Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1620 – Magnetic Resonance Image Guided Radiation Therapy

Applicant: **Elekta Pty Ltd**

Date of MSAC consideration: **MSAC 81st Meeting, 31 March – 1 April 2021**

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

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of Magnetic Resonance Image Guided Radiation Therapy (MR-IGRT) for cancer treatment delivery was received from Elekta Pty Ltd by the Department of Health.

2. 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 the continued Medicare Benefits Schedule (MBS) listing of magnetic resonance image-guided radiation therapy (MR-IGRT) for cancer treatment delivery. MSAC noted limitations in the evidence, but considered that, on balance, that MR-IGRT is non-inferior in terms of comparative safety and effectiveness compared with cone-beam computed tomography-guided radiation therapy (CBCT-IGRT). In addition, MSAC noted that there would be no expected financial impact on the MBS.

MSAC supported that MR-IGRT continue to use MBS item 15275.

Consumer summary
This application is from Elekta Pty Ltd. It seeks to continue funding an interim Medicare Benefits Schedule (MBS) item for magnetic resonance image–guided radiation therapy (MR-IGRT) for cancer treatment delivery. Radiation therapy is used to treat cancer. Image-guided radiation therapy (IGRT) refers to using images of the organs that have the cancer, to help target the cancer with radiation therapy more precisely. Cone-beam computed tomography (CBCT) involves using a CT scanner built into a machine called a linear accelerator. Images are taken just before radiation treatment so that treatment can be adjusted accordingly. By contrast, MR-IGRT provides real-time images

Consumer summary

of tumours at the same time as the radiation therapy is being given. It also gives better images of soft tissue. It is hoped that using MR-IGRT may result in the use of better targeted higher radiation doses for each treatment, but there are fewer treatment sessions and each treatment is shorter. Also, CBCT uses radiation to create an image, and then uses radiation again for the treatment. But, for MR-IGRT, no radiation is used to create an image, but the same radiation is used to give the treatment, which uses less radiation overall.

Although there is limited clinical evidence comparing MR-IGRT with CBCT, MSAC was satisfied that MR-IGRT was about as safe and effective as CBCT. There is also no additional cost to the MBS by allowing MR-IGRT to continue to be used under MBS item 15275.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported the continued Medicare Benefits Schedule (MBS) listing of MR-IGRT for cancer treatment delivery. MSAC accepted that MR-IGRT is safe and effective compared to CBCT. No change to the existing item descriptor is needed.

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

MSAC noted that MR-IGRT is currently not funded in Australia but there is interim approval to use MBS item 15275 for MR-IGRT, and that it is currently being used in two centres in Australia.

MSAC noted that the consumer feedback was generally supportive.

MSAC noted that the proposed population includes all patients with cancer undergoing external beam radiation therapy (EBRT) regardless of the cancer type, but the initial use of MR-IGRT is expected to focus on cancers of the brain, breast, cervix, oesophagus, lung, oropharynx, pancreas, prostate, oligometastatic sites, liver, bladder, and rectum.

MSAC noted that IGRT is used with many types of radiation therapy, namely intensity Modulated Radiation Therapy (IMRT). MSAC noted the comparator CBCT-IGRT can only be used prior to each fraction compared with MR-IGRT where the imaging guidance can be done during each fraction, which was represented as an additional step in the clinical management algorithm for MR-IGRT (see Figure 1).

MSAC noted that there is limited comparative evidence for MR-IGRT *vs*. CBCT-IGRT, with only one retrospective cohort study providing comparative safety data in lung cancer. Due to the lack of comparative evidence, the Department contracted assessment report (DCAR) included a naïve comparison of single-arm MR-IGRT studies and CBCT-IGRT studies assessing toxicity, patient tolerance, survival, quality of life and dosimetric outcomes in patients with lung cancer, prostate cancer, liver and abdominal malignancies. However, the DCAR noted its value is very limited due to the low quality of the methodology of the included studies, considerable heterogeneity in patient populations and treatment modalities, and a large variability in outcome assessment and reporting.

Regarding comparative safety, MSAC noted one comparative study reported no statistically or clinically meaningful difference in lung density between MR-IGRT and CBCT-IGRT on

follow-up CT scans. MSAC noted in two studies, 65% and 80% of patients reported at least some degree of potential MR-IGRT-related complaints, mainly related to feeling uncomfortable during the treatment (noise, temperature, and paraesthesia). MSAC noted no studies informed patient tolerance with CBCT-IGRT.

Regarding clinical effectiveness, MSAC noted the DCAR did not perform a formal GRADE evaluation of the naïve comparison. For the assessment of dosimetric outcomes, MSAC noted there was limited mixed evidence. One comparative cohort study compared the planning target volume (PTV) and the clinically relevant dose-volumetric parameters between the MR-IGRT and CBCT-IGRT plans of patients with lung cancer. MSAC noted dosimetric parameters were significantly more favourable in the CBCT-IGRT group. In contrast, MSAC noted a simulation study with 3mm PTV margin identified some failures with CBCT-IGRT. MSAC considered it is plausible in theory that MR-IGRT can achieve the simulation study findings.

Overall, MSAC noted that a meaningful comparison of treatment safety and effectiveness between the intervention and comparator was difficult to carry out due to the variety of treatment modalities, treatment schedules, total dose delivered and differing patient characteristics encountered. MSAC noted that any theoretical benefits may not be realised based on study data.

Despite the lack of long-term safety and effectiveness data and very low quality evidence, MSAC considered the available data for MR-IGRT appears comparable with CBCT-IGRT. Thus, MSAC concluded that the claim that MR-IGRT is non-inferior in safety and clinical effectiveness compared with CBCT-IGRT may be reasonable given that the radiation delivery technology is the same in both methods.

MSAC agreed with ESC that there was some uncertainty in respect to the clinical claims but also considered that the costing minimisation approach was appropriate. MSAC noted that in the base case, which assumed the same hypofractionation schedule (5 fractions) of MR-guided stereotactic body radiation therapy (SBRT) and CBCT-guided SBRT in prostate cancer patients, the intervention has an incremental cost of $1,930 and is not cost saving. MSAC noted this was mainly due to the increased capital costs with MR-IGRT.

