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ORIGINAL ARTICLE

Multislice computed tomography using a triple-phase contrast protocol for preoperative assessment of hepatic tumor load in patients with hepatocellular carcinoma before liver transplantation

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Summary

For evaluation of triple-phase multislice computed tomography (CT) for assessment of hepatocellular carcinoma (HCC) before liver transplantation. All HCC patients who underwent liver transplantation at our institution between 2001 and 2006 and had contrast-enhanced abdominal 4-/16-slice CT [unenhanced, arterial (20 s delay), portal venous (40 s), and venous (80 s) scan] within 100 days before transplantation were enrolled retrospectively. CT data were reviewed by two observers. Results were correlated to histopathologic findings by means of a lesion-by-lesion evaluation. Thirty-two patients with 76 HCC-lesions were included. The lesion-based sensitivity of observer 1 and 2 was 78% (59/76) and 83% (63/76) (false positives, $n = 6$ and $n = 10$). The sensitivity of observer 1/2 was 89%/95% for lesions >20 mm ($n = 37$), 94% for lesions 11–20 mm ($n = 18$), and 43%/53% for lesions <10 mm ($n = 21$). The mean detection rates of unenhanced, arterial, portal venous, and venous phase scans were 30%, 74%, 59%, and 40%. All detected lesions were visible on arterial and/or portal venous scans (arterial only, 24%; portal venous only, 9%). Arterial and portal venous phase scans are the strongest contributors to the high detection rate of triple-phase multislice-CT in HCC. However, the detection of small HCC measuring <10 mm and false positive findings remains a challenge.

Introduction

Liver transplantation is a potentially curative treatment in patients with hepatocellular carcinoma (HCC) [1–4]. As the number of patients listed for liver transplantation exceeds the number of donor organs, criteria have been developed to select patients with HCC, who most benefit from liver transplantation [1–3]. Recently, the listing criteria have been redefined according to the model of end-stage liver disease (MELD) giving precedence to HCC patients who fulfill the Milan criteria as so called Standard Exceptions. These criteria are based on number and size of hepatic HCC lesions (single lesion up to 5 cm in diameter, or up to three lesions, each up to 3 cm in diameter) as assessed by diagnostic imaging [1,2,5].

Computed tomography (CT) is the most commonly used technique for the detection of HCC, although it is well known that, especially in small tumor lesions, the sensitivity is rather poor [6,7]. However, imaging techniques have improved rapidly over the recent years,

whereby multislice CT devices enable faster scanning at a higher spatial resolution, which is expected to increase lesion detection rates and accuracy of lesion diameter measurements when optimized multiphasic contrast protocols are applied. To the best of our knowledge there is only scarce data on 4-slice-CT and no data published so far for 16-slice data comparing diagnostic accuracy with reference data derived from whole explanted livers.

The purpose of the study presented herein is the evaluation of multidetector CT with a triple-phase contrast protocol for the assessment of the hepatic tumor load in HCC patients before liver transplantation.

Patients and methods

Patients

We retrospectively reviewed all patients who underwent liver transplantation for HCC at our institution between January 2001 and December 2006. Inclusion criteria were a complete digital CT dataset according to our standard protocol, a maximum time interval from CT to transplantation of 100 days, no intermittent neoadjuvant treatment, and presence of a comprehensive histopathologic report. The study was approved by the institutional review board.

Multidetector computed tomography

Computed tomography data were obtained with a 4-channel (Somatom Plus 4; Siemens, Erlangen, Germany) or a 16-channel (Lightspeed 16/Pro16; GE Medical Systems, Milwaukee, WI, USA) multidetector CT scanner. After an unenhanced scan of the upper abdomen, a contrast-enhanced scan of the upper abdomen covering the entire liver in the early arterial and the portal venous phase was performed, followed by a venous phase scan of the entire abdomen and pelvis. The arterial phase scan was initiated 4 s after the contrast bolus [100 ml Iopromide (Ultravist 370®; Schering, Berlin, Germany) followed by 40 ml saline; flow, 4 ml/s] arrived at the aorta (bolus tracking; resulting total delay approximately 20 s). Portal venous phase scanning was initiated with a 40 s delay, the delay for the venous phase was 80 s.

