



Laparoscopic ablation therapies for hepatocellular carcinoma: could specific indications for the laparoscopic approach influence the effectiveness?

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Abstract

Percutaneous thermo-ablation (TA) may be unfeasible for the tumor location: laparoscopic ablation therapies (LATs) are an alternative option. The aim of this study is to assess the efficacy of LATs in the treatment of HCC not eligible for percutaneous TA or surgical resection. LAT was offered to 503 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 surgery; (b) patients not suitable for percutaneous TA; (c) short-term recurrence of HCC (< 3 months). Technical success was achieved with one session in 467 patients (93%). One-month mortality and severe morbidity rates were 0.4% and 2.19%, respectively. During a median follow-up of 38.4 months in the remaining 501 patients, 361 (67%) developed intrahepatic recurrence: it appeared as a local tumor progression (LTP) in 74 cases (15%). Subcapsular lesions showed lower LTP rates ($p=0.008$), as well as HCC nodules contiguous to viscera ($p=0.012$). In the treatment of HCC, LAT has proved to be a safe and effective technique that enables to treat lesions not eligible for percutaneous approach, with a low morbidity rate.

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

Introduction

In the past 20 years, ultrasound (US)-guided thermal ablation (TA) has obtained a dominant role in the curative treatment of small hepatocarcinoma (HCC) less than 3 cm in diameter [1, 2]. Percutaneous US-guided TA is an effective, fast and real-time targeting modality for small HCC [1] and several studies, comparing TA with hepatic resection (HR), have shown similar outcomes in terms of overall and disease-free survival in patients with early-stage HCC [3]. However, percutaneous TA is not always feasible [4–6]

for some lesions due to their location such as adjacent hilar area or liver surface, the top of diaphragm or adjacent to pericardium, large intrahepatic bile ducts or blood vessels, gallbladder or gastrointestinal viscera. To overcome these limitations, laparoscopic TA (LTA) can be used as an alternative ablative method [7]: it combines the advantages of the intracorporeal ultrasound examination with a safer approach to HCC nodules in difficult locations obtaining high necrosis and low complications rates [7, 8].

In the present study, we compared early tumor necrosis rates (technical success) and local progression rates between specific subgroups of patients according to the indications for the laparoscopic approach: the objective is to confirm the effectiveness and safety of the LTA procedure for problematic HCC nodules with difficult approach.

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Methods

Patients

Since 1997 the diagnosis and treatment of HCC patients referred to our Unit were determined by multidisciplinary tumor board [7, 9]. The diagnosis of HCC was made according to the European Association for the Study of the Liver [10] and, after 2005, according to the European Association for the Study of Liver Disease guidelines [2, 11, 12]. Liver function (according to the Child–Pugh classification) was evaluated with history, physical examination, routine laboratory tests, including alpha-fetoprotein (AFP) serum concentration.

LTA was 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 liver transplantation (OLT) (because of age or severe comorbidities);
- (b) patients not eligible to HR because of:
 - severe portal hypertension;
 - impaired liver function;
 - severe comorbidities;
- (c) patients not suitable for percutaneous TA because of:
 - severe impairment of coagulation function (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 ultrasound, or contiguous to primary biliary or portal tributaries).

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 intraoperative ultrasound (IOUS) examination using a laparoscopic ultrasound (LUS) probe with either a rigid shaft (Aloka SSD 500 [1996–1999]) or a flexible head (SSD 1700 [2000–2006], Alfa 10 [2006–2018]; Aloka Co, Tokyo[®]), 10 mm in diameter and 50 cm in length. A 7.5 linear-array transducer was

side-mounted near the tip of the shaft. All examinations were performed by surgeons (RS, MB) trained in IOUS techniques [7, 9].

The technique of ultrasound liver scanning was used for both open IOUS and LUS examination. The technique has been well described in literature [13, 14]. Briefly, the whole liver is initially screened and each tumor is measured in size by ultrasound and described according to the Couinaud classification of liver anatomy. After the lesions have been identified, the therapeutic electrode can be accurately inserted into the tumor.

For all TA, a 200-W, 480 kHz monopolar radiofrequency generator (AMICA-GEN, HS Hospital Service SpA, Aprilia, Italy[®]) was used. An insulated 18-gauge internally-cooled tip electrode was inserted into the tumor under sonographic guidance. Usually, used delivered power was 150–170 W on average, for a total period of 10–12 min. 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. 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. Since April 2017, a 2.45 MHz microwave generator (EMPRINT Microwave Generator, Medtronic[®]) providing energy through a 14 internally-cooled coaxial antenna was also used. This features the technology of “thermosphere” which gives three kinds of spatial energy control (thermal, field and wave-length) ensuring spherical and predictable ablations. According to the tumor size, a single microwave energy application is delivered to the patient, ranging from 70 to 100 W net power at the applicator end, for a total period of 3–10 min.