MSAC also noted that the economic model only included the costs of the treatment related to acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer. However, the basis for the excess toxicity profile and higher costs managing adverse events with CBCT-IGRT in the model was uncertain as it was based on a naïve comparison on a single study (n<30) for MR-IGRT *vs*. eight studies for CBCT-IGRT.

In addition, MSAC agreed with ESC who considered that, depending on the type of cancer and stage, the requirements and the duration of treatment (number of fractions) for interventions (and hence the use of health care resources) are likely to differ, which could impact resource use and thus cost estimates.

MSAC noted that a key driver of the economic model was the assumption that there would be a reduction in the number of fractions given and that this was tested in scenario analyses. However, MSAC noted that the validity of these numbers is difficult to evaluate because there is no evidence to compare the number of fractions between MR-IGRT and CBCT-IGRT. In addition, MSAC noted that assuming different fractions is not clinically relevant, because CBCT-IGRT can treat the same disease with a similar fractionation schedule as MR-IGRT.

MSAC noted the pre MSAC response reiterated that current data from the Australian MR-IGRT sites indicates 87% of patient courses are delivered with SBRT dose levels, resulting in an average number of treatment fractions per patient course totaling 6.9 fractions (75 patients for 520 fractions). However, MSAC agreed with ESC who considered that this analysis cannot be considered reflective of all cancer indications.

MSAC also noted that in the pre-MSAC response the applicant reiterated that it is requesting the same MBS fee for the proposed intervention as for CBCT-IGRT. However, MSAC noted the consumer concern that there are higher capital and staff costs associated with MR-IGRT compared to CBCT-IGRT, and that these costs should not be shifted to patients.

MSAC noted that substitution of services rather than additional services is likely and that it is not likely that there will be an increase in cost to the MBS, nor is it likely to impact the Radiation Oncology Health Program Grants (ROHPG) Scheme. MSAC also discussed that the ROHPG provides a $3 million contribution for eligible linac machines (over 8 years for private providers and 10 years for public providers) but the cost of MR-IGRT is much higher. MSAC was concerned regarding the shortfall, but the ROHPG Scheme only provides a contribution towards eligible linac machines and is not intended to cover the full cost of the radiation therapy equipment.

MSAC noted that the application was not for the more complex adaptive radiotherapy (replanning the radiation treatment before each fraction based on MRI images). MSAC noted this technology may have the potential for smaller margins, higher dose, improved tumour kill, less toxicity and shorter treatments. MSAC considered that if an application was made requesting a new replanning item number for this in the future it would require a superiority claim.

4. Background

This is the first submission for MR-IGRT for patients with cancer undergoing EBRT. MSAC has not previously considered this application.

MR-IGRT is currently not funded or reimbursed in Australia for any indication. Two MR-IGRT devices appear to be currently in operation in Australia (Townsville Cancer Centre of the Townsville University Hospital, Queensland, and GenesisCare St Vincent's Hospital, Darlinghurst, New South Wales), both using the Elekta Unity technology. A third Elekta Unity MR-linac is scheduled to start operating in Victoria in mid 2021. All three facilities have obtained interim approval to use MBS item 15275 for MR-IGRT.

Relevant MSAC applications
MSAC considered applications requesting MBS listing of intensity modulated radiation therapy (IMRT; application 1182) and image guided radiation therapy (IGRT; application 1319) concurrently. MSAC supported public funding of IGRT on a cost neutral basis relative to MBS expenditure on three-dimensional conformal radiotherapy (3D-CRT) [Public Summary Document- Application 1319, 2015, p1).

MBS item 15275 was listed on the 01 January 2016.

5. Prerequisites to implementation of any funding advice

Items on the Australian Register of Therapeutic Goods (ARTG) that are relevant to this application are shown in Table 1.

Table 1 MR-IGRT devices listed on the ARTG

ARTG no.	Product no.	Product description	Product category	Sponsor
319241	GMDN 62147	MRIdian Linac System - Stereotactic teletherapy radionuclide system, MRI-imaging	Medical Device Class IIb	Device Technologies Australia Pty Ltd
307588	GMDN 35159	Elekta Unity – Accelerator system, linear	Medical Device Included Class IIb	Elekta Pty Ltd

Source: Table 9, pp3-4 of the DCAR
ARTG=Australian Register of Therapeutic Goods; GMDN=Global Medical Device Nomenclature code; MRI=magnetic resonance imaging

6. Proposal for public funding

The applicant requested an amendment to the way the service is clinically delivered under existing MBS item 15275 (Table 2). This MBS item is technologically-agnostic, as confirmed by the PASC.

Table 2 Proposed MBS item descriptor (MBS item 15275)

Category 3 – THERAPEUTIC PROCEDURES
RADIATION ONCOLOGY TREATMENT with IGRT imaging facilities undertaken: (a) to implement an IMRT dosimetry plan prepared in accordance with item 15565; and (b) utilising an intensity modulated treatment delivery mode (delivered by a fixed or dynamic gantry linear accelerator or by a helical non C-arm based linear accelerator), once only at each attendance at which treatment is given.
MBS Fee*: $188.65 Benefit: 75% = $141.50 85% = $160.40

Source: Table 1, p xiii of the DCAR
*Fees updated according to current information on mbsonline.gov.au as of 15 October 2020
CT=computed tomography; IGRT=image guided radiation therapy; IMRT=intensity-modulated radiation therapy; MBS=Medical Benefits Schedule

7. Summary of public consultation feedback/consumer Issues

Feedback on the application requesting MBS listing of MR-IGRT for cancer treatment delivery was received from:

- three professional societies: The Faculty of Radiation Oncology of the Royal Australian And New Zealand College of Radiologists (RANZCR); Australian Society of Medical Imaging and Radiation Therapy (ASMIRT); and Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM)
- one charity organisation: Lung Foundation Australia
- one field expert
- Device Technologies Australia (DTA) and Viewray providing a Public Consultation Survey
- Cancer Voices Australia
- Additionally, the ACPSEM and the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) were requested by the Department to provide any comments on the Ratified PICO and on the safety of the technology.

