Australian Government

Department of Health

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Application 1372.1

MRI of liver for patients with colorectal carcinoma (CRC) with suspected hepatic metastases or patients with suspected hepatocellular carcinoma (HCC) for the purposes of staging

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Version Control

Document History

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0.1	10 March 2016	MSAC Reforms	Final for Publication
0.2	19 May 2016	MSAC WEB	Accessibility compliance

Document Approval

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1.0	19 May 2016	MSAC Web	Document released for Online publication

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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	**Patient group 1- CRC** Patients with known colorectal carcinoma (CRC) with suspected or possible liver malignancy, on the basis of confirmed histology or liver lesion as defined on previous CT, who require magnetic resonance imaging (MRI) of the liver for characterisation and intervention planning.
Prior tests (for investigative medical services only)	Liver function tests, ultrasounds and computer tomography (CT) scans. These would not be any different in the absence or presence of the proposed MRI imaging service. Eligibility for MRI would require histology confirmation or evidence of liver lesion defined on previous CT.
Intervention	The intervention is contrast enhanced MRI of the liver.
Comparator	The most relevant comparators in the Australian setting are multiphase CT scan and biopsy. It is possible that contrast enhanced MRI will replace some of these services.
Outcomes	***Safety outcomes*** Adverse reaction to contrast agent Cumulative effects of multiple contrast agent injections Claustrophobia requiring the administration of sedation or general anaesthetic Physical harms from follow-up testing Other adverse events arising from liver MRI ***Clinical effectiveness outcomes*** *Accuracy* • Sensitivity, specificity (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory uninterpretable test results *Change in management (Therapeutic efficacy)* • Avoidance of unnecessary surgery due to resection of benign tumour (noted by expert advice as being a rare outcome) and, • Avoidance of incomplete surgical intervention due to unidentified tumours, suitable for resection, being retained resulting in repeat surgery and, • Avoidance of incorrectly assessed disease stage leading to modification and/or cancellation of surgical intervention.

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Component	Description
	• Avoidance of liver biopsy • Avoidance of follow-up multi-phase CT imaging *Health outcomes* (in the absence of direct evidence on health outcomes, linked evidence approach to assess the indirect impact of MRI on health outcomes will be attempted as per Investigative Guidelines) • Liver disease-specific mortality rate • Overall Survival • Time to initial diagnosis • Time from diagnosis to treatment • Quality of life scores

Component	Description
Patients	**Patient group 2- HCC** Patients with suspected hepatocellular carcinoma (HCC) who require MRI of liver for diagnosis and staging purposes, where: - the patient has a pre-existing chronic liver disease as confirmed by a specialist; and - has an identifiable hepatic lesion over 10mm; and - Child-Pugh class A or B.
Prior tests (for investigative medical services only)	Liver function tests and ultrasounds. Confirmation of pre-existing chronic liver disease. CT scans may or may not be required. These would not be any different in the absence or presence of the proposed MRI imaging service.
Intervention	The intervention is contrast enhanced MRI of the liver.
Comparator	The most relevant comparators in the Australian setting are multiphase CT scan and biopsy. It is possible that contrast enhanced MRI will replace some of these services.
Outcomes	***Safety outcomes*** Adverse reaction to contrast agent Cumulative effects of multiple contrast agent injections Claustrophobia requiring the administration of sedation or general anaesthetic Physical harms from follow-up testing Other adverse events arising from liver MRI

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Component	Description
	<u>Clinical effectiveness outcomes</u> *Accuracy* • Sensitivity, specificity (confirmed by reference standard) • Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard) • ROC curves • Unsatisfactory uninterpretable test results *Change in management (Therapeutic efficacy)* • Avoidance of unnecessary surgery due to resection of benign tumour (noted by expert advice as being a rare outcome) and, • Avoidance of incomplete surgical intervention due to unidentified tumours, suitable for resection, being retained resulting in repeat surgery and, • Avoidance of incorrectly assessed disease stage leading to modification and/or cancellation of surgical intervention. • Avoidance of liver biopsy • Avoidance of follow-up multi-phase CT imaging *Health outcomes* (in the absence of direct evidence on health outcomes, linked evidence approach to assess the indirect impact of MRI on health outcomes will be attempted as per Investigative Guidelines) • Liver disease-specific mortality rate • Overall Survival • Time to initial diagnosis • Time from diagnosis to treatment • Quality of life scores

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PICO or PPICO rationale for therapeutic and investigative medical services only

Population

Two specific populations of patients have been identified to be most suited for the proposed medical service. The two patient groups are:

1. Patients with known colorectal carcinoma (CRC) with suspected or possible liver malignancy, on the basis of confirmed histology or liver lesion as defined on previous CT, who require MRI of the liver for characterisation and intervention planning
2. Patients with suspected hepatocellular carcinoma (HCC) who require MRI of liver for diagnosis and staging purposes, where:
    - the patient has a pre-existing chronic liver disease as confirmed by a specialist; and
    - has an identifiable hepatic lesion over 10mm; and
    - Child-Pugh class A or B.

This application is a resubmission following MSAC's decision to not support public funding of Application 1372 based on uncertainty surrounding clinical effectiveness and cost-effectiveness due to the lack of robust evidence for change in clinical management and translation to improved patient outcomes. The population deemed eligible for the proposed medical service in the current application has narrowed in scope following MSAC's recommendation (Public Summary Document – Application No. 1372). This was in part driven by the availability of data for these populations.

