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 Public Summary Document

Application No. 1597 – Cryoablation for biopsy-confirmed renal cell carcinoma (RCC) ≤4 cm in patients not suitable for partial nephrectomy

**Applicant: Boston Scientific / BTG International Asia Limited**

**Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](http://www.msac.gov.au/)

# Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of cryoablation for the treatment of biopsy-confirmed renal cell carcinoma (RCC) ≤4 cm, in patients not suitable for partial nephrectomy (PN), was received from Boston Scientific/BTG International Asia Limited by the Department of Health.

# MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported Medicare Benefits Schedule (MBS) funding of cryoablation (CA) for biopsy-confirmed renal cell carcinoma (RCC) ≤4 cm in patients not suitable for partial nephrectomy (PN). MSAC accepted that cryoablation in the proposed population was safe, effective and cost-effective compared with active surveillance/delayed therapy. MSAC advised that the Department should liaise with stakeholders to determine a reduced fee from that proposed by the applicant that is commensurate with the time and complexity for the procedure.

| **Consumer summary** |
| --- |
| Boston Scientific/BTG International Asia Limited applied for public funding via the Medicare Benefits Schedule (MBS) for cryoablation for renal cell carcinoma in certain patients.Renal cell carcinoma is a type of kidney cancer. This application relates to patients who have kidney cancer, their tumour measures 4cm or less and they would not benefit from surgery to remove the affected area (partial nephrectomy). Cryoablation (also called cryotherapy or cryosurgery) uses extreme cold to destroy cancer cells. In cryoablation, ultra-thin needles are placed in the tumour, and argon gas is passed into the needles, which quickly cool to a temperature well below −100°C. This forms an ice ball around the needle tip, which freezes the tumour. Helium gas is then passed through the needles to thaw the tissue. The freeze–thaw process is repeated at least twice to destroy the cancer cells and a small number of healthy cells around the edge of the tumour.MSAC considered that cryoablation was safe, effective and good value for money compared with active surveillance (“watch and wait”) or delayed therapy. **MSAC’s advice to the Commonwealth Minister for Health**MSAC supported MBS funding for cryoablation for people with renal cell carcinoma where the tumour is 4cm or less in size and they would not benefit from surgical removal. |

# Summary of consideration and rationale for MSAC’s advice

MSAC noted the purpose of the application was to request MBS listing for CA for the treatment of biopsy-confirmed RCC ≤4 cm (without spread to regional nodes or metastases) in patients not suitable for PN.

MSAC noted the two main comparators presented in the application were active surveillance/delayed therapy (AS/DT) and laparoscopic radical nephrectomy (RN). However, MSAC did not consider laparoscopic RN to be an appropriate comparator, as the application seeks funding for patients who are not suitable for this procedure. MSAC also noted that other thermal ablation (OTA) and PN were included as supplementary comparators in the applicant developed assessment report (ADAR) for clinical comparison only.

MSAC reviewed the evidence on the comparative safety and effectiveness of CA for the proposed indication. MSAC noted that due to a paucity of studies directly comparing CA with AS/DT (the main comparator), the ADAR used studies involving other thermal ablative procedures (OTA, including radiofrequency ablation [RFA] and microwave ablation [MWA]) as a proxy for CA and justified this approach by presenting a supplementary comparison of CA versus OTA.

MSAC reviewed the safety profile of CA versus OTA and accepted that CA had non-inferior safety compared to OTA. MSAC noted that cancer-specific mortality was the same for CA versus OTA, and that non-cancer mortality HR was lower for CA versus OTA. Overall, MSAC considered that CA had likely similar outcomes (i.e. non-inferior safety and effectiveness) compared to OTA.

MSAC accepted CA would have inferior safety compared to AS/DT as some patients on AS would have never received DT. MSAC noted that cancer-specific mortality and non-cancer mortality were significantly lower for CA compared to AS/DT. Overall, MSAC considered CA to have superior clinical effectiveness and inferior safety compared to AS/DT.

MSAC considered the cost-utility analysis for CA versus AS/DT, along with the supplementary analyses provided in the pre-MSAC response. MSAC noted that the time horizon in the model was 10 years, and the model included a percentage of repeat procedures. The model did not account for recurrence, however MSAC noted that RCCs are typically slow-growing tumours. MSAC noted that the incremental cost-effectiveness ratios (ICERs) generated from the economic model showed that CA was dominant in all scenarios, except those including a long inpatient stay, which MSAC considered would be unlikely given that CA is typically a day procedure.

MSAC noted the economic evaluation and budget impact analysis did not take into consideration the cost of consumables (in particular, the cost of CA needles) and that there was uncertainty regarding whether the estimated hospital costs would cover the cost of the CA needles. MSAC noted there could be high out-of-pocket costs for patients if the cost of the CA needles is not covered by the hospital costs. Additional analysis by MSAC indicated that including the CA needle cost as a separate cost in addition to the hospital costs increased the base case ICER from dominant to around $11,000 per quality-adjusted life year gained. This approach would also result in a cost to non-MBS budgets of $3.3 million over 5 years, which MSAC considered had not been adequately accounted for by the applicant.

MSAC considered whether the item descriptor should allow any mode of delivering CA (i.e. laparoscopic, percutaneous and open). MSAC noted that the pre-MSAC response highlighted that percutaneous, laparoscopic and open procedures are all reimbursed under the MBS at the same fee for liver cancer. MSAC considered that the claim of no difference between laparoscopic, percutaneous and open CA was reasonable, but was based on limited evidence and has implications for the cost of the procedure. MSAC noted that for a percutaneous or open CA, the MBS item may be claimed by both the surgeon and the radiologist. MSAC suggested that the Department may wish to consider the potential for co-claiming of laparoscopic procedures and CA for RCC.

MSAC considered whether the proposed MBS item for CA should be broadened to include OTA, as a general item for ablative procedures of the kidney. MSAC noted that CA machines are not widely available, and allowing for use of OTA may improve patient access. MSAC recalled an application for MWA to treat patients with surgically unresectable liver tumours (MSAC Application 1402) which compared MWA against RFA in the liver. MSAC requested that the Department review the evidence presented in MSAC 1402 and inform the MSAC Executive on whether the level of evidence for broadening CA to OTA in the kidney is consistent with MSAC 1402 or whether additional evidence would be required to determine whether OTA could be included in the item descriptor for RCC along with CA.

MSAC considered that the sentence “not to be used as salvage therapy after partial nephrectomy or previous thermal or radiofrequency ablation” should not be included in the item descriptor, as the cost-effectiveness of CA in the proposed indication is predicated on this. MSAC also considered that the item descriptor should state ‘renal cell carcinoma’ rather than ‘localised primary malignant tumour of the kidney’ in line with the presented evidence.

MSAC noted the proposed fee for CA was based on a similar MBS item for ablation of an unresectable primary malignant tumour of the liver. However, MSAC noted lesions in the kidney are likely to be smaller and the procedure is less complex and likely to take less time than in the liver. Therefore, MSAC considered that it was inappropriate for the fee for CA in the kidney to be the same as the fee for ablation of a liver tumour. MSAC advised that the Department should liaise with stakeholders to determine a reduced fee that is commensurate with the time and complexity for the procedure.

The MSAC-supported MBS item descriptor is as follows:

| **Category 3 – THERAPEUTIC PROCEDURES** |
| --- |
| **T8. SURGICAL OPERATIONS** | **XX. CRYOABLATION** |
| CRYOABLATIONRenal cell carcinoma, not more than 4 cm in diameter, destruction of, by percutaneous, laparoscopic or open cryoablation (including any associated imaging services), where malignancy has previously been 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.[Multiple Operation Rule](http://www9.health.gov.au/mbs/fullDisplay.cfm?type=note&q=TN.8.2&qt=noteID&criteria=TN%2E8%2E2)(Anaes.) (See para TN.8.XX1, TN.8.XX2 of explanatory notes to this category)**Fee**: $To be advised  |
| **TN.8.XX1** For the purpose of the proposed item, a multi-disciplinary team typically includes a urologist, interventional radiologist and oncologist. Patients eligible for Medicare-funded cryoablation needs to be considered 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. |
| **TN.8.XX2** For the purpose of the proposed item, the procedure is to be performed by an interventional radiologist specially trained for 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. |

**Other discussion**

MSAC noted the applicant’s suggestion to include the CA needles on Part C of the Prostheses List (PL) at a benefit amount of $**redacted**. MSAC noted that the role of MSAC is not to advise about the PL; this is the role of the Prostheses List Advisory Committee (PLAC).

# Background

This is the first submission (Applicant Developed Assessment Report [ADAR]) for MSAC Application 1597 - cryoablation for the treatment of biopsy-confirmed RCC ≤4 cm, in patients not suitable for PN.

# Prerequisites to implementation of any funding advice

The proposed medical service relies on devices to achieve its intended effect: a CA system (multi-use) and CA needles (single-use consumables). Items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this application are shown in Table 1.

**Table 1 Cryoablation products listed on the ARTG**

| ARTG no. | Product description | Product category | Sponsor |
| --- | --- | --- | --- |
| 221468 | Visual-ICE Cryoablation System - Electronic general cryosurgical system | Medical Device Class IIb | Big Green Surgical Company Pty Ltd., Australia |
| 224583 | Cryotherapy set | Medical Device Class IIb | Big Green Surgical Company Pty Ltd., Australia |
| 308786 | ProSense Unit - Electronic general cryosurgical system | Medical Device Class IIb | Surgeons Choice Australia Pty Ltd., Australia |

Source: Therapeutic Goods Administration, accessed 20 November 2020 [Link to TGA.gov.au](https://www.ebs.tga.gov.au/)

Abbreviations: ARTG no.= Australian Register of Therapeutic Goods number.

# Proposal for public funding

Table 2 presents the applicant proposed MBS item descriptor.

**Table 2 MBS item descriptor proposed by the applicant**

| **Category 3 – THERAPEUTIC PROCEDURES** |
| --- |
| **T8. SURGICAL OPERATIONS** | **XX. CRYOABLATION** |
| CRYOABLATIONLocalised 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~~has previously been 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.[Multiple Operation Rule](http://www9.health.gov.au/mbs/fullDisplay.cfm?type=note&q=TN.8.2&qt=noteID&criteria=TN%2E8%2E2)(Anaes.) (See para TN.8.XX1, TN.8.XX2 of explanatory notes to this category)**Fee**: $830.15 |
| **TN.8.XX1** For the purpose of the proposed item, a multi-disciplinary team typically includes a urologist, interventional radiologist and oncologist. Patients eligible for Medicare-funded cryoablation needs to be considered 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 item, the procedure is to be performed by an interventional radiologist specially trained for 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. |

Source: Table 7, p48 of the ADAR. Red text indicates changes advised by the Evaluation Sub-Committee (ESC).

The applicant proposed item descriptor and fee are consistent with the ratified PICO[[1]](#footnote-1) confirmation. However, the Commentary noted that MSAC may wish to consider whether there is any need to further refine the proposed descriptor wording to align with the evidence presented (e.g. introducing age restrictions, limit to percutaneous CA, etc.) and, or, adding an extra item on salvage CA.

The pre-MSAC response acknowledged and supported ESC’s advice:

* that “where malignancy is confirmed by histopathological examination” be changed to “where malignancy has previously been confirmed by histopathological examination”;
* that ‘hereditary/multiple RCC’ should be removed from the technical note as this is inconsistent with the item descriptor for CA for ‘localised primary malignant tumour’; and
* the proposal to include “tumour of significant complexity not amendable to PN” in the technical note was not supported by any evidence.

