Australian Government

Department of Health

RATIFIED PICO

Application 1620:

Magnetic Resonance Image Guided Radiation Therapy

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

Component	Description
Patients	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	• Safety, including any potential risk of harm to patient ○ Acute and long-term side effects ○ Any adverse events arising from the procedure • Efficacy / effectiveness, including (but not limited to) patient-relevant 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 • Healthcare resources ○ Cost of intervention delivery, including additional physician and medical physicist time • Cost-minimisation analysis • Total Australian Government healthcare costs: ○ Total cost to the Medicare Benefits Schedule (MBS) ○ Total cost to the Pharmaceutical Benefits Scheme (PBS) ○ Total cost to other healthcare services.

POPULATION

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

The Australian Institute of Health and Welfare (AIHW) estimates that approximately 150,000 new cancer cases will be diagnosed in year 2020. Cancer is now the leading cause of death in Australia, and the risk of an individual being diagnosed with cancer by their 85th birthday will be 1 in 2 for both males and females. Although mainly affecting the older population, cancer remains the leading cause of premature death. Many patients live for a number of years with a diagnosis of cancer, potentially requiring ongoing intervention to support quality of life.

Radiation therapy is one of the main treatments for cancer and is an effective treatment 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. 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).

Most people receiving radiotherapy have treatment once a day but the number of treatments vary based on type and stage of the cancer and the size and location. In 2017–18, almost 67,800 courses of radiotherapy were delivered in Australia (Australian Institute of Health and Welfare).

PASC noted the applicant's estimate of 400–500 patient courses delivered in the first year, equating to <1% of the MBS services claimed for items 15275 and 15555 in the last financial year (913,801). However, PASC queried whether there may be an increase in the treated population, if the technology allows treatment for previously untreatable patients (see 'Intervention').

The Applicant advised, the number of previously untreated patients is likely to come from clinical sites with lower incidence and may initially increase the treatment population by <1%.

Rationale

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.

INTERVENTION

The goal of radiation therapy is to deliver sufficient radiation dose to the cancerous tissue to achieve local control while minimising the toxicity to normal surrounding tissue (organs at risk [OARs]). For this reason, radiotherapy treatment usually requires patients to undergo some form of imaging during treatment planning and delivery. These images are needed in order to determine the clinical target volumes (CTV) which in turn determine the planning target volumes (PTV). The CTV contains the gross tumour volume (GTV), i.e. what can be seen, palpated or imaged plus invisible tumour extensions. The PTV is a geometric concept designed to ensure that the radiotherapy dose is delivered to the CTV and includes the CTV and the appropriate margins. In some cases, it may be necessary to add a margin around an OAR to ensure that the organ cannot receive a higher-than-safe dose.

Tumours change shape, size, and their position relative to surrounding tissue over the course of treatment and during individual treatment sessions. This results in uncertainty about the location of tumour and normal tissue during treatment and necessitates increased PTV margins in order to ensure complete dosing of the tumour. Larger PTV margins increase the amount of normal tissue that is dosed, which causes more widespread or more severe toxicity that can lead to acute and long-term side effects and reduced quality of treatment outcomes. Advances in image-guided radiotherapy (RT) have allowed for dose escalation and more precise radiation treatment delivery.

Adaptive radiotherapy (ART) involves incorporation of patient-specific anatomical variations during radiation therapy, in order to feed back into the plan and allow dose-delivery optimisation during the treatment course (Hunt, Hansen, Oelfke, Nill, & Hafeez, 2018). ART can occur over three different timescales: (1) offline, between fractions; (2) online, immediately prior to a fraction; and (3) in real-time, during a fraction.

The proposed medical service is magnetic resonance (MR) image guided radiation therapy (MR-IGRT), also known as MR-linac. This technology combines an MR unit with a linear accelerator (linac), allowing real-time imaging of target volumes and organs at risk, before and during treatment delivery, with re-planning as necessary (Chin et al., 2020). *PASC confirmed the proposed intervention.*

In the *MSAC Public Summary Document for Application 1319 – Image-guided radiation therapy for cancer treatment delivery* (Medical Services Advisory Committee, 2015), MR imaging was identified as a further option for image guided radiation therapy (IGRT). The Applicant stated that the MR-IGRT procedure for every treatment fraction is similar to the standard procedure with conventional linacs: patient set-up, imaging, adaptation, treatment.