Overall, the general conclusion was in favour of listing MR-IGRT on the MBS. Of note, no specific concerns about MR-IGRT safety were raised.

The ACPSEM has also noted the potential of MR-IGRT to change the method of treatment for current high-volume indications, such as prostate and breast cancer.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention

MR-IGRT, also known as MR-linac, combines an MR unit with a linear accelerator (linac). The combination of the two technologies allows real-time imaging of target volumes and organs at risk (OARs) before and during radiation therapy delivery, enabling re-planning for each fraction if necessary.

Description of Medical Condition(s)

The proposed population includes all patients with cancer undergoing external beam radiation therapy (EBRT) regardless of the cancer type.

Initial use of MR-linac is expected to focus on cancers of the brain, breast, cervix, oesophagus, lung, oropharynx, pancreas, prostate, oligometastatic sites, liver, bladder, and rectum.

Clinical place

The current and proposed (green box) clinical management algorithm are depicted in Figure 1. The DCAR stated that the premise is that the current clinical management algorithm would remain largely unchanged, as MR-IGRT is a form of IGRT. MR-IGRT would introduce a new clinical choice for tumour sites that may benefit from reduced target volume margins and hypofractionated courses. The only change compared to standard IGRT is that imaging and treatment adaptation for dose delivery optimisation is ongoing during the radiotherapy session.

Figure 1 Clinical management algorithm for the proposed MR-IGRT relative to current clinical practice (amendment to the current algorithm in green box)

Source: Figure 2, p8 of the DCAR

9. Comparator

The DCAR stated that the comparator is cone-beam computed tomography (CBCT)-guided radiation therapy (CBCT-IGRT). Currently, IGRT can be performed using many systems and techniques, including ultrasound, MR imaging, radiographic and fluoroscopic imaging, and CT-guided systems. The type of system used depends on resources in radiation oncology departments, and accuracy of the type of treatments to be delivered. CBCT is generally understood to be the current standard of care for IGRT for most cancer types (Srinivasan, Mohammadi, & Shepherd, 2014[1]).

10. Comparative safety

The DCARs first literature search identified one comparative retrospective cohort study evaluating patients with lung cancer and 11 case series reporting on toxicity rates, patient tolerance, quality of life and survival rates after receiving MR-IGRT for cancer. The studies

[1] Srinivasan, K., Mohammadi, M., & Shepherd, J. (2014). Applications of linac-mounted kilovoltage Cone-beam Computed Tomography in modern radiation therapy: A review. Pol J Radiol, 79, 181-193.

evaluated patients with lung cancer, prostate cancer, liver and abdominal malignancies, head and neck as well as mixed cancer populations. The DCAR considered that the quality of the evidence for MR-IGRT is very low.

The DCARs second literature search identified 56 studies of which 54 reported on toxicity and survival outcomes in cancer patients that were treated with CBCT-IGRT. Only cancer sites that were identified in the evidence base for MR-IGRT were included.

Two treatment simulation studies compared dosimetric qualities of MR-IGRT and CBCT-IGRT treatment plans for patients that were previously treated with radiotherapy.

Toxicity

Lung cancer

One retrospective cohort study (Kim et al 2018) comparing radiation-induced lung damage (RILD) between MR-IGRT and CBCT-IGRT on follow-up CT scans was identified. The study quality was fair, however, it used outdated MR-IGRT technology and a proxy indicator for lung injury (radiological lung density changes). No statistically significant difference was found between the two image guidance modalities; a clinically meaningful difference has not been established either.

Two single-arm studies reported on the toxicity of MR-IGRT treatment for lung malignancies. One of them reported 15/50 (30%) of patients experienced any grade ≥2 treatment-related toxicity.

Six studies reported on the toxicity of CBCT-IGRT treatment for lung malignancies. Treatment toxicity varied in severity and symptoms across studies; one study reported that 92% of patients experienced any acute or late grade ≥1 treatment-related toxicity.

Prostate cancer

One prospective single-arm case series evaluated acute toxicity of MR-IGRT in patients with localised prostate cancer, reporting 24% and 12% of patients suffering grade 1 and 2 genitourinary (GU) toxicity, and 8% and 4% of patients suffering grade 1 and 2 gastrointestinal (GI) toxicity, respectively. No grade ≥3 events were encountered.

Thirty-three studies reported on the safety of CBCT-IGRT in patients with prostate cancer. Population characteristics ranged from localised to locally-advanced disease, low to high risk, newly-diagnosed or relapsing disease, and both radical or post-prostatectomy radiation therapy. Acute and late treatment-related toxicity was reported, mostly of grade 1-2. Grade ≥3 events were rare, and reported in less than 5% of patients except for one study which reported grade 3 GU toxicity in 6/69 (9%) patients receiving dose-escalated salvage radiotherapy after radical prostatectomy and macroscopic local recurrence.

Abdominal malignancies

Three single-arm case series evaluated the safety of MR-guided stereotactic body radiation therapy (SBRT) for abdominal malignancies (liver or non-liver, primary or metastatic lesions). One study reported 10% of patients experiencing acute grade 1 GI toxicity, one study reported acute grade 2 toxicity in 5% of patients and no acute grade 3 and no late treatment-related toxicity. One study reported acute grade ≥3 GI toxicity of 7%.

Seven retrospective case series and one prospective trial on the safety of CBCT-guided SBRT in abdominal malignancies (e.g. liver, pancreas, and secondary liver oligometastases) were identified. No acute toxicity grade ≥3 was found in seven studies, and one study reported acute toxicity grade ≥3 was found in <1% of patients treated for liver metastases. Similarly,

seven studies observed no cases of late toxicity grade ≥3, whereas one study observed late grade ≥3 toxicity in 4/47 (9%) patients with abdominopelvic tumours, one of them being of grade 5.

