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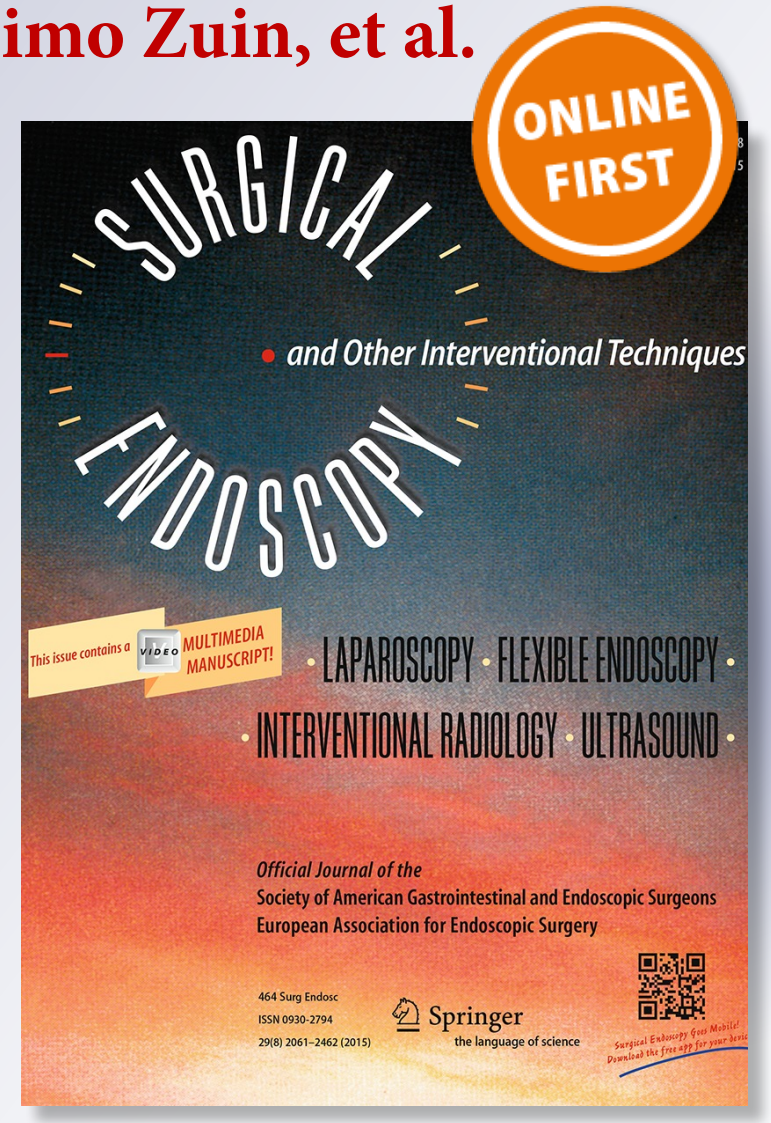

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Long-term outcome of laparoscopic ablation therapies for unresectable hepatocellular carcinoma: a single European center experience of 426 patients

Roberto Santambrogio[1] · Matteo Barabino[1] · Savino Bruno[2] · Mara Costa[1] · Andrea Pisani Ceretti[1] · Maria Rachele Angiolini[1] · Massimo Zuin[3] · Franca Meloni[4] · Enrico Opocher[1]

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Abstract

Background Radiofrequency ablation (RFA) is widely used as a first-line option in patients with hepatocellular carcinoma (HCC). However, since percutaneous approach of RFA may be, in some cases, unfeasible by the tumor size and its location, laparoscopic ablation therapies (LATs) were used as an alternative. Objective of the present study was to assess the efficacy of laparoscopic ultrasound examination in addition to LATs in the treatment of HCC in patients not eligible for percutaneous RFA or surgical resection.

Methods Four hundred and twenty-six patients who underwent LATs were analyzed. Laparoscopic approach was offered to patients fulfilling at least one of the following criteria: (a) patients with a single nodule or up to three nodules smaller than 3 cm not suitable for liver transplantation or not eligible for HR because of severe portal hypertension, impaired liver function, or coexistent comorbidities; (b) patients not suitable for percutaneous RFA because of inconvenient tumor location; and (c) short-term recurrence of HCC (<3 months).

Results Technical success was achieved in one session in 396 patients (93 %). One-month mortality and morbidity rates were 0.23 % (1 patient) and 25 % (106 patients), respectively. During a median follow-up of 37.2 months (range 2–193) in the remaining 425 patients, 276 (65 %) developed intra-hepatic recurrence: It appeared as a local tumor progression in 65 cases (15 %). Patients median survival was 39 months (95 % CI 34.8–47.2), while overall survivals at 1, 3, and 5 years were 88, 55, and 34 %, respectively.

Conclusions In the treatment of HCC, LATs proved to be a safe and effective technique, as they permit to treat with low-morbidity-rate lesions not manageable by percutaneous approach. Moreover, they allow achieving a more accurate staging of the disease in one-fifth of patients, thus better redefining the prognosis of such individuals.

Keywords Hepatocellular carcinoma · Liver cirrhosis · Laparoscopic ultrasound · Radiofrequency interstitial thermal ablation

Liver transplantation (OLT) and hepatic resection (HR) represent treatment modalities with demonstrated good long-term survival and low recurrence rates [1]. However, only a small percentage of patients (10–25 %) is eligible for these therapies [2]. In recent years, radiofrequency ablation (RFA) has been performed with promising results in patients with hepatocellular carcinoma (HCC). Furthermore, some experts [3, 4] recommended RFA as the first-line therapy for patients with early and "very early" (VE) HCC (stage 0), suggesting HR only in patients with failure of or contraindications to RFA.

