Detection of small hepatocellular carcinomas in cirrhotic livers using iodised oil computed tomography

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Abstract

Background—The detection of hepatocellular cancers (HCC) is a major role of preoperative imaging in patients with end stage liver disease being considered for orthotopic liver transplantation (OLT).

Aims—To assess the sensitivity of iodised oil computed tomography (IOCT).

Patients and methods—A prospective evaluation in 50 consecutive patients undergoing OLT included ultrasound scan, contrast enhanced CT, angiography (with intra-arterial injection of iodised oil), and a second CT (IOCT) 10 days later. Following transplantation the explant liver was serially sectioned for pathological evaluation. Soft tissue radiographs of the liver slices were used to match histological lesions with CT findings.

Results—Eleven patients were excluded due to protocol violations. Of the remaining 39, histological evaluation revealed no cancers in 33 explant livers, in keeping with negative preoperative imaging. Six explant livers contained 55 HCCs, 84% of which were less than 1 cm in diameter. Pretransplant IOCT detected 3/6 patients with cancer (50%) but only 7% of cancerous lesions. Ultrasound, contrast CT, and angiography each detected 2/6 patients with cancer and 4% of cancerous lesions.

Conclusion—IOCT is an insensitive method for the detection of small HCCs in livers with advanced cirrhosis but in this study was slightly superior to ultrasound, CT, and angiography.

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Keywords: liver cirrhosis; transplantation; hepatocellular carcinoma; iodised oil; computed tomography

The development of hepatocellular carcinoma (HCC) is a well recognised complication of advanced liver cirrhosis and is a relative contraindication to orthotopic liver transplantation (OLT). The risk of tumour recurrence following transplantation varies with the size of tumour and the presence of multifocal disease.[1] Preoperative imaging for the detection of tumour is therefore essential. The use of iodised oil computed tomography (IOCT), which involves hepatic CT following intrahepatic arterial injection of iodised oil, is reported to be highly sensitive for the detection of HCC.[2–4] However, these reports are based on histological data obtained from resected specimens or needle biopsy rather than an evaluation of the whole liver and are therefore inaccurate. The purpose of this study was to determine the sensitivity of IOCT in the detection of HCC in patients with advanced liver cirrhosis, based on whole liver pathological evaluation.

Patients and Methods

From July 1993 to December 1994, 50 patients underwent a first elective OLT at our centre for end stage chronic liver disease and were included in this study. Preoperative imaging included hepatic ultrasonography (ATL, Ultramark 9) and CT (Somatom DR2, Siemens, Erlangen, Germany) consisting of 1 cm contiguous sections through the entire liver, prior to and after 75 ml of intravenous contrast agent. Visceral angiography was performed to assess the hepatic artery and portal vein. During the selective hepatic study 10 ml of iodised oil (Lipiodol, Laboratoire Guerbet, Roissy Charles de Gaulle, Paris, France) was injected into the hepatic artery proper, or into the left and/or right hepatic artery when anatomical variation was encountered. Ten to 15 days later a further hepatic CT scan was performed. The pattern of iodised oil deposition was recorded from IOCT as follows:

- Nodular: focal deposit(s) >5 mm (fig 1A).
- Heterogeneous: non-focal, wedge shaped, or subcapsular deposition (fig 1B).
- No deposition.

The size, number, and distribution of nodules on the IOCT images were recorded, on a consensus basis, by two experienced radiologists (RD, JS) who were unaware of the clinical details of the patients and the subsequent histological findings of the explant livers.

Following transplantation the explant liver was cut into 10 mm slices. Each slice was closely inspected for atypical nodules according to a standard protocol.[5] Liver slice radiographs were taken of all slices in those with atypical nodules or preoperative suspicion of HCC and from one representative slice in the remaining patients. Each liver slice was compared with its soft tissue radiograph (fig 2). All foci of iodised oil uptake or high soft tissue density on the soft tissue radiograph were noted and the corresponding site on the liver slice biopsied. Tissue samples were also taken from every nodule that was 1 cm or more in diameter, or with an unusual colour. Iodised oil uptake in cancer deposits was verified by specific silver nitrate staining.[6] Each lesion was

