GADOXETIC ACID DISODIUM (GD-EOB-DTPA) LIVER-SPECIFIC MAGNETIC RESONANCE IMAGING CONTRAST AGENT

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EXECUTIVE SUMMARY

Introduction

Magnetic resonance imaging (MRI) has become the key technique for the characterization and detection of focal and diffuse liver disease. In order to adequately characterize focal liver lesions on MRI, it is necessary to utilize contrast agents which are able to modify the signal intensity of either the lesions or the normal liver parenchyma and thus contribute towards the characterization of the lesions. Various contrast agents can be distinguished on the basis of their distribution after intravenous injection; distribute in the extracellular, exclusive distribution to hepatocellular compartment and combined perfusion and hepatocyte-selective properties. Agents of this type include Gadobenate dimeglumine (Gd-BOPTA) and the newer Gadolinium-ethoxybenzyl-diethylenetriamine-pentaacetic-acid (Gd-EOB-DTPA); generic name: Gadoxetic acid disodium which now allows combined dynamic imaging and hepatocyte specific imaging in one examination. This technology review was conducted following a request from Consultant Radiologist, Diagnostic and Imaging Department, Serdang Hospital to look into the diagnostic accuracy of Gadoxetic acid disodium (Gd-EOB-DTPA) liver-specific contrast agent in detecting especially small liver lesions.

Objective/aim

The objective of this systematic review was to assess the safety, efficacy/effectiveness and cost-effectiveness of Gadoxetic acid disodium (Gd-EOB-DTPA) liver-specific MRI contrast agent in the detection and characterization of liver lesions.

Results and conclusions

The studies included consist of four RCTs, 21 diagnostic accuracy studies, one economic evaluation study and two FDA articles.

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was safe.

Comparison with unenhanced MRI

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI improved sensitivity for lesion detection, classification and characterization of focal liver lesions compared with unenhanced MRI.

Comparison with CT

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had the following characteristics:-

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in the detection, classification and characterization of liver lesions especially for lesions equal to or less than two centimetre in diameter compared with spiral CT
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance but may be better for detection of HCC of one centimetre in diameter or smaller compared with triple phase MDCT

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had higher sensitivity for differentiation between hypervascular HCC and hypervascular pseudolesions compared with triple phase MDCT

Comparison with other liver-specific MRI contrast agents

There was fair level of evidence to show that:-

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in detecting HCC than Gadopentetate dimeglumine (Gd-DTPA)-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was as efficacious in detecting liver metastases when compared with SPIO-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in detecting HCC compared with SPIO-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance compared with double-contrast MRI (Gadopentetate dimeglumine-enhanced MRI and SPIO-enhanced MRI) in detection of small HCC
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI showed better enhancement of liver parenchyma at 20 minutes post contrast compared with Gadobenate dimeglumine (Gd-BOPTA) at 40 minutes post contrast
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance as Gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI for detecting HCC

COST/COST-EFFECTIVENESS

There was limited evidence to show that although the cost of Gadoxetic-acid disodium (Gd-EOB-DTPA) liver-specific MRI contrast agent was found to be higher than the extracellular liver-specific MRI contrast agent [Gadopentetate dimeglumine (Gd-DTPA)], the strategy starting with Gd-EOB-DTPA enhanced MRI as a pre-operative diagnostic tool in patients with colorectal liver metastases was shown to be more cost saving.

Methods

Electronic databases were searched, which included PubMed, Medline, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane database of systematic reviews, EBM Reviews - HTA Databases, Horizon Scanning databases, FDA website for published reports. There was no limit in the search. Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and diagnostic studies was graded according to NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2^{nd} Edition).

GADOXETIC ACID DISODIUM: LIVER-SPECIFIC MAGNETIC RESONANCE IMAGING CONTRAST AGENT

1. INTRODUCTION

Magnetic resonance imaging (MRI) has become the key technique for the characterization and detection of focal and diffuse liver disease.[1] Common focal liver lesions are classified as benign versus malignant. Benign lesions include cysts, haemangiomas, focal nodular hyperplasia (FNH), and adenoma. Common malignant lesions include hepatocellular carcinoma (HCC), as well as hyper- and hypovascular metastases.[2] Overall, in Peninsular Malaysia in 2006, liver cancer was the 6th most common cancer. It was the 5th most common cancer among males and the 9th among females.[3]

In order to adequately characterize focal liver lesions on MRI, it is necessary to utilize contrast agents which are able to modify the signal intensity of either the lesions or the normal liver parenchyma and thus contribute towards the characterization of the lesions. The sensitivity of magnetic resonance (MR) to the variations of signal intensity induced by contrast agents has lead to the development of several different types of liver-specific contrast agents which utilise the paramagnetic properties of gadolinium or manganese or the superparamagnetic properties of iron.[4] Initially the use of liver-specific contrast agents has been limited because it has not been possible to perform both proper vascular phase and liver-specific phase within a reasonable time frame and in a single examination after a single injection of contrast agent.[5]