Patients with suspected HCC (patient group 2) were also required to meet the three criteria listed above to be eligible for the proposed medical service. Hepatic lesions greater than 10mm are likely to be malignant and those smaller are usually benign (Oliva et al, 2004; Assy et al, 2009) therefore this aids in narrowing the patient population to those most likely to benefit from using the service. The Child-Pugh classification is a measure of liver functionality and is one of the main prognostic factors related to tumour status. Patients with Child-Pugh class A or B are typically within the early to intermediate stages of HCC where curative treatments remain viable options for the patients while class C patients are usually those not able to be treated with a curative intent (Llovet et al, 2008). As such the proposed criteria appear to adequately capture those patients who are most likely to benefit most from the proposed service and narrow enough to discourage use by populations not targeted for this service.

Colorectal cancer is the second most commonly diagnosed cancer among Australians. In 2017, the estimated number of cases of colorectal cancer diagnosed was 16,682 (9,127 in males and 7,555 in females) with an age-standardised rate of 67.3 (males) and 49.4 (females) per 1000,000 population in 2017. The five-year relative survival for those diagnosed is around 68%, which has increased by about 18% over the last three decades (AIHW, 2017). The liver is often found to be the first site of metastatic disease and in about 20-30% of patients with metastatic colorectal carcinoma the cancer is confined to the liver and may be potentially resectable (Garden et al, 2006).

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Hepatocellular carcinoma is also among the most prevalent cancer in Australia, affecting more men (1,589 cases) than women (527 cases) as estimated in 2017. The age standardised rate is 11.7 and 3.5 per 100,000 population in males and females respectively. Since 1982, there has been a marked increase in the age-standardised incidence of liver cancer from 1.8 to 7.5 per 100,000 population. Although the survival rates have improved over the years, patients with hepatocellular carcinoma experience one of the lowest rates of 5-year survival (17.3%) (AIHW, 2017).

Rationale

Liver lesion characterisation is an important process which differentiates benign hepatic tumours such as cysts from potential malignant tumours. In patients with CRC, the liver has been shown to be the most common site for metastasis occurring in up to 60% of cases (Ismaili, 2011). As such, in these patients where liver metastasis is common, the ability to characterise the lesion to exclude or confirm the presence of hepatic metastasis plays an important role in assisting the clinician or surgeon in determining the next course of action and also in defining the prognosis.

Liver staging examinations are usually performed in patients with known hepatic malignancy such as HCC when liver resection is being considered. The accuracy in determining the number and exact location of each liver metastases is important in determining potential treatment schedules and particularly so for patients where surgical options remain viable (Oliva et al, 2004).

MRI of the liver for characterisation and staging purposes has been shown to be more sensitive than other existing modalities currently being used which in turn can aid decision making in terms of determining a patient management pathway. Additionally, in both these patient populations, surgical resection is considered to be the preferred option with curative intent and is associated with improvements to the 5-year overall survival rate (Llovet et al, 2008). MRI can play a role in pre-operative imaging to produce accurate surgical plans hence minimising deviations from the plan during surgery for which there appears to be some evidence available.

The current management pathway for patient group 1 or 2 involves liver function tests and a series of diagnostic scans using computer tomography (CT) or ultrasound (US) where liver metastasis is suspected and further characterisation or staging is required to confirm diagnosis and determine the course of treatment. The use of MRI is proposed for patient group 1 where evidence of suspected or possible liver malignancy is available via confirmed histology or liver lesion as defined on previous CT scan. In patient population 2 MRI is used where patient has been identified to have a lesion over 10mm and Child-Pugh class A or B and that initial scans show indeterminate pathology and meaning further scans would usually be required. In both these cases, it is likely that the referral for subsequent scans is requested by a specialist (hepatologists, hepatobiliary surgeons or other relevant specialists). However it is noted that for rural and regional access, this restriction may need to include general surgeons or physicians. A more complete description of the management pathway can be found in the Clinical management algorithm section of this report (Figures 2 and 3).

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Prior test (investigative services only - if prior tests are to be included)

As described above, MRI is only indicated following an initial test or testing (imaging or liver function test) which raises suspicions of liver malignancy. As such, prior tests would typically include CT scans and/or US and this would be not be any different in the presence or absence of the proposed MRI medical service. Prior tests under 'current clinical management' for both patient groups 1 and 2 are shown in Figures 2 and 3 respectively.

Prior tests for patient group 1, patients with known CRC with suspected or possible liver metastases, would include liver function tests, CT and US. These tests are conducted to assist in identifying or ruling out the presence of a solid lesion. Eligibility for MRI would require histology confirmation or evidence of liver lesion defined on previous CT.

For patient group 2, patients with HCC with identified lesion over 10mm and having Child-Pugh class A or B liver function will undergo an US scan as the first stage of imaging to determine subsequent treatment options. A prior CT scan may not be required in this population. Eligibility for MRI would also require confirmation of pre-existing chronic liver disease by a specialist.

Intervention

The intervention is contrast enhanced MRI of the liver. No changes to the intervention are proposed from the previous application (1372).

MRI utilises strong, uniform magnetic fields to investigate the anatomy, perfusion, tissue characterisation and function of different organs and systems within the human body. MRI due to its mode of action is particularly useful for imaging soft tissues with a high concentration of water. During the examination patients are required to lie in either a prone or supine position within the MRI machine, with as little movement as possible.