Head and neck cancer

One prospective single-arm case series evaluated the safety of MR-IGRT in patients with head and neck cancer and reported 44% of patients experienced acute grade 3 toxicity. One cohort study reporting on the safety of CBCT-IGRT in head and neck cancer was identified and reported 54% of patients experienced acute grade 3 toxicity and 65% experienced late grade 3 toxicity.

Patient tolerance

Three single-arm studies reported on MR-IGRT-related complaints. In two studies, 65% and 80% of patients reported at least some degree of potential MR-IGRT-related complaints, mainly related to feeling uncomfortable during the treatment (noise, temperature, and paraesthesia).

No studies on patient tolerance of CBCT-IGRT were identified.

11. Comparative effectiveness

No comparative studies of the clinical effectiveness of MR-IGRT versus CBCT-IGRT were identified in the literature search. A naïve comparison of MR-IGRT and CBCT-IGRT was attempted for the patient-relevant outcomes of survival and quality of life.

In addition, given the lack of comparative evidence for clinical effectiveness, three studies comparing the dosimetric parameters of MR-IGRT and CBCT-IGRT were identified and included in this assessment.

Survival outcomes

No comparative evidence was found for survival outcomes. Four single-arm case series reported on survival after MR-IGRT treatment. A naïve comparison with studies on the effectiveness of CBCT-IGRT was attempted. Due to low methodologic quality of included studies, considerable heterogeneity in patient populations and treatment modalities, and a large variability in outcome assessment and reporting, its value is very limited.

Lung cancer

Overall local control in patients treated with MR-IGRT for lung malignancies at one year was reported to be 95.6% (95% confidence interval, CI, 89.8%-100.0%). The overall survival was 82.8% (95% CI 79.4%-97.5%) for early-stage primary lung cancer and 95.2% (95% CI 86.6%-100.0%) for patients with lung metastases.

Nine studies reported survival outcomes after CBCT-IGRT treatment of lung malignancies. Local control rate at one year was reported to be 97% in one study. One-year overall survival ranged between 67-87%, decreasing to 44.4-63% at 3 years and to 42% at 5 years.

Abdominal malignancies

In patients with hepatocellular carcinoma treated with MR-IGRT, freedom from local progression at median follow-up (21.2 months) was 80.4%, progression-free survival at median follow-up was 35%, and one and two year overall survival was 69% and 60%, respectively.

The survival outcomes of patients with hepatocellular carcinoma treated with CBCT-IGRT were similar, with freedom from local progression of 85.7% and 76.3% at 1 and 2 years,

respectively, progression-free survival of 37.8% and 35.6% at 1 and 2 years, respectively, and overall survival ranging between 77-88.5% at 1 year and 60-75% at 2 years.

Three- and 6-month progression-free survival of patients with unresectable abdominal cancers treated with MR-IGRT was reported to be 95% and 89%, respectively, with one year overall survival of 75%.

Head and neck cancer

One prospective case series of patients with head and neck cancer treated with MR-IGRT reported the locoregional control at 1 year was 95%, and the one year progression-free and overall survival rates were 95% and 96%, respectively.

One cohort study reported two year survival outcomes of head and neck cancer treatment with CBCT-IGRT stratified by different target margin sizes. Overall survival was 75%, with two year locoregional control rate of 79-80%.

Quality of life

No comparative evidence was found for quality of life (QoL). Two studies in patients with unresectable abdominal cancer and with prostate cancer treated with MR-IGRT reported no differences in QoL scores on the same questionnaire (EORTC QLQ-C30) over the course of radiotherapy treatment.

One study reported QoL scores after CBCT-IGRT of prostate cancer. However, as no baseline measurements were provided, it is not clear if QoL scores changed during treatment.

Dosimetric outcomes

One comparative cohort study compared the dose-volumetric parameters of MR-IGRT and CBCT-IGRT lung radiation therapy plans. Dosimetric parameters were significantly more favourable in the CBCT-IGRT group. Two simulation studies compared MR-IGRT and CBCT-IGRT plans for patients that had previously undergone radiotherapy treatment for cancer. In one study, all MR-IGRT plans fulfilled the clinical acceptance criteria while a minimal decrease in plan homogeneity was found for MR-IGRT plans compared to current clinical practice for all included patients. In the other simulation study MR-IGRT treatment, resulted in a reduction of violations to the OARs.

The DCARs summary of findings for MR-IGRT is shown in Table 3.

Table 3 Summary of the effect and the overall quality of the evidence on the safety and effectiveness of MR-IGRT

Outcomes	Participants (studies)	Quality of evidence (GRADE)[a,b]	Summary[c]
Toxicity	211 participants (8 studies)	⊕⊙⊙⊙	One comparative study reported no difference in lung density between MR-IGRT and CBCT-IGRT on follow-up CT scans. In one (out of two) lung cancer CS, 15/50 (30%) patients treated with MR-IGRT experienced grade ≥2 toxicity. One CS of patients with prostate cancer treated with MR-IGRT reported 24% and 12% of patients suffering grade 1 and 2 GU toxicity, and 8% and 4% of patients suffering grade 1 and 2 GI toxicity, respectively. One (out of three) CS on abdominal malignancies treated with MR-IGRT reported grade ≥3 GI toxicity in 3/44 (7%) of patients. Any grade ≥3 or higher toxicity was reported in 44% of patients with head and neck cancer treated with MR-IGRT in one CS.
Patient tolerance	194 participants (2 studies)*	⊕⊙⊙⊙	In the two studies, 65% and 89/150 (80%) of patients treated with MR-IGRT reported at least some degree of potential MR-IGRT related complaints, respectively.
Survival	114 participants (4 studies)	⊕⊙⊙⊙	One year OS for patients treated with MR-IGRT: 88% (95%CI 70.1-97.7%) for patients with lung cancer (one CS); 69% for patients with HCC (one CS); 75% in unresectable abdominal cancer (one CS); 96% for patients with head and neck cancer (one CS).
Quality of life	63 participants (3 studies)	⊕⊙⊙⊙	Two studies of patients treated with MR-IGRT (unresectable abdominal cancer and prostate cancer) used the same questionnaire (EORTC QLQ-C30) and both reported no differences in QoL scores over the course of radiotherapy treatment.
Dosimetric outcomes	37 participants (3 studies)	⊕⊙⊙⊙	Dosimetric parameters for MR-IGRT plans were better than dosimetric parameters for CBCT-IGRT in two studies and worse than the CBCT-IGRT plans in one study.

