Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1403 – Lung Microwave Tissue Ablation

Applicant: **N.Stenning & Co. Pty Ltd**

Date of MSAC consideration: **MSAC 68th Meeting, 24-25 November 2016**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application and links to other applications

An application requesting new Medicare Benefits Schedule (MBS) listings of microwave tissue ablation (MTA) for the treatment of primary and secondary lung cancer was received by the Department of Health from N. Stenning & Co. Pty Ltd.

2. MSAC's advice to the Minister

After considering the strength of the available evidence presented in relation to the comparative safety, clinical effectiveness and cost-effectiveness of microwave tissue ablation (MTA) for primary and secondary lung cancer, MSAC did not support public funding due to a lack of evidence to support the comparative benefit of the procedure.

MSAC was concerned that the majority of evidence presented for MTA and its comparators consisted largely of case series studies which resulted in significant uncertainty about the comparative benefit of MTA over existing treatment options. MSAC emphasised that unlike Application 1402 (MTA for the liver) where radiofrequency ablation (RFA) was the only comparator and is MBS-listed, the proposed populations in the current application have access to radiotherapy such as stereotactic body radiation therapy (SBRT) and RFA, although the latter is not MBS-listed.

MSAC noted that any resubmission should include comparative evidence of efficacy compared to radiation therapy (e.g. SBRT) and/or surgery. MSAC also noted that any future application would require consideration by ESC.

3. Summary of consideration and rationale for MSAC's advice

MTA for primary and secondary lung cancer involves the positioning of antennae within tumours through which high frequency electromagnetic waves are emitted, destroying nearby tissue. It can be performed percutaneously or via open or laparoscopic surgery. The applicant proposed that the service would be performed by interventional radiologists, with curative or

palliative intent, in eligible patients. MSAC noted that MTA is not currently reimbursed under the MBS for lung tumours.
MSAC noted that the application included three distinct populations:

- patients with early stage non-small cell lung cancer (NSCLC) who are not eligible for surgical resection and who are receiving treatment with curative intent (population one);
- patients with pulmonary metastases in whom the primary tumour is under control and who are receiving treatment with curative intent (population two); and
- patients with NSCLC or pulmonary metastases who are receiving treatment with palliative intent (population three).

MSAC noted that for populations one and two, MTA would directly replace radiofrequency ablation (RFA) therapy and act as an additional therapeutic option to current best practice radiotherapy (e.g. stereotactic body radiation therapy [SBRT]) ± chemotherapy. For population two, MTA was also considered to be an additional therapeutic option to surgical resection. MSAC highlighted that although the applicant proposed that MTA would replace RFA, there is currently no MBS item for lung RFA.

MSAC noted that for population three, the applicant proposed that MTA would be an additional treatment option to conventional palliative therapies. However MSAC highlighted that MTA would be an unlikely choice for palliative therapy based on current clinical practice, noting that approximately 90% of lung MTA services provided in Australia are for early stage NSCLC (population one) and 10% are used in patients with oligometastatic disease (population two).

MSAC noted that the requested funding was for six new MBS items with graduated fees according to the number of lesions to be ablated and whether the service was to be provided with curative or palliative intent. MSAC noted that the proposed fees were based on those provided in Application 1402 (MTA of liver tumours). MSAC questioned these fees in light of the current flat fee for MBS-listed RFA for liver tumours, both percutaneous (MBS item 50950) and open/laparoscopic (MBS item 50952), and the applicant's claim that MTA has a faster ablation time than RFA which would result in less time spent overall in the radiology suite and may impact on the cost of the procedure.

In its consideration of the evidence provided to support the comparative safety and efficacy of MTA, MSAC noted that no studies which directly or indirectly compared the procedure to a relevant comparator were identified for any of the proposed populations. MSAC indicated that subsequent attempts by the assessment group to identify comparative data for RFA, which is technologically similar to MTA and could have potentially informed decisions about the procedure, against SBRT and/or surgical resection also did not yield any results. Therefore, MSAC considered the data presented for each intervention but noted that no conclusions regarding their comparative safety or effectiveness could be made. MSAC noted that this data was largely derived from case series studies with small sample sizes, variable outcome measures, incomplete reporting and high risk of bias. MSAC summarised that this resulted in significant uncertainty in the clinical evidence which was noted throughout its consideration of the data presented. MSAC noted that the ongoing NCT02455843 and NCT02673021 clinical trials may provide relevant information for consideration in the future.

