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Laparoscopic ablation therapies or hepatic resection in cirrhotic patients with small hepatocellular carcinoma

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ABSTRACT

Background: The Barcelona Clinic Liver Cancer staging system recommends radiofrequency ablation as treatment of choice for patients with "small" (up to 2 cm in size) hepatocellular carcinoma.
Aims: Aim of the study was to assess whether laparoscopic ablation therapies or hepatic resection could be proposed as alternative option if percutaneous approach is not feasible.
Methods: Overall survival and tumour recurrence rate were compared in a retrospective cohort of 176 consecutive patients with small hepatocellular carcinoma on cirrhosis treated by laparoscopic ablation therapies or surgery. To balance the covariates between the two groups, a propensity case-matched analysis was developed to generate a matched sample, which included 76 patients in each arm.
Results: Local tumour progression ($p = 0.005$), intra-segmental recurrence ($p = 0.0001$), and 5-year recurrence rates (80% vs. 60%; $p = 0.0014$) were significantly higher in the ablation therapies group. The 5-year survival rate were 48% after ablation therapies and 69% after hepatic resection ($p = 0.0006$). Multivariate analysis showed that MELD score, alpha-fetoprotein value, procedure category and intraoperative restaging were associated with survival, while the surgery was the only independent predictor of intra-hepatic recurrence.
Conclusions: The present study suggests that, if percutaneous ablation is not feasible, hepatic resection may be considered as a sound option in the treatment of small hepatocellular carcinoma.

1. Introduction

Several comparative studies [1–5] provided evidence that percutaneous radiofrequency ablation (RFA) may be considered the treatment of choice for patients with single, small hepatocellular carcinoma (HCC) (up to 2 cm in size), even if there are no contraindications to hepatic resection (HR) [6–8]. As a matter of fact, previous reports showed that percutaneous RFA gave good results: complete tumour ablation rates of 90–95% and low local tumour progression rates of 5–10% were documented in the majority of series [6,9,10]. However, in daily practice, it is common to find patients with HCC, which were not eligible for this procedure, mainly because the lesion is not identifiable at ultrasound examination [11]. Three studies [11–13] have shown that percutaneous RFA was not feasible in 25–55% of candidates, above all because the impossibility to visualize the nodule with percutaneous ultrasound (due to the subphrenic location of the nodule and the presence of macronodular cirrhosis) prevented this approach. On the other hand, multicentre Italian studies have demonstrated that surgical resection was considered for small HCC only in few patients [14,15].

Laparoscopic ablation therapies (LATs), which were introduced in the past few years [16–18], have been proposed as an alternative option for patients ineligible for other procedures. These treatments allow an improvement in tumour staging by intraoperative ultrasound (IOUS) and gross examination for tumour spread [19]. Additionally, recent studies have proved that a laparoscopic approach provides safe treatment for sub-capsular lesions,

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lesions located in close proximity to the gallbladder or other visceral structures, or lesions with locations unfavourable for percutaneous ablation [16–18,20,21].

Finally, despite no consistent study exists, the laparoscopic approach has been recommended as a reasonable alternative for patients with concurrent severe co-morbidities or poor liver function [17,18].

Aim of the present study was to evaluate the efficacy and safety of laparoscopic ablation in comparison to surgical resection as initial treatment for small HCC in a large cohort of cirrhotic patients ineligible for percutaneous ablation.

2. Patients and methods

2.1. Patients

Prospective databases of treated patients (total, 855 patients: 529 surgical and 326 LATs) from two institutions (San Paolo Hospital, Milan, Italy and Hospital Henri Mondor, Creteil, France) between February 1997 and January 2012 were retrospectively analyzed. Both Centres assessed disease staging according to the Barcelona Clinic Liver Cancer (BCLC) criteria, since they became available [22]. BCLC staging was retrospectively assessed in all patients enrolled before its accessibility.

A multidisciplinary team, including surgeons, radiologists, and hepatologists determined patient eligibility for an invasive treatment. Criteria for staging and treatment evolved over time. However, both were similar amongst the two centres, with only slight differences during the study period. In the Creteil Centre, the possibility of liver transplantation was considered first. Alternatively, liver resection was considered the treatment of choice. For patients referred to the Italian Centre, a transplant centre evaluation was performed even if liver transplant was not available on-site, despite the availability of this procedure was rather limited before 2000.

