could be a comparator, given the proposed population is not considered suitable for partial nephrectomy.*

*The applicant clarified that it included partial nephrectomy as a supplementary comparator, while the HTA group added laparoscopic radical nephrectomy as a main comparator. While the applicant had initially intended to disagree with inclusion of laparoscopic radical nephrectomy, they advised that clinical feedback suggests a subset of patients being referred for cryoablation are those who are initially considered for laparoscopic radical nephrectomy, after being considered not suitable for partial nephrectomy.*

*In addition, PASC queried how the main and supplementary comparators would be treated differently in the clinical and economic evaluations. PASC advised that the assessment report should provide data to substantiate if these comparator distinctions are valid. The applicant informed PASC that they intended to appraise all available evidence and assess which comparisons were possible (and most relevant) to the Australian context.*

*The applicant clarified that its original intention (by including partial nephrectomy as a supplementary comparator, and not a main comparator) was to ensure MSAC had access to data for this comparison, given it is possible that some patients would prefer cryoablation over partial nephrectomy if it is available (i.e. leakage). Radiofrequency ablation was initially included as a main comparator by the applicant, but changed to a supplementary comparator by the HTA group because it is not currently MBS-funded for the proposed indication.*

*The safety and effectiveness of the supplementary comparators should be compared to the proposed intervention, both directly and indirectly, via comparison of the supplementary comparators against the main comparators. Should MSAC recommend that cryoablation be approved for this indication, it would act as an “exemplar” for the other thermal techniques, should an MSAC application for MWA or RFA be made in the future.*

*The applicant advised that evidence for supplementary comparisons will be presented in its ADAR (applicant-developed assessment report) in the same manner that evidence for main comparisons is presented. The distinction between main and supplementary refers only to the degree to which the comparators are likely to be substituted in clinical practice.*

*PASC advised that microwave ablation (MWA) should be included as a supplementary comparator. This could be grouped with radiofrequency ablation, as ‘thermal ablation’ (TA). The applicant agreed with this advice. The assessment group has replaced RFA with TA in Figures 1-3, but recommended that RFA or MWA be in brackets, for clarification - i.e. TA (RFA or MWA) – as there are other types of TA (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4226271/>).*

*The applicant confirmed that data from studies comparing cryoablation with radiofrequency ablation and microwave ablation will be grouped under the comparator heading ‘Other thermal ablation’. This is because cryoablation is simply another method of thermal ablation, and these treatments are often grouped together in clinical practice guidelines.*

The applicant nominated active surveillance/deferred therapy (AS/DT) and radiofrequency ablation (RFA) as two main comparators, and partial nephrectomy (PN) as a supplementary comparator.<sup>123</sup>

The Draft PICO nominated the following comparators for PASC consideration:

- Main comparators: laparoscopic radical nephrectomy (RN) and AS/DT;
- Supplementary comparators: partial nephrectomy (PN) and RFA.

The rationale was as follows:

Currently, for patients with localised primary malignant RCC (T1aN0M0) ( $\leq 4$  cm in diameter), with malignancy and subtype confirmed by biopsy, indicated for intervention after diagnosis (but not suitable for PN), two publicly-funded clinical management options are available (see Figure 1):

- Laparoscopic RN (MBS items 36516 and 36519, **Appendix 6**) if the tumour is of significant complexity, or
- Active surveillance/delayed therapy (AS/DT) with detailed multidisciplinary assessment and serial imaging.

RFA is also another commonly performed ablation technique for SRMs. However, given it is not currently publicly funded (and is only available in the private sector), it is not considered a main comparator for cryoablation for the purpose of this application. Rather, it is included as a supplementary comparator.

The Draft PICO nominated PN as a supplementary comparator. This is because proposed use of CA is for patients not fit for PN (Figure 2). However, should the proposed medical service receive a positive recommendation from MSAC, it is possible that CA will be offered to patients who are suitable/fit for PN, but who prefer a less invasive treatment option (Figure 3).

**Table 4** presents a summary of the nominated main comparators and supplementary comparators and rationale.

**Table 4 Proposed main comparators and supplementary comparators**

Main comparators	Rationale
Laparoscopic RN	A treatment option in patients indicated for intervention after diagnosis but not suitable for PN especially when the tumour is of significant complexity <sup>124</sup>
Active surveillance/delayed therapy (AS/DT)	A treatment option in patients indicated for intervention after diagnosis but not suitable for PN especially in patients aged 70+ with significant comorbidities or competing mortality risks <sup>125</sup>
Supplementary comparators	Rationale
Partial nephrectomy (PN)	Nominated as a supplementary comparator, because if CA becomes available on the MBS, it is anticipated that CA may be offered 'off-label' to patients suitable for PN (but who simply prefer a less invasive approach). Indeed, this is predicted by the applicant. <sup>126</sup>
Thermal ablation (RFA or MWA)	Like CA, both RFA and MWA are local ablative techniques but are only available in private. They are therefore nominated as supplementary comparators for the purpose of this Application.

Abbreviation: AS/DT, Active surveillance/delayed therapy; CA, cryoablation; MBS, Medicare Benefits Schedule; PN, partial nephrectomy; RFA, Radiofrequency ablation; RN, radical nephrectomy; MWA, microwave ablation

#### *Anticipated use of renal cryoablation if approved and substitution of current therapies*

If approved by MSAC, cryoablation would become the third publicly-funded treatment option for patients not suitable for PN (Figure 2). It is anticipated that:

- CA would substitute some of the services currently received with laparoscopic RN and AS/DT. The applicant estimated that 20% of the patients currently receiving AS may choose to receive CA instead.<sup>127</sup>
- Some patients would need re-ablation after CA because of incomplete ablation/local recurrence. However, the applicant reported CA would generally only be a one-off procedure.<sup>128</sup>

It is also anticipated that potential leakage of use of CA beyond the proposed indication is likely:

- As alternative treatment option to patients suitable for but do not prefer PN. The applicant estimated that 10% of the patients currently receiving PN may opt for CA instead if CA is readily available and affordable.<sup>129</sup>
- As salvage treatment option in patients who have treatment failure or local recurrence after initial PN or RFA (Figure 3). The applicant also anticipated that 50% of the patients currently receiving RFA may choose to receive CA instead.<sup>130</sup> In other words, 1 in 2 patients who currently receive RFA in the private market may choose to access CA instead, if public subsidy for CA is approved.

### **Laparoscopic radical nephrectomy (RN)**

RN was the standard of treatment for RCC historically<sup>131</sup> and was usually performed via an open surgical approach. Later, the use of laparoscopic techniques, resulted in reduction of blood loss, shorter length of stay in hospital and earlier ambulation.<sup>132</sup> For localised RCC, PN has been reported to be associated with better overall survival but similar cancer-specific survival and recurrence-free survival than RN.<sup>133</sup> Laparoscopic RN is performed by urologist. The procedure is currently funded via two MBS items numbers (items 36516, 36519) (Appendix 6).

### **Active surveillance/delayed therapy (AS/DT)**

Active surveillance (AS) involves detailed, multidisciplinary assessment of the overall medical and functional status of the patient and serial imaging to monitor the growth of the tumour. Renal tumour biopsy is strongly recommended before AS.

### **Partial nephrectomy (PN)**

As mentioned previously, for patients with localised primary RCC  $\leq 4$  cm early stage T1a RCC and who are indicated for intervention, PN is the current standard of care and can be done via open, laparoscopic or robot-assisted laparoscopic approach. PN is currently listed on the MBS (MBS items 36522, 36525) (Appendix 6)

### **Thermal ablation (radiofrequency ablation or RFA, microwave ablation or MWA)**

RFA is a current-based heating modality. Using grounding pads on the skin and multiple electrodes placed in the tumour, high-frequency alternating current is delivered from a generator through the tumour lesion, generating frictional heat and leading to tumour necrosis.<sup>134</sup> MWA is another thermal ablation technique. It uses electromagnetic microwaves to agitate the water molecules in the tissue thereby producing heat and friction, resulting in cell death by coagulative necrosis.<sup>135</sup> RFA or MWA, via percutaneous, laparoscopic or open approach, are currently listed on the MBS for the destruction of unresectable primary malignant liver tumour (MBS items 50950 and 50952) (Appendix 7).

## **OUTCOMES**

*PASC agreed with the applicant's suggestion to remove 'renal function' from the list of patient-relevant outcomes, as it is already included under functional outcomes.*

*PASC recommended that a repeat procedure be considered as an outcome, and the applicant agreed.*

### **Patient-relevant outcomes**

The types of outcomes that may change by introducing the proposed service relate to:

Clinical effectiveness (including, but not limited to):

- Tumour growth rate (for patients on active surveillance);
- Salvage or repeat procedure rates;
- Oncologic outcomes (local recurrence rates, metastatic rates);
- Survival (local recurrence-free, disease-free, progression-free, cancer-specific, overall), mortality;
- Functional outcomes (physical, renal);
- Patient-relevant outcomes (e.g. pain control, satisfaction, quality of life).

Safety (including, but not limited to):

- Peri- and post-procedure adverse events and complications;
- Major treatment-related: death, haemorrhage, renal injury or injury to adjacent structures, pneumonia, fistula, renal failure or serious infection;
- Minor treatment related: probe site pain, bleeding requiring or not requiring transfusion, transient urinary leakage or minor infection.