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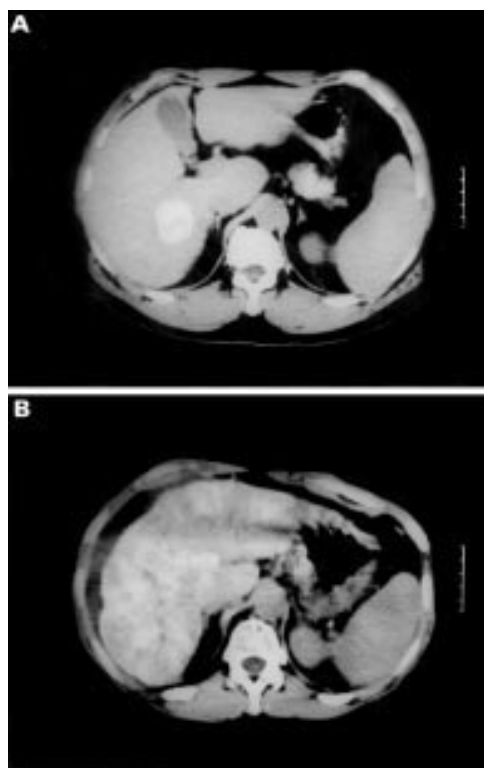
Figure 1: Focal (A) and heterogeneous (B) iodised oil deposition on computed tomography.

classified as either HCC, a regenerative nodule, or an atypical/borderline lesion, using criteria outlined by Ferrell.[7] The findings on preoperative IOCT were then matched for each individual patient with the histological findings of the explant liver. Statistical analysis of the resulting data was performed on a mainframe computer, using the software package SAS (Statistical Analysis System) Version 5 (SAS Institute Inc., Cary, North Carolina, USA, 1985).

Results

Of the 50 cases considered for inclusion, there were protocol violations in 11 due to a donor liver becoming available after Lipiodol administration but prior to IOCT examination. Complete pre-OLT imaging was available in the remaining 39 patients (14 women, 25 men). The underlying causes of chronic liver disease were: hepatitis C (13), alcohol (11), primary sclerosing cholangitis (6), primary biliary cirrhosis (4), chronic active hepatitis (2),

cryptogenic cirrhosis (2), and hepatitis B (1). The median time between IOCT and OLT was 20 days (range 10–80 days). There were no complications related to iodised oil administration.

Histopathological assessment showed no evidence of cancer in the explant livers from 33/39 patients. In 6/39 patients a total of 55 HCCs, 39 regenerative nodules, and nine atypical nodules were found. The aetiology of the liver disease in these patients was alcohol (n=4) and hepatitis C (n=2). The size of histologically detected HCCs ranged from <5 mm to 3.5 cm. Nine of the 55 HCCs were greater than 1 cm in diameter (16%). All nodules greater than 2 cm diameter were HCCs.

Ultrasound, contrast CT, and angiography correctly identified 2/6 patients with histologically proven HCC, but only 2/55 HCCs found on whole liver pathological evaluation (4%). IOCT diagnosed 3/6 patients with cancer in whom four HCCs were demonstrated. Only the largest cancers were found on imaging, IOCT detecting 4/9 HCCs over 1 cm in diameter but none of the smaller lesions. The two largest HCCs were 3.5 cm in diameter and were detected by all preoperative imaging methods. All preoperative imaging modalities failed to identify 3/6 patients with HCCs. There were no false positive results of imaging in the 33 patients without cancer on histology of the explant liver. Table 1 summarises the imaging and histological findings in the six patients with cancer in the explant liver.

The pattern of deposition of iodised oil on IOCT was found to be predictive for the presence of HCC in the explant liver (table 2). The nodular and heterogeneous patterns of IOCT deposition had positive predictive values for the detection of HCC of 100% and 19%, respectively. The no deposition pattern had a negative predictive value of 100%. The presence of iodised oil deposition (either nodular or heterogeneous) was found to have a significant association with the occurrence of HCC, when compared with patients with no deposition (Fisher's exact test, p=0.017).