Until 2012 (when the modified BCLC therapeutic algorithm was published [7]), surgical resection was proposed according to BCLC and AASLD guidelines: patients who had a single lesion were offered surgical resection if they had cirrhosis with preserved liver function. Portal hypertension was not considered a contraindication in all cases [23]. When surgery was not feasible or warranted, patients were evaluated for percutaneous or laparoscopic ablation.

Percutaneous RFA was considered in patients with favourable target tumour for percutaneous access (conspicuous nodule on pre-operative ultrasound), at higher surgical risk (more than 2 segments with a postoperative remnant liver size less than 40–50%), impaired liver function (Child B) or severe comorbidities; laparoscopic approaches were considered for tumours in the dome of the liver or in other dangerous locations (due to proximity with visceral structures such as gallbladder, colon and stomach) or locations difficult to accurately target percutaneously, as confirmed by expert radiologists skilled in interventional procedures. Patients selected for the present cohort analysis fulfilled all of the following criteria at presentation: single lesion, tumour size less than 2 cm and Child–Pugh class A were submitted to liver resection (if they required resection of less than 2 segments); in other cases they were treated by LATs (percutaneous ablation or surgery not indicated). Based on these criteria, 679 patients were excluded and 176 small HCC patients were included in the study: 84 patients who underwent resection and 92 who underwent LATs.

The residual liver function was classified according to the Child–Pugh classification and by MELD (model for end-stage liver disease) score (which was retrospectively re-calculated for patients included before 2000) [19,24,25]. We also retrospectively applied an s-BCLC staging system [26]. Comorbidity was assessed using the Charlson's index [27]: according to this score, patients were categorized as having slight (<2) or severe comorbidities (>3). Furthermore, the diagnosis and staging of HCC was achieved by a sequential contrast-enhanced imaging technique as the percutaneous ultrasound, triple phase helical computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI). Prior to the establishment of the criteria for non-invasive diagnosis of HCC at the European Association of the Study of the Liver in 2000, the diagnosis was established by liver biopsy. As suggested by current guidelines [1,2,7], a preoperative ultrasound-guided percutaneous liver biopsy was performed only in patients with uncertain diagnosis. Based on the BCLC group criteria, the presence of preoperative portal hypertension was defined by esophageal varices detected with endoscopy or by enlarged spleen (major diameter >12 cm) with a platelet count <100,000 mm^{-3} [22,25]. Direct measurements of venous pressure were not routinely performed in the current series.

2.2. Treatment

All surgical procedures included intra-operative ultrasonography (IOUS) examinations by using finger or laparoscopic probes equipped with a multi-frequency linear-array transducer. Similarly to the histological criteria described by Yamashita et al. [28], IOUS definition of micro-invasive HCC in the Italian subgroup was based according to the presence of portal vein, hepatic vein, bile duct infiltration, and/or intra-hepatic metastasis, as previously described [29] (Fig. 1).

Thermo-ablation therapies are described in Appendix A: (Supplementary methods).

Laparotomy for liver resection was carried out following a standardized technique [19,24], while laparoscopic HR was considered in patients with HCC lesions limited to the left lobe or segments IV through VI.

2.3. Assessment and follow-up

Postoperative mortality was defined as occurrence of death within 30 days after treatment. Severity of postoperative morbidity was defined according to the Dindo-Clavien classification of surgical complications [31]. Postoperative hepatic insufficiency was graded according to International Study Group of Liver Surgery (ISGLS) [32].

Liver US and CT (and/or MRI) were performed within one month after treatment to assess the response to either liver resection or ablation. Post-treatment follow-up evaluation was performed by spiral CT (and/or MRI) after 3 months and every 6 months thereafter.

2.4. Technical evaluation

Technical outcome and oncologic response were defined using the International Working Group on Image-Guided Tumour Ablation [33] standardized definitions and according to the guidelines of the International Union Against Cancer (UICC) [34] (Appendix A: Supplementary methods). Local tumour progression was diagnosed when a follow-up exam showed findings of interval development/growth of the tumour along the margin of the ablation or resected zone where the procedures had been considered to be technically effective. Recurrence was categorized as either intra-segmental (including local tumour progression) or extra-segmental based on the segment of the original nodule. HCC recurrence was classified as early or late, using a cut-off of 12 months. Experienced radiologists reviewed all CT scans.