### **Healthcare system outcomes**

Costs (including, but not limited to):

- Pre-procedural costs – e.g. blood tests, renal function tests, imaging, costs associated with pre-ablation biopsy (for ablation, active surveillance) (e.g. anaesthesia, theatre, imaging, professional attendances, pathology);
- Peri-procedural costs - e.g. anaesthesia, imaging, professional attendance, specialist fees, medication use peri-procedure, hospital length of stay, cryoablation equipment and consumables, etc.)
- Post-procedural costs – e.g. post-treatment imaging, monitoring and surveillance (e.g. blood tests, renal function tests, professional attendances, imaging, etc.)
- Costs associated with the management of adverse events or complications peri- and post-procedure

Other healthcare resource use (including but not limited to): costs associated with use of theatre, hospital stay; costs of equipment, consumables.

Total Australian Government healthcare costs: MBS, Pharmaceutical Benefits Scheme (PBS).

## **CURRENT AND PROPOSED CLINICAL MANAGEMENT ALGORITHMS**

*PASC confirmed the proposed clinical management algorithms, but advised there should be separate algorithms for delivery of cryoablation percutaneously, laparoscopically and by open surgery (unless the applicant decides to restrict the application to percutaneous cryoablation, which has been the thrust of the application to date).*

*The applicant disagreed that separate algorithms are required for different modes of delivery of cryoablation. The applicant stated its intention (as noted above) is to present results separately for each mode of delivery of cryoablation, where data is available. The applicant stated that MSAC can use this information to decide whether to limit listing to one or more particular modes, noting the majority of data available for cryoablation is for the percutaneous mode of delivery.*

*PASC also queried whether, given ‘partial nephrectomy’ can be done laparoscopically or by open surgery, they should be separate comparators. The applicant disagreed that different modes of delivering partial nephrectomy should be separate comparators. Regarding the different modes of delivery of cryoablation, the applicant has advised it will present results separately for different modes of delivery of partial nephrectomy (and radiofrequency ablation/microwave ablation), where this information is available.*

*Regarding potential leakage (Figure 3), PASC noted the first potential for leakage is likely to stem from the point at which a patient is considered suitable for partial nephrectomy; not the point at which any intervention is indicated.*



PASC also advised that leakage was possible from the point of active surveillance/delayed therapy. PASC recommended these should be changed in the clinical management algorithm, with details added that potential leakage may be caused by:

- patients preferring cryotherapy over more invasive treatments when the patient may also be eligible for partial nephrectomy;
- patients preferring interventional treatment over conservative treatment;
- clinician preference playing a role in a patient's choice of treatment, especially if an investment in cryotherapy equipment is required by the clinician/service provider.

The applicant agreed with the points regarding patient preference, but has disagreed about clinician preference. The applicant has stated that cryoablation is performed by a different clinician group (interventional radiologists) than those making the initial decision around treatment (urologists) – which in many cases would be whether to perform a nephrectomy (open or laparoscopic, and partial or radical) or put the patient under active surveillance.

The applicant added that the choice to perform cryoablation over nephrectomy or active surveillance should not be impacted by whether the referring clinician has invested in cryotherapy equipment, or appropriate imaging equipment to perform percutaneous cryoablation; the referring clinicians would not have invested in such equipment, because they do not perform those procedures. The applicant clarified that, ultimately, the choice of treatment is likely to be a shared decision between clinician and patient, considering (together) the expected outcomes from approved treatment options and potential treatment risks.

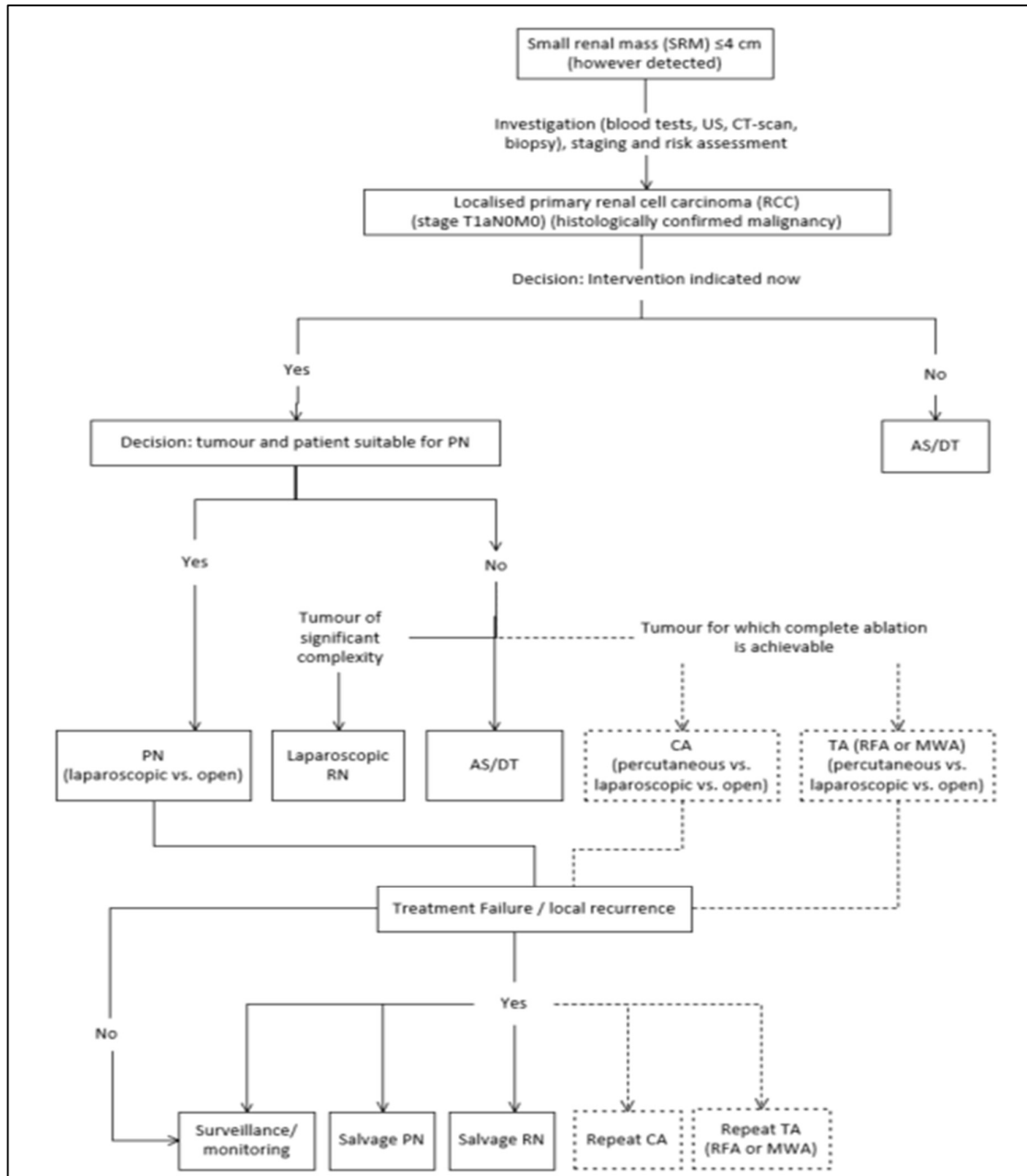
While the applicant provided alternative algorithms in its response to Ratified PASC Outcome 1597 (to depict alternative representations of clinical pathways and choice of main and supplementary comparators), PASC's advice (and agreed algorithms in Figures 1, 2 and 3 below) will stand, as follows:

- *Histologically-confirmed malignancy must be specified, including that this occurs prior to CA (to minimise the risk of over-treatment or unnecessary treatment – as per Table 1 earlier in this PICO). Tumour biopsy should not be conducted during the CA procedure, because of the risk of unnecessary treatment. Knowledge of pathology prior to CA would also guide future surveillance/monitoring (as per Table 1 above).*
- *Different modes of delivery are likely to have different comparative effectiveness and safety outcomes, and will certainly have different costs. Data/evidence may be sparse for anything other than percutaneous delivery, but presenting the differences is necessary.*
- *Specification that partial nephrectomy (PN) may be performed by the laparoscopic or open approach is essential, given differences in outcomes and costs (as stated above). For example, the incremental benefit/harm of percutaneous CA versus laparoscopic PN is likely to be different from the incremental benefit/harm of percutaneous CA versus open PN (resulting in different incremental cost-effectiveness estimates. It is therefore important the assessment report presents results of comparative clinical and cost effectiveness, stratified by type of approach that is used to perform the procedure.*

