LIVER AND BILIARY DISEASE

Prospective comparative study of spiral computer tomography and magnetic resonance imaging for detection of hepatocellular carcinoma


Background: Hepatocellular carcinoma (HCC) is often detected at a relatively late stage when tumour size prohibits curative surgery. Screening to detect HCC at an early stage is performed for patients at risk.

Aim: The aim of this study was to compare prospectively the diagnostic accuracy and classification for management of the two state of the art secondline imaging techniques: triphasic spiral computer tomography (CT) and super paramagnetic iron oxide (SPIO) enhanced magnetic resonance imaging (MRI).

Patients: Sixty one patients were evaluated between January 1996 and January 1998. Patients underwent CT and MRI within a mean interval of 6.75 days.

Methods: CT and MRI were evaluated blindly for the presence and number of lesions, characterisation of these lesions, and classification for management. For comparison of the data on characterisation, the CT and MRI findings were compared with histopathological studies of the surgical specimens and/or follow up imaging. Data of patients not lost to follow up were available to January 2001.

Results: SPIO enhanced MRI detected more lesions and overall smaller lesions than triphasic spiral CT (number of lesions 189 vs 124; median diameter 1.0 vs 1.8 cm; Spearman rank’s correlation coefficient 0.63, p=0.001). There was no significant difference in accuracy between CT and MRI for lesion characterisation. The agreement in classification for management was very good (weighted kappa 0.91, 95% CI 0.83–0.99).

Conclusion: SPIO enhanced MRI detects more and smaller lesions, but both techniques are comparable in terms of classification for management. SPIO enhanced MRI may be preferred as there is no exposure to ionising radiation.

Hepatocellular carcinoma (HCC) is the most common primary liver tumour. Incidence ranges from 1 to 150 cases per 100 000 inhabitants per year, with a wide variation between geographical regions. This wide variation is caused by differences in the prevalence of risk factors such as viral hepatitis, cirrhosis, and metabolic diseases. A recent study has demonstrated an increase in the incidence of HCC in the USA over the last two decades. In these decades the age specific incidence shifted towards younger people. Surgery in selected cases improves survival but only a limited number of patients are suitable for surgery at the time of presentation as clinical symptoms occur later in the course of the disease. Detection and treatment of HCC at an earlier stage can be expected to improve survival as patients with a relatively small tumour have a better prognosis than patients with more extensive disease.

Therefore, screening programmes for patients at risk have been developed to detect HCC at an earlier stage. Current screening programmes comprise serum α fetoprotein (AFP) level and abdominal sonography at six month intervals for high risk patients. Patients positive at screening—that is, with an elevated AFP, an abnormal ultrasound examination, or a combination of the two—require more advanced imaging. Secondline imaging is performed to detect and characterise intrahepatic lesions. Recent developments in computer tomography (CT) and magnetic resonance imaging (MRI) techniques have led to several new strategies for advanced imaging. Spiral CT and MRI with non-specific and especially specific contrast media (for example, super paramagnetic iron oxide (SPIO)) have been advocated but the optimum strategy has not yet been established.

The aim of this prospective study was to compare triphasic spiral CT and SPIO enhanced MRI in establishing the number of hepatic lesions and their nature, and to compare both techniques in terms of classification for management (surgery) in patients suspected of having HCC at screening.

MATERIAL AND METHODS

Patient inclusion

From January 1996 to January 1998, 408 patients participated in a screening programme for HCC at the Erasmus Medical Centre Rotterdam, which is a tertiary referral centre for liver diseases and liver transplantation. Most patients at risk in our hospital population had hepatitis B or C cirrhosis. Screening comprised ultrasound and AFP levels at six month intervals. Patients were included when a new non-cystic focal lesion was detected at ultrasound and/or AFP was elevated to twice the previous value or twice the upper limit of normal (20 µg/l). Patients with a strong clinical suspicion for HCC (for example, weight loss, rapid clinical deterioration) but no abnormal findings at screening were also included. Patients were excluded when there were contraindications for intravenous gadolinium enhanced MRI.

Abbreviations: AFP, α fetoprotein; CT, computer tomography; GRE, gradient echo; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; SPIO, super paramagnetic iron oxide; TSE, turbo spin echo.
low osmolar iodised contrast medium, SPIO, or MRI (for example, pacemaker).