RFA is most commonly performed in radiological setting through a percutaneous approach [3, 5], but there is a

✉ Roberto Santambrogio
rsantambrogio@mclink.it

[1] Chirurgia 2, Epato-bilio-pancreatica e Digestiva, San Paolo Hospital, University of Milan School of Medicine, Via A. di Rudini' 8, 20142 Milan, Italy

[2] Department of Internal Medicine, IRCCS Istituto Clinico Humanitas, Medicine Humanitas University, Rozzano, MI, Italy

[3] Internal Medicine and Hepatology Department, San Paolo Hospital, University of Milan School of Medicine, Milan, Italy

[4] Interventional US Unit, Radiology Department, Valduce Hospital, Como, Italy

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subgroup of patients who may benefit from a laparoscopic approach [6, 7], which combines the advantages of an improved staging, allowed by intra-corporeal ultrasound examination [6]. It guarantees a safer approach to liver lesions whose location would have made a percutaneous treatment difficult or impossible to perform [8]. Aim of this study is to analyze our personal experience with this technique in the treatment of HCC in patients not eligible for HR or percutaneous RFA.

Methods

Patients

Since 1997, the diagnosis and treatment of HCC patients referred to our unit were carried out following a defined and shared protocol [9]. HCC staging was performed on the basis of ultrasonography (US) and contrast-enhanced helical computed tomography (CE-CT) findings. The diagnosis of HCC was made according to the European Association for the Study of the Liver [10] and, after 2005, according to the American Association for the Study of Liver Disease guidelines [11]. Liver function was evaluated with routine laboratory tests including alpha-fetoprotein (AFP) concentration. Complete medical history was obtained in each patient. An overall assessment of the severity of liver disease was made at the time of patient inclusion in the study according to the Child–Pugh classification.

Laparoscopic ablation therapies (LATs) were offered to patients meeting at least one of the following criteria [7, 9]:

(a) Patients with a single nodule or up to three nodules smaller than 3 cm not suitable for OLT (because of age or severe comorbidities);
(b) Patients not eligible for HR because of:
    - Severe portal hypertension;
    - Impaired liver function;
    - Coexistent comorbidities;
(c) Patients not suitable for percutaneous RFA because of:
    - Severe impairment of coagulation tests [platelets < 40.000 and/or international normalized ratio (INR) > 1.20];
    - Superficial lesions adjacent to abdominal viscera, which could be easily displaced during laparoscopy;
    - Deep-sited lesions with very difficult or impossible percutaneous approach (i.e., lesions undetectable at US, or contiguous to primary biliary or portal tributaries);
(d) Short-term recurrence of HCC (<3 months) following percutaneous ethanol injection or RFA or transcatheter arterial chemoembolization (TACE).

The exclusion criteria were complete portal thrombosis and/or a coexisting severe liver disease (class C according to the Pugh–Child classification).

Technical notes

All the patients underwent intra-operative ultrasound (IOUS) examination [Aloka SSD 500 (1996–1999), SSD 1700 (2000–2006), Alfa 10 (2006–2014); Aloka Co., Tokyo]. We used a laparoscopic ultrasound (LUS) probe with either a rigid shaft [Aloka SSD 500 (1996–1999)] or a flexible tip, 10 mm in diameter and 50 cm in length [13]. A 7.5 linear-array transducer was side-mounted near the tip of the shaft. The length of the transducer surface was 38 mm, producing an image footprint of approximately 4 cm in length and 6 cm in depth. All examinations were performed by a surgeon trained in US techniques [7].

The development of LUS liver scanning was based on the standard IOUS examination already defined in the laparotomic approach. The technique has been well described in the literature [6, 12]. Briefly, LUS examination of the liver was performed at the beginning of each surgical procedure, with the patient under general anesthesia. A "protected" technique for liver nodules biopsy was routinely performed using an automatic disposable 18-gauge biopsy needle (Temno, Bauer Medical International S.A., Santo Domingo).

According to our previous report on IOUS pattern classification of HCC [13], which shares some similarities with the histological criteria described by Yamashita et al. [14], we adopted an IOUS definition of microinvasive (MI) HCC considering the possible presence of portal venous, hepatic vein, bile duct infiltration, and/or intra-hepatic metastasis.

A 200-W, 480-kHz monopolar radiofrequency generator (Valleylab, Boulder, CO, USA) was used as the energy source. An insulated 18-gauge internally cooled tip electrode was inserted into the tumor under sonographic guidance; the shaft of this kind of electrode is electrically insulated with only 3–4 cm of exposed metallic tip from which radiofrequency emanates. Electrode tips were selected by matching tip exposure to lesion diameter. Under LUS guidance, the tip of the electrode was advanced until it reached and passed the margin of the lesion, opposite to the point of entrance of the needle. A peristaltic pump was used to infuse into the cooling lumen of the radiofrequency electrode 0 °C normal saline solution with an adequate flow to maintain tip temperature between 18 and 25 °C. Repeated needle placements into the lesion were performed when necessary to obtain maximal lesion

coverage. LAT was repeated until the whole tumor area showed highly echogenic changes.

In some cases, we used clustered electrodes, applying radiofrequency simultaneously with three internally cooled electrodes, spaced 5 mm apart; this devices lead to a substantial increase in the volume of coagulation necrosis obtained at a single treatment session, as previously described in the literature [12].

Since 2004, we performed in selected cases a technical variant known as "intra-hepatic vascular occlusion" (IHVO). This approach produces an ischemic area surrounding the lesion with the aim of increasing the necrosis volume [15]. This effect may reduce the risk of immediate therapy failure (secondary to partial ablation) and of local recurrence. In order to obtain a selective intra-hepatic portal venous occlusion, the primary vessel of the lesion is identified by color Doppler imaging: Using US guidance, the electrode is directed toward this area with direct puncture of the nearby blood vessel; the ablation cycle lasts for 2–4 min or 60–90 s using RFA or microwave ablation (MWA), respectively. A later color Doppler evaluation is therefore performed to confirm a coagulative ablation of the vascular area, also appreciable as a discolored area on the liver surface (Fig. 1). Finally, the lesion is treated with the insertion of the electrode in the usual way.