- *Inclusion of “tumours of significant complexity” in the algorithms is confusing, given the assessment will cover small renal tumours ( $\leq 4$  cm, and  $\leq 3$  cm in the sensitivity analysis). The PICO-agreed algorithms include these for laparoscopic RN only, while the applicant requested inclusion for laparoscopic RN or TA (CA and other TA). The basis for the applicant’s claimed use of TA (CA and other TA) in tumours of significant complexity is not agreed. Only laparoscopic RN is recommended in the ASCO (2017) and CUA (2105) Guidelines (see Appendix 2). It may be relevant to exclude these from the algorithms.*
- *Inclusion of “tumour for which complete ablation is achievable” (as a determinant for using CA [or other TA] in patients/tumours not suitable for PN) may be confusing. CA should only be considered a treatment option for patients where complete tumour ablation is achievable (ASCO Guidelines – Appendix 2).*
- *Surveillance/monitoring as a management option must be included for patients who experience treatment failure/local recurrence after PN, laparoscopic RN or CA. Examples may include a change in patient conditions (e.g. health; preference; complication with initial procedure), or disease progression, etc.*
- *Inclusion of patient and clinician preferences (as causes of potential leakage) is important. The treatment decision should not be based on patient preference alone. The applicant stated that “CA is performed by interventional radiologists, whereas urologists make the initial treatment decision”. This will only be case for laparoscopic CA, which in many cases will involve consideration of whether to perform a nephrectomy (open or laparoscopic, and partial or radical) or put the patient under action surveillance. This is the rationale behind the requirement for review by a multi-disciplinary team (and note TN.8.XX2 in the proposed MBS item descriptor – see Table 6).*
- *While the applicant correctly pointed out that the zero references in TNM coding “T1aN0M0” should be subscripts (as should the letter “a”), it is difficult to present zero references in this way, without them appearing to be lower case references to the letter “o”.*

## Current clinical management algorithm for identified population

Figure 1: Current clinical management algorithm for small renal mass (SRM) in the absence of public funding for the proposed medical service



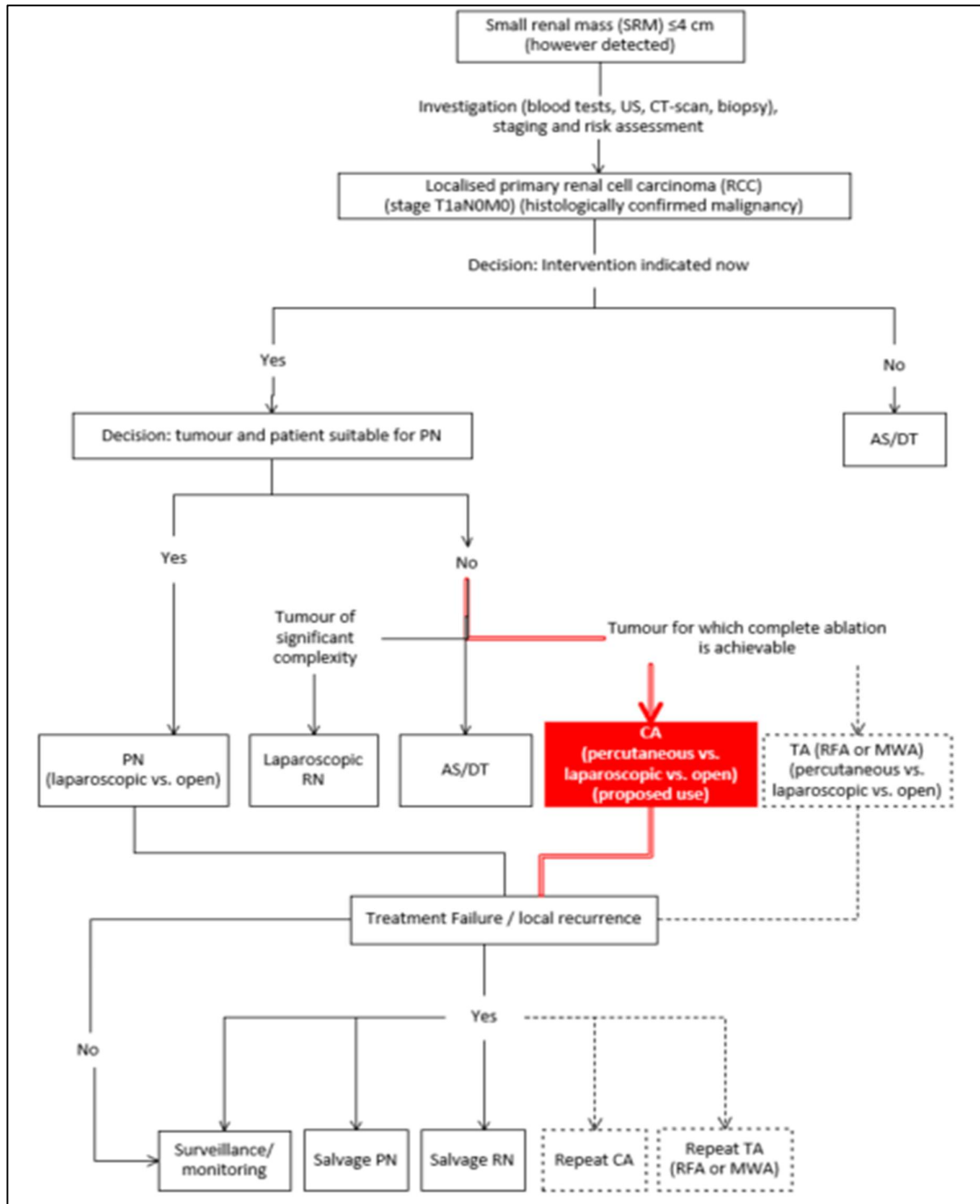
Abbreviations: AS/DT, active surveillance/delayed therapy; CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation; RN, radical nephrectomy; TA, thermal ablation

Note: dotted line refers to treatment options not currently funded on the Medicare Benefits Schedule (MBS).

Clinical management algorithm was constructed during PICO development based on international guidelines (Appendix 2) and current public funding status on the MBS.

## Proposed clinical management algorithm for identified population

Figure 2: Proposed clinical management algorithm for small renal mass (SRM) after the proposed listing

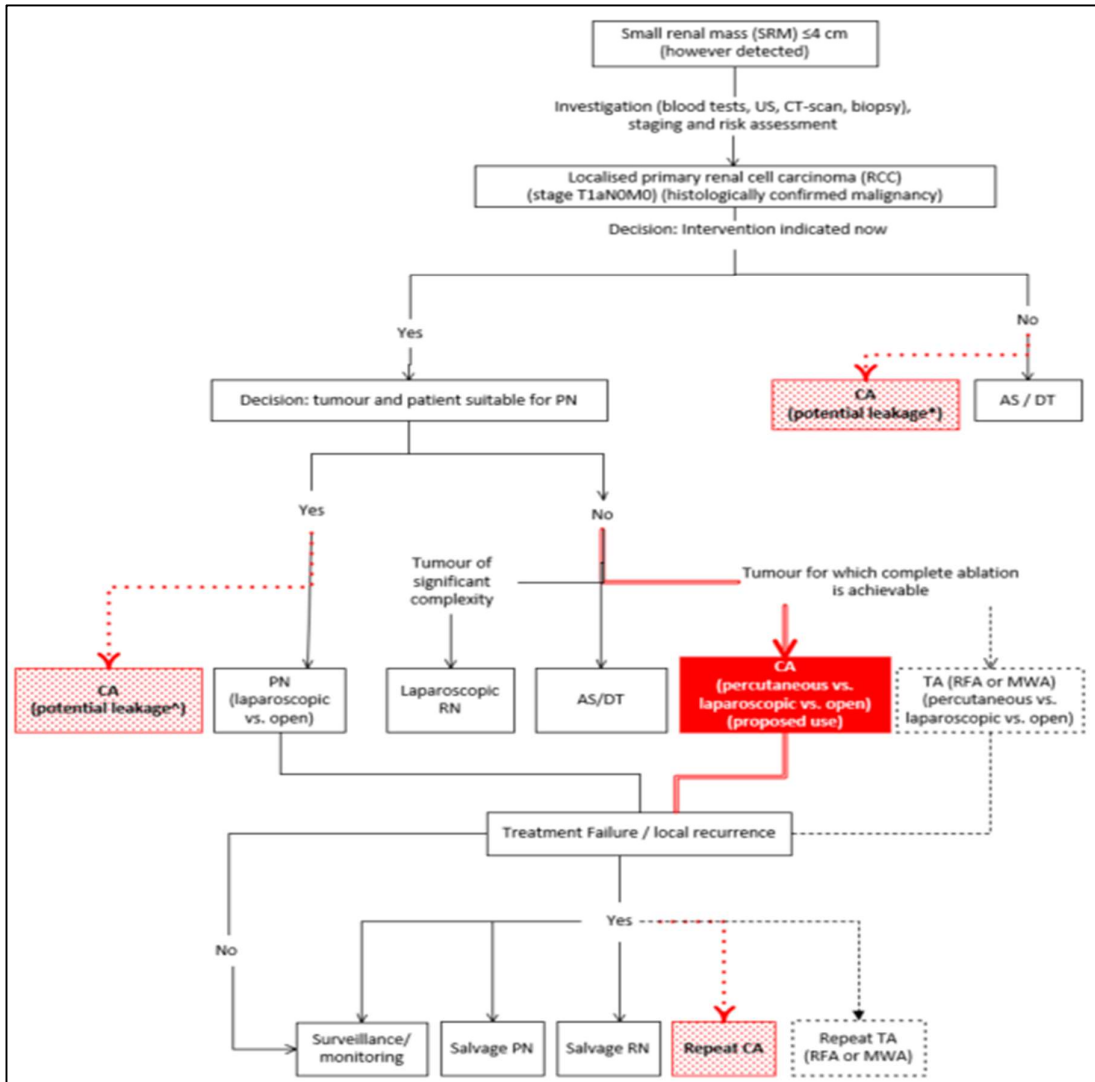


Abbreviations: AS/DT, active surveillance/delayed therapy; CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation; RN, radical nephrectomy; TA, thermal ablation

Note: dotted line refers to treatment options not currently funded on the MBS; line in red refers to the proposed medical service on the Medicare Benefits Schedule (MBS).