Various contrast agents can be distinguished on the basis of their distribution after intravenous injection. Non-specific gadolinium chelates such as Gadolinium-diethylenetriamine penta-acetic acid (Gd-DTPA); generic name: Gadopentetate dimeglumine, and Gd-DTPA-bismethylamide (BMA) which distribute in the extracellular fluid (ECF) space are currently the most widely used contrast agents. These contrast agents are most effective during the dynamic phase of contrast enhancement when differential blood flow between tumour and normal liver parenchyma leads to characteristic lesion enhancement patterns.[4]

Exclusive distribution to the hepatocellular compartment can be obtained using contrast agent which when injected by means of slow infusion can accumulate within the hepatocytes and cause an increase in the proton relaxation rate such as in mangafodipir trisodium (Mn-DPDP). Tumours of non-hepatocytic origin show little or no tumour enhancement resulting in increased in lesion conspicuity.[4]

Other contrast agents demonstrated combined perfusion and hepatocyte-selective properties. Such compounds distribute initially to the vascular-interstitial compartment in an analogous manner to that of conventional, extracellular contrast agent. Thereafter, a fraction of the injected dose is taken up into the hepatocytes causing an increase in the signal intensity of the hepatic tissue. Agents of this type include Gadobenate dimeglumine (Gd-BOPTA) and the newer Gadolinium-ethoxybenzyl-

diethylenetriamine-pentaacetic-acid (Gd-EOB-DTPA); generic name: Gadoxetic acid disodium which now allows combined dynamic imaging and hepatocyte specific imaging in one examination.[4,5] The added value of hepatobiliary phase images obtained after gadoxetic acid-enhanced dynamic MR imaging in the diagnosis of HCC has been demonstrated by Chou *et al*. and Ahn *et al.* [6,7]

Another type of liver imaging contrast agent is superparamagnetic iron oxide (SPIO). These particles accumulate in the reticuloendothelial system (RES) of the liver and darken the healthy liver tissue in T2 weighted images.[4]

This technology review was conducted following a request from a Consultant Radiologist, Diagnostic and Imaging Department, Serdang Hospital to look into the diagnostic accuracy of Gadoxetic acid disodium (Gd-EOB-DTPA) liver-specific contrast agent in detecting especially small liver lesions.

2. OBJECTIVE/AIM

The objective of this systematic review was to assess the safety, efficacy/effectiveness and cost-effectiveness of Gadoxetic acid disodium (Gd-EOB-DTPA) liver-specific MRI contrast agent in the detection and characterization of liver lesions.

3. TECHNICAL FEATURES

Gadoxetic acid disodium (Gd-EOB-DTPA)

3.1. Description

Gadoxetic acid disodium is a paramagnetic contrast agent for MRI. It's salt, gadoxetate disodium is marketed as Primovist® in Europe and Eovist® in the United States by Bayer Healthcare Pharmaceuticals. Eovist® injection is indicated for intravenous use in T1-weighted MRI of the liver to detect and characterize lesions in adults with known or suspected focal liver disease.

Gadoxetate disodium is designated chemically as (4S)-4-(4-Ethoxybenzyl)-2,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioic acid, gadolinium complex, disodium salt with a molecular weight of 725.72 and an empirical formula of $GdC_{23}H_{28}N_3O_{11}Na_2$. Each millilitre (mL) contains 181.43 mg of gadoxetate disodium (equivalent to 0.25 mol/L gadoxetate disodium), and the excipients caloxetate trisodium, trometamol, hydrochloric acid and/or sodium hydroxide (for pH adjustment), and water for injection. It contains no antimicrobial preservative.[8]

3.2. Clinical pharmacology

3.2.1. Mechanism of action

Gadoxetate disodium is a paramagnetic compound and develops a magnetic moment when placed in a magnetic field. The relatively large magnetic moment produced by

gadoxetate disodium results in a local magnetic field, yielding enhanced relaxation rates (shortening of relaxation times) of water photons in the vicinity of paramagnetic agent, which leads to an increase in signal intensity (brightening) of blood and tissue. In MRI, visualisation of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occur with 1) differences in proton density, 2) differences of the spin-lattice or longitudinal relaxation times (T1), and 3) differences in the spin-spin or transverse relaxation time (T2). When placed in a magnetic field, gadoxetate disodium decreases the T1 and T2 relaxation time in target tissue. At the recommended dose, the effect is observed with greatest sensitivity in T1-weighted MR sequences.[8]

3.2.2. Pharmacodynamics

Gadoxetate disodium is a highly water-soluble, hydrophilic compound with a lipophilic moiety, the ethoxybenzyl group (EOB). It shows a weak (<10%), transient protein binding and the relaxivity in plasma is about 8.7 L/mmol/sec at pH 7, 39°C and 0.47T. Gadoxetate disodium is selectively taken up by hepatocytes resulting in increased signal intensity in liver tissue. It exhibits a biphasic mode of action: first, distribution in the extracellular space after bolus injection and subsequently, selective uptake by hepatocytes (and biliary excretion) due to lipophilic (EOB) moiety.[8] The high rate, almost 50% of hepatobiliary uptake ensures that the hepatobiliary phase sequences can be started already at 20 minutes after injection.[5]

3.2.3. Pharmacokinetics

After intravenous administration, the plasma concentration time profile of gadoxetate disodium is characterised by a bi-exponential decline. It does not pass the intact blood brain barrier and diffuses through the placental barrier. It is equally eliminated via the renal and hepatobilliary routes. It is not metabolised.[8]