Since February 2009, a 2.45-MHz microwave generator (AMICA-GEN, HS Hospital Service SpA, Aprilia, Italy) providing energy through a 14- or 16-gauge internally cooled coaxial antenna was also used. This features a miniaturized quarter-wave impedance transformer (referred to as a minichoke) for reflected wave confinement. The minichoke antenna design, protected by an industrial patent (PCT/IB2002/00299) owned by the Italian National Council for Research, ensures a quasi-spherical radiation pattern without increasing the probe diameter (14 gauge at most). According to the tumor size, a single microwave energy application is delivered to the patient, ranging from 45 to 70 W net power at the applicator end, for a total period of 5–10 min.

Pre- and posttreatment imaging evaluation

Preoperative assessment included a US study of the liver and a three-phase spiral contrast-enhanced CT scan allowing the hepatic arterial, portal venous, and delayed phases of hepatic enhancement to be imaged separately. In selected cases, a magnetic resonance imaging (MRI) of the liver was obtained.

US and CT scan were repeated within 1 and 3 months after the procedure. The posttreatment response was later evaluated by CT scan twice a year. A single, experienced radiologist reviewed all CT exams.

Technical outcome and oncologic response were defined using standardized definitions of the International Working Group on Image-Guided Tumor Ablation [16]. Technical success was defined when the tumor resulted completely replaced by RFA zones at the 1-month follow-up exams (total necrosis). Achievement of technique effectiveness was defined when complete ablation of macroscopic tumors was evident at the subsequent follow-up for those patients whose HCC lesions were completely removed by the initial LAT treatment. Local tumor progression (LTP) was defined as the reappearance of enhancing tissue within and around the ablation zone, the latter case secondary to the presence of residual unablated tumor in a patient previously considered as completely treated. Recurrence was classified as either intra-segmental (including LTP) or extrasegmental (appearance of HCC nodules in other hepatic segments). HCC recurrence was further classified as early or late, using a 12-month cutoff.

Patients who did not show a complete local response after the first LAT session underwent further either LAT session or TACE. Patients with LTP or intra-hepatic new distant tumor recurrence were treated with appropriate therapies following the European Association for the Study of the Liver and the American Association for the Study of Liver Disease guidelines [1, 11].

Statistical analysis

Initial evaluation and subsequent follow-up data were collected in a dedicated database (FileMaker Pro, FileMaker Inc., Santa Clara, CA, USA) for personal computer input (Macintosh G4, Apple Computer Inc., Cupertino, CA, USA) and subsequent analysis (Statistica-Mac, Statsoft, Tulsa OK, USA). Cumulative actuarial curves were analyzed by the Kaplan–Meier method and were compared by the log-rank test. Comparison of means between and within groups was done by using the Mann–Whitney *U* test and the Wilcoxon matched pairs test. Data are expressed as mean ± standard deviation. Comparison of proportions was done by the Fisher exact probability test. In all patients, intra-operative variables were recorded and their influence upon the HCC recurrence was assessed using univariate analysis and either logistic regression or Cox's proportional hazards regression model.

The study was approved by the local review boards, and a written informed consent was obtained from all patients before the treatment.

Results

Among 877 patients treated for HCC during the 14 years of the present study period, 444 (322 men/122 women) with a mean age of 68.9 ± 8 years (range 42–90) underwent LATs and were considered for the study. Ninety-six patients