The tip of the electrode or antenna was advanced until it reached the lesion and passed its distal margin, opposite to the point of entrance of the needle. If the ablation zone created with a single application was not sufficient to cover the HCC nodule, additional electrodes or antennae were inserted into the lesion as needed to cover the entire lesion with adequate margin.

Since 2004 we performed in selected cases a technical variant known as “intra-hepatic vascular occlusion” (IHVO): major feeding artery or vessels contiguous to lesion were identified by color power flow imaging and the electrode or antenna was inserted into the vessel area. This approach produces an ischemic area surrounding the lesion with the purpose of increasing the necrosis volume [15]. A later color power flow evaluation is performed following the LTA to confirm a coagulative ablation of the vascular area, also appreciable as a discolored area on the liver surface. Finally the lesion is treated with the insertion of the electrode in the usual way.

Pre- and post-treatment imaging evaluation

Preoperative assessment included a US study of the liver and a triple phase helical computed tomography (CT) scan allowing the hepatic arterial, portal venous and delayed phases of hepatic enhancement to be depicted separately. In selected cases, a magnetic resonance imaging (MRI) of the liver was obtained.

Ultrasound and CT scan (or MRI) were repeated within one month and 3 months after the procedure. Experienced radiologists reviewed all CT exams.

Technical outcome and oncologic response were defined using the International Working Group on Image-Guided Tumor Ablation [16] standardized definitions. Technical success was defined when the tumor resulted completely replaced by TA zones at the 1-month follow-up exams (total necrosis). 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. If complete ablation cannot be achieved within these specified parameters, the tumor should be classified as unsuccessfully treated.

Patients who did not show a complete local response after the first LTA session underwent either further LTA session or TACE. Patients with LTP 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 [2, 12].

Postoperative complications

Severity of postoperative morbidity was defined according to the Dindo-Clavien classification of surgical complications [17]: considering the impact of major complications on postoperative outcome in patients with HCC in high-risk

locations, only complications of Grade III or higher were described.

Definition of problematic lesions

On the basis of our experience and previous literature [7, 18, 19], we defined the following locations as problematic:

- lesions not visible at percutaneous US examination (Fig. 1a);
- lesions in the hepatic dome;
- lesions in the 7 segment;
- lesions in sub-glissonian position;
- lesions located on the liver surface contiguous to intestinal or gastric wall (Fig. 1b);
- lesions located on 4 and 5 segments contiguous to gallbladder;
- lesions adjacent to large vessels or intrahepatic biliary ducts (Fig. 1c), defined as those located ≤ 5 mm from a first or second branch of the Glissonian pedicles, the base of hepatic veins, or the inferior vena cava.

Each location has been compared with all the others by analyzing technical success and LTP rates.

Statistical analysis

Initial evaluation and subsequent follow-up data were collected in a dedicated database (FileMaker Pro, FileMaker Inc., Santa Clara, California, USA) for personal computer input (Macintosh G4, Apple Computer Inc., Cupertino, California, USA) and subsequent analysis (Statistica-Mac, Statsoft, Tulsa OK, USA). Comparison of means between and within groups was done by the Mann–Whitney *U* test and the Wilcoxon matched pairs test. Data are expressed as mean \pm standard deviation. Comparison of proportions was done by the Fisher exact probability test. Each difficult group