Table 3 shows the correlation between size of HCCs and iodised oil uptake on liver slice radiography. Only 45% of cancers retained iodised oil, but its presence was found to correlate very well with the histological diagnosis of HCC (χ^2=15.24, df=1, p=0.0001). Of the 30 lesions that showed iodised oil deposition, 25 were HCCs and two were atypical nodules

TABLE 1 *Imaging and histology in six patients with cancer*

	Imaging				Histology		
Patient	US	CT	Hepatic angiography	IOCT†	HCC	RN	AN
1	Negative	Negative	Negative	Hetergeneous	12	1	0
2	Negative	Negative	Negative	Nodular 2×1 cm⋆	15	1	0
3	Negative	Negative	Negative	Hetergeneous	7	2	0
4	Negative	Negative	Negative	Hetergeneous	11	4	9
5	1×3.5 cm⋆	1×3.5 cm⋆	Blush	Nodular 1×3 cm⋆	9	11	0
6	1×2.5 cm⋆	1×2.5 cm⋆	Blush	Nodular 1×2.5 cm⋆	1	1	0
Total	2 (4%)	2 (4%)	2 (4%)	4 (7%)	55	20	9

US, ultrasound; CT, computed tomography; IOCT, iodised oil CT; HCC, hepatocellular carcionoma; RN, regenerative nodule; AN, atypical nodule; Nodular, nodular uptake of iodised oil.
⋆Transverse diameter of tumour (cm); †iodised oil distribution as outlined in Methods.
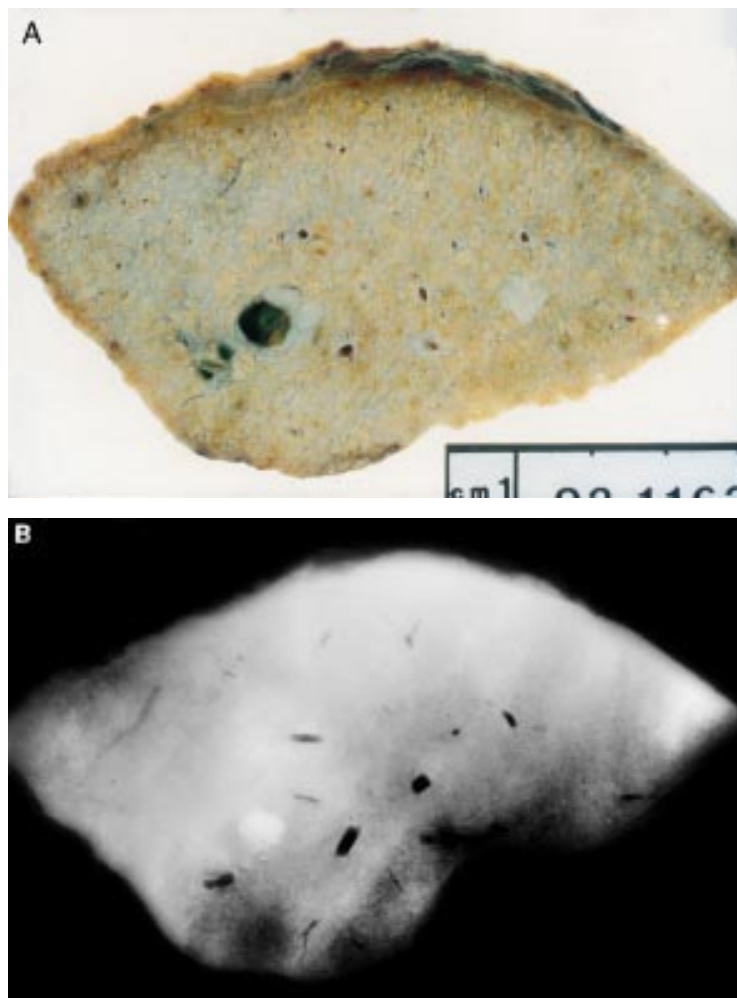
Figure 2:   (A) Naked eye appearance of a liver slice containing two HCCs (central white nodules), one with haemorrhagic change (focal black discolouration). (B) Corresponding soft tissue radiograph demonstrating iodised oil uptake (central opacity) in one of the two cancers.

TABLE 2   *Pattern of iodised oil deposition on IOCT and incidence of HCC*

Pattern of deposition	Number of patients	Number of patients with HCC (%)
Nodular	3	3/3 (100%)
Heterogeneous	16	3/16 (19%)
None	20	0/20 (0%)

TABLE 3   *Size of HCC and iodised oil retention on soft tissue radiograph*

	Iodised oil retention	
Size of HCC	Number of HCCs	Percentage
<5 mm	15/33	45
5–10 mm	6/13	46
>10 mm	4/9	44
Total	25/55	45

(90% specificity). Three regenerative nodules showed only faint uptake in contrast to the HCCs.