MRI is currently approved for public funding under Medicare for a number of indications under the group I5. The following are just a selection of examples: investigation of unexplained seizures (Item 63551), suspected acute meniscal knee tear or anterior cruciate ligament knee tear (Item 63560), septic arthritis of hip (Item 63517), suspected wrist or scaphoid fracture (Items 63522, 63523), or cervical spine trauma (Item 63557). There are some existing funded indications for cancer diagnosis (such as breast cancer Item 63457) and for staging of rectal (Item 63476) and cervical (Item 63470) cancers. There are no Medicare funded current indications for use of MRI of the liver. There are a number of different arrangements for current MRI items regarding the number of times they can be claimed including: no restrictions, once per year, twice per year, three times per year, and once per lifetime. The use of MRI for detection and staging of cancer are often restricted to 'once only' or 'once per year' restrictions. It may be appropriate to consider whether similar restrictions on number of MRIs per period may be appropriate for liver MRI. It is acknowledged that a minority of patients may need follow up when there is a time delay between MRI scan and surgery or to follow up a carcinoma that can only be seen on MRI.

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Currently funded MRI items include restrictions on who can request, who supervises and eligible equipment. All currently funded items are required to be performed under the professional supervision of an eligible provider with eligible equipment and partial eligible equipment. In addition the request of an MRI for most items is by a specialist or consultant physician although some items are available on request by a medical practitioner. For the current proposal for a new item for known colorectal carcinoma and suspected hepatocellular carcinoma it may be appropriate to restrict to referral to a specialists such as hepatologists, hepatobiliary surgeons or other relevant specialists (to minimise limitations for rural or regional access).

Since its introduction to the Medicare Benefits Schedule (MBS), MRI has been managed with careful consideration of requester, provider and item level needs. These needs continue to direct the provision of high quality, safe and cost-effective health care in Australia. The MRI machine is required to meet specific specifications outlined by the Department of Health in order to be used to provide Medicare funded services and the Department maintains a list of Medicare eligible units at list of Medicare eligible units [Accessed 3rd March, 2017]. Conventional MRI is available in private and public facilities across Australia. There were a total of 349 (171 full and 178 partial) Medicare-eligible MRI units in Australia in July 2015 (Assessment Report 1372) that provide services eligible for funding under the MBS.

Current legislative requirements stipulate that Medicare-eligible MRI items must be reported on by a trained and credentialed specialist in diagnostic radiology. The specialist radiologist must be able to satisfy the Chief Executive Medicare that they are a participant in the Royal Australian and New Zealand College of Radiologist's (RANZCR) Quality and Accreditation Program (Health Insurance Regulation 2013 – 2.5.4 – Eligible Providers).

The liver requires use of hepatobiliary extracellular contrast agents for MRI which are selectively absorbed by liver cells. This allows for differentiation of normal liver cells. There are a range of intracellular and extracellular contrast agents available. Those listed with TGA for use in Australia are gadoxetic acid and gadobenate dimeglumine. The two differ in hepatic uptake and therefore the delay in time from delivering contrast agent to taking images. For gadoxetic acid liver cells absorb 50% with a time of 20 minutes wait to take images whereas for gadobenate dimeglumine liver cells absorb 3-5% with a delay of 90 minutes to take images. Hepatobilliary extracellular contrast for MRI is expected to be used for the majority of patients except where contraindicated.

Patients undergoing MRI are not exposed to ionising radiation. Contraindications for liver MRI do not differ from the standard contraindications for MRI which include ferromagnetic implants, electrically or mechanically activated devices (such as pacemakers and infusion pumps), and implanted electrical conductors. There may be some risks associated with contrast agents particularly for groups such as pregnant women (MRI agents relatively contraindicated) and those with severe renal disease (MRI agents contraindicated). Other considerations include patients with claustrophobia, intellectual disability or children aged < 6 years (not relevant for current application) who may not be able to lie still for duration of scan. In these cases MRI with sedation or general anaesthesia may be appropriate.

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Rationale

MRI for investigation of the liver is not currently funded by Medicare. Using hepatobiliary specific contrast agent with MRI for investigation of suspected or possible liver metastases or staging of known liver lesions will allow for differentiation of normal liver cells and, for example, metastases of non-hepatocellular origin which will appear as regions of hypo intensity. Regions of hyper and hypo vascularity are also able to be detected. Information from MRI is likely to directly inform diagnoses and/or treatment pathways.

Comparator

Histology is the reference used in tissue studies (liver biopsy or resection). The availability of data (biopsy vs explant) should be taken into account when assessing the most appropriate comparator. However a range of additional imaging tests are also available for liver lesions:

- multiphase computed tomography (CT) scan
- contrast-enhanced ultrasound (CE-US)
- intraoperative ultrasound (IOUS)
- sulphur colloid scans (for FNH)
- heat-damaged red cell scans (for haemangioma).

Previous advice from PASC indicated that CT portography and positron emission tomography (PET) scans are not appropriate comparators, and are rarely used in Australia for this population. Additional CE-US scan (MBS items 55014 or 55016) is uncommonly used in Australia.

For the majority of patients a MRI scan would most commonly be used as a replacement for:

- multiphase CT scan (MBS items 61352 or 61664) *for patients with known colorectal carcinoma (CRC) with suspected or possible liver malignancy and patients with suspected hepatocellular carcinoma (HCC)*
- biopsy (MBS item 30409) *for patients with known colorectal carcinoma (CRC) with suspected or possible liver malignancy*

MRI is expected to be used in the clinical management algorithm as was indicated in Figures 2 and 3.