MSAC noted that the evidence presented on the safety of MTA indicated that procedure-related mortality and serious adverse events were rare, with pneumothorax the most commonly reported adverse event.

When considering the evidence presented to support the comparative effectiveness of MTA, MSAC reiterated that no comparative studies were identified to inform such an assessment.

Hence, MSAC noted that the applicant's claim of non-inferiority for the comparative effectiveness of MTA compared to current best practice radiotherapy, RFA or surgery remained untested by published evidence.

MSAC concluded that: in population one, MTA has uncertain safety and effectiveness compared to RFA and current best practice radiotherapy ± chemotherapy; in population two, MTA has uncertain safety and effectiveness compared to RFA and current best practice radiotherapy ± chemotherapy and may have superior procedure-related mortality and uncertain effectiveness compared to surgery; and in population three, MTA has uncertain safety and effectiveness compared to best supportive therapy.

MSAC considered the applicant's claim that MTA may be convenient for patients in rural or remote areas, but noted that the strength of this argument was diminished given the availability of alternatives such as SBRT which can be rapidly performed and is MBS funded.

MSAC reviewed the economic evaluation and acknowledged the use of a cost-minimisation approach in light of the uncertain clinical benefit of the proposed intervention. MSAC noted that the analysis presented the total average costs for MTA, SBRT and surgery as a cost per patient over 3 months of treatment according to the proposed population and the number of lesions to be ablated. MSAC noted that as MTA is not currently used for palliative therapy in Australia, population three was not considered in the analysis. MSAC noted that SBRT was consistently the least costly intervention, followed by MTA and then surgery. MSAC considered that the key drivers of MTA costs were the fees for the disposable applicator used during the procedure ($2,960) and overnight hospital stay ($873). MSAC reiterated the concern raised by ESC that the cost of the additional optimal temperature probe for the procedure ($960) had not been included in the economic analysis.

MSAC noted that the projected net cost to the MBS of listing MTA for primary and secondary lung cancer was $614,715 in the first year, increasing to $3,406,068 in the fifth year of listing. MSAC acknowledged that cost-savings were expected as MTA would largely replace SBRT which has a higher MBS rebate. However, MSAC was concerned about additional costs associated with the proposed MTA service which are likely to be borne by private health funds, hospitals or patients, particularly the costs associated with the probes for the procedure. MSAC also considered that the cost of lung MTA is likely to be affected by the choice of treatment modality, particularly whether it is performed as an inpatient or outpatient procedure and whether it is delivered with general or local anaesthetic.

4. Background

MSAC has not previously considered MTA.

5. Prerequisites to implementation of any funding advice

The application refers to the Acculis MTA System with a single use microwave applicator, which is registered to be used in Australia with N Stenning and Co Pty Ltd as the sponsor. In addition to the Acculis MTA system, there are three additional MTA systems currently available in Australia.

6. Proposal for public funding

The application requests the listing of six new 'Category 3 – Therapeutic Procedures' items on the MBS (Table 1).

The proposed items are graduated based on the number of ablated lesions, and are intended to cover the cost of pre-, intra- and post-operative imaging. This includes a limited planning scan, intra-operative image guidance, and a post-ablation control scan. The proposed fee has been adopted from Application 1402 (MTA of liver tumours).

Application 1402 states:

> *"A $1300 fee for ablation of 2–3 lesions, a $1600 fee for ablation of 4–5 lesions and a $2000 fee for ablation of >5 lesions. The higher fee for >5 lesions reflects the increased risk to the patients such as collateral damage as well as more skill, time and expertise required of the physician to ensure better patient outcomes."*

Table 1 Proposed MBS items for microwave tissue ablation of lung cancer

Category 3 – THERAPEUTIC PROCEDURES
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with curative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of up to three lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1300 Benefit: 75% = $975.00 85% = $1105.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of four or five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $1600 Benefit: 75% = $1200.00 85% = $1360.00
NONRESECTABLE PRIMARY LUNG CANCER OR PULMONARY METASTATIC DISEASE, destruction of more than five lesions, by percutaneous microwave tissue ablation (MTA) with palliative intent, including any associated imaging services. (Anaes) Fee: $2000 Benefit: 75% = $1500.00 85% = $1700.00

7. Summary of Public Consultation Feedback/Consumer Issues

The PICO Advisory Sub-Committee (PASC) public consultation feedback received one response from a peak body and one response from the manufacturer.