The scan parameters of the 4-channel CT [arterial and portal venous phase scan: voltage, 120 kV; tube current, 200–300 mA; rotation time, 0.5 s; detector collimation, 4 × 1 mm; table feed, 6–8 mm/gantry rotation; image reconstruction, 1 mm (increment, 0.5 mm) and 3 mm (increment, 3 mm) slice thickness; unenhanced and venous phase scan: 120 kV; 200–300 mA; 0.5 s; 4 × 5 mm; 20–30 mm/rotation; 5 mm slice thickness (5 mm)] resulted in an average scan duration of 12.5–16.7 s for 20 cm scan length in the early contrast phases.

The scan duration of the 16-channel CT [120 kV; 100–350 mA with automatic dose modulation (AutomA; GE Medical Systems)] was 14.9 s per 20 cm for the arterial scan [0.7 s; 16 × 0.625 mm; 9.37 mm/rotation; 0.625 mm (increment, 0.625 mm) and 3.75 mm (3.75 mm) slice thickness] and 5.1 s per 20 cm for the portal venous scan [0.7 s; 16 × 1.25 mm; 27.5 mm/rotation; 1.25 mm (1.25 mm) and 3.75 mm (3.75 mm) slice thickness]. [Unenhanced and venous scan: 0.7 s; 16 × 1.25 mm; 35 mm/rotation; 1.25 mm (1.25 mm) and 5 mm (5 mm) slice thickness.]

Histopathology

Pathologic evaluation of lesions in liver specimens was immediately performed after resection of the liver. First, macroscopic assessment of the entire liver was performed on axial 5 mm slices. Every nodular lesion suspicious for HCC was recorded by size (largest diameter in mm), color, shape, segmental position, as well as distance to the liver hilus and the liver capsule. Secondly, samples of all suspicious lesions were analyzed by means of microscopic evaluation and definite diagnoses were documented. Adjacent lesions were counted as separate tumor deposits when a bridge of benign liver tissue was identified between them. Lesions with confluent growth pattern of tumor satellites were counted as one single lesion. Cases with more than 10 separate hepatic lesions were referred to as disseminated disease.

Interpretation of imaging findings

For CT analysis, a dedicated CT workstation (Advantage-Windows 4.3; GE Medical Systems) was utilized. At retrospective review, CT examinations were analyzed by two independent radiologists (5 and 6 years of experience in abdominal CT reading) who were blinded to clinical and serologic parameters as well as to histologic findings.

First, all visible focal lesions potentially representing tumor (solid nodules delineated by texture, bulging and/or contrast enhancement; simple cysts excluded) were recorded using the same descriptive parameters as in the histopathologic analysis. A judgment regarding the entity of each lesion was made based on morphologic appearance and contrast behavior (early enhancement and wash-out was considered as typical for HCC, determination of the entity of non-HCC-typical lesions was left to the observer's experience). Visualization of each lesion was documented separately for unenhanced, arterial, portal venous and venous phase scans. All scan phases were used for characterization of lesions. Measurement of the largest diameter was performed on the scan phase with best delineation of the evaluated lesion. The lesions' attenuation was analyzed

by measuring Hounsfield units (HU; mean value) with a region of interest (ROI) covering the entire lesion on a central slice in each scan phase. Additionally, the density of healthy liver parenchyma was measured in every unenhanced and enhanced scan by a representative ROI in the mid-level of the liver excluding major vascular structures. CT findings were correlated with the results of the examination of the whole explanted livers by means of a lesion-by-lesion evaluation.