Source: Table 2, ppxviii – xix of the DCAR
GRADE Working Group grades of evidence (Guyatt et al., 2013)
[b] For case series, the GRADE rating commenced at **very low** certainty evidence
[c] The interpretation is limited by the lack of comparative evidence for MR-IGRT *vs.* CBCT-IGRT
**S. U. Tetar et al. (2019) and S. Tetar et al. (2018)CBCT-IGRT
**S. U. Tetar et al. (2019) and S. Tetar et al. (2018) likely included overlapping populations. Only S. Tetar et al. (2018)Only S. Tetar et al. (2018) is included in the summary table
⊕⊕⊕⊕ **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
CBCT=cone beam computed tomography; CT=computed tomography; CS=case series; GI=gastrointestinal; GU=genitourinary; HCC=hepatocellular carcinoma; IGRT=image guided radiation therapy; MR=magnetic resonance; OS=overall survival; QoL=quality of life

Clinical claim

The clinical claim is that MR-IGRT is non-inferior in safety and non-inferior in clinical effectiveness, when compared to current standard of CBCT-IGRT. However, on the basis of the benefits and harms reported in the evidence base (summarised above), the DCAR suggested that, relative to CBCT-IGRT, the MR-IGRT has uncertain safety and uncertain effectiveness. The DCAR considered that the statement of uncertain safety relates to the absence of evidence. Safety concerns were not detected in the available evidence.

12. Economic evaluation

The DCAR considered that the clinical claim of uncertain safety and uncertain effectiveness impacts the choice of the economic model and based on the ratified PICO, it was decided that

a cost-minimisation analysis (CMA) was appropriate (Table 4). The base case of the economic evaluation is generated by a modelled economic evaluation using the evidence derived from two US studies Parikh et al. (2020)[2] and Schumacher et al. (2020)[3] on the healthcare resource utilisation, time spent on each activity, along with relevant capital costs, and relevant healthcare costs in the Australian healthcare setting, and where available, other Australian parameters. Furthermore, the economic model included the costs of the treatment related to acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer. The DCAR acknowledged potential applicability issues with using international data sources to inform the economic evaluation.

The DCAR also acknowledged in the Australian setting, underlying radiation therapy could be delivered using different treatment such as Intensity Modulated Radiation Therapy (IMRT). As such the radiation dose, number of fractions, and healthcare resources utilisation is likely to differ based on the radiation treatment and can impact the cost. Furthermore, depending on the type of cancer and stage, the requirements are likely to differ and impact the overall cost. This is a potential applicability issue, however, due to paucity in the evidence, it was decided to use the evidence available from the literature identified.

Table 4 Summary of the economic evaluation

Perspective	Australian healthcare system
Comparator	Cone-beam computed tomography (CBCT) guided radiation therapy
Type of economic evaluation	Cost-minimisation analysis (CMA)/Cost comparison
Sources of evidence	Systematic review
Time horizon	NA
Outcomes	Cost of MR-guided radiation therapy and CBCT-guided radiation therapy, cost of treatment related to adverse events in prostate cancer patients
Methods used to generate results	Cost-minimisation model
Discount rate	NA
Software packages used	Microsoft Excel 2016 MSO (16.0.8431.2110) 64-bit

Source: Table 3, p xxi of the DCAR
NA=Not applicable; MSO=Microsoft Office

There were several key assumptions for the DCARs economic evaluation:

- That radiation therapy will be delivered using 5 fractions SBRT to reflect the radiation therapy used in the literature and to main consistency in estimating the cost of MR-IGRT and CBCT-IGRT
- The lifetime of the equipment to be 10-years was used in the model, however, this is likely to vary and will impact the overall cost
- Fiducial marker placement was included as a prior step to simulation for all the patients, however, for majority of common cancers treated with radiotherapy, fiducials are not required and likely to overestimate the cost
- The number of treatment courses (volume of patients treated over lifetime) delivered using MR-guided SBRT and CBCT-guided SBRT was adopted from Schumacher et al. (2020). The estimates provided in the paper were for 15 years, however, the DCAR derived number of treatment course to be delivered using MR-guided SBRT and

[2] Parikh, N. R., Lee, P. P., Raman, S. S., Cao, M., et al. (2020). Time-Driven Activity-Based Costing Comparison of CT-Guided Versus MR-Guided SBRT. JCO Oncology Practice, 16(11), e1378-e1385.
[3] Schumacher, L.-E. D., Dal Pra, A., Hoffe, S. E., & Mellon, E. A. (2020). Toxicity reduction required for MRI-guided radiotherapy to be cost-effective in the treatment of localized prostate cancer. The British journal of radiology, 93(1114), 20200028.

CBCT-guided SBRT for 10 years (lifetime of the equipment assumed in the economic evaluation).

The overall costs, and incremental costs as calculated for the intervention and comparator in the model, with the base case assumptions, are shown in Table 5.

Table 5 Overall and incremental costs of MRI-guided radiation therapy and CBCT-guided radiation therapy

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
MRI-guided radiation therapy	$6,056.67	$1,930.39	NA	NA	NA
CBCT-guided radiation therapy	$4,126.29	-	NA	NA	NA

Table 3, p xxi of the DCAR
MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography

The DCAR stated that assuming the same hypofractionation schedule (5 fractions) of MR-guided SBRT and CBCT-guided SBRT in prostate cancer patients, the intervention has an incremental cost of $1,930 and is not cost saving. However, this finding might not extrapolate to all cancers as the underlying radiation treatment, radiation dose, fractionation schedule, healthcare resource utilisation, and cost of toxicities is likely to differ and impact the overall costs.