Issues raised in the responses were:

- That ultrasound is rarely used as an image-guidance method for the intervention
- That Stereotactic Body Radiation Therapy (SBRT) should be a comparator for the intervention; and
- That isolated bone metastases are an emerging indication for Microwave Tissue Ablation.

8. Proposed intervention's place in clinical management

In population 1 (NSCLC), MTA is intended to be a direct replacement for radiofrequency ablation (RFA), and an additional therapeutic option to current best practice radiotherapy with or without chemotherapy. In population 2 (oligometastases), MTA is intended to be a direct replacement for RFA, and an additional therapeutic option to surgical resection or current best practice radiotherapy with or without chemotherapy. In population 3 (palliative), MTA is intended to be an additional treatment option to conventional palliative treatments for NSCLC and pulmonary metastases.

9. Comparator

There are several comparators to MTA including RFA, current best practice radiotherapy and surgery. The number, and type, of comparators to MTA depends on the population, as shown in Table 2.

Table 2 Comparator(s) in the three populations

Population	Comparator(s)
Patients with early stage NSCLC who are not eligible for surgical resection, and who are receiving treatment with curative intent.	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy
Patients with pulmonary metastases, in whom the primary tumour is under control, and who are receiving treatment with curative intent (oligometastatic disease)	1) Radiofrequency ablation 2) Current best practice radiotherapy with or without chemotherapy 3) Surgical resection
Patients with NSCLC or pulmonary metastases, who are receiving palliative treatment	1) Conventional palliative therapy without MTA

10. Comparative safety

A systematic review of published literature was undertaken to identify all studies of MTA in the proposed populations. No studies that directly or indirectly compared MTA to a relevant comparator were identified. As a result, the evidence base was insufficient to inform the comparative safety, effectiveness and cost effectiveness of MTA.

There were no comparative safety studies identified for population 1 or 2, however studies with mixed populations (i.e. primary or secondary cancer) were identified to highlight the safety profile of MTA. Of the 23 studies which reported the safety of MTA (two Level III-2 and 21 Level IV), procedure related mortality was rare (2/916, <1%), mortality within 30 days was (1/739, <1%) and serious adverse events were rarely reported. Pneumothorax was the most frequent adverse event associated with MTA, reported in 27 per cent of ablation sessions (median 30%, range 8–64%). Across studies, chest tube drainage or other intervention was required after 12 per cent (median 10%, range 0–29%) of ablation sessions. The majority of pneumothorax cases were self-limiting.

Nineteen studies reported the safety of RFA, of which one was Level III-3 and 18 were Level IV. Similar to MTA, the procedure-related mortality (1/1,259, 0.08%) and 30-day mortality (2/810, 0.25%) associated with RFA were very low. Pneumothorax was the most commonly reported adverse event, reported after 45 per cent of RFA sessions (median 24%, range 9–67%). Chest tube placement was required after 22 per cent of RFA sessions (median 9%, range 2–39%).

Twenty-two studies reported the safety of radiotherapy in population one and two. There were two cases of procedure-related mortality across all included studies (2/887, 0.2%). Serious adverse events arising from radiotherapy were rare.

Five studies and one recent systematic review reported safety of surgery (Table 4). The review by Pfannschmidt et al (2007) identified four of 20 included studies that reported postoperative mortality, which ranged from 0 to 2.5 per cent of patients. In the case series studies, immediate procedure-related mortality did not occur in any patients (0/365, 0%, 2 studies), and thirty day mortality occurred in 10 of 1,499 patients (0.67%, 4 studies).

11. Comparative effectiveness

No comparative studies were identified to inform an assessment of comparative effectiveness of MTA. The evidence for both the intervention and its comparators is largely characterised by Level IV evidence with variable outcome measures and incomplete reporting. The claim of non-inferiority for the comparative effectiveness of MTA as compared to current best practice radiotherapy, surgery or RFA remains untested by published evidence.

The tables below (Table 3, Table 4, Table 5) provide a summary of findings for selected outcomes that were reported across multiple comparators. It is important to note that information for comparators should not be directly compared with MTA, as data in the tables is drawn largely from case series studies.