3.3. Dosage and administration

The recommended dose of Eovist® / Primovist® is 0.1 mL/kg body weight (0.025 mmol/kg body weight). It is administered undiluted as an intravenous bolus injection at a flow rate of approximately 2 mL/second. The intravenous cannula is flushed with saline solution after the injection. There is no contraindication. However, there is a warning stating that Gadolinium-based contrast agents increase the risk of Nephrogenic Systemic Fibrosis (NSF) among patients with impaired elimination of the drugs. The risk for NSF appears highest among patients with chronic severe kidney disease (GFR < 30 mL/min/1.73m^2) or acute kidney disease.[8]

4. Methodology

4.1. Searching

Electronic databases were searched through the Ovid interface: Medline -1950 to November week 3 2010, EBM Reviews - Cochrane Central Register of Controlled Trials- 4th Quarter 2010, EBM Reviews - Cochrane database of systematic reviews - 2005 to

December 2010, EBM Reviews - Health Technology Assessment - 4th Quarter 2010, NHS economic evaluation database - 4th Quarter 2010. Searches were also run in PubMed, Horizon Scanning database (National Horizon Scanning Centre, Australia and New Zealand Horizon Scanning Network, National Horizon Scanning Birmingham) and FDA website for published literature. Google was used to search for additional web-based materials and information. There was no limit in the search. Additional articles were identified from reviewing the bibliographies of retrieved articles.

The search strategy used the terms which were either used singly or in various combinations;"gadoxetic acid", eovist, primovist, "liver contrast media", "hepatocyte specific MRI contrast media", safe*, "adverse events", sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and "receiver operating characteristic curve".

4.2. Selection

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection.

The inclusion and exclusion criteria were:
Inclusion criteria

Population	Patients with liver lesions or suspected of having liver lesions
Interventions	Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid [Gd-EOB-DTPA (gadoxetic acid disodium)] enhanced MRI
Comparators	1. Unenhanced MRI (precontrast MRI) 2. Enhanced MRI using other liver-specific contrast agent such as Gadobenate dimeglumine (Gd-BOPTA), Gadopentetate dimeglumine (Gd-DTPA) , Gd-DTPA-bismethylamide (BMA), mangafodipir trisodium (Mn-DPDP), superparamagnetic iron oxide 3. Computed tomography (CT)
Outcomes	Lesion detection, lesion characterization, lesion classification, sensitivity, specificity, PPV, NPV, receiver operating characteristic curve, safety, adverse events, economic evaluation
Study design	Health technology assessment, Systematic reviews, Randomised controlled trial, diagnostic accuracy studies, studies with economic evaluation
Type of publication	English full text articles

Exclusion criteria

Study design	Studies conducted in animals and narrative reviews
Type of publication	Non English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) and diagnostic studies was graded according to NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition).

5. RESULTS AND DISCUSSION

The search strategies yielded 28 articles related to Gadoxetic acid disodium (Gd-EOB-DTPA) liver- specific MRI contrast agent for detection, characterization and classification of liver lesions compared with unenhanced MRI, CT and other liver-specific MRI contrast agent. There was no health technology assessment report or systematic review retrieved. The studies included consist of four RCTs, 21 diagnostic accuracy studies, one economic evaluation study and two FDA articles.

5.1. SAFETY

Ten articles related to the safety of Gadoxetic acid disodium (Gd-EOB-DTPA) liver-specific MRI contrast agent were included in this study.

Gadoxetic acid disodium (Gd-EOB-DTPA) has United States Food and Drug Administration (U.S. FDA) approval in 2009 and received approval for Europe in 2004. It is claimed to be approved in more than 40 countries.[9,10]

The safety and dosing of Gadoxetic acid disodium (Gd-EOB-DTPA) have been evaluated in Phase I and Phase II clinical studies. Doses of up to 100 µmol per kilogram Gadoxetic acid disodium has been well tolerated with no side effects or changes in laboratory parameters.[11,12] Several multicentre prospective Phase III diagnostic studies conducted in the U.S, Europe, German and Japan found that the contrast agent was well tolerated by patients and there was no clinically relevant changes in haemodynamic or laboratory parameters due to the contrast agent. No death or any adverse events leading to the discontinuation of patient participation were reported.[13-18 level 2-3.] The most frequently reported adverse events that were definitely, possibly, or probably related to the contrast agent were nausea, vasodilatation, headache, taste perversion and injection site pain.[12 level 2, 14 level 2]

5.2. EEFICACY/EFFECTIVENESS

Seventeen articles related to the efficacy/effectiveness of Gadoxetic acid disodium (Gd-EOB-DTPA) liver specific MRI contrast agent in the detection, characterization and classification of liver lesions when compared with unenhanced MRI, CT and other liver-specific MRI contrast agents were included in this study.