The key difference is that MR-IGRT introduces 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). Additional expected benefits of MR-IGRT include hypofractionated dose to the tumour, and an image can be obtained without an additional radiation dose, unlike standard IGRT.

According to a recently published literature review, two commercial MR-IGRT technologies are currently available, and two technologies are in development (Table 1). Only the Elekta Unity is approved for use in Australia (Australian Register of Therapeutic Goods [ARTG] number 307588). *PASC noted that there were more MR-linacs in development and a TGA approved MRIdian linac system (ARTG 319241). PASC advised that clarification of the TGA approved MRIdian lianc system (ARTG 319241) as a MR-linac technology capable of delivering MR-IGRT is advised.*

The technical nature of the ARTG319241 listing is not completely clear due to listing of the device as "Linac System - Stereotactic teletherapy radionuclide system", suggesting that it is a linac system and a "Stereotactic teletherapy radionuclide system" (i.e., a Co-60 unit), which do not co-exist in the same device.

Table 1 Types of MR-IGRT technologies currently available (adapted from Hall et al 2019)

Commercial name	Manufacturer	MRI field strength	Bore size	Beam strength	ARTG number
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	6 MV	NA
Aurora-RT system	MagnetTx, Edmonton, Alberta, Canada	0.6 T	60 cm	6 MV	NA

MV, megavolatage; Co-60, Cobalt-60; NA, not applicable; ARTG, Australian Register of Therapeutic Goods

The majority of published literature on MR-linacs relates to the ViewRay Co-60 device and is not necessarily translatable to linacs with different beam strengths (Chin et al., 2020). The Co-60 source in the ViewRay device has to be replaced at regular intervals as the radionucleotide decays. Both MRI-linacs approved for use by TGA have had FDA Device Recalls (for software problems):

- ViewRay MRIdian Linac: May 02, 2019; December 12, 2019;
- Elekta Unity: April 08, 2019; July 16, 2019.

PASC considered that the available MR-linac technologies are not interchangeable, and differ in MR field and beam strength. The differences in MRI field strength have implications for image resolution and acquisition times.

While the Applicant agreed with the PASC that the available MR-Linac technologies are not interchangeable, the Applicant noted that clinical IGRT intended through the utilisation of MR imaging to support IGRT workflow is similar. Therefore, the Applicant considered the clinical studies related to the MRIdian device should be accepted as evidence of support for the MR-Linac technology.

The Applicant estimated that, over the next three years, at least 10 MR-linac units will be in operation in Australia, with 400-500 patient courses delivered in the first year. Use of MR-IGRT is logistically challenging, as it requires significant co-operation amongst multidisciplinary teams (consisting of physicians, radiographers and physicists), mainly due to the diversity and complexity of tasks involved in treatment delivery (Chin et al., 2020). Typically, MR-IGRT takes approximately 30-45 minutes to perform, per treatment fraction.

The Application Form states that the cost per treatment fraction of providing MR-IGRT is expected to be higher than existing IGRT. This is due to equipment cost, imaging and treatment fraction times, and professional resources required. The MR-linac cost is approximately 3x higher than a conventional cone beam computed tomography (CBCT) Linac. Imaging and treatment fraction times are expected to be 2-3 times longer than those on a CBCT Linac, due to MR image acquisition, and time to adapt the treatment plan to the daily patient anatomy.

However, total treatment courses may require fewer fractions than those provided by a CBCT Linac. *PASC noted that the applicant in their response to the draft PICO highlighted that MR-IGRT also has the potential to expand case referrals that currently do not receive radiotherapy due to poor target visualisation – example Pancreatic Stereotactic Radiotherapy.*

PASC noted that uptake and utilisation of the intervention (MR-IGRT) is likely to be restricted in the short term due to the capital costs of establishing the technology.

PASC also noted the potential for the new technology to require additional training. Radiation therapists, radiation oncologists, medical physicists and others may not be routinely trained in the use of MRI-IGRT. An accreditation program may be required. PASC advised that these issues should be assessed in the submission.