The DCAR noted from one-way sensitivity analyses, six parameters were found to have highest impact on the incremental cost (Figure 2). The sensitivity analysis demonstrates that number of patients treated over lifetime by MR-IGRT had the largest uncertainty. The DCAR considered that the cost of MR-IGRT equipment is likely to have low uncertainty given the price of the equipment is fixed by the applicant. All the other parameters did not have any substantial impact on the incremental cost on varying their values by 20%. For all the variables, a threshold analysis was further conducted by changing their values by 50%.

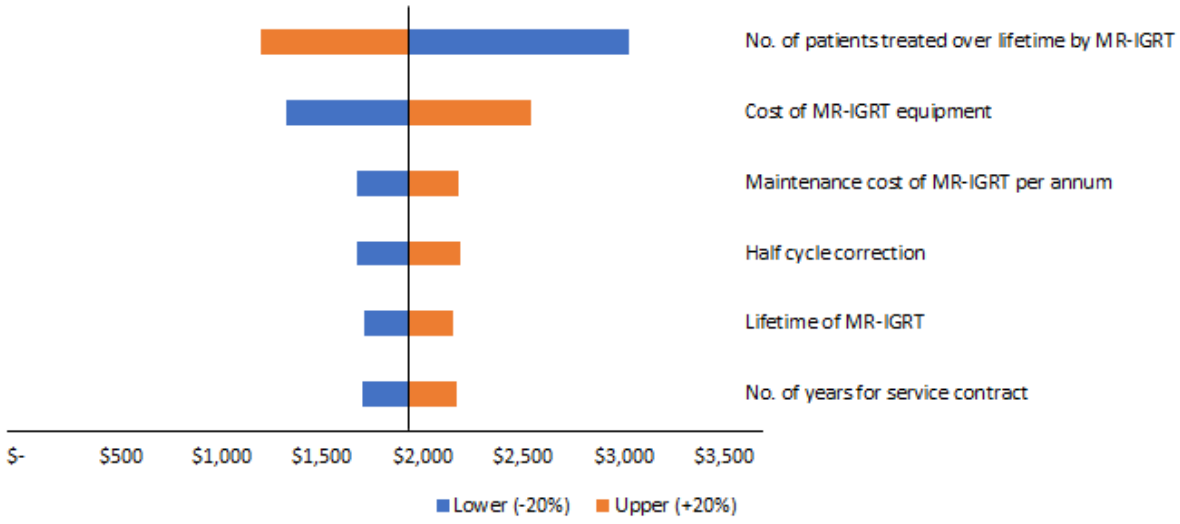

Figure 2 Tornado diagram of main drivers within the economic evaluation (± 20%)
Source: Figure 1, pxxii of the DCAR

In the base case analysis, the DCAR stated that the number of fractions administered by both treatments is 5, however, in scenario analysis, the number of fractions delivered by CBCT-IGRT were changed in the increment of 10 fractions up to 30 fractions per treatment course (Table 6). Expert clinical advice estimates that with CBCT-IGRT, prostate and breast cancer patients currently need between 16-20 fractions per treatment course in Australian clinical settings. This broadly concords with MBS utilisation data for MBS items 15565 (dosimetry planning) and 15275 (single episode of radiation oncology treatment, or fraction). The MBS 2019-20 utilisation data approximately equated to 19.5 fractions per patient undertaking

dosimetry planning for CBCT-IGRT. Based on this, the base case incremental cost reduced by 105% and 176% when CBCT-IGRT is delivered with 20 and 30 fractions respectively and MR-IGRT is delivered with 5 fractions. Unlike the base case result, increasing fractions for CBCT-IGRT is likely to favour MR-IGRT and result in cost-savings.

Table 6 Changing fractions for CBCT-IGRT and impact on the incremental cost

	Incremental Cost ($)			
Base case: MR-IGRT v CBCT-IGRT	$1,930			
MR-IGRT v CBCT-IGRT	**Intervention ($)**	**Comparator ($)**	**Incremental cost ($)**	**% change**
No. of fractions for CBCT-IGRT = 10	$6,056	$4,804	$1,252	-35%
No. of fractions for CBCT-IGRT = 20	$6,056	$6,159	-$103	-105%
No. of fractions for CBCT-IGRT = 30	$6,056	$7,515	-$1,459	-176%

Source: Table 5, pxxiii of the DCAR
MR-IGRT=Magnetic resonance image guided radiation therapy; CBCT-IGRT=Cone beam computed tomography image guided radiation therapy

The DCAR also conducted a scenario analysis by removing cost of fiducial marker placement from the cost of CBCT-IGRT. Based on this, the incremental cost of MR-IGRT *vs*. CBCT-IGRT increased by 11% as the overall cost of CBCT-IGRT reduced.

13. Financial/budgetary impacts

The DCAR stated a pragmatic 'mixed methods' approach was used to estimate the financial implications of the introduction of MR-IGRT (Table 7).

The DCARs financial analysis assumes initial MR-IGRT use for cancer indications (including breast and prostate cancer) where the Applicant and clinical advice has indicated there is emerging evidence for material fraction reductions compared to current CBCT-IGRT fraction rate estimates. The Applicant has indicated MR-IGRT is currently being used in Australia for these indications and is likely to do so upon any MBS listing. The financial implications results therefore reflect assumptions of 'optimal' fractionation.

However, the DCAR considered the financial implications are uncertain given identified uncertainties for the MR-IGRT treatment market including MR-linac deployment and facility capacity, treatment uptake, the patient population receiving treatment and the rate of technology improvement.

The DCAR highlighted that the economic evaluation noted MR-IGRT is more costly to deliver than CBCT-IGRT. However, the Applicant is not requesting a higher MBS fee. The Applicant considered that no net impact to out-of-pocket costs would be expected and any impact would be dependent on the individual MR-IGRT treatment provider. The analysis therefore assumes that any additional costs of MR-IGRT treatment above the MBS fee would be required to be paid by the patient out-of-pocket. However, whether this would happen is uncertain.