CT uses a series of x-rays that are compiled to produce a detailed cross sectional image of a patient's anatomy. CT of the liver is useful for detecting and characterising lesions by providing information on the size, location and type of lesion present (JHM 2014). Multiphase CT is based on the same principles as conventional CT and is commonly used to characterise liver lesions. The liver receives the majority of its blood supply via the portal vein, while lesions receive their supply of blood via the hepatic artery. This difference allows a multiphase CT scan to differentiate between normal liver tissue and tumours. A scan is taken before contrast. Contrast is then administered and two sets of scans are taken; one when the contrast is in the arterial system (arterial phase) and the second when the contrast is in the venous system (venous phase). A final scan is taken to determine

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contrast washout. An assessment of the additional benefit of a hepatobiliary specific contrast agent compared to a standard contrast agent should be included in future assessment and modelling.

A liver biopsy involves taking a small portion of the liver to examine in detail under a microscope. This may be via a percutaneous, transvenous or laparoscopic route. The biopsy may be performed on an uncharacterised liver mass identified previously by imaging (for example, US); however, liver biopsy may not be appropriate to diagnose liver cancer due to the risk of spreading cancer cells outside the liver (CLF 2014; Rockey et al. 2009).

The use of multiphase CT and biopsy are the most likely comparators to be replaced for those able to use MRI to characterise and stage lesions. For the staging of disease it is expected that MRI will largely replace multiphase CT at the proposed position in the algorithm. The proportion of multiphase CT and biopsy replaced will depend on several factors such as the information obtained prior to MRI, the information obtained from the MRI and the details of plans for the proposed treatment pathway. This can be modelled in the cost effectiveness analysis and varied in sensitivity analyses. Given the complexities of cancer and secondary cancer it is unreasonable to assume that MRI will replace all multiphase CT and biopsies but at the indicated place in the algorithm it is likely to replace some of them (See Figures 2 and 3). Currently many liver lesions that are considered indeterminate on CT are observed with serial CT, requiring regular specialist follow up. By providing a more accurate diagnosis, MRI will replace many of these CT examinations and specialist appointments.

Rationale

The rationale for a focus on multiphase CT and biopsy as comparators relates to these being the mostly commonly used practice in Australian usual care. Potential advantages of MRI over the comparators include greater diagnostic accuracy and clarity of staging information, less radiation and less risk of spreading cancer cells (particularly with the avoidance of biopsies).

Outcomes

Patient relevant:

The proposed intervention is likely to lead to greater diagnostic accuracy in terms of characterisation and staging of hepatic lesions in the identified populations. The improved staging has the potential to lead to better decisions surrounding treatment pathways in terms of identifying suitable patients for surgical intervention and specific treatment modalities during surgery. Optimising this decision making has the potential to provide better outcomes for patients both in terms of direct benefit via more tailored surgical interventions, as well as benefits to patients through avoiding risks and decreased quality of life associated with inappropriate surgical interventions. There is international data available on the NPV and PPV for a range of diagnostic options and their impact on surgical management outcomes however direct transferability of this data to the Australian context is uncertain.

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Adverse events:

There are potentially two classes of adverse event that could be considered; those associated with the MRI and those associated with the use of the hepatobiliary extracellular contrast agent.

The primary adverse event for MRI scanning is claustrophobia with data indicating 1.8% of individuals (95% confidence interval, 1.7–1.9%) experiencing sufficient severe symptoms to require mild sedation or cause the termination of a scan. The design of the MRI machine can influence claustrophobia rates (Dewey, Schink, & Dewey, 2007a).

The use of gadolinium-based contrast agent appears well tolerated with mild and transitory adverse events with dyspnoea and nausea being the most commonly reported adverse events (Endrikat, Kim, Sakaguchi, Dohanish, & Breuer, 2015).

The intervention appears to be safe with the most commonly reported side effects being of mild to moderate severity and transitory in nature. CT carries risks for cancer patients associated with radiation, although this is usually minimal given advanced age and competing risks. Biopsy has an important risk of transfer of cancer cells and is more invasive, the rates of biopsy in Australia however are unclear and further work should be undertaken to quantify the current practice in the Australian context.

Health Care relevant:

The addition of a contrast enhanced MRI scan to the patient pathway (see two patient pathways, Figures 2 and 3) for the relevant populations will add an additional phase however the evidence indicates that the use of the MRI has the potential to modify and optimise the treatment provided including surgical treatment. It may also replace some multiphase CT and biopsies.

Patients with known CRC with suspected liver malignancy, on the basis of confirmed histology or liver lesion as defined on previous CT, requiring MRI for characterisation and intervention planning (patient group 1)

Relevant outcomes identified

Accuracy

- Sensitivity, specificity (confirmed by reference standard)
- Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard)
- ROC curves
- Rates of unsatisfactory uninterpretable test results

Comment: There is a moderate pool of evidence indicating that, compared to both CT and US, contrast enhanced MRI has superior sensitivity, positive predictive value (PPV) and receiver operating characteristic (ROC). There is less evidence to suggest there is a comparative advantage, in comparison to CT, with regard to specificity. Clinician assessed confidence in the diagnosis and therapeutic decision was higher when based on a contrast enhanced MRI study compared to CT derived information (C. J. Zech et al., 2014).

