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REVIEW ARTICLE

Laparoscopic thermoablation for hepatocellular carcinoma in patients with liver cirrhosis: an effective procedure for tricky tumors

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Abstract

The optimal treatment for hepatocellular carcinoma (HCC) is surgical resection. However, only a small percentage of patients are amenable to this option. Percutaneous radiofrequency interstitial thermal ablation (TA) proved to be effective in the treatment of unresectable HCC. Recent advances in laparoscopic ultrasound have improved the accuracy in detecting small intrahepatic HCC nodules missed by pre-operative imaging techniques. Our objective was to evaluate an operative combination of laparoscopic ultrasound with laparoscopic thermoablation (LTA) in the treatment of HCC not amenable to liver resection. The aim of our review was to evaluate the advantages and limits of the laparoscopic approach according the criteria of the evidence-based medicine. LTA of HCC proved to be a safe and effective technique both in the short- and long-term follow-up period. This technique may be indicated in selected cases when the percutaneous approach to the lesion is very difficult or contraindicated.

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

Abbreviations

HCC	Hepatocellular carcinoma
LTA	Laparoscopic thermoablation
LTP	Local tumor progression
TA	Thermoablation
HR	Hepatic resection
IOUS	Intraoperative ultrasound
INR	International Normalized Ratio
TACE	Transcatheter arterial chemoembolization
LUS	Laparoscopic ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging

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Introduction

In recent years, radiofrequency interstitial thermal ablation (TA) has been performed with good results in patients with hepatocellular carcinoma (HCC). Furthermore, while TA is most commonly performed through a percutaneous approach [1, 2], there is a sub-group of patients who may benefit from a laparoscopic thermoablation (LTA) approach [3]. The rationale of this technique is to combine the advantages of an improved staging allowed by the intracorporeal ultrasound examination [4] with a safe approach to liver lesions difficult or impossible to be treated percutaneously [3]. The aim of our review was to evaluate the advantages and limits of the laparoscopic approach according the criteria of the evidence-based medicine (www.cebm.net). A systematic research of PubMed, Science Citation Index, and Embase databases was accomplished for articles published before October 2019. We identified 29 articles using the keywords "laparoscopic radiofrequency and hepatocellular carcinoma" and "laparoscopic microwave and hepatocellular carcinoma" to obtain all studies useful for this review analysis. Manual cross-referencing was accomplished, and we also analyzed the reference lists of the included articles to identify further undetected studies. Case reports and abstracts were

excluded. Table 1 shows the characteristics of these 29 studies [4–32].

Basing on its peculiar characteristics, the LTA should be able:

- To stage the intrahepatic HCC disease at best using laparoscopic ultrasound (LUS) [33];
- To treat patients at risk of unsuccessful therapy through a percutaneous access;
- To treat safely those patients at risk of complications;
- To improve the thermoablation results (total necrosis and tumor recurrence).

Staging of the intrahepatic disease

Although intraoperative ultrasound (IOUS) is the most effective tool for detecting focal liver lesions [34], this technique has shown remarkable amount of false positive for what concern HCC definition in cirrhotic patients [35]. The introduction of second-generation US contrast agents, has improved the accuracy of IOUS in this specific field [36]. This technique via laparoscopic approach so-called laparoscopic ultrasound (LUS) uses a linear array high-resolution (7.5 MHz) transducers mounted on probes that are introduced through standard 11.0 mm trocars. Even if few papers have been reported, LUS shown a great value in HCC

Table 1 Characteristics of selected studies

Author	Publication year	Period	Country	Patients number	TA
Ido [4]	1997	1993–1994	Japan	18	MW 2450 MHz
Ito [5]	1999	1996–1998	Japan	14	MW (multiple needle)
Goletti [6]	2000	1997–1998	Italy	7	RF 100-W
Podnos [7]	2001	1999–2000	USA	12	RITA
Hsieh [8]	2004	2000–2003	China	40	RF 100-W
Ballem [9]	2008	1997–2006	USA	104	RF (NR)
Casaccia [10]	2008	2006–2007	Italy	24	RF 200-W
Hirooka [11]	2009	2002–2006	Japan	37	RF 100-W
Panaro [12]	2010	2008–2009	France	12	RF 100-W
Tesche [13]	2010	2000–2008	USA	60	RITA 460 kHz
Simo [14]	2011	2006–2008	USA	22 RF	RF 200-W
				13 MW	MW 915 MHz
Yoon [15]	2012	2003–2009	Korea	107	RF 200-W
Seleem [16]	2012	2010–2012	Egypt	29	RITA 460 kHz
Herbold [17]	2013	2002–2008	Germany	34	RITA 460 kHz
Swan [18]	2013	2007–2011	USA	54	MW 2450 MHz
Iida [19]	2013	2011–2012	Japan	40 MW	MW (NR)
				18 RF	RF 200-W
				13 MW+RF	
Jiang [20]	2013	2002–2011	China	27	RF 200-W
Jiang [21]	2014	NR	China	4	RF 200-W
De La Serna [22]	2015	2000–2013	Spain	41	RF 200-W
Murakami [23]	2015	2000–2008	Japan	6	MW 2450 MHz
Tang [24]	2016	2013–2015	China	30	RF 200-W
Baker [25]	2016	2007–2014	USA	219	MW 915 MHz MW 2450 MHz
Santambrogio [26]	2016	1997–2015	Italy	267 RF	RF 200-W
				98 MW	MW 2450 MHz
				61 TA+IHVO	
Gruttadauria [27]	2016	2013–2016	Italy	35 MW	MW 2450 MHz
Na [28]	2017	2011–2015	Korea	64	RF 200-W
Ding [29]	2017	2009–2012	China	56	RF 100-W
Eun [30]	2017	2005–2016	Korea	71	RF 200-W
Wang [31]	2018	2012–2014	China	51	MW 2450 MHz
Cillo [32]	2019	2009–2016	Italy	674	MW 2450 MHz

