Intraoperative ultrasound patterns predict recurrences after surgical treatments for hepatocellular carcinoma[☆]

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KEYWORDS

Intraoperative ultrasound;
Hepatocellular carcinoma;
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Radiofrequency ablation;
Hepatic resection.

Abstract *Introduction:* Hepatocellular carcinoma (HCC) is associated with a high incidence of postoperative recurrence, despite high rates of complete necrosis with radiofrequency ablation (RFA) and curative hepatic resections (HR). The aim of this study was to identify intraoperative ultrasound patterns observed during HR or RFA that predicting intrahepatic HCC recurrence.

Materials and methods: From January 1997 through August 2008, we treated 377 patients with HCC (158 with HR and 219 with surgical RFA). All patients underwent intraoperative ultrasound (IOUS) examination. Primary HCCs was classified according to diameter, HCC pattern (nodular or infiltrative), echogenicity (hyper- or hypo-), echotexture (homogeneous or inhomogeneous), capsular invasion, mosaic pattern, nodule-in-nodule appearance, and infiltration of portal vessels. Number of HCC nodules was also considered. Comparisons between the groups of possible factors for intrahepatic recurrence of treated tumors were performed using the Kaplan–Meier method and compared using the log-rank test.

Results: Patients were followed for 9–127 months (median: 18.6 months), and intrahepatic recurrence was observed in 198 (52.5%). In 138 patients (36.5%), recurrences were located in different segments with respect to the primary tumor. In 60 HCC tumors (16%), local recurrences were found in the same segment as the primary tumor. At univariate analysis, primary HCC echogenicity and mosaic pattern were the only factors not significant associated with intrahepatic recurrences.

Conclusion: IOUS is an accurate staging tool for use during “surgical” resection or RFA. This study shows that IOUS patterns can also be used to estimate the risk of post-treatment HCC recurrence. In patients at high risk for this outcome, closer follow-up and use of adjuvant therapies could be useful.

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Sommario *Introduzione:* L'epatocarcinoma (HCC) è associato con una elevata incidenza di recidive post-trattamento, nonostante l'elevata incidenza di necrosi totali dopo radiofrequenza (RFA) o una ben riuscita resezione epatica (HR). Scopo dello studio è quello di identificare alcuni patterns ecografici intraoperatori quali fattori predittivi di recidiva.

Materiali e metodi: Dal 1/97 al 8/2008, sono stati trattati 377 pazienti con HCC (158 HR e 219 RFA per via chirurgica). Tutti i pazienti sono stati sottoposti a valutazione ecografica intraoperatoria. Il nodulo primario è stato classificato nel seguente modo: diametro, pattern (nodulare o infiltrativo), ecogenicità (iper- o ipo-ecogeno), eco-struttura (omogeneo o disomogeneo), invasione capsulare, pattern a mosaico, aspetto di nodulo nel nodulo e infiltrazione dei rami portal. Venivano registrati anche il numero di noduli sospetti per HCC. Il confronto fra gruppi dei possibili fattori predittivi di recidiva dei tumori trattati veniva eseguito utilizzando il metodo di Kaplan–Meier con l'uso del log-rank test.

Risultati: I pazienti avevano un range di follow-up di 9–127 mesi (follow-up mediano di 18.6 mesi). In 198 casi (52,5%) sono state riconosciute delle recidive intra-epatiche. Recidive intra-epatiche a distanza (cioè in segmenti differenti da quello trattato) sono state rinvenute in 138 pazienti (36,5%) mentre recidive locali sono state evidenziate in 60 casi (16%). All'analisi univariata, solo l'ecogenicità e il pattern a mosaico si sono rivelati fattori predittivi non significativi di recidiva intra-epatica.

Conclusioni: L'ecografia intraoperatoria consente un accurato staging intraepatico durante le procedure chirurgiche. Questo studio ha dimostrato un ulteriore vantaggio di questa metodica: permette di identificare dei patterns ecografici che possono predire i casi ad alto rischio di recidiva di HCC. In questi pazienti potrebbe essere utile proporre un follow-up di osservazione più stringato e anche delle terapie adiuvanti.