Statistical analysis

Statistical analyses were performed using the SPSS-software (release 11.0.4; SPSS Inc., Chicago, IL, USA). All quantitative data (i.e. patient age, interval between CT and transplant, lesion size, lesion density) are given as mean value (±standard deviation) and range. For assessing interobserver variability in detecting HCC lesions (including all histopathologically proven HCC lesions and all lesions detected by at least one observer on at least one contrast phase scan), kappa statistics were used. Differences in density as compared with the surrounding liver tissue and in absolute HU-contrast of different scan phases were tested for significance using a two-sided paired-samples Wilcoxon signed rank test at a 5%-level of significance (exact). For correlation of lesion diameters measured in CT with reference data the Spearman's rho correlation coefficient was applied for nonparametric data according to the results of the Kolmogorov–Smirnov-test and QQ-plots; to compare the deviations of diameters, the Bland–Altman-Plot was performed (nonvisualized lesions excluded).

Results

Reference data

A total of 32 patients fulfilled the inclusion criteria (Table 1). There was one patient with disseminated intrahepatic tumor and one patient who had radio frequency ablation (RFA) of a single HCC deposit prior to CT without histopathologic evidence of residual viable tumor in the explanted liver. In the remaining 30 patients, there was a total of 76 lesions documented by histopathology (13 patients with one, six patients with two, four patients with three, three patients with four, one patient with five, two patients with six, and one patient with 10 lesions). The mean size of lesions was 27(±20) mm (range, 2–80 mm) with 37 lesions measuring >20 mm, 18 lesions measuring 11–20 mm, and 21 lesions with ≤10 mm diameter. There was one patient with bifocal fibrolamellar HCC. In one patient with unilocular tumor, five high grade dysplastic nodules were additionally present. (Table 1).

Table 1. Patient and lesion characteristics.

Patients	
Number	32
Gender	
Female	4
Male	28
Age (years)	
Mean (±SD)	56.7 (±7.3)
Range	37–67
Cirrhosis	
Child–Pugh score	
A	9
B	19
C	4
Cause	
Alcoholism	10
HBV	5
HCV	17
Time interval	
CT to transplantation (days)	
Mean (±SD)	62.4 (±24.8)
Range	5–100
CT	
Scanner type	
4-slice	9
16-slice	23
HCC Lesions	
Number	76
Size (mm)	
Mean (±SD)	27 (±20)
Range	2–80

CT, computed tomography; HCC, hepatocellular carcinoma; SD, standard deviation; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection.

Detection rate

In the lesion-based analysis, observer 1 detected 87 noncystic focal lesions in the entire set of CT scans, of which 66 were attributed as HCC (true positives, $n = 60$; false positives including the disseminated HCC, $n = 6$); the remaining 21 lesions were judged as non-HCC lesions because of their atypical morphology or contrast behavior. Observer 2 detected a total of 94 noncystic focal lesions, 74 of which were attributed as HCC (true positives, $n = 64$ including the disseminated HCC; false positives, $n = 10$), and 20 as benign. The interobserver variability of observers 1 and 2 for detection of HCC revealed a kappa of 0.722 ($P < 0.001$).

The RFA lesion and the disseminated HCC were excluded from the following lesion-based and size-related analysis. Reading all scan phases side by side, sensitivity of observer 1 was 78% and that of observer 2 was 83% respectively (Table 2). Stratifying for lesion size >20 mm, observer 1 identified 33 of 37 HCC lesions, resulting in a sensitivity and positive predictive value of 89% and

Table 2. Observer, size and contrast phase related detection rates of hepatocellular carcinoma (HCC) lesions in the liver.

HCC lesions	Observer	Sensitivity (%)	PPV (%)	FP
All lesions	1	78	91	6
HCC, $n = 76$	2	83	86	10
Size > 20 mm	1	89	100	0
HCC, $n = 37$	2	95	100	0
Size 11–20 mm	1	94	81	4
HCC, $n = 18$	2	94	71	7
Size ≤ 10 mm	1	43	82	2
HCC, $n = 21$	2	53	79	3

PPV, positive predictive value; FP, false positives.