Clinical management algorithm was constructed during PICO development based on international guidelines (Appendix 2) and current public funding status on the MBS.

Figure 3: Proposed clinical management algorithm for small renal mass (SRM) after the proposed listing (including potential leakage of use)



Abbreviations: AS/DT, active surveillance/delayed therapy; CA, cryoablation; MWA, microwave ablation; PN, partial nephrectomy; RFA, radiofrequency ablation; RN, radical nephrectomy; TA, thermal ablation

Note: dotted line refers to treatment options not currently funded on the MBS; line in red refers to the proposed medical service on the MBS; dotted line in red refers to potential leakage of use.

\* Potential leakage may be caused by patient preferences (e.g. patients preferring interventional treatment over conservative treatment).

^ Potential leakage may be caused by patient preferences (e.g. patients preferring cryotherapy over more invasive treatments even though also eligible for PN). Clinician preferences may also play a role in patients' choice of treatment, especially if an investment in cryotherapy equipment is required by the clinician/service provider.

Clinical management algorithm was constructed during PICO development based on international guidelines (Appendix 2) and current public funding status on the MBS.

## PROPOSED ECONOMIC EVALUATION

PASC confirmed the proposed economic evaluation. The applicant noted that the final economic evaluation will depend on the outcome of the evidence review. Separate economic models are needed for the different modes of delivery (i.e. percutaneous vs. laparoscopic vs. open).

Table 5 presents a summary of the clinical claim as made in the Application Form. Overall, the applicant claimed that CA is non-inferior to its comparators.

**Table 5 Clinical claim in the Application Form**

	Clinical effectiveness			Safety			Overall claim
	Superior	Non-inferior	Inferior	Superior	Non-inferior	Inferior	
CA vs AS/DT	✓					✓	NR
CA vs PN			✓	✓			NR
CA vs RFA		✓			✓		NR
Overall claim for CA in the Application Form	Non-inferior						

Abbreviation: AS/DT, active surveillance/delayed therapy; CA, cryoablation; NR, not reported; PN, partial nephrectomy; RFA, radiofrequency ablation; RN, radical nephrectomy

Source: Question 43, p29 in the Application Form

Laparoscopic RN was not nominated as a comparator in the Application. It is conjectured (at this PICO development stage) that CA is likely to be inferior in clinical effectiveness, and superior in safety, when compared with laparoscopic RN (as is the case when compared with PN).

If the overall claim of non-inferiority of CA versus the nominated comparators is established in the full assessment of comparative clinical effectiveness and safety, then adopting a cost-minimisation approach in the economic evaluation is appropriate.

The economic evaluation and budget impact assessment should consider the following:

- Some patients may receive the proposed procedure more than once at the same session (e.g. having more than one SRM in the same kidney, having SRMs in both kidneys), and/or receive a repeat procedure very soon afterwards (e.g. upon discovery of incomplete ablation via post-treatment imaging).
- Some patients may require repeat CA, or other salvage surgery (PN, RN) because of local recurrence/treatment failure after initial CA.<sup>136</sup>
- Some patients may receive the proposed procedure because of local recurrence/treatment failure after PN or RFA.
- Some patients may receive the proposed procedure and other comparator therapies (e.g. RFA) simultaneously.
- Cost of equipment and consumables associated with cryoablation and comparators.

## **PROPOSED MBS ITEM DESCRIPTOR/S AND MBS FEES (if relevant)**

PASC confirmed the proposed MBS item descriptor and fee, noting the fee (\$830.15) is equivalent to similar MBS items, including hepatic cryotherapy for liver tumours (MBS item 30419), and unresectable liver tumour items 50950 and 50952. PASC highlighted the incorrect fee of \$817.10, detailed in the Application Form and repeated in the Draft PICO document (for existing similar items and the proposed item), noting this is likely to be an error, sourced from earlier MBS versions. The applicant noted the updated MBS fee.

PASC queried if consumables were included in the proposed MBS fee, and recommended the assessment report should justify the cost. The applicant advised that the proposed fee in the Application Form was indicative only (and based on the procedure's similarity to RFA and MWA procedures). The MBS fee that will ultimately be proposed (and justified) in the ADAR will include a consideration of the cost of consumables.

PASC advised that the assessment report should discuss practicalities of an audit mechanism (for example, post service audit) to check the requirement that a multi-disciplinary team be involved.

While the applicant did not entirely agree with the following inclusion in the item descriptor: "a multi-disciplinary team has reviewed treatment options for the patient, and assessed that partial nephrectomy is not suitable", the applicant agreed to discuss reasons for this in its ADAR, including requirement for (and practicalities of) an audit mechanism.

**Table 6 Proposed MBS item descriptor**

<b>Category 3 – THERAPEUTIC PROCEDURES</b>	
<b>T8. SURGICAL OPERATIONS</b>	<b>XX. CRYOABLATION</b>
Localised primary malignant tumour of the kidney, not more than 4 cm in diameter, destruction of, by percutaneous, laparoscopic or open cryoablation (including any associated imaging services), where malignancy is confirmed by histopathological examination and a multi-disciplinary team has reviewed treatment options for the patient and assessed that partial nephrectomy is not suitable	
Not being associated with a service to which item 36522 or 36525 applies.	
<u>Multiple Operation Rule</u> (Anaes.) (See para TN.8.XX1 and para TN.8.XX2 of explanatory notes to this category)	
<b>MBS Fee: \$830.15</b>	

The applicant reported<sup>137</sup> the proposed fee of \$830.15 is the same fee as that for percutaneous RFA or MWA (item 50950) or laparoscopic or open RFA or MWA (MBS item 50952) for the treatment of unresectable primary malignant tumour of the liver (see Appendix 7).

TN.8.XX1 = For the purpose of the proposed MBS item, a multi-disciplinary team typically includes a urologist, interventional radiologist and oncologist. Patients eligible for Medicare-funded cryoablation need to be assessed by the multi-disciplinary team as not suitable for partial nephrectomy, and typically have one or more of the following characteristics:

- Elderly and/or frailty;
- High surgical risk;
- Poor renal function;
- Solitary kidney;
- Bilateral kidney tumours;
- Hereditary/multiple renal cell carcinomas.

TN.8.XX2 - For the purpose of the proposed MBS item, the procedure is to be performed by an interventional radiologist specially trained in the procedure. Percutaneous cryoablation should be the preferred approach, unless the percutaneous approach is considered not suitable for the individual patient by the multi-disciplinary team.

MSAC may also wish to add another MBS item or explanatory note for repeat cryoablation procedures.

It should be noted that this is different from the proposed MBS item descriptor in the Application Form (Table 7 below). Proposed wording of restrictions in the Application Form characterise the renal tumour as 'suspected' primary malignant tumour of the kidney (page 31, Application Form), rather than confirmed by biopsy as proposed here. The Urology Society of Australia and New Zealand disagreed with the applicant's proposed wording of 'suspected primary malignant tumour', arguing that 'biopsy-proven' primary malignant tumour is a more appropriate description for the clinical indications discussed (p5, Targeted Consultation Survey).

**Table 7 Proposed item descriptor in the Application Form**

Category 3 – THERAPEUTIC PROCEDURES
SUSPECTED PRIMARY MALIGNANT TUMOUR OF THE KIDNEY ( $\leq 4$ CM), destruction of, by percutaneous, laparoscopic or open cryoablation (including any associated imaging services), where partial nephrectomy is not considered suitable or feasible.
MBS Fee: \$817.10

Source: Reproduced from p31 of the Application Form: Cryotherapy for small renal mass

## CONSULTATION FEEDBACK

*PASC noted the consultation feedback from RANZCR, which was generally supportive of the proposed PICO.*

## NEXT STEPS

*Upon ratification of PICO 1597, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage.*

*The applicant elected to prepare its own ADAR (applicant-developed assessment report).*



## Appendix 1

Union for International Cancer Control (UICC) tumour, node and metastasis (TNM) 8 staging system of renal cell carcinoma

<b>T</b>		<b>Primary tumour</b>	
TX		Primary tumour cannot be assessed	
T0		No evidence of primary tumour	
T1		Tumour ≤7 cm in greatest dimension, limited to the kidney	
	T1a	Tumour ≤4 cm	
	T1b	Tumour >4 cm but ≤7 cm	
T2		Tumour >7 cm in greatest dimension, limited to the kidney	
	T2a	Tumour >7 cm but ≤10 cm	
	T2b	Tumour >10 cm, limited to the kidney	
T3		Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia	
	T3a	Tumour extends into the renal vein or its segmental branches, or tumour invades the pelvicalyceal system or tumour invades perirenal and/or renal sinus fat (peripelvic) fat but not beyond Gerota fascia	
	T3b	Tumour extends into vena cava below diaphragm	
	T3c	Tumour extends into vena cava above the diaphragm or invades the wall of the vena cava	
T4		Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)	
<b>N</b>		<b>Regional lymph nodes</b>	
NX		Regional lymph nodes cannot be assessed	
N0		No regional lymph node metastasis	
N1		Metastasis in regional lymph node(s)	
<b>M</b>		<b>Distant metastasis</b>	
M0		No distant metastasis	
M1		Distant metastasis	
<b>pTNM pathological classification*</b>			
<b>Stage</b>			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1, T2, T3	N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

pTNM, pathological tumour, node, metastasis

\* pT and pN categories correspond to the T and N categories

Source: Reproduced from Table 2 in Escudier (2019).