During the study period, 61 consecutive patients (41 males, 20 females; mean age 51.9 years, range 30–74) findings at imaging were compared with histopathological findings on the resected specimen or follow up imaging. Ten patients underwent liver transplantation (mean imaging–histopathology interval, 102 days, range 15–306), six patients underwent hemihepatectomy (mean imaging–resection interval, 40 days, range 5–98 days) with follow up imaging of the in situ liver, and 20 patients had follow up imaging only (mean interval 10.6 months, range 6–20). For the 25 remaining patients no histological specimen was available as these patients were not eligible for surgery. No follow up images were made at six months because these patients were in a poor clinical condition (three), had died (11), or were lost to follow up (11). In patients not lost to follow up, clinical follow up was available to January 2001, or until death.

Screening findings
The 61 patients were eligible for the screening protocol because of hepatitis C (23), hepatitis B (20), hepatitis B and C (10), primary biliary cirrhosis (two), secondary biliary cirrhosis (one), Byler's disease (one), and cirrhosis caused by alcohol abuse (three) or α1 antitrypsin deficiency (one). All patients had a biopsy of non-tumorous liver. Forty nine patients had cirrhosis at histopathology.

Seventeen patients had one or more lesions at ultrasound, 10 patients had abnormal elevated AFP levels, 26 patients had abnormal findings both for AFP level and ultrasonography, and eight patients had high clinical suspicion only. At ultrasound, 26 patients had one lesion, eight patients two lesions, two patients three lesions, and seven patients had more than three lesions. Mean AFP level was 15 682 µg/l (range 3–350 000 µg/l).

Imaging
Spiral CT and MRI with SPIO were performed at least 24 hours apart. Mean interval was 6.75 days (range 1–73). For 52 of the 61 patients, CT and MRI were performed within one week.

Spiral CT comprised plain, arterial phase, and portal phase imaging using a single detector row machine (Siemens Somatom Plus; Erlangen, Germany). Plain spiral CT comprised 8 mm slices, 1 mm overlap, and 7 mm reconstruction (pitch 1), and arterial and portal phases comprised 5 mm slices, 1 mm overlap, and 4 mm reconstruction (pitch 1). The arterial phase was performed 20 seconds after the start of injection of 150 ml of low osmolar ionised contrast medium at a rate of 3 ml/s and the portal phase 60 seconds after the start of the injection. No bolus timing technique was used as standard timing gives adequate results whereas contrast timing lengthens the procedure. MRI was performed at 1.5 T (Philips Gyroscan NT 15; Philips Medical Systems, Best, the Netherlands) using the body coil and comprised axial T2w turbo spin echo (TSE), axial T2w TSE with fat saturation and, after administration of SPIO (Endorem; Guerbert Laboratoires, Paris, France), axial T2w TSE with fat saturation, coronal T1w gradient echo (GRE), dynamic multiphase axial T1w GRE (plain, arterial, and portal phases, and a late phase at three minutes) during and after intravenous gadodiamide (Nycomed, Oslo, Norway), and coronal T1w GRE after gadobenate dimeglumine. SPIO was administered intravenously at a dose of 15 pmol/kg (0.075 ml/kg) diluted in a 100 ml 5% glucose solution through a specific filter (median pore diameter 5 µm) in 30 minutes. For further analysis only the axial T2w TSE with fat saturation after SPIO was used as this sequence proved to be the most sensitive. This sequence had a repetition time of 2000 ms, echo time was 70 ms, 7 mm slices (1 mm interslice gap), field of view 300×375 mm, imaging matrix 193×256, and two acquisitions.

Image analysis
As part of the study, CT and MRI were evaluated blindly and separately by two consultants with at least five years of experience in abdominal radiology. The radiologists were informed about the findings at screening. The findings were recorded directly on case record forms. Triphasic spiral CT and MRI with SPIO were evaluated for image quality (good, moderate, poor), artefacts, presence of hepatic lesions, number of hepatic lesions, size of the lesions (<2 cm, 2–<5 cm, ≥5 cm), diagnosis of the lesions (for maximal three lesions), and for establishing the correct classification for management.

For lesion characterisation, the imaging characteristics of HCC, regeneration nodules, benign lesions (for example, haemangioma), and metastasis were used as described in the literature for CT and MRI. CT and MRI were compared for establishing the correct classification for management: no suspect lesion and no surgical treatment; suspect lesion(s) and eligible for curative surgery; and extensive disease without the possibility of curative surgical treatment. Patients without HCC had no hepatic surgery, except for other indications (for example, liver transplantation for deterioration of hepatic function). Patients with a lesion(s) suspected of being HCC were considered as candidates for hepatic surgery when only one lesion was present (<5 cm) or there were two lesions ≤2 cm. Patients were not eligible for surgery when more extensive disease was present.