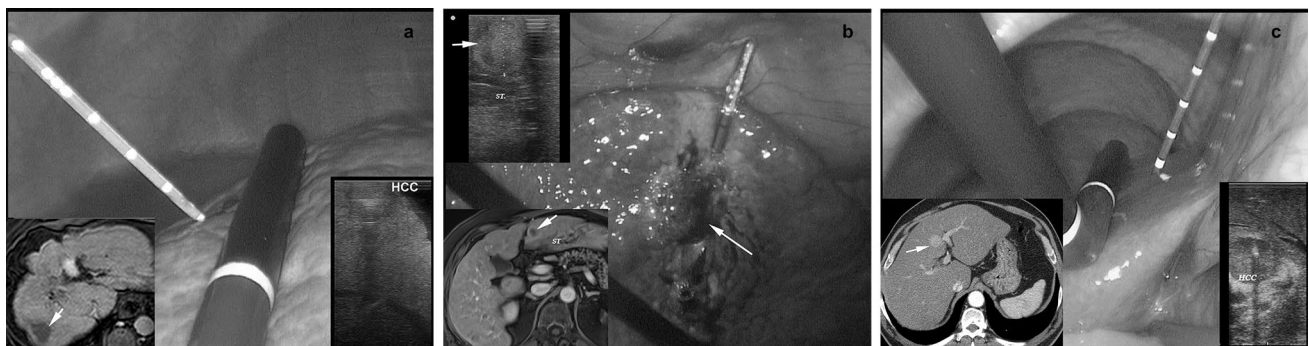


Fig. 1 HCC nodules located in problematic position. **a** HCC nodule in the 7th segment not visible at percutaneous US examination: total necrosis at 1-month RMI (arrow); **b** HCC nodule on the surface of

3rd segment (arrow) contiguous to stomach (ST.); **c** HCC nodule contiguous intrahepatic biliary convergence (arrow in the CT scan)

was compared with the remnant group of patients (control group).

This retrospective study protocol was approved by our Institutional Review Board and waived the requirement for informed consent.

Results

Among 1015 patients treated for HCC during the 20 years of the present study period, 517 (374 men/143 women) with a mean age of 69.2 ± 8.3 years (range 42–90) underwent LTA in our center. Fourteen patients were excluded from statistical analysis because of Barcelona Clinic Liver Cancer (BCLC) class B–C: therefore, 503 patients underwent LTA following the inclusion criteria depicted in Table 1. The

patients' characteristics at the baseline are shown in Table 2. One-hundred sixteen patients (23%) were older than 75 years and 84 (17%) were in Child–Pugh class B; 255 patients (51%) had a tumor size of 20 mm or less, 154 patients (31%) had a tumor size between 21 and 30 mm and 182 cases (36%) had multiple nodules. Three hundred sixty-four patients underwent radiofrequency ablation (RFA) treatment using a “cooled tip” needle and 139 patients (treated since 2009) underwent microwave ablation (MWA). LTA (since 2004) was associated to IHVO in 81 cases: so, 300 patients had “traditional” RFA and 122 patients had “traditional” MWA. Mean total operative time was 84.9 ± 29.5 min (range 30–195 min; median: 79 min); mean total LTA time was 17.6 ± 9.1 min (range 3–60; median: 15 min); the mean number of needle insertions was 2.01 ± 1.04 (range 1–6; median: 2).

Table 1 Reasons to reject percutaneous thermal ablation or hepatic resection for 503 patients submitted to laparoscopic thermal ablation (more than 1 reason for each patient)

Percutaneous thermal ablation	No. (%)	Hepatic resection	No. (%)
HCC contiguous to other structures	166 (33%)	HR > 2 segments	193 (38%)
Superficial or esophytic lesion	183 (35%)	Patients with \geq BCLC A2 stage	356 (71%)
Lesion difficult or impossible to percutaneous US visualization	317 (63%)	Other concomitant severe disease	115 (23%)
Intraoperative US staging (for suspected other nodules)	189 (38%)	Patient refusal	57 (11%)
Pts at risk of bleeding (plts < 50,000 and/or INR > 1.2)	172 (34%)	Age > 75 years	116 (23%)
Multiple lesions	182 (36%)	Child's B class	84 (17%)

HCC hepatocellular carcinoma, HR hepatic resection, US ultrasound, plts platelets

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

Variables	503 pts (%)	IHVO pts (from 2004: 81 pts)	MWA pts (from 2009: 139 pts)
Gender: female/male	142/361 (28/72%)	27/54 (33/67%)	39/100 (28/72%)
Age: ≤ 75 / > 75 years	387/116 (77/23%)	59/22 (73/27%)	94/45 (68/32%)
Etiology: HBV, HCV, other	71/338/94 (14/67/19%)	10/54/17 (12/67/21%)	17/93/29 (12/67/21%)
Child: A/B	419/84 (83/17%)	62/19 (77/23%)	117/22 (84/16%)
BCLC: A1/A2-3/A4	147/126/230 (29/25/46%)	21/22/38 (26/27/47%)	35/39/65 (25/28/47%)
MELD: ≤ 9 / > 9	218/185 (56/46%)	42/35 (55/45%)	82/57 (59/41%)
Charlson index: < 3 / ≥ 3	287/216 (57/43%)	38/43 (47/53%)	71/68 (51/49%)
Bilirubin: ≤ 1 / > 1	215/287 (43/57%)	39/42 (48/52%)	55/84 (40/60%)
Albumin: > 3.5 / ≤ 3.5	322/180 (64/36%)	53/28 (65/35%)	91/48 (65/35%)
AFP: ≤ 20 / > 20	316/101 (65/35%)	50/29 (63/37%)	88/48 (65/35%)
Diameter: ≤ 3 / > 3 cm	402/98 (80/20%)	65/16 (80/20%)	102/37 (73/27%)
US visible: not/yes	317/186 (63/37%)	55/26 (68/32%)	73/66 (52/48%)
Sub-glissonian HCC: not/yes	320/183 (64/36%)	52/29 (64/36%)	76/63 (55/45%)
HCC adjacent to gallbladder: not/yes	469/34 (93/7%)	78/3 (96/4%)	128/11 (92/8%)
HCC adjacent to viscera: not/yes	427/76 (85/15%)	68/13 (84/16%)	106/33 (76/24%)
HCC adjacent to vessels: not/yes	451/52 (90/10%)	78/3 (96/4%)	120/19 (86/14%)
HCC adjacent to intrahepatic biliary ducts: not/yes	471/32 (94/6%)	78/3 (96/4%)	126/13 (91/9%)