5.2.1. Comparison with unenhanced MRI

Two studies assessed the efficacy of postcontrast MRI with Gadoxetic acid disodium (Gd-EOB-DTPA) compared with that of precontrast MRI in patients with known or suspected liver lesions. Bluenke *et al.* conducted a multicentre Phase III study in the U.S. involving 169 patients (94 men and 75 women) who received 25 µmol/kg Gd-EOB-DTPA and underwent dynamic gradient-recalled-echo and delayed MRI 20 minutes after

injection, computed tomography (CT) performed within 6 weeks of MRI. The standard reference used was surgery with intraoperative ultrasonography and biopsy and/or pathologic evaluation of resected liver segments and/or 3 month follow-up of unresected segments if intraoperative ultrasonography was not available. Three blinded reviewers and unblinded site investigators identified liver lesions on segment maps. They found 316 lesions at MRI in 131 patients. They concluded that compared with pre-contrast MRI, post-contrast MRI with Gd-EOB-DTPA demonstrated improved sensitivity for lesion detection in majority of blinded readers.[13 level 3]

Huppertz *et al.* conducted a study to evaluate the safety and efficacy of Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI for the detection of focal liver lesions, with results of histopathological examination and/or intraoperative ultrasound used as a standard reference. One hundred sixty-nine patients who were known to have or suspected of having focal liver lesions and were scheduled for liver surgery were included in the study. Investigators from 14 European centres in six different countries took part in the study. All images were evaluated on site and by three independent and blinded off-site reviewers. The patient-based analysis in both the on-site and off-site was based on results of 129 patients. They found that in the on-site review, the number of patients in whom all lesions were correctly matched increased from 89 of 129 patients (69.0 %) at pre-contrast MRI to 103 of 129 patients (79.8 %) at post-contrast MRI. In the off-site evaluation, the number of patients in whom all lesions were correctly matched and the corresponding sensitivity values increased from 55.8% with pre-contrast images to 68.2% with the post-contrast images for reader 1, from 52.7% to 53.5% for reader 2 and from 51.2% to 58.9% for reader 3. Two of the three blinded readers showed statistically significant difference in lesion detection between pre-contrast and post-contrast MRI ($P < 0.001$ for reader 1 and $P < 0.008$ for reader 3). A large number of additionally correctly detected localized lesions were smaller than one cm. The authors also found that the administration of Gadoxetic acid disodium improved the classification and characterization of focal liver lesions.[14 level 2]

5.2.2. Comparison with CT

Eight studies compared the efficacy/effectiveness of Gadoxetic acid disodium-enhanced MRI with biphasic/triphasic contrast-enhanced spiral CT or triple-phase multidetector row CT (MDCT). The potential of biphasic contrast-enhanced CT and tissue-specific MRI contrast agent (Gadoxetic acid disodium) for liver lesion characterization was evaluated by Halavaara *et al.* The study was conducted in Finland. A total of 176 patients and 252 liver lesions were analysed. There were 104 malignant and 148 benign lesions. They found that both on-site and off-site evaluations demonstrated increases in the lesion classification accuracy and characterization with Gadoxetic acid disodium-enhanced MRI when compared with spiral CT. For on-site evaluation, correct lesion classification showed an increased from 224 of 252 lesions (89%) with biphasic CT to 240 of 252 lesions (95%) with combined MRI. Sensitivity, specificity and accuracy improved with combined MRI by three to four percent. The proportion of correctly characterized lesions with the MRI was 224 of 252 (89%) lesions compared to 201 of 252 [80%; 95% confidence interval (CI), 0.036 to 0.146, $P = 0.0018$]. For off-site evaluation, the numbers of correctly classified lesions improved with MRI by four to seven percent and the

proportion of correct lesion characterization was higher with combined MRI for all 3 readers when compared to biphasic spiral CT. The
numbers increased from 145, 161, and 138 lesions (reader 1, 58%; reader 2, 64%; and reader 3, 55% respectively) with CT to 169, 192, 144 lesions (reader 1, 68%; reader 2, 77%; and reader 3, 58% respectively) with combined MRI. The improvement in lesion characterization was statistically significant with readers 1 and 2 with P=0.0236 and P=0.0014 respectively. They concluded that Gadoxetic acid disodium enhanced MRI offers a safe and diagnostically powerful tool for the evaluation of patients with focal liver lesions with a reliable assessment of lesion classification and characterization compared with spiral CT.[15 level 2]

Hammersting R *et al.* conducted a multicentre study in Germany to evaluate the diagnostic efficacy of MRI using Gadoxetic acid disodium (Gd-EOB-DTPA), Primovist® as opposed to contrast enhanced biphasic spiral CT in the diagnosis of focal liver lesions compared with a standard of reference (SOR). A total of 169 patients with hepatic lesions eligible for surgery underwent Gadoxetic acid disodium-enhanced MRI as well as CT within six weeks. Pathologic liver specimen combined with intraoperative ultrasound established the SOR. They found that the frequency of correctly detected lesions was higher in Gadoxetic acid disodium–enhanced MRI compared with CT in clinical evaluation (10.44%; 95% CI, 4.88 to 16.0). The highest rate of correctly detected lesions with a diameter below one cm was achieved by Gadoxetic acid disodium–enhanced MRI. Differential diagnosis was superior for Gadoxetic acid disodium–enhanced MRI (82.1%) versus spiral CT (71.0%). A change in surgical therapy was documented in 19 of 131 patients (14.5%) post Gadoxetic acid disodium -enhanced MRI.[16 level 2]