Histopathology
An experienced hepatic pathologist performed the histopathological studies. Histopathological studies comprised contiguous 1 cm slices of the complete specimen, additional thinner slices when necessary, and microscopy of all suspicious lesions using haematoxylin-eosin staining. The specimens were evaluated with knowledge of the findings at spiral CT and MRI with SPIO. Each lesion detected at imaging was evaluated histopathologically and the specimens were carefully scrutinised for the presence of lesions not detected at imaging.

Follow up imaging
Follow up imaging comprised repeat triphasic CT and MRI with SPIO. For both repeat studies the parameters were identical to those of the initial studies. The repeat spiral CT and MRI with SPIO were read simultaneously by the two consultants who performed the initial reading. The studies were compared with the initial studies and all relevant data (for example, histopathology). Growth of lesions by at least 20% of the initial diameter or 5 mm or more and/or the presence of new lesions was defined as evidence of malignancy. Lesions with the characteristic findings of cyst or haemangioma on both spiral CT and MRI, a normal AFP level, and no changes on follow up spiral CT and MRI were considered to be cysts and haemangiomas, respectively, and no biopsy was taken. The initial imaging studies were carefully scrutinised in the case of new lesions to determine whether these lesions were already present on the initial studies. New findings were further evaluated (for example, biopsy).

Statistical analysis
Statistical analysis was performed with SAS version 6.12 (SAS Institute Inc., Cary, North Carolina, USA). The number of
lesions per patient at CT and MRI were compared using the Wilcoxon rank's sum test. Correlation of CT and MRI for lesion size was determined using Spearman rank's correlation test. P <0.05 was considered significant. Weighted kappa values were calculated for agreement between CT and MRI in terms of classification for management. Kappa <0.2 was considered poor agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 good agreement, and 0.81 and 1.0 very good agreement.

RESULTS
No patient was excluded because of contraindications for CT or MRI. All spiral CT procedures were performed without complications. Two patients experienced back pain during the SPIO infusion for MRI which resolved uneventfully after the infusion was finished. One patient suffered hypotension after the SPIO infusion for the follow up MRI. Hypotension was transient and required no further treatment. No other imaging procedure related adverse events occurred in this study population. The image quality of the spiral CT was good in all cases. For all CT studies the timing was adequate, as indicated by the enhancement pattern. The image quality of SPIO enhanced MRI was good in 56 cases. For five patients image quality was moderate because of respiratory artefacts.

Fifty three of the 61 patients were found at screening to have an indication for second line imaging: 10 because of an elevated AFP but a normal ultrasound examination and 43 because of a liver tumour at ultrasound with (n=26) or without (n=17) elevated AFP levels. Eight patients were included because of clinical deterioration. In four of 10 patients with only an elevated AFP, HCC was detected by contrast enhanced MRI as well as spiral CT. For the remaining six patients no liver lesions were demonstrated by MRI or CT imaging at six monthly follow up examinations; the elevated AFP levels were attributed to active hepatitis. Fourteen of 43 patients with suspected HCC after ultrasonography but normal AFP levels were found to have a tumour of a different origin at second line imaging and biopsy (six haemangiomas, three regeneration nodules, two metastases, one adenoma, and one focal nodular hyperplasia).

For the 61 patients studied, SPIO enhanced MRI detected more HCC suspect lesions than triphasic spiral CT (124 v 189). The total number of suspect lesions identified with CT or MRI was 197 (table 1). Median number of lesions was 1 (interquartile range 1–3.5) at CT and 2 (interquartile range 1–7) at MRI. With 44 patients one lesion or more and with MRI, 45 patients had one lesion or more. In 39 patients equal numbers of lesions were found, in five patients more lesions were found with CT, and in 18 patients more lesions were found by MRI, indicating that MRI detected more lesions compared with CT scan (p<0.01). In 14 of 15 patients diagnosed with cirrhosis at histopathology, MRI and CT scan showed equal numbers of lesions.