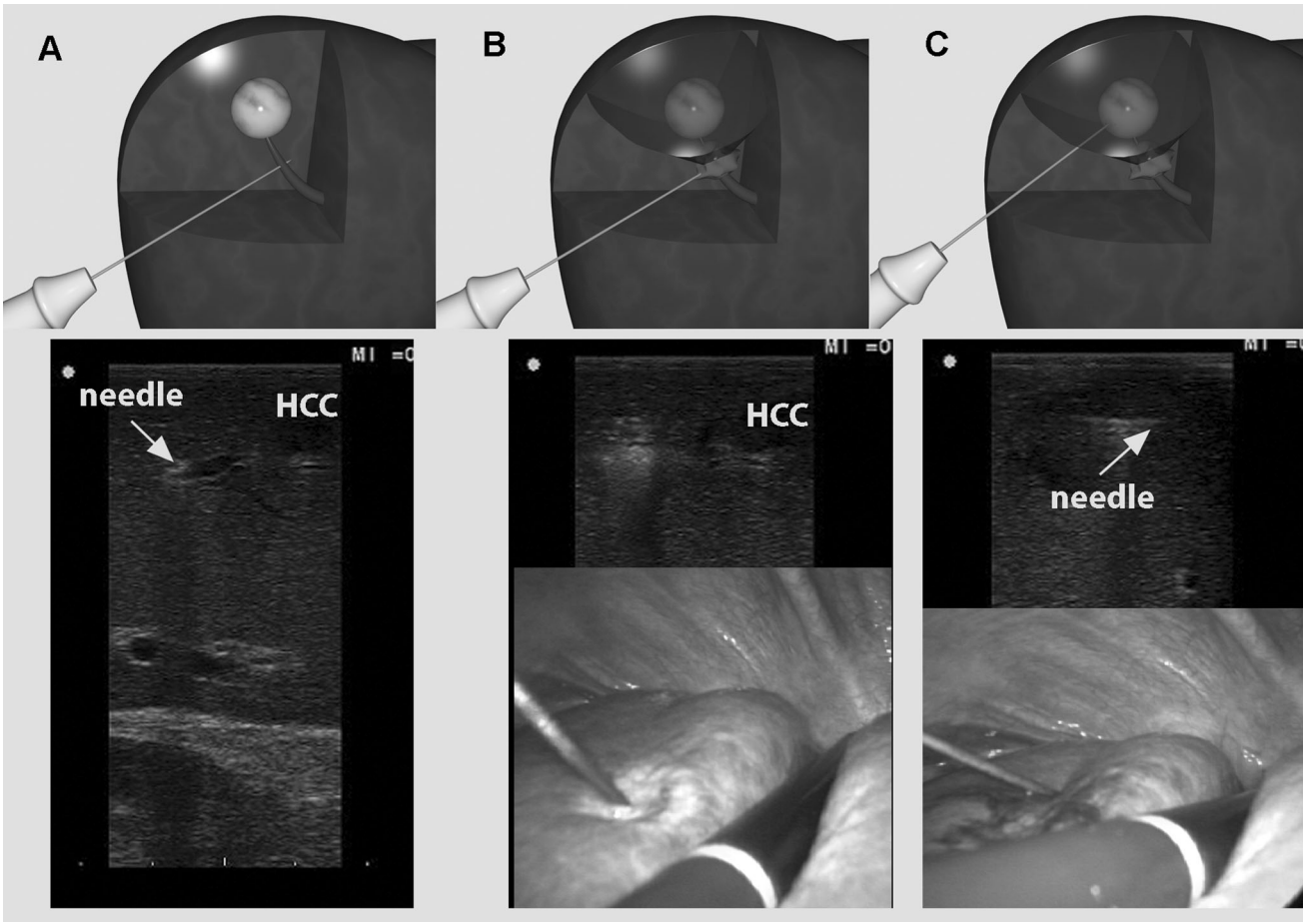

Fig. 1 Primary vessel of the lesion was identified by color Doppler imaging (**A**): Using ultrasonographic guidance, the radiofrequency electrode was directed toward this area with direct puncture of the nearby blood vessel and the ablation cycle lasted 2–4 min (**B**). A discolored area on the liver surface can be also visualized (**B**). Then, the lesion was treated with the insertion of the electrode in the usual way (**C**) (reprinted with permission from Torzilli G. Ultrasound-guided liver surgery. Springer-Verlag Italia 2014. Courtesy of Springer-Verlag)

(22 %) were older than 75 years and 79 (18 %) were in Child–Pugh class B; 49 % of the patients had a tumor size of 20 mm or less, 29 % had a tumor size between 21 and 30 mm (mean tumor size in this subgroup 24.7 ± 11.9 mm), and 38 % had multiple nodules. Main indications for laparoscopic approach are reported in Table 1. The patients' characteristics at the baseline are shown in Table 2. Eighteen patients were excluded from the further statistical analysis because of BCLC class B–C. For these reasons, the final study group included 426 patients treated with LATs: 267 underwent traditional RFA treatment using a "cooled tip" needle, while 61 patients (treated since 2004) underwent treatment with IHVO, and 98 patients (treated since 2009) underwent MWA. Mean total operative time was 89.6 ± 34.5 min (range 30–240 min; median 80 min); mean total LATs time was 18.3 ± 9.1 min (range 3–60; median 16 min); the mean number of needle insertions was 2.03 ± 1.04 (range 1–6; median 2).

IOUS examination detected unrecognized additional nodules in 95 patients (22 %): These new hepatic nodules had a mean diameter of 10.8 ± 4 mm (range 3–26 mm). In 37 cases (39 % of the patients with new nodules), they were contiguous to primary HCC (satellite nodules), while in 58 cases (61 %) they were located in other segments.

Postoperative morbidity and results

The mean postoperative hospital stay was 4.2 ± 1.8 days (range 1–17 days; median 4 days). Thirty-day mortality rate was 0.24 %, with one case of postoperative cardiac failure. Thirty-day morbidity rate was 25 % (106 patients): According to Clavien–Dindo classification, high-grade complications (IIIa/IIIb) appeared in eight cases (1.90 %) and low-grade complications (I/II) in 97 (22.7 %). There were no grade IV complications and, as previously mentioned, one case with grade V.

Table 1 Reasons to reject percutaneous RFA or HR for 444 patients submitted to LATs (more than 1 reason for each patient)

Percutaneous RFA	N[a] (%)	Hepatic resection (HR)	N[a] (%)
HCC contiguous to visceral structures	130 (14 %)	HR > 2 segments	168 (25 %)
Superficial lesion	91 (10 %)	Patients > BCLC A2 stage	268 (40 %)
Lesion difficult or impossible to percutaneous US visualization	284 (30 %)	Other concomitant severe disease	93 (14 %)
LUS staging (for suspected other nodule)	144 (15 %)	Patient refusal	49 (7 %)
Pts at risk of bleeding (plts < 50,000 and/or INR > 1.2)	124 (13 %)	Age > 78 years	21 (3 %)
Multiple lesions	169 (18 %)	Child B class	78 (11 %)

[a] Study group: eighteen patients

Table 2 Demographic and clinical characteristics of all patients enclosed in the study