Table 3 Effectiveness outcomes relevant to population 1

Outcome and intervention/comparator	**№ of studies** Level of evidence	Summary	Quality of the evidence (GRADE)
Overall survival rate			
MTA Assessed with: Kaplan-Meier estimate (95% CI not reported) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 1-year 91.7%, 2-year 76.5%, 3-year 47.9% and 4-year 47.9% Yang et al (2015) [2] 1-year 89%, 2-year 63%, 3-year 43%, and 5-year 16%	⊕⊙⊙⊙ VERY LOW [1]
RFA Assessed with: Kaplan-Meier estimate (95%CI not reported) F/U range 19 to 46 months	1 Level III-3 study 7 Level IV studies	Median survival rate, pooled 1-year 86.3% (range 83–100%) 2-year 74% (range 69.8–86%) 3-year 62.8% (range 40–74%) 5-year 28% (range 14–61%)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Assessed with: varied instruments F/U range 21 to 30.2 months	1 Level II study 1 Level III-1 study[5]	Videtic et al (2015) *1-year survival* 34/1 GY SBRT = 48.6% (95% CI 68.9–92.8%) 48/4 GY SBRT = 91.1 (95% CI 78.0–96.6%) *2-year survival* 34/1 GY SBRT = 61.3% (95% CI 44.2–74.6%) 48/4 GY SBRT = 77.7% (95% CI 62.5–87.3%) Koshy et al (2015) *3-year survival* No therapy = 28% , Conventional radiotherapy = 36%, SBRT = 48% A propensity-matched cohort reported 3 year overall survival with SBRT of 48% and with conventional radiotherapy of 40% (p = 0.001).	⊕⊕⊙⊙ LOW
Median survival time			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 35.0 months (95%CI 22.3–47.7) Yang et al (2014) 33.8 months (95%CI 31.9–35.7) [2]	⊕⊙⊙⊙ VERY LOW [5]

Outcome and intervention/comparator	**№ of studies** Level of evidence	Summary	Quality of the evidence (GRADE)
RFA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 19 to 37 months	6 Level IV studies	Median overall survival 42.8 months (range: 33.4–67)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Not reported	0 studies	NA	NA
Time to local progression			
MTA Assessed with: Kaplan-Meier estimate (95%CI) F/U range 23 to 30 months	2 Level IV studies	Han et al (2015) 28.0 months (95%CI 17.7–38.3) Yang et al (2015) 45.5 months (95%CI: 28.8–61.8)	⊕⊙⊙⊙ VERY LOW [6,7]
RFA Assessed with: Kaplan-Meier estimate (95%CI) F/U 19 to 46 months	1 Level III-3 study[8] 3 Level IV studies	Ambrogi et al (2011) Median of 39 months (range NR) Lanuti et al (2012) mean (SD) of 12 (10) months, range 1–44 Liu et al (2012) mean (SD): 25 (11) months, range 4–35 Safi et al (2015) 11.9 ± 8.1 (1–24) months with RFA and 6.0 ± 3.0 (1–46) months with radiotherapy, p = 0.36 for test of significance	⊕⊙⊙⊙ VERY LOW [9]
Radiotherapy Not reported	0 studies	NA	NA

< F/U = follow-up; CI = confidence interval; MTA = microwave tissue ablation; NA = not applicable; RFA = radiofrequency ablation; SD = standard deviation; ± = SD; SBRT= stereotactic body radiotherapy >GRADE Working Group grades of evidence (Guyatt et al., 2013)**.**

⊕⊕⊙⊙ **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.