# Summary of public consultation feedback/consumer Issues

Consultation feedback was received from one specialist organisation, which was supportive of MBS listing of CA for the proposed MBS population. The response noted that the availability of an alternative ablative technique would increase patient and clinician choice for treatment of small renal masses, and that currently there is no evidence that one form of ablative therapy (CA, radiofrequency ablation [RFA] or microwave ablation [MWA]) is clinically or ontologically superior to the other forms of energy ablation.

# Proposed intervention’s place in clinical management

## Description of Proposed Intervention

Cryoablation (CA), or cryotherapy or cryosurgery, is the use of extreme cold to destroy tissues. The procedure involves the identification and insertion, under image guidance, of ultra-thin probes (CA needles) into the targeted site, followed by rapid freezing and thawing. During the freezing phase, pressurised argon gas delivered into a small chamber inside the tip of the needle expands and cools rapidly to a temperature well below −100°C. An ice ball is produced around the needle and engulfs the tumour, causing its rapid freezing and expansion. During the thawing phase, helium gas delivered into the probe or electrical heating of the needle results in the thawing of the region. The freeze-thaw process is repeated for a minimum of two cycles to ensure adequate freezing and destruction of the tumour cells, and a small margin of surrounding tissues.

## Description of Medical Condition(s)

Kidney cancer is predicted to remain the seventh most commonly diagnosed cancer in Australia in 2020, based on estimates that 4,193 new cases will be diagnosed in 2020, accounting for 2.9% of all new cases of cancer diagnosed.[[2]](#footnote-2) Kidney cancer is estimated to be responsible for 917 deaths in 2020,[[3]](#footnote-3) accounting for 1.9% of all deaths from cancers in 2020. The mean age at diagnosis was 64.1 years (median 65.5 years) in 2016,[[4]](#footnote-4) and the mean age at death was 74.8 years (median 76.5 years) in 2018.[[5]](#footnote-5)

Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for 90% of all kidney cancers. Clear cell RCC is the most common subtype of RCC (about 75%). Papillary and chromophobe RCC makes up about 10-15% and 5% of RCC cases respectively.[[6]](#footnote-6) Owing to the increasing use of diagnostic imaging (ultrasound [U/S], computed tomography [CT]) to investigate abdominal symptoms not related to the kidney, small renal masses (SRMs) are increasingly detected at early asymptomatic stage, which in turn is considered to contribute to the increasing incidence of RCC.

Cryoablation is proposed for use in patients:

* with localised primary malignant renal cell carcinoma (stage T1aN0M0), ≤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, and hereditary/multiple renal cell carcinomas.

The current and proposed clinical management algorithms for the treatment of patients with biopsy-proven T1a RCC, compiled based on international clinical practice guidelines[[7]](#footnote-7), are presented in Figure 1 and Figure 2.



**Figure 1 Current clinical management algorithm for biopsy-proven T1a RCC in the absence of public funding for the proposed medical service**

Source: Figure 2, p53 of the ADAR (reproduced from Figure 1, p18 of the Ratified PICO for 1597, April 2020).

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 and public funding status on the MBS at the time.



**Figure 2 Proposed clinical management algorithm for biopsy-proven T1a RCC after the proposed listing (including potential leakage)**

Source: Figure 3, p54 of the ADAR (reproduced from Figure 3, p20 of the Ratified PICO for 1597, April 2020).

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 and public funding status on the MBS at the time.

# Comparator

The ADAR presented two main comparators:

Active surveillance/delayed therapy (AS/DT)

Active surveillance involves the regular imaging monitoring of patients, with delayed treatment potentially indicated when the tumour reaches a particular growth rate or size, or when the patients decides they want to undergo intervention. Therefore, the ADAR asserted that for many patients, AS/DT is not a lack of active treatment, but simply a delay in treatment.

Laparoscopic radical nephrectomy (RN)

Laparoscopic RN, which involves removal of the whole kidney, is a treatment option for patients with tumours not amenable to PN. The relevant MBS items for reimbursement of RN are: 36516, 36519, 36526, 36528, 36529 and 36575.

Two additional (supplementary) comparators were also presented in the ADAR: Other thermal ablation (OTA; including RFA and MWA) and PN.

The ADAR included OTA as a supplementary comparator on the basis that RFA and MWA are recommended alongside CA in international clinical guidelines and can therefore potentially be used instead of CA. A comparison of CA, RFW and MWA is presented in Table 3. PN was included as a supplementary comparator based on the potential of leakage of use in patients suitable for PN but who prefer percutaneous CA instead.

The ADAR presented both clinical and economic comparison of CA vs the main comparators (AS/DT and RN) and a clinical comparison only of CA versus the supplementary comparators (OTA and PN) (i.e. an economic comparison of CA vs OTA or PN was not provided).

The Commentary noted that the comparators are consistent with the ratified PICO confirmation.

**Table 3 Comparison of CA, RFA and MWA**

|  | **CA** | **OTA** |
| --- | --- | --- |
|  | **RFA** | **MWA** |
| Mechanism of action | Uses alternating freeze/thaw cycles to generate an ice ball with temperatures as low as –140°C. Cell death occurs within the visible ice ball in the range of –20 to –40°C. Tissue destruction can occur directly at the lowest temperatures, and via extracellular ice crystal formation and leading to cell dehydration and death at higher temperatures | High temperature (>55°C) achieved by alternating current which results in vibration of and friction between water molecules, resulting in thermal injury and coagulative necrosis | High temperature achieved by the oscillating microwave field increasing kinetic energy in water molecules, resulting in thermal injury and coagulative necrosis |
| Ablation speed | 28-40 min | 12-30 min | 5-8 min |
| Tumour size | Up to 8cm | < 3 cm | Up to 8cm |
| Relative advantages  | * No grounding pads required so reduced risk of skin burns
* Larger active treatment area than RFA
* Ability of visually monitor the ice ball during treatment using imaging
* Less risk to ureter and collecting systems than methods that use heating
* Better for central tumours than methods that use heating
* Less painful than RFA/MWA
 | * Faster ablation speed than CA
 | * No grounding pads required so reduced risk of skin burns
* Larger active treatment area than RFA
* Faster ablation speed than RFA and CA
 |
| Relative disadvantages | * Slower ablation speed than RFA/MWA
* Higher rate of bleeding than RFA/MWA
 | * Skin pad burns due to use of grounding pads
* Slower ablation speed than MWA (12-30 mins)
* Heating may damage the renal collecting system
 | * Increased treatment zone weighted towards axis of long needle so increases risk of burns to body wall, peritoneum and nearby structures
* Heating may damage the renal collecting system
 |

Source: Table 4, p43 of the ADAR

Abbreviations: CA=cryoablation; DT=delayed therapy; MWA=microwave ablation; N/A=not applicable; OTA=other thermal ablation; RFA=radiofrequency ablation; TA=thermal ablation

# Comparative safety

A total of 39 cohort studies, the majority of which were retrospective registry-based studies in the US, were presented in the ADAR. There were no direct randomised trials that compared CA versus any of the comparators. Studies that reported the use of thermal ablation (TA) were used as a proxy for CA [CA(TA)]. Of the 39 included studies, six cohort studies informed the comparison of CA versus AS/DT (main comparator 1) and seven cohort studies informed the comparison of CA versus laparoscopic RN (main comparator 2). As such, most of the evidence pertained to the comparison of CA versus the supplementary comparators, OTA (k=21) or PN (k=12). None of the studies were Australian.

CA vs. AS/DT (main comparator 1)

The ADAR presented six cohort studies based on three US databases. Two studies were based on data from one US-based prospective DISSRM[[8]](#footnote-8) registry (Alam 2019[[9]](#footnote-9) and Danzig 2019[[10]](#footnote-10)), and the remaining four studies were based on two US-based retrospective databases: SEER[[11]](#footnote-11) (Uhlig 2018[[12]](#footnote-12) and Abdel-Rahman 2017[[13]](#footnote-13)) and SEER-Medicare (Xing 2018[[14]](#footnote-14) and Larcher 2016a[[15]](#footnote-15)). All six studies assessed TA except one study, Uhlig 2018, which assessed cryosurgery, as well as TA, and in patients with histologically confirmed T1a clear cell RCC.

There were no direct randomised data to inform the comparative safety of CA (or TA) versus AS/DT in the proposed MBS population. The ADAR argued that a majority (84% in Alam 2019) of the patients on AS would eventually receive a delayed therapy. Therefore, any adverse events (AEs) associated with the delayed therapy should also be included as the AE profile of the management strategy AS/DT. Because a proportion of patients on AS would never receive any DT, the ADAR claimed inferiority in the safety of CA when compared with AS/DT.

The Commentary noted that the ADAR did not provide any safety data regarding the CA procedure itself. Typical adverse events known to be associated with CA include perioperative bleeding and incomplete treatment necessitating re-treatment. The Commentary considered that inclusion of AEs associated with the therapy delayed to the AE profile of the management strategy AS/DT, but exclusion of AEs associated with re-ablation or salvage therapy after CA, was not appropriate. Despite the lack of evidence presented, the Commentary considered that the claim of inferiority in safety for CA versus AS/DT seemed reasonable from a theoretical perspective: One hundred percent % of the patients receiving CA are at risk of AEs, whereas only patients managed with initial AS and receiving delayed therapy are at risk of intervention-associated AEs.

CA vs. laparoscopic RN (main comparator 2)

The ADAR presented seven cohort studies based on three US databases. Two studies were based on data from the prospective DISSRM registry (Alam 2019 and Danzig 2019), and the remaining five studies were based on two retrospective databases: SEER-Medicare (Talenfeld 2018[[16]](#footnote-16), Xing 2018 and Kowalczyk 2013[[17]](#footnote-17)) and SEER (Moskowitz 2016[[18]](#footnote-18) and Chouieri 2011[[19]](#footnote-19)). Six of the seven studies assessed TA, rather than CA alone. The seventh study, Danzig 2015, assessed CA (n=14, 64% laparoscopic, 36% percutaneous), RN (n=15), AS (n=68) and PN (n=65) but was a study on SRMs. As such there was no data available specifically comparing the safety of percutaneous CA with laparoscopic RN in patients with biopsy-confirmed T1a RCC, rather the ADAR presented data on TA as a proxy for CA.

The primary evidence base presented to inform the comparative safety of CA(TA) vs. laparoscopic RN was Talenfeld 2018, supported by Xing 2018 and Kowalczyk 2013. In patients diagnosed with T1a RCC, acute renal failure and non-urological complications up to 30 days following treatment were significantly higher for RN compared with percutaneous CA(TA); rates for percutaneous CA(TA) compared with RN were 6% versus 12% for acute renal failure, respectively, and 12% versus 27%, respectively for non-urological complications. No complications were seen at a higher rate for CA(TA) compared with RN. Based on the evidence presented, the ADAR claimed superiority in the comparative safety of CA vs. laparoscopic RN.

The Commentary noted that patients in the included studies were not randomised to receive either TA or RN. Provider preference and expertise, availability of equipment, as well as patient and tumour characteristics, all might have contributed to the decision on selection of treatment (TA or RN). Potential impact of selection bias on outcomes could not be ruled out. The ADAR used TA as a proxy for CA, claiming (a) TA is non-inferior to RN, (b) CA is non-inferior to TA, and therefore (c) CA is non-inferior to RN. However, the ADAR did not provide any formal indirect comparison analysis using OTA as a common comparator to establish claim (c). Further, all three studies included only patients aged ≥65 years. As such the Commentary suggested that the applicability of results to the proposed MBS population was not clear.