IHVO intra-hepatic vascular occlusion, MWA micro-wave ablation, HCC hepatocellular carcinoma, AFP alpha feto protein, US ultrasound

Technical success was achieved in one session in 467 patients (93% of the total study group); according to the LTA technique, technical success was obtained in 273 cases out of RFA subgroup (91%), in 113 cases of MWA subgroup (93%) and in 81 cases out of IHVO subgroup (100%) ($p=0.020$).

The mean follow-up period was $38.4 + 33.2$ months (median 30.4; range 2–202 months). One-hundred-sixty-six patients (33%) remained recurrence-free during the study period. Meanwhile, 361 patients (67%) developed intrahepatic recurrence. Regarding the precise location of intrahepatic recurrence, it appeared in same segment in 163 cases (32% of the whole study group), including 74 cases of LTP (equal to 15% of the all patients), while in different segments in 174 patients (35%). Among the 74 patients with LTP, time to develop LTP ranged from 1 to 69 months (mean 13.9 ± 12.9). One-hundred-sixty-six patients (33%) had a single tumor as recurrence, while 171 patients (34%) had multiple recurrent nodules.

Table 3 shows the results according to the specific indication to laparoscopic approach: there were no significant differences between inconspicuous and visible HCC, particularly for lesions located in seven segment or liver dome in comparison to other locations. Subcapsular lesions showed the best results in terms of LTP ($p=0.008$), as well as HCC nodules contiguous to viscera ($p=0.012$). On the other hand, lesions adjacent to vessels had higher rates of LTP ($p=0.009$), while no differences were found for lesions adjacent to intrahepatic biliary ducts.

No differences were found if MWA or IHVO techniques have been used (Table 4).

Postoperative complications

Postoperative mortality rate (30-day mortality) was 0.4% (two patients). Major complications occurred in eleven patients (2.19%): Table 5 shows the characteristics of

Table 3 Outcomes in all patients enclosed in the study according specific indication to the laparoscopic approach

Variables	Technical success	LTP
US-visible vs invisible vs poor visible HCC	94/87/94% $p=NS$	17/9/15% $p=NS$
Liver dome HCC vs other locations	93/93% $p=NS$	14/15% $p=NS$
7 segment vs other locations	89/94% $p=NS$	13.5/15% $p=NS$
Sub-glissonian HCC vs other locations	93.5/93% $p=NS$	9/18% $p=0.008$
HCC adjacent to viscera vs other locations	95/93% $p=NS$	5/16% $p=0.012$
HCC adjacent to gallbladder vs other locations	97/93% $p=NS$	9/15% $p=NS$
HCC adjacent to vessels vs other locations	88.5/93.5% $p=NS$	27/13% $p=0.009$
HCC adjacent to intrahepatic biliary ducts vs other locations	94/93% $p=NS$	25/14% $p=NS$

Bold indicates the significant results

LTP local tumor progression, US ultrasound, HCC hepatocellular carcinoma

Table 4 Outcomes in patients submitted to IHVO (intrahepatic vascular occlusion) or MWA (microwave ablation) according specific indication to the laparoscopic approach