Ichikawa *et al.* in a Japanese Phase III, multicentre trial involving 151 patients also found that sensitivity for lesion detection of combined MRI (Gadoxetic acid disodium-enhanced MRI and unenhanced MRI) for on-site and blinded readers were higher compared with triphasic spiral CT by 6.4% and 3.1 to 9.6%, respectively. The sensitivity for detecting lesions with diameter >20 mm was similar for both combined MRI and spiral CT (approximately 90% correctly detected). Combined MRI resulted in greater sensitivity compared with spiral CT in detection of lesions ≤ 20 mm for all readers. The sensitivity was 30.0% to 55.4% versus 26.1% to 47.3% respectively, for lesions ≤ 10 mm, and 71.1% to 87.3% versus 65.7% to 78.4% respectively, for lesions 10 to 20 mm. The authors concluded that when compared with spiral CT, Gadoxetic acid disodium–enhanced MRI seems to be beneficial especially for the detection of smaller lesions or hepatocellular carcinoma underlying cirrhotic liver.[17 level 3]

Similarly, Raman *et al.* in a study performed in 18 institutions in the U.S. also found that for the clinical evaluation (on-site evaluation), more focal liver lesions were correctly characterized using combined (unenhanced and Gadoxetic acid disodium–enhanced MRI) than using spiral CT (96% versus 85%, P = 0.0008). For the blinded off-site evaluation, all the readers, correctly characterized a greater proportion of the lesions using combined MRI images compared with dual-phase spiral CT. However, the results showed no significant difference for any of the readers.[18 level 2]

Zech CJ *et al.* conducted a study on diagnostic performance and description of morphological features of Focal Nodular Hyperplasia (FNH) in Gadoxetic acid disodium-enhanced liver MRI in comparison with pre-contrast MRI and spiral CT. In 176 patients from a phase III multicentre trial, in 15 European centres in eight different countries, there were 59 confirmed FNH. They found that characterization of FNH provided by combined pre and post MRI was superior to that achieved with biphasic enhanced-spiral CT (88.1% versus 84.7%) in the clinical study (on-site evaluation). For the off-site blinded evaluation, the characterization of FNH by combined pre and post MRI was superior to biphasic enhanced-spiral CT for two of three blinded readers. They concluded that FNH show very similar enhancement characteristics to those of other extracellular contrast agents in the early dynamic phase after bolus injection of Gadoxetic acid disodium. After 20 minutes liver-specific phase enhancement was regularly seen.[19 level 2]

The diagnostic performance of Gadoxetic acid disodium enhanced MRI has also been compared with MDCT in several studies. Kim YK *et al.* compared the diagnostic accuracy and sensitivity of Gadoxetic acid disodium-enhanced MRI with MDCT for the detection of HCC. The study included 62 patients with 81 HCC who underwent MDCT and Gadoxetic acid disodium-enhanced MRI in a tertiary hospital in Korea. Two observers reached a consensus on two sets of images. Diagnostic accuracy and sensitivity were evaluated using the alternative-free response receiver operating characteristic (ROC) method. They found that there was a trend toward increased area under the ROC curve (Az value) for the Gadoxetic acid set (0.963) as compared with the MDCT (0.930), P = 0.41. However, sensitivity of the Gadoxetic acid set (91.4%) was higher than that of the MDCT (71.6%, P = 0.0001).There were 12 lesions that showed only arterial hypervascularization on MDCT but showed arterial hypervascularisation and delayed hypointensity on the gadoxetic acid set. They concluded that gadoxetic acid-enhanced MRI including hepatocyte phase imaging was more sensitive than MDCT for detection of HCC.[20 level 3]

In contrast, Kim SH *et al.* in his prospective study also conducted in a tertiary referral hospital in Korea involving 62 patients with 83 HCCs found that Gadoxetic acid disodium-enhanced MRI and triple-phase MDCT have similar diagnostic performance in the preoperative detection of HCC, but MRI may be better than MDCT in the detection of HCC smaller than one centimetre in diameter. For each observer, the area under the ROC curve were 0.971, 0.959 and 0.967 for MRI and 0.947, 0.950 and 0.943 for CT (P > 0.05).The differences in sensitivity, PPV and NPV for each observer were also not significant. Among ten HCCs which were one cm in diameter or smaller, each of the observers detected seven tumours with MRI. With MDCT, one observer detected five, one observer detected four, and one observer detected three HCCs with no statistically significant difference (P > 0.05). [21 level 2]

The ability of Gadoxetic acid disodium-enhanced MRI in distinguishing small HCCs from hypervascular pseudolesions compared with MDCT was assessed by Sun *et al.* and Motosugi *et al.*[22-23] Sun *et al.* conducted a retrospective study in a tertiary hospital in Korea to determine the characteristic signal intensity (SI) of HCCs and non-neoplastic arterial enhancing pseudolesions (AEP) on Gadoxetic acid disodium (Gd-EOB-DTPA,

Primovist®-enhanced MRI and to assess its performance in differentiating small HCC (≤ 2cm in diameter) from AEP in cirrhotic liver compared with multiphasic CT. A total of 69 patients with 97 small, arterial enhancing hepatic lesions (0.5 cm to 2.0 cm in diameter) that is 44 HCCs and 53 AEPs detected on gadoxetic acid disodium-enhanced MRI were included in the study. HCCs were diagnosed either through histopathology confirmation, or a combination of liver CT, angiographic findings, lipiodol CT and serum alpha feto-protein (AFP) levels. AEPs were diagnosed either through histopathology or based on the angiographic findings, liver CT and follow-up imaging.[22 level 3]