CA vs. OTA (supplementary comparator 1)

The ADAR presented 21 cohort studies based on data from two US-based databases (NCDB[[20]](#footnote-20) and SEER), eight US centres, one European centre (Italy) and one Asian centre (Turkey). There were no direct randomised studies to inform the comparison of CA versus OTA (RFA, MWA) or any Australian study. Six studies specifically provided data on patients with T1a RCC and one study was in patients with T1 RCC (up to 7 cm tumour diameter); the remaining studies included patients with SRM, although some provided subgroup analyses for patients with RCC. Most studies compared CA with RFA; two studies compared CA with MWA and three studies compared CA with RFA and MWA.

Of the 21 studies comparing CA with OTA, nine cohort studies from six treatment centres presented data on complication rates. Two of the studies, De Cobelli 2020[[21]](#footnote-21) and Zhou 2018[[22]](#footnote-22), were excluded from further review with the ADAR citing errors/internal inconsistencies in the studies. The ADAR claimed it was difficult to compare safety across treatment groups due to the differences in patient and disease characteristics seen in each group; i.e. in many of the included studies, percutaneous CA tends to be used in larger and more centrally-located tumours than percutaneous RFA. Bleeding complications tended to be slightly higher following CA and urothelial stricture tended to be slightly higher following RFA. However, the ADAR claimed that these results overall suggest little difference in complications between percutaneous CA and percutaneous RFA and MWA.

The Commentary noted that the seven studies included in the ADAR were unadjusted studies, as such the potential bias of the results of the studies was likely. In addition, all of the presented studies used the percutaneous mode of delivery for CA. Comparative safety of CA via laparocopic or open surgical approach versus OTA (any mode of delivery) is therefore not clear. The pre-ESC response acknowledged that there is a lack of evidence to inform the comparative safety and effectiveness of CA/TA using different modalities, versus the other comparators using different modalities. The applicant claimed the majority of recent evidence relates to the percutaneous mode, which is the preferred methodology due to its being less invasive and highly effective. The applicant claimed this preference is supported by the fact that 90.2% of the 202 RFA/MWA procedures reimbursed for treatment of primary liver cancer in the 2019 to 2020 financial year used the percutaneous mode of delivery.

The Commentary also noted that in three studies (two of which the ADAR excluded) complication rates appeared to be numerically higher with percutaneous CA:

* De Cobrelli 2020, post-procedure complications (percutaneous CA vs. percutaneous MWA) 9.8% vs. 3.6%;
* Zhou 2018, complication rates (percutaneous CA vs. percutaneous MWA), 15% vs. 11%; and
* Camacho 2015[[23]](#footnote-23), total complications (percutaneous CA vs. percutaneous RFA) 12.5% vs. 6.7%.

Overall, the Commentary considered that there is little confidence that the claim of “similar” safety of CA versus OTA (RFA, MWA) is valid.

CA vs. PN (supplementary comparator 2)

The ADAR presented twelve cohort studies based on data from three US-based databases (DISSRM, NCDB and SEER), three US centres (Mayo Clinic, Cleveland Clinic and Washington School of Medicine), one European centre (Milan, Italy) and one Asian centre (Ankara, Turkey). Four studies specifically provided data on patients with T1a RCC; the remaining studies included patients with SRM. Most studies compared CA with PN; only one study comparing TA with PN was included because it provided data for an outcome for which there were no CA versus PN studies available. There was a mix of studies assessing percutaneous CA, laparoscopic CA or both, or where the mode of delivery was not specified.

Of the 12 studies comparing CA with PN, six cohort studies (that included patients with SRMs rather than biopsy-confirmed T1a RCC) presented data on complication rates. The ADAR reported that in a population of patients with T1 SRM aged > 75 years, minor post-operative complications occurred more frequency following PN than CA (25% versus 8%; P=0.009). There was no significant difference in major complications; however, the analysis was based on small patient numbers. Other studies showed no difference in complications between CA and PN, with the exception of one study in which complications occurred more frequently for CA compared with PN (28% versus 20%); in this study the analysis was adjusted for American Society of Anesthesiologists (ASA) score only and did not take into account tumour characteristics. Based on these findings, a clinical claim of superior safety was made in the ADAR, although it was noted that this is based on low quality evidence.

The Commentary considered that the evidence presented in the ADAR did not support a claim of superior safety of CA versus PN in the proposed MBS population.

# Comparative effectiveness

CA vs. AS/DT (main comparator 1)

Based on the evidence presented, the ADAR suggested that CA(TA) is significantly more effective than AS/DT in patients with biopsy-confirmed T1a RCC or SRM. Other-cause mortality (HR 0.47; 95% CI 0.33, 0.67) and cancer-specific mortality (HR 0.69; 95% CI 0.39, 0.88) were significantly lower for CA(TA) compared with AS/DT (moderate quality evidence). In addition, CA(TA) did not appear to impact on renal function, resulting in only a 2.6 mL/min/1.73 m2 reduction in eGFR compared with patients receiving AS/DT (95% CI -6.1, 1.0), and no difference in CKD upstaging-free survival (P=0.98). There was no significant difference in quality of life as measured by the SF-12 total, physical component and mental component scores, with all differences < 2 points. Based on these findings, a clinical claim of superior effectiveness of CA over AS/DT was made in the ADAR.

The balance of clinical benefits and harms of CA(TA) compared with AS/DT is presented in Table 4.

**Table 4 Balance of clinical benefits and harms of CA, relative to AS/DT, and as measured by the critical patient-relevant outcomes in the key studies**

| **Outcomes (units)****Follow-up** | **Participants** **Study type** **(Study ID/location or database)** | **Quality of evidence (GRADE) a** | **Relative effect (95% CI) and/or P value** | **Risk with AS/DT**  | **Risk with CA** |
| --- | --- | --- | --- | --- | --- |
| Other-cause mortality(rate; median FU 34 months) | TA=647; AS/DT=6471 retrospective cohort (Xing 2018/SEER-Medicare) | Moderate(●●●○) | HR 0.47(0.33, 0.67) | 5-year OCM102 per 1000 patients | 5-year OCM48 per 1000 patients |
| Cancer-specific mortality(rate; median FU 34 months) | TA=647; AS/DT=6471 retrospective cohort (Xing 2018/SEER-Medicare) | Moderate(●●●○) | HR 0.69 (0.39, 0.88) | 5-year CSM45 per 1000 patients | 5-year CSM31 per 1000 patients |
| Change in eGFR (mL/min/1.73m2; up to 12 months FU) | TA=27; AS/DT=176; (PN=140)1 prospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD -2.55(-6.07, 0.97) | 12-month change in eGFR–5 mL/min/1.73 m2 | 12-month change in eGFR–7.6 mL/min/1.73 m2 |
| CKD-upstaging(rate; median 18 months FU) | CA=14; AS/DT=681 prospective cohort(Danzig 2015/DISSRM) | Low(●●○○) | P=0.98 | 2-year CKD upstaging70 per 1000 patients | 2-year CKD upstaging70 per 1000 patients |
| Quality of life – change in SF-12 Total score(up to 7 years FU) | TA=37; AS/DT=233; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD 0.98 (-5.48, 7.44) | 7-year change in SF-12 Total score–5 points | 7-year change in SF-12 Total score–4 points |
| Quality of life – change in SF-12 PCS(up to 7 years FU) | TA=37; AS/DT=233; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD 1.78 (-2.68, 6.24) | 7-year change in SF-12 PCS–4 points | 7-year change in SF-12 PCS2 points |
| Quality of life – change in SF-12 MCS(up to 7 years FU) | TA=37; AS/DT=233; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD -0.87 (-4.59, 2.85) | 7-year change in SF-12 PCS2.5 points | 7-year change in SF-12 PCS1.5 points |

Source: Table ES2, p 17 of the ADAR
Abbreviations: AS/DT=active surveillance/deferred therapy; CA=cryoablation; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FU=follow-up; MCS=mental component score; MD=mean difference; min=minute; PCS=physical component score; PN=partial nephrectomy; SF-12=Short Form-12; TA=thermal ablation

Note: outcomes shown in grey shading are statistically significantly in favour of CA(TA) over AS/DT.

a GRADE Working Group grades of evidence (Guyatt et al., 2013): ●●●● **High quality:** We are very confident that the true effect lies close to that of the estimate of effect; ●●●○ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ●○○**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; ●○○○ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Justification for quality of evidence gradings are provided in the source table.

The Commentary noted that the applicability of results from Xing 2018 to the proposed MBS population was uncertain, given the study assessed TA, rather than CA alone, and only in patients aged ≥66 years. It was not clear why Uhlig 2018, a study that assessed cryosurgery, albeit via liquid nitrogen, in patients with histologically confirmed T1a RCC and aged ≥18 years was excluded. The ADAR did not provide any justification on the selection of results from Xing 2018 alone.

The Commentary considered that the claim of overall superiority of TA (any modality, any mode of delivery) over AS/DT appeared reasonable, although the magnitude of difference in treatment benefit is uncertain (Xing 2018 excluded patients aged <66 years, potential selection bias due to non-randomised study design).

The pre-ESC response acknowledged that Uhlig (2018) could have been used, instead of Xing (2018), as the primary evidence base for the comparison of CA vs. AS/DT on the basis that Uhlig (2018) is more applicable to the Australian setting. However, the pre-ESC response clarified that Xing (2018) was selected over Uhlig (2018) on the basis that Xing (2018): more comprehensively factored in potential confounders; provided results for both the AS/DT and RN comparisons (ensuring consistency across the comparisons); and was considered the most conservative of the two studies. The pre-ESC response also claimed that using Uhlig (2018) instead of Xing (2018) would not change the clinical claim that cryoablation is superior to AS/DT in terms of effectiveness.

CA vs. laparoscopic RN (main comparator 2)

Based on the evidence presented, the ADAR suggested that CA(TA) has similar effectiveness to laparoscopic RN in terms of oncological outcomes in patients with biopsy-confirmed T1a RCC or SRM. Other-cause mortality (HR 0.92; 95% CI 0.65, 1.32) and cancer-specific mortality (HR 0.89; 95% CI 0.59, 1.70) were similar for CA(TA) compared with RN (moderate quality evidence). CA(TA) did not appear to impact on renal function, whereas RN did, with RN resulting in a 4.27 mL/min/1.73 m2 reduction in eGFR compared with patients receiving CA(TA) (95% CI 0.26, 8.28). In addition, the rate of renal insufficiency was 19.0 per 100-person years for CA(TA) compared with 38.3 per 100-person years for RN. There was no significant difference in quality of life as measured by the SF-12 total, physical component and mental component scores, with all differences < 2 points. Based on these findings, a clinical claim of non-inferior effectiveness of CA over RN was made in the ADAR.

The balance of clinical benefits and harms of CA(TA) compared with RN is presented in Table 5.

The Commentary considered the overall claim of non-inferiority of CA(TA) (any mode of delivery) vs. RN (any mode of delivery) to be reasonable.