Median diameter of the lesions at MRI was smaller (1.0 cm; interquartile range 1.0–2.5 cm) than at CT (1.8 cm; interquartile range 1.0–4.0 cm) (Spearman rank's correlation coefficient 0.63, p<0.001) (fig 1). When only the largest lesion was considered per patient, median diameter was 5.4 cm (interquartile range 2.7–9.8) for CT and 5.6 cm (interquartile range 2.4–8.4) for MRI.

CT and MRI showed very good agreement (weighted kappa 0.91; 95% confidence intervals 0.83–0.99) in classifying patients for management (table 2). In five patients there were differences in terms of classification for management. MRI classified two patients as candidates for surgery as one lesion (2.0 cm, 2.5 cm) was found, while in both patients the lesion was not visualised at CT. MRI findings proved to be correct at histopathology of the resected liver. One patient was a candidate for surgery based on CT findings as one lesion with a diameter of 2.0 cm was detected, while at MRI the patient was not eligible for surgery as two lesions were detected with one lesion larger than 2.0 cm (1.6 cm, 2.2 cm). At follow up imaging the findings at MRI were confirmed. In another patient, a 3 cm lesion was detected at CT and no lesion at MRI. This lesion proved to be focal nodular hyperplasia at histopathology after biopsy. In a fifth patient, a 5 cm lesion was detected at CT and two lesions (5.6 cm, 1.3 cm) at MRI. As both lesions were closely related within one liver lobe, hemihepatectomy was performed. At histopathology two lesions were detected in the specimen (6.0 cm, 1.3 cm).

At CT, no regeneration nodules were found in 43 patients, seven patients had less than 100 regeneration nodules (median 20; range 5–25), and 11 patients had more than 100 regeneration nodules. At MRI, no regeneration nodules were found in 36 patients, 12 patients had less than 100 regeneration nodules (median 23; range 1–70), and 13 patients had more than 100 regeneration nodules.

For the 36 patients with positive histopathological findings for partial or completely resected liver and follow up imaging, patients. The broken line represents the x=y line.

Table 1 Number of suspected lesions at triphasic spiral computer tomography (CT) and super paramagnetic iron oxide enhanced magnetic resonance imaging (MRI) in 61 patients.

<table>
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<tr>
<th>MRI</th>
<th>CT</th>
<th>&lt;2 cm</th>
<th>2–5 cm</th>
<th>≥5 cm</th>
<th>All</th>
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<tr>
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<td>MRI</td>
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<tr>
<th>Diameter by MRI (cm)</th>
<th>Diameter by CT (cm)</th>
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<td>2</td>
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Table 2 Agreement in terms of classification for management by computer tomography (CT) or magnetic resonance imaging (MRI) in 61 patients.

<table>
<thead>
<tr>
<th>MRI</th>
<th>No surgery necessary</th>
<th>Eligible for surgery</th>
<th>Extensive disease, no surgery</th>
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</tr>
<tr>
<td>CT</td>
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<td>MRI</td>
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Weighted kappa 0.91 (95% confidence interval 0.83–0.99).
findings of CT and MRI in characterising the lesions were comparable (table 3).

For the 10 patients who underwent liver transplantation, CT yielded the correct number of lesions and correct characterisation of the lesions in six cases (MRI in nine cases). With CT, HCC was missed in two patients (1.5 cm, 1.5 cm), two HCC were missed in one patient (0.5 cm, 3 cm), and a lesion was diagnosed as HCC that proved to be a regenerative nodule at histopathology. With MRI, two HCC were missed in one patient (0.5 cm, 3 cm). For the six patients with a resected liver, CT findings were correct in five cases and MRI findings were correct in all cases. With CT, a 3 cm HCC was missed.

**DISCUSSION**

Surgical treatment of HCC can offer cure in selected cases, either by resection for patients without portal hypertension and adequate hepatic reserve or by liver transplantation for cirrhotic patients with inadequate hepatic reserve. As the majority of HCCs tend to grow slowly and metastasise late in the course of the disease, early detection and treatment may improve survival. Screening studies of patients at risk may thus offer an important instrument for improvement of the prognosis for patients with this primary liver tumour. However, in addition to the definition of at risk patients, the success of a screening programme is also dependent on the availability of a secondline imaging technique with high sensitivity and specificity for detection and characterisation of nodules suspected of being HCC. At present, results of prospective controlled studies to determine which secondline imaging technique should be used for the workup and follow up of patients suspected of having HCC are not yet available. Accurate determination of the number of lesions and correct characterisation of these lesions are essential to define homogeneous groups of patients and to evaluate new therapies. The role of state of the art secondline imaging in patient management (for example, eligibility for curative surgery) has not yet been determined.