They found that among the 44 HCCs, 42 (95.4%) demonstrated low SI and only two showed iso or high SI on the hepatobiliary phase of gadoxetic acid disodium-enhanced MRI. Alternatively, most AEPs showed iso SI on the hepatobiliary phase (n=50, 94.3%) and only two AEPs showed low SI. Comparing the diagnostic performance of the two imaging modalities, the mean areas under ROC curves on MRI were 0.975 for reviewer 1 and 0.966 for reviewer 2, whereas those of CT imaging were 0.892 for reviewer 1 and 0.888 for reviewer 2 (P = 0.069 for reviewer 1 and P = 0.106 for reviewer 2). However, the MRI sensitivity of each reviewer for the differentiation of HCC and AEP were greater than 90% (93.9% and 90.9%, respectively) and were significantly higher than the CT sensitivity of 54.5% (in both), P = 0.001 for reviewer 1 and P = 0.0018 for reviewer 2.They concluded that HCCs and AEPs showed different enhancing features on the delayed dynamic and hepatobiliary phases of Gadoxetic acid disodium-enhanced MRI. Gadoxetic acid disodium-enhanced MRI may therefore help to differentiate between HCC and AEP.[22 level 3]

In another retrospective study by Motosugi *et al.* which was conducted in a tertiary hospital in Japan, they found that Gadoxetic acid disodium-enhanced hepatocyte phase MRI and diffusion weighted (DW) imaging could be used to distinguish hypervascular pseudolesions from hypervascular HCCs; a hepatocyte-phase SI ratio below 0.84 and visibility on DW images were findings specific for HCCs rather than pseudolesions.[23 level 3]

5.2.3. Comparison with other liver-specific MRI contrast agents.

Seven studies compared Gadoxetic acid disodium (Gd-EOB-DTPA) enhanced MRI with other liver-specific MRI contrast agents.

Vogl *et al.* conducted a prospective Phase II double-blind randomised trial in Germany to compare the usefulness of Gadoxetic acid disodium (Gd-EOB-DTPA) with conventional Gadolinium chelate; Gadopentetate dimeglumine (Gd-DTPA), in the diagnosis of focal liver lesions. The study involved 31 patients with focal liver lesions, who underwent T2- and T1-weighted spin-echo MRI and fast low-angle shot two-dimensional MRI before, during and after intravenous (IV) administration of three different doses of Gd-EOB-DTPA (12.5 µmol, 25 µmol and 50 µmol per kg body weight). GD-DTPA–enhanced imaging (0.1 mmol/kg body weight) was performed in the same patients within 1 week of Gd-EOB-DTPA. They found that during the hepatobiliary phase (1.5 minutes to 4 hours after injection), Gd-EOB-DTPA enhanced images yielded a dose-independent, statistically significant improvement in the detection rate of additional metastases, HCC,

and haemangiomas compared with unenhanced and Gd-DTPA-enhanced images ($P < 0.05$).[24]

In another study, Park G *et al.* compared the efficacy of Gadoxetic acid disodium-enhanced MRI (Gd-EOB-DTPA) with Gadopentetate dimeglumine (Gd-DTPA) enhanced MRI in the detection of small HCC (size range, 0.5 cm to 2.0 cm). Both MRI techniques were performed on 43 patients with a total of 59 HCCs with a mean interval between the two MRI studies of three days. Two observers reviewed both data sets in consensus. Diagnostic accuracy and sensitivity were evaluated using the alternative-free ROC method. They found that the Gadoxetic acid disodium set of images showed a trend toward increased area under ROC curve (Az value = 0.958) compared with the Gadopentetate dimeglumine set (Az value = 0.927), but the difference was not significant ($P = 0.362$). However, the sensitivity of the Gadoxetic acid disodium set (84.4%) was significantly higher than that of the Gadopentetate dimeglumine set (64.4%), $P = 0.0001$. The authors concluded that Gadoxetic acid disodium-enhanced MRI was more sensitive diagnostic tool for HCC than Gadopentetate dimeglumine-enhanced MRI.[25 level 3]

Kim YK *et al.* conducted two studies in a tertiary hospitals in Korea to compare diagnostic performance of Gadoxetic acid disodium-enhanced MRI with superparamagnetic iron-oxide (SPIO) enhanced MRI for detection of liver metastases and HCC.[26-27] Between June 2007 and April 2008, 36 patients with 80 liver metastases who underwent Gadoxetic acid disodium-enhanced MRI and ferucarbotran (which is a SPIO)-enhanced MRI with a mean interval of seven days were included in the study. Two observers independently interpreted the two sets of images; the Gadoxetic acid set and the ferucarbotran set. Diagnostic accuracy was evaluated using the alternative-free response ROC method. They found that there was a trend toward increased areas under ROC curve (Az values) for the gadoxetic acid set of images (0.950 and 0.948) as compared with ferucarbotran set of images (0.941 and 0.939), but no significance difference was found for both observers ($P < 0.05$). Sensitivity for the Gadoxetic set of images (93.8% and 92.5%) were also slightly better than those of the ferucarbotran set of images (88.8% and 87.7%), $P = 0.13$. The two image sets showed similar PPV (98.7% and 98.6%, respectively). The authors concluded that Gadoxetic acid disodium-enhanced MRI showed comparable diagnostic performance to ferucarbotran-enhanced MRI for detection of liver metastases.[26 level 2]