**Table 5 Balance of clinical benefits and harms of CA, relative to RN, and as measured by the critical patient-relevant outcomes in the key studies**

| **Outcomes (units)****Follow-up** | **Participants** **Study type** **(Study ID/location or database)** | **Quality of evidence (GRADE) a** | **Relative/absolute effect (95% CI) and/or P value** | **Risk with RN** | **Risk with CA** |
| --- | --- | --- | --- | --- | --- |
| Other-cause mortality(rate; median FU 42 months) | TA=733; RN=7331 retrospective cohort (Xing 2018/SEER-Medicare) | Moderate(●●●○) | HR 0.92(0.65, 1.32) | 5-year OCM47 per 1000 patients | 5-year OCM43 per 1000 patients |
| Cancer-specific mortality(rate; median FU 42 months) | TA=733; RN=7331 retrospective cohort (Xing 2018/SEER-Medicare) | Moderate(●●●○) | HR 0.89(0.59, 1.70) | 5-year CSM35 per 1000 patients | 5-year CSM31 per 1000 patients |
| Change in eGFR (mL/min/1.73m2; up to 12 months FU) | TA=27; RN=38; (PN=140)1 prospective cohort (Alam 2019/DISSRM) | Moderate(●●●○) | MD 4.27(0.26, 8.28) | 12-month change in eGFR–22 mL/min/1.73 m2 | 12-month change in eGFR–17 mL/min/1.73 m2 |
| Renal insufficiency(rate per 100-py; median 18 months FU) | TA=211; RN=535 1 prospective cohort (Kowalczyk 2013/SEER-Medicare) | Moderate(●●●○) | No formal test between TA and RN | Rate per 100-py38.3 | Rate per 100-py19.0 |
| Quality of life – change in SF-12 Total score(up to 7 years FU) | TA=37; RN=38; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD 1.55(-5.76, 8.86) | 7-year change in SF-12 Total score5 points | 7-year change in SF-12 Total score6.5 points |
| Quality of life – change in SF-12 PCS(up to 7 years FU) | TA=37; RN=38; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD 1.15(-3.90, 6.20) | 7-year change in SF-12 PCS0 points | 7-year change in SF-12 PCS1 points |
| Quality of life – change in SF-12 MCS(up to 7 years FU) | TA=37; RN=38; (PN=218)1 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD 0.43(-3.77, 4.63) | 7-year change in SF-12 PCS5.5 points | 7-year change in SF-12 PCS6 points |
| Acute renal failure (rate; 30 d FU) | PTA=456; RN=17481 retrospective cohort (Talenfeld 2018/SEER-Medicare) | Moderate(●●●○) | 6% (4, 8)vs12% (10, 14)RR = 0.5b | 30-day acute renal failure120 per 1000 | 30-day acute renal failure60 per 1000 |
| Non-urological complications (rate; 30 d FU) | PTA=456; RN=17481 retrospective cohort (Talenfeld 2018/SEER-Medicare) | Moderate(●●●○) | 12% (10, 15)vs27% (24, 29)RR = 0.44b | 30-day non-urologic complications270 per 1000 | 30-day non-urologic complications120 per 1000 |

Source: Table ES3, p19 of the ADAR

Abbreviations: CA=cryoablation; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FU=follow-up; MCS=mental component score; MD=mean difference; min=minute; OR=odds ratio; PCA=percutaneous cryoablation; PCS=physical component score; PN=partial nephrectomy; RN=radical nephrectomy; SF-12=Short Form-12; TA=thermal ablation

Note: outcomes shown in grey shading are statistically significantly in favour of CA over RN.

a GRADE Working Group grades of evidence (Guyatt et al., 2013): ●●●● High quality: We are very confident that the true effect lies close to that of the estimate of effect; ●●●○ Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ●●○○Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; ●○○○ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Justification for quality of evidence gradings are provided in the source table.

b Post hoc calculation based on adjusted rates

CA vs. OTA (supplementary comparator 1)

Based on the evidence presented, the ADAR stated there were no statistically significant differences between CA and OTA for cancer-specific mortality (HR 1.03; 95% CI 0.45, 2.33) and that the majority of studies reported no difference between CA and OTA for overall mortality/survival. However, the ADAR noted that in the large study providing the primary evidence for overall mortality, there was a small, statistically significant difference in favour of CA over OTA (HR 0.87; 95% CI). The ADAR also reported that there was no statistically significant difference in local recurrence-free survival between CA and RFA (HR 1.37; 95% CI 0.26, 7.32); however, the quality of this evidence was impacted by the small number of events (low quality evidence). Based on these findings, the clinical claim in the ADAR is of non-inferior effectiveness and similar safety of CA compared with OTA (RFA/MWA).

The balance of clinical benefits and harms of CA compared with OTA is presented in Table 6.

The ADAR has used this claim to justify the inclusion of data from studies assessing TA as a group (including CA and RFA/MWA) as a proxy for CA. The applicant noted that MSAC may wish to consider whether consideration of MBS-listing should be extended to RFA and MWA, rather than limited to just CA.

**Table 6 Balance of clinical benefits and harms of CA, relative to OTA, and as measured by the critical patient-relevant outcomes in the key studies**

| **Outcomes (units)****Follow-up** | **Participants** **Study type** **(Study ID/location or database)** | **Quality of evidence (GRADE) a** | **Relative/absolute effect (95% CI) and/or P value** | **Risk with OTA** | **Risk with CA** |
| --- | --- | --- | --- | --- | --- |
| Overall mortality(rate; median FU 30 months) | CA=3936; OTA=2322; 1 retrospective cohort (Wu 2019/NCDB) | Moderate(●●●○) | HR 0.87(0.78, 0.98) | 10-year overall mortality450 per 1000 patients | 10-year overall mortality392 per 1000 patients |
| Cancer-specific mortality(rate; median FU 42 months) | CA=315; OTA=1551 retrospective cohort (Uhlig 2018/SEER) | Moderate(●●●○) | HR 1.03(0.45, 2.33) | 5-year CSM70 per 1000 patients | 5-year CSM72 per 1000 patients |
| Local recurrence(rate; median FU 5 years) | CA=108; RFA=73; (PN=835)1 retrospective cohort (Andrews 2018/SEER) | Low(●●○○) | HR 1.37(0.26, 7.32) | 5-year local recurrence55 per 1000 patients | 5-year local recurrence75 per 1000 patients |
| CKD upstaging(rate; 2 years FU) | CA=26; RFA=244; MWA=27 (tumours)1 retrospective cohort (Zhou 2019/Tufts University) | Very low(●○○○) | No CKD upstaging in any group | - | - |
| Complications(rate; various FU) | 7 retrospective cohorts from the US Europe and Asia | Very low(●○○○) | No clear difference in proportion of patients/ablations with complications between CA, RFA and MWA. Some differences in types of complications related to different tumour types and mechanisms of action of treatments |

Source: Table ES4, p21 of the ADAR

Abbreviations: CA=cryoablation; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FU=follow-up; MCS=mental component score; MD=mean difference; min=minute; PCA=percutaneous cryoablation; PCS=physical component score; PN=partial nephrectomy; RN=radical nephrectomy; SF-12=Short Form-12; TA=thermal ablation

Note: outcomes shown in grey shading are statistically significantly in favour of CA over OTA.

a GRADE Working Group grades of evidence (Guyatt et al., 2013): ●●●● High quality: We are very confident that the true effect lies close to that of the estimate of effect; ●●●○ Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ●●○○Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; ●○○○ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Justification for quality of evidence gradings are provided in the source table.

CA vs. PN (supplementary comparator 2)

Based on the evidence presented, the ADAR suggested that CA has inferior effectiveness to PN in patients with *T1a RCC*. Both overall mortality and cancer-specific mortality were significantly higher for CA compared with PN (HR 1.46; 95% CI 1.32, 1.63 and HR 2.44; 95% CI 1.40, 4.26, respectively). While there was no significant difference in local recurrence between CA and PN (HR 1.90; 95% CI 0.71, 4.26), the evidence for this outcome was considered to be low quality due to imprecision. There was no difference between CA and PN in terms of renal function (moderate quality evidence) and quality of life (low quality evidence). Based on these findings, a claim of inferior effectiveness of CA compared with PN was made in the ADAR.

The balance of clinical benefits and harms of CA compared with PN is presented in Table 7.

The Commentary considered the claim of inferior effectiveness of CA compared with PN to be appropriate.

**Table 7 Balance of clinical benefits and harms of CA, relative to PN, and as measured by the critical patient-relevant outcomes in the key studies**

| **Outcomes (units)****Follow-up** | **Participants** **Study type** **(Study ID/location or database)** | **Quality of evidence (GRADE) a** | **Relative/absolute effect (95% CI) and/or P value** | **Risk with PN** | **Risk with CA** |
| --- | --- | --- | --- | --- | --- |
| Overall mortality(rate; up to > 10 years FU) | CA=6,629; PN=6,6291 retrospective cohort (Kitley 2019; NCDB) | Moderate(●●●○) | HR 1.46(1.32, 1.63) | 8-year OM251 per 1000 patients | 8-year OM366 per 1000 patients |
| Cancer-specific mortality(rate; up to > 10 years FU) | CA=1044; PN=10441 retrospective cohort (Liao 2019; SEER) | Moderate(●●●○) | HR 2.44(1.40, 4.26) | 5-year CSM13 per 1000 patients | 5-year CSM32 per 1000 patients |
| Local recurrence(rate; median FU 5 years) | CA=108; PN=8351 retrospective cohort study(Andrews 2018/SEER) | Low(●●○○) | HR 1.90(0.71, 5.12) | 5-year local recurrence26 per 1000 patients | 5-year local recurrence49 per 1000 patients |
| eGFR(mL/min/1.73m2; 12 months FU)  | CA=65; PN=651 retrospective cohort (Bertolo 2019/Cleveland Clinic) | Moderate(●●●○) | MD 1.2(-6.5, 8.9) | 12-month eGFR56 mL/min/1.73 m2 | 12-month eGFR57 mL/min/1.73 m2 |
| CKD upstaging(rate; up to 3 months FU) | CA=294; PN=310 retrospective cohort(Mason 2017/Mayo Clinic) | Moderate(●●●○) | MD 4.9%P=0.12 | 3-month CKD upstaging168 per 1000 patients | 3-month CKD upstaging217 per 1000 patients |
| Quality of life – change in SF-12 Total score(up to 7 years FU) | TA=37; PN=2181 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD -2.25(-8.09, 3.58) | 7-year change in SF-12 Total score3 points | 7-year change in SF-12 Total score1 point |
| Quality of life – change in SF-12 PCS(up to 7 years FU) | TA=37; PN=2181 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD -1.46(-5.51, 2.58) | 7-year change in SF-12 PCS0 points | 7-year change in SF-12 PCS-1.5 points |
| Quality of life – change in SF-12 MCS(up to 7 years FU) | TA=37; PN=2181 retrospective cohort (Alam 2019/DISSRM) | Low(●●○○) | MD -0.90(-4.27, 2.49) | 7-year change in SF-12 PCS-1.5 points | 7-year change in SF-12 PCS-2.5 points |
| Intraoperative complications(rate; up to 12 months FU) | CA=65; PN=651 retrospective cohort (Bertolo 2019/Cleveland Clinic) | Low(●●○○) | MD -1.5%P=0.5 | Intraoperative complications31 per 1000 patients | Intraoperative complications16 per 1000 patients |
| Postoperative complications(rate; up to 12 months FU) | CA=65; PN=651 retrospective cohort (Bertolo 2019/Cleveland Clinic) | Low(●●○○) | MD -22%P=0.007 | Postoperative complications308 per 1000 patients | Postoperative complications92 per 1000 patients |
| Postoperative complications – Clavien I-II(rate; up to 12 months FU) | CA=65; PN=651 retrospective cohort (Bertolo 2019/Cleveland Clinic) | Low(●●○○) | MD -16.9%P=0.009 | Grade I-II postoperative complications 246 per 1000 patients | Grade I-II postoperative complications77 per 1000 patients |
| Postoperative complications – Clavien III-IV(rate; up to 12 months FU) | CA=65; PN=651 retrospective cohort (Bertolo 2019/Cleveland Clinic) | Low(●●○○) | MD -4.7%P=0.2 | Postoperative complications62 per 1000 patients | Postoperative complications15 per 1000 patients |

Source: Table ES5, p22 of the ADAR

Abbreviations: CA=cryoablation; CI=confidence interval; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate; FU=follow-up; MCS=mental component score; MD=mean difference; min=minute; PCA=percutaneous cryoablation; PCS=physical component score; PN=partial nephrectomy; RN=radical nephrectomy; SF-12=Short Form-12; TA=thermal ablation

Note: outcomes shown in shading are statistically significantly in favour of CA over PN. Outcomes shown in grey text are statistically significantly in favour of RN over CA.

a GRADE Working Group grades of evidence (Guyatt et al., 2013): ●●●● **High quality:** We are very confident that the true effect lies close to that of the estimate of effect; ●●●○ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; ●●○○Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; ●○○○ Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Justification for quality of evidence gradings are provided in the source table.

