Magnetic Resonance Image Guided Radiation Therapy

December 2020

MSAC application no. 1620

Assessment report

© Commonwealth of Australia 2020

ISSN (Online) 1443-7139

Internet site http://www.msac.gov.au/

This work is copyright. You may download, display, print and reproduce this material in unaltered form only (retaining this notice) for your personal, non-commercial use or use within your organisation. Apart from any use as permitted under the Copyright Act 1968, all other rights are reserved. Requests and inquiries concerning reproduction and rights should be addressed to Commonwealth Copyright Administration, Attorney-General's Department, Robert Garran Offices, National Circuit, Barton ACT 2600 or posted at http://www.ag.gov.au/.

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Enquiries about the content of the report should be emailed to hta@health.gov.au.

The technical information in this document is used by the Medical Services Advisory Committee (MSAC) to inform its deliberations. MSAC is an independent committee which has been established to provide advice to the Minister for Health on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC's advice does not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the NHMRC Clinical Trials Centre, the University of Sydney. The report was commissioned by the Australian Government Department of Health.

The suggested citation for this document is:

Berber S, Blaya Novakova V, Agresta B, Shah, K, Fox, N, Raichand, S (2020). *Magnetic Resonance Image Guided Radiation Therapy*. MSAC Application 1620, Assessment Report. Commonwealth of Australia, Canberra, ACT.

CONTENTS

TABLES

BOXES

FIGURES

EXECUTIVE SUMMARY

Main issues for MSAC consideration

- There was insufficient evidence from comparative studies for this assessment consisting of one retrospective matched cohort study in lung cancer patients reporting on a surrogate outcome for pulmonary toxicity following radiotherapy.
- Due to the lack of comparative evidence a naïve comparison was attempted. 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.
- The economic evaluation consisted of a cost-minimisation analysis representing cost of delivering MR-IGRT and CBCT-IGRT with 5 fractions of Stereotactic Body Radiation therapy (SBRT) and included the modelled toxicity in prostate cancer patients. The base case of the economic evaluation was generated using the evidence available from two studies conducted in the United States. Hence, there are considerable applicability issues in using the evidence in the Australian healthcare setting. The healthcare resource utilisation, and time estimates on each activity of MRI-IGRT and CBCT-IGRT from these two studies were multiplied with relevant healthcare costs in the Australian healthcare setting, and where available, other Australian parameters. Furthermore, the economic evaluation only included costs of treatment related to acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer due to the availability of evidence. Toxicity related to other kind of cancers were not included due to the lack of evidence.
- The economic evaluation assumed that radiation therapy will be delivered using 5 fractions of SBRT. However, 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.
- Assuming the capability of MR-IGRT to achieve reductions in the number of fractions required, there is potential for significant cost savings for the MBS. MBS cost savings would be largely driven by reductions in treatment fractions and growth in MR-linac treatment capacity. Given the uncertainties identified including switching rates from CBCT-IGRT, the patient population treated, the progression of technological capabilities and health system capacity, there is the potential for cost savings to vary considerably.

Main issues for MSAC consideration

- These results are in contrast to those of the economic evaluation, which notes MR-IGRT is more costly to deliver than CBCT-IGRT. The Applicant is not requesting a higher MBS fee, considering there to be no expected net impact to out-of-pocket costs, with any impact dependent on the individual MR-IGRT treatment provider. While the Applicant has stated that the difference between the cost to deliver MR-IGRT and the MBS cost would not be transferred to the patient, it is uncertain who would cover this cost.

MAGNETIC RESONANCE IMAGE GUIDED RADIATION THERAPY

This Department contracted assessment report (DCAR) examines the evidence to support listing of Magnetic Resonance Image Guided Radiation Therapy (MR-IGRT) on the Medicare Benefits Schedule (MBS). The service would be used in the inpatient and outpatient setting for the treatment of cancer. The target population are all people with cancer scheduled for external beam radiation therapy (EBRT). The Applicant has claimed that the successful listing of the technology in the target population and setting will introduce a clinical choice for tumour sites benefiting of reduced target volume margins and hypofractionated courses.

ALIGNMENT WITH AGREED PICO CONFIRMATION

This DCAR of MR-IGRT addresses some of the PICO[1] elements that were pre-specified in the PICO Confirmation that was ratified by the PICO Advisory SubCommittee (PASC). The literature search retrieved a single comparative study (Kim et al. 2018), reporting on a surrogate outcome for lung toxicity following radiotherapy in patients with lung cancer. Due to the paucity of comparative evidence a naïve comparison was attempted. The validity of this comparison is very limited due to the variety of treatment modalities, treatment schedules and dose, and differing patient characteristics encountered.

PROPOSED MEDICAL SERVICE

MR-IGRT, also known as MR-linac, combines a 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.

The intervention is not currently used for other clinical indications in Australia.

[1] Population, Intervention, Comparator, Outcomes

PROPOSAL FOR PUBLIC FUNDING

The Applicant requested an amendment to the way the service is clinically delivered under existing MBS item 15275 (Table 1). This MBS item is technologically-agnostic, as confirmed by PASC.

Table 1 Proposed MBS item descriptor

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

*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

POPULATION

The proposed population includes all patients with cancer undergoing 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.

COMPARATOR DETAILS

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).

CLINICAL MANAGEMENT ALGORITHM(S)

The key difference between the current standard of care in IGRT (performed with CBCT) and MR-IGRT is that MR-IGRT delivers a higher level of soft tissue imaging and a more sophisticated adaptive functionality, enabling the user to optimise dose distribution of the treatment plan for every fraction in an online setting (i.e. while the patient is in the machine).

Clinical management algorithm for the proposed MR-IGRT relative to the current clinical practice is depicted in Figure 2 in Section A.

Key Differences in the Delivery of the Proposed Medical Service and the Main Comparator

The procedure for every treatment fraction is similar to the standard IGRT procedure: patient setup, imaging, adaptation, and treatment. Use of MR-linac involves the same professionals as CBCT-linac: radiation oncologists, medical physicists, and radiation therapists. However, more complex workflows may require all these professionals be present collectively at the treatment machine at the same time. The MR-IGRT technique is more time-intensive than the comparator, requiring twice- to three-times as long per fraction as CBCT-IGRT.

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.

Approach Taken to the Evidence Assessment

A systematic literature search of medical literature was undertaken on 02 October 2020 to identify relevant studies and systematic reviews published since 2014. Only literature published since 2014 was included corresponding to the year MR-IGRT was first used for patient treatment (Chin et al., 2020). Due to the paucity of comparative evidence on MR-IGRT and CBCT-IGRT, a second search was conducted on 23 October 2020 with no date limits to capture comparative studies with technical outcomes as well as studies on CBCT-IGRT which could be used for a naïve comparison.

Studies were selected by a single reviewer. Any doubts regarding study selection were discussed with a second reviewer.

Due to a considerable heterogeneity in patient populations, technologies used, and radiation dose received in the included studies on MR-IGRT and CBCT-IGRT, the naïve comparison is of limited validity for evaluating the outcomes pre-specified in the ratified PICO.

Characteristics of the Evidence Base

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

The 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.

Key features of the included evidence on MR-IGRT and CBCT-IGRT are summarised in Section B4.

RESULTS

Safety

Comparative evidence on the safety of MR-IGRT compared to CBCT-IGRT was scarce, with only one retrospective cohort study identified. Therefore, a naïve comparison of single-arm MR-IGRT studies and CBCT-IGRT studies was attempted. The overall contribution of this naïve comparison to the evidence base is limited due to low methodologic quality of the included studies and a considerable heterogeneity in patient populations, technologies used, and radiation dose received.

Toxicity

Lung cancer

One retrospective cohort study 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 (liver, pancreas, 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, paraesthesias).

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

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.

Additionally, 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 summary of findings for MR-IGRT is shown in Table 2.

Table 2 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.

Outcomes	Participants (studies)	Quality of evidence (GRADE)[a,b]	Summary[c]
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.

[a] 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

On the basis of the benefits and harms reported in the evidence base (summarised above), **it is suggested that, relative to CBCT-IGRT, the MR-IGRT has uncertain safety and uncertain effectiveness.** The statement of uncertain safety relates to the absence of evidence. Safety concerns were not detected in the available evidence.

TRANSLATION ISSUES

Applicability issues

The DCAR have used the estimates from the two US based studies (Schumacher et al and Parikh et al) to conduct the economic evaluation. This is a potential applicability issue considering the estimates in these two studies reflect the clinical practice within the US, however, due to paucity of the evidence in the Australian setting, it was decided to use the evidence from these two studies.

Schumacher, Dal Pra, Hoffe, and Mellon (2020) presented toxicity reduction required for MR-IGRT radiotherapy to be cost-effective in the treatment of localized prostate cancer compared with CBCT-guided radiation therapy conducted in the United States population. In this study, two treatment regiments were modelled, conventional fractionation with 39 daily fractions and SBRT with 5 fractions. The study by Parikh et al. (2020) presented time-driven activity-based costing comparison of CBCT-IGRT versus MR-IGRT for patients with unresectable hepatocellular carcinoma as an example in the United States. In this study, CT-guided SBRT and MR-guided SBRT were delivered

with 50 Gy over 5 fractions in patients with localized unresectable hepatocellular carcinoma. In the assessment, the assumption was made that radiation therapy will be delivered using 5 fractions SBRT to reflect the radiation therapy used in both studies and to main consistency in estimating the cost of MR-IGRT and CBCT-IGRT.

However, 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.

The rates of different grades of toxicity related to prostate cancer were based on naïve comparison across different studies presented in Table 20 and Table 21. Relevant treatment costs were applied to the toxicity rates provided to calculate the cost of toxicity associated with MR-IGRT and CBCT-IGRT. This is a potential applicability issue since these studies were conducted internationally, had methodological weaknesses, heterogeneity in the patient population included. However, for the economic evaluation, they were the best source of available evidence on prostate cancer related toxicities post MR-IGRT and CBCT-IGRT.

Any other translation issues

No other translation issues were identified.

ECONOMIC EVALUATION

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. The base case of the economic evaluation is generated by a modelled economic evaluation using the evidence derived from Parikh et al. (2020) and Schumacher et al. (2020) 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 from the studies reported in Table 20 and Table 21.

Table 3 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

NA=Not applicable; MSO=Microsoft Office

Key assumptions of the economic evaluation are:

- As explained in the translational issues, the assumption was made 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 assumption that 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 certain kinds of cancer, it might not require 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 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 the Table 4.

Table 4 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

MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography

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.

From one-way sensitivity analyses, six parameters were found to have highest impact on the incremental cost as provided in Figure 1. The sensitivity analysis demonstrates that number of patients treated over lifetime by MR-IGRT has the largest uncertainty. 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%.

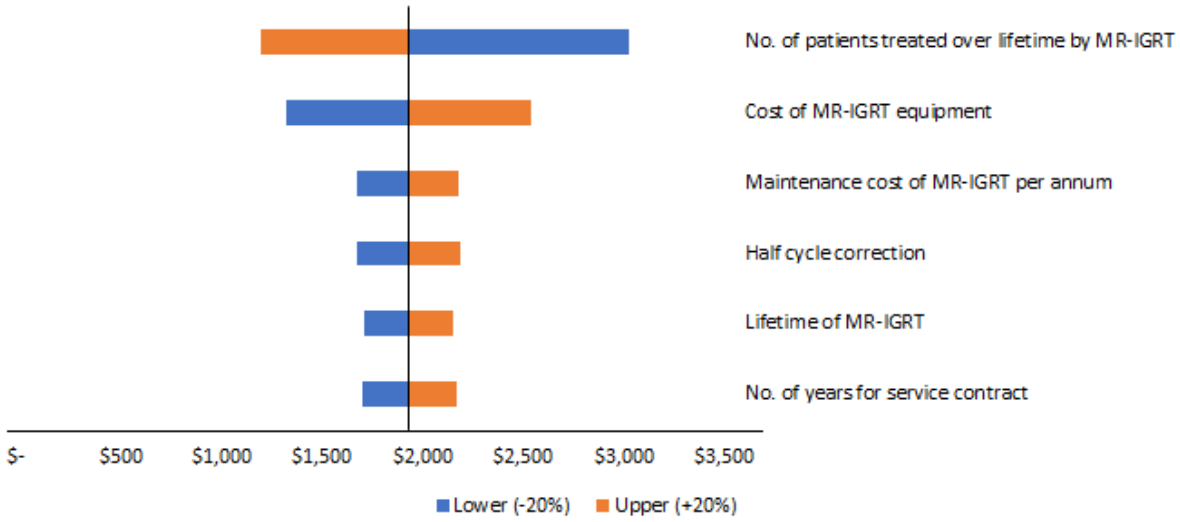

Figure 1 Tornado diagram of main drivers within the economic evaluation (± 20%)

In the base case analysis, the number of fractions administered by both treatment is 5, however, in the 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 as shown in Table 5. Expert clinical advice estimates that with CBCT-IGRT, prostate and breast cancer patients currently need between 16 to 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 5 Changing fractions for CBCT-IGRT and impact on the incremental cost

MR-IGRT v CBCT-IGRT	Intervention ($)	Comparator ($)	Incremental cost ($)	% change
Base case: MR-IGRT v CBCT-IGRT	$6,056.67	$4,126.29	$1,930	-
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%

MR-IGRT=Magnetic resonance image guided radiation therapy; CBCT-IGRT=Cone beam computed tomography image guided radiation therapy

In the base case analysis, fiducial marker placement was included as a prior step to simulation for all the patients, however, for certain kinds of cancer, it might not require and likely to overestimate the cost. The DCAR 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.

ESTIMATED EXTENT OF USE AND FINANCIAL IMPLICATIONS

A pragmatic 'mixed methods' approach was used to estimate the financial implications of the introduction of MR-IGRT.

The financial implications to the MBS resulting from the proposed listing of MR-IGRT are summarised in Table 6. The 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, financial implications are considered 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 economic evaluation notes 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 6 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. Key assumptions underlying analysis include:

- 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-linacs 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); and
- Reduction in average treatment time from 45 minutes to 25 minutes by year three.

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, 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.

Analysis indicates 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

CONSUMER IMPACT SUMMARY

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 RANZCR, Australian Society of Medical Imaging and Radiation Therapy (ASMIRT), and Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM)), one charity (Lung Foundation Australia), one field expert (Prof. Paul Keall, PhD), and a Public Consultation Survey has been received from Device Technologies Australia (DTA) and Viewray. Additionally, the ACPSEM and the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) offered further comments on the Ratified PICO and on the safety of the technology. 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.

ACRONYMS AND ABBREVIATIONS

Acronym/Abbreviation	Meaning
3D-CRT	three-dimensional conformal radiation therapy
ACPSEM	Australasian College of Physical Scientists & Engineers in Medicine
AE	adverse event
AHRQ	Agency for Healthcare Research and Quality
AIHW	Australian Institute of Health and Welfare
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
ARTG	Australian Register of Therapeutic Goods
ASMIRT	Australian Society of Medical Imaging and Radiation Therapy
CBCT	cone-beam computed tomography
CBCT-IGRT	cone-beam computed tomography-guided radiation therapy
CI	confidence interval
CT	computed tomography
CTCAE	The Common Terminology Criteria for Adverse Events
CTV	clinical target volume
DCAR	Department contracted assessment report
DVH	dose-volume histogram
EBRT	external beam radiation therapy
EORTC	European Organisation for Research and Treatment of Cancer
GI	gastrointestinal
GMDN	Global Medical Device Nomenclature
GTV	gross tumour volume
GU	genitourinary
HESP	Health Expert Standing Panel
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy

Acronym/Abbreviation	Meaning
MBS	Medicare Benefits Schedule
MD	mean difference
MR	magnetic resonance
MR-IGRT	magnetic resonance image-guided radiation therapy
MSAC	Medical Services Advisory Committee
NHMRC	National Health and Medical Research Council
NOS	Newcastle-Ottawa Scale
PASC	PICO Confirmation Advisory Sub-Committee of the MSAC
PRO-Q	Patient Reported Outcome Questionnaire
PTV	planning target volume
QALY	Quality Adjusted Life Year
RANZCR	Royal Australian And New Zealand College of Radiologists
RILD	radiation-induced lung damage
OAR	organ at risk
SBRT	stereotactic body radiation therapy
SRS	stereotactic radiosurgery
SRT	stereotactic radiation therapy
TGA	Therapeutic Goods Administration
TROG	Trans-Tasman Radiation Oncology Group
Qol	quality of life
QLQ	Quality of Life Questionnaire

SECTION A CONTEXT

This DCAR of Magnetic Resonance Image-Guided Radiation Therapy (MR-IGRT) for the treatment of cancer is intended for the Medical Services Advisory Committee (MSAC). MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Schedule (MBS) in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

The NHMRC Clinical Trials Centre of the University of Sydney has been commissioned by the Australian Government Department of Health to conduct a systematic literature review and economic evaluation of MR-IGRT. This assessment has been undertaken in order to inform MSAC's decision-making regarding whether the proposed medical service should be publicly funded.

Appendix A provides a list of the people involved in the development of this DCAR.

The proposed use of MR-IGRT in Australian clinical practice was outlined in a PICO Confirmation that was presented to, and accepted by, the PICO Confirmation Advisory Sub-Committee (PASC). The PICO Confirmation was released for public comment on 17 April 2020.

A.1. ITEMS IN THE AGREED PICO CONFIRMATION

This DCAR of MR-IGRT addresses some of the PICO elements that were pre-specified in the PICO Confirmation that was ratified by PASC.

Table 7 PICO Confirmation checkbox

PASC-approved PICO Confirmation Item	Compliance	Change and justification provided in DCAR
Proposed MBS listing	*Yes*	
Population / clinical indication	*Yes*	Evidence was found for the following cancer sites: - Lung cancer - Prostate cancer - Head and neck cancer - Abdominal malignancies (HCC, pancreas, secondary oligometastases in the abdomen, namely liver)
Comparator	*Yes*	
Clinical management algorithm	*Yes*	
Clinical outcomes assessed	*Yes*	Clinical outcomes with available evidence included: Treatment toxicity (short- and long-term), tumour control, survival (OS, PFS, DFS), patient tolerance of treatment, quality of life, dosimetric evidence

PASC-approved PICO Confirmation Item	Compliance	Change and justification provided in DCAR
		No evidence was found for facilitation of radiation therapy dose escalation
Healthcare resources	*Yes*	

DFS=disease-free survival; HCC=hepatocellular carcinoma; MBS=Medical Benefits Schedule; NA=not applicable; OS=overall survival; PASC=PICO Advisory Sub-Committee; PFS=progression-free survival

Due to the paucity of comparative studies between the intervention (MR-IGRT) and the comparator (cone-beam computed tomography [CBCT]-guided radiation therapy; CBCT-IGRT), a naïve comparison was attempted. The findings of this comparison should be interpreted with caution and used for explorative purposes only. Due to a considerable heterogeneity in patient populations, technologies used, and radiation dose received in the included studies on MR-IGRT and CBCT-IGRT, the naïve comparison is of limited benefit in evaluating the outcomes pre-specified in the ratified PICO.

A.2. PROPOSED MEDICAL SERVICE

An application requesting MBS listing of image-guided radiation therapy (IGRT) for cancer treatment delivery was received from the Trans-Tasman Radiation Oncology Group (TROG) and the Faculty of Radiation Oncology within the Royal Australian and New Zealand College of Radiologists (RANZCR) by MSAC in August 2011 (MSAC application number 1319). MSAC supported public funding of IGRT on a cost neutral basis relative to MBS expenditure on three-dimensional conformal radiotherapy (3D-CRT) in April 2015. IGRT may be delivered using a range of technologies including two- and three-dimensional imaging, ultrasound, and magnetic resonance (MR).

The present application concerns MR-IGRT for cancer treatment delivery. This technology, also known as MR-linac, combines a MR imaging unit with a radiation therapy unit (linear accelerator, linac), allowing real-time imaging of target volumes and organs at risk (OAR) before and during treatment delivery, with re-planning as necessary (Chin et al., 2020).

MR-IGRT is expected to be used as a replacement to current practice (CBCT-IGRT), and to introduce a clinical choice for tumour sites benefiting of reduced target volume margins and hypofractionated courses (i.e. receiving the total radiation dose in fewer, but larger fractions given once a day or less often). The extent to which the current standard of IGRT delivery (using CBCT imaging system) would be substituted with MR-IGRT may be difficult to estimate, because MR-IGRT is a relatively novel technique. The uptake of MR-IGRT is likely to depend on access to the service, resources, and clinical indications.

It is proposed that the MR-IGRT treatment is delivered in inpatient and outpatient settings, both public and private.

MARKETING STATUS OF DEVICE / TECHNOLOGY

All therapeutic products marketed in Australia require listing on the Australian Register of Therapeutic Goods (ARTG). MSAC will not consider a therapeutic product for reimbursement if the device is not listed on the ARTG.

According to a recently published literature review (Hall et al., 2019), two commercial MR-IGRT technologies are currently available (ViewRay MRIdian Linac, ViewRay Technologies Inc., Oakwood Village, Ohio, USA, and Elekta Unity, Elekta AB, Stockholm, Sweden). Two additional technologies are currently in development (Australian MRI Linac System by the Australian MRI-Linac Program, and Aurora-RT system by MagnetTx, Edmonton, Alberta, Canada).

The difference between the technologies lies, among parameters, in differing beam penetration and MRI field strength (Table 8).

Table 8 Types of MR-IGRT technologies currently available (adapted from Hall et al. (2019) and Chin et al. (2020))

Commercial name	Manufacturer	MRI field strength	Bore size	Beam strength	ARTG no.
Available					
ViewRay Co-60	ViewRay Technologies Inc, Oakwood Village, Ohio	0.35T	70 cm	Co-60 source	NA
ViewRay Linac	ViewRay Technologies Inc, Oakwood Village, Ohio	0.35T	70 cm	6 MV	319241
Elekta Unity	Elekta AB, Stockholm, Sweden	1.5T	70 cm	7 MV	307588
In development					
Australian MRI Linac System	Australian MRI-Linac Program	1 T	82 cm	4 MV and 6 MV	NA
Aurora-RT system	MagnetTx, Edmonton, Alberta, Canada	0.6 T	60 cm	6 MV	NA

ARTG=Australian Register of Therapeutic Goods; Co-60=Cobalt-60; MRI=magnetic resonance imaging; MV=megavoltage; NA=not applicable

Items on the ARTG that are relevant to this application are shown in Table 9.

Table 9 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: Therapeutic Goods Administration, accessed 15 October 2020 Link to TGA.gov.au
ARTG=Australian Register of Therapeutic Goods; GMDN=Global Medical Device Nomenclature code; MRI=magnetic resonance imaging

OTHER INDICATIONS

The intervention is not currently used for other clinical indications in Australia.

CURRENT FUNDING ARRANGEMENTS

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 supposed to start operating in Victoria in late 2020/early 2021. All three facilities have obtained interim approval to use MBS item 15275 for MR-IGRT.

The Applicant estimated that at least ten MR-linac devices are expected to be installed in Australia in both public and private sector in the upcoming three years, based on the current level of interest from the radiation oncology field, orders in hand and market opportunities. The Applicant considered that no net impact on out-of-pocket costs would be expected and would be dependent on the individual provider, just as the situation currently is for all radiation therapy treatments in Australia.

A.3. PROPOSAL FOR PUBLIC FUNDING

The proposed MBS item descriptor is summarised in Table 10.

The Applicant requested an amendment to the way the service is clinically delivered under existing MBS item 15275. This MBS item is technologically agnostic, as confirmed by PASC.

Table 10 Proposed MBS item descriptor (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

*Fees updated according to current information on mbsonline.gov.au as of 10 December 2020
CT=computed tomography; IGRT=image guided radiation therapy; IMRT=intensity-modulated radiation therapy; MBS=Medical Benefits Schedule

Item 15275 is billed with item 15555 Simulation for intensity-modulated radiation therapy (IMRT; Table 11), as well as item 15565 Preparation of an IMRT dosimetry plan (Table 12). The Applicant claimed that simulation and dosimetry workflows and processes will be consistent with current practice, if implemented with MR-IGRT.

Table 11 Proposed MBS item descriptor (15555)

Category 3 – THERAPEUTIC PROCEDURES
SIMULATION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT), with or without intravenous contrast medium, if: 1. treatment set-up and technique specifications are in preparations for three-dimensional conformal radiotherapy dose planning; and 2. patient set-up and immobilisation techniques are suitable for reliable CT-image volume data acquisition and three-dimensional conformal radiotherapy; and 3. a high-quality CT-image volume dataset is acquired for the relevant region of interest to be planned and treated; and 4. the image set is suitable for the generation of quality digitally-reconstructed radiographic images.
MBS Fee*: $732.75 Benefit: 75% = $549.60 85% = $648.05

*Fees updated according to current information on mbsonline.gov.au as of 10 December 2020
CT=computed tomography; IMRT=intensity-modulated radiation therapy; MBS=Medical Benefits Schedule

Table 12 Proposed MBS item descriptor (15565)

Category 3 – THERAPEUTIC PROCEDURES
Preparation of an IMRT DOSIMETRY PLAN, which uses one or more CT image volume datasets, if: (a) in preparing the IMRT dosimetry plan: (i) the differential between target dose and normal tissue dose is maximised, based on a review and assessment by a radiation oncologist; and (ii) all gross tumour targets, clinical targets, planning targets and organs at risk are rendered as volumes as defined in the prescription; and (iii) organs at risk are nominated as planning dose goals or constraints and the prescription specifies the organs at risk as dose goals or constraints; and (iv) dose calculations and dose volume histograms are generated in an inverse planned process, using a specialised calculation algorithm, with prescription and plan details approved and recorded in the plan; and (v) a CT image volume dataset is used for the relevant region to be planned and treated; and (vi) the CT images are suitable for the generation of quality digitally reconstructed radiographic images; and (b) the final IMRT dosimetry plan is validated by the radiation therapist and the medical physicist, using robust quality assurance processes that include: (i) determination of the accuracy of the dose fluence delivered by the multi-leaf collimator and gantry position (static or dynamic); and (ii) ensuring that the plan is deliverable, data transfer is acceptable and validation checks are completed on a linear accelerator; and (iii) validating the accuracy of the derived IMRT dosimetry plan; and (c) the final IMRT dosimetry plan is approved by the radiation oncologist prior to delivery.
MBS Fee*: $3,417.35 Benefit: 75% = $2,563.05 85% = $3,332.65

*Fees updated according to current information on mbsonline.gov.au as of 10 December 2020
CT=computed tomography; IMRT=intensity-modulated radiation therapy; MBS=Medical Benefits Schedule

A.4. PROPOSED POPULATION

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

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.

The Australian Institute of Health and Welfare (AIHW) estimates approximately 145,000 new cancer cases and 48,000 deaths from cancer in 2020 (Australian Institute of Health and Welfare (AIHW),

2020a). Although mainly affecting population aged 50 years and older, cancer remains the leading cause of premature death. The risk of an individual being diagnosed with cancer by their 85th birthday will be 1 in 2 for both males and females (Australian Institute of Health and Welfare (AIHW), 2019).

Radiation therapy, or radiotherapy, is considered an important part of cancer treatment, effective for a very wide range of cancer types, stages and locations. Radiation therapy uses a controlled dose of radiation to kill cancer cells or damage them so they cannot grow, multiply or spread. The radiation is usually in the form of focused X-ray beams, also known as photons. It is a localised treatment, which means it generally affects only the part of the body where the radiation is targeted, and spares the healthy areas of the body (Cancer Australia, 2020).

There are two types of radiation therapy: internal and external. The internal radiation therapy or brachytherapy involves giving radiation via needle, catheter or another device which is left in place for a few days. The external radiotherapy or EBRT uses a machine that beams radiation onto the tumour such that a precise area receives the radiation while limiting the amount of radiation on the surrounding healthy areas. Utilisation estimates in Australia indicate that 48% of all patients receive external beam radiotherapy at least once during their treatment (Barton et al., 2014). The EBRT uses a radiation machine, usually a linear accelerator (linac), to direct high-energy beams at the cancer. EBRT can be delivered using different techniques: 3D-CRT, IMRT, IGRT, stereotactic radiosurgery (SRS) and stereotactic radiation therapy (SRT), stereotactic body radiation therapy (SBRT), and proton therapy. The IGRT uses a treatment machine that takes an image or scan of the tumour using X-ray or computed tomography (CT) scans, at the start of each treatment session to check that the patient is in the correct position for treatment. Markers are inserted near the cancers so that these are visible in the scans and can guide positioning. IGRT is commonly used with many types of radiation therapy, and is always used when IMRT is being used. It is recommended for areas likely to be affected by movement, e.g. lungs (Cancer Council Australia, 2019).

A prescription of radiation therapy comprises the total dose at a defined volume indicated over one or more treatment courses. Most people receiving radiation therapy have a treatment session once a day, but the number of treatments vary based on type and stage of the cancer and the size and location. One course of treatment is a series of one or more EBRT sessions, and a dose of radiation is divided into smaller doses or fractions. Often patients receive one fraction each day over several days until the total dose is reached. About half of all patients with cancer need radiation therapy for a cure, to improve their chance of survival or to relieve symptoms (Hall et al., 2019). In 2018-19, over 74,200 courses of radiation therapy were delivered in Australia (Australian Institute of Health and Welfare (AIHW), 2020b).

Following a cancer diagnosis in a patient, decisions are made about treatment. There are many different steps involved in a course of treatment for radiation therapy (planning, simulation and treatment), and a unique treatment plan is created for each individual. How these decisions are

made and how a patient is investigated, managed and referred within the Australian healthcare system is dependent on numerous factors including the type of cancer, tumour size and location in the body, general health of the patient and their medical history, other treatments administered as well as age and other medical conditions.

A.5. COMPARATOR DETAILS

The comparator is CBCT-guided radiation therapy. 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 et al., 2014).

Unlike MR-IGRT, CBCT can only be used preceding, not during, each daily treatment, and therefore does not allow optimal imaging of tumours and OARs, when tumour is surrounded by soft tissues (Kerkmeijer et al., 2016).

The MBS item descriptors for the relevant comparator are listed in Table 10, Table 11 and Table 12.

A.6. CLINICAL MANAGEMENT ALGORITHM(S)

The current and proposed (green box) clinical management algorithm are depicted in Figure 2. 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 2 **Clinical management algorithm for the proposed MR-IGRT relative to current clinical practice (amendment to the current algorithm in green box)**

A.7. KEY DIFFERENCES IN THE DELIVERY OF THE PROPOSED MEDICAL SERVICE AND THE MAIN COMPARATOR

The key difference between "standard" IGRT (performed with CBCT, and currently considered the standard of care in IGRT) and MR-IGRT is that MR-IGRT delivers a higher level of soft tissue imaging and a more sophisticated adaptive functionality, enabling the user to optimise dose distribution of the treatment plan on every fraction in an online setting (i.e. while the patient is in the machine).

The procedure for every treatment fraction is similar to the standard IGRT procedure: patient setup, imaging, adaptation, and treatment. Use of MR-linac involves the same professionals as CBCT linac: radiation oncologists, medical physicists, and radiation therapists. However, more complex

workflows may require all of these professionals to be present collectively at the treatment machine at the same time. The MR-IGRT technique is more time-intensive than the comparator, requiring twice- to three-times as long per fraction as CBCT-guided IGRT.

Additional expected benefits of MR-IGRT include hypofractionated dose to the tumour, decreasing the total number of fractions necessary and thus shortening the treatment duration, and that an image can be obtained without an additional radiation dose, unlike standard IGRT.

A.8. 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-guided radiation therapy.

A.9. SUMMARY OF THE PICO

The guiding framework of a PICO Confirmation is recommended by MSAC for each assessment. The PICO Confirmation describes current clinical practice and reflects the likely future practice with the proposed medical service.

The Population, Intervention, Comparator and Outcomes (PICO) that were pre-specified to guide the systematic literature review are presented in Box 1 and Box 2.

Box 1 Criteria for identifying and selecting studies to determine the safety of MR-IGRT in patients with cancer who undergo external beam radiation therapy (EBRT)

Selection criteria	Description
Population	All patients with cancer who undergo external beam radiation therapy (EBRT)
Intervention	Magnetic resonance image guided radiation therapy (MR-IGRT)
Comparator	Cone-beam computed tomography (CBCT) guided radiation therapy
Outcomes	Acute and long-term side effects Any adverse events arising from the procedure
Systematic review question	What is the safety of MR-IGRT, compared to CBCT-guided radiation therapy, in persons with cancer who undergo EBRT?

Box 2 Criteria for identifying and selecting studies to determine the effectiveness of MR-IGRT in patients with cancer who undergo external beam radiation therapy (EBRT)

Selection criteria	Description
Population	All patients with cancer who undergo external beam radiation therapy (EBRT)
Intervention	Magnetic resonance image guided radiation therapy (MR-IGRT)
Comparator	Cone-beam computed tomography (CBCT) guided radiation therapy
Outcomes	Alteration of planned target volume (PTV) margins Treatment toxicity and short-term toxicity Facilitation of radiation therapy dose escalation Treatment-related morbidity Tumour control Overall survival Progression-free survival Disease-free survival Quality of life
Systematic review question	What is the effectiveness of MR-IGRT, compared to CBCT-guided radiation therapy, in persons with cancer who undergo EBRT?

A.10. CONSUMER IMPACT STATEMENT

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 RANZCR, Australian Society of Medical Imaging and Radiation Therapy (ASMIRT), and Australasian College of Physical Scientists and Engineers in Medicine (ACPSEM)), one charity (Lung Foundation Australia), one field expert (Prof. Paul Keall, PhD), and a Public Consultation Survey has been received from Device Technologies Australia (DTA) and Viewray (manufacturer of MR-linacs; competitor of the Applicant). Additionally, the ACPSEM and the Australian Radiation Protection and Nuclear Safety Agency (ARPANSA) offered further comments on the Ratified PICO and on the safety of the technology.

All three professional societies (RANZCR, ASMIRT and ACPSEM) have expressed their support for the use of MBS item 15275 for MR-linacs, noting that the current MBS item was technologically agnostic.

In a further comment to the Ratified PICO, the ACPSEM has noted that there was a potential benefit for patients with soft tissue targets and OARs that were difficult to see on X-ray imaging. Patients with a contraindication to MR imaging (e.g., patients with cardiac implanted electronic devices, metal foreign bodies in ocular cavities, or claustrophobia) were not eligible for the intervention. Additionally, standard risks related to MRI would apply (e.g., peripheral nerve stimulation, local heating, acoustic noise, etc.) The benefits of MR-IGRT would include:

- reduced safety margins, decreasing the amount of healthy tissue being irradiated,
- increased dose per fraction, thus reducing the number of visits required for treatment and less impact on patient's lives and less burden on healthcare system, and
- reduced radiation dose from daily CBCT to tissues outside of the treatment area.

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. No specific concerns about MR-IGRT safety were raised.

Prof. Paul Keall, PhD, leader of the Australian MRI-Linac Program, has also expressed his support for using item 15275 for MR-linac treatment.

The charity Lung Foundation Australia has supported the application of Elekta Pty Ltd for delivering services in Australia, noting that MR-linac is expected to have utility in the treatment of tumours that are not amenable to current radiation therapy approaches.

A Public Consultation Survey submitted by DTA (distributor of Medical Devices Viewray, manufacturer of MRIdian) has commented on the benefits of MR-linacs, noting better effectiveness outcomes, lower toxicity, decrease in the number of fractions, and lower overall costs per patient treated. The disadvantages of the technology mentioned included limited availability and awareness of the treatment option. DTA strongly disagrees with the proposed MBS fee, arguing that MR-IGRT requires additional reimbursement due to increased resources (capital equipment and staff time) required to deliver adaptive planning during treatment delivery.

The ARPANSA was requested to comment on the safety of MR-IGRT. They considered that while there was a well-known risk associated with powerful magnetic fields, this was well understood and could be managed in the controlled clinical setting in which MR-linacs existed, and that the radiation risk to staff was similar to a standard linac.

The ARPANSA also pointed out that one of the key points of adaptive radiotherapy (ART) was the fact that it involved incorporation of patient-specific anatomical variations during radiotherapy, in order to feed back into the plan and allow dose-delivery optimisation during the treatment course. Therefore, if the daily pre-treatment MR imaging identified a significant difference between the imaging used to plan the radiation treatment and the set-up of the patient on the day, the system would re-calculate the radiation distribution. Any encompassing quality dosimetry testing of an MR-linac system would need to incorporate a situation where the test object being imaged was not setup correctly, i.e., identical to the planning scan. This arrangement would force the re-calculation, or rejection if the difference were too great. As ART is becoming more common on conventional linear accelerators, the risk profile of MR-IGRT would be very similar.

SECTION B CLINICAL EVALUATION

B.1. LITERATURE SOURCES AND SEARCH STRATEGIES

The medical literature was searched on 02 October 2020 to identify relevant studies and systematic reviews published during the period 2014 to 2020. Only literature published since 2014 was included, corresponding to the year MR-IGRT was first used for patient treatment (Chin et al., 2020). Due to the paucity of comparative evidence on clinical outcomes comparing MR-IGRT and CBCT-IGRT, a second search with no date limits was conducted on 23 October 2020 to capture comparative studies with technical outcomes as well as studies on the CBCT-IGRT for a naïve comparison. The databases and sources where the searches were conducted are described in Appendix B. Search terms for the two literature searches are also detailed in Appendix B.

B.2. RESULTS OF LITERATURE SEARCH

Two PRISMA flowcharts (Figure 3 and Figure 4) provide a graphic depiction of the two literature searches and the application of the study selection criteria (listed in Box 1 and Box 2) (Liberati et al., 2009). Identified comparative evidence was limited, therefore, studies without a comparator arm were also included. Literature search of the clinical trial registries (clinicaltrials.gov, ANZCTR[2]) found no ongoing comparative studies either. The second literature search aimed to identify studies reporting clinical outcomes in patients treated with IGRT using CBCT for image guidance, as well as studies contributing comparative data on technical outcomes for IGRT guided by MR imaging and CBCT.

Studies were selected by a single reviewer using Covidence, a web-based tool for selecting and synthesising results of studies, in addition to EndNote, a desktop-based reference management software. Any doubts regarding study selection were discussed with a second reviewer.

