Research Article

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Pre-operative liver biopsy in cirrhotic patients with early hepatocellular carcinoma represents a safe and accurate diagnostic tool for tumour grading assessment

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Background & Aims: Knowledge of pre-operative tumour grade is crucial in the management of hepatocellular carcinoma (HCC) because it can influence recurrence and survival after surgery. The accuracy of pre-operative needle core biopsy (NCB) in tumour grading has been assessed in only a few studies with conflicting results.

Our aim was to determine the long-term safety and the overall accuracy of NCB in assessing tumour grading in subjects who had undergone liver resection for a single HCC.

Methods: Eighty-one cirrhotic patients with HCC who had undergone NCB before liver resection were selected. Only patients with a single HCC and with at least a five-year-follow-up were included. Tumour grading was scored according to a modified Edmondson–Steiner classification: well/moderately (low grade) vs poorly-differentiated (high grade).

Results: In the 81 patients with a solitary HCC (mean size 4.1 ± 2.3 cm) tumour grade was correctly identified by NCB in 74 out of 81 (91.4%) HCCs. NCB overall sensitivity and specificity were 65% and 98.1%, respectively, with a PPV of 92% and an NPV of 91%. No major complications (in particular tumour seeding) were observed. The overall survival rates at 1, 3, and 5 years were 83%, 62%, and 44%, respectively; the recurrence rate after a 5-year-follow-up was 56.2% for low grade and 82.3% for high grade tumours (p <0.007).

Conclusions: Pre-operative NCB can be performed on early (<5 cm) HCC cirrhotic patients because it provides histologically useful information for HCC management with good accuracy and a low complication rate.

Keywords: Liver resection; Liver transplantation; Hepatocellular carcinoma; Liver cirrhosis; Liver biopsy.

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Abbreviations: HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; NCB, needle core biopsy; CEUS, contrast enhancement ultrasonography; AFP, α-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus.

Introduction

Hepatocellular carcinoma (HCC) represents the most common liver cancer and the third main cause of cancer-related deaths [1,2]. Its annual incidence is similar to that of mortality; thus, its prognosis is poor with an overall survival rate of 3–5% at 3 years [2]. This being the situation, an appropriate diagnostic work-up and effective therapeutic strategies could play a key role in increasing overall survival. Liver transplantation (OLT) is currently the best therapeutic strategy for selected candidates with HCC; in fact, up to now, according to the Milan criteria [3], post-OLT survival in HCC patients is similar to that of patients having benign liver disease [4,5]. However, the Milan criteria are based only on strict morphologic evaluations, without any consideration of the tumour histology. On the contrary, the histological characteristics of the tumour could have the same clinical significance as the radiological criteria in determining patient outcome after OLT [6,7] Moreover, histological evaluation could play an important role in confirming the diagnosis of HCC and in the assessment of the biological behaviour of the tumour. Furthermore, imaging can either understage or overstage HCC; in fact, in a review of the United Network for Organ Sharing (UNOS) database, 31% of patients who underwent OLT for HCC based on imaging results were found not to have HCC [8]; on the contrary, others [9] have observed that pre-OLT imaging understaged the disease in 15–25% of cases. It has been shown that tumour grade is correlated to microvascular invasion which represents a marker of HCC recurrence [10–12] and survival [13,14]. Moreover, the histological specimen can be used to carry out biomolecular analysis [7] which can also be useful in predicting early and late recurrence and overall survival [15,16].

Needle core biopsy (NCB) represents the most utilized method of obtaining a pre-operative specimen useful for both HCC diagnosis and grading. NCB has a consolidated role in HCC diagnosis [17], even in small HCCs (<2 cm) [18], although, according to

the recent guidelines of the American Association for the Study of Liver Disease (AASLD) [19], its use is limited to a specific setting. In fact, liver biopsy is advisable when an HCC >2 cm does not show concordant behaviour at CT, MR, or contrast enhancement ultrasonography (CEUS) and when CT, MR, or CEUS is not concordant for nodules of 1–2 cm in size [19]. Surprisingly, the accuracy of pre-operative NCB in tumour grading has been assessed in only a few studies with conflicting results [11,20]. The aim of our study was to determine the long-term safety and overall accuracy of NCB in tumour grading in subjects who had undergone liver resection for a single HCC.

Materials and methods

Patients

Eighty-one cirrhotic patients, who had undergone NCB from 1990 to 2000 before liver resection for HCC, were retrospectively identified in our database. Standard demographic and clinical-pathologic data, including age, sex, tumour size and number, aetiology of HCC, Child–Pugh score, and α-fetoprotein (AFP) level, were collected for all patients. Inclusion criteria were: (i) patients with a single nodule of HCC, (ii) availability of both histological biopsy and surgical specimens for each patient, and (iii) at least 1-year-follow-up after surgical resection and until 5 years. Patients treated by loco-regional therapies and/or with multiple nodules and/or without a suitable follow-up (i.e. 5 years) were excluded.