## Clinical claim

### CA vs. AS/DT (main comparator 1)

The ADAR claimed that relative to AS/DT, CA has inferior safety and superior effectiveness, with an overall claim of superiority.

The Commentary considered that:

* the claim of inferior safety was not based on evidence (no evidence presented);
* the claim of superior effectiveness of TA (any modality, any mode of delivery) over AS/DT appears reasonable (Xing 2018), although the magnitude of difference in treatment benefit is uncertain (Xing 2018 excluded patients aged <66 years, potential selection bias due to non-randomised study design).

### CA vs. laparoscopic RN (main comparator 2)

The ADAR claimed that relative to laparoscopic RN, CA has superior safety and non-inferior effectiveness, with an overall claim of non-inferiority.

The Commentary considered that:

* the claim of superior safety appears reasonable though potential selection bias due to inherent limitation on study design cannot be ruled out;
* The validity of the claim of non-inferiority in effectiveness depends on validity of the claim that CA is equivalent to TA.

### CA vs. OTA (supplementary comparator 1)

The ADAR claimed that relative to other TA (RFA, MWA), CA has similar safety and non-inferior effectiveness, with an overall claim of non-inferiority.

The Commentary considered that this claim seemed acceptable, noting (a) the lack of direct randomised data comparing CA vs. RFA/MWA and (b) very limited evidence on CA (laparoscopic CA, open CA) vs. RFA (any mode of delivery).

### CA vs. PN (supplementary comparator 2)

The ADAR claimed that relative to PN, CA has superior safety and inferior effectiveness, with an overall claim of inferiority.

The Commentary considered that the overall claim of non-inferiority of CA with PN was supported by the evidence base.

# Economic evaluation

Based on clinical claims that CA has 1) inferior safety and superior effectiveness compare to AS/DT, and 2) superior safety and non-inferior effectiveness compared to laparoscopic RN, the ADAR presented two economic evaluations:

1. A cost-utility analysis comparing CA with AS/DT (main comparator 1)
2. A cost analysis comparing CA with laparoscopic RN (main comparator 2).

## CA vs. AS/DT (main comparator 1)

The economic evaluation for CA vs. AS/DT is summarised in Table 8.

**Table 8 Summary of the economic evaluation**

| **Perspective** | Australian healthcare |
| --- | --- |
| **Comparator** | AS |
| **Type of economic evaluation** | Cost-utility |
| **Sources of evidence** | Systematic review and ABS for safety and effectivenessMBS, PBS, NHCDC public cost weights, Reeve (2018) for costsMaxwell (2016) for utilities |
| **Time horizon** | 10 years in the model base case |
| **Outcomes** | Costs, Life Years, and QALYs |
| **Methods used to generate results** | Cohort expected value analysis |
| **Health states** | Alive, dead |
| **Cycle length** | 6 months |
| **Discount rate** | 5% p.a. on costs and outcomes |
| **Software packages used** | Microsoft Excel |

Source: Table 8, p22 of the Commentary
Abbreviations: ABS = Australian Bureau of Statistics, AS = active surveillance, MBS = Medicare benefits schedule, NHCDC = National hospital cost data collection, PBS = pharmaceutical benefits scheme, QALY = quality adjusted life year

The Commentary noted the following limitations with the economic model:

* CA was nominated as the delayed therapy for the comparator arm, but this was incorrect since the decision problem is whether CA is cost-effective compared with current management (AS/DT) and CA is not currently listed on the MBS.
* The types of costs included in the model were considered to be appropriate, but a detailed breakdown of CA equipment costs for laparoscopic, percutaneous, and open CA should have been provided.

The overall estimated costs and QALYs for the intervention and comparator in the model, using the base case assumptions and including the Commentary respecified base case (*italics)* to include the costs associated with RN as the delayed therapy intervention, are shown in Table 9.

**Table 9 Base case results of the economic evaluation**

|  | Cost | Incremental cost | Effectiveness (QALYs) | Incremental effectiveness | ICER |
| --- | --- | --- | --- | --- | --- |
| Cryoablation | $16,857$*16,193* |  | 5.785 |  |  |
| AS/DT | $16,942*$21,807* | -$85*-$4,901* | 5.682*5.676* | 0.104*0.110* | -$825 (dominant)*-$44,662 (dominant)* |

Source: Table 9, p23 of the Commentary. *Base case respecified so RN is the delayed therapy intervention. Updated MBS and PBS costs are included.*

Abbreviations: AS/DT = active surveillance/delayed therapy, CA = cryoablation, ICER = Incremental Cost Effectiveness Ratio, QALY = quality adjusted life year

The Commentary also noted that the results of the economic evaluation are likely to be biased since the modelled incremental effectiveness is based on a trial not applicable to the intended population. The Commentary considered that cancer-specific survival from Uhlig (2018), which compares CA and other TA with DT, may be more appropriate.

Table 10 presents the sensitivity analyses conducted by the ADAR and Commentary.

The Commentary noted that the Australian Defined diagnosis-related groups (AR-DRGs) selected for treatment of T1a RCC (≤4cm) are inappropriate and favour CA.
AR-DRG L62C (used for CA), and L62A and L62B (used for RN) are partitioned as medical DRGs which means they do not involve an operating room procedure[[24]](#footnote-24). A more appropriate DRG might be L03C (Kidney, Ureter and Major Bladder Procedures for Neoplasm, Minor Complexity) which is partitioned as a surgical DRG. The impact of applying alternate DRGs was explored in an additional sensitivity analysis (Table 10) and has a substantial effect on the ICER. The Commentary considered that the ICER presented in the ADAR does not accurately represent the cost effectiveness of CA.

**Table** **10 Sensitivity analysis of the cost utility analysis - respecified base case**

| **Analyses** | **Incremental cost** | **Incremental QALY** | **ICER** | **% change to ICER** |
| --- | --- | --- | --- | --- |
| **Base case *(respecified)*** | ***-$4,893.63*** | ***0.110*** | ***-$44,662*** | ***0%*** |
| Demographics |  |  |  |  |
| Increase age to 80 | *-$5,063.23* | *0.100* | *-$50,845* | *14%* |
| Decrease age to 70 | *-$4,793.09* | *0.115* | *-$41,560* | *-7%* |
| Discounting |  |  |  |  |
| No discounting on outcomes | *-$4,893.63* | *0.144* | *-$33,976* | *-24%* |
| No discounting on costs | *-$5,678.27* | *0.110* | *-$51,823* | *16%* |
| Undiscounted (0%) | *-$5,678.27* | *0.144* | *-$39,424* | *-12%* |
| Reduce discount to 3.5% | *-$5,119.94* | *0.119* | *-$43,159* | *-3%* |
| Time horizon |  |  |  |  |
| 7 years | *-$4,989.31* | *0.063* | *-$79,381* | *78%* |
| 5 years | *-$5,048.80* | *0.034* | *-$147,023* | *229%* |
| Efficacy |  |  |  |  |
| Use lower 95% CI for HR of AS/DT vs CA | *-$4,260.72* | *0.036* | *-$119,552* | *168%* |
| Use upper 95% CI for HR of AS/DT vs CA | *-$7,148.37* | *0.373* | *-$19,167* | *-57%* |
| Use digitised CSS curves for CA and AS/DT | *-$4,987.82* | *0.164* | *-$30,381* | *-32%* |
| Use digitised OS curves for CA and AS/DT | *-$6,145.63* | *0.562* | *-$10,935* | *-76%* |
| *Change % receiving delayed therapy to 100%* | *-$6,336.57* | *0.110* | *-$57,831* | *29%* |
| Change % receiving delayed therapy to 50% | *-$1,827.38* | *0.110* | *-$16,678* | *-63%* |
| *Change % receiving delayed therapy to 0%* | *$2,681.81* | *0.110* | *$24,475* | *-155%* |
| Change time of delayed therapy to 1.6 years | *-$5,122.75* | *0.100* | *-$51,328* | *15%* |
| Change time of delayed therapy to 5 years | *-$4,443.32* | *0.109* | *-$40,891* | *-8%* |
| Change time of delayed therapy to 7 years | *-$4,000.52* | *0.108* | *-$37,097* | *-17%* |
| *Change rate of repeat CA to 9%* | *-$4,755.51* | *0.109* | *-$43,455* | *-3%* |
| Costs |  |  |  |  |
| Remove cost of death | *-$3,983.10* | *0.110* | *-$36,352* | *-19%* |
| Halve cost of death | *-$4,438.37* | *0.110* | *-$40,507* | *-9%* |
| *Change hospital costs to surgical DRGs* | *$3,643.26* | *0.103* | *$35,444* | *-179%* |
| *Change hospital costs to private costs* | *-$5,093.09* | *0.117* | *-$43,526* | *-3%* |
| *Reduce average cost of non-urological AEs from $1000 to $0* | *-$4,812.72* | *0.110* | *-$43,923* | *-2%* |
| *Reduce average cost of non-urological AEs from $1000 to $500* | *-$4,853.17* | *0.110* | *-$44,292* | *-1%* |
| *Increase average cost of non-urological AEs from $1000 to $1500* | *-$4,934.09* | *0.110* | *-$45,031* | *1%* |
| Quality of Life |  |  |  |  |
| Background utility = 1 | *-$4,893.63* | *0.127* | *-$38,457* | *-14%* |
| Background utility = 0.7 | *-$4,893.63* | *0.089* | *-$54,939* | *23%* |
| Multivariate analyses |
| Change % receiving delayed therapy to 81%, change hospital costs to surgical DRGs | *$4,169* | *0.103* | *$40,558* | *-191%* |

Source: Table 85, p166 of the Commentary*. Base case respecified so RN is the delayed therapy intervention. Updated MBS and PBS costs are included.*

Abbreviations: AS/DT = active surveillance/delayed therapy, CA = cryoablation, CSS = cancer specific survival, DRG = diagnosis related group, AEs = adverse events, HR = hazard ratio, ICER = incremental cost effectiveness ratio, OS = overall survival, QALY = quality adjusted life year

The respecified base case is sensitive to the model time horizon, efficacy inputs from Xing (2018), the cost of hospitalisation, and the proportion of patients receiving DT (Table 11).