Additional pre-specified criteria for excluding studies were:

1. Publication type: Non-systematic reviews, letters, editorials, animal, in vitro, laboratory studies, conference abstracts and technical reports
2. Language: non-English language articles

Studies that were excluded are listed as Excluded Studies in Appendix E. All other studies that met the inclusion criteria are listed in Appendix C.

[2] Australian New Zealand Clinical Trials Registry

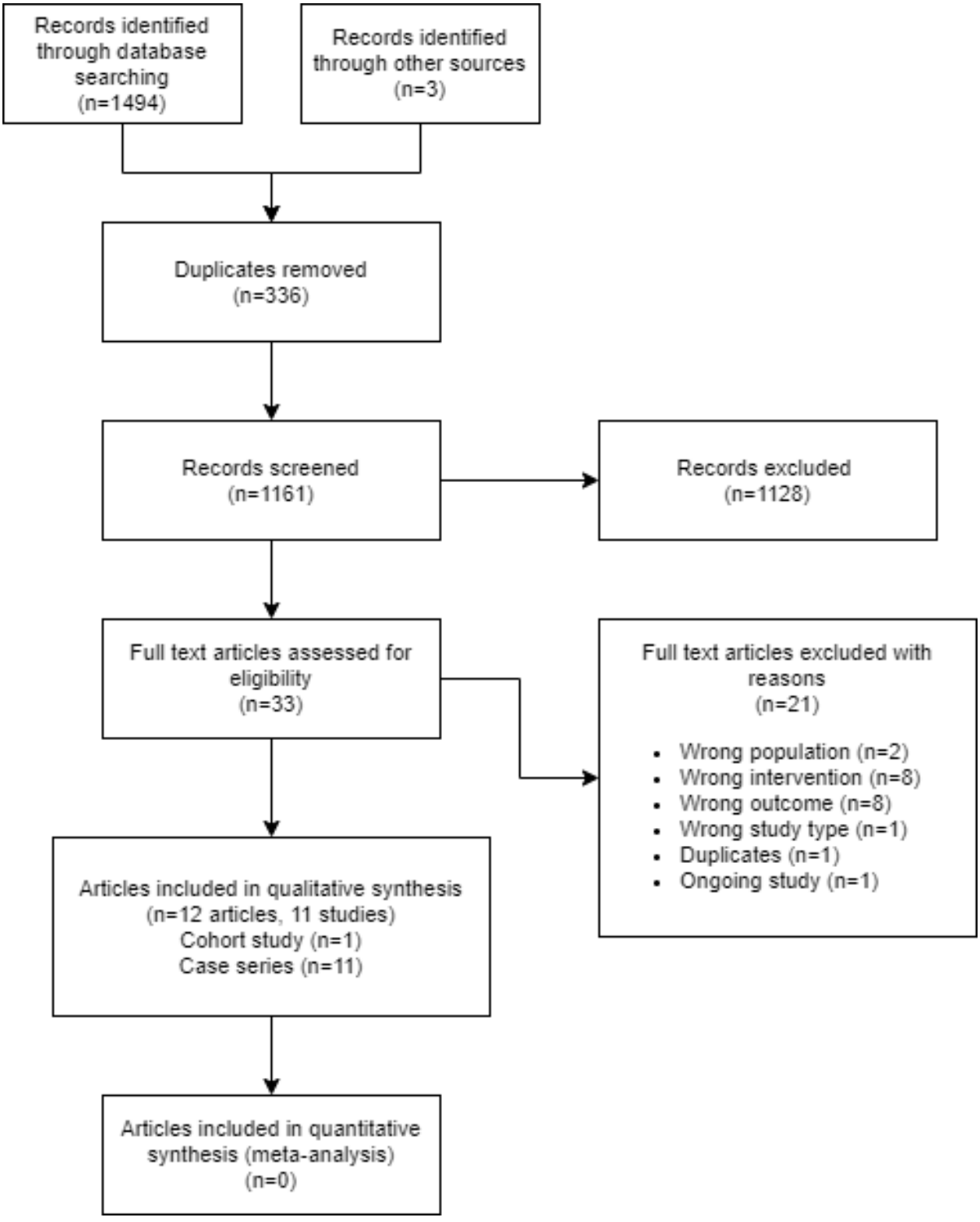

Figure 3 **Summary of the process used to identify and select studies on MR-IGRT for the assessment**

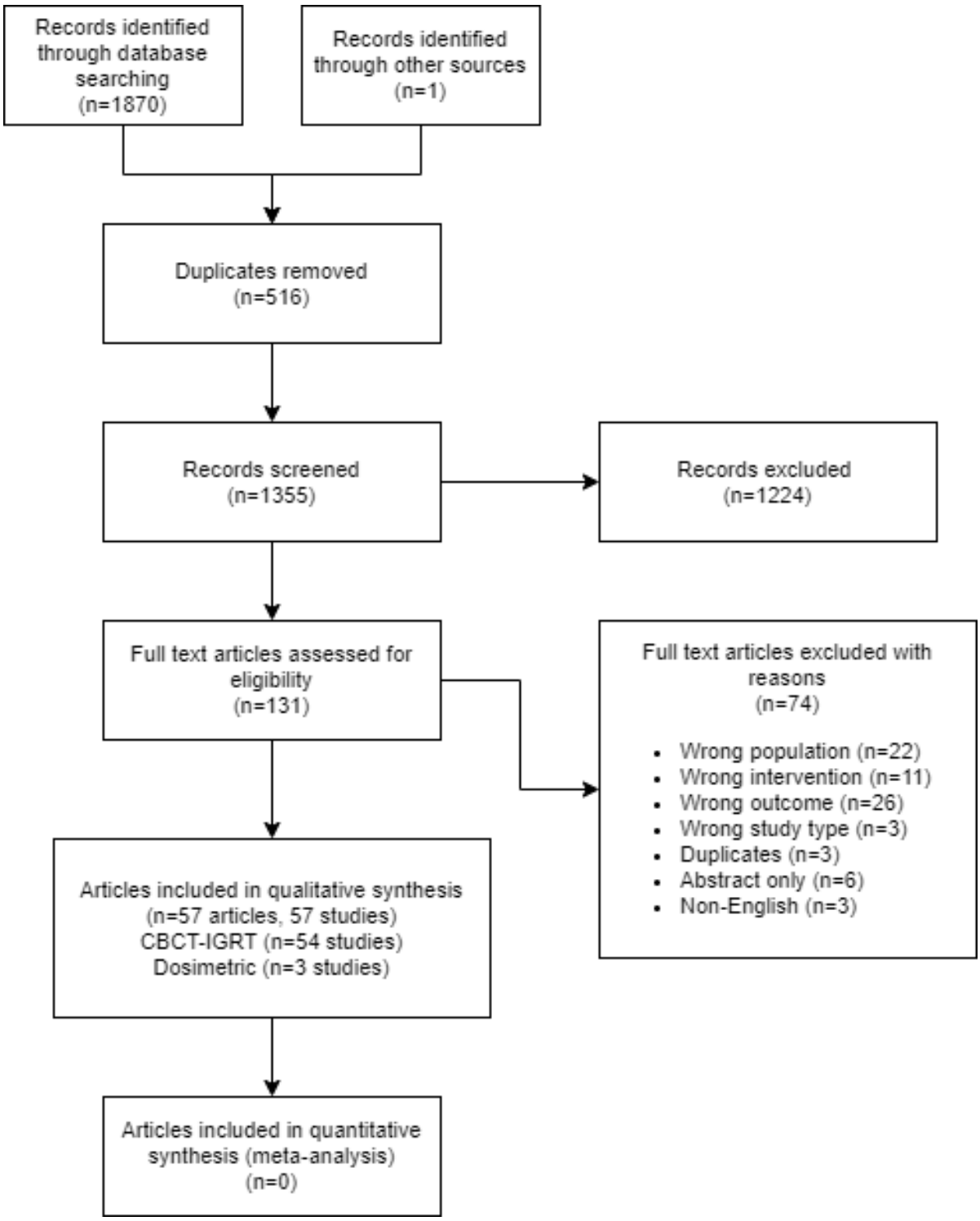

Figure 4 Summary of the process used to identify and select studies on CBCT-IGRT and dosimetric outcomes for the assessment

A profile of each included study for MR-IGRT is given in Appendix C , describing the authors, publication year, study design and quality (level of evidence and risk of bias), study location, setting, length of patient follow-up, study population characteristics, description of the intervention, description of the comparator, and the relevant outcomes assessed. Study characteristics are also summarised in a shorter format in Section B.4.

APPRAISAL OF THE EVIDENCE

Appraisal of the evidence was conducted in four stages:

Stage 1: Appraisal of the risk of bias within individual studies (or systematic reviews) included in the review (Section B.3).

Stage 2: Extraction of the pre-specified outcomes for this assessment, narrative synthesis to determine an estimate of effect per outcome.

Stage 3: Rating the overall quality of the evidence per outcome across studies, based on the study limitations (risk of bias), imprecision, inconsistency of results, indirectness of evidence, and the likelihood of publication bias. This was done to provide an indication of the confidence in the estimate of effect in the context of Australian clinical practice (Evidence profile tables, Appendix D).

Stage 4: Integration of this evidence for conclusions about the net clinical benefit of the intervention in the context of Australian clinical practice (Sections B.6-8).

B.3. RISK OF BIAS ASSESSMENT

The Newcastle Ottawa Scale (NOS) was used for assessing the quality of the included comparative cohort study (Wells et al., 2000). The quality of the single-arm case series was assessed with the Three-Minute Checklist (Chan & Bhandari, 2011), which was found to be the most applicable to the studies available.

The single identified comparative cohort study by E. Kim et al. (2018) scored 5 points on the NOS[3]. To aid interpretation, the score was translated according to the Agency for Healthcare Research and Quality (AHRQ) standards[4], indicating a fair quality score. The quality assessment for this study is summarised in Table 13. One score was not awarded in the Selection domain was not awarded as only patients with lung cancer treated with SBRT using the tri-^{60}Co system were included in the study. The non-exposed cohort was drawn from the same community and treated at the same location during the same period. Exposure was ascertained from treatment records. Patients were matched at a 1:1 ratio in the following order of importance: dose/fractionation, tumour size, tumour location, and age. Investigators used CT images and deformable registration software to determine lung density change, however, it is not clear if they were blinded. Moreover, the study was

[3] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

[4] Available at: https://www.ncbi.nlm.nih.gov/books/NBK115843/bin/appe-fm3.pdf.

retrospective, and the second follow-up CT scan had a wide timing range (16-31 weeks after the end of radiation therapy treatment).

Table 13 Assessment of the quality of the included cohort study using NOS

Study	Selection score (max =4)	Comparability score (max =2)	Outcome score (max =3)	Total score (max =9)	Study quality
E. Kim et al. (2018)	3 stars	1 star	1 star	5 stars	Fair quality*

*Thresholds for converting the NOS rating to AHRQ standards:
Good quality: 3 or 4 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain
Fair quality: 2 stars in Selection domain AND 1 or 2 stars in Comparability domain AND 2 or 3 stars in Outcome domain
Poor quality: 0 or 1 star in Selection domain OR 0 stars in Comparability domain OR 0 or 1 stars in Outcome domain

A study quality summary for the included case series on MR-IGRT is shown in Table 14. Eight case series collected data prospectively, however, none of the included case series met all the criteria on the Three-Minute Checklist. Two studies met 7/8 criteria of the checklist, only lacking a specified time interval for patient recruitment. Four studies were judged to meet 4/8 or 5/8 criteria, suggesting fair study quality. Five studies scored 3/8 or less, indicating low quality.

The quality assessment of the included studies on CBCT-IGRT was not undertaken since the naïve comparison is of extremely limited use for making conclusions for the outcomes relevant to this assessment.

Table 14 Assessment of the quality of the included case series on MR-IGRT using the Three-Minute Checklist

Study	Clear study objective/ question	Well defined study protocol	Explicit inclusion and exclusion criteria	Specified time interval for patient recruitment	Consecutive patient enrolment	Clinically relevant outcomes	Prospective outcome data collection	High follow-up rate	Study quality[a]
Alongi et al. (2020)	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
Chen et al. (2018)	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Good
Feldman, Modh, Glide-Hurst, Chetty, and Movsas (2019)	No	No	No	Unclear	Yes	Yes	No	Unclear	Poor
Finazzi, Haasbeek, et al. (2020)	Yes	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Fair

Study	Clear study objective/ question	Well defined study protocol	Explicit inclusion and exclusion criteria	Specified time interval for patient recruitment	Consecutive patient enrolment	Clinically relevant outcomes	Prospective outcome data collection	High follow-up rate	Study quality[a]
Finazzi, van Sornsen de Koste, et al. (2020)	No	Unclear	No	Unclear	Unclear	Yes	Yes	Yes	Poor
Henke et al. (2018)	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Good
Kluter et al. (2020)	No	Unclear	No	Yes	Yes	Yes	Yes	Unclear	Fair
Rosenberg et al. (2019)	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Fair
Rudra et al. (2019)	No	Unclear	Yes	Unclear	Unclear	Yes	No	Unclear	Poor
S. Tetar et al. (2018)	Yes	Unclear	Yes	Unclear	Unclear	No	Yes	Unclear	Poor
S. U. Tetar et al. (2019)	No	Unclear	No	Unclear	Unclear	No	No	Unclear	Poor

[a] The Three-Minute Checklist conversion to quality (developed for this assessment):
Good quality: at least 6 of 8 criteria met; Fair quality: 4 or 5 criteria met; Poor quality: 3 or less criteria met

B.4. CHARACTERISTICS OF THE EVIDENCE BASE

No randomised controlled trials comparing MR-IGRT with CBCT-IGRT were identified in the literature search.

One comparative retrospective cohort study (E. Kim et al., 2018), and 11 case series reports (Alongi et al., 2020; Chen et al., 2018; Feldman et al., 2019; Finazzi, Haasbeek, et al., 2020; Finazzi, van Sornsen de Koste, et al., 2020; Henke et al., 2018; Kluter et al., 2020; Rosenberg et al., 2019; Rudra et al., 2019; S. Tetar et al., 2018; S. U. Tetar et al., 2019) were included in the assessment of MR-IGRT. See Appendix C for details on the individual studies included in the evidence base. A summary is provided in Table 15. MR-IGRT was administered using the ViewRay system (either the older technology with tri-^{60}Co source or the newer MR-linac) in all included studies except for one, in which patients were treated with Elekta Unity MR-linac (Alongi et al., 2020). In the Ratified PICO, the PASC considered that the available MR-linac technologies were not interchangeable and differed in field and beam strength; and that the differences in MRI field strength would have implications for image resolution and acquisition times. The Applicant as well as the ACPSEM considered that while the beam characteristics of the tri-^{60}Co device differed from an MR-linac, the results of these studies were probably a good indicator of what MR imaging and EBRT could achieve.

Patients in the comparative cohort study (E. Kim et al., 2018) and in eight of the 11 case series included in the evidence base were treated with the SBRT technique. Two studies included patients with various techniques (Kluter et al., 2020; Rudra et al., 2019), and IMRT technique was used in one study (Chen et al., 2018).

The retrospective cohort study by E. Kim et al. (2018) has limited contribution to the overall evidence base as the study only reported on lung density changes as a predictive parameter for radiation induced lung damage (RILD) following SBRT treatment for lung cancer using MR-IGRT or CBCT-IGRT. The study also reported on dose-volumetric parameters.

Dosimetric outcomes were reported in four studies (E. Kim et al., 2018; van de Schoot et al., 2019; Winkel et al., 2020; Winkel et al., 2018).

Table 15 Key features of the included evidence on MR-IGRT

Study	N	Design/	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
E. Kim et al. (2018)	16	Retrospective matched Coh	SBRT	Lung cancer, early stage or lung metastases	Toxicity (lung density change*) Dose-volumetric parameters	Not used
Alongi et al. (2020)	25	Prospective CS	SBRT	Prostate cancer, low and intermediate risk	Toxicity QoL	Not used
Chen et al. (2018)	18	Prospective CS	IMRT	Head and neck cancer	Toxicity OS PFS Patient-reported QoL	Not used
Feldman et al. (2019)	29	Retrospective CS	SBRT	Liver tumours, one or more biopsy-proven unresectable HCC or liver metastases	Toxicity	Not used
Finazzi, Haasbeek, et al. (2020)	50	Retrospective CS	SBRT	Lung cancer at high risk of toxicity, primary or lung metastases	Toxicity OS DFS LC	Not used
Finazzi, van Sornsen de Koste, et al. (2020)	10	Prospective CS	Single-fraction SBRT	Lung cancer, early stage	Toxicity Local recurrence	Not used
Henke et al. (2018)	20	Prospective CS	SBRT	Abdominal malignancies, liver or non-liver, oligometastatic or unresectable primary malignancies	Toxicity OS PFS Patient-reported QoL	Not used
Kluter et al. (2020)	43	Prospective CS	SBRT, other non-specified	Various malignancies and metastases	Toxicity Patient tolerance	Not used
Rosenberg et al. (2019)	26	Prospective CS	SBRT	Liver cancer, HCC or liver metastases	OS PFS	Not used

Study	N	Design/	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Rudra et al. (2019)	44	Retrospective Coh	SBRT (conventional fractionated, conventional SBRT, high-dose SBRT, hypo-fractionated)	Pancreatic cancer, biopsy-proven, inoperable	Toxicity	Not used
S. Tetar et al. (2018)	150	Prospective CS	SBRT	Cancer patients (majority prostate cancer)	Patient-reported outcomes	Not used
S. U. Tetar et al. (2019)	140	Retrospective CS	SBRT	Prostate cancer	Patient-reported experience	Not used
van de Schoot et al. (2019)	16	Retrospective review	NA	Rectal and prostate cancer	Dosimetric outcomes	Not used
Winkel et al. (2018)	5	Retrospective review	NA	Pelvic and para-aortic lymph nodes	Dosimetric outcomes	Not used
Winkel et al. (2020)	20	Retrospective review	NA	Pelvic and para-aortic lymph nodes	Dosimetric outcomes	Not used

Coh=cohort; CS=case series; DFS=disease-free survival; HCC=hepatocellular carcinoma; IMRT=intensity modulated radiation therapy; LC=local control; MR-IGRT=magnetic resonance image guided radiation therapy; NA=not assessed; OS=overall survival; PFS=progression-free survival; SBRT=stereotactic body radiation therapy; QoL=quality of life

*Lung density is regarded as an objective predictive parameter for clinical radiation-induced lung damage (RILD)

Fifty-four studies on the safety and clinical effectiveness of CBCT-IGRT were included in an attempt to perform a naïve comparison: 11 for lung malignancies, 34 for prostate cancer, eight for abdominal malignancies and one for head and neck cancer. Their key features are described in Table 16. Studies were either single-arm or comparative in nature. In comparative studies, only the subset of patients relevant to the comparator (IGRT with daily CBCT confirmation) were considered.

Table 16 Key features of the included evidence on CBCT-IGRT

Study	N	Design	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Lung cancer						
Appel et al. (2020)	58	Retrospective CS	3D-CRT, IMRT/ VMAT, or hybrid	NSCLC and SCLC (locally advanced) treated with chemoradiation	OS DFS LC	Not used
Baschnagel et al. (2013)	32 (47 lesions)	CS	SBRT	Lung metastases	Toxicity OS LC	Not used
Boda-Heggemann et al. (2014)	43 (50 lesions)	Retrospective consecutive CS	SABR	NSCLC or lung metastases	OS PFS	Not used
Frakulli et al. (2015)	24 (68 lesions)	Retrospective consecutive CS	SBRT	Lung metastases from bone and soft-tissue sarcomas	OS LC	Not used

Study	N	Design	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Grills et al. (2012)	483 (505 tumours)	Prospective multicentric SA Coh	SBRT	NSCLC (early stage)	OS	Not used
Guckenberger, Baier, et al. (2010)	59	Retrospective consecutive CS	SBRT	NSCLC or lung metastases	Toxicity	Not used
Kestin et al. (2014)	483 (505 tumours)	Retrospective multicentric SA Coh	SBRT	NSCLC (T1-2N0M0)	OS CSS Recurrence rates	Not used
Kilburn et al. (2016)	62* (total 169)	Retrospective Coh, comparative (with IGRT vs without IGRT)	3D-CRT or IMRT	NSCLC (locally advanced, stage IIB-IIIB) treated with curative intent	Toxicity OS PFS Failure-free survival	Not used
Shen et al. (2010)	20 (32 tumours)	CS	SBRT	NSCLC or lung metastases	Toxicity	Not used
Stone, Mangona, Johnson, Ye, and Grills (2015)	127	Prospective SA Coh	SBRT	NSCLC (peripheral stage I)	OS	Not used
Yegya-Raman et al. (2018)	76* (total 124)	Retrospective Coh, comparative (CBCT vs kV CT imaging for IGRT)	3D-CRT, IMRT or both	NSCLC (inoperable, locally advanced or stage IV oligometastases)	Toxicity OS Progression incidence rates	Not used
Prostate						
Becker-Schiebe, Abaci, Ahmad, and Hoffmann (2016)	102* (total 198)	Retrospective Coh, comparative (before-after, standard RT vs IGRT)	NR DE	Prostate cancer	Toxicity	Not used
Berlin et al. (2015)	68	Prospective SA Coh (phase II trial)	IMRT	Prostate cancer, post RP	Toxicity QoL	Not used
Byrne et al. (2017)	300	CS	IMRT DE	Prostate cancer, localised	Toxicity	Not used
Byun, Kim, Ahn, and Kim (2018)	170	Retrospective consecutive CS	WP IMRT, salvage	Prostate cancer, high-risk, post-RP, biochemical recurrence	Toxicity	Not used
Callan et al. (2019)	30	Prospective SA Coh (phase I/II trial)	SABR	Prostate cancer, high-risk	Toxicity	Not used
Correa et al. (2020)	451	Retrospective Coh, comparative (3D-CRT vs VMAT)	3D-CRT or VMAT (hypofractionated)	Prostate cancer, localised	Toxicity	Not used
Duffton et al. (2018)	41	Prospective SA Coh	SABR	Prostate cancer, low/intermediate risk	Toxicity	Not used

Study	N	Design	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Eldredge et al. (2011)	68* (total 218)	Retrospective consecutive Coh, comparative (before-after, weekly port films vs CBCT)	3D-CRT	Prostate cancer, post RP	Toxicity	Not used
Faria, Petrucelli, Cury, Duclos, and Souhami (2016)	105	Retrospective CS	IMRT (hypofractionated)	Prostate cancer, high-risk, locally advanced	Toxicity	Not used
Girelli et al. (2015)	104	Consecutive CS	IMRT (hypofractionated, SIB)	Prostate cancer	Toxicity	Not used
Guckenberger, Ok, Polat, Sweeney, and Flentje (2010)	100	Prospective consecutive Coh	IMRT DE, SIB	Prostate cancer	Toxicity	Not used
Guckenberger, Lawrenz, and Flentje (2014)	150	Retrospective consecutive CS	IMRT (hypofractionated)	Prostate cancer, localised	Toxicity	Not used
Hopper, Sandhu, Parsons, Rose, and Einck (2018)	8	Retrospective CS	IMRT, salvage DE	Prostate cancer, failure after cryotherapy	Toxicity	Not used
Ingrosso et al. (2017)	118	Retrospective CS	3D-CRT	Prostate cancer, post RP	Toxicity	Not used
Ingrosso et al. (2018)	294	Retrospective CS	3D-CRT	Prostate cancer, localised	Toxicity	Not used
Ishii et al. (2016)	224	Consecutive Coh, comparative (PORT vs WP)	VMAT	Prostate cancer, localised, high-risk	Toxicity	Not used
Keall et al. (2020)	48	Prospective multicentric SA Coh (trial)	SABR	Prostate cancer, intermediate risk (96%)	Toxicity	Not used
Levin-Epstein et al. (2020)	205	Prospective Coh	SBRT	Prostate cancer, localised	Toxicity	Not used
Nakamura et al. (2018)	96* (total 192)	Consecutive Coh, comparative (before-after, bony structure-based vs prostate-based IGRT)	IMRT	Prostate cancer, localised, low and intermediate risk	Toxicity	Not used
Naoi et al. (2019)	73	CS	VMAT	Prostate cancer, locally advanced	Toxicity	Not used
Nath et al. (2010)	50	Consecutive CS	IMRT	Prostate cancer, localised, post RP	Toxicity	Not used
Ost et al. (2011)	80* (total 196)	Coh, comparative (before-after, EPID vs CBCT)	IMRT	Prostate cancer, post RP, biochemical recurrence	Toxicity	Not used

Study	N	Design	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Pryor et al. (2019)	135	Prospective multicentric Coh (phase 2 trial)	SBRT boost and conventional IMRT via VMAT	Prostate cancer, stage ≤T3N0M0, intermediate- and high-risk	Toxicity	Not used
Shelan et al. (2019)	69	Retrospective consecutive CS	IMRT, salvage DE	Prostate cancer, post RP, macroscopic local recurrence	Toxicity	Not used
Simpson et al. (2011)	23* (total 50)	Retrospective Coh, comparative (CBCT without radiopaque clips vs kV planar CT with radiopaque clips for IGRT)	IMRT	Prostate cancer, localised, post RP	Toxicity	Not used
Swamy et al. (2009)	12	Retrospective consecutive CS	IMRT DE	Prostate cancer, localised	Toxicity	Not used
Tamihardja et al. (2020)	346	Retrospective consecutive CS	VMAT (moderately hypofractionated, SIB)	Prostate cancer, localised	Toxicity	Not used
Tondel et al. (2018)	128* (total 257)	RCT (weekly offline imaging vs daily online CBCT-IGRT)	NR	Prostate cancer, non-metastatic, intermediate or high-risk	QoL	Not used
Valeriani, Bracci, et al. (2013)	69* (total 105)	Prospective multicentric Coh, comparative (with IGRT vs without IGRT)	3D-CRT (hypofractionated)	Prostate cancer, intermediate risk	Toxicity	Not used
Valeriani, Carnevale, et al. (2013)	59	Prospective SA Coh	IMRT (hypofractionated, SIB)	Prostate cancer, high risk	Toxicity	Not used
Valeriani et al. (2018)	85* (total 175)	Prospective multicentric Coh, comparative (with IGRT vs without IGRT)	IMRT (hypofractionated)	Prostate cancer, low risk	Toxicity	Not used
Vargas et al. (2019)	79* (no BRT; total 106)	RCT (with/without ADT and with/without BRT), not blinded	IMRT with or without BRT	Prostate cancer, intermediate risk	Toxicity QoL	Not used
Vassis, Noldeke, Christiansen, von Klot, and Merten (2020)	55* (total 110)	Retrospective Coh, comparative (moderately hypofractionated VMAT vs conventional RT)	VMAT (moderately hypofractionated, SIB)	Prostate cancer, localised	Toxicity	Not used
Wang et al. (2018)	40	Prospective Coh, comparative (two risk-based groups)	IMRT or VMAT (moderately hypofractionated)	Prostate cancer, localised	Toxicity	Not used
Abdominal malignancies						

Study	N	Design	Radiation delivery	Patient population	Key outcome(s)	Result used in economic model
Amendola, Amendola, Blanco, Perez, and Wu (2017)	27	Retrospective CS	SBRT via VMAT	Liver metastases	Toxicity	Not used
Andratschke et al. (2018)	474 (623 lesions)	Retrospective multicentric CS	SBRT	Liver metastases	Toxicity	Not used
Barney et al. (2012)	47 (50 lesions)	Retrospective CS	SBRT	Abdominopelvic tumours	Toxicity	Not used
N. Kim et al. (2019)	105* (114* tumours; total n=773)	Retrospective multicentric Coh, comparative (SBRT vs RFA; PSM analysis)	SBRT via VMAT, CyberKnife, Tomotherapy or 3D-CRT	Liver (HCC) BCLC stage 0-A: 38.1%, stage B-C: 61.9%	Toxicity OS PFS Freedom from progression	Not used
Mazzola et al. (2018)	33	Retrospective CS	SBRT via VMAT	Pancreatic cancer, locally advanced, unresectable	Toxicity	Not used
Price et al. (2012)	26	Prospective Coh (phase 1-2 trial)	SBRT	Liver (HCC), not surgical candidates	OS	Not used
Valakh, Gresswell, and Kirichenko (2018)	15	Retrospective consecutive CS	SBRT	Liver (HCC), Class B-C Child-Pugh cirrhosis CP≥8	Toxicity OS Freedom from progression	Not used
Voglhuber et al. (2020)	31 (34 lesions)	Retrospective CS	SBRT	Adrenal gland metastases	Toxicity	Not used
Head and neck						
Navran et al. (2019)	414	Consecutive Coh, comparative (before-after, CTV-PTV margin 5mm vs 3 mm)	VMAT	Head and neck cancer	Toxicity OS DFS LC	Not used

3D-CRT=3-dimensional conformal radiation therapy; BCLC=Barcelona Clinic Liver Cancer; BRT=brachytherapy; CBCT=cone-beam computed tomography; Coh=cohort; CS=case series; CSS=cancer-specific survival; DE=dose-escalated; DFS=disease-free survival; EPID=electronic portal imaging device; HCC=hepatocellular carcinoma; IGRT=image-guided radiation therapy; IMRT=image modulated radiation therapy; LC=local control; MR-IGRT=magnetic resonance image guided radiation therapy; NA=not assessed; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; PORT=prostate-only radiotherapy; PSM=propensity score matching; RCT=randomised controlled trial; RFA=radiofrequency ablation; RP=radical prostatectomy; SA=single-arm; SABR=stereotactic ablative radiotherapy; SBRT=stereotactic body radiation therapy; SCLC=small-cell lung cancer; SIB=simultaneous integrated boost; QoL=quality of life; VMAT=volumetric modulated arc therapy; WP=whole-pelvic

* Only patients treated with daily CBCT-guided IGRT were included in the assessment

B.5. Outcome Measures and Analysis

See Appendix C for details on the outcomes measured in the included studies, along with the statistical methods used to analyse the results.

A meta-analysis was not conducted as there were no studies identified for which this would be appropriate.

E. Kim et al. (2018) reported the lung density changes following completion of radiation therapy on one-month and four to six-month follow-up CT scans. CT density changes were taken as an objective and quantitative method to assess lung toxicity after radiotherapy. However, the study authors acknowledged the fact that a clinically significant cut-off value of the lung density change had not been proposed.

The Common Terminology Criteria for Adverse Events (CTCAE)[5] version 4 or higher was used in studies assessing treatment toxicity.

Clinical effectiveness was assessed in terms of survival. A wide array of survival measures (overall survival, disease progression, treatment failure rates, control rates, etc.) was reported by the included studies.

Quality of life (QoL) measures were assessed using validated questionnaires including the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, a questionnaire used to assess the quality of life of patients with cancer, and the EORTC QLQ-PR25, developed for assessing quality of life of patients with prostate cancer.

Various dosimetric outcomes were evaluated; each of the three included studies reported on different outcomes.

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.

[5] CTCAE available from https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

B.6. RESULTS OF THE SYSTEMATIC LITERATURE REVIEW

IS IT SAFE?

Summary – What is the safety of MR-IGRT, compared to CBCT-guided radiation therapy, in persons with cancer who undergo EBRT?

Comparative evidence on the safety of MR-IGRT compared to CBCT-IGRT was scarce, with only one study identified. Therefore, a naïve comparison of single-arm MR-IGRT studies and CBCT-IGRT studies was attempted. The overall contribution of this naïve comparison to the evidence base is limited due to low methodologic quality of the included studies and a considerable heterogeneity in patient populations, technologies used, and radiation dose received.

Lung cancer

One retrospective cohort study 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 (lung density changes on CT). No statistically significant difference was found between the two image guidance modalities; and a clinically significant difference for lung density change has not been proposed 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-radical prostatectomy radiation therapy. Both 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 case series evaluated the safety of MR-guided SBRT for abdominal malignancies (liver or non-liver, primary or metastatic lesions). One study reported 2/20 (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 cumulative grade ≥3 GI toxicity of 7%.

Seven retrospective case series and one prospective trial on the safety of CBCT-guided SBRT in abdominal malignancies (liver, pancreas, 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. A total of 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. A total of 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 89/150 (80%) of patients reported at least some degree of potential MR-IGRT-related complaints.

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

TOXICITY

One comparative study on the safety of MR-IGRT for treatment of lung cancer (primary or lung metastases) was identified (E. Kim et al., 2018).

Additional single-arm studies on MR-IGRT safety were identified for lung cancer (Finazzi, Haasbeek, et al., 2020; Finazzi, van Sornsen de Koste, et al., 2020), prostate cancer (Alongi et al., 2020), liver cancer (hepatocellular carcinoma and liver metastases (Feldman et al., 2019; Henke et al., 2018; Rudra et al., 2019)), head and neck cancer (Chen et al., 2018), and for mixed cancer population (Kluter et al., 2020).

In the absence of comparative evidence, a naïve comparison was attempted, using single-arm studies of CBCT-IGRT toxicity for those same cancer sites.

Lung cancer

E. Kim et al. (2018) reported on the early radiological lung density changes following completion of SABR for primary or metastatic lung cancer at one-month and four to six-month follow-up CT scans. Lung density was regarded as a quantitative parameter for early detection of RILD. The authors noted that in general, radiological changes would occur at least 3 months after completing a course of conventional EBRT and would stabilise after about 9-12 months. Patients were treated with an older MR-IGRT technology, which used cobalt-60 radiation beams.

Comparison of lung density in Hounsfield units (HU) between MR-linac SBRT and conventional CBCT-guided SBRT for different isodose regions at first and second follow up is summarised in Table 17 and Figure 5. There were no significant differences in lung density changes by treatment modality for all dose regions assessed.

Table 17 Results of toxicity: mean lung density changes in isodose (HU) - E. Kim et al. (2018)

Study ID	Isodose	MR-IGRT (HU)	CBCT-IGRT (HU)	P-value
E. Kim et al. (2018)	> 48 Gy (one month follow-up)	-37.79 (95% CI, − 78.38 to 2.8)	10.98 (95% CI, −34.65 to 56.61)	P > 0.05 for all dose regions
	Four to six months follow-up scan			
	6 - 12 Gy	25.6	23.6	0.871
	12 - 18 Gy	38.5	45.4	0.999
	18 - 24 Gy	69.9	74.5	0.982
	24 - 36 Gy	122.4	92.7	0.978
	36 - 48 Gy	167.1	91.8	0.545
	> 48 Gy	154.2	100.8	0.665

CBC=cone-beam computed tomography; CI=confidence interval; Gy=Gray; HU=Hounsfield unit; IGRT=image-guided radiation therapy; MR=magnetic resonance

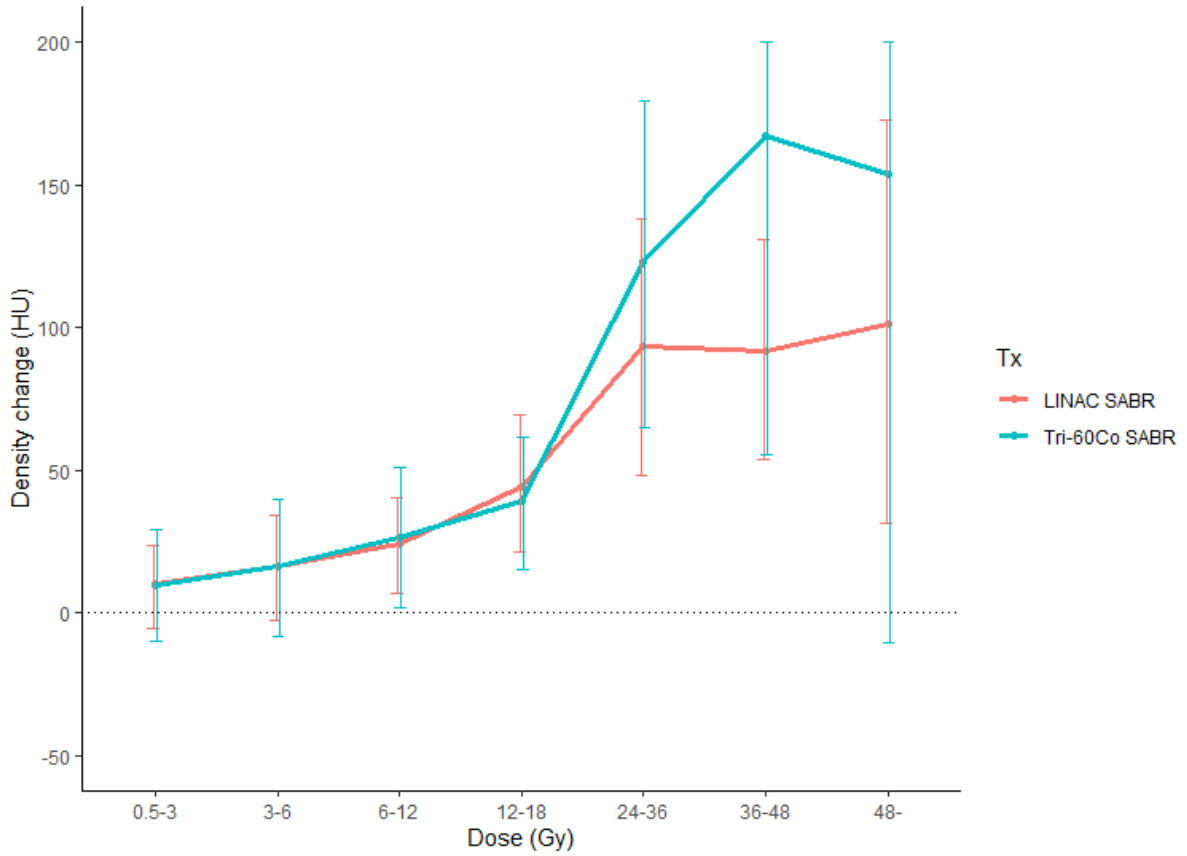

Figure 5 **Mean lung density changes according to treatment modality for different isodose regions**

Error bars represent 95% confidence interval
Source: E. Kim et al. (2018), p 6, Fig 2B

Two case series reported toxicity rates in patients with lung cancer (Finazzi, Haasbeek, et al., 2020; Finazzi, van Sornsen de Koste, et al., 2020). Finazzi, Haasbeek, et al. (2020) reported that 15 of 50 (30%) of patients with lung cancer at high risk of radiation toxicity (owing to tumour location, motion or pulmonary comorbidity) experienced grade ≥2 toxicities. In a case series of early-stage lung cancer, two out of 10 patients experienced grade 2 toxicities (Finazzi, van Sornsen de Koste, et al., 2020). All reported toxicities are summarised in Table 18.