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Introduction

The potentially curative approaches to the treatment of hepatocellular carcinoma (HCC) in patients with liver cirrhosis include hepatic resection (HR), liver transplantation, and radiofrequency ablation (RFA) [1,2]. The perioperative complication rates and long-term survival associated with these treatments in cirrhotic livers have improved in recent years, but the rate of postoperative HCC recurrence remains high, ranging from 60% to 100% at 5 years [3,4]. Identification of possible risk factors for recurrence is of fundamental importance to improve the results of HCC treatment and increase disease-free survival. Numerous studies have been performed to analyze the prognostic values of clinical, pathological, and biological factors in this setting [5,6]. Less is known about the predictive value of the ultrasound characteristics of the tumor nodule, despite their undisputed role in the differential diagnosis of HCC [7,8].

In the present study, we prospectively evaluated the intraoperative ultrasound (IOUS) characteristics of primary HCC nodules treated with HR or RFA to estimate their ability to predict postoperative intrahepatic HCC recurrence. The results are useful for identifying patients at high risk for tumor recurrence and planning more effective treatment and follow-up.

Materials and methods

The study population consisted of 377 patients who were consecutively treated for HCC in our surgical unit between January 1997 and August 2008: 158 with HR and 219 with RFA (laparoscopic in 195 cases; via laparotomy in 24).

Written informed consent was obtained from all 377. Liver cirrhosis was present in 372 (98.7%) of the patients. The characteristics of the patients are shown in Table 1. The protocols used for the diagnosis and treatment of HCC patients referred to our Unit have been described elsewhere [9]. In particular, HR and RFA were both excluded as treatment options if there were signs of neoplastic portal thrombosis on preoperative imaging studies.

All surgical procedures included intraoperative ultrasonography (IOUS) examinations performed with the following scanners (all from Aloka, Tokyo, Japan): Model SSD 500 (1996–1999), Model SSD 1700 (2000–2006), Model alfa 10 (2006–2008). During laparotomy procedures, we used a T-shaped linear-type US transducer at frequencies of 5 MHz and 7.5 MHz; during laparoscopy, we used a flexible-tip laparoscopic ultrasound probe (10 mm in diameter, 50 cm in length) and a 5–7.5 MHz linear-array transducer side-mounted near the tip of the shaft.

From the baseline IOUS features of the primary HCC nodule [10], the surgeon was asked to classify the primary tumor in terms of diameter (≤ 20 mm versus > 20 mm), echogenicity (hyperechoic or hypoechoic), echotexture (homogeneous or inhomogeneous), presence of a pseudo-capsule (hypoechoic or echogenic rim versus infiltrative aspect [Fig. 1]), capsular invasion (interruption of pseudo-capsule [Fig. 2a]), nodule-in-nodule appearance (Fig. 2b), mosaic architecture (Fig. 2c), and vascular infiltration (suspected microencasement of subsegmental portal veins [Fig. 3]). The number of HCC nodules was also considered.

Laparoscopic RFA was performed with a 200-watt, 480-kHz monopolar radiofrequency generator (Valleylab, Boulder, CO) and an insulated, internally cooled electrode (18 G at the tip). The electrode was inserted into the tumor under US guidance, and tissue impedance was continuously

Table 1 Baseline characteristics of patients treated for HCC.