Methods

All patients were studied as outpatients at the Ultrasound Section, Gastroenterology Unit of the Department of Clinical Medicine of the University of Bologna. Pre-operative NCB was performed under ultrasound control using a semiautomatic modified Menghini system 19-gauge needle (HS Hospital Service, SPA, Italy); the biopsy was carried out within the lesion (1–3 passages based on the amount of material obtained). The biopsy was performed on fasting (>12 fasting hours) patients if the following conditions were satisfied: prothrombin activity >50% and a platelet count >50,000 μl.

Histological classification

HCC was graded according to a modified version of the Edmonson-Steiner classification [21]: G1–G2: well differentiated, G3: moderately differentiated, and G4: poorly differentiated. In tumours exhibiting several regions of differentiation, grading was established according to the highest grade observed.

In our analysis, as well as in other studies [20,22], Edmonson's classification [21] was modified to include only two groups: low grade (well/moderately-differentiated) and high grade (poorly-differentiated) HCC. This simplified model was chosen because well- and moderately-differentiated tumours seem to have similar long-term survival after OLT while patients with poorly-differentiated tumours have a significantly worse outcome following OLT [11,13,23–25]. Furthermore, when the same differentiation grade was found in the overall lesion, HCC was defined as a homogeneously-differentiated carcinoma while, when several differentiation grades were present simultaneously, HCC was defined as heterogeneous. In our analysis, according to patient outcome, HCCs were classified as very highly heterogeneous when they showed the simultaneous presence of low and high grades in the same nodule.

Statistical analysis

The patient's baseline characteristics are expressed as mean (ranges) for continuous data and as frequencies (percentages) for categorical data.

χ^2 test was used to compare categorical variables (tumour size, grade, and microvascular invasion).

Logistic regression analysis (uni- and multi-variate analyses) was performed in order to evaluate the possible predictors (age, sex, tumour size, Child–Pugh score, α-fetoprotein levels, and liver disease aetiology) of tumour grade on the surgical specimen. Logistic regression analysis (uni- and multi-variate analyses) was also performed in order to evaluate risk factors (age, sex, tumour size, Child–Pugh score, α-fetoprotein levels, liver disease aetiology, and presence of microvascular invasion) for tumour recurrence.

Overall survival and recurrence rates were calculated using the Kaplan–Meier method and were compared using the log-rank test. The agreement of tumour grade assessment between the pre-operative needle biopsy and the final surgical specimen was evaluated using the k statistics [26]. Statistical significance was defined as p <0.05. Statistical analyses were performed using SPSS 13.0.

Results

Patients

Patient baseline characteristics are summarized in Table 1. There were 63 men and 18 women (mean age 62.78 ± 7.2 years); mean tumour size was 4.1 ± 2.3 (range 1–15 cm). In almost all patients, liver cirrhosis had a viral aetiology (HCV = 60.5%; HBV = 17.3%). Seventy-five (92.6%) patients were classified as Child–Pugh score A and 6 (7.4%) patients as Child–Pugh score B, while no patient was classified as Child–Pugh score C. Only 13 (16%) patients presented an AFP level >100 ng/ml.

No significant NCB major side effect was recorded; in 25 (31%) out of 81 patients a transient pain in the site of liver biopsy was documented. Furthermore, no case of tumour seeding along the needle tract was documented.

Histologic data

On the basis of the pre-operative NCB, 69 out of 81 (85.1%) cases were classified as low grade HCC while 12 (14.9%) cases were classified as high grade HCC. Instead, on the basis of the final surgical specimen, 64 out of 81 (79.0%) HCCs were classified as low

Table 1. Patient clinical and pathological features (n = 81).

Variable		Value
Mean age (years)		62.78 ± 7.2
Male / Female		63/18
Solitary tumor n (%)		81 (100)
Mean tumor size / Larger tumor (cm)		4.1 ± 2.3/15
Tumor size n (%)		
	≤3 cm	30 (37)
	≤5 cm	64 (79)
	≤6.5 cm	72 (89)
	>6.5 cm	9 (11)
Microvascular Invasion		40 (49.3)
Aetiology n (%)		
	HBV	14 (17.3)
	HCV	49 (60.5)
	Alcohol	8 (9.9)
	Cryptogenic	10 (12.3)
Child-Pugh score n (%)	A / B	75 (92.6)/6 (7.4)
α fetoprotein levels (ng/ml) (%)		
	1-10	34 (42)
	11-100	34 (42)
	101-1000	13 (16)

n (%); HBV = hepatitis B virus; HCV = hepatitis C virus.