Table 18 **Results of toxicity across the studies, lung cancer, MR-IGRT**

Study ID	Toxicity	Any (acute or late)			
	Grade	0	1	2	3
Finazzi, Haasbeek, et al. (2020)	Any toxicities, Grade ≥2			15/50 (30%)	
	Radiation pneumonitis			4/50 (8%)	1/50 (2%)
	Chest wall pain			3/50 (6%)	1/50 (2%)
	Esophagitis			2/50 (4%)	
	Pleural effusion			2/50 (4%)	
	Fatigue			1/50 (2%)	
	Atelectasis			1/50 (2%)	

Study ID	Toxicity	Any (acute or late)			
	Grade	0	1	2	3
	Pneumothorax				2/50 (4%)
Finazzi, van Sornsen de Koste, et al. (2020)	Radiation pneumonitis			1/10 (10%)	
	Fatigue			1/10 (10%)	
	Any G3-G5 toxicity				0/10 (0%)

For a naïve comparison, six studies reporting on the toxicity of CBCT-guided IGRT in lung cancer were identified (Baschnagel et al., 2013; Guckenberger, Baier, et al., 2010; Kilburn et al., 2016; Shen et al., 2010; Stone et al., 2015; Yegya-Raman et al., 2018). Their findings are summarised in Table 19.

Table 19 Results of pulmonary toxicity across the studies, lung cancer, CBCT-IGRT

Study ID	Toxicity	Acute				Late			
	Grade	0	1	2	3	0	1	2	3
Baschnagel et al. (2013)	Radiation pneumonitis		6/32 (19%)	1/32 (3%)	1/32 (3%)				
	Dyspnoea		3/32 (9%)	1/32 (3%)	0/32 (0%)		2/32 (6%)	2/32 (6%)	1/32 (3%)
	Cough		6/32 (19%)	0/32 (0%)	1/32 (3%)				
	Rib fracture		3/32 (9%)	1/32 (3%)	1/32 (3%)				
	Myositis		0/32 (0%)	1/32 (3%)	0/32 (0%)				
	Pain		0/32 (0%)	2/32 (6%)	1/32 (3%)				
	Oesophagitis		1/32 (3%)	1/32 (3%)	0/32 (0%)				
	Dermatitis		8/32 (25%)	1/32 (3%)	0/32 (0%)				
	Fatigue		3/32 (9%)	0/32 (0%)	0/32 (0%)				
Guckenberger, Baier, et al. (2010)	Radiation pneumonitis							11/59 (19%)	
Kilburn et al. (2016)	Any toxicity (acute or late)		57/62 (92%)						
	Any toxicity		56/62 (91%)				21/62 (35%)		
	Toxicity			48/62 (76%)	6/62 (10%)			16/62 (25%)	4/62 (6%)
Shen et al. (2010)	Pulmonary toxicity		3/20 (15%)	1/20 (5%)			2/20 (10%)		
	Acute esophagitis		3/20 (15%)						

Study ID	Toxicity	Acute				Late			
	Grade	0	1	2	3	0	1	2	3
	Dysphagia						1/20 (5%)		
	Skin toxicity		0%	0%	0%		0%	0%	0%
	Haemotoxicity		0%	0%	0%		0%	0%	0%
Stone et al. (2015)	Pneumonitis, 12 months							3.1%	0.8%
Yegya-Raman et al. (2018)	Radiation pneumonitis			Grade ≥2: 24%[1]					

CBCT-IGRT=cone-beam computed tomography image-guided radiation therapy
[1]One year cumulative rate

Prostate cancer

Toxicity in patients who underwent MR-guided prostate SBRT was reported in one prospective case series (Alongi et al., 2020). Alongi et al. (2020) evaluated acute genitourinary (GU) and gastrointestinal (GI) toxicities in patients with localised prostate cancer. Grade 1 and grade 2 GU toxicity was reported by 6/25 (24%) and 3/25 (12%) patients, respectively. Two patients experienced grade 1 GI toxicity and one (4%) experienced grade 2 GI toxicity. No grade 3 or higher toxicities were experienced in the study population. Results are summarised in Table 20.

Table 20 Results of toxicity across the studies, prostate cancer, MR-IGRT

Study ID	Toxicity	Acute		Late	
	Grade	1	2	1	2
Alongi et al. (2020)	GI (rectal pain)	2/25 (8%)	1/25 (4%)		
	GU (frequency, urgency, pain)	6/25 (24%)	3/25 (12%)		

GI=gastrointestinal; GU=genitourinary; MR-IGRT=magnetic resonance image-guided radiation therapy

Thirty-three studies reporting on the toxicity of CBCT-IGRT treatment of prostate cancer were identified for the naïve comparison (Becker-Schiebe et al., 2016; Berlin et al., 2015; Byrne et al., 2017; Byun et al., 2018; Callan et al., 2019; Correa et al., 2020; Duffton et al., 2018; Eldredge et al., 2011; Faria et al., 2016; Girelli et al., 2015; Guckenberger et al., 2014; Guckenberger, Ok, et al., 2010; Hopper et al., 2018; Ingrosso et al., 2018; Ingrosso et al., 2017; Ishii et al., 2016; Keall et al., 2020; Levin-Epstein et al., 2020; Nakamura et al., 2018; Naoi et al., 2019; Nath et al., 2010; Ost et al., 2011; Pryor et al., 2019; Shelan et al., 2019; Simpson et al., 2011; Swamy et al., 2009; Tamihardja et al., 2020; Valeriani et al., 2018; Valeriani, Bracci, et al., 2013; Valeriani, Carnevale, et al., 2013; Vargas et al., 2019; Vassis et al., 2020; Wang et al., 2018). All patients had localised or locally advanced, non-metastatic prostate cancer of varying risk (low, intermediate, high, or mixed). Eight studies involved patients receiving radiotherapy into prostatic bed after radical prostatectomy (Berlin et al., 2015; Byun et al., 2018; Eldredge et al., 2011; Ingrosso et al., 2017; Nath et al., 2010; Ost et al., 2011; Shelan et al., 2019; Simpson et al., 2011), and three studies involved patients with recurrent disease

receiving salvage radiotherapy (Byun et al., 2018; Hopper et al., 2018; Shelan et al., 2019). The outcomes are summarised in Table 21.

Table 21 Results of toxicity across the studies, prostate cancer, CBCT-IGRT

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
Becker-Schiebe et al. (2016)	GI	44/102 (43%)	39/102 (38%)	14/102 (14%)	2/102 (2%)	3/102 (3%)	51/102 (50%)	34/102 (33%)	17/102 (17%)	0/102 (0%)	0/102 (0%)
	GU	20/102 (20%)	48/102 (47%)	29/102 (28%)	5/102 (5%)	0/102 (0%)	50/102 (49%)	35/102 (34%)	17/102 (17%)	0/102 (0%)	0/102 (0%)
Berlin et al. (2015)	Diarrhea	28/68 (41%)	34/68 (50%)	6/68 (9%)							
	Nausea	61/68 (90%)	6/68 (9%)	1/68 (1%)							
	Vomiting	68/68 (100%)	0/68 (0%)	0/68 (0%)							
	Proctitis	22/68 (32%)	38/68 (56%)	8/68 (12%)							
	Bladder spasms	53/68 (78%)	13/68 (19%)	2/68 (3%)							
	Cystitis	36/68 (53%)	29/68 (43%)	3/68 (4%)							
	Urinary frequency	26/68 (38%)	29/68 (43%)	13/68 (19%)							
	Incontinence	38/68 (56%)	22/68 (32%)	8/68 (12%)							
	Haematuria	63/68 (93%)	5/68 (7%)	0/68 (0%)							
Byrne et al. (2017)	GU								57/300 (19%)	11/300 (4%)	
Byun et al. (2018)	GI		26/170 (15%)	12/170 (7%)	1/170 (1%)			6/170 (4%)	1/170 (1%)	1/170 (1%)	
	GU		31/170 (18%)	11/170 (6%)	1/170 (1%)			22/170 (13%)	16/170 (9%)	5/170 (3%)	

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
Callan et al. (2019)	GI Baseline:		3/28 (11%)	0/28 (0%)							
	GI 6 weeks		8/27 (30%)	1/27 (4%)							
	GI 6 months							12/28 (43%)	0/28 (0%)		
	GI 1 year							9/23	0/23 (0%)		
	GU baseline		10/28 (36%)	1/28 (4%)							
	GU 6 weeks		15/27 (56%)	4/27 (15%)							
	GU 6 months							17/28 (61%)	5/28 (18%)		
	GU 1 year							15/23 (65%)	5/23 (22%)		
Correa et al. (2020)	GI		86/451 (19%)					12/451 (3%)			
	GU		46.1%	25.9%	0.7%			91/451 (20%)			
Duffton et al. (2018)	GI baseline		2/41 (5%)								
	GI		Grade 1-2: 31/41 (76%)	3/41 (7%)	0/41 (0%)						
	GU baseline		22/41 (54%)								
	GU		Grade ≥1: 41/41 (100%)	Grade ≥2: 14/41 (34%)	2/41 (5%)						
Eldredge et al. (2011)	GI			9/68 (13%)					2/43 (5%)		
	GU			9/68 (13%)	1/68 (1%)				3/43 (7%)		
Faria et al. (2016)	GI	40/105 (38%)	47/105 (45%)	17/105 (16%)	1/105 (1%)		78/105 (74%)	20/105 (19%)	5/105 (5%)	2/105 (2%)	
	GU	34/105 (32%)	53/105 (50%)	15/105 (14%)	3/105 (3%)		81/105 (77%)	16/105 (15%)	6/105 (6%)	2/105 (2%)	
Girelli et al. (2015)	GI		11/104 (10%)	3/104 (3%)	1/104 (1%)			6/104 (5.7%)	8/104 (7.6%)	2/104 (1.9%)	
	GU		27/104 (26%)	3/104 (3%)	2/104 (2%)			6/104 (5.8%)	5/104 (4.8%)	0/104 (0%)	
Guckenberger, Ok, et al. (2010)	Diarrhea		14%	1%	0%			1.5%	1.5%	0%	
	Proctitis		20%	7%	0%			1.5%	0%	0%	

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
	Rectal bleeding		1%	0%	0%			0%	0%	1.5%	
	Faecal incontinence		1%	0%	0%			1.5%	0%	0%	
	Urinary frequency		53%	32%	1%			11%	3.1%	0%	
	Dysuria		41%	2%	0%			4.6%	0%	0%	
	Haematuria		2%	0%	0%			1.5%	3.1%	0%	
	Urinary incontinence		12%	0%	0%			11%	1.5%	0%	
Guckenberger et al. (2014)	Diarrhea		17%	2.7%	0%			2.9%	0%	0%	
	Proctitis		19%	5.3%	0%			4.8%	0%	0%	
	Rectal bleeding		4.7%	0%	0%			5.7%	0%	0%	
	Faecal incontinence		2.7%	0.7%	0%			3.8%	1%	1%	
	Urinary frequency		48%	32%	3.3%			20%	11%	4.8%	
	Dysuria		39%	2.7%	0.7%			4.9%	4.9%	0%	
	Haematuria		5.3%	0.7%	0%			9.6%	6.7%	1.9%	
	Urinary incontinence		16%	1.3%	0%			17%	9.7%	1.9%	
Hopper et al. (2018)	GI (diarrhea)		2/8	0/8	0	0		0	0	0	0
	Dysuria		4/8	1/8	0	0		0	0	0	0
	Nycturia		1/8	0/8	0	0		0	0	0	0
Ingrosso et al. (2017)	GI		25/118 (21%)	3/118 (3%)	0/118 (0%)			4/118 (3%)	4/118 (3%)	0/118 (0%)	
	GU		37/118 (31%)	5/118 (4%)	3/118 (3%)			19/118 (16%)	1/118 (1%)	4/118 (3%)	
Ingrosso et al. (2018)	GI		40/294 (14%)	34/294 (12%)	2/294 (1%)			4/294 (1%)	8/294 (3%)	7/294 (2%)	
	GI actuarial 4-year toxicity grade ≥2								3%		
	GI actuarial 5-year toxicity grade ≥2								4%		
	GU		89/294 (30%)	94/294 (32%)	6/294 (2%)			21/294 (7%)	22/294 (7%)	10/294 (3%)	
	GU actuarial 4-year toxicity grade ≥2								6%		
	GU actuarial 5-year toxicity grade ≥2								10%		
Ishii et al. (2016)	GI (PORT)			7/105 (7%)							
	GI (WPRT)			17/119 (14%)							
	GU (PORT)			11/105 (10%)							
	GU (WPRT)			15/119 (13%)							

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
Keall et al. (2020)	GI 12 months								2/48 (4%)		
	GU 12 months								2/48 (4%)		
Levin-Epstein et al. (2020)	GI or GU toxicity grade ≥3				6/205 (3%)						
Nakamura et al. (2018)	Any toxicity grade ≥3				0/96 (0%)					0/96 (0%)	
	GI grade ≥2		3/96 (3%)		0/96 (0%)			1.1%[1]			
	Proctitis grade ≥2		3/96 (3%)		0/96 (0%)						
	Rectal haemorrhage grade ≥2		0/96 (0%)		0/96 (0%)						
	Diarrhoea grade ≥2		0/96 (0%)		0/96 (0%)						
	GU grade ≥2		45/96 (47%)		0/96 (0%)			5.1%[1]			
	Haematuria grade ≥2		0/96 (0%)		0/96 (0%)						
	Urinary tract pain grade ≥2		2/96 (2%)								
	Urinary incontinence grade ≥2		0/96 (0%)		0/96 (0%)						
	Urinary urgency grade ≥2		6/96 (6%)								
	Urinary retention grade ≥2		29/96 (30%)								
	Urinary frequency grade ≥2		30/96 (31%)								
Naoi et al. (2019)	Rectal bleeding							9/73 (12%)	4/73 (5%)	1/73 (1%)	
	Urinary frequency							12/73	4/73		
	Haematuria							5/73	1/73		
Nath et al. (2010)	GI		30/50 (60%)	4/50 (8%)				4/50 (8%)	1/50 (2%)		
	GI two year cumulative incidence rate grade ≥2								2% (95% CI 0.3-14%)		
	GU		28/50 (56%)	7/50 (14%)				4/50 (8%)	8/50 (16%)	1/50 (2%)	
	GU two year cumulative incidence rate								Grade ≥2: 16% (95%	Grade ≥3: 2% (95%	

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
									CI 9-30%)	CI 0.3-14%)	
Ost et al. (2011)	GI		45/80 (56%)	10/80 (14%)	0/80 (0%)						
	GU		44/80 (55%)	13/80 (16%)	1/80 (1%)						
Pryor et al. (2019)	GI			6/135 (4%)	0/135 (0%)				Grade ≥2: 4.5%[2]	Grade ≥3: 2%[2]	
	GU			36/135 (27%)	0/135 (0%)				Grade ≥2: 24.9%[2]	Grade ≥3: 3/135 (2.2%)[2]	
Shelan et al. (2019)	GI			7/69 (10%)	0/69 (0%)				2/69 (3%)	1/69 (1%)	
	GU			12/69 (17%)	6/69 (9%)				12/69 (17%)	6/69 (9%)	
Simpson et al. (2011)	GI		6/23 (26%)	3/23 (13%)							
	GU		10/23 (43%)	2/23 (9%)							
Swamy et al. (2009)	GI: Proctitis 12 months							1/12 (8%)			
	GU							0%			
Tamihardja et al. (2020)	GI			Grade ≥2: 13.0%					Grade ≥2: 12.1%[3]	4/346 (1%)	0/346 (0%)
	GU			Grade ≥2: 30.1%					Grade ≥2: 26.3%[3]	14/346 (4%)	
Valeriani, Bracci, et al. (2013)	GI during RT		8/69 (12%)	9/69 (13%)							
	GI 3-month FU		2/69 (3%)	1/69 (1%)							
	GI late cumulative rate grade ≥2								Grade ≥2: 1.6%		
	GU during RT		32/69 (46%)	5/69 (7%)							
	GU 3-month FU		20/69 (29%)	2/69 (3%)							
	GU late cumulative rate grade ≥2								Grade ≥2: 6.5%		

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
Valeriani, Carnevale, et al. (2013)	GI during RT		3/59 (5%)	4/59 (7%)							
	GI 1-month FU		1/59 (2%)								
	GI 3-month FU		1/59 (2%)								
	GU during RT		14/59 (24%)	1/59 (2%)	1/59 (2%)						
	GU 1-month FU		7/59 (12%)	1/59 (2%)							
	GU 3-month FU		4/59 (7%)								
Valeriani et al. (2018)	GI during RT (grade 1-2)		13/85 (15%)								
	GI 2-month FU (Grade 1-2)		4/85 (5%)								
	GI 6-month FU (Grade 1-2)							6/85 (7%)			
	GI last FU							4/85 (5%)	0/85 (0%)	1/85 (1%)	
	GU during RT (Grade 1-2)		31/85 (36%)								
	GU 2-month FU (Grade 1-2)		6/85 (7%)								
	GU 6-month FU							16/85 (19%)	0/85 (0%)	1/85 (1%)	
	GU last FU (Grade 1-2)							25/85 (30%)			
Vargas et al. (2019)	GI			1/79 (1%)					1/79 (1%)		
	GU			39/79 (49%)					23/79 (29%)		

Study ID	Toxicity	Acute					Late				
	Grade	0	1	2	3	4	0	1	2	3	4
Vassis et al. (2020)	Proctitis		5/55 (9%)								
	Diarrhea		2/55 (4%)	1/55 (2%)							
	Colitis		2/55 (4%)	1/55 (2%)							
	Colonic obstruction		1/55 (2%)								
	Defecation frequency		1/55 (2%)								
	Small intestine toxicity							1/55 (2%)			
	Colon toxicity							8/55 (15%)			
	Urinary frequency		20/55 (36%)	2/55 (4%)							
	Cystitis non-infective		3/55 (5%)	2/55 (4%)	1/55 (2%)						
	Dysuria		8/55 (15%)								
	Bladder/uretheral toxicity							9/55 (16%)	2/55 (4%)	2/55 (4%)	
	Fatigue		3/55 (5%)								
	Dermatitis		3/55 (5%)								
Wang et al. (2018)	GI			Grade ≥2: 13/40 (33%)	3/40 (8%)				Grade ≥2: 2/40 (5%)	0/40 (0%)	1/40 (3%)
	GU			Grade ≥2: 17/40 (43%)	1/40 (3%)				Grade ≥2: 7/40 (18%)	2/40 (5%)	0/40 (0%)
	Sexual toxicity						9/40 (23%)	10/40 (40%)	6/40 (23%)	1/40 (3%)	

CI=confidence interval; FU=follow-up; GI=gastrointestinal; GU=genitourinary; MR-IGRT=magnetic resonance image-guided radiation therapy; RT=radiation therapy; PORT=prostate-only radiotherapy; WPRT=whole-pelvic radiotherapy

[1] 3-year incidence rate; [2] Late cumulative incidence rate; [3] 3-year cumulative rate

Abdominal malignancies

A total of 1/29 patients with primary or metastatic unresectable liver tumours who underwent MRI-guided SBRT experienced nausea and vomiting, and one case reported abdominal pain with bloody diarrhoea (Feldman et al., 2019). Henke et al. (2018) noted no grade 3 or higher acute or late toxicities in a case series of 20 patients with oligometastatic or unresectable liver or non-liver abdominal malignancies. One patient developed an asymptomatic grade 2 ulcer of the gastric

antrum discovered on follow-up imaging four months after therapy completion. Rudra et al. (2019) reported 3/44 (7%) patients with inoperable pancreatic cancer treated with MR-IGRT experienced acute GI toxicity grade ≥3. Two patients developed abdominal infections requiring hospitalisation and once patient developed a grade 4 duodenal ulcer requiring admission into an intensive care unit. Results are summarised in Table 22.

Table 22 Results of toxicity across the studies, hepatocellular carcinoma and hepatic metastases, MR-IGRT

Study ID	Toxicity	Acute				Late
	Grade	0	1	2	3	
Feldman et al. (2019)	Nausea and vomiting		1/20 (5%)			
	Abdominal pain with bloody diarrhea		1/20 (5%)			
Henke et al. (2018)	Toxicity			1/20 (5%)	0/20 (0%)	0/20 (0%)
Rudra et al. (2019)	GI, cumulative grade ≥ 3				3/44 (7%)	

GI=gastrointestinal

Seven studies reporting on the toxicity of CBCT-IGRT treatment of hepatocellular carcinoma and other abdominal malignancies (hepatocellular carcinoma, k=2 studies (N. Kim et al., 2019; Valakh et al., 2018); liver metastases, k=2 studies (Amendola et al., 2017; Andratschke et al., 2018); pancreatic cancer, k=1 study (Mazzola et al., 2018); metastases in adrenal glands, k=1 study (Voglhuber et al., 2020); abdominopelvic tumours, k=1 study (Barney et al., 2012)) were identified for the naïve comparison. Their outcomes are summarised in Table 23.

Table 23 Results of toxicity across the studies, abdominal malignancies, CBCT-IGRT

Study ID	Toxicity	Acute					Late					
	Grade	0	1	2	3	4	0	1	2	3	4	5
HCC												
N. Kim et al. (2019)	RILD (no grade)						7/105 (7%)					
	Fatigue		5/105 (5%)	2/105 (2%)				4/105 (4%)	1/105 (1%)			
	Nausea		10/105 (10%)	0/105 (0%)								
	Anorexia		11/105 (10%)	0/105 (0%)				3/105 (3%)	0/105 (0%)			
	Esophagitis		2/105 (2%)	0/105 (0%)								
	Abdominal pain		2/105 (2%)	1/105 (1%)								
	Burn		0/105 (0%)	0/105 (0%)				0/105 (0%)	0/105 (0%)			
	Abscess		0/105 (0%)	0/105 (0%)								
	Bile duct injury		0/105 (0%)	0/105 (0%)				0/105 (0%)	0/105 (0%)			
	Intra-abdominal haemorrhage		0/105 (0%)	0/105 (0%)								
	Pleural haemorrhage		0/105 (0%)	0/105 (0%)								
	Pneumothorax		0/105 (0%)	0/105 (0%)								
	Pleural effusion		0/105 (0%)	0/105 (0%)				0/105 (0%)	0/105 (0%)			
	Pneumonitis							5/105 (5%)	3/105 (3%)			
Valakh et al. (2018)	Toxicity grade 1-2		4/15 (27%)									
Liver metastases												
Amendola et al. (2017)	Toxicity	22/27 (81%)	5/27 (19%)	1/27 (4%)	0/27 (0%)	0/27 (0%)						
Andratschke et al. (2018)	Toxicity		23%		<1%							
Pancreas												
Mazzola et al. (2018)	GI				0/33 (0%)					0/33 (0%)		
	Nausea		5/33 (15%)	3/33 (9%)								

Study ID	Toxicity	Acute					Late					
	Grade	0	1	2	3	4	0	1	2	3	4	5
Metastases in adrenal glands												
Voglhuber et al. (2020)	Nausea		2/31 (6%)	4/31 (13%)								
	Vomiting		0/31 (0%)	1/31 (3%)								
	Abdominal pain		2/31 (6%)	2/31 (6%)								
	Loss of weight		1/31 (3%)	1/31 (3%)				0/31 (0%)	1/31 (3%)			
	Loss of appetite		2/31 (6.5%)	1/31 (3%)								
	Diarrhea		2/31 (6%)									
	Constipation		1/31 (3%)	1/31 (3%)								
	Fatigue		6/31 (19%)	5/31 (16%)				1/31 (3%)	3/31 (10%)			
	Throbbing pain		0/31 (0%)	2/31 (6%)								
	Adrenal insufficiency		0/31 (0%)	2/31 (6%)								
	Radiogenic gastritis		0/31 (0%)	1/31 (3%)								
	Flatulence		1/31 (3%)	1/31 (3%)								
	GI		48.4%					4/31 (13%)	0/31 (0%)			
	Headache							0/31 (0%)	2/31 (6%)			

Study ID	Toxicity	Acute					Late					
	Grade	0	1	2	3	4	0	1	2	3	4	5
Abdominopelvic tumours												
Barney et al. (2012)	Any toxicity		42/47 (89%)	11/47 (23%)				10/47 (21%)	4/47 (9%)	3/47 (6%)	0/47 (0%)	1/47 (2%)
	Nausea		15/47 (32%)	5/47 (11%)				1/47 (2%)				
	Fatigue		12/47 (26%)									
	GI pain		7/47 (15%)	3/47 (6%)				4/47 (9%)	2/47 (4%)			
	Diarrhea		4/47 (9%)					4/47 (9%)	1/47 (2%)			
	Abdominal distension		2/47 (4%)					1/47 (2%)				
	Musculoskeletal pain		2/47 (4%)						1/47 (2%)			
	Oesophagitis			2/47 (4%)								
	Dermatitis			1/47 (2%)								
	Biliary stenosis									2/47 (4%)		
	Perforation									1/47 (2%)		1/47 (2%)

GI=gastrointestinal; HCC=hepatocellular carcinoma; RILD=radiation-induced liver damage

Head and neck

Chen 2018 reported the rate of grade 3 acute toxicities in patients with head and neck cancer treated with MR-IMRT. These toxicities are summarised in Table 24. Some degree of acute skin erythema, odynophagia, taste alterations or xerostomia occurred in essentially all patients. In the late toxicity setting, 11/18 (61%) of patients complained of some subjective degree of xerostomia. One patient was found to have oesophageal stricture and 17% of patients were gastrostomy tube-dependent at six months and 6% at one year. No cases of osteoradionecrosis, neurological toxicity or central nervous system toxicity were observed.

Table 24 Results of toxicity across the studies, head and neck cancers, MR-IGRT

Study ID	Toxicity	Acute			
	Grade	0	1	2	3
Chen et al. (2018)	Any toxicity grade 3				44%
	Skin desquamation				6/18 (33%)
	Odynophagia/dysphagia				6/18 (33%)
	Mucositis				5/18 (28%)
	Anorexia				4/18 (22%)
	Laryngeal oedema				1/18 (6%)

One study reporting on the toxicity of CBCT-IGRT treatment of head and neck cancer (Navran et al., 2019) was identified for the naïve comparison. Its outcomes are summarised in Table 25.

Table 25 Results of acute toxicity, head and neck cancers, CBCT-IGRT

Study ID	Acute toxicity	3-mm CTV-PTV margin				5-mm CTV-PTV margin			
	Grade	0	1	2	3	0	1	2	3
Navran et al. (2019)	Any acute toxicity			Grade ≥2: 98.6%	53.8%			Grade ≥2: 98.1%	65.0%
	Dermatitis			Grade ≥2: 77.4%	27.4%			Grade ≥2: 71.8%	25.2%
	Mucositis			Grade ≥2: 74.5%	30.8%			Grade ≥2: 78.2%	42.2%
	Dysphagia			Grade ≥2: 62.0%	22.1%			Grade ≥2: 71.4%	33.5%
	Xerostomia			Grade ≥2: 33.7%				Grade ≥2: 37.9%	

CTV=clinical target volume; PTV=planning target volume

Mixed cancer population

Acute toxicity rates from case series that included a mixed cancer population were reported by Kluter et al. (2020). Twenty of the 43 included patients (47%) were eventually able to undergo MR-guided SBRT, and the most common treated sites included lymph node metastases and liver lesions. No grade ≥3 acute toxicities were observed in the included patient population. Four patients reported grade 2 fatigue and various grade 1 toxicities were reported, with fatigue (n=19) and nausea (n=12) noted as the most common. All acute toxicities observed in the study are listed in Table 26.

Table 26 Results of toxicity across the studies, mixed cancer population, MR-IGRT

Study ID	Toxicity	Acute	
	Grade	1	2
Kluter et al. (2020)	Fatigue	19/43 (44%)	4/43 (9%)
	Nausea	12/43 (28%)	
	Coughing	7/43 (16%)	
	Flatulence	6/43 (14%)	
	Diarrhea	4/43 (9%)	
	Dyspnoea	2/43 (5%)	
	Dyspepsia	7/43 (16%)	
	Pain in thoracic wall	2/43 (5%)	
	Dysphagia	1/43 (2%)	

Due to the population heterogeneity and lack of detail in reporting, no naïve comparison was attempted for the mixed cancer population.

PATIENT TOLERANCE

Three case series reported on patient experiences and complaints of undergoing treatment with MR-IGRT (Kluter et al., 2020; S. Tetar et al., 2018; S. U. Tetar et al., 2019). All three studies utilised an in-house developed patient-reported outcome questionnaire (PRO-Q) including questions on potential MR-related complaints and experiences.

In a case series reported by Kluter et al. (2020), patients with cancer treated with MRI-guided SBRT were asked to complete an in-house developed PRO-Q after each fraction. The results presented in the study report compare ratings after first fraction and at the end of treatment. These are summarised in Table 27. Authors further report that 65% of patients reported some degree of potential MR-related complaints at least once (score ≥4). The main complaints were related to the unsuitable temperature in the room (24%) and of feeling too warm or too cold in some particular body parts (27%). Furthermore, 18% of the patients experienced paraesthesia during treatment, and 12% rated the positioning as well as having to lie still for at least half an hour during treatment negatively (score ≥4).

Table 27 Results of the patient-reported outcome questionnaires, Kluter et al. (2020)

How do you rate[a] ...	After the first fraction (N = 34) Mean (range)	At the end of treatment (N = 34) Mean (range)	*p-value*
... the treatment at the MRlinac in total?	1.3 (1–4)	1.4 (1–3)	0.739
... the information provided by the staff before treatment?	1.1 (1–2)	1.1 (1–2)	1.000
... the friendliness of the staff?	1.0 (1–2)	1.0 (1–2)	0.317
... the duration of treatment?	2.2 (2–5)	2.1 (2–4)	0.741
... the size of the MRI bore?	1.9 (1–4)	1.8 (1–4)	1.000
... the positioning during RT?	2.2 (1–4)	2.2 (1–4)	0.604
... having to lie still?	2.0 (1–3)	1.8 (1–4)	0.662
... the noise in the MRI?	2.1 (1–4)	2.0 (1–3)	0.817
... the temperature in the MRI?	3.6 (1–4)	3.4 (1–3)	0.067
... the local temperature of your body parts?	3.5 (1–3)	3.2 (1–4)	0.302
... potential tingling sensations in your fingers and toes?	1.9 (1–4)	1.7 (1–4)	0.090
... the breathing instructions?	1.1 (1–3)	1.2 (1–2)	0.102
... holding your breath during RT?	1.4 (1–3)	1.5 (1–3)	0.305
Were you anxious during treatment?	1.4 (1–3)	1.3 (1–3)	0.157
Respiratory gated dose delivery (*N* = 22)			
Was it difficult to control the target by holding your breath?	1.3 (1–3)	1.2 (1–2)	0.739

How do you rate[a] ...	After the first fraction (N = 34) Mean (range)	At the end of treatment (N = 34) Mean (range)	*p-value*
Was it confronting to watch your tumor on the monitor?	1.2 (1–2)	1.1 (1–2)	0.564
How did you like the possibility to have an active role in control- ling the duration of treatment?	1.2 (1–2)	1.1 (1–2)	1.000

[a] Items were scored using a five-point scale with higher score indicating more concern.

In another cross-sectional study by S. Tetar et al. (2018) potential MR-IGRT related complaints and experiences, such as anxiety, temperature, and noise were assessed through study's own in-house PRO-Q. Questionnaires were collected once, immediately following the last SBRT fraction. Some degree of anxiety during treatment delivery was reported by 25/150 (17%) patients, with seven of these patients (5%) reporting anxiety to be considerable. None of the patients needed medication for anxiety. S. Tetar et al. (2018) noted that 89/150 (80%) patients reported at least some degree of one of the potential MR-related complaints included in the questionnaire. However, only 44/150 (29%) scored at least one of them as considerable. The proportion of patients reporting each of the seven assessed MR-related complaints in S. Tetar et al. (2018) are summarised in Table 28.

Table 28 MR-IGRT related complaints, S. Tetar et al. (2018)

MR-related complaints[a]	Troubled a little (N=150) n (%)	Considerably troubled (N=150) n (%)
Noise	90 (60%)	26 (17%)
Cold	44 (29%)	15 (10%)
Paraesthesia	42 (28%)	9 (6%)
Dizziness	16 (11%)	2 (1%)
Local heat sensations	13 (9%)	2 (1%)
Metallic taste	3 (2%)	-
Light flashes	3 (2%)	-

Source: S. Tetar et al. (2018), p 8

[a] Items could be scored on a 4-point scale as: "not at all", "a little", "moderate", and "very much". the scores "moderate" and "very much" for any question were combined and denominated "considerable" in this manuscript.

The population evaluated by S. U. Tetar et al. (2019) included only patients with prostate cancer, with 68 out of 89 of these assumed to be included in another study published by S. Tetar et al. (2018). The findings from the 2019 study of patients with prostate cancer were therefore very comparable to the findings presented in S. Tetar et al. (2018) and were presented as a graph in S. U. Tetar et al. (2019) (see Figure 6).

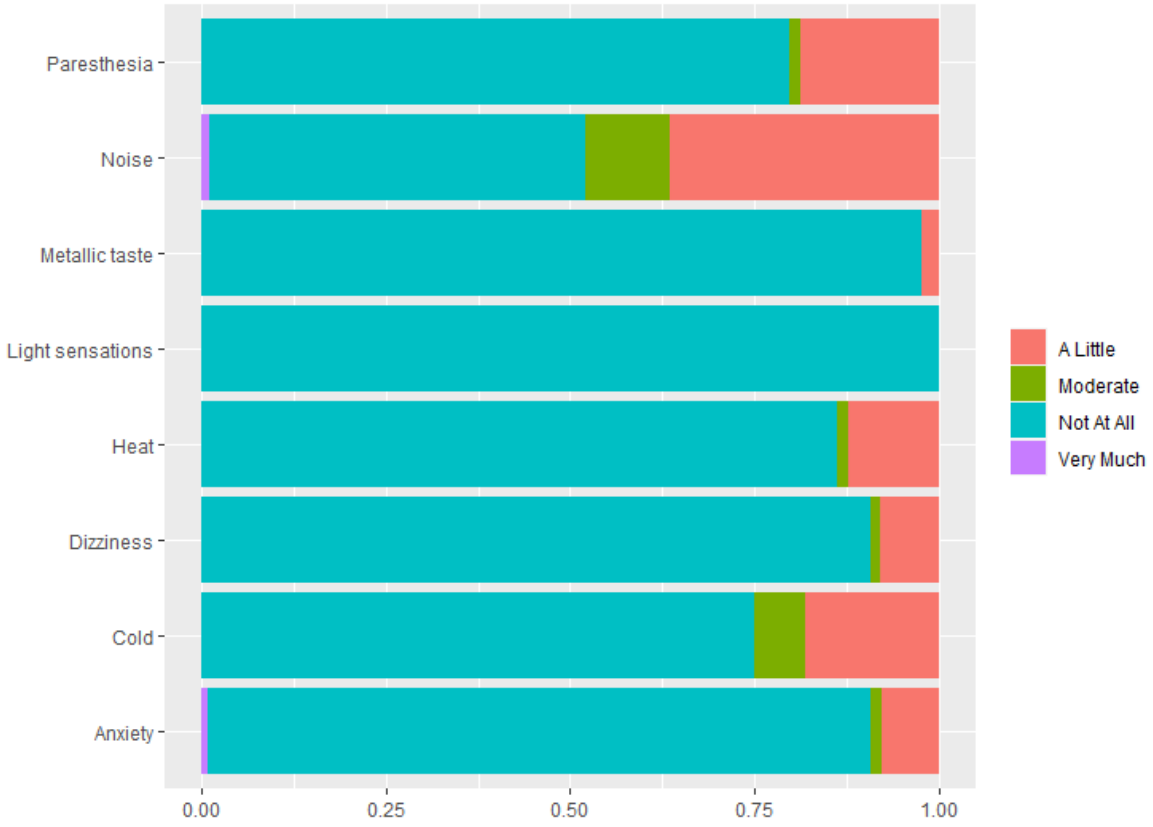

Figure 6 Patient reported complaints during MR-IGRT for prostate cancer (N=89)

Source: S. U. Tetar et al. (2019), p 75

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

IS IT EFFECTIVE?

Summary – What is the effectiveness of MR-IGRT, compared to CBCT-guided radiation therapy, in persons with cancer who undergo EBRT?

Dosimetric outcomes

One comparative cohort study compared the PTV and the clinically relevant dose-volumetric parameters between the MR-IGRT and CBCT-IGRT plans of patients with lung cancer. 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 organs at risk (OARs).

Survival outcomes

No comparative evidence was found for survival outcomes. Four 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 70.1%-97.7%) for patients with 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 44-63% 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 one year and 60-75% at 2 years.

Three- and six-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 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 in patients with prostate cancer. However, as no baseline measurements were provided, it is not clear if QoL scores changed during treatment.

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

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

DOSIMETRIC OUTCOMES

E. Kim et al. (2018) compared the PTV and the clinically relevant dosimetric parameters in lung between the MR-linac and CBCT-linac plans. These parameters are summarised in Table 29. Planning target volume (PTV) was smaller in the MR-linac plans (p=0.036), although there was no significant difference in tumour size between the two groups. The mean doses to both ipsi- and contralateral lung were statistically significantly higher and the volume of normal lung receiving 10 and 20 Gy were significantly larger for MR-linac than for CBCT-linac. E. Kim et al. (2018) stated that "the shown dosimetric parameters were worse in the tri-^{60}Co system. However, both treatment systems kept the normal organ dose constraint suggested in the Radiation Therapy Oncology Group (RTOG)".