## Appendix 2

### International treatment guidelines and recommendations for the management of SRMs

<b>American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for SRMs (Finelli 2017)</b>	
Clinically localized SRMs ( $\leq 4$ cm) (usually consistent with stage T1a RCC)	Biopsy: <ul style="list-style-type: none"> <li>All patients with an SRM should be considered for renal tumour biopsy when the results may alter management.</li> </ul>
	AS should be an initial management option for patients who have significant comorbidities and limited life expectancy. <ul style="list-style-type: none"> <li>Absolute indication: high risk for anaesthesia/intervention or life expectancy <math>&lt; 5</math> years;</li> <li>Relative indication: significant risk of ESRD if treated, SRM <math>&lt; 1</math> cm, or life expectancy <math>&lt; 10</math> years.</li> </ul>
	PN is the standard treatment for SRMs and should be offered to all patients <ul style="list-style-type: none"> <li>for whom an intervention is indicated and</li> <li>who possess a tumor that is amenable to this approach</li> </ul>
	RN <ul style="list-style-type: none"> <li>should be reserved only for patients who possess a tumour of significant complexity that is not amenable to PN or</li> <li>where PN may result in unacceptable morbidity even when performed at centres with expertise.</li> </ul>
	Percutaneous TA <ul style="list-style-type: none"> <li>should be considered an option for patients who possess tumors such that complete ablation will be achieved.</li> <li>A biopsy should be obtained before or at the time of ablation.</li> </ul>
<b>American Urological Association (AUA) Guideline for renal mass and localized renal cancer (Campbell 2017)</b>	
cT1a RM	PN: <ul style="list-style-type: none"> <li>When intervention is indicated, PN is the top priority treatment choice.</li> </ul>
cT1a RM $< 3$ cm	TA is an alternate approach: <ul style="list-style-type: none"> <li>A percutaneous technique is preferred over a surgical approach</li> <li>Both RFA and CA are options.</li> <li>A renal mass biopsy should be performed prior to ablation to provide pathologic diagnosis and guide subsequent surveillance.</li> </ul>
SRM, solid or Bosniak $\frac{3}{4}$ complex cystic ( $< 2$ cm)	AS: <ul style="list-style-type: none"> <li>When oncologic risks are particularly low, AS is an acceptable initial management option for all patients, not just those with limited life expectancy or poor performance status.</li> </ul>
<b>Canadian Urological Association (CUA) Guideline for SRM (Jewett 2015)</b>	
Early stage T1a RCC	PN is recommended (open, laparoscopic or robotic-assisted laparoscopic). <ul style="list-style-type: none"> <li>Open PN is preferable to laparoscopic nephrectomy.</li> </ul>
	Laparoscopic RN is reserved for tumours not amenable to PN.
	Probe ablation by RFA or CA is an option. <ul style="list-style-type: none"> <li>An attractive approach in elderly and infirm patients.</li> <li>A biopsy should be obtained before or at the time of ablation for follow-up planning and outcome analysis.</li> <li>Success rates decrease in tumours <math>&gt; 3</math> cm.</li> <li>Requires long-term follow-up with imaging.</li> </ul>
	AS with regular radiographic follow-up should be a primary consideration for SRMs in: <ul style="list-style-type: none"> <li>elderly and/or</li> <li>infirm patients with multiple comorbidities rendering them high risk for interventions, and</li> <li>those with limited life expectancy.</li> </ul>
<b>Europe Association of Urology (EAU) Guidelines on RCC 2019 update (Ljungberg 2019)</b>	
Localised T1a-b tumours	Surgery is the only curative treatment. <ul style="list-style-type: none"> <li>PN (open, pure laparoscopic or robot-assisted approach)</li> </ul>

<b>American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for SRMs (Finelli 2017)</b>	
	<p>AS</p> <ul style="list-style-type: none"> <li>• can be offered to a select category of patients (elderly, comorbid, with incidentally detected SRMs – because this category of patients has low RCC-specific mortality and significant competing-cause mortality);</li> <li>• Defined as initial serial abdominal imaging (US, CT or MRI) to monitor the tumour size, then delayed intervention for those tumours that show clinical progression during follow-up.</li> <li>• Renal biopsy recommended prior to surveillance.</li> </ul>
	<p>Ablative therapies:</p> <ul style="list-style-type: none"> <li>• Most commonly performed: percutaneous RFA, laparoscopically assisted or percutaneous CA.</li> <li>• Considered experimental: MWA, stereotactic radiosurgery, laser ablation, high-intensity focused US ablation.</li> </ul> <p>Indications for thermal ablation:</p> <ul style="list-style-type: none"> <li>• Elderly, comorbid, SRM, considered unfit for surgery;</li> <li>• Genetic predisposition to develop multiple tumours;</li> <li>• Bilateral tumours or solitary kidney</li> <li>• High risk of complete loss of renal function after PN.</li> </ul> <p>Ablation is not recommended for larger tumours or tumours located at the hilum or near the proximal ureter.</p>
<b>European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for RCC (Escudier 2019)</b>	
T1 tumours (<7 cm)	<p>Surgery:</p> <ul style="list-style-type: none"> <li>• PN is the preferred treatment option for organ-confined T1 tumours.</li> <li>• PN is the standard of care, with no tumour size limitation, in patients with compromised renal function, solitary kidney or bilateral tumours.</li> <li>• Laparoscopic RN is recommended if PN not technically feasible.</li> </ul>
	<p>RFA, MWA, CA:</p> <ul style="list-style-type: none"> <li>• Are treatment options in patients with small cortical tumours (<math>\leq 3</math> cm), especially in patients who are frail, present a high surgical risk and those with a solitary kidney, compromised renal function, hereditary RCC or multiple bilateral tumours.</li> <li>• Renal biopsy is recommended to confirm malignancy and subtype in this setting.</li> </ul>
	<p>AS:</p> <ul style="list-style-type: none"> <li>• Is an option in elderly patients with significant comorbidities or those with a short life expectancy and solid renal tumours &lt;4 cm.</li> <li>• Renal tumour growth rate is low (mean 3 mm/year) in most cases and only 1-2% progress to metastatic disease.</li> <li>• Renal biopsy is recommended to select patients with small masses for AS, because of the incidence of non-malignant tumours in this setting.</li> </ul>
T2 tumours (>7 cm)	Laparoscopic RN is the preferred treatment option.
Locally advanced RCC (T3, T4)	Open RN is the standard of care
<b>NCCN Clinical Practice Guidelines in Oncology for Kidney Cancer (Jonasch 2019)</b>	
Stage I-III RCC	<p>Primary treatment: (a) PN or (b) RN or (c) AS (in selected patients).</p> <p>Further treatment: is typically not recommended.</p>

CA, cryoablation; CT, computer tomography; ESRD, of end-stage renal disease; MRI, magnetic resonance imaging; MWA, microwave ablation; NCCN, National Comprehensive Cancer Network; PN, partial nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RM, renal mass; RN, radical nephrectomy; SRM, small renal mass; TA, thermal ablation; US, ultrasound.