Variables	Technical success		LTP	
	MWA	IHVO	MWA	IHVO
US-visible vs invisible vs poor visible HCC	93/75/95%	100/100/100%	26/12.5/9%	11.5/0/12%
Liver dome HCC vs other locations	95%/92%	100/100%	19/17%	15/9%
7 segment vs other locations	92/93%	100/100%	11.5/18.5%	17/9%
Sub-glissonian HCC vs other locations	94.5/91%	100/100%	13/20.5%	10/9.5%
HCC adjacent to viscera vs other locations	92/93%	100/100%	7.5/19.5%	7.5/10%
HCC adjacent to gallbladder vs other locations	89/93%	100/100%	22/17%	0/10%
HCC adjacent to vessels vs other locations	82/94%	100/100%	29/15%	0/10%
HCC adjacent to intrahepatic biliary ducts vs other locations	82/94%	100/100%	27/16%	0/10%

LTP local tumor progression, US ultrasound, HCC hepatocellular carcinoma

Table 5 Characteristics of each patient which suffered of severe complications

Complication	Procedures	Dindo class	Child class	Charlson index	High risk of bleeding	Portal hypertension	HCC number	HCC location
Liver failure	Intensive care	5	B8	8	Yes	Yes	1	4 s—near the hilum
Cardiac failure	Intensive care	5	B7	5	No	Yes	1	4 s—near the hilum
Trocar access hematoma	Local drainage	3A	A6	1	No	Yes	2	4–8 s
Biliary fistula	ERCP	3A	A5	2	No	No	1	4 s—near the hilum
Pneumothorax	Pleural drainage	3A	B7	3	Yes	Yes	1	8 s
Pleural effusion—ascites	Pleural drainage	3A	A6	1	Yes	Yes	1	8 s
Trocar access hematoma	Surgical hemostasis	3B	A6	1	No	Yes	1	4 s—near the hilum
Trocar access hematoma	Surgical hemostasis	3B	B8	4	No	No	2	3–8 s
Trocar access hematoma	Surgical hemostasis	3B	A6	3	No	No	2	6–8 s
Trocar access hematoma	Surgical hemostasis	3B	B7	4	No	No	2	3–4 s—near stomach
Duodenal perforation (during dissection from HCC nodule)	Surgical suture	3B	A6	8	No	Yes	1	6 s—near duodenum

HCC hepatocellular carcinoma

patients with major complications and 30-day mortality. The 90-day mortality was 2.2% (11 patients): deaths secondary to liver failure were 5, to variceal bleeding were 2, to cardiovascular disease were 2, to sepsis were 1 and to diffuse recurrent HCC were another patient.

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 BCLC Staging System): RFA should become the first-line therapy and HR should be considered only in patients with failure or contraindications to RFA [2, 12]. However, more recent reviews and cohort analysis proved the opposite, that is RFA showed a higher LTP rates and it cannot be conclusively shown to prolong overall survival compared with HR [20–22]. Percutaneous RFA showed lower rates of technical success and higher rates of LTP in patients with large nodules, multifocal tumors and lesions in high-risk locations [18, 19, 23]. Furthermore, percutaneous RFA under ultrasound guidance is not always feasible and the rate of feasibility could be considerably low [4–6]. In some of those cases, RFA with a laparoscopic approach can be a valid option [22]. 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 LTA more flexible than the percutaneous approach while remaining minimally invasive [7, 8, 24]. However, if the percutaneous procedure is unfeasible, this can be considered a problematic situation also for the laparoscopic approach, influencing the LTA results. This study seems to confirm that in this setting the laparoscopic

approach is able to obtain similar results to those obtained by percutaneous RFA for feasible lesions.

As regards LTA efficacy, technical success was achieved in a single session in 93% of all patients and it is in the expected range (90–98%) according to the most important percutaneous series [1, 3, 25–27]. In our series, as shown in Table 1, the laparoscopic approach was indicated for 317 patients (63%) due to difficult or impossible trans-abdominal ultrasound visualization of the lesion. Nevertheless, a technical success rate was obtained in a group of patients at high risk of treatment failure (for difficult tumor location or unfavorable anatomic conditions) or complications after a percutaneous procedure.

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 [16, 25–29], depending on the tumor size and the difficult location of the nodules. Furthermore, current Literature concerning LTP rates after MWA or IHVO versus RFA remain controversial [17, 30–32] and the effectiveness of these techniques should be validated with further prospective studies [33]: LTA with IHVO could obtain a 100% of technical success, however only a small group of patients had a HCC nodule with a tributary vessel to permit this technique and LTP rates were similar to traditional RFA [15]. On the other hand, several Authors showed that subcapsular tumors and/or lesions contiguous to viscera had an independent statistical association with LTP after percutaneous ablation [8, 16, 30, 34]. In subcapsular nodules, artificial ascites (providing a thermal barrier between the ablation zone and surrounding structures) could be an effective method to widen the extrahepatic space before the RFA procedure reducing the risk of visceral complications [35]. However, in the current study