Table 29 Dose-volumetric parameters in lung, E. Kim et al. (2018)

Variable	tri-^{60}Co MR-linac (n = 8) Mean ± SD	CBCT-linac (n = 8) Mean ± SD	p-value*
PTV	9.06 ± 7.02	14.78 ± 3.97	0.036
Ipsilateral lung mean dose (Gy)	7.17 ± 1.55	4.66 ± 2.42	0.012
Contralateral lung mean dose (Gy)	1.35 ± 0.6	0.67 ± 0.35	0.036
V_{5Gy} (cc)	603.41 ± 280.21	313.02 ± 158.21	0.050
V_{10Gy} (cc)	396.62 ± 201.28	186.42 ± 83.23	0.036
V_{20Gy} (cc)	218.36 ± 153.51	92.09 ± 40.43	0.017
D_{1000cc} (Gy)	2.07 ± 1.92	0.89 ± 0.64	0.069
D_{1500cc} (Gy)	0.94 ± 0.9	0.37 ± 0.24	0.071

Source: E. Kim et al. (2018), Table 1 and Table 2, p 5/11
V_{nGy}=total normal lung volume receiving n Gy; D_{ncc}=dose received by at least n volume of a total normal lung; PTV=planning target volume; SD=standard deviation
*Wilcoxon signed-rank test

Three simulation studies comparing dosimetric outcomes between MR-IGRT and CBCT-IGRT were identified (van de Schoot et al., 2019; Winkel et al., 2020; Winkel et al., 2018). Winkel et al. (2018) investigated whether online replanning for SBRT of pelvic and para-aortic lymph node oligometastases on the MR-linac yields beneficial dosimetric values compared to online position correction as performed on CBCT-linacs in current clinical practice. For each of the 17 included lymph nodes (from five patients with locally advanced cervical cancer), five plans were generated to simulate the different treatment approaches: (1) pre-treatment plan with a 3mm PTV margin and (2) calculated on daily anatomy after CBCT-online position correction, (3) pre-treatment plan with a 8mm PTV margin and (4) calculated on daily anatomy after CBCT-online position correction, and (5) complete new plan generated on the daily anatomy (full online replanning for the MR-linac with 3mm PTV margin). Plans were evaluated against dose criteria for PTV and surrounding OARs including bladder, bowel, rectum and sigmoid.

Winkel et al. (2018) stated that compared to the current clinical practice of online position correction, "full online replanning, simulating MR-linac treatment, resulted in a reduction of

violations to the OARs. The number of instances of violation was reduced from 6 to 2 (66%) and 8 to 2 (75%) for lymph node oligometastases with a 3 and 8mm margin, respectively." Diagram provided in the study report is shown in Figure 7.

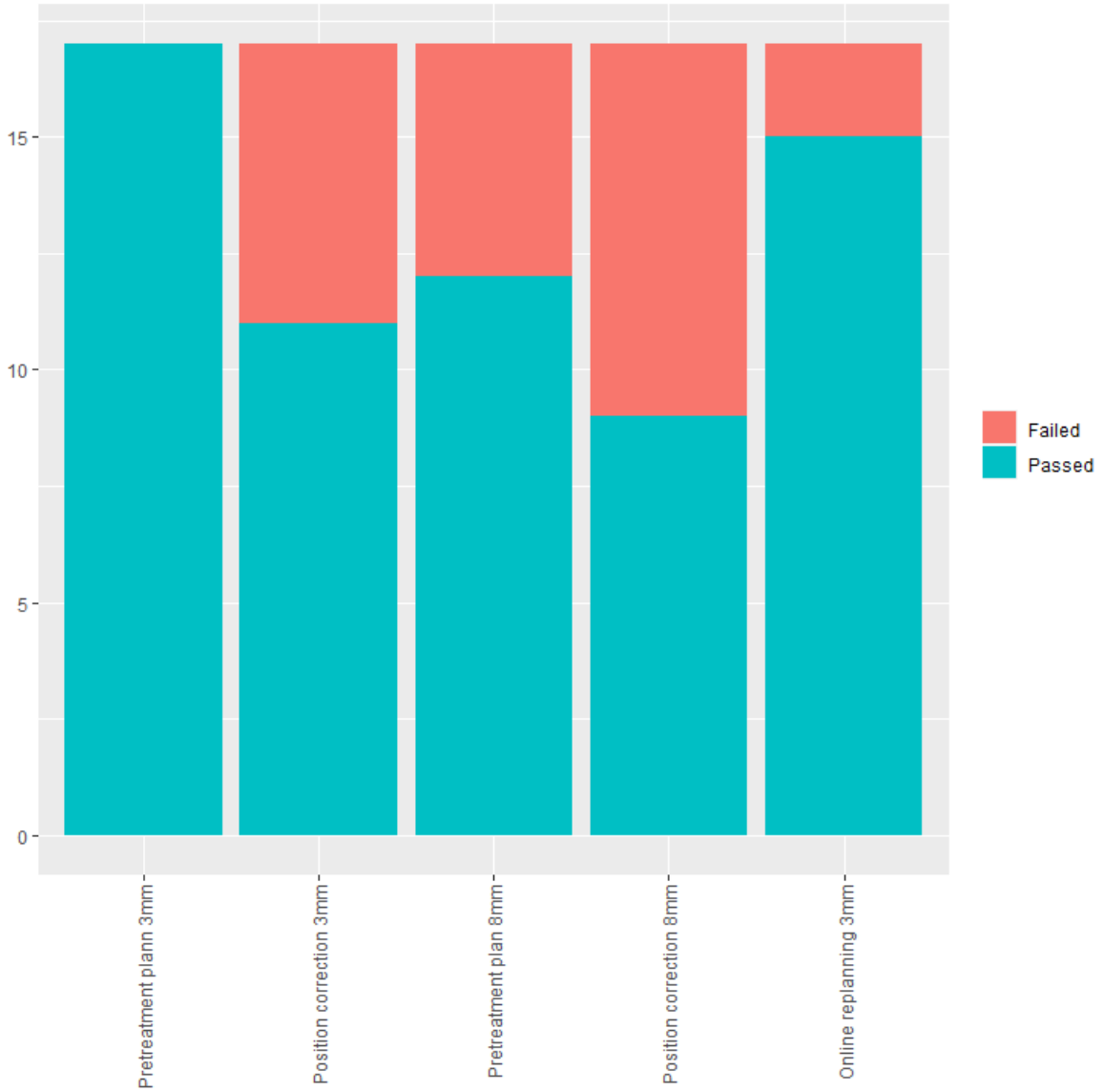

Figure 7 Number of plans (N=17) that passed or failed based on dose criteria for the initial plan, the initial plan calculated on the daily anatomy and full online replanning (simulating MR-linac treatment)

Source: Winkel et al. (2018), Figure 3, p 1708

A dosimetric study by van de Schoot et al. (2019) aimed to compare MR-linac plan quality with the current clinical practice of positioning and adaptation based on CBCT. Data of eight patients with rectal cancer and eight patients with prostate cancer treated on a conventional CBCT-integrated linac were included in the retrospective treatment planning study. Clinical treatment planning for conventional CBCT-integrated linac and MR-linac was performed using a volumetric modulated arch therapy (VMAT) and an IMRT delivery technique, respectively. Compared to clinical plans, MR-linac

plans showed a statistically significant decrease in plan homogeneity, an increase in PTV D_{mean} (prostate: 0.6 Gy; rectum: 0.8 Gy) and $D_{1\%}$ (prostate: 1.9 Gy; rectum: 2.0 Gy) and increases in OAR dose. Dose-volume histogram (DVH) parameter differences between MR-linac plans compared to current clinical practice reported in the study are summarised in Table 30. van de Schoot et al. (2019) stated that all MR-linac plans fulfilled the clinical acceptance criteria, and MR-linac plans were considered clinically equivalent to current clinical practice. A significant decrease in plan homogeneity was found for MR-linac plans compared to current clinical practice for all included patients.

Authors stated that "differences between MR-linac plans and clinical plans are mainly due to a larger washout of the low dose region and an increase in target inhomogeneity. This leads to changes in OAR dose in the low-dose region and around the near-maximum. The increased dose in the low-dose region is due to the use of the 7 MV beam of the MR-linac instead of our conventional choice for pelvic cases of 10 MV beams."

Table 30 Median (min-max) DVH parameter differences between MR-linac plans compared to current clinical practice, van de Schoot et al. (2019)

DVH parameter	MR-linac – Clinical	Clinical
Rectal cancer		
PTV D_{mean} (Gy)	0.8 (0.2-1.3)*	49.5 (49.2-50.0)
PTV $D_{1\%}$ (Gy)	2.0 (1.1-2.4)*	50.6 (50.0-51.4)
Bladder D_{mean} (Gy)	2.9 (- 0.5-6.0)*	29.1 (11.3-37.7)
Bowel area D_{mean} (Gy)	4.1 (2.1-5.9)*	16.9 (11.6-26.3)
EXT D_{mean} (Gy)	2.4 (1.1-2.9)*	18.2 (12.1-21.1)
EXT-PTV_{2cm} D_{mean} (Gy)	2.5 (1.1-3.2)*	12.4 (8.80-14.2)
EXT-PTV_{2cm} $D_{1\%}$ (Gy)	4.2 (2.1-6.8)*	29.5 (26.2-31.2)
GI grade ≥ 2 acute toxicity NTCP (%)	0.013 (- 0.61-0.41)	0.08 (0.00-21.2)
Prostate cancer		
$PTV_{64.6Gy}$ D_{mean} (Gy)	0.6 (- 0.1-1.3)*	64.6 (64.2-64.8)
$PTV_{64.6Gy}$ $D_{1\%}$ (Gy)	1.9 (0.5-2.4)*	66.5 (65.6-66.8)
$PTV_{57.8Gy}$ $D_{95\%}$ (%)	-0.3 (- 0.6- -0.2)*	100 (99.1-100)
Rectum D_{mean} (Gy)	0.8 (- 2.5-3.7)	25.3 (12.7-29.7)
Anal sphincter D_{mean} (Gy)	0.7 (- 2.0 - -0.9)	12.3 (3.80-31.3)
EXT D_{mean} (Gy)	- 1.7 (- 2.7- -1.4)*	7.45 (5.70-8.20)
EXT-PTV_{2cm} D_{mean} (Gy)	- 1.2 (- 2.0 - -0.9)*	5.56 (4.50-5.90)
EXT-PTV_{2cm} $D_{1\%}$ (Gy)	0.2 (- 2.4-2.7)	29.8 (28.1-32.4)
Late rectal bleeding grade ≥2 toxicity NTCP (%)	0.17 (- 2.31-1.81)	10.4 (3.88-13.7)

Source: van de Schoot et al. (2019), Table 3, p 22
D_{mean}=mean dose; EXT=indicates the patient volume; EXT-PTV_{2cm}=indicates the patient volume with the PTV, along with an additional 2 cm margin removed; NTCP=normal tissue complication probability; PTV=planned target volume;
Positive values indicate higher DVH parameters for the MR-linac plans.
*Statistically significant difference (Wilcoxon $p < 0.05$)
Also listed are the median (min – max) DVH parameters for the clinical plans.

Winkel et al. (2020) performed a target coverage and dose criteria-based evaluation of the clinically delivered online ART compared with conventional CBCT-linac treatment of patients with single or multiple (2-3) pelvic and para-aortic lymph node oligometastases. Patients were treated with 1.5T MR-linac and CBCT plans were also created for each patient. MR-linac improved the percentage of plans that met all dose constraints (PTV coverage and OAR constraints) from 19% to 84% for single oligometastases and from 20% to 67% for multiple metastases. There was a smaller amount of unplanned violations of high dose criteria in the MR-linac plans. The authors concluded that the benefit was particularly gained in patients with multiple lymph node oligometastases.

Table 31 Comparison of MR-linac and CBCT-linac plans, Winkel et al. (2020)

DVH parameter	MR-linac, clinically delivered	CBCT-linac
Single oligometastases		
Median GTV V_{35Gy}	100% (99.7-100%)	100% (98.7-100%)
Median PTV V_{35Gy}	100% (90.7-100%)*	94.9% (47.7-100%)
All criteria met (PTV coverage + OAR constraints)	59/70 (84%)	13/70 (19%)
Violations of OAR criteria (above the set threshold)	Max 3 Gy	Max 2.5 Gy/0.1 cc
Multiple lymph nodes		
Median GTV V_{35Gy}	100% (100-100%)	100% (8.9-100)
Median PTV V_{35Gy}	100% (93.4-100%)*	94.7% (31.6-100%)
All criteria met (PTV coverage + OAR constraints)	20/30 (67%)	6/30 (20%)
Violations of OAR criteria (above the set threshold)	Max 0.5 Gy /0.1 cc	Max 0.5 Gy/0.7 cc

GTV=gross tumour volume; PTV=planned target volume;
*Statistically significant difference (Wilcoxon $p < 0.01$)
Also listed are the median (min – max) DVH parameters for the clinical plans.

SURVIVAL OUTCOMES AND TUMOUR CONTROL

Four case series reported survival outcomes after MR-IGRT for different cancers including lung cancer (Finazzi, Haasbeek, et al., 2020), hepatocellular cancer (Rosenberg et al., 2019), unresectable abdominal malignancies (Henke et al., 2018), and head and neck cancers (Chen et al., 2018).

Lung cancer

Survival outcomes at one year in patients with lung malignancies treated with MR-IGRT were reported in Finazzi, Haasbeek, et al. (2020) and are summarised in Table 32. Separate data for primary lung cancer (early-stage non-small cell lung cancer, NSCLC) and lung metastases populations were also provided in the study report.

Table 32 Results of key patient-relevant outcomes across the studies, lung cancer, MR-IGRT

Study ID	Cancer	Outcome	One year survival rate (%) (95% CI)
Finazzi, Haasbeek, et al. (2020)*	Lung cancer	OS	88.0% (70.179.4-97.5%)
		DFS	63.6% (51.5-78.5%)
		LC	95.6% (89.8-100.0%)
	Early stage NSCLC	OS	82.8% (70.1-97.7%)
		DFS	68.4% (53.2-87.8%)
		LC	95.8% (88.2-100.0%)
	Lung metastases	OS	95.2% (86.6-100.0%)
		DFS	57.1% (39.5-82.8%)
		LC	95.5% (87.1-100.0%)

CI, confidence interval; DFS, disease-free survival; LC, local control; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

* Survival data reported for all lung cancers and separately for patients with primary lung cancers and patients with lung metastases

Nine studies reported on survival outcomes in patients with lung cancer, predominantly various stages of NSCLC or lung metastases, after treatment with CBCT-IGR (Appel et al., 2020; Baschnagel et al., 2013; Boda-Heggemann et al., 2014; Frakulli et al., 2015; Grills et al., 2012; Kestin et al., 2014; Kilburn et al., 2016; Stone et al., 2015; Yegya-Raman et al., 2018). The results are summarised in Table 33.

Table 33 Results of key patient-relevant outcomes across the studies, lung cancer, CBCT-IGRT

Study ID	Cancer	Outcome	Survival rate (%) (95% CI)			
			1 year	2 years	3 years	5 years
Appel et al. (2020)	Lung cancer (locally advanced NSCLC and SCLC)	OS			44.4% (36-61.3%)	
		DFS			37% (18-56%)	
		LC		60.7% (34.5-79.2%)	52% (25.4-73.3%)	
Baschnagel et al. (2013)	Lung metastases	OS	83%	76%	63%	
		LC	97%	92%	85%	
Boda-Heggemann et al. (2014)	NSCLC	OS	67%	43%		42%
		PFS	28%			

Study ID	Cancer	Outcome	Survival rate (%) (95% CI)			
			1 year	2 years	3 years	5 years
Frakulli et al. (2015)	Lung metastases (bone and soft-tissue sarcoma)	OS		66.4%		
		LC		85.9%		
Grills et al. (2012)	NSCLC (early)	OS	60%	48%		
Kestin et al. (2014)	NSCLC (early stage T1-2 N0M0)	OS		60%		
		CSS		89%		
		LRR		6%		
		RRR		11%		
		DMR		20%		
Kilburn et al. (2016)	NSCLC stage IIB-IIIB with curative intent	OS		47%		
		LFFS		75%		
		RFFS		84%		
		DFFS		58%		
		PFS		43%		
Stone et al. (2015)	NSCLC stage I peripheral	OS	87%		62%	
Yegya-Raman et al. (2018)	NSCLC (unresectable, locally advanced or stage IV oligometastases)	OS		50%		
		Cumulative locoregional progression incidence		38% 50%*		
		Cumulative distant meta incidence		38%		
		Cumulative any progression incidence		62%		

CI=confidence interval; CSS=cancer-specific survival; DFFS=distant failure-free survival; DFS=disease-free survival; DMR=distant metastasis rate; LC=local control; LFFS=local failure-free survival; LRR=local relapse rate; NSCLC=non-small cell lung cancer; OS=overall survival; PFS=progression-free survival; RFFS=regional failure-free survival; RRR=regional relapse rate; SCLC=small-cell lung cancer;
* Adjusted for distant metastases

Abdominal malignancies

Rosenberg et al. (2019) reported survival outcomes for patients with hepatocellular carcinoma and metastases to the liver deemed inappropriate for surgical treatment treated with MR-guided liver SBRT. Henke et al. (2018) reported survival in a case series of patients with unresectable abdominal cancers (primary liver and non-liver malignancies). The results of the two studies are summarised in Table 34.

Table 34 Results of key patient-relevant outcomes, abdominal malignancies, MR-IGRT

Study ID	Outcome	Survival rate n /N (%)			
		3 months	6 months	1 year	2 years
Henke et al. (2018)	OS			15/20 (75%)	
	Local PFS	95%	89.1%		
Rosenberg et al. (2019)	OS			69%	60%
	FFLP at median follow-up (21.2 months)				80.4%
	PFS (local, regional, distant) at median follow-up (21.2 months)				35%

FFLP=freedom from local progression; OS=overall survival; PFS=progression-free survival

Three studies evaluated survival outcomes in hepatocellular carcinoma patients treated with CBCT-IGRT (N. Kim et al., 2019; Price et al., 2012; Valakh et al., 2018). Results of these studies are summarised in Table 35.

Table 35 Results of key patient-relevant outcomes, abdominal malignancies, CBCT-IGRT

Study ID	Outcome	Survival (%) (95% CI)		
		6 months	1 year	2 years
N. Kim et al. (2019)	OS		88.5%	74.8%
	PFS		37.8%	35.6%
	FFLP		85.7%	76.3%
Price et al. (2012)	OS		77%	60%
Valakh et al. (2018)	OS	26.7% (4.4-49%)		
	Freedom from in-field tumour failure	100%		
	Freedom from intrahepatic cancer relapse	91%		

CI=confidence interval; DFS=disease-free survival; FFLP=freedom from local progression; OS=overall survival; PFS=progression-free survival

Head and neck cancer

Survival data for patients with head and neck cancer treated with MR-IGRT were reported by Chen et al. (2018) and are summarised in Table 36.

Table 36 Results of key patient-relevant outcomes, head and neck cancer, MR-IGRT

Study ID	Outcome	One year survival rate (%)
Chen et al. (2018)	OS	96%
	PFS	95%
	LRC	95%

LRC=loco-regional control; PFS=progression-free survival; OS=overall survival

One study reported two-year survival rates for patients with head and neck cancer treated with CBCT-IGRT, summarised in Table 37.

Table 37 Results of key patient-relevant outcomes, head and neck cancer, CBCT-IGRT

Study ID	Outcome	Two year survival rate (%)	
		Margin 3 mm	Margin 5 mm
Navran et al. (2019)	OS	75.2%	75.1%
	DFS	71.5%	72.7%
	LRC	79.9%	79.2%

LRC=loco-regional control; PFS=progression-free survival; OS=overall survival

QUALITY OF LIFE

For MR-IGRT, QoL was measured in three of the included case series (Alongi et al., 2020; Chen et al., 2018; Henke et al., 2018). Alongi et al. (2020) and Henke et al. (2018) reported the EORTC QLQ-C30 QoL scores in patients with localised prostate cancer and unresectable abdominal malignancies, respectively. Alongi et al. (2020) also utilised the EORTC QLQ-PR25 which is designed for patients with prostate cancer. EORTC QLQ-PR25 has 25 items examining urinary and bowel symptoms, sexual activity and function, and treatment-related symptoms, using a four-point Likert response scale. Chen et al. (2018)used the University of Washington QoL instrument (UW-QOL), v4, to measure the QoL of patients with head and neck cancerChen et al. (2018).

Henke et al. (2018) reported no significant difference in the median global QoL scores during the treatment period and in the acute post-treatment time (p=0.29). Single-item QoL scores such as for diarrhea, constipation, nausea, emesis, appetite, pain, or activity tolerance, were also unchanged.

Alongi et al. (2020) reported no clinically or statistically relevant difference on the functional scales of the EORTC QLQ-C30 questionnaire with the exception of physical functioning, which decreased from 94.5% ±10.4% at baseline to 91.6% ± 12.6% at the end of MR-guided SBRT. On the symptom scale, insomnia and constipation worsened relative to baseline. Global health status values were 72.5% and 72.1% at baseline and at the end of treatment, with no statistically significant difference. All scores are shown in Table 38.

Table 38 QoL scores on EORTC QLQ-C30 at baseline and post-treatment with MR-IGRT for patients with prostate cancer Alongi et al. (2020)

EORTC QLQ-C30*	Baseline (mean ± SD)	Post-RT (mean ± SD)	P value
Functioning scale			
Physical Functioning	94.5 ± 10.4	91.6 ± 12.6	0.04
Role Functioning	94.6 ± 9.9	88.8 ± 17.3	0.10
Emotional Functioning	82.2 ± 18.7	79.7 ± 16.6	0.23
Cognitive Functioning	94.9 ± 11.7	92 ± 12.2	0.16
Social Functioning	65.5 ± 40.5	73.2 ± 35.8	0.29
Global Health Status	72.5 ± 13.4	72.1 ± 15.8	0.91
Single item			
Fatigue	12.1 ± 15.3	17.4 ± 18.3	0.22
Nausea and Vomiting	0.7 ± 3.5	0.7 ± 3.5	0.23
Pain	1.5 ± 4.8	7.2 ± 17.3	0.12
Dyspnoea	10.1 ± 18.6	8.7 ± 20.6	0.72
Insomnia	10.1 ± 15.7	26.1 ± 26.5	0.005
Appetite Loss	1.4 ± 6.9	2.9 ± 9.6	0.33
Constipation	11.6 ± 19.1	17.4 ± 19.8	0.04
Diarrhoea	5.8 ± 12.9	7.2 ± 17.3	0.71
Financial Difficulties	2.9 ± 9.6	2.9 ± 9.6	0.23

Source: Alongi et al. (2020), Table 6
SD=standard deviation; RT=radiation therapy
* The EORTC QLQ-C30 includes functional scales and single-item questions. All scales and single-item scores range from 0 to 100. A high functional scale score represents a healthy level of functioning; a high score for the global health status represents a high QoL, while a high score for a symptom scale, bowel score or urinary score represents a high level of symptomatology.

The EORTC QLQ-PR25 urinary symptom scale also showed no significant worsening during the treatment Alongi et al. (2020). The results of the EORTC QLQ-PR25 questionnaire are provided in Table 39.

Table 39 QoL scores on EORTC QLQ-PR25 at baseline and post-treatment with MR-IGRT for patients with prostate cancer Alongi et al. (2020)

EORTC QLQ-PR25*	Baseline (Mean ± SD)	Post-RT (Mean ± SD)	P value
Urinary Symptoms	10.2 ± 3.1	10.3 ± 3	0.21
Incontinent Aid	1.1 ± 0.5	1.1 ± 0.5	1
Bowel Symptoms	4.3 ± 0.6	4.5 ± 1.8	0.33
Hormonal-treated Related Symptoms	6.9 ± 1	6.8 ± 1.2	0.19
Sexual Activity	3.2 ± 1.7	3.2 ± 1.5	0.71
Sexual Functioning	7.2 ± 4	6.3 ± 3.4	0.76

Source: Alongi et al. (2020), Table 4
RT=radiation therapy; SD=standard deviation
* All items and scale scores of the QLQ-PR25 are linearly transformed to a 0–100 scale, with higher scores reflecting either more symptoms (urinary, bowel, hormonal treatment-related symptoms) or higher levels of functioning (sexual).

Chen et al. (2018) provided a narrative summary of the QoL findings: "The proportion of patients rating their health-related quality of life as ''very good'' or ''outstanding'' at 6-months and one year after MR-IGRT was 60 and 70%, respectively. With global QoL on the UW-QOL, the corresponding proportions reporting ''very good'' or ''outstanding'' scores were 53 and 60%, respectively." Unfortunately, baseline QoL measurements were not reported in the study.

One study included in the CBCT-IGRT evidence base reported health-related QoL scores obtained from EORTC QLQ-C30 questionnaire in patients with intermediate- or high-risk non-metastatic prostate cancer. Mean scores on functioning scales and single items of EORTC QLQ-C30 at the end of radiotherapy are summarised in Table 40.

Table 40 QoL scores on EORTC QLQ-C30 at baseline and post-treatment with CBCT-IGRT for patients with prostate cancer Tondel et al. (2018)

EORTC QLQ-C30*	Post-RT (mean ± 95%CI)
Functioning scale	
Physical Functioning	83.6 (82.0-85.3)
Role Functioning	78.1 (75.8-80.4)
Emotional Functioning	87.7 (86.4-89.1)
Cognitive Functioning	86.9 (85.4-88.4)
Social Functioning	82.0 (80.3-83.8)
Global Health Status	76.2 (74.4-77.9)
Single item	
Fatigue	30.2 (28.4-32.1)
Nausea and Vomiting	1.7 (1.2-2.2)
Pain	12.2 (10.4-14.0)
Dyspnoea	20.7 (18.3-23.1)
Insomnia	22.4 (20.1-24.7)
Appetite Loss	4.2 (3.1-5.2)
Constipation	17.0 (15.0-19.0)
Diarrhoea	20.6 (18.6-22.6)
Financial Difficulties	4.1 (2.8-5.5)

Source: Tondel et al. (2018), Table 3
CI=confidence interval; RT=radiation therapy
* The EORTC QLQ-C30 includes functional scales and single-item questions. All scales and single-item scores range from 0 to 100. A high functional scale score represents a healthy level of functioning; a high score for the global health status represents a high QoL, while a high score for a symptom scale, bowel score or urinary score represents a high level of symptomatology.

B.7. EXTENDED ASSESSMENT OF HARMS

An extended assessment of harms was not conducted for this DCAR.

B.8. INTERPRETATION OF THE CLINICAL EVIDENCE

On the basis of the evidence profile (summarised in Table 41), it is suggested that, relative to CBCT-IGRT, the MR-IGRT has uncertain safety and uncertain effectiveness.

There is insufficient high-quality evidence to enable the comparison of safety and effectiveness between MR-IGRT and CBCT-IGRT for the population of interest (all patients with cancer eligible for EBRT). Due to the paucity of comparative studies, a naïve comparison was attempted. The summary of findings for MR-IGRT is shown in Table 41.

Table 41 Summary of findings for the critical patient-relevant outcomes in the MR-IGRT studies

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 with lung cancer 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 reported (one CS); 96% for patients with head and neck cancer (one CS); 75% in unresectable abdominal cancer (one CS).
Quality of life	63 participants (3 studies)	⊕⊙⊙⊙	Two studies on patients treated with MR-IGRT(unrespectable 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.

[a] 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) likely included overlapping populations. 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

A formal GRADE evaluation of the quality of evidence provided by the single-arm studies of CBCT-IGRT included in the naïve comparison was not carried out. Evidence was found for the outcomes of toxicity (k=47 studies), survival (k=13 studies) and QoL (k=1 study). The evidence base was generally of level IV-V, with concerns about the methodological quality and risk of bias, small sample size (and, consequently, concerns about imprecision of the reported results), wide variations in outcome measurement and reporting, and poorly matched to the patient populations treated with MR-IGRT (indirectness concerns).

SECTION C TRANSLATION ISSUES

C.1. OVERVIEW

Based on the evidence reported in Section B, it is suggested that, relative to CBCT-IGRT, MR-IGRT has uncertain safety and uncertain effectiveness. It was therefore decided that a cost-minimisation analysis would be most appropriate approach for the economic evaluation. Furthermore, PASC confirmed that a cost-minimisation analysis was appropriate.

The base case of the economic evaluation is generated by a modelled economic evaluation using the evidence derived from Parikh et al. (2020) and Schumacher et al. (2020) on the healthcare resource utilisation, time spent by healthcare professionals on each activity along with capital costs, and relevant healthcare costs in the Australian healthcare setting, and where available, other Australian parameters. Furthermore, the economic model included costs of treatment related to acute and late gastrointestinal (GI) and genitourinary (GU) toxicity in prostate cancer. The rates of different grades of toxicity related to prostate cancer for MR-IGRT and CBCT-IGRT are provided in Table 20 and Table 21 to which relevant treatment costs were applied.

C.2. APPLICABILITY TRANSLATION ISSUES

The patient population for whom public funding of the proposed medical service is intended includes patients with cancer who undergo external beam radiation therapy (EBRT).

In this assessment, the cost of delivering 5 fractions MR-IGRT and CBCT-IGRT was used in the model and adverse event modelling for prostate cancer patients. A search of the economic literature was unsuccessful in identifying, in the Australian setting, the resource use of healthcare professionals required at each step of delivering MR-IGRT and CBCT-IGRT, time spent on each activity, and relevant healthcare resources required to estimate costs. From our literature search, two US based studies were identified, conducted in prostate cancer and hepatocellular carcinoma patients, relevant to this assessment. While from the literature search, healthcare resources required for treating toxicity in prostate cancer patients were available (Schumacher et al., 2020), the DCAR did not identify resources required for treating toxicity related to hepatocellular carcinoma. The amount of available identified evidence was discussed with the Department of Health and it was agreed that the most pragmatic evaluation was to provide a cost-minimisation analysis of MR-IGRT versus CBCT-IGRT based on the two studies along with economic modelling of adverse events in prostate cancer patients.

From the literature search, Schumacher et al. (2020) presented toxicity reduction required for MR-IGRT radiotherapy to be cost-effective in the treatment of localized prostate cancer compared with CBCT-guided radiation therapy conducted in the united states population. This study employed a

markov model to simulate annual transitions between health states over 15 years after receiving prostate cancer treatment with CBCT-guided radiation therapy. The study by Parikh et al. (2020) presented time-driven activity-based costing comparison of CBCT-guided radiation therapy versus MR-guided stereotactic body radiation therapy (SBRT) for patients with unresectable hepatocellular carcinoma as an example in the United States. The estimates provided in these two studies were used to conduct the cost-minimisation analysis. This is a potential applicability issue considering the estimates reflect the clinical practice within the United States, however, due to paucity of the evidence in the Australian setting, it was decided to use the evidence from these two studies. To reduce uncertainty, Australian specific costs of healthcare professionals involved with SBRT was obtained and multiplied them with time and probability estimate from these two studies to derive Australian specific cost of delivering MR-guided SBRT and CBCT-guided SBRT. A range of one-way sensitivity analysis were also conducted in the economic section to reduce uncertainty.

The economic evaluation assumed that radiation therapy will be delivered using 5 fractions SBRT, and derived costs of delivering 5-fractions MR-guided SBRT and CBCT-guided SBRT. However, 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. Hence the assumption of 5 fractions SBRT was made to reflect the radiation therapy used in both studies and to main consistency in estimating the cost of MR-IGRT and CBCT-IGRT. To reduce uncertainty, one-way sensitivity analysis on the number of fractions delivered using CBCT-IGRT alongside other key variables within the economic section were included.

The cost-minimisation model comprised of modelling acute and late GI/GU toxicity in prostate cancer patients. The rates of different grades of toxicity related to prostate cancer were based on naïve comparison across different studies presented in Table 20 and Table 21. Relevant treatment costs were applied to the toxicity rates provided to calculate the cost of toxicity associated with MR-IGRT and CBCT-IGRT. This is a potential applicability issue since these studies were conducted internationally, had methodological weaknesses, heterogeneity in the patient population included. However, for the economic evaluation, these studies were the best source of available evidence on prostate cancer related toxicities post MR-IGRT and CBCT-IGRT. To reduce uncertainty, a one-way sensitivity analysis on the toxicity rates was included within the economic section.

C.3. EXTRAPOLATION TRANSLATION ISSUES

No data was extrapolated in the model and thus no extrapolation translation issues were identified.

C.4. TRANSFORMATION ISSUES

No data was transformed in the model and thus no transformation translation issues were identified.

C.5. ANY OTHER TRANSLATION ISSUES

No other translation issues were identified.

SECTION D ECONOMIC EVALUATION

D.1. OVERVIEW

The clinical evaluation suggested that, relative to CBCT-guided radiation therapy, MR-IGRT has uncertain safety and uncertain effectiveness based on the evidence profile given in Table 41. Table 42 sets out the framework that was used to classify the clinical evidence in Section Bso that a decision could be made about the type of economic analysis to undertake (if any) in this Section.

Table 42 Classification of the comparative effectiveness and safety of the proposed therapeutic medical service compared with its main comparator and guide to the suitable type of economic evaluation

Comparative safety	**Comparative effectiveness**			
	Inferior	**Uncertain[a]**	**Non-inferior[b]**	**Superior**
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Non-inferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'non-inferiority' is the preferred basis for demonstrating equivalence

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. The base case of the economic evaluation was generated by a modelled economic evaluation using the evidence derived from Parikh et al. (2020) and Schumacher et al. (2020) 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 from the studies reported in Table 20 and Table 21.

D.2. POPULATIONS AND SETTINGS

The proposed population for whom MBS listing is sought 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.

It is estimated that of all cancers that occur in Australia, approximately 48.2% to 49.4% are related to cancers for which MR-linac may be used based on the Applicant's stated intentions.

For this application, the DCAR provided an example of cost minimisation analysis of delivering 5 fractions MR-IGRT and CBCT-IGRT and adverse event modelling in prostate cancer patients. Due to paucity in evidence on economic evaluation of MR-IGRT and CBCT-IGRT for other kinds of cancer, it was decided to create a cost-minimisation analysis based on the evidence available within the prostate cancer patients. The DCAR discussed the available evidence and the challenges in developing an economic model for all kinds of cancer with the Department, and agreed to provide a cost-minimisation analysis of MR-IGRT versus CBCT-guided radiation therapy in prostate cancer patients.

As described in Section A Context, 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.

The key difference between "standard" IGRT (performed with CBCT, and currently considered the standard of care in IGRT) and MR-IGRT is that MR-IGRT delivers a higher level of soft tissue imaging and a more sophisticated adaptive functionality, enabling the user to optimise dose distribution of the treatment plan on every fraction in an online setting (i.e. while the patient is in the machine).

The procedure for every treatment fraction is similar to the standard IGRT procedure: patient setup, imaging, adaptation, and treatment. Use of MR-linac involves the same professionals as CBCT linac: radiation oncologists, medical physicists, and radiation therapists. However, more complex workflows may require these professionals to be present collectively at the treatment machine at the same time. The MR-IGRT technique is more time-intensive than the comparator, requiring twice- to three-times as long per fraction as CBCT-guided IGRT. The DCAR identified studies providing details on the workflow at each activity associated with the delivery of 5 fractions MR-guided Stereotactic Body Radiation Therapy (SBRT) and CBCT-guided SBRT in prostate cancer and hepatocellular carcinoma patients. The economic evaluation was performed for 5 fractions MR-guided SBRT and CBCT-guided SBRT based on the estimates on healthcare resources identified, time and probability estimates provided in the two studies from the United States (Parikh et al., 2020; Schumacher et al., 2020).

D.3. STRUCTURE AND RATIONALE OF THE ECONOMIC EVALUATION

A summary of the key characteristics of the economic evaluation is given in Table 43.

Table 43 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)
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

NA=Not applicable; MSO=Microsoft Office

LITERATURE REVIEW

A literature review was conducted on 18th September 2020 using OVID MEDLINE, EMBASE, NHS Economic Evaluation Database, and the HTA websites (https://www.journalslibrary.nihr.ac.uk, https://www.cadth.ca) for the studies published since 16th September 2020. The literature search of the publications on economic evaluation is provided in Table 44 and Table 45. A total of 418 citations were retrieved, and one relevant cost-effectiveness analysis of MR-IGRT vs CBCT-IGRT in prostate cancer patients in United States (Schumacher et al., 2020) was found to be relevant from the literature search. In addition, one peer-review publication was identified from the United States (Parikh et al., 2020) on time-driven activity-based cost comparison of MR-guided SBRT vs CBCT-guided SBRT in patients with localized unresectable hepatocellular carcinoma to be relevant for this assessment. The DCAR modelled estimates on acute and late GI/GU toxicity of prostate cancer patients as reported in Table 20 and Table 21.

Schumacher et al. (2020) presented toxicity reduction required for MR-IGRT radiotherapy to be cost-effective in the treatment of localized prostate cancer compared with CBCT-guided radiation therapy conducted in the United States population. This study employed a markov model to simulate annual transitions between health states over 15 years after receiving prostate cancer treatment with CBCT-guided radiation therapy. For the purposes of this assessment, the DCAR used the healthcare resources identified in delivering MR-IGRT and CBCT-guided radiation therapy with 5 fractions SBRT.

The study by Parikh et al. (2020) presented time-driven activity-based costing comparison of CBCT-IGRT versus MR-IGRT for patients with unresectable hepatocellular carcinoma as an example in the United States. The DCAR used the healthcare resources identified and the time estimates to calculate Australian relevant costs of delivering MR-IGRT and CBCT-IGRT.

Overall, none of the economic evaluations identified in the literature search were directly applicable to the proposed use of MR-IGRT in Australia. Due to paucity in evidence specific to the Australian setting it was decided to use the estimates provided in the two studies mentioned.