The Applicant noted that MRI Simulation is a regular process in many clinical cases currently receiving radiation therapy, so the MRI training topic is in part already in place. The Applicant advised that the IGRT workflow on the MR-Linac is the component of training associated with this technology, much like IGRT with CBCT is covered in conventional Linac training. MR-IGRT training is part of all installation programs. As with CBCT-IGRT, individual providers will have required competencies for staff.

MR-linac workflows are still developing, and the professional resources (radiation oncologist; physicist; and radiation therapist) needed at treatment delivery may be higher, than with current conventional CBCT Linacs.

The Applicant stated that 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. The Applicant provided the current utilisation breakdown of MR-linac patient indications to date, along with 2015 cancer statistics for the Australian population (Table 2).

MRIGRT is currently not funded or reimbursed in Australia for any indication.

Table 2 Applicant-provided current utilisation breakdown of MR-linac patient indications to date

Indications	Utilisation of MR-linac	2015 Incidence in Australia	2015 Number of deaths Australia
Brain/GBM	1%	1,787	1,365
Breast	6%	17,004	2,924
Oesophagus	1%	1,469	1,312
Head&Neck	2%	3,697	1,121
Liver	8%	2,079	1,785
Pancreas	3%	3,307	2,911
Prostate	29%	18,878	3,159
Rectum	17%	5,120	2,527
Oligometastatic	22%		
Bone	6%	255	101
Nodal boosts	1%		
Lung	1%	11,788	8,416
Larynx	2%	638	212

COMPARATOR

The comparator is cone beam computed tomography (CBCT)-guided radiation therapy. Unlike MR-IGRT, CBCT can only be used preceding, not during, each daily treatment, and therefore does not allow optimal imaging of tumours and OAR, when tumour is surrounded by soft tissues (Kerkmeijer et al., 2016).

PASC confirmed the proposed comparator.

The Applicant proposed that MR-IGRT is expected to be used as a replacement to current practice. 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. The Application Form states that MR-linac will introduce a clinical choice for tumour sites, which demonstrates the benefit of reduced target volume margins and hypofractionated (shorter) courses.

The Applicant advised that the application is specifically for use of the IGRT MBS Item with MR-Linac devices, with MRI being the imaging for IGRT.

Rationale

Currently, IGRT can be performed using many systems and techniques, including ultrasound, magnetic resonance imaging (MRI), radiographic and fluoroscopic imaging and CT guided systems. The type of system used depends on resources in departments, and accuracy of the type of treatments to be delivered. However, CBCT is generally understood to be the current standard of care for IGRT, for most cancer types (Srinivasan, Mohammadi, & Shepherd, 2014).

OUTCOMES

The Applicant provided a list of four relevant ongoing studies, two feasibility studies and two prospective observational studies. One of these is a multi-institutional international observational cohort study, aiming to collect technical and clinical patient data in cancer patients receiving treatment and/or imaging on an MR-linac.

- Safety, including any potential risk of harm to patient
    - Acute and long-term side effects
    - Any adverse events arising from the procedure
- Efficacy / effectiveness, including (but not limited to) patient-relevant outcomes
    - Alteration of 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
- Healthcare resources
    - Cost of intervention delivery, including additional physician and medical physicist time

- Cost-effectiveness:
    - Cost per life-year gained
    - Cost per quality-adjusted life year (QALY) gained
- Total Australian Government healthcare costs:
    - Total cost to the Medicare Benefits Schedule (MBS)
    - Total cost to the Pharmaceutical Benefits Scheme (PBS)
    - Total cost to other healthcare services.

PASC noted that the majority of the proposed safety and effectiveness outcomes are patient-relevant outcomes, but due to the level of evidence provided in the application, queried whether other technical measurements should be included (such as dosimetry outcomes [e.g. dose to tumour]) when the patient relevant outcomes were not available. PASC recommended that the applicant seek expert advice on this.