1. Neither Han et al (2015) nor Yang et al (2015) provide confidence intervals associated with the point estimates, therefore the precision of these estimates is unclear. Similarly only Yang et al (2015) report maximum follow-up of >60 months (5 years).
2. Note that: Yang et al (2015) examined a subgroup of patients with tumours > 3.5 cm versus ≤ 3.5 cm and found that tumours ≤ 3.5 cm were associated with better survival than were tumours >3.5 cm (p = 0.016). The distribution in number of patients with tumours >3.5 cm across the two studies will affect the consistency of outcomes.
3. There is a wide range of survival rates reported with reporting becoming more and more limited over time. This should be a relatively homogenous group in terms of cancer stage and extent of disease. There is substantial concern that outcomes have been measured very differently across studies. For example Hiraki et al (2011) has a 5-year survival of 61% whilst Ridge et al (2014) reports only 14%.
4. Koshy et al (2015) is a Level III-1 retrospective propensity-matched cohort, Videtic et al (2015) is Level II study.
5. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95%CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.
6. It has been observed that authors appear to use the term recurrence/progression interchangeably. Han et al (2015): A focal enhancement at the ablation site or enlargement of the ablated tumour after a series of shrinkage was considered local recurrence if technical success had been confirmed. Yang et al (2015): Local progression was referred to as the contrast-enhancement by CT scans in the site of ablation.
7. Studies include relatively few patients (total N = 75), with the study by Yang et al (2014) having a substantially narrower 95%CI than Han et al (2015), around the estimate of the effect. In this case, with only two studies reporting this outcome there is substantial uncertainty regarding precision.
8. Safi et al (2015) is a Level III-3 retrospective cohort study that compared RFA and radiotherapy.
9. Estimates across different studies are markedly different; it may be due to differences in measurement, reporting or outcome.

Table 4 Effectiveness outcomes relevant to population 2

Outcome and intervention/comparator	**№ of Studies** and level of evidence	Summary	Quality of the evidence (GRADE)
Overall survival rate			
MTA Assessed with: n/N (%) at 1 and 2 years Median F/U 9 months	1 Level IV study	Vogl et al (2015) 12 month survival 91% (73/80 patients alive), 24 month survival 75% (60/80 patients alive). Survival greater than 24 months NR.	⊕⊙⊙⊙ VERY LOW
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U range 12 to 38 months	10 Level IV studies	Median survival rate, pooled 1-year 87.8% (range 73.4–100%) 2-year 59.3% (range 41.1–94%) 3-year 53.0% (range: 30–85%)	⊕⊙⊙⊙ VERY LOW
Radiotherapy Assessed with: Kaplan-Meier estimate (95%CI) F/U range 13 to 55 months	3 Level III-2 studies 14 Level IV studies	Median survival rate, pooled 1-year 86.0% (60.5–98%) 2-year 65.1% (31.2–86%) 3-year 61.5% (50.1–73%) 5-year 46.2% (39–56.2%)	⊕⊙⊙⊙ VERY LOW [1]
Surgery assessed with: varied measures Minimum F/U 30 days	2 Level I studies (of Level IV evidence) 2 Level IV studies	Young et al (2015) Meta-analysis of 5 year overall survival from 11 studies (387 patients) : 29.1% (95%CI; 24.1–35.3); I2 =0%, p = 0.462, d.f = 10 Pfannschmidt et al (2007) Median 5-year survival 48%, range 41%–56% Reza et al (2014) 3-year 48%, 5-year 42%, 10-year 31% Kitano et al (2012) 2-year 53.9%, 5-year 40.9%	⊕⊙⊙⊙ VERY LOW
Median survival time			
MTA Not reported	0 studies	NA	NA
RFA Assessed with: Kaplan-Meier estimates (95%CI) F/U range 12 to 38 months	10 Level IV studies	Median overall survival 44 months (range 21–67)	⊕⊙⊙⊙ VERY LOW [2]
Radiotherapy Assessed with: Kaplan-Meier estimates (95%CI) F/U range 13 to 55 months	1 Level III-2 study 10 Level IV studies	Median overall survival 27.8 months (range 12–42.8)	⊕⊙⊙⊙ VERY LOW [2]
Surgery assessed with: Kaplan-Meier estimate (95 % CI) F/U not reported	3 Level IV studies	Renaud et al (2014) No lymph node involvement: 94 months (95%CI, 76.3–111.7) positive lymph node involvement: 42 months (95%CI, 30.1–53.9; p<0.0001) Hilar location of lymph node involvement: 47 months (95%CI, 29.9–64.1) Mediastinal location of lymph node involvement: 37 months (95%CI, 14.0–60.0; p>0.05) Solitary pulmonary metastasis: 81 months (95%CI, 60.8–101.2) Multiple metastases: 55 months (95%CI, 35.1–74.9; p<0.01) Hepatic metastases: 47 months (95%CI, 21.6–72.4) No hepatic metastases: 74 months (95%CI, 60.7–87.3;. p<0.01) Reza et al (2014) 35 months (95%CI 23–61) Kitano et al (2012) 26.5 months (range: 0.7–165)	⊕⊙⊙⊙ VERY LOW [2]
Time to local progression			
MTA Assessed with: Mean time in months (range) F/U range 9 to 14 months	2 Level IV studies	Qi et al (2015) 7.2 months (range 4–20) Vogl et al (2015) 6 months (range: 1–18)	⊕⊙⊙⊙ VERY LOW