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Change in management (Therapeutic efficacy)

Relevant outcomes include:

- Avoidance of unnecessary surgery due to resection of benign tumour (noted by expert advice as being a rare outcome) and,
- Avoidance of incomplete surgical intervention due to unidentified tumours, suitable for resection, being retained resulting in repeat surgery and,
- Avoidance of incorrectly assessed disease stage leading to modification and/or cancellation of surgical intervention.
- Avoidance of liver biopsy with associated risks
- Avoidance of follow-up multi-phase CT imaging with associated radiation (although we note that radiation is of minor relevance in this population)

Comment: The primary reported benefit of contrast enhanced MRI compared to CT was more complete identification of metastatic lesions. Where metastatic lesions are appropriately identified and characterised then an appropriate surgical plan can be developed; reducing the requirement for peri-operative alterations causing prolonged surgery (Christoph J Zech et al., 2016) or a reduced risk of repeat surgeries/ return to theatre. There appears to be limited data to support any conclusions on the avoidance of liver biopsies or additional imaging although the increased confidence in diagnosis and therapeutic decisions (C. J. Zech et al., 2014) may support this conclusion.

Health outcomes

Relevant outcomes include:

- Liver disease-specific mortality rate
- Overall survival
- Time to initial diagnosis
- Time from diagnosis to treatment
- Quality of life scores

Comment: There is limited direct evidence of changes in health outcomes, neither Wiggans (Wiggans et al., 2014) nor Titu (Titu, Breen, Nicholson, Hartley, & Monson, 2006) described direct health benefits to individual who underwent MRI in comparison to those who only underwent CT. Titu reported improved accuracy in identifying patients who were candidates for resection (covered in change in management) using MRI and ascribed better outcomes to the resected population however made no direct claim of superiority for contrast enhanced MRI so the assessment of benefit will be via linked evidence associated with change in patient management. The impact of the intervention on patient quality of life should be assessed independent of other clinical outcomes. Care should be taken in providing a plausible mechanism for QoL modification post intervention if it is not linked to one of the previously established clinical or change in management outcomes. Furthermore if the data sources are from non-randomised studies the implications of both observation bias and effects of regression to the mean should be taken into account.

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Patients with pre-existing chronic liver disease and suspected HCC with a hepatic lesion of over 10mm and Child-Pugh class A or B who require MRI for the purposes of diagnosis and staging (patient group 2)

Relevant outcomes include:

Accuracy

- Sensitivity, specificity (confirmed by reference standard)
- Positive likelihood ratio, negative likelihood ratio (confirmed by reference standard)
- ROC curves
- Rates of unsatisfactory uninterpretable test results

Comment: There is good evidence indicating that, compared to CT, contrast enhanced MRI has superior sensitivity, PPV and ROC characteristics. In addition to data analysed in the previous application a large meta-analysis (242 studies and 15,713 participants) has been published subsequently further supporting the superior sensitivity and PPV properties of MRI compared when compared to both CT and US (Hanna et al., 2016).

Change in management (Therapeutic efficacy)

Relevant outcomes include:

- Avoidance of unnecessary surgery due to resection of benign tumour (noted by expert advice as being a rare outcome) and,
- Avoidance of incomplete surgical intervention due to unidentified tumours, suitable for resection, being retained resulting in repeat surgery and,
- Avoidance of incorrectly assessed disease stage leading to modification and/or cancellation of surgical intervention.
- Avoidance of liver biopsy with associated risks
- Avoidance of follow-up multi-phase CT imaging with associated radiation

Comment: Studies indicate that the use of MRI leads to a change in patient management primarily by changing the assessed stage of disease progression (Hanna et al., 2016; Rostambeigi et al., 2016; Wang et al., 2016). The proposed intervention should lead to more accurate characterisation and staging of HCC. There is evidence for improved characterisation of lesions that are <=20mm (Hanna et al., 2016) and <=30mm (Duncan, Ma, Vreugdenburg, Cameron, & Maddern, 2017), which are key threshold for the widely used BCLC staging algorithm (Attwa & El-Etreby, 2015) (Figure 1).The primary benefit of correct staging of HCC is the selection of the most appropriate interventional method. In addition to a staging benefit the complete identification of lesions of importance is key for optimal surgical planning and management. The literature reports that the correct allocation of patient to operative status can be impacted by the use of MRI (Wang et al., 2016).