Table 44 Literature search from MEDLINE

#	Search terms	Hits
1	("Magnetic Resonance Imaging" or MRI).mp. and (guidance or guided).ab,kf,ti. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	13587
2	(RADIOTHERAPY or RADIATION).ab,kf,ti.	498569
3	1 and 2	1922
4	Economics/	27229
5	exp "Costs and Cost Analysis"/	238443
6	Economics, Nursing/	3999
7	Economics, Medical/	9100
8	Economics, Pharmaceutical/	2953
9	exp Economics, Hospital/	24679
10	Economics, Dental/	1911
11	exp "Fees and Charges"/	30403
12	exp Budgets/	13743
13	budget*.ti,ab,kf.	29994
14	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	231689
15	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.	864336
16	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	165349
17	(value adj2 (money or monetary)).ti,ab,kf.	2428
18	exp models, economic/	15160
19	economic model*.ab,kf.	3377
20	markov chains/	14453
21	markov.ti,ab,kf.	22808
22	monte carlo method/	28506
23	monte carlo.ti,ab,kf.	49805
24	exp Decision Theory/	12129
25	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	24653
26	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	1182430
27	3 and 26	144

Table 45 Literature search from EMBASE

#	Search terms	Hits
1	(("Magnetic Resonance Imaging" or MRI) and (guidance or guided)).ab,kw,ti.	24414
2	(RADIOTHERAPY or RADIATION).ab,kw,ti.	722110
3	1 and 2	4459
4	Economics/	241652
5	Cost/	61989
6	exp Health Economics/	872560
7	Budget/	29851
8	budget*.ti,ab,kw.	40439
9	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.	292843
10	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab.	1171663
11	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.	233595
12	(value adj2 (money or monetary)).ti,ab,kw.	3382
13	Statistical Model/	161380
14	economic model*.ab,kw.	4991
15	Probability/	111124
16	markov.ti,ab,kw.	30197
17	monte carlo method/	40857
18	monte carlo.ti,ab,kw.	51154
19	Decision Theory/	1772
20	Decision Tree/	13337
21	(decision* adj2 (tree* or analy* or model*)).ti,ab,kw.	35336
22	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	2199668
23	3 and 22	408

STRUCTURE OF THE ECONOMIC EVALUATION

For the economic evaluation, Microsoft Excel 2016 MSO (16.0.8431.2110) 64-bit was used to develop the cost-minimisation model.

A cost-minimisation model was developed to estimate the costs of MR-IGRT compared with CBCT-IGRT. As requested in the PICO, the economic evaluation presented the distribution of costs between the intervention and comparator, including capital costs, and resource costs (including procedural time). Furthermore, adverse event profile modelling to assess the risk-benefit trade-offs has been assessed for prostate cancer. Since prostate cancer is one of the most common cancers in Australia, it made practical sense to use it as an example within this report. The economic modelling

of MR-IGRT and CBCT-IGRT for prostate cancer related adverse events was discussed with the Department.

From Schumacher et al. (2020) and Parikh et al. (2020) the healthcare resources and time estimates provided were used to derive the cost of delivering 5 fraction SBRT with MR-IGRT and CBCT-IGRT. Using data from these studies two separate costs were estimated for MR-IGRT and CBCT-IGRT.

Parikh et al. (2020) provided process maps (online supplementary) for each step identifying the relevant healthcare professional, time spent, and probability estimate specific to delivering MR-guided SBRT and CBCT-guided SBRT for patients with localized unresectable heapatocellular carcinoma. In both settings, patients were to be treated with 50 Gy over 5 fractions. The steps identified were new patient consultation, treatment simulation, fiducial placement that occurs prior to simulation (for CBCT-guided radiation therapy only), prior to simulation steps (for MR-IGRT specific patients), treatment planning, treatment, management of patient while on-treatment, follow-up. Since the study was conducted in the United States, the DCAR obtained Australian specific costs of healthcare professionals involved and multiplied them with time and probability estimate to derive Australian specific cost of delivering MR-guided SBRT and CBCT-guided SBRT.

Schumacher et al. (2020) provided estimates on personnel time spent and costs at each step of delivering two treatment regiments: conventional radiotherapy with daily 39 fractions using CBCT and MRI and 5 fractions SBRT using CBCT and MRI. In this report, 5-fractions was used and the estimate for MR-guided SBRT and CBCT-guided SBRT in prostate cancer patients. The steps identified were consultation, simulation, planning, treatment, on-treatment visit, follow-up visit. Australian specific costs were obtained as mentioned in the paragraph above.

As guided by the PICO, capital costs were included for both MRI guided SBRT and CBCT-guided SBRT which includes one-off cost (installation cost, software, imaging, Linac, professional development, training and accreditation, maintenance for first two years). The DCAR assumed a lifetime of 10 years over which the value of equipment will depreciate at 10% per annum and have added it to the capital cost. In addition, the DCAR have assumed a cost of borrowing capital at an interest rate of 5% per annum (reflecting discount rate) and added it to the capital cost. A half-cycle correction was factored to avoid overestimation of the capital cost.

The DCAR included annual service and maintenance cost of both equipment up to 8 years. As mentioned above, the cost of borrowing capital and a half cycle correction was applied.

The Australian specific costs estimated from Parikh et al. (2020) and Schumacher et al. (2020) were averaged to derive the cost of MR-guided SBRT and CBCT-guided SBRT per treatment course to be used in the cost-minimisation model.

The cost-minimisation model comprised of modelling acute and late GI/GU toxicity in prostate cancer patients. The rates of different grades of toxicity related to prostate cancer are provided in

Table 20 and Table 21 to which relevant treatment costs were applied. The final costs consisted of the cost of delivering 5 fractions MR-guided SBRT and CBCT-guided SBRT and the cost of treating adverse events in patients with prostate cancer.

Assumptions incorporated into the model structure:

In this assessment, the DCAR has provided an example on cost of delivering 5 fractions MR-guided radiation therapy and CBCT-guided radiation therapy and adverse event modelling for prostate cancer patients. The DCAR did not find relevant economic literature in the Australian setting regarding healthcare professionals required at each step of delivering MR-IGRT and CBCT-IGRT, time spent on each activity, and relevant healthcare resources required to estimate costs. Two US based studies were identified, conducted in prostate cancer and hepatocellular carcinoma patients relevant to this assessment. While from the literature, healthcare resources required for treating toxicity in prostate cancer patients were available (Schumacher et al., 2020), the DCAR did not identify healthcare resources required for treating toxicity related to hepatocellular carcinoma. The amount of available identified evidence was discussed with the Department of Health and it was agreed that the most pragmatic evaluation was to provide a cost-minimisation analysis of MR-IGRT versus CBCT-IGRT based on the two studies along with economic modelling of adverse events in prostate cancer patients.

The DCAR assumed that radiation therapy will be delivered using 5 fractions SBRT, and have derived costs of delivering MR-guided SBRT and CBCT-guided SBRT. However, 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. Due to paucity in the available evidence, it was decided to use the available evidence from the two studies on healthcare resources, time spent by health professionals, and probabilities to estimate cost of delivering MR-guided SBRT and CBCT-guided SBRT in Australian setting. Furthermore, it is likely that CBCT-IGRT may require higher number of fractions per treatment course. The DCAR conducted a sensitivity analysis by increasing number of fractions with CBCT-IGRT from 5 fractions to 30 fractions per treatment course.

The DCAR assumed lifetime of the equipment to be 10-years, however, this is likely to vary and will impact the overall cost. A sensitivity analysis was conducted on lifetime of the equipment and subsequent variables such as interest rate and depreciation. Cost of equipment and maintenance accounted for the largest proportion in overall cost, so to avoid uncertainty, a sensitivity analysis was developed testing these costs.

The DCAR included fiducial marker placement as a prior step to simulation for all the patients, however, for certain kinds of cancer, it might not require and likely to overestimate the cost. A sensitivity analysis was included by removing cost of fiducial marker placement.

The DCAR estimated the number of treatment courses (volume of patients treated over lifetime) delivered using MR-guided SBRT and CBCT-guided SBRT from Schumacher et al. (2020). The estimates provided in the paper were for 15 years, however, the DCAR derived number of treatment courses to be delivered using MR-guided SBRT and CBCT-guided SBRT for 10 years (lifetime of the equipment assumed in the economic evaluation). The number of treatment courses delivered over the lifetime of the equipment are likely to vary and create uncertainty in estimating cost. A sensitivity analysis was included by increasing and decreasing number of treatment courses delivered from base case value to see its impact on the overall costs.

D.4. INPUTS TO THE ECONOMIC EVALUATION

The DCAR acknowledges uncertainty in the inputs used in the economic evaluation. The assessment group contacted the Department of Health, The Royal Australian and New Zealand College of Radiologists (RANZCR), and the Applicant to provide inputs for economic evaluation as no Australian specific literature comparing MR-IGRT versus CBCT-IGRT could be found. The DCAR reviewed previous MSAC application on IGRT technologies, and some inputs provided by the Applicant which were useful for the economic evaluation. Majority of the inputs in the economic evaluation were derived from the US based studies.

COSTS

Table 46 presents a summary of the costs used in the cost minimisation analysis.

Table 46 Cost inputs

Total Cost	*Per treatment course*
Cost of MR-guided SBRT (average of cost estimate derived from Parikh et al and Schumacher et al)	$5,906.05
Cost of CBCT-guided SBRT (average of cost estimate derived from Parikh et al and Schumacher et al)	$2,533.34
Cost of Acute toxicity 1-2 grade (GI/GU)	$404.34
Cost of Acute toxicity grade 3 and above (GI/GU)	$4,305.72
Cost of Late toxicity grade 2 (GI)	$819.67
Cost of Late toxicity grade 3 and above (GI)	$4,058.81
Cost of Late toxicity grade 2 (GU)	$1,393.81
Cost of Late toxicity grade 3 and above (GU)	$4,221.35

MR=Magnetic resonance; CBCT=Cone-beam computed tomography; SBRT=Stereotactic body radiation therapy; GI=Gastrointestinal; GU=Genitourinary

Detail breakdown of the healthcare resources and their costs to estimate the overall cost related to MR-guided SBRT and CBCT-guided SBRT are provided in Table 47 and Table 48. Detail breakdown of the healthcare resources and their costs to estimate the overall cost related to the treatment of prostate cancer toxicities are provided in Table 49. Unit costs were obtained from the MBS 2020, AR-DRG 2018-19, and PBS 2020 databases.

Table 47 List of steps, healthcare resources, time estimates and their costs to derive cost of MRI-guided SBRT and CBCT-guided SBRT from Parikh et al (Base case)

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Capital cost				
Cost of equipment	1	-	$9,900,000	$3,000,000
Lifetime of the equipment (in years)	10	-	-	-
Depreciation (10%)	10%	-	$4,950,000	$1,500,000
Cost of borrowing money (interest rate of 5%)	5%	-	$2,475,000	$750,000
Total capital cost over lifetime			**$17,325,000**	**$5,250,000**
Maintenance cost				
Service contract (for 8 years, first 2 years included)	8	-	$6,000,000	$2,520,000
Service provision/Maintenance cost with interest	5%	-	$1,200,000	$504,000
Total cost of Service provision/Maintenance over lifetime		**-**	**$7,200,000**	**$3,024,000**
Estimation of cost from Parikh et al. (2020)				
Step - Process map reflecting new patient consultation				
Register patient				
Obtain referral from patient directly, referring provider, or work queue	Front desk (x1)	7	$2.75	$2.75
Obtain medical records and insurance authorization for consultation	Front desk (x1)	9	$3.54	$3.54
Prepare chart; register patient in medical records	Front desk (x1)	3	$1.18	$1.18
Pre-clinic charting				
Review records in advance; prepare note	Radiation Oncologist (x1)	25	$44.61	$44.61

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Clinic Visit				
Check-in patient for appointment	Front desk (x1)	10	$3.94	$3.94
Take vitals; perform medication reconciliation; update medical history in medical records	Medical Assistant (x1)	13	$5.33	$5.33
See patient and complete consult (H&P; informed consent; place simulation orders)	Radiation Oncologist (x1)	45	$80.29	$80.29
Print-post-visit-summary	Nurse (x1)	2	$1.23	$1.23
Complete consent paperwork with patient	Nurse (x1)	3	$1.85	$1.85
Check-out patient; schedule simulation and orders	Front desk (x1)	8	$3.15	$3.15
Post-clinic visits				
Revise/sign consult note	Radiation Oncologist (x1)	10	$17.84	$17.84
Run insurance authorization for simulation and treatment	Front desk (x1)	13	$5.12	$5.12
MR clearance process				
Perform MR clearance process	Radiation Therapist (x1)	8	$6.07	-
MR safety officer to further investigate if patient does not pass initial clearance	Radiation Therapist (x1) (probability 0.05)	45	$1.71	-
Total			**$178.60**	**$170.82**
Step - Process map reflecting steps prior simulation (fiducial marker placement)				
Check-in patient for fiducial placement that occurs prior to simulation	Front Desk (x1)	10	-	$3.94
Pre-op time			-	
Place IV; draw labs; perform initial assessment	Nurse (x1)	20	-	$12.33
Obtain consent and answer questions prior to procedure	Interventional Radiologist (x1)	15	-	$44.14
Fiducial placement				
Place 3 fiducial seeds under image guidance	Interventional Radiologist (x1)	45	-	$132.41
	Nurse (x1)	45	-	$27.75
	Imaging Technologist (x1)	45	-	$29.74

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Post-op time			-	
Monitor patient post-op	Nurse (x1)	60	-	$37.00
Assess patient post-op; place orders; complete documentation; clear for discharge	Interventional Radiologist (x1)	45	-	$132.41
Disposables			-	
Fiducial markers (x3) including sterile pack			-	$142.60
Total			-	$562.31
Step - Process map reflecting simulation				
Pre-Huddle	Radiation Therapist (x2)	3	$4.55	$4.55
Huddle review of each patient's checklist	Radiation Therapists (including Chief Therapist) (x3)	3	$6.82	$6.82
	Nurse (x1)	3	$1.85	$1.85
	Dosimetrist (x1)	3	$3.11	$3.11
CT Simulation				
Patient check-in	Front Desk (x1)	2	$0.79	$0.79
Place IV; complete patient education; perform initial clinical assessment	Nurse (x1)	30	$18.50	$18.50
Verify patient and check 3 P's; obtain contact info; review setup and mark device; give contrast and perform free-breathing scan	Radiation Therapist (x2)	28	$42.46	$42.46
Provide DIBH instructions and perform DIBH scan	Radiation Therapist (x2)	6	$9.10	-
Review of images				
Review images	Radiation Oncologist (x1)	3	$5.35	$5.35
	Dosimetrist (x1)	3	$3.11	$3.11
	Radiation Therapist (x2)	3	$4.55	$4.55

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
After CT simulation				
Mark patient and device; answer questions; schedule treatment; complete documentation; clean equipment; finish reconstructing scan	Radiation Therapist (x2)	13	$19.71	$19.71
Remove IV from patient	Nurse (x1)	8	$4.93	$4.93
Total			**$124.83**	**$115.73**
Step - Process map reflecting simulation (specific to MR-guided SBRT)				
Transfer patient from CT; review MR simulation orders and set up instructions	Radiation Therapist (x2)	5	$7.58	-
Perform MR clearance; administer Eovist; position patient; coach patient on DIBH	Radiation Therapist (x2)	18	$27.29	-
MR simulation/ review				
Perform MR simulation; page MD and physicist	Radiation Therapist (x2)	15	$22.75	-
Review imaging and localize tumor	Radiation Oncologist (x1)	3	$5.35	-
Provide guidance on scan limits and protocol	Medical Physicist (x1)	8	$5.47	-
After MR simulation				
Mark patient, answer questions, clean equipment, complete documentation	Radiation Therapist (x2)	13	$19.71	-
Total			**$88.16**	-
Step - Process map reflecting treatment planning				
Contour structures				
Fuse CT simulation to other diagnostic imaging	Dosimetrist (x1) (probability 0.85)	13	$11.45	$11.45
Review fusion	Medical Physicist (x1) (probability 0.85)	8	$4.65	$4.65
Contour OARs	Dosimetrist (x1)	45-60	$62.18	$46.64
Check fusion/OARs and contour target structures	Radiation Oncologist (x1)	30	$53.53	$53.53
Create Treatment Plan				
Prescribe dose, provide guidance on dose constraints	Radiation Oncologist (x1)	5	$8.92	$8.92
Create treatment plan	Dosimetrist (x1)	180	$186.54	$186.54

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Review treatment plan	Medical Physicist (x1)	15-20	$13.68	$10.26
Review treatment plan and approve documents	Radiation Oncologist (x1)	15	$26.76	$26.76
Deliver plan to phantom	Technician (x1)	30	$22.76	$19.83
Analyse results	Dosimetrist (x1)	15	$15.55	$15.55
Create documentation for treatment plan	Dosimetrist (x1)	45	$46.64	$46.64
Perform "second check" and review documentation	Medical Physicist (x1)	30	$20.52	$20.52
Chart Rounds				
Present for chart rounds	Dosimetrist (x1)	3	$3.11	$3.11
	Medical Physicist (x1)	3	$2.05	$2.05
	Radiation Oncologist (x1)	3	$5.35	$5.35
Total			**$483.67**	**$461.78**
Step - Process map reflecting steps prior treatment				
Prior to first treatment				
Obtain vitals and weight	Medical Assistant (x1)	4	$1.64	$1.64
Perform medication and reconciliation	Medical Assistant (x1)	6	$2.46	$2.46
Manage symptoms; address patient concerns	Nurse (x1) (probability 0.50)	8	$2.47	$2.47
Meet patient prior to initial SBRT treatment; complete OTV note	Radiation Oncologist (x1)	8	$14.27	$14.27
After last treatment complete				
Print post-visit summary	Nurse (x1)	2	$1.23	$1.23
Check-out patient and schedule follow-up visit and next imaging	Front desk (x1)	5	$1.97	$1.97
Complete radiation treatment summary	Radiation Oncologist (x1)	10	$17.84	$17.84
Total			**$41.88**	**$41.88**
Step - Process map reflecting treatment (specific to CBCT-guided SBRT)				
Treatment Setup				
Position patient and take CBCT	Radiation Therapist (x2)	12	-	$18.20
Make adjustments and page MD/ Physicist	Radiation Therapist (x2)	4	-	$6.07

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Image verification			-	
Review images	Medical Physicist (x1) (probability 0.20)	8	-	$1.09
Approve images	Radiation Oncologist (x1)	5	-	$8.92
Therapists present and apply shifts if necessary	Radiation Therapist (x2)	8	-	$12.13
Treatment			-	
Treatment of all arcs	Radiation Therapist (x2)	8	-	$12.13
Help patient off machine; clean equipment; finish documentation	Radiation Therapist (x2)	3	-	$4.55
Total				**$63.09**
Step - Process map reflecting treatment (Specific for MRI-guided SBRT)				
Treatment Setup				
Check-in patient	Front desk (x1)	2	$0.79	-
Place IV	Nurse (x1)	8	$4.93	-
Perform metal detector screen; give Eovist; position patient; coach through DIBH; take targeted MR images; adjust gating	Radiation Therapist (x2)	15	$22.75	-
Make adjustments and page MD/Physicists	Radiation Therapist (x2)	4	$6.07	-
Image verification				-
Review images	Medical Physicist (x1) (probability 0.20)	8	$1.09	-
Approve images	Radiation Oncologist (x1)	8	$14.27	-
Therapists present and apply shifts if necessary	Radiation Therapist (x2)	8	$12.13	-
Treatment				-
Treatment of all fields	Radiation Therapist (x2)	14	$21.23	-
Help patient off machine; clean equipment; finish documentation	Radiation Therapist (x2)	3	$4.55	-
Remove IV from patient	Nurse (x1)	4	$2.47	-
Total			**$90.27**	

Category	Number of items in natural unit of measurement/ %/ Personnel (Base case)	Time (mins) (Base case)	MRI-guided radiation therapy (Base case)	CBCT-guided radiation therapy (Base case)
Step - Process map reflecting follow-up visit				
Check-in-patient	Front desk (x1)	3	$1.18	$1.18
Take vitals; perform medication reconciliation; update medical history in EMR	Medical Assistant (x1)	4	$1.64	$1.64
Meet and examine patient; place imaging orders for next visit	Radiation Oncologist (x1)	15	$26.76	$26.76
Print post-visit summary	Nurse (x1)	2	$1.23	$1.23
Check-out patient and schedule next follow-up visit/ imaging	Front desk (x1)	5	$1.97	$1.97
Complete follow-up visit note	Radiation Oncologist (x1)	15	$26.76	$26.76
Total			**$59.55**	**$59.55**
Step - Annual time spent on machine QA, minutes (MRI-guided SBRT)	Medical Physicist	156600	$107,088.30	**-**
Step - Annual time spent on machine QA, minutes (CBCT-guided SBRT)	Medical Physicist	87600	-	**$59,903.80**
Total cost per treatment course				
Allocation of capital cost per patient			$3,032.03	$437.50
Allocation of maintenance cost per patient			$1,260.06	$252.00
New Patient Consultation			$178.60	$170.82
Simulation			$212.99	$678.04
Planning			$483.67	$461.78
Treatment			$660.78	$524.84
Follow-up visit			$297.74	$297.74
QA cost per patient			$18.74	$4.99
Total cost per patient's treatment course from Parikh et al			**$6,144.60**	**$2,827.72**

MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography; SBRT=Stereotactic body radiation therapy; IV=Intravenous; OAR=Organs at risk; DIBH=Deep inspiration breath hold; OTV=On-treatment visit; QA=Quality assurance

Table 48 List of steps, healthcare resources, time estimates and their costs to derive cost of MRI-guided SBRT and CBCT-guided SBRT from Schumacher et al. (2020) (Base case)

Category	Quantity (Base case)	MRI Guided Radiation Therapy (Base case)	Quantity (Base case)	Cone-beam CT Scan guided radiation therapy (Base case)
Capital cost				
Cost of equipment	1	$9,900,000	1	$3,000,000
Lifetime of the equipment (in years)	10		10	
Depreciation (10%)	10%	$4,950,000	10%	$1,500,000
Cost of borrowing money (interest rate of 5%)	5%	$2,475,000	5%	$750,000
Total capital cost over lifetime		$17,325,000		$5,250,000
Maintenance cost				
Service contract (for 8 years, first 2 years included)	8	$6,000,000	8	$2,520,000
Service provision/Maintenance cost with interest	5%	$1,200,000	5%	$504,000
Total cost of Service provision/Maintenance over lifetime		**$7,200,000**		**$3,024,000**
Estimation of cost from Schumacher et al. (2020)				
Consultation				
Radiation Oncologist	1 hr * 5714 patients	$611,705	1hr * 12000 patients	$1,284,645
Nurse	1 hr * 5714 patients	$211,418	1hr * 12000 patients	$444,000
Receptionist	1 hr * 5714 patients	$134,908	1hr * 12000 patients	$283,320
Simulation				
Radiation Therapist	1.5 hr * 5714 patients	$389,895	0.5 hr * 12000 patients	$272,940
Receptionist	1.5 hr * 5714 patients	$202,361	0.5 hr * 12000 patients	$141,660
Planning				
Radiation Oncologist	1 hr * 5714 patients	$611,704.91	1 hr * 12000 patients	$1,284,644.53
Medical Physicist	1 hr * 5714 patients	$234,445.42	1 hr * 12000 patients	$492,360.00
Dosimetrist	4 hr * 5714 patients	$1,421,186.08	4 hr * 12000 patients	$2,984,640.00
Treatment				
Radiation Therapist	0.5 hr * 5 * 5714 patients	$649,824.65	0.33 hr * 5 * 12000 patients	$900,702.00
Receptionist	0.5 hr * 5 * 5714 patients	$337,268.85	0.33 hr * 5 * 12000 patients	$467,478.00
On-treatment visit				
Radiation Oncologist	0.25 hr * 1 * 5714 patients	$152,926.23	0.25 hr * 1 * 12000 patients	$321,161.13

Category	Quantity (Base case)	MRI Guided Radiation Therapy (Base case)	Quantity (Base case)	Cone-beam CT Scan guided radiation therapy (Base case)
Nurse	0.25 hr * 1 * 5714 patients	$52,854.50	0.25 hr * 1 * 12000 patients	$111,000.00
Receptionist	0.25 hr * 1 * 5714 patients	$33,726.89	0.25 hr * 1 * 12000 patients	$70,830.00
CT-specific costs				
Fiducial marker placement	-	-	1 * 12000 patients	$1,711,200.00
Ultrasound image guidance	-	-	1 * 12000 patients	$1,329,000.00
Specialist attendance	-	-	1 * 12000 patients	$1,074,600.00
Anaesthesia	-	-	1 * 12000 patients	$1,224,000.00
Prophylactic antibiotics	-	-	1 * 12000 patients	$219,360.00
MRI-specific costs				
MR-Immobilization equipment	1	$36,446.30	-	-
Ancillary MR-equipment	1	$17,836.55	-	-
MR-physics equipment	1	$365,465.30	-	-
Follow-up visit				
Radiation Oncologist	0.5 hr * 24 * 5714 patients	$1,529,262.26	0.5 hr * 24 * 12000 patients	$3,211,611.34
Nurse	0.5 hr * 24 * 5714 patients	$528,545.00	0.5 hr * 24 * 12000 patients	$1,110,000.00
Receptionist	0.5 hr * 24 * 5714 patients	$337,268.85	0.5 hr * 24 * 12000 patients	$708,300.00
Total cost per treatment course				
Allocation of capital cost per patient		$3,032.03	$437.50	$3,032.03
Allocation of maintenance cost per patient		$1,260.06	$252.00	$1,260.06
New Patient Consultation		$167.66	$79.84	$167.66
Simulation		$103.65	$497.73	$103.65
Planning		$396.80	$396.80	$396.80
Treatment		$288.13	$155.93	$288.13
Follow-up visit		$419.16	$419.16	$419.16
QA cost per patient		-	-	-
Total cost per patient's treatment course from Schumacher et al		**$5,667.49**	**$2,238.96**	**$5,667.49**

MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography; QA=Quality assurance

Table 49 List of healthcare resource items and their costs for treating prostate cancer related toxicities (Base case)

Type of resource item	Number of items in natural unit of measurement (Base case)	Unit cost (Base case)	AR-DRG/MBS/PBS Code Source (Base case)	Total cost (Base case)
Acute toxicity grade 1-2 (GI/GU)				**$404.34**
Cost of GP visits in grade 1 - 2 acute toxicity	2	$38.75	23 (100% MBS)	$77.50
Cost of loperamide to treat diarrhoea in acute toxicity grade 1-2	9	$13.51	10592L (PBS)	$121.59
Cost of specialist visits in grade 1 - 2 acute toxicity	2	$45.00	105 (100% MBS)	$90.00
Cost of Ural sachets in acute toxicity grade 1- 2	5	$18.22	4049D (PBS)	$91.10
Cost of urine flow study in 1-2 grade acute toxicity	1	$28.15	11900 (85% MBS)	$24.15
Acute toxicity grade ≥3 (GI/GU)				**$4,305.72**
Cost of GP visits in grade 3 or more acute toxicity	5	$38.75	23 (100% MBS)	$193.75
Cost of suppositories in acute toxicity 3 or more	85	$41.60	1502C (PBS)	$3,536.00
Cost of hydrocortisone tubes in acute toxicity 3 or more	2	$17.19	10831C (PBS)	$34.38
Cost of loperamide to treat diarrhoea in acute toxicity grade 3 or more	9	$13.51	10592L (PBS)	$121.59
Cost of panadeine forte in acute toxicity grade 3 or more	5	$15.73	4275B (PBS)	$78.65
Cost of specialist visits in grade 3 or more acute toxicity	3	$45.00	105 (85% MBS)	$135.00
Cost of Ural sachets in acute toxicity grade 3 and more	10	$18.22	4049D (PBS)	$182.20
Cost of urine flow study in acute toxicity grade 3 or more	1	$24.15	11900 (85% MBS)	$24.15
Late GI toxicity grade 2				**$819.67**
Diarrhea				**$1,201.31**
Cost of outpatient visit - GP	3	$38.75	23	$116.25
Cost of outpatient visit - specialist	3	$45.00	105	$135.00
Cost of Loperamide	20.00	$13.51	10592L	$493.12
Cost of Magnesium	50	$18.04	4321K	$131.69
Cost of Psyllium powder	10	$25.28	4422R	$252.80
Cell blood count test (CBC)	1	$14.45	65070	$14.45
Complete Panel test	1	$58.00	-	$58.00
Anal/rectal haemorrhage				**$421.35**

Type of resource item	Number of items in natural unit of measurement (Base case)	Unit cost (Base case)	AR-DRG/MBS/PBS Code Source (Base case)	Total cost (Base case)
Cost of outpatient visit - GP	3	$38.75	23	$116.25
Cost of outpatient visit - specialist	3	$45.00	105	$135.00
Cell blood count test (CBC)	1	$14.45	65070	$14.45
Complete Panel test	1	$58.00	-	$58.00
Sigmoidoscopy for bleeding	1	$97.65	32084	$97.65
Constipation				**$814.94**
Cost of outpatient visit - GP	3	$38.75	23	$116.25
Cost of outpatient visit - specialist	3	$45.00	105	$135.00
Cell blood count test (CBC)	1	$14.45	65070	$14.45
Complete Panel test	1	$58.00	-	$58.00
Thyroid Stimulating Hormone quantification	1	$21.30	66716	$21.30
Abdominal X-Ray	1	$30.85	58900	$30.85
Magnesium Citrate	50	$18.04	4321K	$131.69
Psyllium Powder	10	$25.28	4422R	$252.80
Dietician consult	1	$54.60	10954	$54.60
Anal Pain				**$841.10**
Cost of outpatient visit - GP	3	$38.75	23	$116.25
Cost of outpatient visit - specialist	3	$45.00	105	$135.00
Anoscopy (Used Colonoscopy instead)	1	$97.65	32084	$97.65
Psyllium Powder	10	$25.28	4422R	$252.80
Lidocaine tube	12	$19.95	-	$239.40
Late GI toxicity grade 3 and +				**$4,058.81**
Diarrhea				**$3,275.03**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Loperamide	20	$13.51	10592L	$493.12
Cost of Magnesium	50	$18.04	4321K	$131.69
Cost of Psyllium powder	10	$25.28	4422R	$252.80
Hospital admission for diarrhea	1	$2,062.42	G67A/G67B	$2,062.42
Anal/rectal haemorrhage				**$3,561.08**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cell blood count test (CBC)	1	$14.45	65070	$14.45
Complete Panel test	1	$58.00		$58.00

Type of resource item	Number of items in natural unit of measurement (Base case)	Unit cost (Base case)	AR-DRG/MBS/PBS Code Source (Base case)	Total cost (Base case)
Hospital admission for rectal bleeding	1	$3,153.63	G61A/G61B	$3,153.63
Constipation				**$5,892.03**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Magnesium	50	$18.04	4321K	$131.69
Cost of Psyllium powder	10	$25.28	4422R	$252.80
Dietician consult	1	$54.60	10954	$54.60
Hospital admission for constipation	1	$5,117.94	G70A/G70B	$5,117.94
Radiation Proctitis				**$3,507.10**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Sucralfate	120	$27.61	2055E	$83.98
Hospital admission for radiation proctitis	1	$3,088.12	G46A/G46B	$3,088.12
Late GU toxicity grade 2				**$1,393.81**
Urinary Retention				**$2,285.64**
Cost of outpatient visit - GP	3	$38.75	23	$116.25
Cost of outpatient visit - specialist	3	$45.00	105	$135.00
Cost of Tamsulosin	30	$63.78	4070F	$775.99
Cost of catheterisation with lubrication	52	$24.20	36800	$1,258.40
Urinary Incontinence				**$501.98**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Oxybutynin	100	$15.83	8039D	$57.78
Cost of Physical therapy	2	$54.60	10960	$109.20
Late GU toxicity grade 3 and +				**$4,221.35**
Urinary Retention				**$2,980.84**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Tamsulosin	30	$63.78	4070F	$775.99
Cost of catheterisation with lubrication	52	$24.20	36800	$1,258.40
Cost of Renal Ultrasound	1	$146.25	55278	$146.25
Cost of Cystoscopy with stent	1	$465.20	36823	$465.20

Type of resource item	Number of items in natural unit of measurement (Base case)	Unit cost (Base case)	AR-DRG/MBS/PBS Code Source (Base case)	Total cost (Base case)
Urinary Incontinence				**$5,461.85**
Cost of outpatient visit - GP	4	$38.75	23	$155.00
Cost of outpatient visit - specialist	4	$45.00	105	$180.00
Cost of Oxybutynin	100	$15.83	8039D	$57.78
Cost of Physical therapy	2	$54.60	10960	$109.20
Cost of Artificial Urinary Sphincter	1	$4,959.87	L08A/L08B	$4,959.87

Abbreviations: AR-DRG= Australian refined-diagnosis related groups; GI=Gastrointestinal; GU=Genitourinary; MBS=Medicare benefits schedule; PBS=Pharmaceutical benefits schedule; GP=General Practitioner

Capital costs

The cost of equipment including cost of installation, software, imaging, Linac, professional development, training and accreditation was provided by the Applicant. The cost of annual service contract (for 8 years, first 2 years included in the cost of equipment) were also provided by the Applicant. The depreciation (10% per annum) and cost of borrowing (interest of 5% per annum) were added to the total capital costs. A depreciation of 10% annually was assumed for the cost of equipment, however this rate may be lower or higher than the current accounting practice and might impact the overall capital costs. An interest rate of 5% for capital to purchase the equipment was assumed, however this rate may be lower or higher than the current market rate and might impact the overall capital costs. A half-cycle correction was applied to account for any overestimation of cost.

Costs of delivering MR-IGRT and CBCT-guided radiation therapy estimated from Parikh et al

Parikh et al. (2020) presented time-driven activity-based costing at an academic referral center to compare the direct costs of SBRT using MR-IGRT and CBCT-guided radiation therapy. The analysis was focussed on patients with localized unresectable hepatocellular carcinoma. In both the settings, patients were treated with 50 Gy over 5 fractions. They presented the process maps and their subcomponents, including the probability of time spent during the activity, were formulated and validated on the basis of input from nurses, dosimetrist, physicists, attending physicians from radiation oncology and interventional radiology, front office personnel, and radiation therapists. In addition, they validated the treatment times for MR-IGRT and CBCT-IGRT with patient level data. The DCAR estimated hourly wage of all the professional staff involved in delivering radiation therapy relevant within the Australian setting and multiplied with the probability and time estimates provided in Parikh et al. (2020) to estimate Australian specific costs. This method was applied to estimate the cost of new patient consultation; fiducial marker placement (for CBCT-IGRT); simulation step; planning step; treatment step; follow-up; and quality assurance.

Costs of delivering MR-IGRT and CBCT-guided radiation therapy estimated from Schumacher et al

Schumacher et al. (2020) presented time-driven activity-based costing to determine the costs of all steps of patient care including: consultation, simulation, planning, treatment, on-treatment visits, and follow-up visits (over 15 years). The analysis was focussed on patients with prostate cancer. The costs of MRI-IGRT and CBCT-IGRT were obtained by conducting interviews with staff at two academic institutions in the United States. They presented time estimate for each healthcare professional at each step of the activity. The DCAR estimated hourly wage of all the professional staff involved in delivering radiation therapy relevant within the Australian setting and multiplied with the time estimates provided in Schumacher et al. (2020) to estimate Australian specific costs.

Cost of MR-IGRT and CBCT-guided radiation therapy

An average of the cost derived from Parikh et al. (2020) and Schumacher et al. (2020) was taken to arrive at the cost of MRI-guided SBRT and CBCT-guided SBRT. This cost was used in the cost-minimisation model.

Cost of Acute toxicity in prostate cancer

The cost of acute GI/GU toxicity grade 1-2 and grade 3 and above are provided below.

Cost of Acute toxicity 1-2 grade (GI/GU)

The healthcare resource utilisation in the acute toxicity health state was determined based on published data (Carter et al., 2014). The value of the healthcare resources (costs) were updated using MBS and PBS 2020. The frequency of visits to the general practitioner (GP) and specialists and medication use were calculated based on estimates provided in Carter et al. The cost was assumed to be similar for patients with acute and late GI/GU toxicity grade 0, and late GI/GU toxicity grade 1.

Cost of Acute toxicity grade 3 and above (GI/GU)

The healthcare resource utilisation in the acute toxicity health state was determined based on published data (Carter et al., 2014). The value of the healthcare resources (costs) were updated using MBS and PBS 2020. The frequency of visits to the general practitioner (GP) and specialists and medication use were calculated based on estimates provided in Carter et al. (2014).

Cost of Late toxicity in prostate cancer

The cost of late GI/GU toxicity grade 2 and grade 3 and above are provided below:

Cost of Late GI toxicity (grade 2 and grade 3 +)

The healthcare resource utilisation in the acute toxicity health state was determined based on published data (Schumacher et al., 2020). The value of the healthcare resources (costs) were

updated using MBS and PBS 2020, published literature, and online resources. The frequency of visits to the general practitioner (GP) and specialists and medication use were calculated based on the estimates provided in Schumacher et al. (2020).

Cost of Late GU toxicity (grade 2 and grade 3 +)

The healthcare resource utilisation in the acute toxicity health state was determined based on published data (Schumacher et al., 2020). The value of the healthcare resources (costs) were updated using MBS and PBS 2020. The frequency of visits to the general practitioner (GP) and specialists and medication use were calculated based on the estimates provided in Schumacher et al. (2020).

CLINICAL INPUTS

The clinical inputs used for modelling prostate cancer related toxicities are provided in Table 20 and Table 21. An average was taken where more than one estimate was available across different studies. This simplifying assumption was considered to be appropriate. Sensitivity analysis was performed on the GI/GU toxicity rate. The base case toxicity rates used in the economic model are provided in Table 50.

Acute GI/GU toxicity related to MRI-guided radiation therapy

Acute GI/GU toxicity grade 1-2 rates were obtained from Alongi et al. (2020). These were multiplied with the relevant treatment cost to calculate cost of acute GI/GU toxicity.

Acute GI/GU toxicity related to CBCT-guided radiation therapy

Multiple studies were identified in Table 20 and Table 21 reporting toxicities related to CBCT-guided radiation therapy in prostate cancer. However, the DCAR took estimates from studies with sample size of 100 or more and studies published in 2015 or later to get robust estimates. This was reasonable. Grade 0 toxicity was obtained from Becker-Schiebe et al. (2016), Faria et al. (2016). Grade 1-3 toxicity were obtained from Becker-Schiebe et al. (2016), Byun et al. (2018), Correa et al. (2020), Faria et al. (2016), Girelli et al. (2015), Ingrosso et al. (2017) and Ingrosso et al. (2018). Grade 4 toxicity was obtained from Becker-Schiebe et al. (2016). An average was taken where multiple sources were available for a specific toxicity grade.