the laparoscopic approach obtain higher rates of success for superficial lesions [7, 8, 32]: we ascribe the improved LTP rates to the fact that both LUS and direct visualization can become more precise in targeting and more aggressive ablation with a better evaluation of the ablation process. Also, for lesions contiguous to viscera, they can safely be mobilized away from the target lesion decreasing the risk of LTP after LTA, decreasing the risk of complications. Furthermore, our study does not confirm that proximity to gallbladder interferes in post-treatment LTP [8, 36]: this is likely secondary to surgeons' improved experience over time [7, 14]. On the other hand, also for the laparoscopic approach, the presence of LTP after treatment of lesions adjacent to large blood vessels due to the heat-sink phenomenon (tissue cooling by blood flow that causes thermal loss) remains a real problem: larger studies including either MWA or IHVO should confirm that these techniques could improve LTP and technique effectiveness for HCC nodules adjacent to large vessels [16, 17, 37].

With regards to the safety of LTA, the present study found a low incidence of severe postoperative complications (Dindo-Clavien classes superior to 3A and 3B) rates (about 2%). These values are comparable to the safety profiles found in previous clinical ablation studies [1, 38]. A recent systematic review comparing both ablation modalities (RFA and MWA) also reported similar data for both techniques with low rates of complications: severe complication rates associated with RFA and MWA was 4.1% and 4.6%, respectively [39].

On the other hand, TA with laparoscopic approach has some limitations including the inevitable selection bias of a retrospective evaluation within a long recruitment period. The second limitation in the evaluation of LATs' results could be the presence of massive adhesions within the abdominal cavity due to previous surgery in some patients, with consequent difficult access to the liver. A group of patients qualified for LTA have undergone either HR before (48 cases in our study group) and these operations are responsible for the development of adhesions. Massive adhesiolysis to gain free access to the liver leads higher risk of damaging other organs, especially large and small bowel, and extends operative time [40]. The third limitation to the application of LATs is the technical difficulty of puncturing deep tumors. While it is undeniable that some skill is required for laparoscopic nodule puncture using a LUS probe, appropriate patients' selection for laparoscopic approach is essential, as well as surgeon experience in this kind of procedure [41].

In conclusion, the present study represents the largest single-center series on LATs for HCC in cirrhosis available to date. In our opinion, laparoscopic approach should be considered the first technique of choice for TA if percutaneous TA or hepatic resection is not feasible. As these

patients represent a group at risk for complications related to their underlying disease and to HCC location, however, they should be optimally prepared for LATs, safely treated through the laparoscopic approach and closely observed in the postoperative period. At these conditions, LATs for HCC are safe and feasible, and achieve good results in selected patients.

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Data availability Data are collected in database which could be checked.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest or financial ties to disclose.

Ethics approval This retrospective study protocol was approved by our Institutional Review Board and waived the requirement for informed consent.

Research involving human participants and/or animals Institutional review research board approval was granted by Ospedale San Paolo, and appropriate good clinical and research practices were followed.

Informed consent We have obtained consent to publish from the participants to report individual patient data.

References

1. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S (2008) Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? *Hepatology* 47:82–89
2. Forner A, Reig M, Bruix J (2018) Hepatocellular carcinoma. *Lancet* 391:1301–1314
3. Jia JB, Zhang D, Ludwig JM, Kim HS (2017) Radiofrequency ablation versus resection for hepatocellular carcinoma in patients with Child–Pugh A liver cirrhosis: a meta-analysis. *Clin Radiol* 72:1066–1075
4. Rhim H, Lee MH, Kim YS, Choi D, Lee WJ, Lim HK (2008) Planning sonography to assess the feasibility of percutaneous radiofrequency ablation of hepatocellular carcinomas. *AJR* 190:1324–1330
5. Kim JE, Kim YS, Rhim H, Lim HK, Lee MW, Choi D, Shin SW, Cho SK (2011) Outcomes of patients with hepatocellular carcinoma referred for percutaneous radiofrequency ablation at a tertiary center: analysis focused on the feasibility with the use of ultrasonography guidance. *Eur J Radiol* 79:e80–e84
6. Kim PN, Choi D, Rhim H, Rha SE, Hong HP, Lee J, Choi J, Kim JW, Seo JW, Lee EJ, Lim HK (2012) Planning ultrasound for percutaneous radiofrequency ablation to treat (%3c 3 cm) hepatocellular carcinomas detected on computed tomography or magnetic resonance imaging: a multicenter prospective study to assess factors affecting ultrasound visibility. *J Vasc Interv Radiol* 23:627–634