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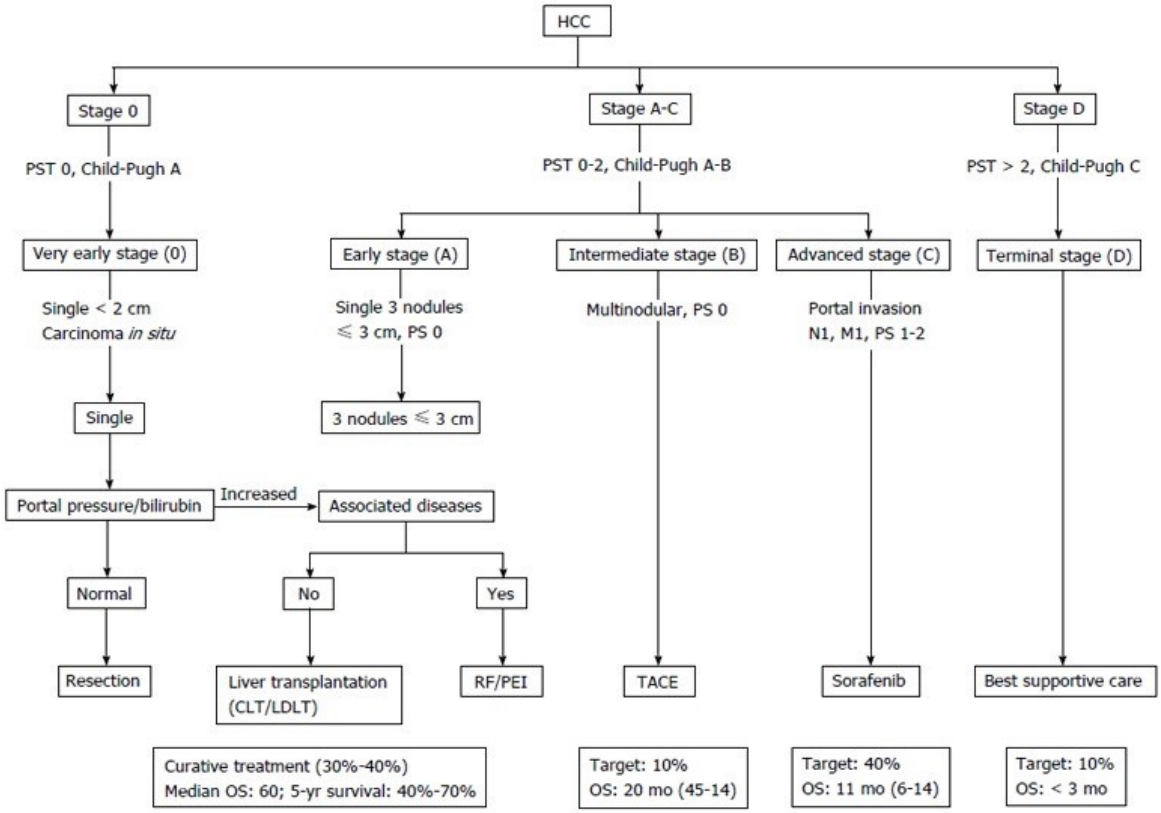

Figure 1. Updated Barcelona Clinic Liver Cancer staging system and treatment strategy. The BCLC algorithm classifies HCC into five stages-based on the extent of disease, Child-Pugh score, and ECOG performance status-that enables prognostication and informs allocation of first-line treatment. BCLC: Barcelona Clinic Liver Cancer (group); HCC: Hepatocellular carcinoma; PST: Performance status test; TACE: Transarterial chemoembolization; RF: Radiofrequency; PEI: Percutaneous ethanol infusion; CLT: Cadaveric liver transplant; LDLT: Living donor liver transplant (Attwa & El-Etreby, 2015).

Health outcomes

Relevant outcomes include:

- Liver disease-specific mortality rate
- Overall survival
- Time to initial diagnosis
- Time from diagnosis to treatment
- Quality of life scores

Comment: There is evidence that the use of MRI can provide benefits in terms of overall mortality (Kim et al., 2015) and recurrence-free survival (Matsuda et al., 2014) however the level of evidence is not currently strong and so the assessment of benefit may need to be via linked evidence associated with change in patient management. The impact of the intervention on patient quality of life should be assessed independent of other clinical outcomes. Care should be taken in providing a

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plausible mechanism for QoL modification post intervention if it is not linked to one of the previously established clinical or change in management outcomes. Furthermore if the data sources are from non-randomised studies the implications of both observation bias and effects of regression to the mean should be taken into account.

Current clinical management algorithm for identified population

Figures 2 and 3 depict the clinical management algorithms for patient groups 1 and 2 respectively, and where the proposed service would fit into the current management pathways. The current clinical management follows the route marked 'Comparators' with black arrows in both the figures.

Figure 2: Clinical decision pathway for patients with known colorectal carcinoma (CRC) with suspected or possible liver metastases, on the basis of confirmed histology or liver lesion as defined on previous CT, for characterisation and intervention planning [Patient group 1]