## Appendix 3

### Preliminary comparison between the current Application and the previous Application

	Application No. 1597 5-6 December 2019 PASC Meeting		Application No. 1124 11 September 2009 MSAC Meeting
	Current PICO Confirmation	Application Form	Previous Application
Applicant	Boston Scientific/BTG International Asia Limited (Australian distributor: Big Green)		Scanmedics Pty. Ltd.
Proposed medical service	Percutaneous cryoablation for localised primary RCC (T1aN0M0), ≤4 cm in diameter, with malignancy and subtype confirmed in pre-ablation biopsy, indicated for intervention after diagnosis but not suitable for PN (see population below)	Cryoablation for the treatment of SRMs (i.e. T1a tumours ≤4 cm) in patients considered not suitable for PN (see population below)	Cryotherapy for the treatment of small localised renal cancer (<4 cm) in patients with significant co-morbidities and/or renal impairment requiring a nephron-sparing approach (see population below)
Proposed eligible population	Patients with localised primary RCC (T1aN0M0), ≤4 cm in diameter, with malignancy and subtype confirmed by biopsy; <ul style="list-style-type: none"> <li>Indicated for intervention after diagnosis (e.g. LE ≥5 years); and</li> <li>Not suitable for PN</li> </ul>	Patients with SRM and considered not suitable for PN: <ul style="list-style-type: none"> <li>Increased age and/or frailty;</li> <li>Presence of comorbidities;</li> <li>Solitary kidney;</li> <li>Compromised renal function;</li> <li>Bilateral tumours;</li> <li>Technical difficulty in performing PN</li> </ul>	Patients with small localised renal cancer (<4 cm) and with significant co-morbidities and/or renal impairment requiring a nephron-sparing approach: <ul style="list-style-type: none"> <li>Single functioning kidney;</li> <li>Bilateral tumours;</li> <li>Pre-existing kidney disease;</li> <li>Not fit for radical nephrectomy (RN).</li> </ul>
Comparator(s)	Main comparators: <ul style="list-style-type: none"> <li>Laparoscopic RN;</li> <li>AS/DT.</li> </ul> Supplementary: <ul style="list-style-type: none"> <li>PN;</li> <li>RFA.</li> </ul>	Nominated main comparators: <ul style="list-style-type: none"> <li>AS/DT;</li> <li>RFA.</li> </ul> Supplementary comparator: <ul style="list-style-type: none"> <li>PN</li> </ul>	Considered by the MSAC as appropriate: <ul style="list-style-type: none"> <li>PN;</li> <li>Surveillance.</li> </ul> Considered by the MSAC as less appropriate: <ul style="list-style-type: none"> <li>RFA (procedure was under investigation for clinical effectiveness without long-term outcome data).</li> </ul>
Device(s) associated with the proposed medical service	<ul style="list-style-type: none"> <li>Big Green Surgical Company Pty Ltd - Electronic general cryosurgical system<sup>^</sup> (ARTG <a href="#">221468</a>; GMDN 45738; manufacturer: Galil Medical Inc., USA)</li> <li>Big Green Surgical Company Pty Ltd - Cryotherapy set<sup>#</sup> (ARTG <a href="#">224583</a>; GMDN 45140; manufacturer: Galil Medical Ltd., Israel)</li> </ul>		Third-generation cryosurgical unit (ARTG 144069; manufacturer: Galil Medical, Israel) (no longer registered on the ARTG)

<sup>^</sup> Intended purpose as stated in the ARTG Public Summary: 'The Visual-ICE Cryoablation System is intended for cryoablative destruction of tissue during minimally invasive, transient surgical procedures. The System is indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology, thoracic surgery, ENT,

gynecology, oncology, proctology, and urology. This system is designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, skin lesions, and warts) by the application of extremely cold temperatures.’

# Procedure packs containing cryoablation needles and accessories intended to be used with a cryoablation system for the destruction of tissue during minimally invasive, transient surgical procedures (Public Summary for ARTG 224583, TGA)

Abbreviations: ARTG, Australian Register of Therapeutic Goods; AS, active surveillance; CA, cryoablation; DT, delayed therapy; GMDN, Global Medical Device Nomenclature; LE, life expectancy; MSAC, Medical Services Advisory Committee; PASC, PICO Advisory Sub-committee; PN, partial nephrectomy; RCC, renal cell carcinoma; RFA, radiofrequency ablation; RN, radical nephrectomy; SRM, small renal mass.

Source: [Public Summary Document](#) and [Assessment Report](#), Part B for Application No. 1124 Cryotherapy for Recurrent Prostate Cancer and Renal Cancer, 11 September 2009 MSAC Meeting; [Application Form](#) for Application no. 1597 Cryoablation for small renal mass, to be considered at the December 2019 PASC Meeting.

## Appendix 4

### Current MBS-listed items for cryotherapy or cryosurgery (list not exhaustive)

#### Category 3 – THERAPEUTIC PROCEDURES

T8. SURGICAL OPERATIONS		1. GENERAL
30196	<p>Malignant neoplasm of skin or mucous membrane that has been:</p> <ul style="list-style-type: none"> <li>(a) proven by histopathology; or</li> <li>(b) confirmed by the opinion of a specialist in the specialty of dermatology where a specimen has been submitted for histologic confirmation;</li> </ul> <p>removal of, by serial curettage, or carbon dioxide laser or erbium laser excision-ablation, including any associated cryotherapy or diathermy</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$128.30    <b>Benefit:</b> 75% = \$96.25    85% = \$109.10 (See para <a href="#">TN.8.10</a> of explanatory notes to this Category)</p>	
30202	<p>Malignant neoplasm of skin or mucous membrane proven by histopathology or confirmed by the opinion of a specialist in the specialty of dermatology—removal of, by liquid nitrogen cryotherapy using repeat freeze thaw cycles</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$49.10    <b>Benefit:</b> 75% = \$36.85    85% = \$41.75 (See para <a href="#">TN.8.10</a> of explanatory notes to this Category)</p>	
30419	<p>LIVER TUMOURS, destruction of, by hepatic cryotherapy, not being a service associated with a service to which item 50950 or 50952 applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$830.15    <b>Benefit:</b> 75% = \$622.65    85% = \$745.45</p>	
T8. SURGICAL OPERATIONS		7. NEUROSURGICAL
39118	<p>PERCUTANEOUS NEUROTOMY for facet joint denervation by radio-frequency probe or cryoprobe using radiological imaging control</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) (See para <a href="#">TN.8.4</a> of explanatory notes to this Category) <b>Fee:</b> \$302.60    <b>Benefit:</b> 75% = \$226.95    85% = \$257.25</p>	
39323	<p>PERCUTANEOUS NEUROTOMY by cryotherapy or radiofrequency lesion generator, not being a service to which another item applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$281.25    <b>Benefit:</b> 75% = \$210.95    85% = \$239.10</p>	
T8. SURGICAL OPERATIONS		9. OPHTHALMOLOGY
42587	<p>TRICHIASIS (due to causes other than trachoma), treatment of by cryotherapy, laser or electrolysis - each eyelid</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$52.80    <b>Benefit:</b> 75% = \$39.60    85% = \$44.90</p>	
42588	<p>TRICHIASIS (due to trachoma), treatment of by cryotherapy, laser or electrolysis - each eyelid</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$52.80    <b>Benefit:</b> 75% = \$39.60    85% = \$44.90</p>	
42680	<p>CONJUNCTIVA, cryotherapy to, for melanotic lesions or similar using CO<sup>2</sup> or N<sup>2</sup>O</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$305.55    <b>Benefit:</b> 75% = \$229.20    85% = \$259.75</p>	
42818	<p>RETINA, CRYOTHERAPY TO, as an independent procedure, or when performed in conjunction with item 42809 or 42770</p>	

	<a href="#">Multiple Operation Rule</a> (Anaes.) <b>Fee:</b> \$595.90 <b>Benefit:</b> 75% = \$446.95 85% = \$511.20
<b>T8. SURGICAL OPERATIONS</b> <span style="float: right;"><b>13. PLASTIC AND RECONSTRUCTIVE SURGERY</b></span>	
45882	The treatment of a premalignant lesion of the oral mucosa by a treatment using cryotherapy, diathermy or carbon dioxide laser. <a href="#">Multiple Operation Rule</a> <b>Fee:</b> \$43.70 <b>Benefit:</b> 75% = \$32.80 85% = \$37.15
45939	PERIPHERAL BRANCHES OF THE TRIGEMINAL NERVE, cryosurgery of, for pain relief <a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$454.25 <b>Benefit:</b> 75% = \$340.70 85% = \$386.15

Source: [Medicare Benefits Schedule \(MBS\) online](#) [accessed 1 November 2019].

## Appendix 5

### Devices associated with the proposed medical service

Product name	Visual-ICE Cryoablation System - Electronic general cryosurgical system	Cryotherapy set	ProSense Unit - Electronic general cryosurgical system
Sponsor	Big Green Surgical Company Pty Ltd., Australia	Big Green Surgical Company Pty Ltd., Australia	Surgeons Choice Australia Pty Ltd., Australia
ARTG ID	<a href="#">221468</a>	<a href="#">224583</a>	<a href="#">308786</a>
ARTG Start Date	19 March 2014	17 June 2014	30 August 2018
Status	Active	Active	Active
Product category	Medical Device Class IIb	Medical Device Class IIb	Medical Device Class IIb
Manufacturer	Galil Medical Inc., USA	Galil Medical Ltd., Israel	IceCure Medical Ltd., Israel
GMDN	45738 Electronic general cryosurgical system	45140 Cryotherapy set	45738 Electronic general cryosurgical system
Product Type	Medical device system	Procedure pack	Medical device system
Effective date	19 March 2014	17 June 2014	30 August 2018
Intended purpose	The Visual-ICE Cryoablation System is intended for cryoablative destruction of tissue during minimally invasive, transient surgical procedures. The System is indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology, thoracic surgery, ENT, gynecology, oncology, proctology, and urology. This system is designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, skin lesions, and warts) by the application of extremely cold temperatures.	Procedure packs containing cryoablation needles and accessories intended to be used with a cryoablation system for the destruction of tissue during minimally invasive, transient surgical procedures.	The ProSense™ cryoablation system may be used with an ultrasound device to provide real-time visualization of the cryosurgical procedure. An assembly of mains electricity (AC-powered) devices designed to apply cold from a gaseous or liquid refrigerant (cryogen) [e.g., liquid nitrogen (LN2), nitrous oxide (N2O), carbon dioxide (CO2)] to a target tissue for its destruction and removal. The system typically includes an electronic control unit with LCD display to control the flow of cryogen from an attached cylinder, and sometimes to monitor skin temperature; and cryogen-cooled probes to apply the cold to tissues upon contact. It is typically used across clinical specialties (e.g., general surgery, dermatology, oral surgery, gynaecology, urology, ENT, proctology, oncology) to remove malignant or abnormal benign tissues.
Specific conditions	No Specific Conditions included on Record	No Specific Conditions included on Record	None reported