Outcome and intervention/comparator	**№ of Studies** and level of evidence	Summary	Quality of the evidence (GRADE)
RFA Assessed with: mean (range) months/Kaplan-Meier estimate (95%CI) F/U range 12 to 38 months	5 Level IV studies	Median time to local progression 12 months (range: 8.2–15 months)	⊕⊙⊙⊙ VERY LOW [3]
Radiotherapy Assessed with: median months until progression F/U range 15 to 24 months	1 Level III-2 study 6 Level IV studies	Median time to local progression 10.8 months (range: 5–18)	⊕⊙⊙⊙ VERY LOW [3]
Surgery Not reported	0 studies	NA	NA

< CI = confidence interval; F/U = follow up; MTA = microwave tissue ablation; NA = not applicable; RFA = radiofrequency ablation >

GRADE Working Group grades of evidence (Guyatt et al., 2013)**.**
⊕⊙⊙⊙ **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.

1. Studies report a large range of survival rates with many studies not providing any indication of the variance associated with point estimates. At later time points less results are available.
2. Studies included investigated a range of prognostic factors and different studies reported on patients with different primary cancers. This is likely to have affected the overall survival time of included patients.
3. Studies report a range of time to progression estimates and it is not clear whether they were measured in a consistent manner.

Table 5 Effectiveness outcomes relevant to population 3

Outcome and intervention/comparator	**№ of Studies** and level of evidence	Summary	Quality of the evidence (GRADE)
1 year survival			
MTA versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U range 6 to 35 months	1 Level III-2 study (Sun et al 2015)	MTA: 9/18 (50%) MTA + chemotherapy: 17/22 (77.3%)	⊕⊙⊙⊙ VERY LOW[1,2]
2-year survival			
MTA versus MTA + chemotherapy Assessed with: n/N (%) at 1 and 2 years F/U range 6 to 35 months	1 Level III-2 study (Sun et al 2015)	MTA: 5/18 (27.7%) MTA + chemotherapy: 13/22 (79.1%)	⊕⊙⊙⊙ VERY LOW[1,2]
Median survival time			
Chemotherapy versus MTA + chemotherapy Assessed with: Kaplan-Meier estimate F/U median 21 months	1 Level III-2 study (Wei et al 2015)	MTA + chemotherapy: 23.9 (95%CI15.2–32.6) months Chemotherapy: 17.3 (95%CI 15.2–19.3) months, difference p = 0.140	⊕⊙⊙⊙ VERY LOW[1,3,4]
MTA alone Assessed with: Median and range F/U median 17.7 months	1 Level III-2 study (Wei et al 2015)	Median OS: 17.7 months (range of 5–45) and from the time of MTA until death it was 10.6 months (range: 3.1–36.2).	⊕⊙⊙⊙ VERY LOW[1,5]

< CI = confidence interval; F/U = follow-up; MTA = microwave tissue ablation; NA = not applicable >

GRADE Working Group grades of evidence (Guyatt et al., 2013),
⊕⊙⊙⊙ **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.

1. Based on the results of one study with 22patients in one arm and 18 in the other, study reporting quality was low.
2. Measures of variance are not available. The small sample size reduces the reliability of the outcomes
3. Wei et al (2015) reports on small sample sizes and inherent drawbacks in study design are problematic
4. Measures of variance show wide confidence intervals associated with OS. The small sample size reduces the reliability of the outcomes.
5. Due to inherent limitations in case series evidence

12. Economic evaluation

A cost-minimisation analysis was undertaken to examine the cost implications of MTA, versus SBRT in populations one and two, and also against surgery in population two.

Model inputs
Costs for MTA, RFA and surgery were obtained from MBS, the applicant, and the National Hospital Cost Data Collection Australia Public Hospitals Cost Report Round 18. They are specified for patients with < 3 lesions and 3–5 lesions as the protocol proposed a graduated fee structure for MTA based on this lesion grouping. Discussion with clinicians indicated that patients with more than five lesions and those undergoing palliative care would rarely receive MTA. Costs are not estimated for these patients.