Late GI/GU toxicity related to CBCT-guided radiation therapy

Multiple studies were identified in Table 20 and Table 21 reporting toxicities related to CBCT-guided radiation therapy in prostate cancer. However, the DCAR took estimates from studies with sample size of 100 or more and studies published in 2015 or later to get robust estimates. Grade 0 toxicity was obtained from from Becker-Schiebe et al. (2016), Faria et al. (2016). Grade 1-3 toxicity were obtained from Becker-Schiebe et al. (2016), Byun et al. (2018), Correa et al. (2020), Faria et al.

(2016), Girelli et al. (2015), Ingrosso et al. (2017) and Ingrosso et al. (2018). An average was taken where multiple sources were available for a specific toxicity grade.

Table 50 Prostate cancer related acute and late GI/GU toxicity used in economic model

	MRI-guided radiation therapy		CBCT-guided radiation therapy	
GI toxicity	**Acute**	**Late**	**Acute***	**Late***
Grade 0	-	-	41%	62%
Grade 1	8%	-	23%	14%
Grade 2	4%	-	10%	5%
Grade 3	-	-	1%	1%
Grade 4	-	-	3%	3%
GU toxicity	**Acute**	**Late**	**Acute***	**Late***
Grade 0	-	-	26%	63%
Grade 1	24%	-	36%	16%
Grade 2	12%	-	16%	11%
Grade 3	-	-	2%	2%
Grade 4	-	-	-	-

MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography; GI=Gastrointestinal; GU=Genitourinary. * Average was taken across studies reporting the same toxicity data.

D.5. RESULTS OF THE ECONOMIC EVALUATION

DISAGGREGATED COSTS

The frequency of each type of resource item multiplied by the appropriate unit cost of the resource item is summarised in Table 47, Table 48, and Table 49. The disaggregated costs for each step of MRI-guided radiation therapy and CBCT-guided radiation therapy and the adverse events cost for prostate cancer patients is provided in Table 51.

Table 51 Disaggregated costs

Category	MRI-guided radiation therapy	CBCT-guided radiation therapy	Incremental costs (MR-IGRT v CBCT-IGRT)
Allocation of capital cost per patient	$3,032.03	$437.50	$2,595.53
Allocation of maintenance cost per patient	$1,260.06	$252.00	$1,008.06
New patient consultation	$173.13	$125.33	$47.80
Simulation	$158.32	$587.89	$429.57
Planning	$440.24	$429.29	$10.95
Treatment	$474.45	$340.39	$134.06
Follow-up visit	$358.45	$358.45	-
QA cost per patient	$18.74	$4.99	$13.75

Category	MRI-guided radiation therapy	CBCT-guided radiation therapy	Incremental costs (MR-IGRT v CBCT-IGRT)
Total cost per patient's treatment course	$5,906.05	$2,533.34	$3,372.71
Cost associated with prostate cancer toxicities	$150.63	$1,592.95	-$1,442.32

MR-IGRT=Magnetic resonance imaging guided radiation therapy; CBCT-IGRT= Cone beam computed tomography guided radiation therapy; QA= Quality assurance

COST MINIMISATION ANALYSIS

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

Table 52 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

MRI=Magnetic resonance imaging; CBCT=Cone beam computed tomography

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.

D.6. SENSITIVITY ANALYSES

A thorough and systematic approach was used to identify key drivers estimating the cost of MR-IGRT and CBCT-IGRT and the cost of their associated toxicities. Each variable was deviated by an arbitrary but a constant proportion. A 20% deviation was chosen to mitigate any issues relating to upper bound or lower bound values (such as proportions deviating above 100% or below 0%). Using this systematic approach, parameters can be identified which impacted the model estimates the most and allows the identification of parameters having disproportionate large effects. The parameter increasing or decreasing the CMA base case output by more than an arbitrary 10% were further scrutinised for parameter uncertainty.

From one-way sensitivity analysis, six parameters were found to have highest impact on the incremental cost.. The number of patients treated over lifetime (10 years) by MR-IGRT had the largest impact on the incremental cost followed by the cost of the MR-IGRT equipment and its maintenance cost. The key parameters impacting the incremental cost are provided in the Tornado Diagram Figure 8 and in Table 53. All remaining parameters did not have any substantial impact on the incremental cost on varying their values by 20%.

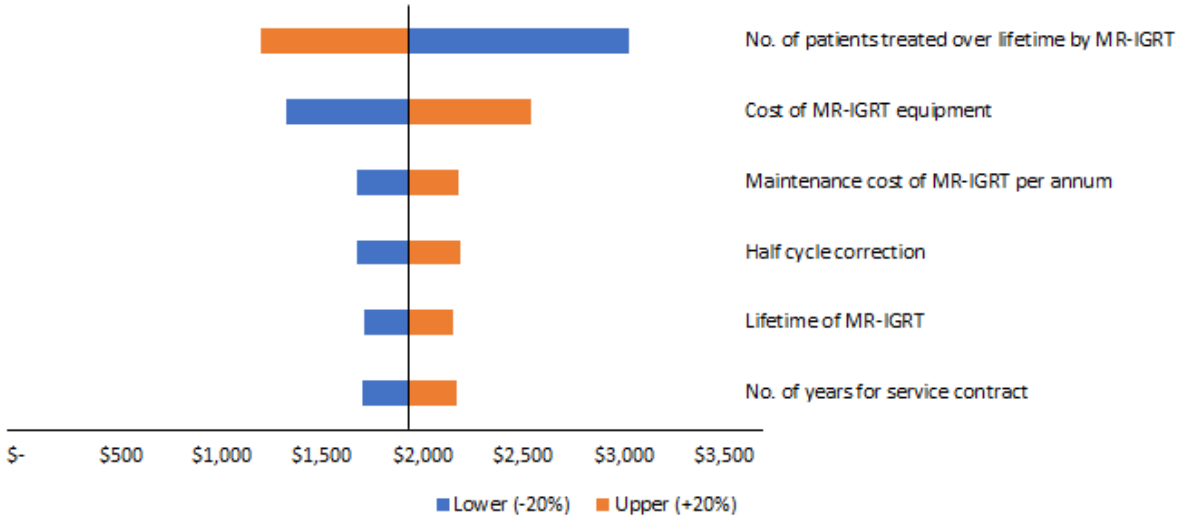

Figure 8 **Tornado diagram of main drivers within the economic evaluation (± 20%)**

Table 53 **Key drivers of economic model – MR-IGRT v CBCT-IGRT (± 20%)**

MR-IGRT v CBCT-IGRT	-20%	Incremental cost ($)	% change	+20%	Incremental cost ($)	% change
Base case: MR-IGRT v CBCT-IGRT		$1,930				
No. of patients treated over lifetime by MR-IGRT	4571	$3,023	57%	6857	$1,199	-38%
Cost of MR-IGRT equipment	$7,920,000	$1,324	-31%	$11,880,000	$2,537	31%
Maintenance cost of MR-IGRT per annum	$600,000	$1,678	-13%	$900,000	$2,182	13%
Half cycle correction	0.4	$1,674	-13%	0.6	$2,186	13%
Lifetime of MR-IGRT	8	$1,708	-12%	12	$2,153	12%
No. of years for service contract	6	$1,702	-12%	10	$2,172	13%

MR-IGRT=Magnetic resonance image guided radiation therapy; CBCT-IGRT=Cone beam computed tomography image guided radiation therapy

The sensitivity analysis presented in this section demonstrates the number of patients treated over lifetime by MR-IGRT has the largest uncertainty. Cost of MR-IGRT equipment is likely to have low uncertainty given the price of the equipment is fixed by the Applicant. For all the variables, a threshold analysis was further conducted by changing their values by 50%. The key parameters impacting the incremental cost are provided in the Tornado Diagram Figure 8, Figure 9 and in Table 54.

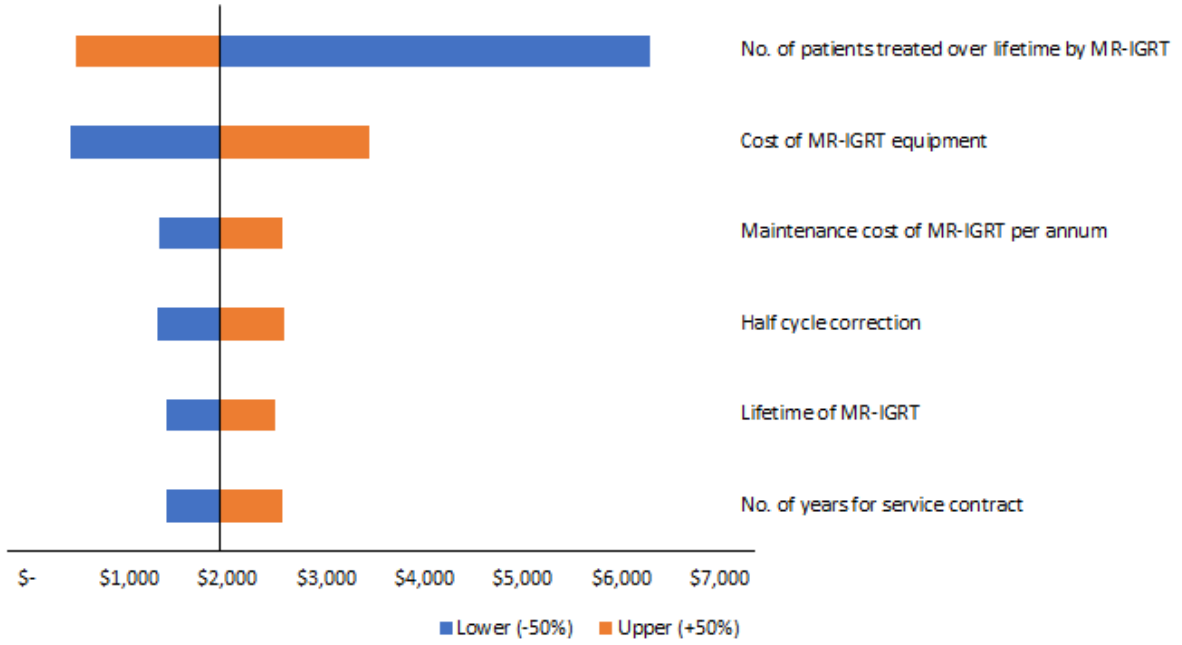

Figure 9 **Tornado diagram of main drivers within the economic evaluation (± 50%)**

Table 54 **Key drivers of economic model – MR-IGRT v CBCT-IGRT (± 50%)**

MR-IGRT v CBCT-IGRT	-50%	Incremental cost ($)	% change	+50%	Incremental cost ($)	% change
Base case: MR-IGRT v CBCT-IGRT	$1,930					
No. of patients treated over lifetime by MR-IGRT	2857	$6,289	226%	8571	$464	-76%
Cost of MR-IGRT equipment	$4,950,000	$414	-79%	$14,850,000	$3,446	79%
Maintenance cost of MR-IGRT per annum	$375,000	$1,300	-33%	$1,125,000	$2,560	33%
Half cycle correction	0.3	$1,290	-33%	0.8	$2,570	33%
Lifetime of MR-IGRT	5	$1,374	-29%	15	$2,486	29%
No. of years for service contract	4	$1,384	-28%	12	$2,560	33%

MR-IGRT=Magnetic resonance image guided radiation therapy; CBCT-IGRT=Cone beam computed tomography image guided radiation therapy

From further threshold analysis by changing the value of variables by 50%, the parameter on number of patients treated by MR-IGRT had the biggest impact on the incremental cost followed by cost of MR-IGRT equipment. On reducing the number of patients treated by MR-IGRT over lifetime, the incremental cost increases by 226%, and reduces by 76% if the number of patients increases. Furthermore, on increasing values of other variables by 50% the incremental cost increases in the range of 29% to 33%. As mentioned earlier, although the incremental cost increases by increasing the cost of MR-IGRT equipment, the cost is likely to remain fixed since it was provided by the Applicant.

In the base case analysis, the number of fractions administered by both treatment is 5, however, in the sensitivity analysis, the number of fractions delivered by CBCT-IGRT were changed in the increment of 10 fractions up to 30 fractions per treatment course as shown in Table 55. Expert clinical advice estimates that with CBCT-IGRT, prostate and breast cancer patients currently need between 16 to 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, this is likely to favour MR-IGRT and result in cost-savings.

Table 55 Changing fractions for CBCT-IGRT and impact on the incremental cost

MR-IGRT v CBCT-IGRT	Intervention ($)	Comparator ($)	Incremental cost ($)	% change
Base case: MR-IGRT v CBCT-IGRT	$1,930			
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%

MR-IGRT=Magnetic resonance image guided radiation therapy; CBCT-IGRT=Cone beam computed tomography image guided radiation therapy

In the base case analysis, fiducial marker placement was included as a prior step to simulation for all the patients, however, for certain kinds of cancer, it might not require and likely to overestimate the cost. A sensitivity analysis was included by removing cost of fiducial marker placement from the cost of CBCT-IGRT. The results are provided in Table 56. Based on this, the incremental cost changed by 11% as the overall cost of CBCT-IGRT reduced.

Table 56 Removing cost of fiducial marker placement from the overall cost of CBCT-IGRT

MR-IGRT v CBCT-IGRT	Intervention ($)	Comparator ($)	Incremental cost ($)	% change
Base case: MR-IGRT v CBCT-IGRT	$6,056.67	$4,126.29	$1,930	-
Cost of fiducial marker placement removed from CBCT-IGRT	$6,056	$3,916	$2,104	11%

SECTION E FINANCIAL IMPLICATIONS

E.1. JUSTIFICATION OF THE SELECTION OF SOURCES OF DATA

The financial implications analysis considers the estimated financial impact to the MBS of MR-IGRT use of MBS items 15275, 15555 and 15565 for MR-IGRT and an estimation of per patient treatment related adverse event (TRAE) costs for patients considered likely to initially use MR-IGRT.

Given the relatively new and evolving nature of MR-IGRT technology, analysis draws on Applicant-provided information, clinical advice, evidence presented in this DCAR, pragmatic literature search and MBS historical utilisation data. Given the MR-linac is in early stages of use in Australia, analysis is subject to uncertainty, with ultimate resulting outcomes dependent on a number of interdependent factors which are currently uncertain.

As per Section D.4, TRAE analysis focuses on prostate cancer treatment only. Analysis presented is not to be considered reflective of all cancer indications for which MR-IGRT may be used or all current CBCT-IGRT treatment practice. However, it serves as a useful estimate of per patient adverse-event related costs, given the prostate cancer indication has been one for which MR-IGRT has been most commonly studied and used and is expected by the Applicant to reflect a significant portion of initial utilisation upon any MBS listing.

It is acknowledged there are currently uncertainties regarding, or a lack of available information for, certain inputs and assumptions. This reflects the relatively 'new' nature of the technology, the limited current use of MRI-linac in Australia and uncertainty regarding the scale of future deployment and its application to specific cancer indications. Subsequent analysis in Section E acknowledges these uncertainties and considers the impact of these in sensitivity analyses in Section E.6.

ELIGIBLE PATIENT POPULATION

A pragmatic 'mixed methods' approach was used to estimate the eligible patient population. Three separate calculations or sources were used:

1. The Applicant's literature-based estimate of the proportion of all cancer patients likely to use EBRT at least once during their treatment (48%, Barton et. al. 2014) was applied against the estimated overall Australian cancer incidence projections (145,000; AIHW, Cancer Australia). For the individual cancers where the MRI-linac use has been indicated as likely or possible, including prostate cancer, incidence projections based on AIHW and Cancer Australia data were applied against ABS-sourced population projections.

2. AIHW data on historical trends in radiation therapy use in Australia and MBS utilisation data for relevant items 15275, 15555 and 15565 since their January 2016 commencement. MBS

utilisation data for other forms of radiation therapy were also analysed to assess the overall size of the radiation therapy population which may use MR-IGRT.

3. Utilisation data and information on MRI-linac use by indication to date in Australia (provided by the Applicant). To date in Australia, two MRI-linac facilities are in operation: the 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. These facilities have obtained interim approval to use MBS item 15275 for MR-IGRT. A third Elekta Unity MR-linac is supposed to start operating in Victoria in late 2020 or early 2021. All three facilities have obtained interim approval to use MBS item 15275 for MR-IGRT.

CAPACITY

Balanced against the potential patient population is consideration of capacity in Australia to meet potential patient demand. This reflects patient treatment capacity per MR-linac and the number of MR-linacs deployed. Ultimate capacity of MR-linac treatment relative to CBCT-IGRT reflects:

- Procedural steps of the respective technologies.
- Associated health care resource utilisation requirements, including required treatment facilities and services and clinical specialists.
- Treatment course duration, reflecting both individual treatment fraction duration and the required number of fractions.
- Overall health care system capacity (including the availability and geographical location of the respective devices) in Australia.

The Ratified PICO, information provided by the Applicant and clinical advice were used to consider the respective procedures, associated health care resource utilisation requirements and assumptions regarding treatment course specifications (including course duration and fraction requirements).

The total number of treatment courses able to be delivered will be a function of the number of MR-linacs deployed in Australia. The Applicant provided assumptions about the intended projected MRI-linac facility rollout pathway for the five-year analysis period. Clinical advice on the Applicant's proposed rollout pathway, as well as that of PASC, was also considered.

UPTAKE

As per Section A.2, MR-IGRT is expected to substitute current practice (CBCT-IGRT). The extent of this is difficult to estimate because MR-IGRT is a relatively novel technique. The Applicant and clinical advice stated uncertainty regarding potential substitution rates.

Uptake of MR-IGRT will depend on factors including access to the service, resources, clinical indications targeted, and operational efficiency and fractionation achieved in clinical practice. The Applicant provided estimates of likely patient throughput per MRI-linac both initially and over time, as a function of expected average fractions per patient treatment course, based on its own data, as well as that for the CBCT-linac, based on the Radiation Oncology Health Program Grant (ROHPG) scheme guidelines.

Applicant and clinical advice indicated the likely cancer indications MR-IGRT is currently used for and likely to be used for upon any MBS listing. In particular, advice noted indications where significant reductions in treatment course duration, as measured by fractions per course, had been achieved relative to other potential indications.

COST INPUTS

Cost inputs were sourced from the MBS for relevant items 15275, 15555 and 15565 and from the PBS to determine the cost impact of the respective toxicities of MR-IGRT and CBCT. Fiducial marking costs of CBCT-IGRT were as per Section D.4, sourced from relevant MBS items and one PBS item. TRAE costs and associated health care resource utilisation assumptions reflect those from Section D.4.

E.2. USE AND COSTS OF MR-IGRT

ELIGIBLE POPULATION

Cancer incidence: overall and by indication

The AIHW estimates approximately 145,000 new cancer cases were diagnosed in Australia in 2020 (AIHW, 2020a).

The Applicant stated initial clinical cases treated in Australia have included oligometastatic (original sources of the cancer not specified), prostate, bladder, pancreas, and spinal indications, with initial use of MR-linac upon any MBS listing expected to focus on cancers of the brain, breast, cervix, bone, oesophagus, lung, oropharynx, pancreas, prostate, oligometastatic sites, liver, bladder, and rectum.

Historical incidence of these cancers between 1982 and 2019 (in some instances up to 2015) was sourced from Cancer Australia (2019) and the AIHW (2020). The simple linear average rate of historical growth in overall incidence for each cancer was generally (examples of exceptions include prostate cancer, which has seen a marked decline in incident cases since 2004) applied against ABS population projection estimates from series 3222.0 (ABS, 2018) to determine forecast cancer incidence by indication.

The projected incidence of these cancers in Australia between 2021 and 2025 is summarised in Table 57, with comparison to forecast overall cancer incidence (based on historical AIHW data) also

provided. It is estimated that between 147,000 and 155,000 incident cancer cases will occur in Australia between 2021 and 2025, with approximately 48.2% to 49.4% related to cancers for which MR-linac may be used based on the Applicant's stated intentions.

Table 57 Forecast Australian incidence of selected cancer indications and overall cancer incidence forecasts, 2021 to 2025

Indication	2021	2022	2023	2024	2025
Bladder	3,354	3,451	3,550	3,653	3,759
Bone	296	300	305	309	312
Breast	20,636	21,302	21,954	22,601	23,237
Brain/glioblastoma	1,913	1,940	1,967	1,993	2,018
Cervix	987	1,006	1,025	1,045	1,065
Head and neck (excluding lip)	4,323	4,386	4,447	4,505	4,561
Larynx	567	557	547	537	527
Liver	2,699	2,738	2,776	2,812	2,847
Lung	13,331	13,660	13,951	14,221	14,481
Oligometastatic (prostate)	1,951	1,980	2,007	2,033	2,059
Oesophagus	1,598	1,622	1,644	1,666	1,686
Pancreas	3,983	4,040	4,096	4,150	4,202
Prostate	16,952	17,199	17,437	17,666	17,885
Rectum	4,742	4,811	4,878	4,942	5,003
Total	**73,978**	**75,541**	**77,035**	**78,479**	**79,882**
All cancers	**147,327**	**149,471**	**151,540**	**153,530**	**155,437**
Selected cancers as % of overall	**50.2%**	**50.5%**	**50.8%**	**51.1%**	**51.4%**

Source: Based on projections of historical data from Cancer Australia, 2019 (https://ncci.canceraustralia.gov.au/diagnosis/cancer-incidence/cancer-incidence) and the AIHW, 2020 (https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation)
Note: Cancer indications reflect those identified by the Applicant as currently being use for, and likely to, or having the potential to, be treated by MR-IGRT. No indication-specific data on oligometastatic data was found; based on oligometastatic treatment to date in Australia, the oligometastatic projections assume the underlying cancer is prostate cancer. Applying estimated proportions of prostate cancers that are locally advanced as a proxy for oligometastatic disease state.

Radiation therapy use in Australia

The AIHW has reported on the use of radiation therapy in Australia from the 2013-14 calendar year. The AIHW annual report defines radiotherapy as a series of one or more EBRT treatments prescribed by a radiation oncologist. Table 58 summarises estimated annual courses of radiation therapy since 2013-14. Growth in radiation therapy use has steadily risen during this period. It should be noted data is reflective of the proportion of radiation therapy centres in Australia participating in data collection, with full participation in the annual reporting achieved in 2016-17. Overall, there has been steady growth in in the use of EBRT therapy in Australia in the last six financial years, with courses of EBRT approaching 50% of all Australian cancer incidence numbers.

Table 58 Courses of EBRT delivered in Australia, 2013-14 to 2018-19

Financial year	Courses of Radiation therapy	% radiation centres participating
2013–14	47,657	81%
2014–15	56,376	93%
2015–16	60,580	97%
2016–17	63,531	100%[(a)]
2017–18	67,773	99%
2018–19	74,199	99%

Source: AIHW, 2020. Radiotherapy in Australia, 2018-19
Note: a) Rounded to 100%, 0.4% of records (250 records) were missing waiting times data.
Abbreviations: EBRT=external beam radiation therapy

The breakdown of radiation therapy courses by indication between 2013-14 and 2018-19 is summarised in Table 59.

Table 59 EBRT courses by cancer indication, 2013-14 to 2019

Indication	2013-14	2014-15	2015-16	2016-17	2017-18	2018-19
Bladder cancer	464	535	612	557	666	639
Breast cancer	10,831	12,716	13,969	14,376	15,133	14,933
Colorectal cancer	2,251	1,628	1,795	1,805	1,838	1,878
Head and neck cancers	1,808	2,152	2,395	2,475	2,423	2,574
Kidney	363	414	450	464	507	550
Leukaemia	165	130	135	126	131	164
Lung cancer	5,718	3,921	4,518	4,254	5,025	5,151
Lymphoma	1,417	957	996	1,041	1,137	1,162
Melanoma of skin	1,129	903	816	849	907	864
Non cancer	289	198	130	107	128	151
Not stated	1,716	719	124	530	495	452
Other cancer	11,727	7,447	8,384	9,164	10,540	12,479
Ovarian cancer	147	154	213	206	190	207
Pancreatic cancer	274	207	218	237	249	312
Prostate cancer	6,139	7,319	8,335	7,993	9,282	9,626
Secondary cancers	2,528	2,119	2,018	1,376	1,591	2,412
Thyroid cancer	72	72	88	105	96	87
Uterine cancer	574	654	783	907	934	960
Total	**47,612**	**56,373**	**60,545**	**63,516**	**67,773**	**74,195**

Source: AIHW, 2020. Radiotherapy in Australia 2018-19 (https://www.aihw.gov.au/reports/radiotherapy/radiotherapy-in-australia-2018-19/contents/radiotherapy-courses) Note: A patient can receive more than one course of radiotherapy at the same time (courses that are simultaneous or overlap). One course of radiotherapy may cover multiple phases and multiple treatment plans. Sum of individual cancer indications may not add up to aggregate annual totals. Full participation in data collection was not achieved until 2016-17. Annual rates of participation have been 81%, 93%,, 97%, 100%, 99% and 99%.
Abbreviations: EBRT=external beam radiation therapy

It is noted that not all cancer indications for which MR-IGRT would potentially be used for are listed in Table 59, including bone, brain/glioblastoma, liver, oesophagus, oligometastatic (prostate) and

the rectum. These may be covered by the categories 'not stated', 'other cancer' or 'secondary cancers'. Table 60 summarises the estimated use of EBRT by cancer indication.

Table 60 Estimated proportion of all cancer indications treated by EBRT by indication, 2013-14 to 2018-19

Indications	2013-14	2014-15	2015-16	2016-2017	2017-18	2018-19
Breast	22.7%	22.6%	23.1%	22.6%	22.3%	20.1%
Head and Neck (excluding lip)	3.8%	3.8%	4.0%	3.9%	3.6%	3.5%
Lung	12.0%	7.0%	7.5%	6.7%	7.4%	6.9%
Pancreas	0.6%	0.4%	0.4%	0.4%	0.4%	0.4%
Prostate	12.9%	13.0%	13.8%	12.6%	13.7%	13.0%

Source: AIHW, 2020. Radiotherapy in Australia 2018-19 (https://www.aihw.gov.au/reports/radiotherapy/radiotherapy-in-australia-2018-19/contents/radiotherapy-courses)
Abbreviations: EBRT=external beam radiation therapy

Table 61 summarises historical use of EBRT in Australia between 2013-14 and 2018-19 for cancer indications where specific use for that indication was identified.

Table 61 Estimated proportion of selected cancer indications treated by EBRT in Australia, 2013-14 to 2018-19 (% of overall annual incidence)

Indications	2015-16	2016-2017	2017-18	2018-19
Breast	80%	78%	80%	77%
Head and Neck (excluding lip)	64%	63%	60%	62%
Lung	37%	34%	40%	40%
Pancreas	6%	6%	7%	8%
Prostate	43%	43%	52%	55%

Source: AIHW, 2020. Radiotherapy in Australia 2018-19 (https://www.aihw.gov.au/reports/radiotherapy/radiotherapy-in-australia-2018-19); AIHW, 2020. Cancer data in Australia. (https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation); Cancer Australia, 2020. Cancer Incidence.
Note: EBRT courses of radiation therapy reported on financial year basis, while incidence reported on calendar year basis. As such, there may be some deviation of %s from those reflecting perfect alignment of data by year.
Abbreviations: EBRT=external beam radiation therapy

It is noted that as of 2019, these cancer indications account for approximately 41% of all incident cancer cases and 44% of courses of EBRT. One noted uncertainty relates to head and neck cancer treatment. Data in the AIHW's report "Head and Neck Cancers in Australia" (2014) estimated 124 hospitalisations for radiation therapy for head and neck cancer (inclusive of larynx cancer), in comparison to 3,952 for chemotherapy.

Estimates of future EBRT utilisation in Australia based on historical utilisation are summarised in Table 62. While subject to uncertainty, they can provide an indicative pathway of future use in Australia. The number of radiation therapy centres in Australia has grown from 73 in 2013-14 to 93 in 2018-19, or an annualised growth rate of 5.0%. In November 2020, the National Oncology Alliance (NOA) released "Vision 20-30: Building an Australian Cancers Future Framework". It estimated only one in three cancer patients receive radiation therapy treatment, but that approximately 50% would benefit.

This concords with AIHW estimates: the AIHW reports 58% to 60% of all radiation therapy has been curative in intent between 2014-15 and 2018-19 (AIHW, 2019), currently meaning an estimated 32% of cancer patients are receiving curative EBRT treatment. Assuming the approximate 6% historical annual growth rate in EBRT treatment courses experienced since 2014-15 (accounting for previously identified data completion issues), an estimated 112,000 treatment courses would be provided in Australia by 2025-26.

Table 62 Actual and forecast EBRT utilisation in Australia, 2021 to 2025

Financial year	Forecast utilisation
2019-20	78,651
2020-21	83,370
2021-22	88,372
2022-23	93,674
2023-24	99,294
2024-25	105,252
2025-26	111,567

Abbreviations: EBRT=external beam radiation therapy
Note: These are indicative estimates only based on historical utilisation to date.

EBRT is covered by existing MBS items for 2DCRT, 3DCRT, IMRT and stereotactic radiosurgery. Table 63 summarises historical utilisation of respective dosimetry MBS item numbers between 2010 and 2019. It is noted these numbers broadly concord with those reported by the AIHW annual radiotherapy reports. In 2015, IMRT was used by an estimated 37% of patients using radiation therapy (Bridge et al., 2015). With MBS item 15565 for IMRT first listed in 2015, there has been rapid growth in its use on the MBS, with accompanying decline in use of corresponding MBS item numbers for 2DCRT and 3DCRT (Table 63).

Table 63 Historical utilisation of MBS-funded EBRT with reference to dosimetry planning item utilisation, 2010 to 2019

Calendar Year	Intensity Modulated Radiation Therapy (15565)	2DCRT (15518,15521, 15524, 15527,15530,15533)	3DCRT (15556,15559, 15562)	Stereotactic radiosurgery (15600)	MBS utilisation data total all EBRT
2010	N/A	20,321	26,162	249	46,732
2011	N/A	19,577	28,432	294	48,303
2012	N/A	19,433	29,878	331	49,642
2013	N/A	17,683	33,128	420	51,231
2014	N/A	15,749	40,496	514	56,759
2015	7,388	14,450	44,022	493	66,353
2016	26,842	12,300	27,618	638	67,398
2017	34,183	10,997	22,664	667	68,511
2018	43,158	9,936	19,308	699	73,101

Calendar Year	Intensity Modulated Radiation Therapy (15565)	2DCRT (15518,15521, 15524, 15527,15530,15533)	3DCRT (15556,15559, 15562)	Stereotactic radiosurgery (15600)	MBS utilisation data total all EBRT
2019	50,906	9,115	18,138	724	78,883
Historical Annualised growth rate	**23.8%**	**-9.5%**	**-13.1%**	**4.3%**	**6.0%**

Source: Department of Human Services, 2020
Abbreviations: 2DCRT= Two-Dimensional Conformal Radiotherapy; 3DCRT= Three-Dimensional Conformal Radiotherapy, EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Since first listing in 2015, use of IMRT on the MBS has grown 23.8% per annum. Conversely, use of 2DCRT (9.5% per annum) and 3DCRT (13.1% per annum) items has decreased over the same time period. Overall, the use of EBRT has increased approximately 6% per annum since 2010. It is noted that in 2019, MBS EBRT utilisation, as reflected by dosimetry planning broadly concords with AIHW EBRT radiation therapy estimates.

Estimates of future MBS-listed IMRT utilisation in Australia based on historical utilisation are summarised in Table 64. Key assumptions include:

- Overall EBRT grows at approximately 6.0% per annum; and
- IMRT maintains a steady-state of 70% of all EBRT.

It is estimated EBRT utilisation would increase to up to 112,000 treatment courses by 2025, with IMRT increasing to approximately 78,000 treatment courses. It is acknowledged there is uncertainty with these forecasts and the impact of these will be tested in sensitivity analysis in Table 64.

Table 64 Forecast utilisation of MBS-funded EBRT with reference to dosimetry planning item utilisation, 2021 to 2025

Calendar Year	Intensity Modulated Radiation Therapy (15565)
2021	62,043
2022	65,766
2023	69,712
2024	73,894
2025	78,328

Abbreviations: 2DCRT= Two-Dimensional Conformal Radiotherapy; 3DCRT= Three-Dimensional Conformal Radiotherapy, EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule
Note: These are indicative estimates only based on historical utilisation to date.

Present MR-linac utilisation in Australia

The Applicant presented data estimating MR-IGRT utilisation by cancer indication to date in Australia at its two treatment centres in Townsville and Sydney. Table 65 summarises the proportions of patients by indication. Predominantly, utilisation has been for prostate, rectum and oligometastatic

indications. The Applicant did not disclose the total volume of treatments undertaken, nor whether it anticipated the respective weighting of patients would likely be similar should MR-linac capacity expand upon approval for use of the MBS items.

Table 65 Applicant-provided current utilisation breakdown of MR-linac patient indications to date

Indications	Utilisation of MR-linac
Prostate	29%
Oligometastatic	22%
Rectum	17%
Liver	8%
Breast	6%
Bone	6%
Pancreas	3%
Head & neck	2%
Larynx	2%
Brain/GBM	1%
Oesophagus	1%
Nodal boosts	1%
Lung	1%

Source: Department of Health, 2020. Ratified PICO 1620: Magnetic Resonance Image-Guided Radiation Therapy
Abbreviations: MR=magnetic resonance

Contraindications to MR-IGRT

The Applicant stated many clinical tumour sites would be appropriate for use with MR-IGRT, excluding patients with contraindications for MRI, and obese patients unable to fit into the device (Ratified PICO 1620, p.6). The Applicant did not indicate the likely proportion of potential patient populations that may be ineligible.

The Royal Australian College of General Practitioners (RACGP) outlines MRI contraindications as those with prostheses and implants (e.g., pacemakers, internal hearing devices, neurostimulators, orthopaedic and dental implants, programmable shunts, vascular clips), metallic foreign bodies or conductors (e.g., wires, metallic surgical staples) (RACGP, 2013). The MR-linac technologies currently available (Ratified PICO 1620, p.5) have a width of 70 cm: it is not clear what proportion of patients this may preclude from treatment.

Patient Eligibility

Advice from both the Applicant and Australian clinicians indicates multidisciplinary team meetings covering patient cases are expected to be a channel for identification and referral of patients for MR-IGRT.

Aside from indicating which cancers MR-IGRT is likely to initially treat, the Applicant has not specified any characteristics of patients who are proposed to be eligible for the proposed medical service or how patients would be investigated, managed, and referred within the Australian health care system in the lead up to being considered eligible for the service.

The Applicant's premise is the current clinical management algorithm would remain largely unchanged, as MR-IGRT is a form of IGRT (Ratified PICO, p.9). 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.

CAPACITY

Capacity has several dimensions which would ultimately affect the ability for the MR-linac to deliver treatment courses to patients. The number of patients capable of being treated is a function of the number of estimated fractions per treatment course, the number of treatment courses delivered per MR-linac and the number of MR-linacs deployed in Australia.

The MR-IGRT technique is more time-intensive than CBCT-IGRT, requiring twice- to three-times as long per fraction as CBCT-guided IGRT. However, this is intended to be offset by hypofractionation. Ultimately, more complex workflows may require professionals to be present collectively at the treatment machine at the same time. The respective availability and geographical location of CBCT-IGRT and MR-IGRT in Australia will also influence uptake.

There are currently two MR-linac systems operating in Australia: one at 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 supposed to start operating in Victoria in late 2020 or early 2021. All three facilities have obtained interim approval to use MBS item 15275 for MR-IGRT.

The Applicant has stated that over the next three years, at least 10 MR-linac units will be operating in Australia (Ratified PICO, p.5). It has not made any statement regarding capacity expansion beyond this time period.

The Applicant assumes MR-linac availability 230 days a year (i.e., a 46 work-week equivalent). Further, it estimates a capability to deliver 400 to 500 treatment courses per MR-linac in the first year, with 900 to 1,000 treatment courses per MR-linac possible over time, based on a treatment course duration of five fractions (Ratified PICO, p.5). Any rate of progression towards this annual throughput has not been specified. The Applicant estimates average fractions per MR-linac treatment currently is five, with average treatment time of 45 minutes. Presuming a nine-hour operational day based on the ROHPG Scheme guidelines, this equates to 12 treatment fractions per day (Ratified PICO, p.5)

The majority of MR-IGRT treatment in Australia to date has been for prostate, oligometastatic, rectum, liver, and breast cancers (82%). Clinical advice indicates that while initial evidence suggests a significant proportion of patients with prostate and breast cancer can be treated with five fractions, other cancers such as oesophageal cancer may see moderate reduction in fractions and head and neck cancers are unlikely to see any reduction in fractions.

The Applicant states reduction in average treatment time would drive additional treatment throughput per MR-linac site. The best fraction time in Australia to date is 25 minutes, which if achieved consistently would imply the ability to deliver 1,012 fractions per MR-linac per year.

The Applicant notes the current distribution of fractionation schedules in Australia as: 80% of patients receiving less than ten fractions and 20% receiving more than ten fractions. However, further break down, including breakdown by cancer indication or more definitive utilisation averages for above and below ten fractions use, was not provided.

Clinical advice estimates that with CBCT-IGRT, prostate and breast cancer treatments currently need between 16 to 20 fractions per treatment course in Australian clinical settings. Information provided by the Applicant notes a recent survey by the Royal Australian and New Zealand College of Radiation Oncologists (RANZCR) that estimates the overall average fractions per radiation course is delivered in Australia is currently 19. These broadly concord with MBS utilisation data for MBS items 15565 (dosimetry planning) and 15275 (single episode of radiation oncology treatment, or fraction). In 2019-20, 50,906 items for dosimetry planning and 968,287 items for fractions were claimed, equating to approximately 19.5 fractions per patient undertaking dosimetry planning. While the Applicant notes continual MR-linac fraction reductions, CBCT-linacs have also seen reduced average fractions per treatment course, decreasing from an estimated 22.7 in 2015-16.

Table 66 summarises information provided by the Applicant. It should be noted it is unclear whether the stated current courses per year for the MR-linac (i.e., 552) is considered to be operational capacity or actual throughput of patients.