Source: Public ARTG summaries of the products, available at the [Australian Register of Therapeutic Goods \(ARTG\)](#)



## Appendix 6

### Current MBS-listed items for nephrectomy (list not exhaustive)

#### Category 3 – THERAPEUTIC PROCEDURES

T8. SURGICAL OPERATIONS		5. UROLOGICAL
36516	NEPHRECTOMY, complete <a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$939.50 <b>Benefit:</b> 75% = \$704.65	
36519	NEPHRECTOMY, complete, complicated by previous surgery on the same kidney <a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$1,311.75 <b>Benefit:</b> 75% = \$983.85	
36522	NEPHRECTOMY, partial <a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$1,125.70 <b>Benefit:</b> 75% = \$844.30	
36525	NEPHRECTOMY, partial, complicated by previous surgery on the same kidney <a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) <b>Fee:</b> \$1,599.65 <b>Benefit:</b> 75% = \$1199.75	

Source: [Medicare Benefits Schedule \(MBS\) online](#) [accessed 1 November 2019].

## Appendix 7

### Current MBS-listed items for radiofrequency or microwave ablation (list not exhaustive)

#### Category 3 – THERAPEUTIC PROCEDURES

T8. SURGICAL OPERATIONS		1 GENERAL
30687	<p>ENDOSCOPY with RADIOFREQUENCY ABLATION of mucosal metaplasia for the treatment of Barrett's Oesophagus in a single course of treatment, following diagnosis of high grade dysplasia confirmed by histological examination</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (See para <a href="#">TN.8.17</a>, <a href="#">TN.8.20</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$483.70 <b>Benefit:</b> 75% = \$362.80 85% = \$411.15</p>	
T8. SURGICAL OPERATIONS		3. VASCULAR
32523	<p>Varicose veins, abolition of venous reflux by occlusion of a primary or recurrent great (long) or small (short) saphenous vein of one leg (and major tributaries of saphenous veins as necessary), using a radiofrequency catheter introduced by an endovenous catheter, if it is documented by duplex ultrasound that the great or small saphenous vein (whichever is to be treated) demonstrates reflux of 0.5 seconds or longer:</p> <p>(a) including all preparation and immediate clinical aftercare (including excision or injection of either tributaries or incompetent perforating veins, or both); and (b) not including endovenous laser therapy or cyanoacrylate embolisation; and (c) not provided on the same occasion as a service described in any of items 32500, 32504 and 32507</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (See para <a href="#">TN.8.33</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$542.15 <b>Benefit:</b> 75% = \$406.65 85% = \$460.85 <b>Extended Medicare Safety Net Cap:</b> \$81.35</p>	
35526	<p>Varicose veins, abolition of venous reflux by occlusion of a primary or recurrent great (long) and small (short) saphenous vein of one leg (and major tributaries of saphenous veins as necessary), using a radiofrequency catheter introduced by an endovenous catheter, if it is documented by duplex ultrasound that the great and small saphenous veins demonstrate reflux of 0.5 seconds or longer:</p> <p>(a) including all preparation and immediate clinical aftercare (including excision or injection of either tributaries or incompetent perforating veins, or both); and (b) not including endovenous laser therapy or cyanoacrylate embolisation; and (c) not provided on the same occasion as a service described in any of items 32500, 32504 and 32507</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (See para <a href="#">TN.8.33</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$806.00 <b>Benefit:</b> 75% = \$604.50 85% = \$721.30 <b>Extended Medicare Safety Net Cap:</b> \$80.60</p>	
T8. SURGICAL OPERATIONS		4. GYNAECOLOGICAL
35616	<p>ENDOMETRIUM, endoscopic examination of and ablation of, by microwave or thermal balloon or radiofrequency electrosurgery, for chronic refractory menorrhagia including any hysteroscopy performed on the same day, with or without uterine curettage</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.)</p> <p><b>Fee:</b> \$456.80 <b>Benefit:</b> 75% = \$342.60</p>	
T8. SURGICAL OPERATIONS		5. UROLOGICAL
37201	<p>PROSTATE, transurethral radio-frequency needle ablation of, with or without cystoscopy and with or without urethroscopy, in patients with moderate to severe lower urinary tract symptoms who are not medically fit for transurethral resection of the prostate (that is, prostatectomy using diathermy or cold punch) and including services to which item 36854, 37203, 37206, 37207, 37208, 37245, 37303, 37321 or 37324 applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (See para <a href="#">TN.8.53</a> of explanatory notes to this Category)</p>	

	<b>Fee:</b> \$842.10 <b>Benefit:</b> 75% = \$631.60
37202	<p>PROSTATE, transurethral radio-frequency needle ablation of, with or without cystoscopy and with or without urethroscopy, in patients with moderate to severe lower urinary tract symptoms who are not medically fit for transurethral resection of the prostate (that is prostatectomy using diathermy or cold punch) and including services to which item 36854, 37245, 37303, 37321 or 37324 applies, continuation of, within 10 days of the procedure described by item 37201, 37203 or 37207 which had to be discontinued for medical reasons</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (See para <a href="#">TN.8.53</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$422.70 <b>Benefit:</b> 75% = \$317.05 85% = \$359.30</p>
37230	<p>PROSTATE, high-energy transurethral microwave thermotherapy of, with or without cystoscopy and with or without urethroscopy and including services to which item 36854, 37203, 37206, 37207, 37208, 37303, 37321 or 37324 applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.)</p> <p><b>Fee:</b> \$1,058.80 <b>Benefit:</b> 75% = \$794.10 85% = \$974.10</p>
37233	<p>PROSTATE, high-energy transurethral microwave thermotherapy of, with or without cystoscopy and with or without urethroscopy and including services to which item 36854, 37303, 37321 or 37324 applies, continuation of, within 10 days of the procedure described by item 37201, 37203, 37207, 37230 which had to be discontinued for medical reasons</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.)</p> <p><b>Fee:</b> \$567.05 <b>Benefit:</b> 75% = \$425.30 85% = \$482.35</p>
<b>T8. SURGICAL OPERATIONS</b>	
<b>7. NEUROSURGICAL</b>	
39109	<p>TRIGEMINAL GANGLIOTOMY by radiofrequency, balloon or glycerol</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.)</p> <p><b>Fee:</b> \$450.80 <b>Benefit:</b> 75% = \$338.10 85% = \$383.20</p>
39118	<p>PERCUTANEOUS NEUROTOMY for facet joint denervation by radio-frequency probe or cryoprobe using radiological imaging control</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.) (See para <a href="#">TN.8.4</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$302.60 <b>Benefit:</b> 75% = \$226.95 85% = \$257.25</p>
39323	<p>PERCUTANEOUS NEUROTOMY by cryotherapy or radiofrequency lesion generator, not being a service to which another item applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.) (Assist.)</p> <p><b>Fee:</b> \$281.25 <b>Benefit:</b> 75% = \$210.95 85% = \$239.10</p>
<b>16. RADIOFREQUENCY AND MICROWAVE TISSUE ABLATION</b>	
<b>T8. SURGICAL OPERATIONS</b>	
50950	<p>Unresectable primary malignant tumour of the liver, destruction of, by percutaneous radiofrequency ablation or percutaneous microwave tissue ablation (including any associated imaging services), other than a service associated with a service to which item 30419 or 50952 applies</p> <p><a href="#">Multiple Operation Rule</a> (Anaes.)</p> <p><b>Fee:</b> \$830.15 <b>Benefit:</b> 75% = \$622.65 85% = \$746.75</p>
50952	<p>Unresectable primary malignant tumour of the liver, destruction of, by open or laparoscopic radiofrequency ablation or open or laparoscopic microwave tissue ablation (including any associated imaging services), if a multi-disciplinary team has assessed that percutaneous radiofrequency ablation or percutaneous microwave tissue ablation cannot be performed or is not practical because of one or more of the following clinical circumstances:</p> <ul style="list-style-type: none"> <li>(a) percutaneous access cannot be achieved;</li> <li>(b) vital organs or tissues are at risk of damage from the percutaneous radiofrequency ablation or percutaneous microwave tissue ablation procedure;</li> </ul>

<p>(c) resection of one part of the liver is possible, however there is at least one primary liver tumour in an unresectable portion of the liver that is suitable for radiofrequency ablation or microwave tissue ablation;</p> <p>other than a service associated with a service to which item 30419 or 50950 applies.</p> <p><a href="#">Multiple Operation Rule</a></p> <p>(Anaes.)</p> <p>(See para <a href="#">TN.8.120</a> of explanatory notes to this Category)</p> <p><b>Fee:</b> \$830.15    <b>Benefit:</b> 75% = \$622.65    85% = \$746.75</p>
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Source: [Medicare Benefits Schedule \(MBS\) online](#) [accessed 1 November 2019].