100%, respectively. For observer 2 with 35 of 37 true positives, the values were 95% and 100%. Analyzing 11–20 mm lesions, the sensitivity of observer 1 and 2 were 94% (17 of 18 HCC lesions) each, with a PPV of 81% and 71%, respectively. For lesions with 10 mm in diameter and less, the sensitivity of observer 1 and 2 was 43% (9 of 21 HCC lesions) and 53% (11 of 21 HCC lesions); the PPV was 82% (nine of 11) and 79% (11 of 14) (Table 2).

The average proportion of visible HCC lesions recorded by the two observers was 30% on unenhanced scans, 74% on arterial phase scans, 59% on portal venous phase scans, and 40% on venous phase scans. When comparing arterial and portal venous phases, an average of 50% of lesions were seen on both, 33% were seen only on either arterial (24%) or portal venous phase scans (9%) (Figs 1 and 2), and 17% were not seen on either scan. To this, unenhanced and venous phase scans did not depict any additional lesion.

Lesion density

Mean density of HCC lesions was significantly different from liver parenchyma in arterial phase scans [lesions, 79(±25) mean HU; liver, 60(±7) HU; $P < 0.001$] and portal venous phase scans [lesions, mean 98(±25) HU; liver, 84(±13) HU; $P < 0.001$], where HCC lesions tended to appear hyperattenuating. Unenhanced scans [lesions, 52(±6) mean HU; liver, 53(±5) HU; $P = 0.066$] and venous phase scans [lesions, 94(±16) mean HU; liver, 97(±13) HU; $P < 0.010$] visualized HCC lesions rather as iso- and hypoattenuating, respectively (Fig. 3). The difference in lesion density (absolute HU-differences, regardless whether positive or negative contrast) to liver parenchyma was the highest in the arterial phase [mean, 23(±22) HU] when compared with the portal venous phase [16(±21) HU; $P = 0.090$], the venous phase [7(±11); $P < 0.001$], and unenhanced phase [3(±6); $P < 0.001$].

Lesion size

Comparing the size measurements of the histologically proven HCC lesions derived from CT to the measurements obtained from the explanted liver, the correlation was $r = 0.784$ ($P < 0.001$) for observer 1 and $r = 0.888$ ($P < 0.001$) for observer 2. The lesion diameters measured in CT were within a narrow range and in direction

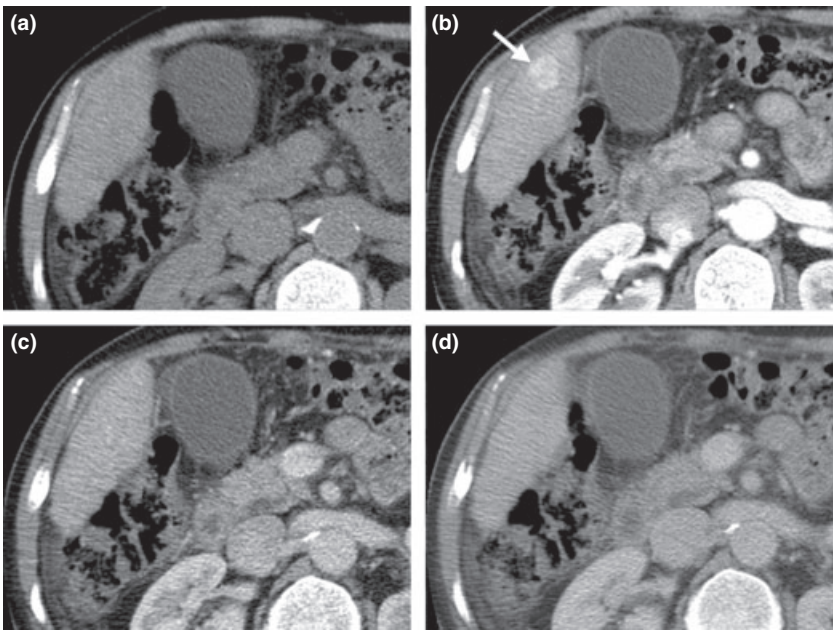

Figure 1 Example of a 20 mm hepatocellular carcinoma in the segment 5/6 of the liver visualized in the early arterial phase scan (b) and invisible on unenhanced (a) and barely visible on late contrast phase images (c, portal venous phase; d, late venous phase).