Table 7 Net MBS financial impact of MR-IGRT listing

Item	2021	2022	2023	2024	2025
Estimated utilisation impact					
Incremental number of services (courses of therapy)[1]	0	0	0	0	0
Number of services (courses of therapy substituted)[1]	1,656	3,312	10,120	10,120	10,120
MBS item 15565 (planning)[1]	0	0	0	0	0
MBS item 15555 (simulation)[1]	0	0	0	0	0
MBS item 15275 (fraction)[2]	-21,528	-43,056	-131,560	-131,560	-131,560
Estimated financial impact					
Fiducial marker placement	-$626,382	-$1,252,764	-$3,827,890	-$3,827,890	-$3,827,890
MBS item 15565 (planning)[1]	$0	$0	$0	$0	$0
MBS item 15555 (simulation)[1]	$0	$0	$0	$0	$0
MBS item 15275 (fraction)[2]	-$3,453,091	-$6,906,182	-$21,102,224	-$21,102,224	-$21,102,224
Total cost of MR-IGRT to the MBS	**-$4,079,473**	**-$8,158,946**	**-$24,930,114**	**-$24,930,114**	**-$24,930,114**

Abbreviations: "MBS"=Medical Benefits Schedule, "MR-IGRT"=magnetic resonance image-guide radiation therapy
Note: No changes to course numbers, planning episodes or simulation would be anticipated assuming patient substitution of CBCT-IGRT for MR-IGRT, as analysis assumes substitution of CBCT-IGRT for MR-IGRT only and planning episodes and simulation are assumed to occur only once per patient treatment course, regardless of radiation therapy technology used.
Financial implications analysis is based on assumptions regarding potential achievable fraction reductions per treatment course specifically for the prostate and breast cancer indications. Based on Applicant and clinical advice, analysis assumes an average of five treatment fractions per course for MR-IGRT versus an average of 18 treatment fraction per course for CBCT-IGRT.

The financial model estimates the MBS per patient cost (assumed at an 85% rebate rate) of MR-IGRT treatment to be $4,783 compared to $7,246 with CBCT-IGRT. There were several key assumptions underlying the analysis:

- Substitution of CBCT-IGRT treatment for MR-IGRT (i.e., no patients from alternative treatments e.g. surgery or chemotherapy are assumed)
- Three MR-linac facilities in operation from year one, increasing to ten by year three and remaining at that level thereafter
- The locations of MR-linac machines deployed in Australia provides for CBCT-IGRT and MR-IGRT to be equally feasible patient treatment options
- As above, initial utilisation of MR-IGRT for cancer indications it has already been used for to date in Australia, including indications where the Applicant and clinical advice indicate significant fraction reductions have already occurred (e.g. breast and prostate cancer)
- Reduction in average treatment time from 45 minutes to 25 minutes by year three.

The DCAR considered as there is no anticipated change to the number of radiation therapy courses there would be no expected changes to use of MBS items 15565 (dosimetry planning) and 15555 (simulation).

Referencing the economic evaluation, the DCAR noted that indicative analysis estimates reduced per person adverse event related costs for MR-IGRT patients relative to CBCT-IGRT patients with prostate cancer. It should be noted this analysis assumes a five fractions treatment for both MR-IGRT and CBCT-IGRT. As such it may not be applicable to other cancer indications or current CBCT-IGRT practice, with clinical advice indicating current CBCT-IGRT treatment fractions used being higher. The analysis estimates MBS savings of $778 per patient and PBS savings of $641 per patient.

The DCAR stated that should MR-IGRT market parameters and treatment input assumptions

progress as estimated by the Applicant, there would be potentially significant MBS cost savings. However, it should be noted these financial implications estimates do not necessarily reflect the potential outcomes that may occur should any resulting MR-IGRT use upon MBS listing be under different circumstances. This includes in particular treatment fraction reductions achieved for the treated patient populations and MR-linac treatment facility capacity.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Evidence base	There is a lack of long-term safety and effectiveness data; however, available data appears comparable with the comparator, which is expected given the radiation delivery hardware is the same as the comparator.
Future potential of MR-IGRT is not explored in the DCAR	The potential benefits of the more complex replanning/adaptive radiotherapy are not included in the DCAR. There is potential for a future MSAC application for a replanning item number.
Economic evaluation	The limited comparative evidence on safety and effectiveness impacts the validity of the economic evaluation.
Translation/economic caveat	Using different fractions for sensitivity analysis for MR-IGRT *vs.* CBCT-IGRT in the DCARs scenario analysis is not clinically relevant, because CBCT-IGRT can treat the same disease with a similar fractionation schedule as MR-IGRT.

ESC discussion

ESC noted that this application was for a Medicare Benefits Schedule (MBS) listing of magnetic resonance image–guided radiation therapy (MR-IGRT or MR-linac) for the treatment of cancer. ESC noted that MRI provides improved soft tissue resolution and MR-IGRT allows real time imaging and differentiation of tumour and surrounding normal tissue before/during treatment, with no additional radiation dose. The applicant had requested an amendment to the way the service is clinically delivered under the existing MBS item number 15275. ESC noted that as item 15275 is technologically agnostic, and the applicant is not seeking a higher fee, no amendments would be required to this item to allow MR-IGRT use.

ESC noted there are currently two operational MR-linac machines in Australia (Townsville and Sydney) and a third Elekta Unity MR-linac is planned to start operating in Victoria (Austin hospital) in mid 2021. ESC also noted that the applicant estimates that in the next three years, 10 MRI-Linac machines will be installed in Australia. ESC noted that all three facilities have obtained interim approval to use MBS item 15275 for MR-IGRT.

ESC noted that consultation feedback was received from several societies, a charity group (Lung Foundation) and industry, all in support of the intervention. ESC noted that consumer issues concerned equity of access, given that there are only 2-3 centres currently offering this treatment in Australia.

ESC noted Department advice that should the application be successful, there is a high probability that radiotherapy facilities will seek Commonwealth funding for MR-linac through the Radiation Oncology Health Program Grants (ROHPG) scheme. However, the Department does not expect significant financial impact on the ROHPG scheme. It is anticipated that ROHPG applications for MR linac funding will primarily be for "replacement" i.e. linacs replacing equipment due to be decommissioned. However, ESC

considered it was uncertain whether MR-linacs will replace current linacs given that MR-linac is more time intensive than the comparator and is a relatively new technology. The amount of funding received under the ROHPG scheme is not dependent on the type of linac being installed i.e. successful applicants for ROHPG funding receive a flat rate of $3 million per linac.