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## END NOTES

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- <sup>1</sup> Table 3, page ix in AIHW (2019a).
- <sup>2</sup> Ibid., online Supplementary Table S5.5.
- <sup>3</sup> Ibid., online Supplementary Table S5.3.
- <sup>4</sup> Table T8, online, AIHW (2019b).
- <sup>5</sup> Table 3, page ix in AIHW (2019a).
- <sup>6</sup> Ibid., online Supplementary Table S8.5.
- <sup>7</sup> Ibid., online Supplementary Table S8.4.
- <sup>8</sup> Table T8, online, AIHW (2019b).
- <sup>9</sup> Relative survival refers to the probability of being alive for a given amount of time after diagnosis compared with the general population. It is the ratio of the observed survival of a group of persons diagnosed with cancer to the expected survival of those in the corresponding general population after a specified interval following diagnosis (such as 5 or 10 years). A 5-year relative survival of 100% means that the cancer has no impact on the person's chance of still being alive 5 years after diagnosis, whereas a 5-year relative survival of 50% means that the cancer has halved that chance (pp74 and 146 in AIHW 2019a).
- <sup>10</sup> Table 4c, web report, AIHW (2019c).
- <sup>11</sup> The number of people alive at 31 December 2014 who have been diagnosed with kidney cancer in the past 1 and 5 years respectively.
- <sup>12</sup> Escudier (2019).
- <sup>13</sup> Ljungberg (2019).
- <sup>14</sup> Ljungberg (2019).
- <sup>15</sup> Escudier (2019), Ljungberg (2019).
- <sup>16</sup> Cancer Council Australia (2019).
- <sup>17</sup> Campbell (2017).
- <sup>18</sup> Ljungberg (2019).
- <sup>19</sup> Crestani (2016).
- <sup>20</sup> Jewett (2015).
- <sup>21</sup> Appendix 1 presents details of the Union for International Cancer Control (UICC) TNM 8 staging system for renal cell carcinoma (RCC) as recommended by the European Society of Medical Oncology (ESMO).
- <sup>22</sup> Crestani (2016), AHRQ (2017), Elstob (2016).
- <sup>23</sup> Organ (2019).
- <sup>24</sup> Ljungberg (2019).
- <sup>25</sup> Crestani (2016).
- <sup>26</sup> Organ (2019).
- <sup>27</sup> Finelli (2017).
- <sup>28</sup> Organ (2019), AHRQ (2017).
- <sup>29</sup> Lee (2016).
- <sup>30</sup> Jewett (2019).
- <sup>31</sup> Escudier (2019), Krokidis (2018).
- <sup>32</sup> Organ (2019).
- <sup>33</sup> AHRQ (2017).
- <sup>34</sup> Ljungberg (2019).
- <sup>35</sup> Among surgical cases, risk of malignancy was 0% in Bosniak I and II cysts, 10% in Bosniak IIF, 50% in Bosniak III and 100% in Bosniak IV cysts (Ljungberg 2019).
- <sup>36</sup> Ljungberg (2019).
- <sup>37</sup> Escudier (2019), Ljungberg (2019).
- <sup>38</sup> Ljungberg (2019).
- <sup>39</sup> Ljungberg (2019).
- <sup>40</sup> Shakeri (2019).
- <sup>41</sup> Patel (2016), Shakeri (2019).
- <sup>42</sup> Finelli (2017), Campbell (2017), Jewett (2015), Ljungberg (2019), Escudier (2019), Jonasch (2019).
- <sup>43</sup> Campbell (2017).
- <sup>44</sup> Finelli (2017), Campbell (2017).
- <sup>45</sup> Escudier (2019).
- <sup>46</sup> Escudier (2019).
- <sup>47</sup> Jewett (2015), Finelli (2017).
- <sup>48</sup> Escudier (2019).

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- <sup>49</sup> Ljungberg (2019).
- <sup>50</sup> Finelli (2017).
- <sup>51</sup> For example some patients may simply do not want any type of invasive treatment no matter what.
- <sup>52</sup> Escudier (2019).
- <sup>53</sup> Question 25, Application Form.
- <sup>54</sup> Question 13, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>55</sup> Questions 25 and 50, Application Form.
- <sup>56</sup> Escudier (2019).
- <sup>57</sup> Jewett (2015), Finelli (2017).
- <sup>58</sup> Campbell (2017), Escudier (2019).
- <sup>59</sup> Shakeri (2019).
- <sup>60</sup> Organ (2019), Ljungberg (2019), Shakeri (2019).
- <sup>61</sup> Filippiadis (2019).
- <sup>62</sup> Question 25, Application Form.
- <sup>63</sup> Campbell (2017)
- <sup>64</sup> Escudier (2019).
- <sup>65</sup> Campbell (2017)
- <sup>66</sup> Jewett (2015).
- <sup>67</sup> NCCN (2019).
- <sup>68</sup> Escudier (2019).
- <sup>69</sup> Escudier (2019).
- <sup>70</sup> Elstob (2016).
- <sup>71</sup> Ljungberg (2019).
- <sup>72</sup> Campbell (2019).
- <sup>73</sup> Question 8, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>74</sup> Ljungberg (2019).
- <sup>75</sup> Targeted Consultation feedback from the Royal Australian and New Zealand College of Radiologists (RANZCR)
- <sup>76</sup> Question 46, Application Form
- <sup>77</sup> Question 49, Application Form.
- <sup>78</sup> Questions 46 and 49, Application Form.
- <sup>79</sup> Mahnken (2018).
- <sup>80</sup> Mahnken (2018).
- <sup>81</sup> Mahnken (2018).
- <sup>82</sup> Filippiadis (2019)
- <sup>83</sup> And/or via indirect ischaemic effect from micro-vascular changes (Ismail 2018).
- <sup>84</sup> Krokidis (2018).
- <sup>85</sup> The Joule-Thomson effect is the ability of a gas to extract thermal energy from the surrounding area during fast expansion (Mahnken 2018).
- <sup>86</sup> Shakeri (2019).
- <sup>87</sup> Argon has a high inversion temperature so experiences cooling under expansion (up to  $-185^{\circ}\text{C}$ ) whereas helium as a low inversion temperature so undergo warming (Mahnken 2018).
- <sup>88</sup> Shakeri (2019).
- <sup>89</sup> Shakeri (2019).
- <sup>90</sup> Krokidis (2018).
- <sup>91</sup> Shakeri (2019).
- <sup>92</sup> p31, Application Form.
- <sup>93</sup> Krokidis (2018).
- <sup>94</sup> Filippiadis (2019).
- <sup>95</sup> Shakeri (2019).
- <sup>96</sup> Krokidis (2018).
- <sup>97</sup> Mahnken (2018).
- <sup>98</sup> Shakeri (2019).
- <sup>99</sup> Krokidis (2018).
- <sup>100</sup> Page 23, Application Form.
- <sup>101</sup> Question 10, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>102</sup> Common perioperative complications include paraesthesia, pain, fever, parenchymal fracture, bleeding, pulmonary complications, urinary tract infection, etc. (Ismail 2018).
- <sup>103</sup> Krokidis (2018).
- <sup>104</sup> Ismail (2018).



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- <sup>105</sup> Question 4, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>106</sup> Question 34, Application Form; Targeted Consultation feedback from the Royal Australian and New Zealand College of Radiologists (RANZCR).
- <sup>107</sup> Filippiadis (2019).
- <sup>108</sup> Question 8, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>109</sup> Question 8, Targeted Consultation Survey by the Urology Society of Australia and New Zealand.
- <sup>110</sup> Ismail (2018).
- <sup>111</sup> Question 27, Application Form.
- <sup>112</sup> Ismail (2018).
- <sup>113</sup> Targeted Consultation feedback from the Royal Australian and New Zealand College of Radiologists (RANZCR).
- <sup>114</sup> Ismail (2018).
- <sup>115</sup> Ismail (2018).
- <sup>116</sup> Pessoa (2017).
- <sup>117</sup> Question 50, Application Form.
- <sup>118</sup> Question 12, Application Form.
- <sup>119</sup> Question 12, Application Form.
- <sup>120</sup> Question 13, Application Form.
- <sup>121</sup> Question 11, Application Form.
- <sup>122</sup> Shprits (2019) [Safety, feasibility and oncologic efficacy of treatment for small renal masses using an innovative liquid nitrogen-based cryogenic device](#). *European Urology Supplements* 2019; 18(1):e1749.
- <sup>123</sup> Question 38, Application Form.
- <sup>124</sup> Finelli (2017).
- <sup>125</sup> Finelli (2017).
- <sup>126</sup> Question 41, Application Form.
- <sup>127</sup> Question 41, Application Form.
- <sup>128</sup> Question 48, Application Form.
- <sup>129</sup> Question 41, Application Form.
- <sup>130</sup> Question 41, Application Form.
- <sup>131</sup> Shakeri (2019).
- <sup>132</sup> Patel (2016).
- <sup>133</sup> Gu (2016).
- <sup>134</sup> Krokidis (2018), Cronan (2019).
- <sup>135</sup> Zondervan (2019).
- <sup>136</sup> Abarzua-Cabezas (2015).
- <sup>137</sup> Question 53, Application Form.