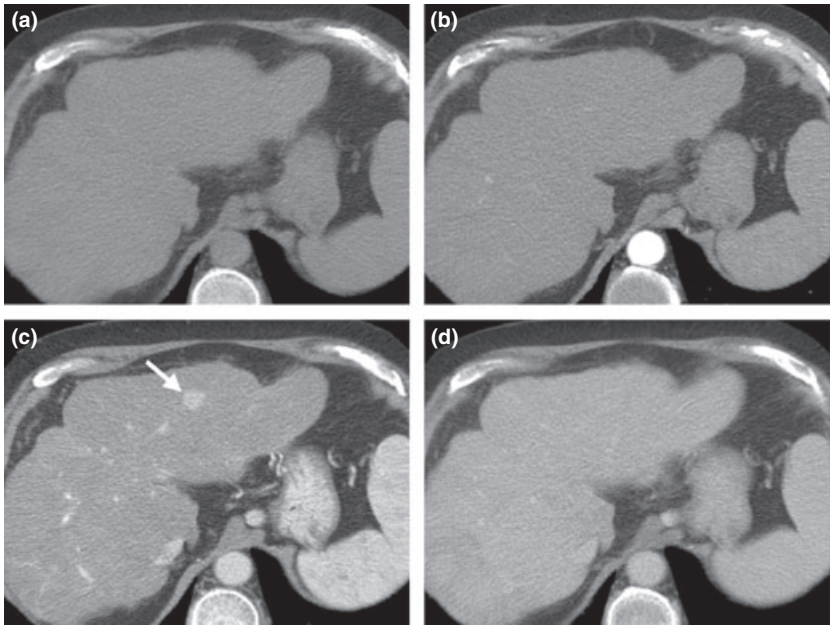

Figure 2 Example of a 15 mm hepatocellular carcinoma visualized in the portal venous phase scan (c) and invisible on unenhanced (a), early arterial phase (b) and late venous phase (d) images.

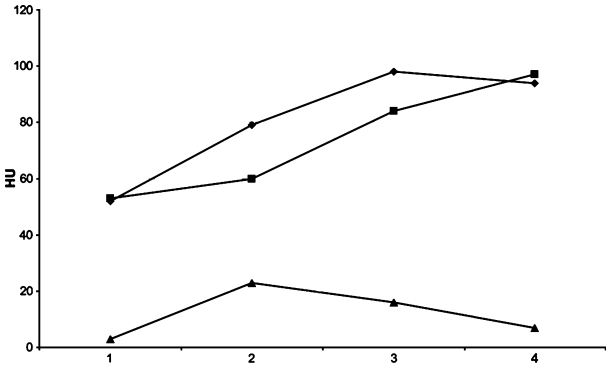

Figure 3 Attenuation shownig liver tissue (■) and HCC lesions (◆) as measured in unenhanced (1), arterial phase (2), portal venous phase (3) and venous phase (4) CT scans with linear interpolation. (▲, absolute difference in HU between liver and HCC lesions).

smaller compared with the diameters measured in the explanted specimen [observer 1, −1.6(±7.1) mm (range, −15 to +22); observer 2, −0.1(±5.2) mm (range, −14 to +14)] (Fig. 4).

False positive and false negative findings

Among the false positive lesions were five dysplastic nodules, which were detected and interpreted as HCC by observer 2. Observer 1 recorded only one of these five lesions and read it as HCC. The other false positive lesions were regenerative nodules (observer 1, $n = 2$; observer 2, $n = 4$); in three (observer 1) and one (observer 2) case, there was no corresponding focal lesion seen in histopathology. False negative lesions in CT were either not visualized (observer 1, $n = 15$; observer 2, $n = 11$) or misinterpreted as hemangioma (both observers, $n = 2$).