**Table 11 Key drivers of the economic model – *respecified base case***

| Description | Method/Value | ImpactBase case: -$44,662/ QALY gained (dominant) |
| --- | --- | --- |
| Time horizon | Reducing the time horizon increases the dominance of CA versus AS/DT. The time horizon is reasonable and may be too short. Since the clinical data was not extrapolated the impact of extending the time horizon cannot be evaluated. | Uncertain |
| Efficacy inputs from Xing (2018) | Base case applies a point estimate hazard ratio based on Xing (2018). Sensitivity analyses using the upper and lower 95% confidence intervals (CI) show that the ICER is sensitive to this parameter | UncertainUpper 95% CI = -$19,167/QALYLower 95% CI = -$119,552/QALY |
| Hospitalisation costs | Hospitalisation costs are based on AR-DRGs L62C for CA and a weighted average of L62A and L62B for RN. These are medical DRGs and should be substituted by surgical DRGs (e.g. L03C) | High, favours CAIncorporating L03C increased the ICER to +$35,444/QALY |
| Proportion receiving delayed therapy (DT) | Base case assumes 84% of patients in the comparator arm receive DT. Sensitivity analyses using alternate proportions show the ICER is sensitive to this parameter | Uncertain0% receiving DT = +$24,475/QALY100% receiving DT = -$57,831/QALY |

Source: Table 86, p169 of the Commentary

Abbreviations: AR-DRG = Australian refined diagnostic related group, CA = cryoablation, QALY = quality adjusted life year, RN = radical nephrectomy

**Redacted.**

The pre-ESC response acknowledged that Uhlig (2018) may be more applicable to the Australian setting than Xing (2018). However, the applicant claimed that the alternative
AR-DRG suggested in the Commentary (L03C) is inappropriate on the basis that it is not a good fit for the reduced invasiveness and simplicity of CA (noting that most procedures would be performed percutaneously). Further, the average length of stay for L03C (3.3 days) substantially exceeds the average length of stay for CA that was identified in the ADAR (1 day). Therefore, the applicant proposed modifying the cost of AR-DRG L03C to reflect a length of stay of 1 day, i.e. all costs except for operating room costs are divided by 3 (i.e. 3.3 days length of stay in L03C versus 1 for CA). Using this approach, the applicant proposed a hospital cost of $10,207 (indexed to $10,832) for the CA arm that contains $7,523 (indexed to $7,983) in operating room costs, which the applicant claimed is more than sufficient to cover consumable costs.

Based on the above, the applicant presented updated results to show the impact of using Uhlig 2018 on the cost-utility analysis (with and without the other changes to the model inputs suggested in the Commentary), which were verified by the assessment group and shown in Table 12. The applicant claimed CA remained cost effective even when the modified AR-DRG hospital costs and effectiveness data from Uhlig (2018) are used.

**Table 12 Original and updated results of the cost-utility analysis**

| Analysis | Effectiveness data | Costings | ICER ($/LYG) | ICER ($/QALY) |
| --- | --- | --- | --- | --- |
| 1. ADAR base case | Xing 2018 (HR) | As per ADAR | -$707 (dominant) | -$825 (dominant) |
| 2. Commentary  | Xing 2018 (HR) | Update PBS and MBS costs and use RN as DT as per Commentary suggested changes | -$40,530 (dominant) | -$44,662 (dominant) |
| 3. Commentary – modified 1 | Xing 2018 (HR) | As #2 but change AR-DRG to L03C and change LOS to 3.3 for both CA and RN | $30,676 | $36,034\* |
| 4. Commentary – modified 2 | Uhlig 2018 (HR) | As #3 but use Uhlig HR of 4.0 instead of Xing 1.45# *(0.25 CA vs DT)* | -$1,664 (dominant) | -$1,936 (dominant) |
|  |  | *As #3 but use Uhlig HR of 0.14 (lower 95% CI)* | *-$4,584 (dominant)* | *-$5,328 (dominant)* |
|  |  | *As #3 but use Uhlig HR of 0.45 (upper 95% CI)* | *$6,637* | *$7,740* |
|  |  | *As #3 but use Uhlig HR of 0.60 (comorbidity-adjusted)* | *$18,311* | *$21,429* |
| 5. Response – modified 1 | Xing 2018 (HR) | As #3 (but hospitalisation costs and LOS adapted as per Issue 4 below) | -$17,579 (dominant) | -$19,610 (dominant) |
| 6. Response – modified 2 | Uhlig 2018 (HR) | As #5 but use Uhlig HR of 4.0 instead of Xing 1.45# | -$8,902 (dominant) | -$10,276 (dominant) |
| 7. Response – modified 2 | Uhlig 2018 (HR) | As #6 but change DT to 81% from 84% | -$8,246 (dominant) | -$9,517 (dominant) |

Source: Table 2, p3 of the pre-ESC response. *The values presented in the table were verified by the assessment group.*

Abbreviations: ADAR=Applicant Developed Assessment Report; AR-DRG=Australian Refined Diagnosis Related Groups; DT=delayed therapy; HR=indicates hazard ratio methodology used, i.e. the digitised curves were not used; ICER=incremental cost-effectiveness ratio; LOS=length of stay; LYG=incremental life-year gained; QALY=quality adjusted life year
\* Critique reported $35,444. Incremental QALYs are identical at 0.103 but costs differ slightly at $3,643 in the critique vs $3,704 in this response
# The CA arm is unchanged, just the AS/DT arm changes.

In the pre-MSAC response, the applicant respecified the baseline population in the economic model by updating Analysis 7 from Table 12 to use age and gender from Uhlig 2018. The result indicated that the ICER ($/QALY) changes from -$9,517 (dominant) to -$8,669 (dominant). The difference in discounted costs reduces by 2% to a -$6,496 saving (from -$6,637) and the difference in discounted QALYs increases by 7% to 0.749 (from 0.697).

## CA vs. laparoscopic RN (main comparator 2)

The ADAR acknowledged that based on a clinical claim of non-inferior effectiveness and superior safety of CA compared to laparoscopic RN, a cost-utility analysis is the preferred economic evaluation. However, the ADAR claimed that despite the safety advantage, the clinical evidence did not detect a statistically significant difference in quality of life between the two interventions, making any attempt to quantify the benefit of a reduction in AEs subject to uncertainty. Therefore, the ADAR presented a cost analysis, quantifying the cost offsets associated with resources used to treat adverse events as well as the costs of providing the index procedure, for the economic evaluation of CA versus laparoscopic RN.

The cost analysis is summarised in Table 13.

**Table 13 Summary of the economic evaluation (cost analysis)**

| **Perspective** | Australian healthcare |
| --- | --- |
| **Comparator** | Radical nephrectomy (RN) |
| **Type of economic evaluation** | Cost analysis |
| **Sources of evidence** | Systematic review and ABS for safety and effectivenessMBS, PBS, NHCDC public cost weights for costsRowley (2011) for conversion from laparoscopic to open RN |
| **Time horizon** | One year |
| **Outcomes** | Costs, adverse events |
| **Methods used to generate results** | Trial-based |
| **Discount rate** | Not applicable |
| **Software packages used** | Microsoft Excel |

Source: Table 11, p25 of the Commentary
Abbreviations: RN = radical nephrectomy

The Commentary noted that the clinical claim of non-inferior effectiveness is primarily based on clinical evidence derived from Xing (2018). As noted for the economic evaluation of CA vs. AS/DT, the population and comparator in Xing (2018) are not representative of the scenario for which MBS listing of cryoablation is sought. As such, the Commentary considered that the results of the economic evaluation are uncertain.

The ADAR predicted the overall cost of treatment with CA as $4,625, compared with $11,280 for RN (Table 14). This translates to a cost saving of $6,655 per patient per course of treatment. The base case was respecified to include current MBS and PBS costs. This resulted in an estimated cost saving of $6,657 per patient per course of treatment.

**Table 14 Results of the cost analysis of cryoablation versus radical nephrectomy – respecified base case**

|  | **Cryoablation** | **Radical Nephrectomy** | **Difference****(CA – RN)\*** |
| --- | --- | --- | --- |
| **Costs associated with the performance of the procedure** |
| Professional attendance (initial specialist) | *$89.55* | *$89.55* | *$0.00* |
| Professional attendance (subsequent specialist) | *$46.80* | *$45.00* | *$1.80* |
| Pre-treatment pathology | *$23.14* | *$22.25* | *$0.89* |
| Pre-treatment imaging - CT | *$380.02* | *$365.40* | *$14.62* |
| Biopsy | *$177.90* | *$177.90* | *$0.00* |
| Pre-anaesthesia consultation and General anaesthesia | *$64.74* | *$249.00* | *-$184.26* |
| Local Anaesthesia | *$26.61* | *$0.00* | *$26.61* |
| Procedure | *$876.30* | *$1,069.42* | *-$193.12* |
| Medication use peri-procedure | *$69.32* | *$66.65* | *$2.67* |
| Hospitalisation | $1,411.21 | $7,137.93 | -$5,726.72 |
| **Subtotal** | ***$3,165.59*** | ***$9,223.11*** | ***-$6,057.52*** |
| **Costs associated with monitoring or surveillance** |
| Blood tests - renal function | *$35.40* | *$35.40* | *$0.00* |
| Professional attendances (subsequent specialist) | *$90.00* | *$90.00* | *$0.00* |
| Imaging - ultrasound | *$225.90* | *$0.00* | *$225.90* |
| Imaging – CT | *$36.54* | *$0.00* | *$36.54* |
| **Subtotal** | ***$387.84*** | ***$125.40*** | ***$262.44*** |
| **Costs associated with the management of adverse events or complications** |
| Move from laparoscopic to open (Nb. cost difference) | $0.00 | $102.86 | -$102.86 |
| Non-urological (within 30 days) | $124.80 | $270.00 | -$145.20 |
| Acute renal failure (within 30 days) | $300.01 | $576.94 | -$276.93 |
| Renal insufficiency (31-365 days) | $673.10 | $1,009.65 | -$336.55 |
| **Subtotal** | ***$1,097.91*** | ***$1,959.45*** | ***-$861.54*** |
| **Total Health care cost to the Australian Government** | **$4,651.34** | **$11,307.96** | **-$6,656.62** |

Source: Table 91, p179 of the Commentary. *Base case respecified to include updated MBS and PBS costs.*
Abbreviations: CA = cryoablation, RN = radical nephrectomy, \* a number less than zero means cryotherapy is less expensive than radical nephrectomy

The ADAR presented univariate sensitivity analyses on all variables using plausible extremes and multivariate sensitivity analyses combining variables from the univariate analyses. As noted for the cost utility analysis versus AS/DT, the AR-DRGs selected for treatment of T1a RCC (≤4cm) are inappropriate and favour CA. The impact of applying alternate DRGs was explored in sensitivity analysis and has a substantial impact on the result (Table 15). The Commentary therefore considered that the cost savings presented do not accurately represent the costs of listing CA.