Discussion

This is the first study which compares imaging, including IOCT, in patients with end stage liver disease, with a careful histological assessment of the entire explant liver. The sensitivity of IOCT for the detection of HCC was 44% for tumour size equal to or greater than 1 cm. This is considerably lower than the widely reported sensitivity of IOCT to be in excess of 80%.[2–4] However, this study compared the results of imaging with a careful histological examination of the entire liver rather than a surgical partial resection or needle biopsy evaluation. Failure to detect multifocal disease because of an inability to evaluate the entire liver may be an important cause of the variation in reported sensitivities. The stage of the liver disease may also be a factor as transplant candidates have more advanced liver disease than those considered for surgical resection and are therefore more likely to have multifocal cancers. In addition to differences in methodology between the reported studies most of the data on IOCT and liver cancers relate to patients from the Far East and the natural history of these cancers may be different in a Western population.[8]

The sensitivity of ultrasound, CT, and angiography in detecting primary liver cancers over 1 cm in diameter was 33%, which is again lower than is generally reported.[3] HCCs less than 1 cm in diameter were not detected using these modalities. This figure, however, may underestimate the value of these modalities in detecting HCC as the number of patients with cancers over 1 cm in diameter was small. The study is based only on patients who have undergone transplantation; patients with end stage liver disease who are known preoperatively to have large or multifocal cancers are not considered for OLT.

In this study both nodular and heterogeneous uptake of iodised oil were significantly associated with the presence of HCC. However in patients with heterogeneous uptake this association was insufficient to identify reliably patients with HCC. Three of the 16 patients with heterogeneous deposition on IOCT had a total of 30 cancers found on histological examination of their explant livers, the remaining 13 having no evidence of cancer. Although previous studies have suggested that a heterogeneous distribution on IOCT may be related to the presence of small cancers[9] the explant histology has clearly shown that in the majority of cases with heterogeneous iodised oil deposition there are no underlying cancers. In these cases the iodised oil retention may be due to slow clearance by the lymphatics or arterioportal shunts.[10] Nodular deposition on IOCT was always associated with cancers in the explant liver. However, nodular deposition was only found with cancers over 1 cm in diameter and no smaller cancers were demonstrated on IOCT. Because of the difficulty in identifying cancers less than 1 cm on IOCT the majority of published studies have calculated their sensitivities based on lesions greater than 1 cm. Taourel *et al*[11] compared IOCT findings with whole liver pathological examination. They reported a sensitivity of 53% for the detection of HCC, using IOCT criteria established by Ngan.[2] However, no HCCs smaller than 11 mm in diameter were detected on IOCT and pathological assessment excluded lesions smaller than 8 mm. As the majority of HCCs in

our study (46/55) were less than 1 cm diameter their exclusion in Taourel *et al*'s study may have allowed the sensitivity of IOCT to be overestimated. The sensitivity of 53% for lesions over 1 cm in Taourel *et al*'s study is similar to our sensitivity of 44% for lesions of this size. There was no attempt to demonstrate iodised oil uptake in sampled lesions either by using soft tissue radiography or histological stains for iodised oil. We found that soft tissue radiography guided biopsy of lesions in the liver slices is a useful method of ensuring that lesions seen on IOCT are accurately sampled. The no deposition pattern on IOCT is potentially clinically useful, there being no cancers on histology in this group.

Whole liver pathological data are essential for assessing the true sensitivity of any imaging modality in cirrhosis. The pathological data from the present study have highlighted the difficulty of preoperative imaging in this group of patients, 46/55 cancers (84%) being less than 1 cm in diameter. The correlation between cancer size and iodised oil retention is well recognised and probably relates to the alteration in blood supply of HCC with increased size, small HCCs often being hypovascular[12] and larger lesions being hypervascular with an arterialised circulation.[13] New imaging modalities are obviously required as IOCT is limited by the uptake of iodised oil in small cancers. Less than half the cancers in the current study retained iodised oil.

We would conclude that in patients with end stage liver cirrhosis IOCT is more sensitive than ultrasound, CT, or angiography for the detection of HCC but is unable to detect the majority of cancers which are <1 cm in diameter.

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