Patient-based analysis

In a correlative patient-based analysis of all available scans, the presence of HCC was correctly detected in 31 patients. The patient with disseminated disease was correctly identified by both observers in the portal venous as well as in the arterial phase. In the remaining patient, both observers correctly excluded residual tumor tissue after complete radiofrequency ablation. Correct identification of all HCC lesions in a patient by observer 1 and 2 was present in 22 (69%) and 23 (72%) of cases, while the number of HCC lesions was underestimated in seven (22%) and six (19%) patients, and overestimated in three patients (9%) each, respectively.

Discussion

This analysis comprises data of 32 patients with HCC. The reliability of MSCT with a triple-phase contrast protocol for assessment of hepatic tumor load before liver transplantation was analyzed retrospectively.

To focus on the situation of a patient who undergoes liver transplantation for HCC, only patients with the pretransplant diagnosis of HCC were included, and therefore, the detection rates for HCC found in this study, cannot be directly transferred to patients with chronic liver disease who are screened for HCC. This implies, that in con-

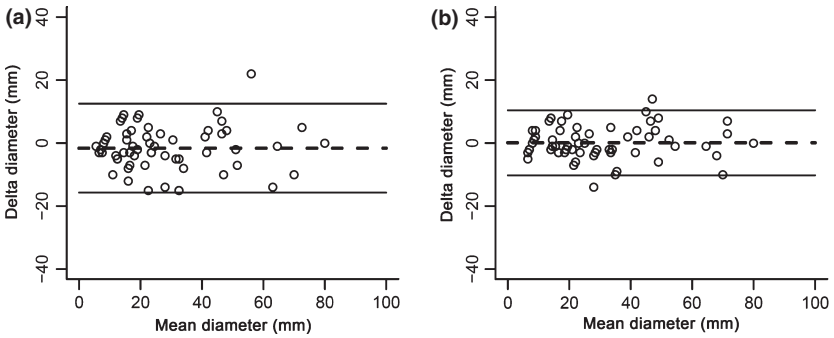

Figure 4 Bland–Altman-plot of deviations in size measurements of HCC lesions obtained in CT by observer 1 (a) and 2 (b) versus those obtained by histopathology.

trast to other studies [6,8,9], patients who received hepatic resection instead of transplantation, or histologic diagnosis obtained by biopsy or imaging follow-up only were not enrolled in this study. The advantage of a correlation to whole explanted livers is the exclusion of possibly undetected tumor deposits in the remaining liver [10]. The inclusion of patients who underwent living related liver transplantation beyond the listing criteria enabled an analysis of a broad spectrum with unifocal and multifocal disease. An important limitation of the study is the retrospective approach to data collection.

In this study, all patients had a multislice (four or 16 slice) triple contrast phase CT scan for pretransplant evaluation. In all patients, the presence of HCC was correctly identified. The lesion-based analysis in this study revealed overall sensitivities of 78% to 81%. Stratified for tumor size, the sensitivity was 89–95% for lesions >20 mm in diameter, 94% for 11–20 mm lesions, and 43–53% for lesions measuring 10 mm or less.

Compared with studies with helical single-slice CT, this appears to be a substantial improvement, especially for small lesions. A study on single-slice CT in 15 patients with 22 lesions in the explanted livers revealed a sensitivity of only 20% for lesions with a diameter of 5–10 mm, while 82% of 11–20 mm lesions, 86% of 21–30 mm lesions, and 100% of lesions >30 mm in diameter were detected [6]. Valls *et al.* [11] reported a sensitivity of 61% for all lesions smaller than 2 cm (lesions <1 cm not stratified) using a biphasic examination protocol at a single detector CT. In a study by Zacherl *et al.* [10] using single-slice CT with a triple-phase scan protocol, the mean diameter of all false negative lesions was 10 mm. Three other studies using single-detector CT scanners and at least dual phase contrast protocols on 30, 23, and 41 HCC patients, respectively, revealed sensitivities of 0–20% for lesions <1 cm and 33%, 47%, and 82%, respectively, for lesions measuring 10–20 mm in diameter [12–14]. Using four-channel multidetector-CT in a large series with 195 patients, the sensitivity for lesions smaller than 20 mm was 88–89% indicating the superiority of multislice CT; however, the reference data in this study consisted of partial liver resection, biopsy, or imaging follow-up only and was not stratified for lesions smaller than 1 cm [9].