**Table 15 Sensitivity analysis of the cost analysis - respecified base case**

| Analyses | Cryoablation | Radical Nephrectomy | Difference |
| --- | --- | --- | --- |
| *Base case (respecified)* | *$4,651.34* | *$11,307.96* | *-$6,656.62* |
| Univariate |  |  |  |
| Identical hospitalisation costs (lower RN to $1,356.93 from $7137.93) | $4,651.34 | $5,526.96 | -$875.62 |
| Reduce average costs for non-urological AEs from $1000 to $0 | $4,651.34 | $11,307.96 | -$6,656.62 |
| Reduce average costs for non-urological AEs from $1000 to $500 | $4,588.94 | $11,172.96 | -$6,584.02 |
| Increase average costs for non-urological AEs from $1000 to $1500 | $4,713.74 | $11,442.96 | -$6,729.22 |
| Remove difference in renal insufficency AE, i.e. both groups = cryo rate | $4,651.34 | $10,971.41 | -$6,320.07 |
| *Use Surgical DRGs* | *$20,331.77* | *$20,683.85* | *-$352.08* |
| Multivariate |  |  |  |
| Identical hospitalisations and reduce average costs for non-urological AEs to $500 | $4,588.94 | $5,391.96 | -$803.02 |
| Identical hospitalisations and reduce average costs for non-urological AEs to $500 plus identical renal insufficiency rates | $4,588.94 | $5,055.41 | -$466.47 |

Source: Commentary respecified section D workbook*. Base case respecified to include updated MBS and PBS costs.*

Abbreviations: AS/DT = active surveillance/delayed therapy, CA = cryoablation, CSS = cancer specific survival, DRG = diagnosis related group, AEs = adverse events, HR = hazard ratio, ICER = incremental cost effectiveness ratio, OS = overall survival, QALY = quality adjusted life year

Overall, the main driver of the cost difference is higher hospitalisation costs associated with RN (Table 16).

**Table 16 Key drivers of the economic model - *respecified base case***

| Description | Method/Value | ImpactBase case: -$6,657 |
| --- | --- | --- |
| Hospitalisation costs | Base case assumes different hospitalisation costs for CA and RN. Applying identical hospitalisation costs for CA and RN has a significant impact on the result | High, favours CA,Equal hospitalisation costs increase the cost to -$876 |
| Hospitalisation costs are based on AR-DRGs L62C for CA, a weighted average of L62A and L62B for laparoscopic RN and L62A for open RN. *These are medical DRGs and should be substituted for surgical DRGs (e.g. L03C)* | *High, favours CAIncorporating L03C for CA and laparoscopic RN and L03B for open RN increased the cost to -$352* |

Source: Table 12, p25 of the ADAR. *Commentary in italics*
Abbreviations: AR-DRG = Australian refined diagnostic related group, CA = cryoablation, RN = radical nephrectomy

# Financial/budgetary impacts

The ADAR employed an epidemiological approach to estimate the impact of providing CA to Australians with confirmed T1a RCC by substituting CA for AS/DT, laparoscopic RN regimen and privately funded RFA/MWA. The financial implications to the MBS resulting from the proposed listing of CA are summarised in Table 17. The ADAR estimated CA listing would incur an MBS cost $106,803 in Year 1 and an overall cost over five years of $382,782.

The Commentary noted that it was not clear how the applicant estimated MBS costs for CA and laparoscopic RN, nor what proportion of patients would avail these services in inpatient and outpatient settings, or as private and public patients. Inpatient services are assumed to attract a 75% MBS rebate and costs are updated in the Commentary to rebate proportions (Table 17). The respecified analysis estimated $42,565 in MBS costs in Year 1, while a saving of -$28,032 is realised in Year 5. The overall 5-year net MBS cost (respecified) is estimated to be $78,553 under this scenario.

**Table 17 Total costs to the MBS associated with listing CA**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Description** | **2021** | **2022** | **2023** | **2024** | **2025** |
| **Submission** |  |  |  |  |  |
| MBS costs of CA | $287,795 | $344,029 | $399,072 | $453,054 | $505,945 |
| Change in MBS Costs (AS/DT + RN) | -$180,992 | -$227,188 | -$272,372 | -$453,612 | -$472,950 |
| **Net Impact to MBS** | **$106,803** | **$116,841** | **$126,700** | **-$558** | **$32,996** |
| ***Commentary*** |  |  |  |  |  |
| *MBS costs of CA* | *$174,462* | *$208,782* | *$242,374* | *$275,317* | *$307,595* |
| *Change in MBS Costs (AS/DT + RN)* | *-$131,897* | *-$160,949* | *-$189,375* | *-$312,129* | *-$335,627* |
| ***Net Impact to MBS*** | ***$42,565*** | ***$47,833*** | ***$52,999*** | ***-$36,812*** | ***-$28,032*** |

Source: Table 13, p26 of the Commentary. *Commentary in italics*

Abbreviations: AS/DT=active surveillance/delayed therapy; CA=cryoablation; MBS=Medicare benefits Schedule; RN=radical nephrectomy

The ADAR included sensitivity analyses for uptake of CA (Table 18). Increasing uptake to 100% from 50%, had the largest impact on costs. Additional sensitivity analyses included in the Commentary relating to proportion of kidney cancer cases <=4cm and % malignant did not have a large impact on net MBS costs. The largest uncertainties are in the assumptions used in the ADAR to estimate MBS unit costs for CA and comparators (compared to the estimates presented in the Commentary) and proportion of AS being treated with RN.

**Table 18 MBS net impact sensitivity analysis**

| **Uncertainty analysis** | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| **Net Impact to MBS** | **2021** | **2022** | **2023** | **2024** | **2025** |
| Base case | $106,803 | $116,841 | $126,700 | -$558 | $32,996 |
| **Changed Uptake** |  |  |  |  |  |
| Reduce uptake to 25% from 50% | $53,401 | $58,421 | $63,350 | -$279 | $16,498 |
| Increase uptake to 75% from 50% | $160,204 | $175,262 | $190,050 | -$838 | $49,494 |
| Increase uptake to 100% from 50% | $213,606 | $233,682 | $253,401 | -$1,117 | $65,991 |
| ***Commentary*** |  |  |  |  |  |
| *Base case* | *$42,565* | *$47,833* | *$52,999* | *-$36,812* | *-$28,032* |
| *Proportion of kidney cancer <=4cm, 43%* | *$46,821* | *$52,616* | *$58,299* | *-$40,493* | *-$30,835* |
| *Kidney cancer* growth rate (5%) | *$42,565* | *$49,995* | *$55,429* | *-$34,120* | *-$25,082* |
| *67% malignant*  | *$38,800* | *$43,603* | *$48,312* | *-$33,556* | *-$25,553* |
| *80% malignant.* | *$46,329* | *$52,063* | *$57,686* | *-$40,067* | *-$30,511* |
| *50% AS treated with RN in Year 3* | *$42,565* | *$47,833* | *$52,999* | *$1,596* | *$8,840* |
| *75% AS treated with RN in Year 3* | *$42,565* | *$47,833* | *$52,999* | *-$26,645* | *-$18,272* |
| *100% AS treated with RN in Year 3* | *$42,565* | *$47,833* | *$52,999* | *-$54,886* | *-$45,383* |

Source: Table 108, p195 of the Commentary. *Commentary in italics*

Abbreviations: MBS=Medicare benefits Scheme; RN=radical nephrectomy

The total government impact (MBS, PBS, and State Hospital) of CA listing is presented in Table 19, which the ADAR estimated to generate savings of -$228,516 over 5-years However, when the amended MBS rebate and DRG costs are included and budget impact recalculated, an overall government saving of -$697,000 over 5-years is estimated. The Commentary cautioned that these results are uncertain as it is unclear who would bear hospital costs, and there are differences in CA and comparator MBS unit costs.

**Table 19 Total impact to Government health budgets**

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** | **5-year impact** |
| --- | --- | --- | --- | --- | --- | --- |
| **Description** | **2021** | **2022** | **2023** | **2024** | **2025** |  |
| **Submission** |  |  |  |  |  |  |
| MBS | $106,803 | $116,841 | $126,700 | -$558 | $32,996 | $382,782 |
| PBS | $8,266 | $8,379 | $8,494 | $3,558 | $3,881 | $32,578 |
| State Hospital | $134,588 | $134,400 | $134,297 | -$537,046 | -$510,115 | -$643,876 |
| **Net Impact** | **$249,657** | **$259,620** | **$269,491** | **-$534,046** | **-$473,238** | **-$228,516** |
| ***Commentary*** |  |  |  |  |  |  |
| *MBS* | *$42,565* | *$47,833* | *$52,999* | *-$36,812* | *-$28,032* | *$78,553* |
| *PBS* | *$10,740* | *$10,857* | *$10,977* | *$4,219* | *$4,623* | *$41,416* |
| *State Hospital* | *$77,897* | *$74,579* | *$71,387* | *-$530,784* | *-$509,763* | *-$816,684* |
| ***Net Impact*** | ***$131,202*** | ***$133,268*** | ***$135,363*** | ***-$563,377*** | ***-$533,172*** | ***-$696,715*** |

Source: Table 107, p of the Commentary. *Commentary in italics*

Abbreviations: MBS=Medicare Benefits Schedule; PBS=Pharmaceutical Benefits Schedule

# Key issues from ESC for MSAC

| ESC key issue | ESC advice to MSAC |
| --- | --- |
| Evidence – other TA as proxy for CA | Due to the paucity of comparative studies of CA vs the main comparators (AS/DT or RN), studies that reported the use of other TA (i.e. RFA or MWA) were used as a proxy for CA [CA(TA)]. This approach was supported by results of the supplementary comparison between CA and other TA modalities, which suggests there are no differences in safety or effectiveness between the different modalities. |
| Applicability of study populations to the Australian population | ESC considered that the population in Uhlig 2018 was more applicable to the Australian MBS population than Xing 2018 which was applied in the ADAR economic analysis. ESC noted that the pre-ESC response had addressed this by applying the data from Uhlig 2018 but without re-specifying the baseline population in economic model. |
| Costs of equipment and consumables | The ADAR did not include the capital cost of the equipment or the cost of CA needles, but that these were included in the pre-ESC response. However, ESC considered that it remained unclear who would bear the cost of the CA needles ($**redacted** per procedure), and whether there was potential for significant out-of pocket costs for patients.  |
| Item descriptor – eligibility  | The proposed item descriptor does not explicitly require a patient to have a confirmed renal malignancy prior to ablation. ESC considered that the item descriptor should be amended to “where malignancy has been previously confirmed by histopathological examination”.  |
| Item descriptor – CA only or general item for CA, RFA and MWA | MSAC may wish to consider whether MBS listing for CA should be broadened to also include RFA and MWA, as a general item for ablative procedures of the kidney.  |
| Item descriptor - technical note | ESC considered that ‘hereditary/multiple RCC’ should be removed from the technical note as this is inconsistent with the item descriptor for CA for ‘localised primary malignant tumour’. ESC considered that the applicant proposal to include “tumour of significant complexity not amendable to PN” in the technical note was not supported by any evidence. |
| Item descriptor - mode of delivery of treatment | ESC noted the item descriptor and clinical evidence base included CA of any delivery mode (i.e. percutaneous, laparoscopic or open). ESC considered it was reasonable to use data based on a mix of percutaneous and laparoscopic CA procedures to estimate the comparative effectiveness and safety of percutaneous CA, but noted that the evidence presented for the T1a RCC population was very limited. MSAC may wish to consider whether more data are needed to clarify whether these outcomes are similar. |
| Item descriptor - Inadequate justification of the proposed MBS fee | The proposed fee ($842.60) is benchmarked to the MBS fees for CA, RFA and MWA of the liver. ESC considered that surgical advice should be sought to assess the validity of this comparison in terms of relative complexity of procedures.  |

**ESC discussion**

ESC noted the purpose of the application was to request MBS listing for CA for the treatment of biopsy-confirmed RCC ≤4 cm in patients not suitable for PN.

ESC noted consultation feedback supported MBS listing of CA in the proposed population and claimed potential advantages of CA to consumers.