The Applicant advised that there is already an ARPANSA ACDS process covering MR-Linac systems in Australia. The ACDS is the dosimetry accreditation provider in Australia and already has a program which the Applicant strongly supports. Level 1b and III Audits have been completed successfully in Townsville before the first patient treatment[1] and are being completed (June 2nd-3rd 2020) for the Sydney system. The Applicant emphasised that MRI is an imaging capability which has been in use for many years with proven safety and clinical effectiveness and that training for MR-Linacs aligns with the existing MR safety and clinical use training in place for dedicated MRI devices. MR-IGRT also enables imaging with no radiation dose to the patient. The Applicant considered the Viewray MRIdian clinical papers submitted on Prostate, Liver, Lung, Pancreas, Breast, Oligomets in the Public Consultation also support the clinical use of MR-Linac technologies.

CURRENT AND PROPOSED CLINICAL MANAGEMENT ALGORITHMS

Current clinical management algorithm for identified population

The current clinical management pathway provided in the Application Form was taken from earlier Application 1319, publicly available on MSAC's website (Medical Services Advisory Committee, 2015).

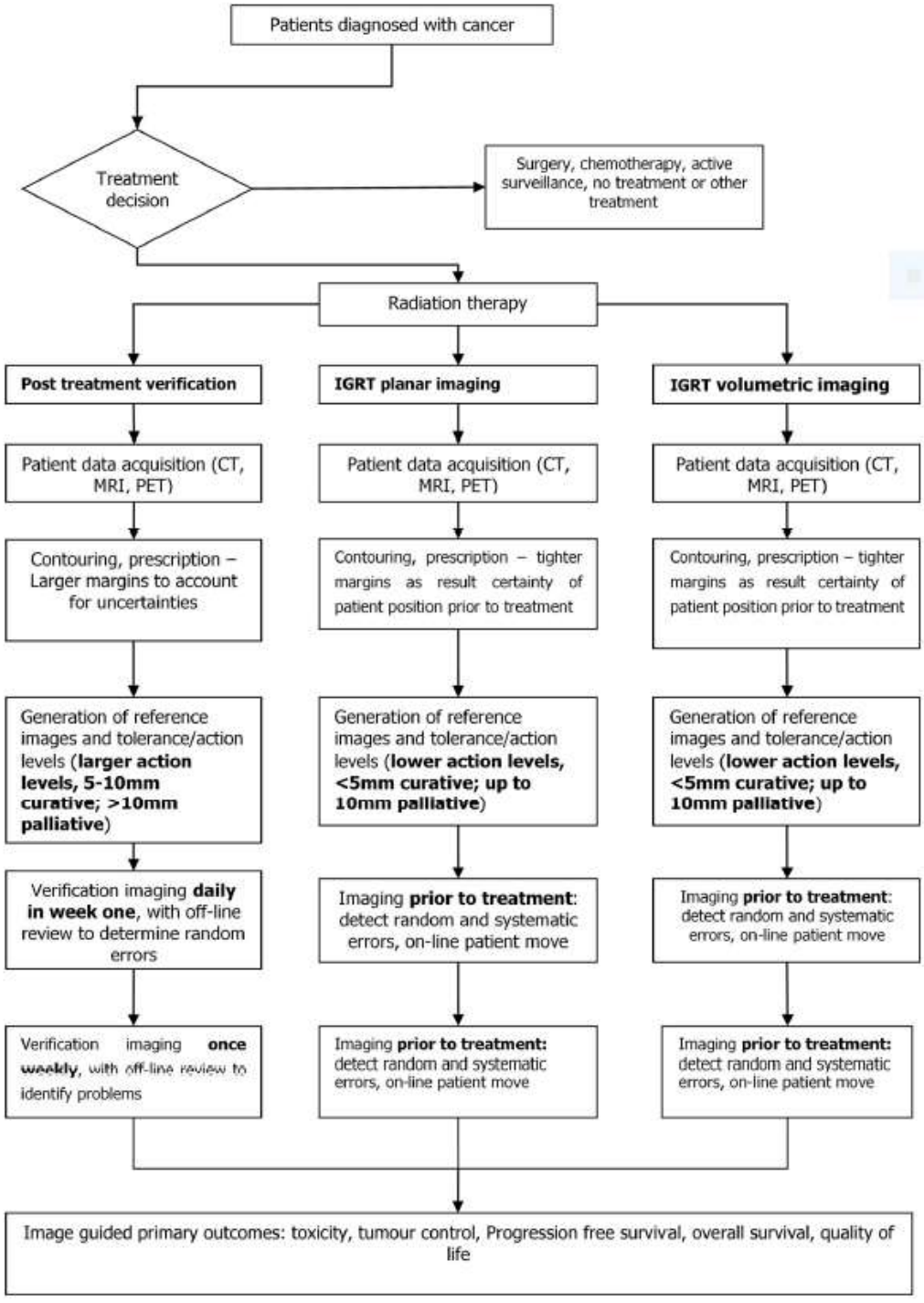
Proposed clinical management algorithm for identified population