Table 66 Estimated current and project EBRT treatment course capacity with CBCT-IGRT and MR-IGRT

Item	CBCT Linac	MR-Linac current	MR-Linac planned
Treatment Days / Year	230	230	230
Treatment Hours / Day	9	9	9
Treatment minutes/day	540	540	540
Time (minutes) / Treatment (fraction)	15	45	25
Fractions / Day	36	12	22
Fractions / Year	8,280	2,760	4,968
Average Fractions / Course	19	5	5

Item	CBCT Linac	MR-Linac current	MR-Linac planned
Courses / Year	436	552	1,012

Source: Department of Health, 2020. Ratified PICO 1620: Magnetic Resonance Image-Guided Radiation Therapy
Abbreviations: CBCT=cone beam computer tomography, EBRT=external beam radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy, MR-linac=magnetic resonance linac

Analysis assumes average fractions per treatment course of five, with three operational MR-linacs in year one, increasing to ten by year three and remaining so thereafter. Assuming consistent growth in deployment of MR-linac machines, analysis further assumes six will have been deployed and operational by year two. Further, analysis assumes average treatment courses per year capacity of approximately 1,000 per MR-linac by year three and thereafter.

Overall, these assumptions would indicate the potential to provide 1,656 courses of treatment in year one and 5,520 courses of treatment from year three onwards assuming Applicant-indicated optimal fraction rates of five per treatment course. Assuming the treatment fraction length reached a consistent 25-minutes by year three, this would mean the potential to provide 10,120 courses of treatment from year three onwards. These assumptions are tested in sensitivity analysis in Section E.6.

UPTAKE

PASC has noted estimating substitution of CBCT-IGRT for MR-IGRT may be difficult given the novel technique (Ratified PICO, p.7), but considered rollout of MR-linac facilities is likely to be constrained in the short-term by the capital costs of the machine (Ratified PICO, p.6). Clinical advice notes radiation therapy has seen gradual advances in particular with on-treatment visualisation, starting with CT and now with MRI. As such, advice indicated any emerging technology with strong technical and dosimetric justification will likely result in rapid uptake in routine practice, preceding high level randomised clinical evidence.

Ultimate uptake will depend on numerous interdependent factors including achieving MBS listing, the number of MR-linacs deployed and their geographical location relative to CBCT-IGRT, achievable fraction numbers per cancer indication and reduction in average fractionation time, cancer indications targeted, improvement in fraction delivery schedules and availability and training as required of health care resources.

Analysis assumes patients from the current mix of cancer indications treated by MR-linac centres in Australia, as provided by the Applicant, including prostate and breast cancers. Information provided by the Applicant and clinical advice indicates these patients have the possibility to achieve low average fraction rates per treatment course for a significant proportion of patients, giving an estimate of maximum initial potential for MR-IGRT treatment utilisation subject to capacity constraints.

It is assumed the locations of MR-linacs deployed in Australia provides for CBCT-IGRT and MR-IGRT to be equally feasible patient treatment options.

The first step of analysis assumes that without capacity constraints, 10% of patients would switch to MR-IGRT in year one, increasing to 50% by year five. Estimates are then modified to reflect projected annual capacity constraints. Given the inherent uncertainties, including current absolute utilisation, sensitivity analysis tests these assumptions (Section E.6).

Table 67 summarises estimated maximum MR-IGRT utilisation assuming the projected MR-linac capacity and cancer indications being treated. Total treatment courses (patients) potentially being delivered are estimated to increase from 1,656 patients in year one to 10,120 patients by year five.

Table 67 Estimated utilisation of MR-IGRT (substitution of CBCT-IGRT), assuming predominantly prostate and breast cancer indication targeting, 2021 to 2025

Item	2021	2022	2023	2024	2025
Capacity constraints					
MR-linacs	3	6	10	10	10
Treatment fractions delivered per day	12	12	22	22	22
Annual treatment courses (patients)	1,656	3,312	10,120	10,120	10,120
Treatment assumptions					
Weighted-fractions (MR-IGRT)	5	5	5	5	5
Prostate MBS EBRT IMRT patient numbers (estimated)	7,571	8,026	8,507	9,017	9,559
Breast cancer MBS EBRT IMRT patient numbers (estimated)	11,745	12,450	13,197	13,989	14,828
MR-linac uptake rate (overall)	10%	20%	30%	40%	50%
Estimated utilisation					
Total patient numbers without capacity constraints (prostate and breast)	1,932	4,095	6,511	9,203	12,194
Total maximum uptake accounting for capacity constraints	1,656	3,312	6,511	9,203	10,120

Abbreviations: CBCT=cone beam computer tomography, EBRT=external beam radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy, MR-linac=magnetic resonance linac
Note: This analysis is indicative only and is not intended to make prediction about the ultimate cancer indications for which MR-IGRT may be used or the relative proportions of patients from different cancer indications that may use it.

Clinical advice estimates that with CBCT-IGRT, prostate and breast cancer patients currently are using between 16 to 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). In 2019-20, 50,906 items for dosimetry planning and 968,287 items for fractions were claimed, equating to approximately 19.5 fractions per patient

undertaking dosimetry planning. Assuming this, there would be expected to be reductions in use of MBS item 15275 (single episode of radiation oncology treatment, or fraction). Table 68 summarises estimated reduction in utilisation of this item, assuming a CBCT-IGRT treatment fraction total of 18 and an MR-IGRT treatment fraction total of five. This would lead to a reduction in utilisation of MBS item 15275 of 21,528 in year one, increasing to 131,560 in year three and remaining at that level thereafter.

Table 68 Estimated reduction in utilisation of episodes of radiation oncology treatment, 2021 to 2025

Item	2021	2022	2023	2024	2025
Weighted-average fractions MR-IGRT	5	5	5	5	5
Weighted-average fractions CBCT-IGRT	18	18	18	18	18
Fraction difference	13	13	13	13	13
Estimated MR-IGRT utilisation	1,656	3,312	6,511	9,203	10,120
Total difference in fractions (MBS item 15275)	-21,528	-43,056	-131,560	-131,560	-131,560

Abbreviations: CBCT=cone beam computer tomography, EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule, MR-IGRT=magnetic resonance image-guided radiation therapy, MR-linac=magnetic resonance linac

It is noted that Section D.4 analysis, which considers potential adverse event costs with reference to hypofractionated treatment courses assumes treatments compared both use five fractions per patient for prostate cancer. As such, assuming there was no treatment fraction differential, then there would be no difference in use of MBS items 15565 and 15275. However, as stated above, clinical advice and MBS utilisation data would tend to indicate current treatment course fraction requirements is close to 16 to 20 per patient.

COST INPUTS

Cost items relate to pre-treatment, treatment, and post-treatment costs (adverse event costs). Both Applicant and clinical advice indicates multidisciplinary team meetings covering these clinical cases are expected to be a channel for identification and referral of these patients.

Cost inputs were previously considered in Section D.4. Cost of treatment delivery reflecting dosimetry planning, simulation and individual treatment sessions are captured by MBS items 15555, 15565 and 15275, respectively. CBCT-IGRT also requires fiducial marking. Adverse events costs as a function of CBCT-IGRT and MR-IGRT were also considered in Section D.4. Both the Applicant and clinical advice do not anticipate any difference in post-treatment patient management or monitoring aside from those associated with adverse events. This reflects the Applicant's claim of MR-IGRT having a reduced toxicities relative to CBCT-IGRT. Relevant cost items for financial implications analysis are summarised in Table 69. These cost items are applied as appropriate in Sections E.2 to E.6.

Table 69 Relevant cost inputs for MR-IGRT and CBCT-IGRT

MBS/PBS/AR-DRG/PLAC item number	Description	Cost/DPMQ/Fee	MBS 85% Benefit	MBS 75% Benefit
Pre-treatment				
While both the Applicant and clinical advice indicate multidisciplinary team meetings covering these clinical cases are expected to be a channel for identification and referral of these patients, specific processes were not identified and therefore not explicitly costed. As per Section A.6, patients are assumed to proceed through the same clinical management algorithm as other radiation therapy patients, with MR-IGRT a proposed additional treatment option. However, as processes and procedures for potential MR-IGRT patients evolve, clinical advice suggests such MDT workflows will become more clearly defined.				
Treatment				
Fiducial Marking (CBCT only)				
37217	Prostate, implantation of radio-opaque fiducial markers into the prostate gland	$142.60	$121.25	$106.95
55603	Cost of ultrasound scan	$110.75	$94.15	$83.10
104	Cost of specialist attendance	$89.55	$76.15	$67.20
21980	Cost of anaesthesia	$102.00	$86.70	$76.50
1209P	Cost of antibiotics	$18.28	N/A	N/A
CBCT and MR-IGRT				
15275 (fraction)	Radiation oncology treatment with IGRT imaging facilities	$188.65	$160.40	$141.50
15555 (simulation)	Simulation for IMRT with or without intravenous contrast medium.	$732.75	$648.05	$549.60
15565 (IMRT dosimetry plan)	Preparation of an IMRT DOSIMETRY PLAN, which uses one or more CT image volume datasets	$3,417.35	$3,332.65	$2,563.05
Adverse Events				
23	Professional attendance	$38.75		
105	Specialist consultation (subsequent)	$45.00		
10592L	Loperamide	$13.51		
1502C	Hydrocortisone Suppositories	$41.60		
4049D	Ural Sachets	$18.22		
10831C	Hydrocortisone tubes	$17.19		
11900	Urine flow study	$28.40	$24.15	$21.30
4321K	Magnesium	$18.04		
4422R	Psyllium Husk Powder	$25.28		
4275B	Panadeine forte	$15.73		
65070	Pathology service	$16.95	$14.45	$12.75
32084	Sigmoidoscopy or colonoscopy	$114.85	$97.65	$86.15
66716	TSH quantitation	$25.05	$21.30	$18.80

MBS/PBS/AR-DRG/PLAC item number	Description	Cost/DPMQ/Fee	MBS 85% Benefit	MBS 75% Benefit
58900	Abdominal diagnostic imaging	$36.25	$30.85	$27.20
10954	Dietetic services	$64.20	$54.60	
2020-21 NEP	2020-21 NEP	$4,998.00		
G67A/G67B	Oesophagitis and Gastroenteritis, Major/Minor Complexity	$2,062.42		
G61A/G61B	Gastrointestinal Haemorrhage, Major/Minor Complexity	$3,153.63		
G70A/G70B	Other Digestive System Disorders, Major/Minor Complexity	$5,117.94		
Other Post-treatment patient management				
No difference in post-treatment patient management assumed.				

Abbreviations: AR-DRG=Australian Refined Diagnosis Related Groups, CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, DPMQ=Dispensed Price Maximum Quantity, IMRT=intensity-modulated radiation therapy, MBS=Medical Benefits Schedule, MR-IGRT=magnetic resonance image-guided radiation therapy, NEP=National Efficient Price, PBS=Pharmaceutical Benefits Schedule, PLAC=Prosthesis List Advisory Committee,TSH=Thyroid Stimulating Hormone

COST OF MR-IGRT

The analysis of the financial implications of listing MR-IGRT on the MBS considers the potential financial impact given assumptions about the market for MR-IGRT and treatment settings. Most of these assumptions are subject to uncertainty and are considered in sensitivity analysis in Section E.6. The MBS financial implications analysis for MR-IGRT assumes:

- Substitution of CBCT-IGRT for MR-IGRT only. The Applicant and clinical advice stated MR-IGRT may potentially see patients who would otherwise use alternative treatment modalities be using, or be able to use, radiation therapy as a result of the improved tumour targeting. However, consistent with the Ratified PICO (p.7), which expects MR-IGRT to be used as a replacement for CBCT-IGRT, analysis assumes only those who would otherwise already use CBCT-IGRT are part of the potentially eligible population.

- Based on Applicant advice, MRI-linac capacity in Australia is increasing from three centres in year one, to ten by year three. Analysis assumes it remains at that level thereafter.

- The locations of MR-linacs deployed in Australia provides for CBCT-IGRT and MR-IGRT to be equally feasible patient treatment options.

- While the Applicant has requested listing for both inpatient and outpatient settings, MRI-linacs in Australia to date have been in outpatient settings. Analysis assumes this to be the case, meaning an 85% MBS item rebate.

- MR-linac facilities operating or operational for nine hours per day as per Applicant-provided information.

- Initially, Applicant projections of current MR-linac average fractions per treatment course (five fractions) and duration of treatment fraction (45 minutes), meaning the potential to provide 1,656 courses of treatment across Australia in year. From year three and thereafter, analysis assumes average treatment courses per year of approximately 1,000 per MR-linac, reflecting treatment fraction duration reaching a consistent 25-minutes by year three. In contrast, CBCT-linac throughput rates are assumed stable.

- Only patients from the current mix of cancer indications treated by MR-linac centres in Australia, as provided by the Applicant, are assumed to be treated with MR-IGRT, including prostate and breast cancers. Information provided by the Applicant and clinical advice indicates these patients have the possibility to achieve low average fraction rates per treatment course for a significant proportion of patients. This concords with information publicly released by St. Vincent's Health Australia in June 2020 (St. Vincent's Health Australia, 2020).

- Estimated fractions per CBCT treatment course reflect Applicant, clinical advice, and historical MBS utilisation data to date.

The cost to the MBS of MR-IGRT adverse events is considered separately in Section E.2. Table 70 summarises the estimated final impact of listing MR-IGRT on the MBS. Annual costs to the MBS as a result of MR-IGRT increase by $7,920,151 in year one rising to $48,400,924 by year three and remaining at that level thereafter.

It should be noted the results presented may not necessarily reflect the financial implications to the MBS under different subsequent MR-IGRT market and treatment settings. Different ultimate market and treatment settings upon any MBS listing may see different financial impacts. In particular, financial impacts are sensitive to assumptions about per treatment course fraction reductions achieved. These assumptions are tested in sensitivity analysis in Section E.6.

Table 70 Estimated financial impact of listing MR-IGRT on the MBS, 2021 to 2025

Item	2021	2022	2023	2024	2025
Estimated utilisation impact					
MR-IGRT	1,656	3,312	10,120	10,120	10,120
MBS item 15565 (planning)	1,656	3,312	10,120	10,120	10,120
MBS item 15555 (simulation)	1,656	3,312	10,120	10,120	10,120
MBS item 15275 (fraction)	8,280	16,560	50,600	50,600	50,600

Item	2021	2022	2023	2024	2025
Estimated financial impact					
MBS item 15565 (planning)	$5,518,868	$11,037,737	$33,726,418	$33,726,418	$33,726,418
MBS item 15555 (simulation)	$1,073,171	$2,146,342	$6,558,266	$6,558,266	$6,558,266
MBS item 15275 (fraction)	$1,328,112	$2,656,224	$8,116,240	$8,116,240	$8,116,240
Total cost of MR-IGRT to the MBS	**$7,920,151**	**$15,840,302**	**$48,400,924**	**$48,400,924**	**$48,400,924**

Abbreviations: MBS=Medical Benefits Schedule, MR-IGRT=magnetic resonance image-guided radiation therapy

E.3. CHANGES IN USE AND COST OF OTHER MEDICAL SERVICES

Both the Applicant and clinical advice indicated multidisciplinary team meetings covering potential eligible clinical cases are expected to be a channel for identification and referral of these patients. However, the exact nature of this, including resourcing and costs, was not indicated by the Applicant or clinical advice. As per Section A.6, patients are assumed to proceed through the same clinical management algorithm as other radiation therapy patients, MR-IGRT a proposed additional treatment option. However, as processes and procedures for potential MR-IGRT patients evolve, clinical advice suggests such MDT workflows will become more clearly defined.

Table 71 summarises the change in MBS item utilisation and costs over the five-year analysis period. Assuming an approximate 13 fraction reduction in treatment course duration and no fiducial market costs, substitution of CBCT-IGRT for MR-IGRT is estimated to save the MBS $11,999,624 in year one, with annual savings of $73,331,038 in year three and every year thereafter.

Table 71 Financial impact of decreased use of other medical services on the MBS, 2021 to 2025

Item	2021	2022	2023	2024	2025
CBCT-IGRT: Treatment					
Estimated utilisation impact					
Fiducial marker placement	1,656	3,312	10,120	10,120	10,120
MBS item 15565 (planning)	1,656	3,312	10,120	10,120	10,120
MBS item 15555 (simulation)	1,656	3,312	10,120	10,120	10,120
MBS item 15275 (fraction)	29,808	59,616	182,160	182,160	182,160
Estimated financial impact					
Fiducial marker placement	$626,382	$1,252,764	$3,827,890	$3,827,890	$3,827,890
MBS item 15565	$5,518,868	$11,037,737	$33,726,418	$33,726,418	$33,726,418
MBS item 15555 (simulation)	$1,073,171	$2,146,342	$6,558,266	$6,558,266	$6,558,266
MBS item 15275 (fraction)	$4,781,203	$9,562,406	$29,218,464	$29,218,464	$29,218,464
Total cost of CBCT-IGRT to the MBS	**$11,999,624**	**$23,999,249**	**$73,331,038**	**$73,331,038**	**$73,331,038**

Abbreviations: CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, MBS=Medical Benefits Schedule, MR-IGRT=magnetic resonance image-guided radiation therapy

Differences in per patient adverse event costs for prostate cancer treatment were considered in Section D.5. This analysis assumes five fraction treatment courses for both the intervention and the comparator, and therefore the applicability to broader patient groups and current CBCT-IGRT

treatment practice is unclear. These costs are therefore considered indicative, however they serve as a useful estimate of potential initial adverse-event related costs for MR-IGRT, given prostate cancer treatment is expected by the Applicant to reflect a significant portion of initial utilisation upon any MBS listing.

Per patient MBS-specific acute toxicity costs are summarised in Table 72, with MR-IGRT patients estimated to save $222 relative to CBCT-IGRT patients.

Table 72 Estimated financial impact of treatment-related adverse events on the MBS: per patient acute toxicity costs, prostate cancer only

Item	Total acute toxicity costs per patient
CBCT-IGRT	$313.62
MR-IGRT	$91.99
Net difference	**$221.63**

Abbreviations: CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy

Similarly, Table 72 summarises late toxicity costs, with MR-IGRT patients estimated to save $566 relative to CBCT-IGRT patients. In contrast to CBCT-IGRT, MR-IGRT is considered to have no 'late' (i.e., post-acute) toxicity costs.

Table 73 Estimated financial impact of treatment-related adverse events on the MBS: per patient late toxicity costs, prostate cancer only

Item	Total late costs per patient
CBCT-IGRT	$565.75
MR-IGRT	$0.00
Net difference	**$565.75**

Abbreviations: CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy

E.4. FINANCIAL IMPLICATIONS FOR THE MBS

The financial implications to the MBS resulting from the proposed listing of MR-IGRT are summarised in Table 74. It is estimated that assuming MR-IGRT five fraction treatment course duration and a current estimated average CBCT-IGRT treatment course duration of 18 fractions, annual cost savings to the MBS will be $4,079,473 in year one, increasing to $24,930,114 by year three and remaining at that level thereafter. It should be noted that no additional courses of treatment are assumed, but that there is substitution of CBCT-IGRT treatment for MR-IGRT treatment.

Table 74 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 substituted (courses of therapy)[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.

These financial implications rest primarily on the assumption of reduced treatment course duration as a result of reduced fractions per patient. However, they are considered uncertain given the uncertainties previously identified including MR-linac deployment, treatment uptake, the patient population receiving treatment, the rate of technology improvement and capacity. It should be noted that these estimates do not necessarily reflect potential financial implications for MR-IGRT under other different MR-IGRT treatment scenarios. Sensitivity analysis in Section E.6 test the impact of variations in key assumptions on financial implications.

E.5. Financial Implications for Government Health Budgets

The Broader Impact on the MBS

The Applicant has not considered any broader impacts on the MBS, including Extended Medicare Safety Net costs. PASC queried if there would be Extended Medicare Safety Net costs (Ratified PICO, p.12).

Other Government Impacts

Consistent with Applicant-provided information, no PBS costs while taking radiation therapy treatment courses are assumed.

Reduced use of CBCT-IGRT would mean reduced use of fiducial marking procedures. The procedure requires use of both MBS and PBS items. MBS items have been previously considered in Section E.3.

PBS costs are estimated at $18.28 per procedure for antibiotics (PBS item 1209P). Cost savings increase from $30,272 in year one to $184,994 in year three and thereafter (Table 75).

Table 75 PBS cost offsets associated with reduced fiducial marking procedures, 2021 to 2025

Item	2021	2022	2023	2024	2025
PBS item 1209P	1,656	3,312	10,120	10,120	10,120
Fiducial Marker Placement	$30,272	$60,543	$184,994	$184,994	$184,994

Abbreviations: PBS=Pharmaceutical Benefits Schedule

Both the Applicant and clinical advice do not anticipate any difference in post-treatment patient management or monitoring aside from adverse events. An indicative analysis of adverse events costs as a function of CBCT-IGRT and MR-IGRT were also considered in Section D.4.

Per patient MBS-specific cost offsets were considered in Section E.3. Per patient PBS-specific cost offsets are presented in this section. As per Section E.3, they are not to be considered necessarily reflective of all cancer indications for which MR-IGRT may be used or current CBCT-IGRT treatment practice. However, they serve as useful estimates of adverse-event related costs, given the prostate cancer indication has been one for which MR-IGRT has been most commonly studied and used and is expected by the Applicant to reflect a significant portion of initial utilisation upon any MBS listing.

PBS-specific acute toxicity costs are summarised in Table 76. The MR-IGRT is estimated to save $372 per patient in acute toxicity costs.

Table 76 Financial impact of treatment-related adverse events: acute toxicity costs, prostate cancer only

Item	Total acute toxicity costs per patient
CBCT-IGRT	$430.72
MR-IGRT	$58.64
Net difference	**$372.08**

Abbreviations: CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy

Similarly, Table 77 summarises late toxicity costs. In contrast to CBCT-IGRT, based on analysis in Section D.4, MR-IGRT is considered to have no 'late' (i.e., post-acute) toxicity costs. The MR-IGRT is estimated to save $269 per patient in late toxicity costs.

Table 77 Financial impact of treatment-related adverse events: late toxicity costs, prostate cancer only

Item	Total late costs per patient
CBCT-IGRT	$269.06
MR-IGRT	$0.00
Net difference	**$278.29**

Abbreviations: CBCT-IGRT=cone beam computer tomography image-guided radiation therapy, MR-IGRT=magnetic resonance image-guided radiation therapy

Given these analyses are intended to be indicative and not necessarily reflective of broader TRAE-related implications for the PBS, impacts on overall PBS script utilisation have not been assessed.

STATE AND TERRITORY GOVERNMENT HEALTH BUDGETS

Although the Applicant has indicated that to achieve alignment with current radiation oncology services provided across multiple settings, the proposed settings for delivery include public and private inpatient and outpatient settings, analysis in this DCAR assumes an outpatient setting. GenesisCare St Vincent's Hospital, Darlinghurst, New South Wales currently treats patients in an outpatient setting.

As such no inpatient admissions or emergency department visits are included in this analysis. Outpatient clinic patients would change as a function of the number of individual fractions of treatments received by patients. Assuming a 13-fraction reduction per treatment course, analysis estimates a resulting decrease of 21,528 outpatient visits in year one, with the reduction increasing to 131,560 by year five. The cost of individual fractions of treatment covered by MBS item 15275 has been previously considered in Section E.2. As per previous sections, this is subject to assumptions about MR-linac facility roll-out, cancer indications targeted, health care system capacity and procedure technology developments.

As per Section D.5, patients with prostate cancer using MR-IGRT are estimated to have reduced TRAE-associated costs compared to those using CBCT-IGRT. These costs include hospitalisation costs. However, the analysis assumes five fraction treatment courses for both the intervention and the comparator, and therefore the applicability to broader patient groups and current CBCT-IGRT treatment practice is unclear.

E.6. IDENTIFICATION, ESTIMATION AND REDUCTION OF UNCERTAINTY

The financial implications analysis is subject to uncertainty regarding several interdependent factors including:

- Continued growth in the EBRT treatment market. While overall growth in MBS-listed EBRT has averaged approximately 6.0% in the most recent decade and overall EBRT growth has been higher in recent years, the future growth pathway is unclear, being dependent on the

role of radiation therapy in the cancer patient treatment mix. Cancer treatment is an evolving therapeutic space, so the proportion of patients with cancer treated with EBRT is uncertain.

- The number of MR-linac facilities. While the Applicant has stated intent to have 10 MR-linac facilities operational within three years, PASC expressed uncertainty regarding this given the significant initial capital costs per machine (Ratified PICO, p.6).

- The MR-IGRT technology progression pathway is uncertain, including:

    - The fraction reductions achievable across cancer indications;

    - Cancer indications for which MR-IGRT would be used in the Australian market and timing of this use;

    - The expansion of cancer indications possible due to improved tumour targeting, and procedural process improvements achieved (i.e., time per treatment fraction); and

This impacts the maximum achievable 'throughput' from the given mix of cancers being treated and subsequently patient uptake.

Several sensitivity analyses have been undertaken addressing these issues. Their impacts on five-year financial implications for the MBS have been tested, with results in Table 78 to Table 85. MBS financial implications are driven by interacting assumptions about MR-linac facility capacity, fraction reduction and time per fraction. Analysis indicates that should these parameters and inputs progress as estimated by the Applicant, there would be potentially significant MBS cost savings.

No sensitivity analysis has been conducted on TRAE cost estimates, given original analysis was on a per patient basis and intended to be indicative in nature only as they may not necessarily be applicable to other cancer indications for which MR-IGRT may be used.

It should be noted the Ratified PICO states "*the Applicant considered there would be no net impact to out-of-pocket costs*" (p. 11). As per Section D.5, it appears the MR-IGRT technology is more expensive than the comparator (CBCT-IGRT). However, the Applicant is not requesting a higher MBS fee. As per the Ratified PICO (p.12), "*The Applicant advised that the Application seeks equivalent reimbursement for MR-Linac systems to existing Linacs and considered the current modelling for IGRT for Linacs would be appropriate analysis. The Applicant considered that no net impact to out-of-pocket costs would be expected and would be dependent on the individual provider, just as the situation currently is for all radiation therapy treatments. The Applicant noted that MR linacs are going in to both public and private sector sites in Australia."*

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 78 Sensitivity analysis: Financial implications for MBS – EBRT growth rate halves to 3% per annum

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,252,764	-$3,827,890	-$3,827,890	-$3,827,890
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$3,453,091	-$6,906,182	-$21,102,224	-$21,102,224	-$21,102,224
Financial Implications for the MBS	**-$4,079,473**	**-$8,158,946**	**-$24,930,114**	**-$24,930,114**	**-$24,930,114**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 79 Sensitivity analysis: Financial implications for MBS – average of 10 fractions of treatment per treatment course with MR-IGRT

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$313,191	-$626,382	-$1,913,945	-$1,913,945	-$1,913,945
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$1,062,490	-$2,124,979	-$6,492,992	-$6,492,992	-$6,492,992
Financial Implications for the MBS	**-$1,375,681**	**-$2,751,361**	**-$8,406,937**	**-$8,406,937**	**-$8,406,937**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 80 Sensitivity analysis: Financial implications for MBS – average duration per MR-IGRT treatment fraction remains at 45 minutes

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,252,764	-$2,087,940	-$2,087,940	-$2,087,940
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$3,453,091	-$6,906,182	-$11,510,304	-$11,510,304	-$11,510,304
Financial Implications for the MBS	**-$4,079,473**	**-$8,158,946**	**-$13,598,244**	**-$13,598,244**	**-$13,598,244**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 81 Sensitivity analysis: Financial implications for MBS – number of MR-linacs grows to five by year two, seven by year three, remaining steady thereafter

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,043,970	-$2,679,523	-$2,679,523	-$2,679,523
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$3,453,091	-$5,755,152	-$14,771,557	-$14,771,557	-$14,771,557
Financial Implications for the MBS	**-$4,079,473**	**-$6,799,122**	**-$17,451,080**	**-$17,451,080**	**-$17,451,080**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 82 Sensitivity analysis: Financial implications for MBS – number of MR-linacs grows to 12 by year four, and 15 by year five

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,252,764	-$3,827,890	-$4,593,468	-$5,741,835
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$3,453,091	-$6,906,182	-$21,102,224	-$25,322,669	-$31,653,336
Financial Implications for the MBS	**-$4,079,473**	**-$8,158,946**	**-$24,930,114**	**-$29,916,137**	**-$37,395,171**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 83 Sensitivity analysis: Financial implications for MBS – uptake rate of given pool of initial cancer indications (e.g. prostate and breast) with low average fraction rate (five) increases to 15%, 30%, 45%, 60%, 75% and number of MR-linacs grows to eight, 11, 14 and 17 in years two to five, respectively.

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,670,352	-$4,210,679	-$5,359,046	-$6,507,413
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$3,453,091	-$9,208,243	-$23,212,446	-$29,543,114	-$35,873,781
Financial Implications for the MBS	**-$4,079,473**	**-$10,878,595**	**-$27,423,125**	**-$34,902,160**	**-$42,381,194**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 84 Sensitivity analysis: Financial implications for MBS – CBCT-IGRT fraction rate reduces to an average of 16 per patient

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$626,382	-$1,252,764	-$3,827,890	-$3,827,890	-$3,827,890
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	-$2,921,846	-$5,843,693	-$17,855,728	-$17,855,728	-$17,855,728
Financial Implications for the MBS	**-$3,548,228**	**-$7,096,457**	**-$21,683,618**	**-$21,683,618**	**-$21,683,618**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Table 85 Sensitivity analysis: Financial implications for MBS – no fraction reduction, fiducial market cost-offset only

Item	2021	2022	2023	2024	2025
Fiducial marker placement	-$173,617	-$347,234	-$1,062,883	-$1,062,883	-$1,062,883
MBS item 15565 (planning)	$0	$0	$0	$0	$0
MBS item 15555 (simulation)	$0	$0	$0	$0	$0
MBS item 15275 (fraction)	$0	$0	$0	$0	$0
Financial Implications for the MBS	**-$173,617**	**-$347,234**	**-$1,062,883**	**-$1,062,883**	**-$1,062,883**

Abbreviations: EBRT=external beam radiation therapy, MBS=Medical Benefits Schedule

Appendix A Clinical Experts and Assessment Group

ASSESSMENT GROUP

NHRMC Clinical Trials Centre

Name	Position
Blaise Agresta	HTA Lead
Dr. Slavica Berber	Senior Project Officer
Dr. Vendula Blaya-Novakova	Project Officer
Nathan Fox	Senior Evidence Analyst
Smriti Raichand	Senior Evidence Analyst
Karan Shah	Research Fellow

Noted conflicts of interest

There were no conflicts of interest.

APPENDIX B SEARCH STRATEGIES

BIBLIOGRAPHIC DATABASES

Electronic database	Time period searched
02 October 2020	
Embase via Ovid SP	2014-2020
Medline via Ovid SP	2014-2020
EMB Reviews* via Ovid SP	2014-2020
23 October 2020	
Embase via Ovid SP	No limits
Medline via Ovid SP	No limits
EMB Reviews* via Ovid SP	No limits

*Cochrane Database of Systematic Reviews 2005 to September 17, 2020, Database Field Guide EBM Reviews - ACP Journal Club 1991 to August 2020, Database Field Guide EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, Database Field Guide EBM Reviews - Cochrane Clinical Answers August 2020, Database Field Guide EBM Reviews - Cochrane Central Register of Controlled Trials August 2020, Database Field Guide EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, Database Field Guide EBM Reviews - Health Technology Assessment 4th Quarter 2016, Database Field Guide EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

ADDITIONAL SOURCES OF LITERATURE (INCLUDING WEBSITES)

Source	Location
Australian Clinical Trials Registry	http://www.anzctr.org.au/TrialSearch.aspx
National Institutes of Health	https://clinicaltrials.gov/

SEARCH STRATEGIES

Medline (via OvidSP) searched 02 October 2020

1 exp Magnetic Resonance Imaging/mt [Methods] 130055

2 (MRI or magnetic resonance imaging or magnetic-resonance imaging or MR imag$).ti,ab. 405799

3 (Magnetic Resonance Imaging Guided or MRgRT).ti,ab. 758

4 (MR-linac or MRI-linac or MR linac or MRI linac or ViewRay co-60 or View Ray Linac or Elekta Unity or MRIdian).ti,ab. 286

5 exp Radiotherapy, Image-Guided/ 3124

6 (IGRT or image guided).ti,ab. 12819

7 exp Radiotherapy, Intensity-Modulated/ 10233

8 (IMRT or intensity modulated radiation therapy).ti,ab. 11125

9 1 or 2 or 3 or 4 449619

10 5 or 6 or 7 or 8 28523

11 9 and 10 3564

12 ((men or women or patient* or participant*) adj6 treat*).ti,ab. 1238669

13 11 and 12 781

14 limit 13 to yr="2014 -Current" 514

15 animals/ not humans/ 4705549

16 14 not 15 512

Medline (via OvidSP) on 23 October 2020

1 exp Magnetic Resonance Imaging/mt [Methods] 130710

2 (MRI or magnetic resonance imaging or magnetic-resonance imaging or MR imag$).mp. 591420

3 (Magnetic Resonance Imaging Guided or MRgRT).mp. 791

4 (MR-linac or MRI-linac or MR linac or MRI linac or ViewRay co-60 or View Ray Linac or Elekta Unity or MRIdian).mp. 327

5 exp Radiotherapy, Image-Guided/ 3139

6 (IGRT or image guided).mp. 18918

7 (imag$ adj3 guid$).mp. 29834

8 exp Cone-Beam Computed Tomography/ 10393

9 (CBCT or cone beam comp$ or cone-beam comp$ or cone beam CT or cone-beam CT or cone beam-comp$).mp. 15891

10 1 or 2 or 3 or 4 598068

11 5 or 6 or 7 30064

12 8 or 9 15891

13 exp Radiotherapy/ 186764

14 10 and 11 and 12 and 13 74

15 treat*.mp. 6050551

16 11 and 12 and 13 and 15 822

17 14 or 16 839

18 exp Brachytherapy/ or brachytherapy.ti. 21563

19 17 not 18 829

20 limit 19 to humans 780

APPENDIX C STUDIES INCLUDED IN THE SYSTEMATIC REVIEW

Profiles of studies on MR-IGRT included in the systematic literature review

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
E. Kim et al. (2018)	Retrospective matched Coh 2015-2016	Level III Fair quality	South Korea Median follow-up: 4-6 months post treatment	N=16 Intervention: 8 patients (4 men, 4 women), mean age 73 (SD ± 7) years; Control: 8 patients (6 men, 2 women), mean age 71 (SD ± 9) years; Patients who received SABR for lung cancer within one institution were included (excluded if they had previous RT to thorax or showed locoregional recurrence during follow-up period) Patients matched 1:1 based on dose/fractionation, tumour size, tumour location and age	SBRT using the tri-^{60}Co MR-guided system called MRIdian™ (ViewRay Inc., Cleveland, United States) Patients were treated with either 52 or 60 Gy in four fractions	LINAC-based SABR The volumetric modulated arc therapy (VMAT) plans were delivered with a 6 MV flattening filter-free beam of Truebeam STxTM (Varian Medical Systems, Palo Alto, CA) after imaging with a kV cone-beam CT. Patients were treated with either 52 or 60 Gy in four fractions	Paired differences between lung density changes PTV Dosimetric outcomes	Lung density changes were determined based on the first and second follow-up CT scans. Post-treatment CT scans were overlaid on a planning CT scan at end-inspiration phase using deformable registration with MIMTM version 5.4 (MIM Software Inc., Cleveland, OH), and changes in the lung density (measured in HU) were assessed.

Alongi et al. (2020)	Prospective CS October 2019 - January 2020	Level IV Good quality	Italy Follow-up NR	N=25 Median age 68 years (range, 54-82) Localised prostate cancer	Unity Elekta MR-linac (Elekta Unity, Stockholm, Sweden) The SBRT schedule consisted of five daily fractions of 7 Gy (total prescription dose, Dp = 35 Gy within 2 weeks	NA	Toxicity QoL	The QLQ-C30 includes functional scales and single-item questions. All scales and single-item scores range from 0 to 100. A high functional scale score represents a healthy level of functioning; a high score for the global health status represents a high QoL, while a high score for a symptom scale, bowel score or urinary score represents a high level of symptomatology. The EORTC QLQ-PR25 is complementary to the general cancer EORTC QLQ30 questionnaire and is designed for PC patients. This questionnaire has 25 items examining urinary and bowel symptoms, sexual activity and function, and treatment-related symptoms, using a 4-point Likert response scale

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Chen et al. (2018)	Prospective Coh October 2014-October 2016	Level III Good quality	USA, Median follow-up: 18 months	N=18, Median age: 58 (range 15-76) years, 15 men, 3 women. Patients with newly-diagnosed head and neck cancer with biopsy-proven evidence of malignancy, measurable disease, and the ability to consent for treatment. No patient had evidence of distant metastasis	IMRT treatment with 0.35-T MRI scanner with a tri-source ^{60}Co therapy source (ViewRay system) Prescription dose 66-70 Gy (median 70 Gy) to PTV1 (2.0 or 2.12 Gy per fraction), and 60–63 Gy to the PTV2 (1.8 Gy per fraction per day), total fractions not reported	No comparator	Toxicity QoL 1-year PFS 1-year OS 1-year local–regional disease control	Response to treatment was determined using RECIST criteria. Acute and late normal tissue effects were graded according to the National Cancer Institute's CTCAE, UW-QOL version 4 instrument was administered at follow-up visits to evaluate patient-reported outcomes
Feldman et al. (2019)	Retrospective CS August 2017-October 2018	Level IV Poor quality	USA 2-3 months	N=29 Age NR 19 male, 10 females patients had one or more biopsy-proven primary or metastatic unresectable liver lesions.	SBRT using MRIdian Linac system (ViewRay, Oakwood Village, OH) Patients received 45 to 50 Gy prescribed to at least 95% of the PTV in five fractions except for two patients who received 27-30 Gy in three fractions.	NA	Toxicity	Toxicity information was obtained by reviewing radiation treatment completion notes and follow-up clinic visit notes.