	HR (n = 158)	RFA (n = 219)	Total (n = 377)
Preoperative features			
Male sex – no. (%)	116 (73%)	161 (73%)	277 (73%)
Age (years, mean $\pm$ SD)	68 $\pm$ 8	68 $\pm$ 7	68 $\pm$ 7
Cause of cirrhosis – no. (%)			
HCV	111 (72%)	155 (70%)	266 (71%)
HBV	23 (15%)	24 (11%)	47 (13%)
Child-Pugh class A – no. (%)	137 (88%)*	133 (60%)*	270 (72%)
MELD score (mean $\pm$ SD)	8.7 $\pm$ 2.4*	9.6 $\pm$ 2.4*	9.2 $\pm$ 2.4
LCSGJ stage I/II – no. (%)	64 (50%)	117 (57%)	181 (54%)
BCLC A1 – no. (%) #	78 (61%)*	84 (41%)*	162 (49%)
Esophageal varices >F0 – no. (%)	21 (16%)*	52 (31%)*	73 (24%)
Single HCC – no. (%)	116 (73%)	141 (64%)	257 (68%)
HCC lesion diameter (mm, mean $\pm$ SD)	38 $\pm$ 27*	27 $\pm$ 11*	32 $\pm$ 20
Portal vein diameter (mm, mean $\pm$ SD)	12.2 $\pm$ 1.4	12.5 $\pm$ 1.4	12.4 $\pm$ 1.4
Longitudinal diameter spleen (cm, mean $\pm$ SD)	11.7 $\pm$ 2.4*	12.8 $\pm$ 2.9*	12.4 $\pm$ 2.8
Platelet count ($\times 10^3/\text{mm}^3$, mean $\pm$ SD)	137 $\pm$ 64*	109 $\pm$ 62*	121 $\pm$ 64
Total bilirubin (mg/dl, mean $\pm$ SD)	1.0 $\pm$ 0.6*	1.4 $\pm$ 1.0	1.2 $\pm$ 0.9
Serum albumin (g/l, mean $\pm$ SD)	3.8 $\pm$ 0.6	3.7 $\pm$ 0.6	3.7 $\pm$ 0.6
Prothrombin time (INR, mean $\pm$ SD)	1.12 $\pm$ 0.11*	1.18 $\pm$ 0.13*	1.16 $\pm$ 0.13
AFP level <40 ng/ml – no. (%)	110 (74%)	143 (70%)	253 (72%)
Intraoperative US findings			
HCC diameter (mm, mean $\pm$ SD)	37 $\pm$ 27*	27 $\pm$ 11*	31 $\pm$ 20
Infiltrative type – no. (%)	59 (37%)*	112 (51%)*	171 (45%)
Hyperechogenicity – no. (%)	52 (33%)	78 (36%)	130 (34%)
Inhomogeneous texture – no. (%)	140 (89%)	203 (93%)	343 (91%)
Capsular invasion – no. (%)	109 (69%)	153 (70%)	262 (69%)
Mosaic pattern – no. (%)	41 (26%)	43 (20%)	84 (22%)
Nodule-within-nodule – no. (%)	66 (42%)	78 (36%)	144 (38%)
Vascular invasion (subsegmental portal branches) – no. (%)	59 (37%)	73 (33%)	132 (35%)
IOUS new HCC nodules – no. (%)	21 (13%)*	52 (24%)*	73 (19%)

Abbreviations: HR, hepatic resection; RFA, radiofrequency ablation; HCV, hepatitis C virus; HBV, hepatitis B virus; MELD, Model for End-Stage Liver Disease; LCSGJ, Liver Cancer Study Group of Japan; BCLC A1, Barcelona Clinic Liver Cancer classification A1; AFP, Alpha fetoprotein; IOUS, intraoperative ultrasound; SD, standard deviation.

* $p < 0.05$ HR versus RFA.

monitored by means of circuitry incorporated within the generator. A peristaltic pump was used to infuse cold (0 °C) saline into the cooling lumen of the radiofrequency electrode at a rate sufficient to maintain the tip temperature within the 18–25 °C range. When necessary, the electrode tip was repositioned within the lesion and multiple thermal lesions created to obtain maximal lesion coverage. Laparotomic HR was carried out following a standardized technique [10]; laparoscopic HR was considered only in patients whose HCC lesions were confined to the left hepatic lobe or to segments V and VI.