The Applicant sought modification to the way service is clinically delivered under the existing MBS item. The premise is that the current clinical management algorithm (below) would remain unchanged, given MR-IGRT is a form of IGRT.

PASC noted that changes in prior imaging or marker procedures were not well captured in the algorithm. Also, the proposed clinical management algorithm does include imaging during treatment, which is a proposed benefit of the intervention. PASC advised this should be rectified in the final PICO. The clinical management algorithms below (Figure 1 and Figure 2) have been updated by the Applicant to reflect PASC's advice.

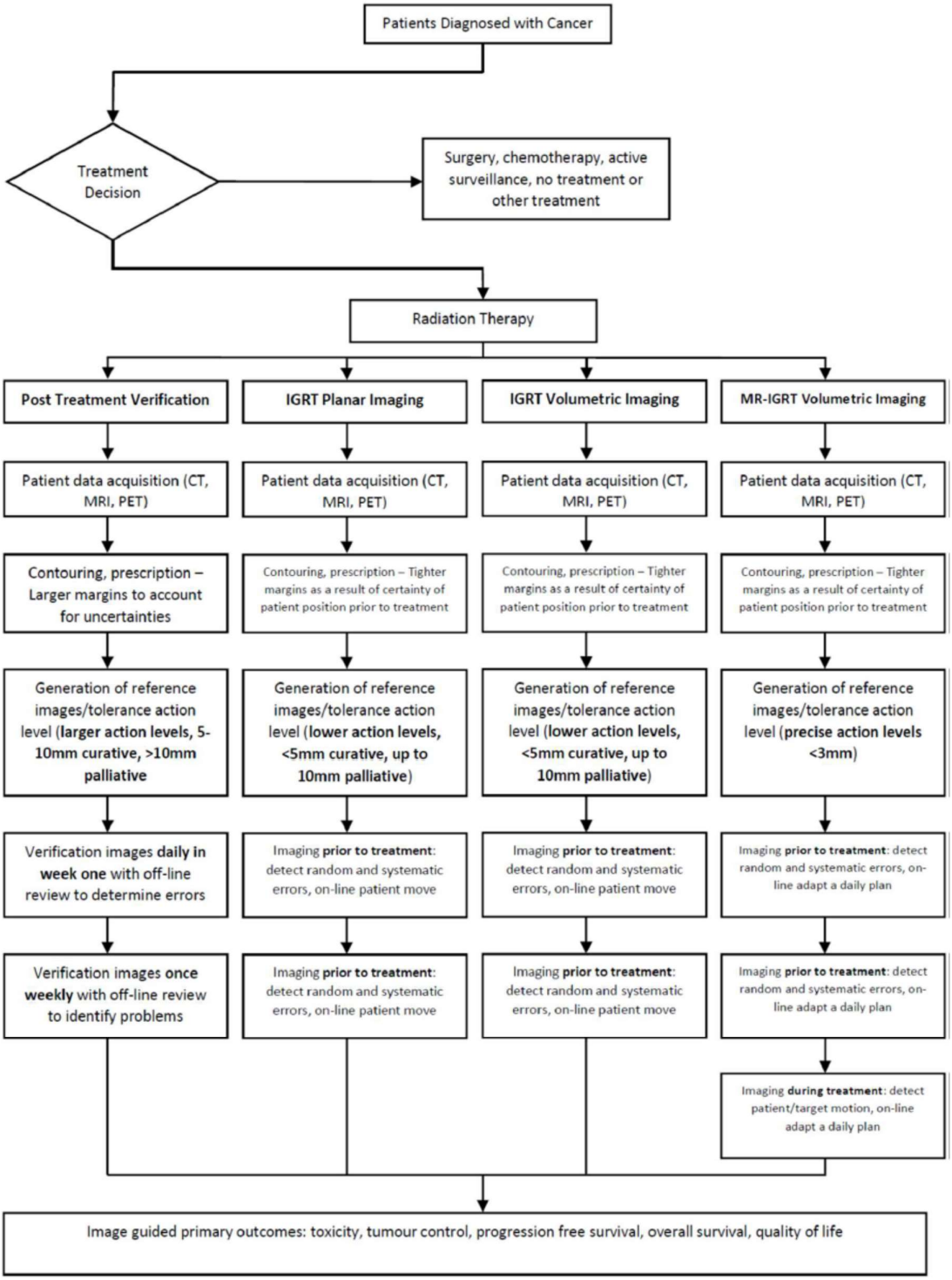
[1] *https://www.arpansa.gov.au/news/arpansadevelops-audit-new-mri-linac*