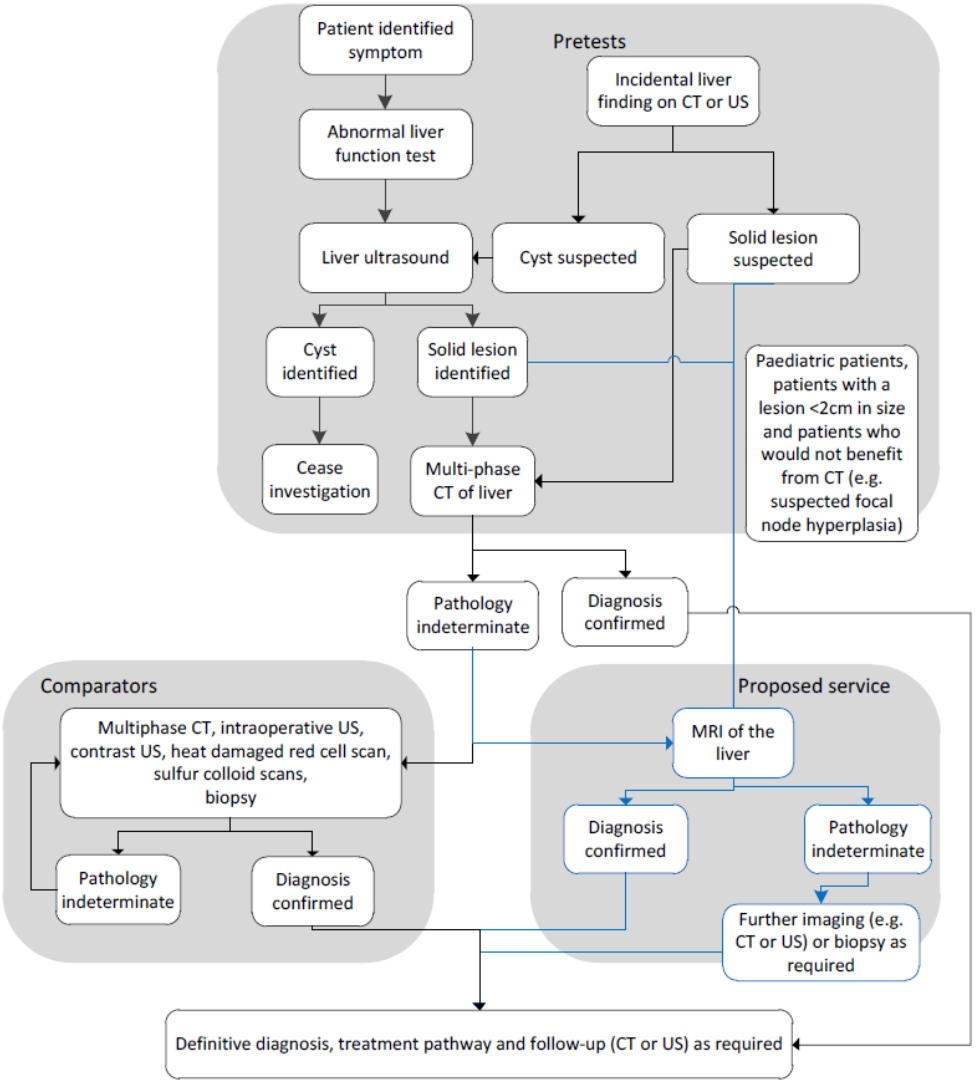
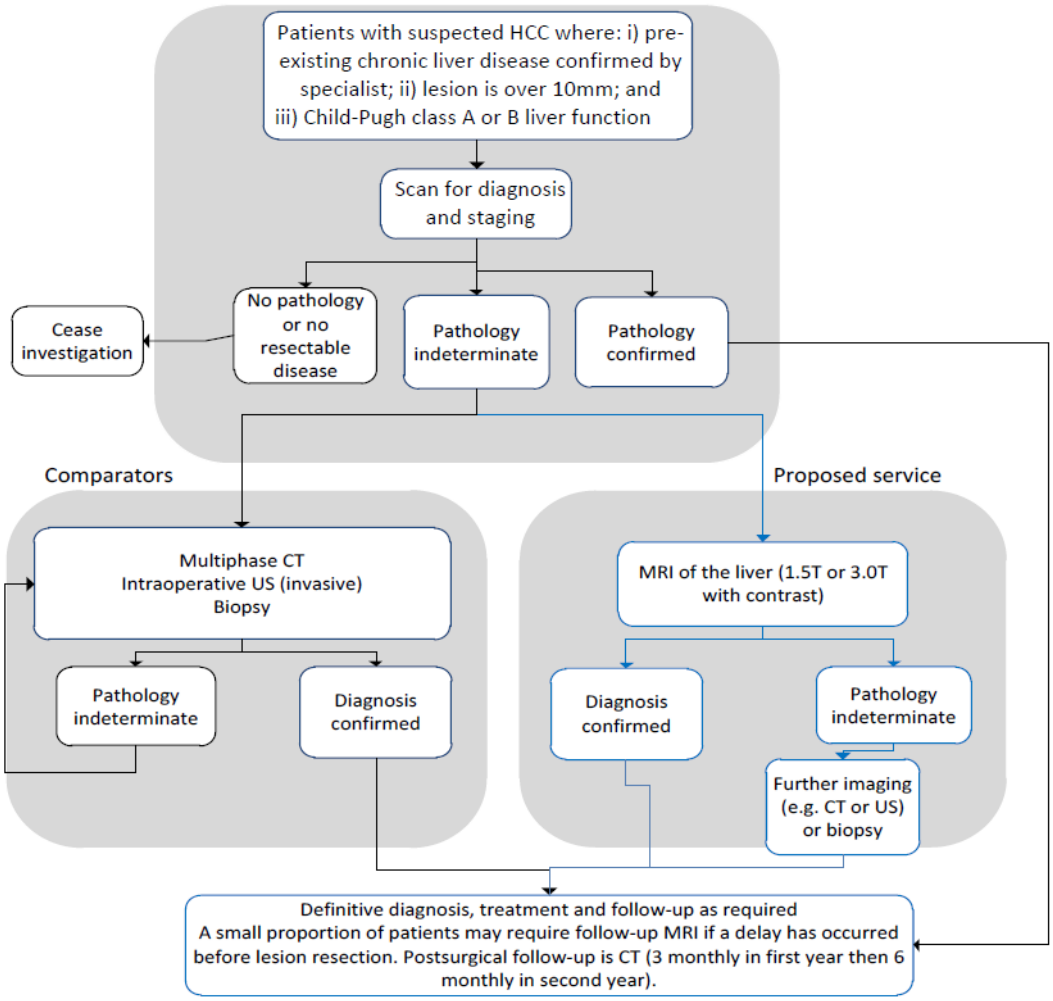


Figure 3: Clinical decision pathway for patients with hepatocellular carcinoma (HCC) for diagnosis and staging purposes [Patient group 2]



Proposed clinical management algorithm for identified population

MRI is proposed to be used largely in place of currently available imaging modalities or diagnostic procedure such as multiphase CT, biopsy (with other comparators less commonly used in Australia). It is expected that in both the patient populations, the use of MRI will not change the clinical management pathway but will be available as an alternative (or preferred) means of imaging to improve liver malignancy characterisation, diagnosis and staging. This is shown in the above figures marked in blue and highlighted as the 'Proposed Service' in Figures 2 and 3 above.