ESC noted that the comparator is cone-beam computed tomography (CBCT)-guided radiation therapy (CBCT-IGRT), and that the only difference in the algorithm is that MR-IGRT has an additional step to allow imaging during treatment.

ESC noted that there is limited comparative evidence on safety and effectiveness (including quality of life), with only one retrospective cohort study included in the Department-contracted assessment report (DCAR). Due to this absence of comparative evidence, ESC noted the DCAR included a naïve comparison of MR-IGRT *vs.* CBCT-IGRT assessing toxicity, patient tolerance, survival, quality of life and dosimetric outcomes in patients with lung cancer, prostate cancer, liver and abdominal malignancies. However, ESC noted the results should be interpreted with caution due to the significant heterogeneity in patient populations, technologies and radiation dose. ESC considered that very low quality evidence base is mainly due to the fact that the technology is relatively new with limited current use in Australia, and that the applicant had acknowledged this.

ESC noted that the DCAR stated that on the basis of the benefits and harms reported in the evidence base, relative to CBCT-IGRT, that MR-IGRT has uncertain safety and uncertain effectiveness. The statement of uncertain safety relates to the absence of evidence, as safety concerns were not able to be addressed in the available evidence. However, ESC noted that the applicant's claim of non-inferior safety and effectiveness may be reasonable given that although MRI-IGRT is a new technology, it is the same radiation delivery hardware as current CBCT-IGRT. However, evidence would still be required to support this assumption.

ESC noted that the applicant is requesting the same MBS fee for the proposed intervention as for CBCT-IGRT, which was confirmed in the pre-ESC response. However, given there are higher capital and staff costs compared to CBCT-IGRT, ESC was concerned that there may be higher out-of-pocket costs.

Given that the clinical claim is uncertain safety and uncertain clinical effectiveness, the applicant developed a costing model as a cost comparison.

ESC noted that while the level of details included in the costing model is appropriate, there are applicability issues in the sources used to estimate the number and type of health care resources and toxicity rates. Two US-based studies (Schumacher et al. 2020 and Parikh et al. 2020) were used, so differences in clinical practice could impact the type and quantity of resources used in the costing model. In addition, both studies used stereotactic body radiation therapy (SBRT). However, in the Australian setting, different treatment is commonly used (e.g. intensity-modulated radiation therapy), and this could impact the radiation dose, number of fractions and the use of heath care resources. ESC noted the DCARs base-case costing model assumed 5 fractions SBRT for MR-IGRT and CBCT-IGRT based from the literature.

In terms of the toxicity data, ESC noted that the economic model only included the costs of the treatment related to acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer informed from the literature review, noting averaging was taken where more than one estimate was available across studies. It was conducted internationally, used different treatment regiments and had heterogeneity in the patient population. Therefore, this could impact resource use and hence cost estimates. ESC also noted the only comparative

study (Kim 2018) in the DCAR found no significant difference in radiation toxicity in patients with lung cancer.

Furthermore, ESC considered that, depending on the type of cancer and stage, the requirements and the duration of treatment (number of fractions) for interventions (and hence the use of health care resources) are likely to differ, which could impact resource use and thus cost estimates.

ESC noted that the DCARs sensitivity analyses used arbitrary 20% and 50% thresholds, which it considered might be appropriate due to the limited evidence base. ESC also noted that the key driver of the costing model was the number of fractions between MR-IGRT and CBCT-IGRT. However, ESC considered that using different fractions for MR-IGRT *vs*. CBCT-IGRT in the DCARs scenario analysis is not clinically appropriate, because currently CBCT-IGRT can treat the same disease with similar fractionation schedule as MR-IGRT.

ESC noted that a mixed approach was used to estimate the financial implications. The net cost savings associated with the use of MR-IGRT to the MBS is estimated to be ~$4 million in year 1 increasing to $24.9 million by year 5. However, the DCARs financial analysis assumes initial MR-IGRT use for cancer indications (including breast and prostate cancer) where the Applicant and clinical advice has indicated there is emerging evidence for material fraction reductions compared to current CBCT-IGRT fraction rate estimates. In terms of average fractions per treatment course, 5 fractions were used for the proposed intervention (mainly based on information on prostate cancer) and 18 fractions for CBCT (i.e. a 13-fraction reduction). However, ESC noted that the validity of these numbers is difficult to evaluate as stated before.

ESC noted that, in the pre-ESC response, the applicant stated that Australian MR-IGRT sites indicates 87% of patient courses are delivered with SBRT dose levels, resulting in an average number of treatment fractions per patient course totaling 6.9 fractions (75 patients for a total of 520 fractions). As noted in the DCAR, MBS data provided an average of 19.5 fractions per patient for CBCT-IGRT. However, ESC considered that this analysis cannot be considered reflective of all cancer indications. As an example, the impact on the number of fractions might be more applicable in some cancer types, such as those in a soft-tissue area (e.g. the abdomen and liver malignancies).

ESC noted the possibility of using the more complex adaptive radiotherapy (replanning the radiation treatment before each fraction based on MRI images) with MG-IGRT in the future, having the potential for smaller margins, higher dose, improved tumour kill, less toxicity and shorter treatments; but that this was not assessed in the current application. ESC noted it could be explored in a future MSAC application requesting a new replanning item number.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Elekta and the Clinical Expert team, as the Applicant for the MSAC 1620 submission, are pleased with the outcome to support eligibility of MR-Linacs to utilise the existing IGRT MBS Item for MR-IGRT. The reported decision in this Public Summary Document is of great importance to Radiation Therapy patients and will contribute to enable patients access to MR-Linac treatments. MR-Linac treatments have the potential to increase patient outcomes through advanced imaging, smaller planning/treatment margins and reduced

toxicity. The availability of MR-Linacs for the Australian population ensures the continued advancement in Radiation Therapy services available and progress in the resulting patient outcomes.

17. Further information on MSAC

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