Variables	444 pts (%)	426 pts[a] (%)	IHVO pts (from 2004: 61 pts)	MWA pts (from 2009: 98 pts)
Gender: female/male	122/322 (27/73 %)	119/307 (28/72 %)	17/44 (28/72 %)	27/71 (28/72 %)
Age: ≤75/>75 years	348/96 (78/22 %)	335/91 (79/21 %)	45/16 (74/26 %)	68/30 (69/31 %)
Etiology: HBV, HCV, other	58/304/82 (13/68/19 %)	57/292/77 (13/69/18 %)	6/39/16 (10/64/26 %)	12/68/18 (12/69/19 %)
Child: A/B	365/79 (82/18 %)	350/76 (82/18 %)	46/15 (75/25 %)	79/19 (81/19 %)
BCLC: A1–A3/A4/B–C	224/202/18 (51/45/4 %)	224/202/0 (53/47 %)	34/27/0 (56/44 %)	48/50/0 (49/51 %)
MELD: ≤9/>9	218/185 (54/46 %)	208/178 (54/46 %)	28/27 (51/49 %)	57/41 (58/42 %)
Charlson index: <3/≥3	254/190 (57/43 %)	244/182 (57/43 %)	28/33 (46/54 %)	51/47 (52/48 %)
Bilirubin: ≤1/>1	176/267 (40/60 %)	172/253 (40/60 %)	29/32 (48/52 %)	35/63 (36/64 %)
Albumin: >3.5/≤3.5	302/141 (68/32 %)	292/133 (69/31 %)	40/21 (66/34 %)	69/29 (70/30 %)
AFP: ≤20/>20	268/162 (62/38 %)	264/148 (64/36 %)	39/20 (66/34 %)	60/36 (62/38 %)
IOUS MI: not/yes	208/233 (47/53 %)	205/219 (48/52 %)	19/42 (31/69 %)	50/48 (51/49 %)
Diameter: ≤3/>3 cm	346/98 (78/22 %)	341/85 (80/20 %)	51/10 (84/16 %)	73/25 (74/26 %)
Capsule: yes/not	236/206 (53/47 %)	227/197 (54/46 %)	37/24 (61/39 %)	52/46 (53/47 %)
Capsule invasion: not/yes	141/301 (32/68 %)	136/288 (32/68 %)	16/45 (26/73 %)	25/73 (26/74 %)
Mosaic pattern: not/yes	371/70 (84/16 %)	359/64 (85/15 %)	53/8 (87/13 %)	80/17 (82/18 %)
Nodule-in-nodule: not/yes	293/149 (66/34 %)	283/141 (67/33 %)	37/24 (61/39 %)	61/37 (62/38 %)
Vascular microinvasion: not/yes	311/131 (70/30 %)	304/120 (72/28 %)	24/37 (39/61 %)	76/22 (78/22 %)
US–visible: yes/not	173/271 (39/61 %)	159/267 (37/63 %)	18/43 (30/70 %)	51/47 (52/48 %)
Superficial HCC: yes/not	167/277 (38/62 %)	158/268 (37/63 %)	18/43 (30/70 %)	46/52 (47/53 %)
HCC adjacent to gallbladder: not/yes	413/31 (93/7 %)	396/30 (93/7 %)	60/1 (98/2 %)	91/7 (93/7 %)
HCC adjacent to vessels: not/yes	400/44 (90/10 %)	388/38 (91/9 %)	60/1 (98/2 %)	88/10 (90/10 %)
Recurrent HCC: not/yes	249/195 (56/44 %)	236/190 (55/45 %)	37/24 (61/39 %)	50/48 (51/49 %)

IOUS MI intra-operative ultrasound microinvasive pattern, *IHVO* intra-hepatic vascular occlusion, *MWA* microwave ablation

[a] Eighteen patients were excluded from the further statistical analysis because of BCLC class B–C. For these reasons, the final study group included 426 patients treated with LATs

Technical success was achieved in one session in 396 patients (93 % of the total study group), in 61 cases out of IHVO subgroup (100 %) and in 90 cases of MWA subgroup (92 %). Technical success rate significantly differed according to tumor size ($p = 0.001$): No apparent viable portions were appreciable in 324 (95 %) of the 341 patients with smaller tumors (≤3.0 cm), while this proportion resulted inferior (72 cases, equal to 85 %) among the 85 patients with larger tumors (>3.0 cm). No differences were found for single versus multiple lesions (procedure technical success: 94 versus 91 %, respectively; $p = 0.326$). Treatment failure was observed in 30 patients (7 %): Of these patients, 7 received another LAT, while 16 patients underwent TACE; the remaining 7 patients were not further treated because of liver failure o multiple new HCC nodules.

Technique effectiveness (follow-up period)

Excluding one patient with in-hospital mortality, the median follow-up of the remaining 425 patients was 37.2 months (range 2–193 months). One hundred and forty-nine patients (35 %) remained recurrence-free during the study period. Meanwhile, 276 patients (65 %) developed intra-hepatic recurrence. Regarding the precise location of intra-hepatic recurrence, it appeared in same segment in 128 cases (30 % of the whole study group, including 65 cases of local tumor progression, equal to 15 % of the patients) and in different segments in 148 patients (35 %). One hundred and thirty-three patients (31 %) had a single tumor as recurrence, while 143 patients (34 %) had multiple nodules.

Among the 65 patients with local tumor progression, time to develop local tumor progression ranged from 1 to 54 months (mean 12.8 ± 10.8). On the other hand, as regards timing of intra-hepatic recurrence, in 148 patients (35 %), it appeared "early," meaning within 12 months from LAT.

Cumulative intra-hepatic tumor recurrence rates at 1, 3, and 5 years were 33, 69, and 78 % (Fig. 2A), while local tumor progression and intra-segmental recurrence rates at 1, 3, and 5 years were 9, 18, and 20 and 15, 33, and 40 %, respectively (Fig. 2B, C).

In 87 out of 276 HCC recurrences (31 %), it was not possible to retreat the patient; the reasons were multiple tumors development (53 cases), liver insufficiency occurrence (22 cases), patient's refusal (6 cases), US-undetectable lesion (3 cases), and extrahepatic tumors development (3 cases).

On the other hand, 189 out of 276 HCC recurrences (69 %) have been treated: 78 patients underwent TACE, 72 had LATs, 22 received percutaneous RFA, 16 patients were candidate for hepatic resection, and 1 patient underwent OLT; among these patients, technical success has been obtained in 147 cases (78 %).

Univariate and multivariate analysis of factors contributing to intra-hepatic recurrence

At the univariate analysis, AFP > 20 ng/ml, IOUS microinvasive pattern, IOUS infiltrative pattern, superficial lesion, and recurrent HCC nodule appeared significantly contributing to intra-hepatic recurrence. The multivariate analysis confirmed AFP > 20 ng/ml, IOUS MI pattern, superficial lesion, and recurrent HCC nodule as independent risk factors for intra-hepatic recurrence.