Liver US and CT (and/or MRI) were performed within one month of treatment to assess the response to RFA or HR. The response to RFA was classified as *complete* when the ablation site presented no enhancement at all or only a thin peripheral rim of enhancement, which is the result of an inflammatory response. An incomplete response to RFA was defined as persistent nodular enhancement. Spiral CT scans were repeated 3 months after treatment and every 6 months thereafter to detect post-treatment intrahepatic recurrence. The latter was diagnosed when there was a new appearance of contrast enhancement.

Recurrence was classified as local when the enhanced area was located within 2 cm from the margins of the ablated nodule or within 2 cm from the surgical margin. New areas of enhancement in other areas of the liver were classified as distant HCC recurrence. Intrahepatic recurrences were also classified as early and late. The cut-off for early recurrence, 9 months after the initial surgical treatment, had been shown in preliminary analyses to be the most accurate discriminator between early and late recurrences compared with other cut-offs.

For normally distributed data, results were expressed as means $\pm$ standard deviations; for nonparametric data, medians and ranges are reported. Intergroup comparisons of factors regarded as potential predictors of intrahepatic HCC recurrence were based on the Kaplan–Meier method, and differences between groups were compared using the log-rank test. All analyses were two-tailed, and P values < 0.05 were considered as significant throughout the study. Baseline and follow-up data were collected in a dedicated database (FileMaker Pro for Macintosh, FileMaker Inc., Santa Clara, CA) and analyzed with Stata software (Intercooled Stata 10.0 for Macintosh, College Station, TX).

Fig. 1 IOUS findings: HCC nodule type: pseudocapsular (with an echogenic rim) (A) versus infiltrative (B).

Fig. 2 IOUS findings: HCC with capsular infiltration (A: white arrows); HCC with nodule-in-nodule appearance (B); mosaic architecture (C).

Fig. 3 IOUS findings: HCC (T) with subsegmental portal vein encasement (white arrows).

Results

The patients were followed for 9–127 months (mean: 26.8 ± 24.8 months, median: 18.6 months). In 198 patients (52.5%), intrahepatic recurrences were observed during the follow-up. Sixty of these patients (16%) had local recurrences. In 91 patients (24%), the recurrence was observed within the 9 months after treatment (early recurrence). Overall recurrence rates were similar in the RFA and HR

Table 3 IOUS findings and early HCC recurrence (within 9 months).

IOUS variables	Early HCC rec.	<i>p</i>
HCC numbers: 1 versus >1	23% vs 28%	NS
HCC diameter: <20 versus > 20 mm	17% vs 27%	0.034
Pseudocapsular versus infiltrative type	15% vs 34%	0.0001
Echogenicity: hypoechoic vs. hyperechoic	23% vs 26%	NS
Echotexture: homogeneous vs. inhomogeneous	22% vs 44%	0.004
Capsular invasion: no/yes	16% vs 27%	0.022
Mosaic architecture: no/yes	23% vs 30%	NS
Nodule-in-nodule appearance: no/yes	21% vs 30%	0.041
Subsegmental portal vein encasement: no/yes	21% vs 30%	0.040
IOUS new HCC nodules; no/yes	22% vs 34%	0.025

subgroups (56% and 47%, $p = \text{NS}$). However, local recurrence was more common in patients treated with RFA (21% versus 8% in the HR subgroup, $p = 0.001$).

At univariate analysis, HCC diameter (>20 mm), infiltrative tumor, a nodule-within-a-nodule appearance, and capsular infiltration were statistically associated with intrahepatic recurrences in general (Table 2). At univariate analysis using actuarial curves, only echogenicity and mosaic architecture were unrelated to this outcome. Early recurrences (Table 3) were statistically correlated with HCC diameter (>20 mm), infiltrative tumor, inhomogeneous texture, capsular infiltration, nodule-in-nodule appearance, subsegmental portal vein encasement, and IOUS detection of new HCC nodules, while infiltrative tumor was the only factor significantly that showed significant correlation with local recurrences (Table 4).