Model results
The total average costs for MTA, SBRT and surgery are presented as the cost per patient over the course of 3 months of treatment. They are presented in Table 6 for populations one and two, by lesion grouping. It is evident that the total average cost of SBRT is less than that of MTA for populations one and two across all included lesion groupings. For less than three lesions, the average cost of MTA is $2,471 higher than for SBRT. The key items driving increased costs are the costs of the disposable applicator and the overnight hospital stay. In the case of the applicator this cost is $2,960 and the hospital stay is $873 per night. In the longer term, the MTA procedure may be delivered on an outpatient basis, which would reduce the cost margin.

Table 6 Health care costs per patients (3 months) for base-case analysis

Resource item description	MTA	SBRT	Incremental cost of MTA vs SBRT	Surgery	Incremental cost of MTA vs Surgery
Population and Lesions	Population 1 and 2, <3 lesions			Population 2 , <3 lesions	
Specialist services – screening prior to intervention	1,557.55	1,557.55	0.00	1,557.55	0.00
Specialist services – intervention (MBS supported)[1]	1,866.68	3,168.90	-1,302.22	2,814.33	-947.65
Specialist services – intervention (Hospital)	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	293.50	2,916.50	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	7,843.83	5,372.95	2,470.88	19,472.05	-11,628.22
	Population 1 and 2, <3–5 lesions			Population 2 , <3–5 lesions	
Specialist services – screening prior to intervention	1,557.55	1,557.55	0.00	1,557.55	0.00
Specialist services – intervention (MBS supported)	2,166.68	3,494.90	-1,328.22	2,814.33	-647.65
Specialist services – intervention (Hospital)	932.10	0.00	932.10	14,822.67	-13,890.57
Specialist services – post intervention follow-up	277.50	353.00	-75.50	277.50	0.00
Prostheses or equipment costs	3,210.00	329.62	2,880.38	0.00	3,210.00
Adverse events	0.00	0.00	0.00	0.00	0.00
Total	8,143.83	5,735.07	2,408.76	19,472.05	-11,328.22

13. Financial/budgetary impacts

Within Australia it is expected that 3,215 patients in year one will have early stage NSCLC and 1,833 of them will be ineligible for, or not elect, surgery, increasing to 2,031 patients in Year 5. Additionally, a smaller number of patients with pulmonary metastases, in whom the primary tumour is under control, will be eligible for MTA under the proposed MBS items. This is estimated to be equivalent to 10 per cent of the early stage eligible population. An uptake rate of 10% for MTA among these patients has been assumed for the first 5 years to account for developing treatment capacity and educating radiologists. A total of 202 MTA procedures are estimated in Year 1 increasing to 1,117 in Year 5.

The number of MTA procedures is disaggregated by lesion groupings. Discussions with clinical experts indicated most ablation would involve less than 3 lesions. Correspondingly, 90% of the 202 MTA procedures forecast for Year 1 will involve the proposed fee associated with less than three lesions. While 181 MTA procedures are estimated for <3 lesions, around 10% of all MTA procedures, or 20%, are estimated for 3–5 lesions. No MTA procedures are estimated for patients with more than 5 lesions. The cost to the MBS from MTA uptake is estimated to be $0.61 million in Year 1, increasing to $3.41 million in Year 5 based on these projections. MTA would largely replace SBRT, which entails a higher MBS rebate. Consequently, there is an annual net MBS cost saving of $0.30 million in Year 1 to a saving of $1.64 million in Year 5. These budget impacts are outlined in Table 7.