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Finazzi, Haasbeek, et al. (2020)	Retrospective CS May 2016 – November 2018	Level IV Good quality	The Netherlands Median follow-up 21.7 months (95% CI, 19.9-28.1)	N=50 Median age 68.5 years (range, 34-86) Male 68% primary lung cancer (n=29); lung metastases (n=21) At high risk to experience toxicity due to central tumour location (n=30), previous thoracic RT (n=17), interstitial lung disease (n=7)	Gated SBRT was delivered during repeated breath-holds under continuous MR guidance. MRIdian (ViewRay Inc, USA) Cobalt-60 system for 34 treatments, a MRIdian MR Linac for 18 treatments, and both units in 2 patients Dose 54-60Gy in 3-12 fractions	NA	OS DFS LC Toxicity	Patients were followed for clinical outcomes and treatment related toxicities, with outcome information, including imaging studies, obtained from external institutions when necessary. Reported toxicities were verified by at least 2 radiation oncologists and scored using the CTCAE version 5.0.17 OS, DFS, and LC were estimated using the Kaplan-Meier method
Finazzi, van Sornsen de Koste, et al. (2020)	Prospective CS October 2017-November 2019	Level IV Fair quality	The Netherlands Median follow-up 5 months (range, 2-12 months)	N=10 Median age 73 years (range, 58-80 years) Patients with early-stage lung cancer	Single-fraction SBRT on the MRIdian MR-linac (ViewRay Inc., USA).	NA	Toxicity Local recurrence	Toxicities were scored by at least two radiation oncologists, and graded using the CTCAE version 5.0

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Henke et al. (2018)	Prospective CS NR	Level IV Good quality	USA Median follow-up: 15 months (range 4–22 mos)	N=20 Median age 64 (range 48-79) Patients with oligometastatic or unresectable primary liver or non-liver-abdominal malignancies who were considered technical and clinical candidates for SBRT	SBRT using the tri-^{60}Co MRI guided system called MRIdian™ (ViewRay Inc., Cleveland, United States) Prescribed dose for all plans was 50 Gy/5 fractions	NA	Toxicity QoL PFS OS	Treatment response assessed using RECIST Patient-reported QoL scores at zero, six, and 26 weeks post-treatment using EORTC QLQ-C30 Version 3.0. Survival outcomes were prospectively assessed at 12 and 26 weeks post-treatment and subsequently through chart review and routine clinical appointments. Acute toxicities were assessed prospectively by clinical research coordinators and late toxicities were assessed through routine care and chart review.

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Kluter et al. (2020)	Prospective CS April 2018-April 2019	Level IV Good quality	Germany Follow-up NR	N=43 Mean age 64 years (range 32-87) Male 58% Various cancer types	MRIdian Linac® system (ViewRay Inc.; Oakwood, USA), which combines a 0.35T MR scanner with a 6-MV linear accelerator with 20/43 patients treated with SBRT. Unclear how other 23 patients were treated. Mean dose 37Gy (range 4-66) Mean fractions: 9 (range 2-33)	NA	Patient reported outcomes Toxicity	Patient-reported acceptance of the whole treatment procedure was documented using an in-house developed patient- reported outcome questionnaire (PRO-Q) which was completed after the first fraction, weekly during the treatment, and after the last fraction. Items were scored using a five-point scale with higher score indicating more concern.
Rosenberg et al. (2019)	Prospective Coh 2014-2017	Level III Good quality	USA, Median follow-up: 21.2 months	N=26, Median age: 70 (range 30-90) years, 65% males, at 3 institutions, patients with HCC of liver or metastatic tumours to the liver for which surgery was not appropriate.	0.35-T MR-guided SBRT with a tri-source ^{60}Co therapy source, called MRIdian system Prescription dose to PTV: median 50 Gy (30-60), Median Dose per fraction: 10 (6-12), Median dose to liver: 12.7 Gy (3.2-21.9), total fractions not reported	No comparator	Toxicity Freedom from local progression Overall survival	Freedom from local progression and overall survival were analysed with Kaplan-Meier and a c2 test. Toxicity was determined using National Cancer Institute CTCAE Version 4 as a chart review with a focus on grade 3 or higher toxicity

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Rudra et al. (2019)	Retrospective Coh 2014-2016	Level III/IV Poor quality	USA, Multi-centre Median follow-up: 17 months	N= 44 (high dose, n= 24; standard dose, n=20) Median age 66 (range 47-85) 59.1% male, 40.9% female Patients with biopsy-proven, inoperable, pancreatic cancer	MR-IGRT (ViewRay MRIdian System, Oakwood Village, OH) with concurrent chemotherapy in all but two patients. Conventional fractionated (n=13): 40-55 Gy in 25-28 fractions; Conventional SBRT (n=6): 30-35 Gy in 5 fractions; High-dose SBRT (n=16): 40-52 Gy in 5 fractions; Hypo fractionated (n=9): 50-67.5 Gy in 10-15 fractions.	NA	Acute gastrointestinal toxicity	All time to endpoint calculations were performed from start date of RT. Acute GI toxicity was graded based on the Common Terminology Criteria for Adverse Events version 4 and recorded from start of RT until 6 weeks after completion of RT.

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
S. Tetar et al. (2018)	Prospective Coh, May 2016 to August 2017	Level III Good quality	The Netherlands, Median follow-up: 21.2 months	N=150, Median age 69 (35-92) years, 114 males (76%), majority prostatic tumour, exclude claustrophobic patients Patients with claustrophobia are excluded.	MRIdian® system (ViewRay, Inc., Mountain View, CA), which combines a split 0.35 Tesla (T) MR scanner with ^{60}Co therapy, provided with SMART delivery. Dose not reported. Most patients were treated using a five-fraction stereotactic scheme, except for several lung and liver lesions that received eight to 12 fractions.	No comparator	Patient reported outcomes related to the MRI guided radiotherapy procedure	Mean scores compared using ANOVA. Response from patients gathered using an in-house PRO-Q including questions on potential MR-related complaints and experiences,

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
S. U. Tetar et al. (2019)	Retrospective CS May 2016-June 2018	Level IV Poor quality	The Netherlands Follow-up NR	N=140 Age NR All patients treated with MR-IGRT for prostate cancer	SBRT using MR-IGRT initially with the tri-^{60}Co system (n=130), currently with the MR-Linac (n=10) Most patients were treated with 5 fractions of 7.25 Gy per fraction delivered on the prostate with a simultaneous integrated sparing (SIS) of the urethra with a dose of 32.5 Gy in 5 fractions (6.5 Gy per fraction). In some cases (n=10) with tumour near the urethra, the SBRT was delivered in fractions of 7 Gy up to a total dose of 35 Gy without urethral sparing.	NA	Patient reported experiences	An in-house developed PRO-Q. Included questions on potential MR-related complaints and experiences, such as anxiety, temperature, and noise. These items could be scored on a 4- point scale as: “not at all”, “a little”, “moderate”, and “very much”. PRO-Qs were collected once, immediately following the last MR-IGRT fraction, taking the completion of the PRO-Q on average 5 min.

van de Schoot et al. (2019)	Retrospective review	Level III-3 NA	The Netherlands Follow-up: NA	N= 16 (8 rectal and 8 prostate) who received radiotherapy on conventional CBCT-linac	MR-linac treatment plans were generated using Monaco 5.4 (Elekta AB, Stockholm, Sweden), a version of the Monaco TPS developed for MR-linac treatment planning. Target and OAR dose criteria, as well as margins, were identical to those for the clinical plans. All MR-linac plans were created using a 9-beam step-and shoot IMRT technique. MR-linac plan optimisation was started using a predefined set of objectives and objective values were individually optimized to achieve PTV coverage while minimizing OAR dose. MR-linac dose calculation was performed on a uniform 3mm dose grid with an overall 1% Monte Carlo statistical uncertainty.	Clinical treatment planning for a conventional linac was performed using Pinnacle3 9.10 (Philips, Best, the Netherlands). According to departmental protocols, clinical plans for both rectal cancer (25×2.0 Gy) and prostate cancer (19×3.4 Gy) used a VMAT delivery technique. Plan optimisation objectives were individually optimized in order to minimize OAR dose while maintaining PTV dose constraints. For rectal cancer patients, a single dose level treatment technique was used. Prostate cancer patients were treated using SIB with prescribed doses of 57.8 Gy and 64.6 Gy.	Dosimetric parameters	MR-linac plans were compared with clinical plans using dose-volume histogram (DVH) parameters. Since all plans were normalized to identical target coverage (V95%), the mean dose (Dmean) and the near maximum dose (D1%) of the PTV (rectum) or the PTV64.6Gy (prostate), were measures of the homogeneity of the dose distribution in the target. Dose to surrounding OARs was evaluated using criteria defined in local protocols. Integral dose differences were determined by calculating the mean dose to the patient (EXT Dmean). Given the applied plan normalisation, the Dmean and D1% of the patient excluding the 2.0 cm uniformly expanded PTV (EXT – PTV2cm) were determined to verify dose fall-off differences. For the prostate plans the normal tissue

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
								complication probability (NTCP) was calculated for grade 2 and higher late rectal bleeding toxicity using the QUANTEC-recommended Lyman-Kutcher-Burman model with parameters n=0.09, m=0.13, and TD50=76.9 Gy.

Authors Study ID Publication Year	Study design/ duration	Level of evidence[a] and risk of bias assessment[b]	Location Setting Length of follow-up	Study population characteristics	Description of Intervention	Description of Comparator	Relevant outcomes assessed (ie related to outcomes specified in PICO)	Measurement of outcomes and methods of analysis
Winkel et al. (2018)	Retrospective review	Level III-3 NA	The Netherlands Follow-up: NA	N= 17 pelvic and para-aortic pathological lymph nodes were included from five female patients with locally advanced cervical cancer	To simulate replanning in a full-online workflow for the MRIinac, one new fully optimized treatment plans was created for each lymph node using daily target and OAR definitions based on the simulated daily patient anatomy. The used beam angles for online replanning were equal to those in the pre-treatment plan. For these plans, a PTV margin of 3mm was applied, simulating the good visibility of lymph nodes on MRI. As the 1.5T MR-linac only allows for movement in superior–inferior direction, the isocenter is fixed in the center of the bore for the other directions. The isocenter position in the superior–inferior direction is set as close to center of the PTV as possible.	To simulate the daily anatomy, a MRI dataset obtained at least one week into treatment was used. The target and the OARs were manually contoured. Electron density information was considered by matching and deforming the initial planning CT to the MRI data. CBCT-based online correction was performed by matching using a 0.5 cm mask around the GTV or a clipbox with nearby structures for lymph nodes with good or poor visibility, respectively. The reference point of this correction is equal to the center of the PTV and placed the plan isocenter at the center of the PTV according to the daily anatomy.	Dosimetric parameters	All plans were generated with a prescribed dose of 57 Gy to 95% of the PTV using the Monaco treatment planning software (TPS) research version 5.19.03d by Elekta AB (Stockholm, Sweden). To eliminated differences in machine characteristics all plans were created with the 7MV FFF beam model of the Elekta MR-linac and the 1.5 T magnetic field in superior– inferior patient direction which is present when treatingpatients on the MR-linac.

Winkel et al. (2020)	Retrospective review Since August 2018	Level III-3 NA	The Netherlands Follow-up: NA	N= 20 patients with metastases in the pelvic and para-aortic region (n=14 single oligometastasis, n=6 2-3 metastases)	1.5T MR-linac with a prescribed dose of 5 x 7 Gy to 95% of the PTV. For each patient, a 6-, 7- or 10-beam MR-linac IMRT pre-treatment plan was created with a GTV-PTV margin of 3mm using Monaco TPS (Elekta AB, Stockholm, Sweden).	A CBCT-linac VMAT back-up plan was created for each patient. A PTV margin of 8 mm was used for poorly visible lymph nodes and 3 mm for visible lymph nodes. For patients with multiple lymph node oligometastases, the plans consisted of one, two or three PTV's. A medical physicist and radiation oncologist decided on one or two separate plans, placement of the isocenter, depending on the specific anatomical situation of the patient and PTV margins. OAR dose was lowered as much as possible, while maintaining a sufficient PTV coverage of V_{35Gy} > 95% and a D_{max} between 120–135%. Clinical dose criteria for the OARs were based on the UK SABR consortium guidelines (2016).	Dosimetric parameters	The differences in target coverage between the clinically delivered MR-linac and the CBCT-linac plans were compared for each treatment session. Additionally, the plans were evaluated based on the clinical dose criteria for the target coverage and OAR dose. The CBCT-linac plan was recalculated on the daily MRI and using the contours from the online treatment.

CBCT=cone-beam computed tomography; CI=confidence interval; Coh=cohort; CS=case series; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; DVH=dose volume histogram; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FFF=flattening filter free; GTV=gross tumour volume; Gy=Gray; HCC=hepatocellular carcinoma; HU=Hounsfield unit; IMRT=image-guided radiation therapy; LC=local control; LINAC=linear accelerator; MR=magnetic resonance; MRI=magnetic resonance imaging; MR-IGRT=magnetic resonance-guided radiation therapy; NA=not assessed; NR=not reported; OAR=organs at risk; OS=overall survival; PFS=progression-free survival; PRO-Q=patient reported outcomes questionnaire; PTV=planned target volume; QoL=quality of life; RECIST=Response Evaluation Criteria in Solid Tumours; RT=radiation therapy; SABR=stereotactic ablative radiotherapy; SBRT=stereotactic body radiation therapy; SD=standard deviation; SMART=stereotactic MR-guided adaptive radiation therapy; tri-^{60}Co=tri-^{60}Co magnetic-resonance image guided system; UW-QOL=University of Washington Quality of Life instrument; VMAT=volumetric modulated arc therapy

[a] source: see NHMRC hierarchy of evidence; [b] risk of bias as it relates to primary outcomes of the systematic review

APPENDIX D EVIDENCE PROFILE TABLES

Table 86 Evidence profile table for MR-IGRT

Outcome	No. of participants No of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (publication bias)
Toxicity	211 participants (1 matched cohort study and 7 case series) **Very low quality evidence**	Good quality - 2 studies Fair quality - 4 studies Poor quality - 2 studies **Some concern**	Magnitude of effect could not be determined in non-comparative studies. Grade ≥3 toxicities were reported in 2 studies **Serious concern**	Differences in populations, interventions, outcome measures and follow-up durations E. Kim et al. (2018) (comparative study) reported a surrogate outcome for toxicity **Serious concern**	Small numbers of patients evaluated in the studies **Serious concern**	Not suspected, the search for studies was comprehensive **No concern**
Patient tolerance	194 participants (2 case series)* **Very low quality evidence**	Fair quality - Kluter et al. (2020) Poor quality - S. Tetar et al. (2018) **Some concern**	Magnitude of effect could not be determined as studies were non-comparative In Kluter et al. (2020), 65% reported an MR-IGRT related complaint In S. Tetar et al. (2018), 80% reported an MR-IGRT related complaint **Serious concern**	Both studies included mixed cancer populations Differences in interventions, setting, outcome measures **Serious concern**	Small numbers of patients evaluated in the studies **Serious concern**	Not suspected, the search for studies was comprehensive **No concern**

Outcome	No. of participants No of studies and study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (publication bias)
Survival	114 participants (4 case series) **Very low quality evidence**	Good quality - Henke et al. (2018), Chen et al. (2018) Fair quality - Finazzi, Haasbeek, et al. (2020), Rosenberg et al. (2019) **Some concern**	Magnitude of effect could not be determined as studies were non-comparative **Serious concern**	Differences in populations (unresectable abdominal - Henke et al. (2018), lung - Finazzi, van Sornsen de Koste, et al. (2020), head and neck - Chen et al. (2018), liver - Rosenberg et al. (2019)), interventions, outcome measures and follow-up durations **Serious concern**	Small numbers of patients evaluated in the studies **Serious concern**	Not suspected, the search for studies was comprehensive **No concern**
Quality of life	63 participants (3 case series) **Very low quality evidence**	Good quality - Henke et al. (2018), Chen et al. (2018) Fair quality - Alongi et al. (2020) **No concern**	Magnitude of effect could not be determined as studies were non-comparative **Serious concern**	Henke et al. (2018) and Alongi et al. (2020) used the same questionnaire. Both reported no differences in QoL over the course of treatment. **Some concern**	Small numbers of patients evaluated in the studies **Serious concern**	Not suspected, the search for studies was comprehensive **No concern**
Dosimetric outcomes	37 participants (1 comparative cohort study, 2 planning studies) **Very low quality evidence**	Fair quality - E. Kim et al. (2018) **Some concern**	MR-IGRT plans had better or equivalent quality dosimetry variables **No concern**	Differences in populations, interventions, outcome measures **Some concern**	Small numbers of patients evaluated in the studies **Serious concern**	Not suspected, the search for studies was comprehensive **No concern**

MR-IGRT=magnetic resonance image guided radiation therapy; QoL=quality of life
*S. U. Tetar et al. (2019) and S. Tetar et al. (2018) likely included overlapping populations. S. Tetar et al. (2018) only included in the summary table

APPENDIX E EXCLUDED STUDIES

Study reference	Reason for study exclusion
Acharya, S., Fischer-Valuck, B. W., Kashani, R., Parikh, P., Yang, D., Zhao, T., . . . Olsen, J. (2016). Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications. Int J Radiat Oncol Biol Phys, 94(2), 394-403. doi:https://dx.doi.org/10.1016/j.ijrobp.2015.10.015	N=5, considered to be too small
Cuccia, F., Mazzola, R., Nicosia, L., Figlia, V., Giaj-Levra, N., Ricchetti, F., . . . Alongi, F. (2020). Impact of hydrogel peri-rectal spacer insertion on prostate gland intra-fraction motion during 1.5 T MR-guided stereotactic body radiotherapy. Radiation Oncology, 15(1). doi:http://dx.doi.org/10.1186/s13014-020-01622-3	Duplicate, study population included in Alongi et al. (2020)

REFERENCES

Alongi, F., Rigo, M., Figlia, V., Cuccia, F., et al. (2020). 1.5 T MR-guided and daily adapted SBRT for prostate cancer: Feasibility, preliminary clinical tolerability, quality of life and patient-reported outcomes during treatment. *Radiation Oncology, 15*(1).

Amendola, B., Amendola, M., Blanco, J. M., Perez, N., et al. (2017). Radiosurgery for liver metastases. A single institution experience. *Reports of Practical Oncology and Radiotherapy, 22*(2), 118-125.

Andratschke, N., Alheid, H., Allgauer, M., Becker, G., et al. (2018). The SBRT database initiative of the German Society for Radiation Oncology (DEGRO): patterns of care and outcome analysis of stereotactic body radiotherapy (SBRT) for liver oligometastases in 474 patients with 623 metastases. *BMC Cancer, 18*(1), 283.

Appel, S., Bar, J., Alezra, D., Ben-Ayun, M., et al. (2020). Image-guidance triggered adaptive replanning of radiation therapy for locally advanced lung cancer: an evaluation of cases requiring plan adaptation. *Br J Radiol, 93*(1105), 20190743.

Australian Institute of Health and Welfare (AIHW). (2019). Cancer in Australia 2019. Cat no. CAN 123. Retrieved from https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019

Australian Institute of Health and Welfare (AIHW). (2020a). Cancer data in Australia. Cat. no. CAN 122. *Cat. no. CAN 122.* Retrieved from https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation

Australian Institute of Health and Welfare (AIHW). (2020b). Radiotherapy in Australia 2018–19. Cat. no. HSE 248. Retrieved from https://www.aihw.gov.au/reports/radiotherapy/radiotherapy-in-australia-2018-19

Barney, B. M., Olivier, K. R., Macdonald, O. K., Fong de Los Santos, L. E., et al. (2012). Clinical outcomes and dosimetric considerations using stereotactic body radiotherapy for abdominopelvic tumors. *Am J Clin Oncol, 35*(6), 537-542.

Barton, M. B., Jacob, S., Shafiq, J., Wong, K., et al. (2014). Estimating the demand for radiotherapy from the evidence: a review of changes from 2003 to 2012. *Radiother Oncol, 112*(1), 140-144.

Baschnagel, A. M., Mangona, V. S., Robertson, J. M., Welsh, R. J., et al. (2013). Lung metastases treated with image-guided stereotactic body radiation therapy. *Clin Oncol (R Coll Radiol), 25*(4), 236-241.

Becker-Schiebe, M., Abaci, A., Ahmad, T., & Hoffmann, W. (2016). Reducing radiation-associated toxicity using online image guidance (IGRT) in prostate cancer patients undergoing dose-escalated radiation therapy. *Reports of Practical Oncology and Radiotherapy, 21*(3), 188-194.

Berlin, A., Cho, E., Kong, V., Howell, K. J., et al. (2015). Phase 2 trial of guideline-based postoperative image guided intensity modulated radiation therapy for prostate cancer: Toxicity, biochemical, and patient-reported health-related quality-of-life outcomes. *Pract Radiat Oncol, 5*(5), e473-e482.

Boda-Heggemann, J., Frauenfeld, A., Weiss, C., Simeonova, A., et al. (2014). Clinical outcome of hypofractionated breath-hold image-guided SABR of primary lung tumors and lung metastases. *Radiat, 9*, 10.

Byrne, K., Hruby, G., Kneebone, A., Whalley, D., et al. (2017). Late Genitourinary Toxicity Outcomes in 300 Prostate Cancer Patients Treated With Dose-escalated Image-guided Intensity-modulated Radiotherapy. *Clinical Oncology, 29*(9), 617-625.

Byun, S. J., Kim, Y. S., Ahn, H., & Kim, C. S. (2018). Image-guided, whole-pelvic, intensity-modulated radiotherapy for biochemical recurrence following radical prostatectomy in high-risk prostate cancer patients. *PLoS ONE, 13*(1), e0190479.

Callan, L., Bauman, G., Chen, J., Lock, M., et al. (2019). A Phase I/II Trial of Fairly Brief Androgen Suppression and Stereotactic Radiation Therapy for High-Risk Prostate Cancer (FASTR-2): Preliminary Results and Toxicity Analysis. *Advances in Radiation Oncology, 4*(4), 668-673.

Cancer Australia. (2020). Radiation Therapy. Retrieved from https://www.canceraustralia.gov.au/affected-cancer/treatment/radiation-therapy

Cancer Council Australia. (2019). Understanding Radiation Therapy- A guide for people with cancer, their familes and friends. Retrieved from https://www.cancercouncil.com.au/cancer-information/cancer-treatment/radiation-therapy/

Carter, H. E., Martin, A., Schofield, D., Duchesne, G., et al. (2014). A decision model to estimate the cost-effectiveness of intensity modulated radiation therapy (IMRT) compared to three dimensional conformal radiation therapy (3DCRT) in patients receiving radiotherapy to the prostate bed. *Radiotherapy and Oncology, 112*(2), 187-193.

Chan, K., & Bhandari, M. (2011). Three-minute critical appraisal of a case series article. *Indian J Orthop, 45*(2), 103-104.

Chen, A. M., Hsu, S., Lamb, J., Yang, Y., et al. (2018). MRI-guided radiotherapy for head and neck cancer: initial clinical experience. *Clin Transl Oncol, 20*(2), 160-168.

Chin, S., Eccles, C. L., McWilliam, A., Chuter, R., et al. (2020). Magnetic resonance-guided radiation therapy: A review. *J Med Imaging Radiat Oncol, 64*(1), 163-177.

Correa, R., Navarro, I., Lobato, M., Otero, A., et al. (2020). Influence of the technique and comorbidities in hypofractionated radiotherapy for prostate cancer. *Clinical and Translational Oncology, 22*(3), 311-318.

Duffton, A., Sadozye, A., Devlin, L., MacLeod, N., et al. (2018). Safety and feasibility of prostate stereotactic ablative radiotherapy using multimodality imaging and flattening filter free. *Br J Radiol, 91*(1084), 20170625.

Eldredge, H. B., Studenski, M., Keith, S. W., Trabulsi, E., et al. (2011). Post-prostatectomy image-guided radiation therapy: evaluation of toxicity and inter-fraction variation using online cone-beam CT. *J Med Imaging Radiat Oncol, 55*(5), 507-515.

Faria, S., Petrucelli, M., Cury, F., Duclos, M., et al. (2016). Acute and late toxicity in high-risk prostate cancer patients treated with androgen suppression and hypofractionated radiotherapy (HypoRT) to the prostate and pelvic nodes. *Radiotherapy and oncology, 120*.

Feldman, A. M., Modh, A., Glide-Hurst, C., Chetty, I. J., et al. (2019). Real-time Magnetic Resonance-guided Liver Stereotactic Body Radiation Therapy: An Institutional Report Using a Magnetic Resonance-Linac System. *Cureus, 11*(9), e5774.

Finazzi, T., Haasbeek, C. J. A., Spoelstra, F. O. B., Palacios, M. A., et al. (2020a). Clinical Outcomes of Stereotactic MR-Guided Adaptive Radiation Therapy for High-Risk Lung Tumors. *International Journal of Radiation Oncology Biology Physics, 107*(2), 270-278.

Finazzi, T., van Sornsen de Koste, J. R., Palacios, M. A., Spoelstra, F. O. B., et al. (2020b). Delivery of magnetic resonance-guided single-fraction stereotactic lung radiotherapy. *Physics and Imaging in Radiation Oncology, 14*, 17-23.

Frakulli, R., Salvi, F., Balestrini, D., Parisi, A., et al. (2015). Stereotactic radiotherapy in the treatment of lung metastases from bone and soft-tissue sarcomas. *Anticancer Research, 35*(10), 5581-5586.

Girelli, G., Franco, P., Sciacero, P., Cante, D., et al. (2015). Image-guided Intensity-modulated Radiotherapy for Prostate Cancer Employing Hypofractionation and Simultaneous Integrated Boost: Results of a Consecutive Case Series with Focus on Erectile Function. *Anticancer Res, 35*(7), 4177-4182.

Grills, I. S., Hope, A. J., Guckenberger, M., Kestin, L. L., et al. (2012). A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. *J Thorac Oncol, 7*(9), 1382-1393.

Guckenberger, M., Baier, K., Polat, B., Richter, A., et al. (2010a). Dose-response relationship for radiation-induced pneumonitis after pulmonary stereotactic body radiotherapy. *Radiother Oncol, 97*(1), 65-70.

Guckenberger, M., Lawrenz, I., & Flentje, M. (2014). Moderately hypofractionated radiotherapy for localized prostate cancer: long-term outcome using IMRT and volumetric IGRT. *Strahlenther Onkol, 190*(1), 48-53.

Guckenberger, M., Ok, S., Polat, B., Sweeney, R. A., et al. (2010b). Toxicity after intensity-modulated, image-guided radiotherapy for prostate cancer. *Strahlenther Onkol, 186*(10), 535-543.

Hall, W. A., Paulson, E. S., van der Heide, U. A., Fuller, C. D., et al. (2019). The transformation of radiation oncology using real-time magnetic resonance guidance: A review. *European Journal of Cancer, 122*, 42-52.

Henke, L., Kashani, R., Robinson, C., Curcuru, A., et al. (2018). Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen. *Radiother Oncol, 126*(3), 519-526.

Hopper, A. B., Sandhu, A. P. S., Parsons, J. K., Rose, B., et al. (2018). Salvage image guided radiation therapy to the prostate after cryotherapy failure. *Advances in Radiation Oncology, 3*(1), 52-56.

Ingrosso, G., Carosi, A., Cristino, D. D., Ponti, E., et al. (2018). Volumetric image-guided conformal radiotherapy for localized prostate cancer: Analysis of dosimetric and clinical factors affecting acute and late toxicity. *Reports of Practical Oncology and Radiotherapy, 23*(5), 315-321.

Ingrosso, G., Carosi, A., di Cristino, D., Ponti, E., et al. (2017). Volumetric image-guided highly conformal radiotherapy of the prostate bed: Toxicity analysis. *Reports of Practical Oncology and Radiotherapy, 22*(1), 64-70.

Ishii, K., Ogino, R., Hosokawa, Y., Fujioka, C., et al. (2016). Comparison of dosimetric parameters and acute toxicity after whole-pelvic vs prostate-only volumetric-modulated arc therapy with daily image guidance for prostate cancer. *Br J Radiol, 89*(1062), 20150930.

Keall, P., Nguyen, D. T., O'Brien, R., Hewson, E., et al. (2020). Real-Time Image Guided Ablative Prostate Cancer Radiation Therapy: Results From the TROG 15.01 SPARK Trial. *International Journal of Radiation Oncology Biology Physics, 107*(3), 530-538.

Kerkmeijer, L. G., Fuller, C. D., Verkooijen, H. M., Verheij, M., et al. (2016). The MRI-Linear Accelerator Consortium: Evidence-Based Clinical Introduction of an Innovation in Radiation Oncology Connecting Researchers, Methodology, Data Collection, Quality Assurance, and Technical Development. *Front Oncol, 6*, 215.

Kestin, L., Grills, I., Guckenberger, M., Belderbos, J., et al. (2014). Dose-response relationship with clinical outcome for lung stereotactic body radiotherapy (SBRT) delivered via online image guidance. *Radiotherapy and Oncology, 110*(3), 499-504.

Kilburn, J. M., Soike, M. H., Lucas, J. T., Ayala-Peacock, D., et al. (2016). Image guided radiation therapy may result in improved local control in locally advanced lung cancer patients. *Pract Radiat Oncol, 6*(3), e73-e80.

Kim, E., Wu, H. G., Park, J. M., Kim, J. I., et al. (2018). Lung density change after SABR: A comparative study between tri-Co-60 magnetic resonance-guided system and linear accelerator. *PLoS ONE, 13*(4), e0195196.

Kim, N., Kim, H. J., Won, J. Y., Kim, D. Y., et al. (2019). Retrospective analysis of stereotactic body radiation therapy efficacy over radiofrequency ablation for hepatocellular carcinoma. *Radiotherapy and Oncology, 131*, 81-87.

Kluter, S., Katayama, S., Spindeldreier, C. K., Koerber, S. A., et al. (2020). First prospective clinical evaluation of feasibility and patient acceptance of magnetic resonance-guided radiotherapy in Germany. *Strahlentherapie und Onkologie, 196*(8), 691-698.

Levin-Epstein, R., Qiao-Guan, G., Juarez, J. E., Shen, Z., et al. (2020). Clinical Assessment of Prostate Displacement and Planning Target Volume Margins for Stereotactic Body Radiotherapy of Prostate Cancer. *Frontiers in Oncology, 10 (no pagination)*.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ, 339*, b2700.

Mazzola, R., Fersino, S., Aiello, D., Gregucci, F., et al. (2018). Linac-based stereotactic body radiation therapy for unresectable locally advanced pancreatic cancer: risk-adapted dose prescription and image-guided delivery. *Strahlenther Onkol, 194*(9), 835-842.

Nakamura, K., Mizowaki, T., Inokuchi, H., Ikeda, I., et al. (2018). Decreased acute toxicities of intensity-modulated radiation therapy for localized prostate cancer with prostate-based versus bone-based image guidance. *Int J Clin Oncol, 23*(1), 158-164.

Naoi, Y., Yamada, K., Kurokawa, C., Kunogi, H., et al. (2019). Late rectal bleeding after volumetric-modulated arc therapy for localised prostatic cancer. *Journal of Radiotherapy in Practice, 18*(2), 165-168.

Nath, S. K., Sandhu, A. P., Rose, B. S., Simpson, D. R., et al. (2010). Toxicity analysis of postoperative image-guided intensity-modulated radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys, 78*(2), 435-441.

Navran, A., Heemsbergen, W., Janssen, T., Hamming-Vrieze, O., et al. (2019). The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT). *Radiother Oncol, 130*, 25-31.

Ost, P., De Gersem, W., De Potter, B., Fonteyne, V., et al. (2011). A comparison of the acute toxicity profile between two-dimensional and three-dimensional image-guided radiotherapy for postoperative prostate cancer. *Clin Oncol (R Coll Radiol), 23*(5), 344-349.

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.

Price, T. R., Perkins, S. M., Sandrasegaran, K., Henderson, M. A., et al. (2012). Evaluation of response after stereotactic body radiotherapy for hepatocellular carcinoma. *Cancer, 118*(12), 3191-3198.

Pryor, D., Sidhom, M., Arumugam, S., Bucci, J., et al. (2019). Phase 2 multicenter study of gantry-based stereotactic radiotherapy boost for intermediate and high risk prostate cancer (PROMETHEUS). *Frontiers in Oncology, 9*(APR).

Rosenberg, S. A., Henke, L. E., Shaverdian, N., Mittauer, K., et al. (2019). A Multi-Institutional Experience of MR-Guided Liver Stereotactic Body Radiation Therapy. *Adv Radiat Oncol, 4*(1), 142-149.

Rudra, S., Jiang, N., Rosenberg, S. A., Olsen, J. R., et al. (2019). Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med, 8*(5), 2123-2132.

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.

Shelan, M., Odermatt, S., Bojaxhiu, B., Nguyen, D. P., et al. (2019). Disease control with delayed salvage radiotherapy for macroscopic local recurrence following radical prostatectomy. *Frontiers in Oncology, 9*(FEB).

Shen, Y., Zhang, H., Wang, J., Zhong, R., et al. (2010). Hypofractionated radiotherapy for lung tumors with online cone beam CT guidance and active breathing control. *Radiat, 5*, 19.

Simpson, D. R., Einck, J. P., Nath, S. K., Sethi, R. A., et al. (2011). Comparison of daily cone-beam computed tomography and kilovoltage planar imaging for target localization in prostate cancer patients following radical prostatectomy. *Practical Radiation Oncology, 1*(3), 156-162.

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.

Stone, B., Mangona, V. S., Johnson, M. D., Ye, H., et al. (2015). Changes in Pulmonary Function Following Image-Guided Stereotactic Lung Radiotherapy: Neither Lower Baseline Nor Post-SBRT Pulmonary Function Are Associated with Worse Overall Survival. *Journal of Thoracic Oncology, 10*(12), 1762-1769.

Swamy, K., Narayanan, V. K. S., Basu, S., Maiya, V., et al. (2009). Dose escalation in image-guided, intensity-modulated radiotherapy of carcinoma prostate: Initial experience in India. *Journal of Cancer Research and Therapeutics, 5*(4), 277-283.

Tamihardja, J., Schortmann, M., Lawrenz, I., Weick, S., et al. (2020). Moderately hypofractionated radiotherapy for localized prostate cancer: updated long-term outcome and toxicity analysis. *Strahlentherapie und Onkologie.*

Tetar, S., Bruynzeel, A., Bakker, R., Jeulink, M., et al. (2018). Patient-reported Outcome Measurements on the Tolerance of Magnetic Resonance Imaging-guided Radiation Therapy. *Cureus, 10*(2), e2236.

Tetar, S. U., Bruynzeel, A. M. E., Lagerwaard, F. J., Slotman, B. J., et al. (2019). Clinical implementation of magnetic resonance imaging guided adaptive radiotherapy for localized prostate cancer. *Physics and Imaging in Radiation Oncology, 9*, 69-76.

Tondel, H., Lund, J., Lydersen, S., Wanderas, A. D., et al. (2018). Dose to penile bulb is not associated with erectile dysfunction 18months post radiotherapy: A secondary analysis of a randomized trial. *Clinical and Translational Radiation Oncology, 13*, 50-56.

Valakh, V., Gresswell, S., & Kirichenko, A. (2018). Outcomes of stereotactic body radiotherapy for hepatocellular carcinoma with severe cirrhosis and ineligibility for transplant. *Anticancer Research, 38*(12), 6815-6820.

Valeriani, M., Bonfili, P., Reverberi, C., Marinelli, L., et al. (2018). Moderate hypofractionation in patients with low-risk prostate cancer: Long-term outcomes. *Anticancer Research, 38*(3), 1671-1676.

Valeriani, M., Bracci, S., Osti, M. F., Falco, T., et al. (2013a). Intermediate-risk prostate cancer patients treated with androgen deprivation therapy and a hypofractionated radiation regimen with or without image guided radiotherapy. *Radiat, 8*, 137.

Valeriani, M., Carnevale, A., Osti, M. F., Minniti, G., et al. (2013b). Hypofractionated intensity-modulated simultaneous integrated boost and image-guided radiotherapy in the treatment of high-risk prostate cancer patients: a preliminary report on acute toxicity. *Tumori, 99*(4), 474-479.

van de Schoot, A. J. A. J., van den Wollenberg, W., Carbaat, C., de Ruiter, P., et al. (2019). Evaluation of plan quality in radiotherapy planning with an MR-linac. *Physics and Imaging in Radiation Oncology, 10*, 19-24.

Vargas, C. E., Alam, N. B., Terk, M., Niska, J. R., et al. (2019). Initial results of a randomized phase III trial of high dose image guided radiation with or without androgen deprivation therapy for intermediate-risk prostate cancer. *Cancer treatment and research communications, 19*.

Vassis, S., Noldeke, B., Christiansen, H., von Klot, C. A., et al. (2020). Moderately HRT vs. CRT for localized prostate cancer using image-guided VMAT with SIB: evaluation of acute and late toxicities. *Strahlentherapie und Onkologie, 196*(7), 598-607.

Voglhuber, T., Kessel, K. A., Oechsner, M., Vogel, M. M. E., et al. (2020). Single-institutional outcome-analysis of low-dose stereotactic body radiation therapy (SBRT) of adrenal gland metastases. *BMC Cancer, 20*(1).

Wang, W. G., Yan, D., Ye, H., Gustafson, G., et al. (2018). Outcomes and toxicity from a prospective study of moderately hypofractionated radiation therapy for prostate cancer. *Advances in Radiation Oncology, 3*(2), 163-169.

Wells, G., Shea, B., O'Connell, D., Peterson, j., et al. (2000). The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Non-Randomized Studies in Meta-Analysis. , .

Winkel, D., Bol, G. H., Werensteijn-Honingh, A. M., Intven, M. P. W., et al. (2020). Target coverage and dose criteria based evaluation of the first clinical 1.5T MR-linac SBRT treatments of lymph node oligometastases compared with conventional CBCT-linac treatment. *Radiother Oncol, 146*, 118-125.

Winkel, D., Kroon, P. S., Werensteijn-Honingh, A. M., Bol, G. H., et al. (2018). Simulated dosimetric impact of online replanning for stereotactic body radiation therapy of lymph node oligometastases on the 1.5T MR-linac. *Acta Oncol, 57*(12), 1705-1712.

Yegya-Raman, N., Kim, S., Deek, M. P., Li, D., et al. (2018). Daily Image Guidance With Cone Beam Computed Tomography May Reduce Radiation Pneumonitis in Unresectable Non-Small Cell Lung Cancer. *Int J Radiat Oncol Biol Phys, 101*(5), 1104-1112.