Early recurrence and local recurrence rates were lower in the HR group than in patients treated with RFA (Table 5). At univariate analysis using actuarial curves, HCC recurrences (any type) in the HR and RFA groups were associated

Table 2 IOUS findings and overall HCC recurrence (rate and actuarial analysis).

IOUS variables	Overall HCC recurrences	<i>p</i>	Actuarial HCC rec. (5 years)	<i>p</i>
HCC numbers: 1 versus >1	50% vs 56%	NS	74% vs 86%	0.0006
HCC diameter: ≤ 20 versus >20 mm	43% vs 57%	0.011	70% vs 82%	0.0046
Pseudocapsular versus infiltrative type	44% vs 63%	0.0001	74% vs 83%	0.0012
Echogenicity: hypoechoic vs. hyperechoic	50% vs 57%	NS	74% vs 86%	NS
Echotexture: homogeneous vs. inhomogeneous	51% vs 65%	NS	78% vs 83%	0.0101
Capsular invasion: no/yes	43% vs 56%	0.020	62% vs 86%	0.0005
Mosaic architecture: no/yes	51% vs 59%	NS	77% vs 83%	NS
Nodule-in-nodule appearance: no/yes	47% vs 62%	0.005	74% vs 84%	0.0071
Subsegmental portal vein encasement: no/yes	51% vs 55%	NS	74% vs 88%	0.0003
IOUS new HCC nodules; no/yes	51% vs 60%	NS	76% vs 87%	0.0159

Table 4 IOUS findings and local HCC recurrence.

IOUS variables	Local HCC rec.	<i>p</i>
HCC numbers: 1 versus >1	16% vs 16%	NS
HCC diameter: ≤20 versus >20 mm	14% vs 17%	NS
Pseudocapsular versus infiltrative type	12% vs 21%*	0.013
Echogenicity: hypoechoic vs. hyperechoic	14% vs 19%	NS
Echotexture: homogeneous vs. inhomogeneous	15% vs 21%	NS
Capsular invasion: no/yes	13% vs 17%	NS
Mosaic architecture: no/yes	16% vs 14%	NS
Nodule-in-nodule appearance: no/yes	15% vs 18%	NS
Subsegmental portal vein encasement: no/yes	15% vs 17%	NS
IOUS new HCC nodules; no/yes	14% vs 22%	NS

with the same baseline IOUS features of the primary HCC nodule: nodule diameter (>20 mm), infiltrative tumor, and subsegmental portal vein encasement (Table 6).

Discussion

IOUS has been used at several surgical centers to improve intrahepatic staging of HCC in patients with cirrhosis [11] and to establish the precise topographical characteristics of the lesion and achieve safe resection margins [12]. During HR for HCC, IOUS reveals new lesions in 13.1–30% of cases, and in 4.9–67% of cases IOUS findings lead to modifications in the preoperative surgical plan [13,14]. The characteristic IOUS findings in HCC nodules included

Table 5 IOUS findings and HCC recurrence rates according to treatment group.

	HR (<i>n</i> = 158)	RFA (<i>n</i> = 219)	Total (<i>n</i> = 377)
Any type of HCC recurrence	75 (47%)	123 (56%)	198 (52%)
Early HCC recurrences	27 (17%)*	64 (29%)*	92 (24%)
Local HCC recurrences	13 (8%)*	47 (21%)*	60 (16%)

Abbreviations: HR: hepatic resection; RFA: radiofrequency ablation.

**p* < 0.05 HR versus RFA.

a mosaic pattern of internal echoes, posterior echo enhancement, halo, and lateral shadowing. Hypoechoic lesions and those with mosaic patterns are more likely to be malignant [10].

IOUS detection rates for liver nodules can be expected to improve even more with routine intraoperative use of new US contrast agents. Contrast-enhanced IOUS may also be useful in determining whether the new nodule is malignant [15].

IOUS allows accurate three-dimensional reconstruction of the tumor's relations with branches of the portal veins and hepatic veins, and this information is fundamental step for defining an appropriate surgical strategy. With the aid of IOUS, it is now possible to carry out surgical procedures that preserve residual liver function and are safe and oncologically radical [9,12,16,17].