Proposed economic evaluation

The clinical claim is that MRI will be superior in safety and effectiveness compared to CT and biopsy. It is also noted that MRI will be more costly. There may be some savings associated with MRI in terms of reduced inappropriate surgeries or avoided adverse events for biopsy, CT or avoided surgery. The appropriate economic evaluation will be a decision analytic model that incorporates information on both the accuracy of testing combined with treatment outcomes and provides estimates of cost-effectiveness and possibly cost utility. Both the investigative and therapeutic Technical Guidelines will provide relevant guidance as to the appropriate structure and methods for the economic evaluation which will be informed by this PICO confirmation.

Proposed item descriptor

Currently there are no MBS items listed for the MRI of liver. The applicant has proposed an estimated fee of $1,200 for this service. PASC noted that the current market rate for the service for private patients in Australia is between $500 and $800. The applicant indicated that the higher fee is based on the time required in the scanner. There are existing MRI-related MBS items for the evaluation of breast implant and small bowel Crohn's disease, with fees ranging from $201.60 (MBS item 63747) to $1440.00 (MBS item 63489). The scan times for these existing services are not currently available for comparison and justification of the proposed MBS fee is warranted. The use of these MRI services is attached to a modifying item (MBS item 63491 with a fee of $44.80) for the use of a contrast agent eligible for current MRI items. During the modelling phase a sensitivity analysis should be undertaken to explore the impact of the cost of the procedure on the overall cost effectiveness of the interventions. Logical upper and lower bounds for the cost per scan could be gained from the current maximum and minimum values for MRI-related MBS items currently listed. Alternately a survey of market pricing, where the current mean price is estimated by PASC to fall between $500 and $800, could be undertaken to establish a maximum, minimum and probable distribution for the purposes of a sensitivity analysis. Given the relatively wide broad range of pricing for existing procedures, with the largest listed cost being 7 times that of the lowest, a survey of existing market conditions is likely to provide a more realistic distribution of possible pricing scenarios.

Hepatobiliary specific contrast agents (particularly gadoxetic acid) were used in the evidence presented for MRI, and the use hepatobiliary specific contrast agents with MRI for the proposed population appears indicated. Therefore a new MBS item for the use of hepatobiliary specific agent accompanying the MRI of liver would be ideal to support the application for a new MBS item number for MRI. It should be noted that the currently proposed MBS item only covers the provision of the service. The cost of the recommended hepatobiliary contrast agent, Primovist (gadoxetate disodium), is expected to cost around $250 (current market rate) which is borne by the patient as an out-of-pocket expense. Further clarification and justification with evidence of superiority for use of the more expensive hepatobiliary contrast agent is warranted.

As described in the Intervention section, some current MRI-related MBS items have additional restrictions on the number of times they can be claimed. Considerations to limit one liver MRI per year (with US monitoring in between) is deemed appropriate.

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A number of the existing MRI-related MBS items are listed with an additional condition (capital sensitivity measure) labelled as (K) or (NK) which relates to the age of the equipment and level of schedule fee. PASC may need to consider if such an assignment is relevant to the proposed service.

Category 5 – DIAGNOSTIC IMAGING SERVICES
Item [proposed MBS item number 1] (specialist referral) MAGNETIC RESONANCE IMAGING performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist – scan of liver for: (a) patients with known colorectal carcinoma with suspected or possible liver metastases for the purpose of characterisation and intervention planning where: ▪ the patient has confirmed histology or liver lesion as defined on previous CT (R) (contrast as clinically indicated), OR (b) patients with suspected hepatocellular carcinoma for the purposes of diagnosis and staging where: ▪ the patient has a pre-existing chronic liver disease as confirmed by a specialist; and ▪ has an identified hepatic lesion over 10mm; and ▪ has been assessed as having a Child-Pugh class A or B liver function. (R) (contrast as clinically indicated) (Anaes.) Note: Benefits are payable on only one occasion for diagnostic purposes in any 12-month period Bulk bill incentive Fee: $1,200 Benefit: 75% = $900 85% = $1,020 (See para DIQ of explanatory notes to this category)

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Category 5 – DIAGNOSTIC IMAGING SERVICES
Item [proposed MBS item number 2] NOTE: Benefits in Subgroup 22 are only payable for modifying items where claimed simultaneously with MRI services. Modifiers for sedation and anaesthesia may not be claimed for the same service. Modifying items for use with MAGNETIC RESONANCE IMAGING or MAGNETIC RESONANCE ANGIOGRAPHY performed under the professional supervision of an eligible provider at an eligible location where the service requested by a specialist or by a consultant. Scan performed: - involves the use of HEPATOBILIARY SPECIFIC contrast agent as clinically indicated for [proposed MBS item number 1] Bulk bill incentive Fee: $TBA (See para DIQ of explanatory notes to this category)

RATIFIED

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