In another diagnostic accuracy study involving 89 patients with 118 HCCs who underwent Gadoxetic acid disodium-enhanced MRI and SPIO (ferucarbotran)-enhanced MRI, they found that the area under the ROC curve (Az value) and the sensitivity of the Gadoxetic acid disodium set of images were significantly higher than those of the SPIO set of images. The Az value of Gadoxetic acid disodium set of images was 0.964 versus 0.830 for the SPIO set of images, ($P = 0.004$). The sensitivity of Gadoxetic acid disodium set of images was 90.7% versus 84.7%, for the SPIO set of images ($P = 0.08$). Although there was no difference between the sensitivity of the Gadoxetic acid disodium set of images and that of the SPIO set of images for lesions larger than 1.5 cm diameter (97.5% for both), 14 lesions $\leq$ 1.5 cm were verified on Gadoxetic acid set only and seven lesions $\leq$ 1.5 cm were verified on SPIO set only. The authors concluded that Gadoxetic acid

disodium enhanced MRI was better than SPIO-enhanced MRI for detection of HCCs.[27] level 3

Kim YK *et al.* also conducted another diagnostic accuracy study to investigate whether Gadoxetic acid disodium-enhanced MRI has the diagnostic capability and sensitivity comparable to the combination of Gadopentetate dimeglumine (Gd-DTPA)-enhanced MRI and SPIO-enhanced MRI (double-contrast MRI) in the detection of small HCCs. Forty-one patients with 56 HCCs (size range 0.5 cm to 2.0 cm) who underwent both Gadoxetic acid disodium-enhanced MRI and double-contrast MRI with a mean interval of four days were included in the study. They found that the area under ROC curve (Az value) and sensitivity were similar for both sets of images [(Az value = 0.955 and Sensitivity = 83.9%) for Gadoxetic acid disodium set) and (Az value = 0.952 and Sensitivity = 80.4%) for double-contrast MRI set), $P > 0.05$]. There were five HCCs that were clearly identifiable on the Gadoxetic acid disodium set, but were not verifiable on the dual contrast MRI. There were three HCCs that were clearly discerned on the dual contrast MRI, but not verifiable on the Gadoxetic set (confidence rating one or two). There were six HCCs that could not be verified on both image sets. All lesions were confirmed by pathologic analysis of surgical specimens or percutaneous biopsy. They concluded that Gadoxetic acid disodium-enhanced MRI could replace double-contrast MRI for detection of HCCs.[28 level 2]

Two studies compared the diagnostic performance of Gadoxetic acid disodium-enhanced MRI with Gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI in detecting liver lesions.[29-30] Filippone A *et al.* conducted a multicentre (16 centres) Phase III study to compare the enhancement of liver parenchyma after injection of gadoxetic acid disodium (Gd-EOB-DTPA) and Gadobenate dimeglumine (Gd-BOPTA). The study involved 264 patients with known or suspected focal liver lesions who were randomly assigned to receive 0.025 mmol gadoxetic acid/per kg body weight or 0.05 mmol Gadobenate dimeglumine/kg body weight by means of bolus injection. They found that the relative liver enhancement in the overall study population was superior with Gadoxetic acid disodium (57.24%) versus Gadobenate dimeglumine (32.77%) in the delayed imaging phase. The ratio between both contrast media was 1.75; 95% CI, 1.46-2.13 indicating statistically significant superiority of Gadoxetic acid disodium at 20 minutes post contrast over Gadobenate dimeglumine at 40 minutes postcontrast with regard to enhancement of liver parenchyma. In subgroup of patients with underlying liver cirrhosis, the enhancement in liver parenchyma with Gadoxetic acid disodium (57.00%) was comparable to that in the study population (57.24%), whereas the enhancement with Gadobenate dimeglumine was inferior in patients with liver cirrhosis (26.85%) compared with overall population (32.77%). [29]

Park Y *et al.* conducted a diagnostic accuracy study in Korea to compare the diagnostic performance of Gadoxetic acid disodium-enhanced MRI with Gadobenate dimeglumine-enhanced MRI for preoperatively detecting HCC. Eighteen consecutive patients with 22 HCCs underwent examinations with Gadoxetic acid disodium-enhanced MRI and Gadobenate dimeglumine-enhanced MRI on a 3.0-Tesla unit. Three observers independently reviewed each MR image in random order on a tumour-by-tumour basis.