On the other hand, as regards local tumor progression, AFP > 20 ng/ml, and IOUS MI pattern resulted significantly associated with LTP at univariate analysis. A multivariate analysis involving these two factors together with other four conditions showing a weaker association with LPT ($p < 0.1$), which were Child–Pugh A, A1–A3 BCLC stage, deep-sited lesion and proximity to intra-hepatic vessels, only AFP > 20 ng/ml and IOUS MI pattern confirmed their independent association. Hazard ratios and

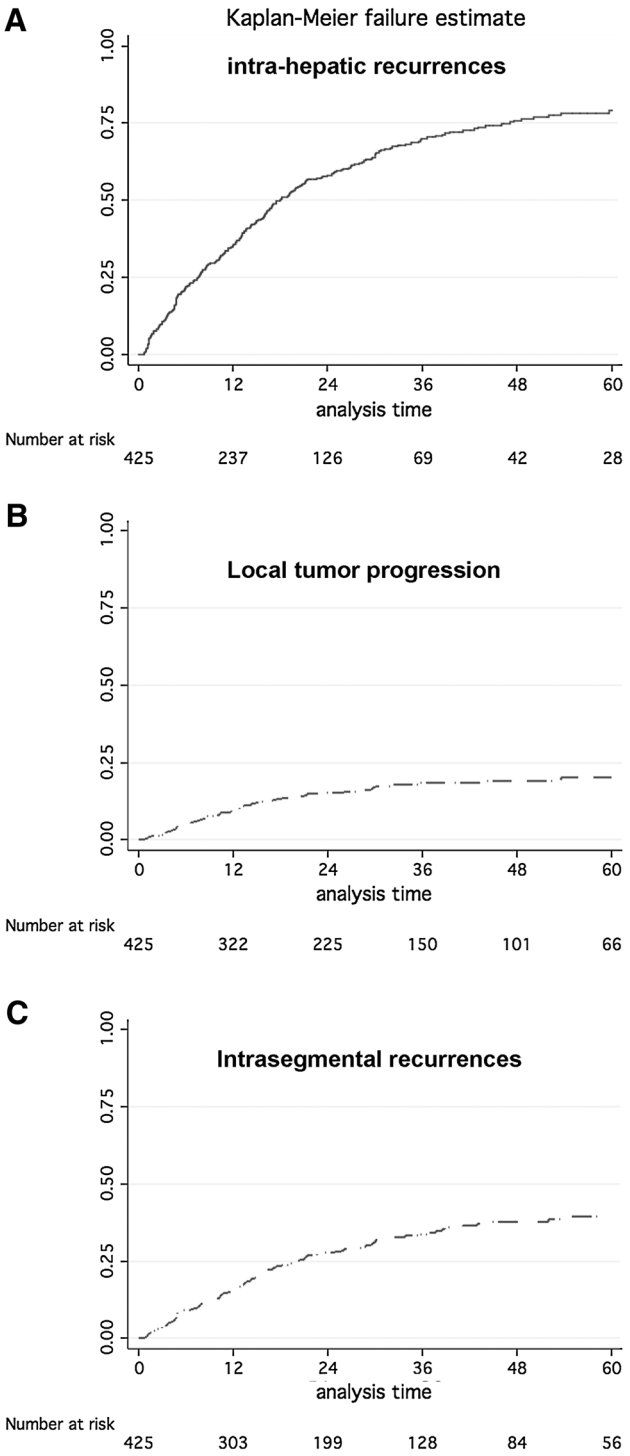

Fig. 2 Graph shows Kaplan–Meier overall HCC recurrences (**A**), local tumor progression (**B**), and intra-segmental recurrences (**C**) for 425 patients who underwent LATs for unresectable HCC

95 % confidence intervals (CI) regarding all these analysis are detailed in Table 3.

Survival analysis

During the follow-up, 269 of 426 patients (61 %) died: 116 (43 %) because of neoplastic progression, 83 (31 %) because of progressive liver failure or acute upper gastrointestinal hemorrhage, and 70 (26 %) because of other nonliver-related diseases or accidents. Patients' median survival was 39 months (95 % CI 34.8–47.2); overall survivals at 1, 3, and 5 years were 88, 55, and 34 %, respectively (Fig. 3).

Univariate and multivariate analysis of factors contributing to survival

At the univariate analysis, Child–Pugh classification, MELD score >9, serum albumin <3.5 g/dl, total bilirubin >1.0 mg/dl, AFP >20 ng/ml, superficial lesions, recurrent HCC, and uncompleted necrosis at 1 month were significantly associated with a poor prognosis (Table 4). At the multivariate analysis, total bilirubin >1.0 mg/dl, albumin <3.5 g/dl, AFP >20 ng/ml, recurrent HCC, and uncompleted necrosis resulted independently associated with worse survival. Hazard ratios and 95 % CI are detailed in Table 4.

Discussion

In recent years, several authors suggested a major change in BCLC therapeutic algorithm regarding the specific subgroup of patients with "very early" and "early" HCC (stage 0 and A of Barcelona Clinic Liver Cancer Staging System): RFA should become the first-line therapy, and HR should be considered only in patients with failure or contraindications to RFA [1, 3, 4].

However, percutaneous RFA and HR cannot always be performed because of nodule location, poor liver function, and severe comorbidities [7, 8, 17]. In our series, as shown in Table 1, 284 patients (30 %) have not been proposed percutaneous RFA because of difficult or impossible transabdominal US visualization of the lesion. This finding is confirmed by a recent publication by Kim et al. [17] who described a 25.3 % rate of HCC undetectable at percutaneous US. The ability to identify and treat lesions located at the dome of the liver, peripheral in the liver, or in proximity to other organs makes this procedure more flexible than the percutaneous approach while remaining minimally invasive [8].