Previously reported predictors of postoperative HCC recurrence included preoperative factors such as hepatitis C carriage, high serum α -fetoprotein concentrations, high

Table 6 IOUS findings and global HCC recurrence (actuarial analysis) according the treatment (HR: hepatic resection; RFA: radiofrequency ablation).

IOUS variables	HR (<i>n</i> = 158)	<i>p</i>	RFA (<i>n</i> = 219)	<i>p</i>
HCC numbers: 1 versus >1	67% vs 89%	0.0006	80% vs 84%	NS
HCC diameter: ≤20 versus >20 mm	58% vs 77%	0.0088	77% vs 85%	0.0490
Pseudocapsular versus infiltrative type	69% vs 77%	NS	79% vs 86%	0.0114
Echogenicity: hypoechoic vs. hyperechoic	66% vs 84%	NS	80% vs 87%	NS
Echotexture: homogeneous vs. inhomogeneous	72% vs 78%	NS	81% vs 89%	NS
Capsular invasion: no/yes	55% vs 83%	0.025	69% vs 88%	0.0066
Mosaic architecture: no/yes	68% vs 85%	0.0022	83% vs 81%	NS
Nodule-in-nodule appearance: no/yes	65% vs 79%	NS	80% vs 85%	0.0149
Subsegmental portal vein encasement: no/yes	66% vs 85%	0.0091	79% vs 88%	0.0067

CLIP scores, elevated serum ALT level, and tumor characteristics, such as multiplicity, large size, venous invasion, tumor rupture, and mitotic grade. However, various studies have yielded conflicting results concerning the predictive value of these factors, and debate continues over the relative importance of each [18–22].

In our study, we evaluated the recurrence-predicting capacity of morphologic features of the HCC nodules on baseline IIOUS. Baseline US or IIOUS findings have already been used to differentiate HCC from other liver tumors [7,8,23]. Contrast-enhancement patterns have also been used for differentiating among the liver tumors [8,15,24]. In the present study, we prospectively classified the baseline IIOUS characteristics of primary HCC nodule, and the aim of this study was to determine whether any of these characteristics were able to predict the postoperative recurrence risk.

Univariate analysis (Table 2) indicated that a nodule diameter greater than 20 mm, tumor infiltration, capsular invasion, and a nodule-within-a-nodule appearance were significantly related to HCC recurrence. These tumor characteristics, along with tumor number, inhomogeneous texture, a subsegmental portal vein encasement, and the detection of new HCC nodules during IIOUS were significantly related to HCC recurrence when actuarial curves were analyzed. These findings confirm that HCC recurrence after a local treatment is likely to be associated with aggressive tumor properties that can be identified by IIOUS. With the exception of echogenicity and mosaic architecture, these IIOUS variables also seem to be capable of predicting early recurrence (i.e., that developing within 9 months of treatment). In contrast, the local versus nonlocal nature of the recurrence seems to depend less on these IIOUS factors and more on the type of treatment. Anatomic HR is fundamental for reducing the risk of local recurrences [12,25,26]. The need for an anatomic approach is based on the theory that intrahepatic spread of HCC occurs through branches of the portal vein [27]. A modified technique of laparoscopic RFA with selective intrahepatic vascular occlusion seems to increase the rate of total necrosis and reduce the frequency of local recurrence [28].

In conclusion, open-sky or laparoscopic IIOUS seems to be a fundamental tool for safe and effective HR or RFA of HCC. IIOUS also provides better intrahepatic staging of the disease. Our study confirms that certain HCC characteristics defined by IIOUS can also be used to estimate the risk of postoperative HCC recurrence. In patients with these IIOUS risk factors, closer follow-up should be considered, with more frequent computed tomography scans and perhaps with magnetic resonance imaging studies of the liver to ensure more timely detection of disease recurrence.

Conflict of interest statement

The authors have no conflict of interest.

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