The present prospective study demonstrated that SPIO enhanced MRI was superior to spiral CT for detection of lesions. Detection of the number of lesions is important for patient management and prognosis. Others have already reported on the outcome of either contrast enhanced MRI or spiral CT of cirrhotic or non-cirrhotic livers. Portal phase spiral CT and to a lesser extent plain CT or delayed phase spiral CT can add some information. The wide range can be explained by inclusion of a variety of patient groups, differences in technique, and lack of follow up imaging or histopathological evidence of HCC. In the present study, histological specimens were studied if available or follow up imaging was performed at six month intervals by repeating both imaging studies. In this study the sensitivity of spiral CT was 76%.

MRI is a rapidly evolving technique, with growing evidence that SPIO enhanced MRI is the optimum approach. With MRI, detection of HCC can be based on arterial phase imaging, as in spiral CT, but the high intrinsic contrast resolution of MRI also offers the possibility of using T2 weighted sequences. T2 weighted sequences, especially T2 weighted TSE sequences after SPIO, have been demonstrated to be valuable techniques for the detection of hepatic lesions, including HCC. SPIO enhanced MRI has been demonstrated to be superior to gadolinium enhanced dynamic MRI for detection of focal hepatic lesions, including HCC. In an ex vivo study with correlation with pathology, MRI with T1 weighted spin echo and T2 weighted TSE sequences detected 41 of 42 non-regenerative nodules in 28 explanted cirrhotic livers.

A major problem is differentiation between benign nodules (regenerative nodules and dysplastic nodules) and HCC in cirrhotic livers. MRI has been advocated as the optimum imaging technique for differentiation between these benign nodules and HCC. The use of SPIO, as in the present study, can be expected to lead to an increase in accuracy. In this study some hypointense nodules proved to be HCC. One explanation for this limitation lies in the pathogenesis of HCC in cirrhotic livers. Dysplastic nodules, formerly called macroregenerative nodules or adenomatous hyperplastic nodules, are thought to be precursors of HCC with a gradual progression to HCC. This gradual progression of a benign premalignant lesion to HCC is only partly reflected in changes in the imaging characteristics. Normal liver parenchyma, regenerative nodules, and dysplastic nodules demonstrate uptake of SPIO by Kupffer cells. A significant decrease in the number of Kupffer cells is found predominantly in moderately and poorly differentiated HCC. These types of HCC will remain hyperintense in T2 weighted sequences after SPIO. Highly differentiated HCC may become hypointense like benign lesions.

In the present study, lesion by lesion proof of diagnosis was demonstrated for 36 of 61 patients. This proof was based on histopathological studies of the resected specimen and radiological and clinical follow up for up to two years. Biopsies were taken only when histopathology would have implications for further management. Complete histopathological data available for those patients who underwent total hepatectomy or liver transplantation support the findings for the entire study population.

Importantly, detection of more lesions at MRI compared with CT in this study did not lead to improved classification for treatment (for example, curative surgery). The major reason is that the difference in detection of lesions was predominantly in patients with extensive disease (more than two lesions).
These patients are not candidates for curative surgery and therefore differences in the number of lesions higher than two do not influence management.

Both spiral CT and MRI are rapidly developing techniques with new improvements yet to come. For MRI the widespread use of phased array coils, new imaging sequences, and protocols (for example, multiphasic breath hold three dimensional gadolinium enhanced MR) and further developments in liver specific contrast media will enhance the efficacy of the technique. A recent innovation is the introduction of the next generation of CT scanners with the possibility of very thin slices (1–3 mm) which may improve lesion detection with spiral CT. A drawback is the further increase in radiation dose, especially for patients who need multiple secondline imaging procedures during the screening period. The CT technique used in the present study produces an effective dose of approximately 12 mSv, leading to an estimated risk of a fatal radiation induced cancer of 1:1700 per examination for the general population. This risk, which is age dependent, decreases with increasing age.

Triphasic spiral CT and SPIO enhanced MRI are both valuable advanced imaging techniques but the absence of ionising radiation exposure makes SPIO enhanced MRI preferable for the workup and follow up of patients suspected of having HCC. As a result, future studies on HCC may become more accurate in the identification and monitoring of this malignancy.

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