Another advantage of the laparoscopic approach is represented by IOUS examination [6, 7]: In 14 % of patients, other neoplastic nodules located in different segments have been identified and treated, thus permitting a better staging and a true radical treatment. In addition, the related pneumoperitoneum allows for an up to 40 % reduction in the portal venous flow, thereby enabling an increase in the size of the ablation site [7]. Furthermore, despite being a surgical procedure, in our experience, LAT is related to minimal perioperative stress and allows fast recovery, short hospital stay, and low morbidity, especially regarding severe postoperative complications: Only one patient died because of cardiac accident and grade IIIa/IIIb complications were 1.9 %. This is a very good result if we consider the baseline unfavorable clinical features of these patients: 18 % of patients in Child B class, 47 % with A4 BCLC stage, 46 % with MELD score >9, 60 % with abnormal preoperative bilirubin, and 43 % with Charlson comorbidity index >3.

Furthermore, LATs are associated with a lower adhesion than open surgery and dissection around the liver hilum is not required in this approach [7, 12]. Thus, LATs would be a good bridge therapy for prevention of tumor progression and downstaging of multiple lesions before OLT.

As regards LAT efficacy, technical success was achieved in a single session in 93 % of patients and it is in the expected range (90–98 %) according to the most important percutaneous series [3, 5, 18–20]; this is a very important result as it was obtained in a group of patients at high risk of treatment failure or complications following the percutaneous approach, in example because of difficult tumor location or unfavorable anatomic conditions. Furthermore, our experience confirms that residual unablated tissue is a relatively common occurrence after LAT in patients with HCC nodule larger than 3 cm, as reported by several authors [20–23] who suggested that the larger the lesion, the higher the probability of incomplete ablation.

During the follow-up period, LTP in a RFA ablated site is a serious occurrence, with described rates ranging from 17 to 38 % after PEI and from 3.2 to 26 % after RFA [18, 20, 24]. LTP after RFA may be due to insufficient ablation of the primary tumor and/or to the presence of tumor venous invasion or satellite nodules in the adjacent liver [8, 14, 15]. This finding was confirmed in our experience, as the presence of a MI-HCC pattern at IOUS represents an independent risk factor for LTP. This is a further confirmation of the advantages of the laparoscopic approach: Allowing a disease intra-operative restaging, IOUS improves the immediate results as well as the further therapeutic strategies [6, 7, 9]. Other studies, too, suggested the superiority of LAT in LTP risk reduction compared with percutaneous RFA [25]: Unfortunately, no prospective studies comparing the two approaches confirmed it [26]. In addition, none of the proposed technical variants (IHVO LAT) or new technologies (MW) seems to improve

Table 3 Univariate and multivariate analysis for 5-year total HCC recurrences and local tumor progression (LTP)

Variables	5-year total recurrence	Hazard ratio	95 % CI	5-year LTP	Hazard ratio	95 % CI
Gender: female/male	73 %/80 %			27 %/18 %		
Age: ≤75/>75 years	77 %/81 %			19 %/23 %		
Etiology: HBV, HCV, other	79 %/81 %/ 65 %			13 %/21 %/ 23 %		
Child: A/B	80 %/67 %			22 %/10 % ($p = 0.0641$)		
BCLC: A1–A3/A4	80 %/76 %			25 %/14 % ($p = 0.0727$)		
MELD: ≤9/>9	79 %/76 %			20 %/22 %		
Bilirubin: ≤1/>1	77 %/80 %			20 %/20 %		
Albumin: >3.5/≤3.5	79 %/76 %			22 %/14 %		
AFP: ≤20/>20	77 %/79 % ($p = 0.0121$)	1.3253	1.030–1.705 ($p = 0.028$)	16 %/28 % ($p = 0.0003$)	2.4734	1.505–4.066 ($p = 0.0001$)
IOUS MI: not/yes	69 %/86 % ($p = 0.0001$)	1.6316	1.274–2.089 ($p = 0.0001$)	14 %/26 % ($p = 0.0024$)	2.078	1.204–3.587 ($p = 0.009$)
Diameter: ≤3/>3 cm	79 %/75 %			20 %/23 %		
Capsule: yes/not	73 %/85 % ($p = 0.0242$)			17 %/24 %		
Capsule invasion: not/yes	73 %/81 %			19 %/20 %		
Mosaic pattern: not/yes	78 %/80 %			21 %/16 %		
Nodule-in-nodule: not/yes	78 %/78 %			20 %/22 %		
Vascular microinvasion: not/yes	77 %/81 %			18 %/25 %		
US–visible: yes/not	84 %/75 %			25 %/18 %		
Superficial HCC: yes/not	86 %/74 % ($p = 0.0094$)	1.3447	1.046–1.728 ($p = 0.021$)	16 %/23 % ($p = 0.0946$)		
HCC adjacent to gallbladder: not/yes	79 %/63 %			21 %/3 %		
HCC adjacent to vessels: not/yes	77 %/87 %			19 %/31 % ($p = 0.0755$)		
Recurrent HCC: not/yes	73 %/85 % ($p = 0.0001$)	1.635	1.279–2.089 ($p = 0.0001$)	19 %/21 %		
MWA/RFA	79 %/79 %			28 %/19 %		
HIVO/LATs	70 %/80 %			14 %/22 %		

IOUS MI intra-operative ultrasound microinvasive pattern, *MWA* microwave ablation, *RFA* radiofrequency ablation, *IHVO* intra-hepatic vascular occlusion

the LTP rate, even though large reports at this regard are still missing in the literature [15, 27, 28].

Distant recurrence accounts for most of HCC recurrences in our patients; its high frequency is not an unexpected finding, being a universally recognized feature of HCC natural history after whatsoever kind of treatment: The reported tumor recurrence cumulative rate after HR or RFA is 60–80 % [3, 9, 29, 30]. However, it is difficult and sometimes impossible to determine whether the development of a new HCC lesion apart from the primary nodule is due to intra-hepatic metastasis associated with local recurrence or to multicentric tumor genesis in a predisposing substrate, such as liver cirrhosis [31, 32].