7. Santambrogio R, Barabino M, D'Alessandro V, Galfrascoli E, Zappa MA, Piccolo G, Zuin M, Opocher E (2020) Laparoscopic thermoablation for hepatocellular carcinoma in patients with liver cirrhosis: an effective procedure for tricky tumors. *Med Oncol* 37:32–39
8. De la Serna S, Vilana R, Sanchez-Cabus S, Calatayud D, Ferre J, Molina V, Fondevila C, Bruix J, Fuster J, Garcia Valdecasas JC (2015) Results of laparoscopic radiofrequency ablation for HCC. Could the location of the tumour influence a complete response to treatment? A single European centre experience. *HPB* 17:387–393
9. Santambrogio R, Barabino M, Bruno S, Mariani M, Maroni N, Bertolini E, Franceschelli G, Opocher E (2018) Surgical resection versus ablative therapies through a laparoscopic approach for hepatocellular carcinoma: a comparative study. *J Gastrointest Surg* 22:650–660
10. Llovet JM, Bru' C, Bruix J (1999) Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 19:329–338
11. Bruix J, Sherman M (2005) Management of hepatocellular carcinoma. *Hepatology* 42:1208–1236
12. European Association for the Study of the Liver (2018) EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 69:182–236
13. Lo CM, Lai ECS, Liu CL, Fan ST, Wong J (1998) Laparoscopy and laparoscopic ultrasonography avoid exploratory laparotomy in patients with hepatocellular carcinoma. *Ann Surg* 227:527–532
14. Santambrogio R, Bianchi P, Pasta A, Palmisano A, Montorsi M (2002) Ultrasound-guided interventional procedures of the liver during laparoscopy: technical considerations. *Surg Endosc* 16:349–354
15. Santambrogio R, Costa M, Barabino M, Opocher E (2008) Laparoscopic radiofrequency of hepatocellular carcinoma using ultrasound-guided selective intrahepatic vascular occlusion. *Surg Endosc* 22:2051–2055
16. Ahmed M (2014) Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update. *Radiology* 273: 241–260
17. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications. A new proposal with evaluation in a cohort of 633 patients and results of a survey. *Ann Surg* 240:205–213
18. Lee MW, Kang D, Lim HK, Cho J, Sinn DH, Kang TW, Song KD, Rhim H, Cha DI, Lu DSK (2020) Updated 10-year outcomes of percutaneous radiofrequency ablation as first-line therapy for single hepatocellular carcinoma ≤ 3 cm: emphasis on association of local tumor progression and overall Survival. *Eur Radiol* 30:2391–2400
19. Huang S, Yu J, Liang P, Yu X, Cheng Z, Han Z, Li Q (2014) Percutaneous microwave ablation for hepatocellular carcinoma adjacent to large vessels: a long-term follow-up. *Eur J Radiol* 83:552–558
20. Xu XL, Liu XD, Liang M, Luo BM (2018) Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. *Radiology* 287:461–472
21. Jiang YQ, Wang ZX, Deng YN, Yang Y, Wang GY, Chen GH (2019) Efficacy of hepatic resection vs radiofrequency ablation for patients with very-early-stage or early stage hepatocellular carcinoma: a population-based study with stratification by age and tumor size. *Front Oncol* 9:113. <https://doi.org/10.3389/fonc.2019.00113>
22. Si MB, Yan PJ, Hao XY, Du ZY, Tian HW, Yang J, Han CW, Yang KH, Guo TK (2019) Efficacy and safety of radiofrequency ablation versus minimally invasive liver surgery for small hepatocellular carcinoma: a systematic review and meta-analysis. *Surg Endosc* 33:2419–2429
23. Lee S, Kang TW, Cha DI, Song KD, Lee MW, Rhim H, Lim HK, Sinn DH, Kim JM, Kim K (2018) Radiofrequency ablation versus surgery for perivascular hepatocellular carcinoma: propensity score analyses of long-term outcomes. *J Hepatol* 69:70–78
24. Cillo U, Noaro G, Vitale A, Neri D, D'Amico F, Gringeri E, Farinati F, Vincenzi V, Vigo M, Zanus G (2014) Laparoscopic microwave ablation in patients with hepatocellular carcinoma: a prospective cohort study. *HPB* 16:979–986
25. Brunello F, Cantamessa A, Gaia S, Carucci P, Rolle E, Castiglione A, Ciccone G, Rizzetto M (2013) Radiofrequency ablation: technical and clinical long-term outcomes for single hepatocellular carcinoma up to 30 mm. *Eur J Gastroenterol Hepatol* 25:842–849