They found that the average value of the area under ROC curve (Az value) for Gadoxetic acid-enhanced MRI (0.887) was not significantly different from the Az value for Gadobenate diglumine-enhanced MRI (0.899), P > 0.05. There was also no significant difference in the sensitivity and PPV for the two contrast agents. They concluded that the diagnostic performance of Gadoxetic acid disodium-enhanced MRI and Gadobenate dimeglumine-enhanced MRI for preoperatively detecting HCC was quite similar.[30 level 3]

5.3 COST/COST-EFFECTIVENESS

There was only one economic evaluation retrieved. Zech CJ *et al.* performed an economic evaluation of Gd-EOB-DTPA enhanced MRI as a pre-operative diagnostic tool in patients with colorectal liver metastases (CLM) compared with MDCT and extracellular contrast media-enhanced MRI (ECCM-MRI). The economic evaluation was performed with a decision-tree model designed to estimate all aggregated costs depending on the initial investigation. Probabilities on the need for further imaging to come to a treatment decision were collected through interviews with 13 pairs of each a radiologist and a liver surgeon in Germany, Italy and Sweden. The rate of further imaging needed was 8.6% after initial Gd-EOB-DTPA enhanced MRI, 18.5% after ECCM-MRI and 23.5% after MDCT. Considering the cost of all diagnostic work-up, intra-operative treatment changes and unnecessary surgery, a strategy starting with Gd-EOB-DTPA enhanced MRI with 959 € was cost-saving compared to ECCM-MRI (1,123 €) and MDCT (1,044 €) in Sweden. In Italy and Germany, Gd-EOB-DTPA enhanced MRI was cost-saving compared to ECCM-MRI and had total costs similar to MDCT. They concluded that Gd-EOB-DTPA enhanced MRI was cost-saving by improving pre-operative planning and decreasing intra-operative changes. The higher cost of imaging with Gd-EOB-DTPA enhanced MRI is offset in such a scenario by lower costs for additional imaging and less intra-operative changes.[31]

The price per bottle (10 ml) of Gadoxetic acid disodium [Gd-EOB-DTPA (Primovist®)] was estimated at RM [redacted]. The price for Gadopentetate dimeglumine (Gd-DTPA) was about RM [redacted] per bottle (10 ml) and the price for Gadobenate dimeglumine (Gd-BOPTA) is about RM [redacted] per bottle (15 ml).(Via personal communication with Bayer Healthcare representative).

5.4 LIMITATIONS

This technology review has several limitations. The selection of studies was done by one reviewer. Although there was no restriction in language during the search but only English full text articles were included in this report. Most of the diagnostic accuracy studies suffered from differential use of reference standard (not all of the lesions were confirmed histopathologically). Some of the diagnostic studies were conducted retrospective instead of prospective. There was only one economic evaluation study retrieved which was based on a decision-tree model. Economic analyses that were conducted in other countries can have limited generalizibility to the Malaysian health care system.

6. CONCLUSION

6.1. SAFETY

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI is safe. However, there was a warning stating that Gadolinium-based contrast agents increased the risk of Nephrogenic Systemic Fibrosis (NSF) among patients with impaired elimination of the drugs.

6.2. EFFICACY/EFFECTIVENESS

6.2.1. Comparison with unenhanced MRI

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI improved sensitivity for lesion detection, classification and characterization of focal liver lesions compared with unenhanced MRI.

6.2.2. Comparison with CT

There was fair level of evidence to show that Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had the following characteristics:-

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in the detection, classification and characterization of liver lesions especially for lesions equal to or less than two centimetre in diameter compared with spiral CT
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance but may be better for detection of HCC of one centimetre in diameter or smaller compared with triple phase MDCT
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had higher sensitivity for differentiation between hypervascular HCC and hypervascular pseudolesions compared with triple phase MDCT

6.2.3. Comparison with other liver-specific MRI contrast agents

There was fair level of evidence to show that:-

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in detecting HCC than Gadopentetate dimeglumine (Gd-DTPA)-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was as efficacious in detecting liver metastases when compared with SPIO-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI was more effective in detecting HCC compared with SPIO-enhanced MRI
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance compared with double-contrast MRI (Gadopentetate dimeglumine-enhanced MRI and SPIO-enhanced MRI) in detection of small HCC
- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI showed better enhancement of liver parenchyma at 20 minutes post contrast compared with Gadobenate dimeglumine (Gd-BOPTA) at 40 minutes post contrast

- Gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced MRI had similar diagnostic performance as Gadobenate dimeglumine (Gd-BOPTA)-enhanced MRI for detecting HCC

6.3. COST/COST-EFFECTIVENESS

There was limited evidence to show that although the cost of Gadoxetic-acid disodium (Gd-EOB-DTPA) liver-specific MRI contrast agent was found to be higher than the extracellular liver-specific MRI contrast agent [Gadopentetate dimeglumine (Gd-DTPA)], the strategy starting with Gd-EOB-DTPA enhanced MRI as a pre-operative diagnostic tool in patients with colorectal liver metastases was shown to be more cost saving.

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8. APPENDIX

8.1 Appendix 1

HIERARCHY OF EVIDENCE FOR TEST ACCURACY STUDIES

Level	Description	
1.	A blind comparison with reference standard among an appropriate sample of consecutive patients	
2.	Any one of the following	Narrow population spectrum
3.	Any two of the following	Differential use of reference standard
4.	Any three or more of the following	Reference standard not blind
		Case control study
5.	Expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.	

SOURCE: NHS Centre for Reviews and Dissemination (CRD) University of York, Report Number 4 (2nd Edition)