Our results showed that an increased level of serum AFP is associated with intra-hepatic HCC recurrences after LATs. Although the reason why AFP production is related to tumor recurrence is not clear, other reports support this association [33, 34]. Furthermore, other tumor features, as MI-HCC pattern and recurrent HCC contribute in this direction: HCC recurrence tends to be multicentric in the liver remnant furthest from the ablation area, being related to the carcinogenic potential of hepatocytes affected by

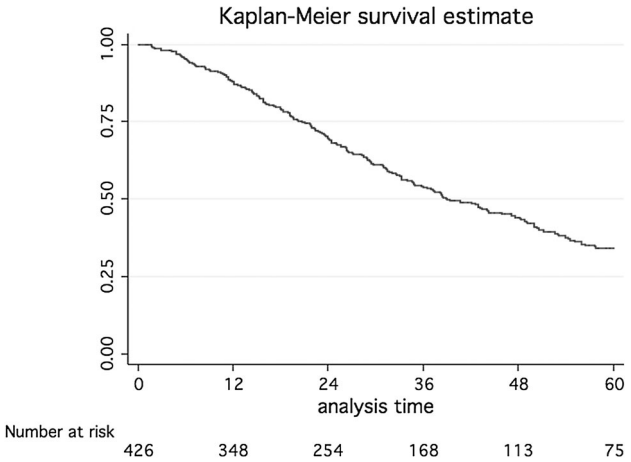

Fig. 3 Graph shows Kaplan–Meier overall survival estimation for 426 patients who underwent LATs for unresectable HCC

cirrhosis or to the development of HCC nodules from microsatellites or microthrombosis [14, 31, 32]. Our results confirm that identification of risk factors and close follow-up are important because recurrences that are confined to the liver may be amenable to additional treatment, with improvement in long-term survival.

According to our experience, total bilirubin >1.0 mg/dl and albumin <3.5 g/dl independently influenced overall survival after LATs. Bilirubin and albumin levels reflect liver function. As shown in previous reports, liver function strongly influences survival [35]. On the other hand, also tumor-related factors as AFP levels or recurrent HCC seem to influence survival rates. These observations confirmed the importance of liver function, as well as HCC own invasiveness, as prognostic factors among patients undergoing LAT for HCC. Furthermore, this study confirmed that initial complete response to LATs is associated with an improved survival as previously described in a percutaneous RFA series [36].

On the other hand, the LATs have some limitations. The limitations of the present study include the inevitable selection bias of a retrospective evaluation within a long recruitment period. The second limitation could be the presence of massive adhesions within the abdominal cavity due to previous surgery in some patients, which make access to the liver difficult. A group of patients qualified for LAT have undergone either HR before (48 cases in our study group) or other abdominal operations, and these operations are responsible for the development of adhesions. Releasing adhesions in order to gain free access to the liver carries higher risk of causing damage to other organs of the abdominal cavity, especially the intestine, and extends the surgery time [37]. The third limitation to the application of LATs is the technical difficulty of puncturing deep-situated tumors. While it is undeniable that some skill is required for laparoscopic tumor puncture

Table 4 Univariate and multivariate analysis for 5-year overall survival

Variables	5-year OS	HR	95 % CI
Gender: female/male	33 %/35 %		
Age: ≤75/>75 years	36 %/30 %		
Etiology: HBV, HCV, other	45 %/34 %/28 %		
Child: A/B	37 %/22 % ($p = 0.0130$)		
BCLC: A1–A3/A4	36 %/32 %		
MELD: ≤9/>9	46 %/25 % ($p = 0.0001$)		
Charlson index: <3/≥3	36 %/32 %		
Bilirubin: ≤1/>1	45 %/26 % ($p = 0.0001$)	1.555	1.122–2.155 ($p = 0.008$)
Albumin: >3.5/≤3.5	40 %/20 % ($p = 0.0006$)	1.438	1.031–2.005 ($p = 0.032$)
AFP: ≤20/>20	42 %/21 % ($p = 0.0001$)	1.682	1.277–2.215 ($p = 0.0001$)
IOUS MI: not/yes	39 %/30 %		
Diameter: ≤3/>3 cm	35 %/32 %		
Capsule: yes/not	36 %/33 %		
Capsule invasion: not/yes	37 %/33 %		
Mosaic pattern: not/yes	36 %/28 %		
Nodule-in-nodule: not/yes	35 %/33 %		
Vascular microinvasion: not/yes	35 %/33 %		
US–visible: yes/not	33 %/35 %		
Superficial HCC: yes/not	26 %/39 % ($p = 0.0415$)		
HCC adjacent vessels: not/yes	33 %/45 %		
Recurrent HCC: not/yes	39 %/27 % ($p = 0.0162$)	1.361	1.029–1.801 ($p = 0.031$)
Total necrosis at 1 month: not/yes	19 %/35 % ($p = 0.0298$)	2.340	1.425–3.844 ($p = 0.001$)

using a laparoscopic US probe, appropriate patients selection for laparoscopic approach is essential, as well as surgeon experience in this kind of procedure.

In conclusion, the present study describes a wide experience on LATs in patients with cirrhosis and HCC and it represents the largest single-center series on LATs for HCC on cirrhosis available to date. In our opinion, laparoscopic approach should be considered the first-choice technique for RFA if percutaneous RFA or hepatic resection is not feasible. As these patients represent a group at risk of complications related to their underlying disease and to comorbidities, however, they should be optimally prepared for LATs and closely observed in the postoperative period. At these conditions, LATs for HCC are safe and feasible, achieving good results in selected patients.

Compliance with ethical standards

Disclosures Roberto Santambrogio, M.D., Matteo Barabino, M.D., Savino Bruno, M.D., Mara Costa, M.D., Andrea Pisani Ceretti, M.D., Maria Rachele Angiolini, M.D., Massimo Zuin, M.D., Franca Meloni, M.D., and Enrico Opocher, M.D., have no conflicts of interest or financial ties to disclose.

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