The two main comparators presented in the application were AS/DT and laparoscopic RN. ESC noted that OTA and PN were included as supplementary comparators in the ADAR for clinical comparison only. ESC noted the proposed clinical management algorithms, and considered that some patients who are suitable for PN or AS/DT may prefer a non-surgical intervention such as CA, which may result in use outside the MBS item descriptor

ESC noted that the clinical evidence base consisted of 39 cohort studies, but that there were no direct comparative studies to inform the comparison of CA with the main comparators (AS/DT and laparoscopic RN). ESC noted that, due to the paucity of comparative studies of CA vs AS/DT or RN, the intervention in the application was expanded to include thermal ablation (TA – that is RFA or MWA as a proxy for CA). The appropriateness of this was explored through the comparison of CA *vs.* OTA (supplementary comparator 1).

Six cohort studies (CA k=2; CA+TA k=1; TA k=3) informed the comparison of CA *vs.* AS/DT (main comparator 1). ESC noted the claim that CA had inferior safety compared to AS/DT was based on the argument that all patients treated with CA are at risk of intervention-related AE, whereas not all patients on AS/DT are at risk of intervention-related AE (following DT) as a proportion of patients on AS would never receive DT. The claim that CA had superior clinical effectiveness over AS/DT was based on evidence suggesting that CA(TA) had significantly lower all-cause and cancer-specific mortality, no impact on renal function and no significant difference in quality of life.

ESC noted seven cohort studies (CA k=1; TA k=6) informed the comparison of CA *vs.*laparoscopic RN (main comparator 2). ESC noted the claim that CA has superior safety compared to laparoscopic RN was based on observations that acute renal failure and non-urological complication rates were lower for CA(TA) than for RN. The claim CA had non-inferior clinical effectiveness compared to laparoscopic RN was based on evidence that CA(TA) was similar to RN in oncological outcomes, all-cause and cancer-specific mortality, and quality of life.

ESC noted 21 cohort studies informed the comparison of CA *vs.* OTA (RFA and/or MWA; supplementary comparator 1). ESC noted the difficulty in comparing the safety of CA *vs.* OTA due to differences in patient and disease characteristics between studies. However, the evidence suggested there was little difference in the complication rates between percutaneous CA and percutaneous RFA/MWA and therefore claimed to have similar safety. CA was claimed to have non-inferior clinical effectiveness compare to OTA, based on evidence that there was no significant difference in cancer-specific or overall mortality and no significant difference in local recurrence-free survival. ESC noted that the results of the supplementary comparison between CA and OTA, which suggests no differences in safety or effectiveness between the different modalities, supported the use of TA as a proxy for CA.

ESC noted 12 cohort studies informed the comparison of CA *vs.* PN (supplementary comparator 2). ESC noted the evidence on comparative safety was of low quality but that CA was claimed to have superior safety compared to PN based on findings that minor post-operative complications occurred more frequently following PN than CA and that there was no significant difference in major complications. CA was claimed to have inferior clinical effectiveness compared to PN based on significantly higher overall mortality and cancer-specific mortality rates in CA patients. ESC noted this comparison supports the clinical positioning of CA as a treatment option only for patients who are not suitable for PN.

ESC noted the applicant proposed MBS item descriptor and agreed with the Commentary’s proposal that “where malignancy is confirmed by histopathological examination” be changed to “where malignancy has previously been confirmed by histopathological examination”. ESC noted that the proposed fee was based on similar MBS items for ablative techniques of the liver; however, ESC considered that surgical advice should be sought to assess the validity of this comparison.

ESC noted conflicting terminology between the item descriptor for ‘localised primary malignant tumour’ and the accompanying technical note that suggests “patients who are not suitable for PN” includes people with hereditary/ multiple RCC. As such, ESC proposed that hereditary/ multiple RCC be removed from the technical note. ESC also noted that the applicant sought to include “tumour of significant complexity not amendable to PN” in the technical note. ESC considered that patients with multiple or complex lesions may be more appropriately treated with RN than PN as noted in international clinical guidelines[[25]](#footnote-25); however, evidence to support the use of CA in tumours of significant complexity not amenable to PN was not presented in the ADAR.

ESC noted that CA is recommended alongside RFA or MWA in international clinical practice guidelines, but RFA and MWA are not currently MBS listed. Given the evidence suggests there is no difference in safety and effectiveness between the different TA modalities, ESC agreed with the applicant’s proposal that MSAC may wish to consider whether for the proposed MBS item for CA should be broadened to also include TA, as a general item for ablative procedures of the kidney.

ESC noted the item descriptor and clinical evidence base included CA of any delivery mode (i.e. percutaneous, laparoscopic or open). This was based on the applicants claim that the evidence suggested there was no difference in outcomes for patients receiving percutaneous versus laparoscopic CA, other than operative outcomes such as length of stay (shorter for percutaneous) and incomplete ablation (higher for percutaneous). ESC considered it was reasonable to use data based on a mix of percutaneous and laparoscopic CA procedures to estimate the comparative effectiveness and safety of percutaneous CA, but noted that the evidence presented for the T1a RCC population was very limited. ESC advised MSAC that it may wish to consider whether more data are needed to clarify these outcomes.

ESC reviewed the economic evaluation, comprising a cost-utility analysis comparing CA *vs.* AS/DT (main comparator 1) and a cost analysis comparing CA *vs.* laparoscopic RN (main comparator 2). Regarding the cost-utility analysis for CA *vs.* AS/DT, ESC noted CA was dominant to AS/DT even when the base cases was respecified to correctly include RN as the DT (and updated MBS/PBS fees). ESC noted that the drivers of the model were hospital costs and the proportion patients who received DT. ESC agreed with the Commentary that the applicability of results from Xing 2018 (primary source for model) to the proposed MBS population was uncertain, given the Xing 2018 assessed TA, rather than CA alone, and only in patients aged ≥66 years. ESC noted the Commentary considered that Uhlig 2018 (a study that assessed cryosurgery in patients with histologically confirmed T1a RCC and aged ≥18 years) was a more appropriate study. ESC noted that the applicant attempted to address the applicability issues through the pre-ESC response, which provided justification for using Xing 2018 but also provided revised ICERs using hazard ratios from Uhlig 2018. ESC noted that the revised ICERs using Uhlig 2018 indicated CA remains dominant but that this only partially resolved issues with the model as the baseline population in the model was not respecified to better reflect the proposed MBS population.

ESC discussed model issues including hospital costs, the exclusion of capital costs of the CA machine, and the claim that the costs of consumables (i.e. CA needles) would be covered under the hospital costs. ESC noted the Commentary’s assertion that the ADAR had incorrectly applied a medical AR-DRG[[26]](#footnote-26) instead of a surgical AR-DRG, and noted that the medical AR-DRG applied would not cover the costs of consumables. ESC noted that the pre-ESC response confirmed the capital equipment and consumables costs, and provided revised ICERs using updated hospital costs. However, ESC noted that the consumable costs would make up a significant proportion of the hospital costs and considered that it remained unclear who would bear the cost of the CA needles. ESC considered there was potential for cost-shifting resulting in significant out-of-pockets costs for patients, particularly if performed on outpatient basis.

Regarding the cost analysis for CA *vs.* laparoscopic RN, ESC considered that the economic evaluation used simplistic modelling that did not fully account for the negative health impacts of RN. ESC noted that CA appeared cost saving over one year but as with the CUA for CA *vs.* AS/DC. ESC noted that the cost analysis of CA *vs.* laparoscopic RN has the same issues with hospital and consumable costs as the CUA of CA *vs.* AS/DT. ESC noted that when the cost analysis was respecified (in the Commentary and pre-ESC response) to apply a more appropriate hospital cost, the cost-saving with CA is reduced but still less expensive than laparoscopic RN. However, the potential for significant out-of-pockets costs for patients remained.

ESC noted that the budget projections in the ADAR did not account for the fact that many small renal masses are “incidentalomas” (asymptomatic lesions detected when individuals undergo imaging for other reasons); however, the requirement for histological confirmation of RCC would mean that this would not lead to inappropriate treatment. ESC noted that the financial estimates were based solely on the use of CA and that if the MBS item descriptor was broadened to include all ablative techniques, the financial analysis may need to be revised.

# Other significant factors

Nil

# Applicant comments on MSAC’s Public Summary Document

The applicant had no comment.

# Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](http://www.msac.gov.au/)

1. Population, Intervention, Comparator, Outcomes [↑](#footnote-ref-1)
2. Kidney cancer in Australia statistics, Cancer Australia, Australian Government, page updated: 7 July 2020 [available: <https://kidney-cancer.canceraustralia.gov.au/statistics>; accessed 17 July 2020]. [↑](#footnote-ref-2)
3. Data tables: Cancer data in Australia – Book 2 Mortality supplementary tables, AIHW, June 2020 [available: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>; accessed 17 July 2020]. [↑](#footnote-ref-3)
4. Data tables: Cancer data in Australia – Book 1: Incidence supplementary tables, AIHW, June 2020 [available: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>; accessed 17 July 2020]. [↑](#footnote-ref-4)
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6. Kidney cancer, Cancer Council Victoria [available: <https://www.cancervic.org.au/cancer-information/types-of-cancer/kidney_cancer/kidney-cancer-overview.html>; accessed 17 July 2020]. [↑](#footnote-ref-6)
7. Summarised in Appendix 2 of [MSAC 1597 ratified PICO confirmation](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1597-public); American Society of Clinical Oncology (ASCO) Clinical Practice Guideline for SRMs (Finelli 2017), American Urological Association (AUA) Guideline for renal mass and localized renal cancer (Campbell 2017), Canadian Urological Association (CUA) Guideline for SRM (Jewett 2015), Europe Association of Urology (EAU) Guidelines on RCC 2019 update (Ljungberg 2019), European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for RCC (Escudier 2019), NCCN Clinical Practice Guidelines in Oncology for Kidney Cancer (Jonasch 2019). [↑](#footnote-ref-7)
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11. Surveillance, Epidemiology and End Results (SEER) [↑](#footnote-ref-11)
12. Uhlig, A. et al. (2018). CardioVascular and Interventional Radiology 41(2): 277-283. [↑](#footnote-ref-12)
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16. Talenfeld, A. D. et al . (2018). Annals of Internal Medicine 169(2): 69-78. [↑](#footnote-ref-16)
17. Kowalczyk, K. J. et al. (2013). BJU International 112(4): E273-E280. [↑](#footnote-ref-17)
18. Moskowitz, D. et al. (2016). Journal of Urology 196(4): 1000-1007. [↑](#footnote-ref-18)
19. Choueiri, T. K. et al. (2011). Urology 78(1): 93-98. [↑](#footnote-ref-19)
20. National Cancer Database (NCDB) [↑](#footnote-ref-20)
21. De Cobelli, F. et al. (2020). CardioVascular and Interventional Radiology 43(1): 76-83. [↑](#footnote-ref-21)
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24. AIHW, Australian refined diagnosis-related groups (AR-DRG) data cubes user guide, <https://www.aihw.gov.au/reports/hospitals/ar-drg-data-cubes/contents/user-guide> 23-May-2019, accessed 23-Jul-2020 [↑](#footnote-ref-24)
25. [National Comprehensive Cancer Network (NCCN) 2019 Clinical Practice Guidelines in Oncology](https://www.nccn.org/professionals/physician_gls/default.aspx#site) and American Society of Clinical Oncology (ASCO) Clinical Practice Guideline 2017 [Finelli, A. et al. (2017) Journal of Clinical Oncology. 35(6): 668-680]. [↑](#footnote-ref-25)
26. Australian refined diagnosis-related groups (AR-DRG) [↑](#footnote-ref-26)