Table 7 Total estimated additional costs to MBS of changes in services ($)

	Year 1	Year 2	Year 3	Year 4	Year 5
Uptake estimate	10%	20%	30%	40%	50%
Anticipated total number of MTA procedures per year	202	414	636	871	1,117
Procedures by Lesion Grouping					
1–3 lesions; total cost per patient (90%)	181	372	573	784	1,005
3–5 lesions; total cost per patient (10%)	20	41	64	87	112
>5 lesions; total cost per patient (0%)	0	0	0	0	0
Total	202	414	636	871	1,117
MTA MBS Costs by Lesion Grouping					
1–3 lesions; total cost per patient (90%)	549,161	1,126,565	1,733,634	2,371,868	3,042,840
3–5 lesions; total cost per patient (10%)	65,554	134,480	206,946	283,133	363,228
>5 lesions; total cost per patient (0%)	0	0	0	0	0
Total	614,715	1,261,044	1,940,581	2,655,001	3,406,068
SBRT MBS Costs by Lesion Grouping (Item 15600)					
1–3 lesions; total cost per patient (90%)	815,107	1,672,134	2,573,194	3,520,509	4,516,418
3–5 lesions; total cost per patient (10%)	96,829	198,638	305,678	418,213	532,779
>5 lesions; total cost per patient (0%)	0	0	0	0	0
Total	911,937	1,870,773	2,878,872	3,938,722	5,049,197
Net MBS Costs	-296,546	-608,343	-936,160	-1,280,805	-1,643,129

MBS = Medicare benefits schedule; MTA = microwave tissue ablation for primary and secondary lung cancer.

The costs of the MTA machine, and probes are borne by private health funds, patients or hospitals (state and territory budget). The base case estimate assumed the number of MTA patients increases from 202 to 1,117 per year, leading to a total cost of the machines of $0.05 million in year one increasing to $0.28 million in year five. The cost of probes and hospital stays also increase. Probes are the largest cost item – increasing from $0.60 million in Year 1 to $3.31 million in Year 5. The total cost to private health funds and hospitals in Year 5 is $13.42 million. This is substantially more than the net impact to the MBS. Variables such as

the proportion of lung cancer that is NSCLC, the relative size of population one and two patient numbers, and assumed uptake have an impact on net MBS expenditures. Increases in these parameters generally increase the MBS net cost savings, as a higher number of SBRT procedures are being substituted.

14. Key issues from ESC for MSAC

ESC noted that lung MTA is administered percutaneously for pulmonary lesions and is delivered with image guidance by CT or ultrasound. MTA is currently not reimbursed under the MBS for lung tumours and is currently performed largely within the public system.

ESC noted that there is lack of evidence, no studies and significant uncertainty regarding the comparative benefit of MTA tumour destruction over existing treatment options and potential out of pocket expenses for patients. Approximately 90% of lung MTA in Australia is performed for early stage non-small cell lung cancer (NSCLC) and 10% for oligometastatic disease.

ESC noted the 3 populations as follows:

- Population 1: Early stage non-small cell lung cancer;
- Population 2: Oligometastatic disease; and
- Population 3: Palliative therapy – unlikely to be used according to clinical experience.

ESC noted that MTA is proposed to replace radiofrequency ablation (RFA), and that currently there is no MBS item for RFA for lung tumours.

ESC noted that the evidence for MTA is Level IV (case series). The evidence base for the comparator interventions – RFA, radiotherapy and surgical resection – is also limited by study design (predominantly Level IV case series).

ESC discussed the safety and agreed pneumothorax was the most common adverse event associated with MTA (median 30%, range 8–64%, 20 studies) and that procedure-related deaths were rare (0.2%, 2/916, 23 studies).

ESC noted that the cost of lung MTA is affected by the choice of treatment modality: that is, whether it is performed as an inpatient or outpatient procedure, or under general or local anaesthetic.

ESC noted the clinical input suggesting that lung MTA is not used for palliative therapy in Australia, as patients would be more likely to receive systemic therapies. Studies have shown that surgical resection is effective for population 2; however, without randomised control trial data it is difficult to assess MTA's comparative effectiveness against surgery.

ESC noted the costs for treatment of base case primary lung cancer with: stereotactic body radiotherapy (SBRT) (over three months for fewer than three lesions) is $5,372.95; MTA is $7,843.83 and surgery is $19,472.05.

ESC noted that clinical advice suggests MTA may be useful in rural or remote areas on the basis of convenience (only one treatment usually required) and price, particularly in those areas where access to radiation therapy is limited.

ESC also noted, the annual MBS costs are projected to decrease over the 5-year horizon, related to substitution for SBRT, which has a higher rebate, with an increasing capacity to provide lung MTA services over time.

ESC noted potential out of pocket cost of the disposable probe $2,960 each, plus additional optimal temperature probe cost of $960 (which was not included in the economic analysis).

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website