One major advantage of multidetector CT using four- and even more so 16-slice scanners as compared with single slice helical CT is the increased scan speed at a high spatial resolution, which allows acquisition of three scans within the first pass of contrast material through the liver as realized in this study. A study on 44 HCC patients examined with 16-slice CT and two scan phases in the early and late arterial phase revealed a sensitivity of 77% for all HCC lesions; however, the reference data consisted of resections and needle biopsies, stratification for lesion size was impossible [8].

Taking early arterial and portal venous phases at 20 and 40 s delay together, the detection rate for HCC was acceptably high, even though other groups recommend different delays, e.g. 14–30 s after reaching the 100 HU threshold in the aorta using bolus tracking, or a fixed delay of 30 s for one single early phase regardless of the circulation time of an individual patient [15,16]. The high detection rate observed in this study was achieved by correlative reading of both early scans, whereas a high proportion (33%) of HCC lesions was visible in the early arterial (24%) or the portal venous phase (9%) only, while 50% were visualized in both scan phases. The wide variations of the contrast behavior of HCC lesions, which are responsible for different detection rates of the early scan phases, are well known [17]. The venous phase scan with a detection rate of 40% did not depict any additional lesions; nevertheless it was helpful for lesion characterization. The rate of visualized lesions in the unenhanced scan, however, was even lower (30%) and therefore this scan appears to be unnecessary, which is in line with the results of other studies [9].

Lesion size is an important prognostic parameter. In this study, there is a strong correlation of lesion diameters in CT and macroscopic assessment of the resected specimens. Comparable data of other studies on HCC patients before liver transplantation to the best of our knowledge do not exist to date.

False positive findings are an important issue when assessing HCC patients before transplantation. Cirrhotic livers contain parenchymal scarring along with regenerative areas and thus, are often inhomogeneous on CT images. This may result in false positive findings [18]. The false positive findings in this study were predominantly caused by dysplastic nodules and regenerative nodules. Some lesions, which did not meet a correlate in pathologic evaluation of the explanted liver, were seen as early contrast blush probably caused by shunts and irregularly perfused cirrhotic tissue. This spectrum is similar to other reports and is of course a major problem for CT reading in the pretransplant setting [11,18,19].

Comparing CT with other imaging modalities, it has been reported that magnetic resonance imaging (MRI), particularly with the use of liver-specific contrast agents and early dynamic sequences was superior to helical multiphasic CT for the evaluation of HCC patients before transplantation [8,8,10,14,20,21]. However, there are no studies on direct comparison of CT and MRI in state of the art techniques in a pretransplant setting yet. A recent retrospective analysis of the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS; OPTN) database (2003–2005) resulted in the conclusion that current imaging modalities (CT, MRI and US) alone and in combination are unacceptably inaccurate for staging prior to liver transplantation [7]. This study shows that the recent technical refinements of CT and a short time interval between CT and transplantation can improve the HCC detection rates. Trials comparing state-of-the-art MRI and CT in a pretransplant setting are warranted.

In conclusion, multi-row detector CT with a multiphase contrast protocol comprising two first pass contrast phases at the beginning of arterial and portal venous inflow of contrast material into the liver facilitated a higher detection rate of small HCC lesions in cirrhotic livers as compared with historic data on single-slice helical CT. Arterial and portal venous phase scans are the strongest contributors to the high HCC detection rate of triple-phase multislice-CT. However, the detection of small HCC measuring less than 10 mm and false positive findings remain a challenge.

Authorship

TD: designed and performed study, collected and analyzed data, wrote the paper. VF: performed study, collected and analyzed data, wrote the paper. CG, IGS, BR: analyzed data. LS, LL, FS, JL, PN: collected data. ELH: designed and performed study, collected data, wrote the paper.

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