26. Lee DH, Lee JM, Lee JY, Kim SH, Yoon JH, Kim YJ, Han JK, Choi BI (2014) Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology* 270:900–909
27. Eun HS, Lee BS, Kwon IS, Yun GY, Lee ES, Joo JS, Sung JK, Moon HS, Kang SH, Kim JS, Shin HJ, Kim TK, Chun K, Kim SH (2017) Advantages of laparoscopic radiofrequency ablation over percutaneous radiofrequency ablation in hepatocellular carcinoma. *Dig Dis Sci* 62:2586–2600
28. Ayav A, Germain A, Marchal F, Tierris I, Laurent V, Bazin C, Yuan Y, Robert L, Brunaud L, Bresler L (2010) Radiofrequency ablation of unresectable liver tumors: factors associated with incomplete ablation or local recurrence. *Am J Surg* 200:435–439
29. Lencioni R, De Baere T, Martin RC, Nutting CW, Narayanan G (2015) Image-guided ablation of malignant liver tumors: recommendations for clinical validation of novel thermal and non-thermal technologies—a western perspective. *Liver Cancer* 4:208–214
30. Chinnaratha MA, Chuang MA, Fraser RJ, Woodman RJ, Wigg AJ (2016) Percutaneous thermal ablation for primary hepatocellular carcinoma: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 45:1230–1235
31. Poulou LS, Botsa E, Thanou I, Ziakas PD, Thanos L (2015) Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. *World J Hepatol* 7:1054–1063
32. Santambrogio R, Chiang J, Barabino M, Meloni FM, Bertolini E, Melchiorre F, Opocher E (2017) Comparison of laparoscopic microwave to radiofrequency ablation of small hepatocellular carcinoma (≤ 3 cm). *Ann Surg Oncol* 24:257–263
33. Vietti Violi N, Duran R, Guiu B, Cercueil JP, Aubè C, Digkila A, Pache I, Deltenre P, Knebel JF, Denys A (2018) Efficacy of microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with chronic liver disease: a randomized controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 3:317–325
34. Chua JME, Lam YMP, Tan BS, Tay KH, Gogna A, Irani FG, Lo HGR, Too CW (2019) Single-centre retrospective review of risk factors for local tumour progression and complications in radiofrequency ablation of 555 hepatic lesions. *Singap Med J* 60:188–192
35. Kim JW, Shin SS, Heo SH, Hong JH, Lim HS, Seon HJ, Hur YH, Park CH, Jeong YY, Kang HK (2015) Ultrasound-guided percutaneous radiofrequency ablation of liver tumors: how we do it safely and completely. *Korean J Radiol* 16:1226–1239
36. Choi IY, Kim PN, Lee SG, Won HJ, Shin YM (2017) Efficacy and safety of radiofrequency ablation for focal hepatic lesions adjacent to gallbladder: reconfiguration of the ablation zone through probe relocation and ablation time reduction. *J Vasc Interv Radiol* 28:1395–1399
37. Cheng YT, Jeng WJ, Lin CC, Chen WT, Sheen IS, Lin CY, Lin SM (2016) Percutaneous radiofrequency ablation of tumor feeding artery before target tumor ablation may reduce local tumor progression in hepatocellular carcinoma. *Carcinoma Biomed J* 39:400–406
38. Livraghi T, Meloni F, Solbiati L, Zanus G, For the Collaborative Italian Group Using AMICA System (2012) Complications of

- microwave ablation for liver tumors: results of a multicenter study. *Cardiovasc Intervent Radiol* 35:868–874
39. Bertot LC, Sato M, Tateishi R, Yoshida H, Koike K (2011) Mortality and complications rates of percutaneous ablative techniques for the treatment of liver tumors: a systematic review. *Eur Radiol* 21:2584–2596
 40. Santambrogio R, Costa M, Barabino M, Zuin M, Bertolini E, De Filippi F, Bruno S, Opocher E (2012) Recurrent hepatocellular carcinoma successfully treated with laparoscopic thermal ablation. *Surg Endosc* 26:1108–1115
 41. Cillo U, Bertacco A, Fasolo E, Carandina R, Vitale A, Zanusi G, Gringeri E, D'Amico F, Bassi D, Neri D, Dadduzio V, Farinati F, Aliberti C (2019) Videolaparoscopic microwave ablation in patients with HCC at a European high-volume center: results of 815 procedures. *J Surg Oncol* 120:956–965

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