Figure 1: Current clinical management pathway for cancer patients receiving radiation therapy



Source: Applicant's comment to PASC Outcomes

Figure 2: Proposed clinical management pathway for cancer patients receiving radiation therapy



Source: Applicant's comment to PASC Outcomes

Proposed economic evaluation

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. According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Therapeutic,* the required economic analysis is therefore a cost-minimisation analysis against the comparator (CBCT guided radiation therapy).

PASC confirmed that a cost-minimisation analysis (CMA) was appropriate.

PASC queried if the comparator would be a complete substitution, or would there be any changes in healthcare resource use. PASC noted the applicant's advice indicating there would be a reduction in fiducial marker procedures, increased case referral and changes in treatment schedule with MR-IGRT compared with CBCT.

PASC advised that the evaluation should be clear on whether the intervention is budget neutral.

PASC noted that the distribution of costs between the intervention and comparator should be evaluated, including capital costs, and resource costs (including procedural time). PASC queried if there would be a net impact to out-of-pocket costs and Extended Medicare Safety Net costs, although noted these are not always included in economic modelling.

PASC noted that changes in the treatment schedule (such as increased hypofractionation or facilitation of dose escalation) and adverse event profile may need to be modelled to assess the risk–benefit trade-offs.

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.

Proposed MBS item descriptor and MBS fee

The Applicant requested an amendment to the way the service is clinically delivered under existing MBS item 15275. Item 15275 is billed with item 15555 SIMULATION FOR INTENSITY-MODULATED RADIATION THERAPY (IMRT), as well as item 15565 Preparation of an IMRT DOSIMETRY PLAN. The Applicant claimed that Simulation and Dosimetry workflows and processes will be consistent with current practice, if implemented with MR-IGRT.

MBS item 15275:

Category 3 - THERAPEUTIC PROCEDURES
RADIATION ONCOLOGY TREATMENT with IGRT imaging facilities undertaken: (a) to implement an IMRT dosimetry plan prepared in accordance with item 15565; and (b) utilising an intensity modulated treatment delivery mode (delivered by a fixed or dynamic gantry linear accelerator or by a helical non C-arm based linear accelerator), once only at each attendance at which treatment is given. **MBS Fee: $185.85 Benefit: 75% = $139.40 85% = $158.00**

MBS item 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: $721.90 Benefit: 75% = $541.45 85% = $637.20**

MBS item 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 gantryposition (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: $3,366.85 Benefit: 75% = $2,525.15 85% = $3,282.15**

PASC confirmed that the proposed existing MBS items and fees were appropriate, noting the item was technologically agnostic.

Consultation feedback

PASC noted the consultation feedback received, which was supportive of the application. PASC also noted that the consultation feedback discussed the advantages of proposed service included fewer adverse events, shorter radiotherapy courses and reduced procedures for markers, and disadvantages include access to the proposed service.

The Applicant noted that peak professional body letters of support from RANZCR, ASMIRT and ACPSEM were presented with the application. Further, the Applicant noted the Elekta MR-linac Whitepaper covers the advantages of MR-IGRT.

Next steps

PASC advised that, upon ratification of the post-PASC PICO, the application can proceed to the Evaluation Sub-Committee (ESC) stage of the MSAC process.

The Applicant elected to progress the application as a Department Contracted Assessment Report (DCAR).

References

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