diagnosis and staging (Table 2); better staging, by detecting new suspect HCC in 8–22% of cases [6, 7, 10, 12, 17, 26], means to avoid unnecessary laparotomy with a remarkable percentage of patients (16.5%) as reported by Lai et al. who shown 44 out of 122 consecutive patients with HCC and liver cirrhosis found to be unresectable after laparoscopic staging [37]. Authors concluded that LUS have a significant effect both on identifying surgically untreatable disease and in selecting the optimal treatment strategy. The key point is to be sure of histology of new suspect HCC found by LUS.

Moreover, Ido et al. [38] reported power of LUS in detecting new suspect HCC nodules in 64 out of 186 patients (34.4%); LUS guided biopsy was made on all 134 new lesions with a histological confirm in 28 cases (21%). Nevertheless, this quite low yield of LUS in detecting true HCCs, the authors outlined that when new nodular lesions are detected by LUS, these patients must be considered at high risk for recurrence, even if there is no histological evidence of HCC. We reported similar results in our personal series with 22% out of 68 patients submitted to LUS showing new malignant nodules. These findings support the validity of a single-stage approach with discovery and immediate treatment of new HCC nodules allowed by the LUS use [26].

Moreover, Klegar et al. [39] remarked high yield of LUS in changing operative management in 9/20 (45%) of HCC scheduled for liver resection. Management was changed because of LUS finding of severe nodular cirrhosis in four cases, more extensive staging in six cases either for number of nodules or for intrahepatic satellites metastases or carcinomatosis discover. On the contrary LUS shown a down staging in two cases, thus allowing a gentler procedure.

Among opponents of considering LUS as a crucial staging tool in HCC surgical treatment, Reddy et al. [40] reported his experience on 16 patients scheduled for liver transplantation (LT), all submitted to LUS as first step, thus showing to be suitable to LT in 100% of cases. Finally, at laparotomy, one patient was found to have extrahepatic disease; thus, the procedure was abandoned. One patient was found to have lesser curvature lymphadenopathy. Two patients had major vascular involvement noted in the explanted liver. Finally, authors concluded that laparoscopy cannot be routinely performed as a staging tool in a pre-transplant program due to low yield.

Any way on the basis of these data, there is a reasonable evidence that laparoscopic staging is useful and may alter patient management and treatment in patients with HCC and liver cirrhosis (level 2b of evidence).

Outcomes

Fulfilling criteria for thermoablation laparoscopic approach are shown in Table 3, including patients not suitable to HR, or patients with HCC not visible to percutaneous route (liver dome) or deep next to hilum (high risk of biliary stricture), or superficial lesions juxta visceral structures (gallbladder, colon, or stomach) as regards laparoscopic approach is effective and safe, allowing the direct visualization of surrounding structures and their active protection by performing specific laparoscopic maneuvers (separating or cooling techniques) thus reducing the risk of visceral injuries [26].

Table 4 shows the outcomes in the published series. However, until 2013, the articles included few patients and the results reflect a pioneering period for the LTA. 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 [22, 26, 32]. However, if the percutaneous procedure is unfeasible, this can be considered a problematic situation also for the laparoscopic approach, influencing the LTA results. In the last years, as regards LTA

Table 2 Studies with staging liver tumors with LUS

	No of points submitted to LUS	Median time for LUS (+TA)	No of new HCC (%)	Change of therapeutic strategy (%)
Podnos [7]	12	–	1 (8%)	1 (8%)
Casaccia [10]	24	148′	13 (20%)	13 (20%)
Goletti [6]	7	–	1 (14%)	1 (14%)
Panaro [12]	12	96′	4 (20%)	4 (20%)
Herbold [17]	34	–	7 (20%)	7 (20%)
Santambrogio [26]	426	89.6′	95 (22%)	95 (22%)
Lo [33]	91	45′	11 (12%)	15 (16%)
Ido [4]	186	–	23 (12%)	18 (10%)
Montorsi [49]	68	38′	15 (22%)	–
Klegar [39]	20	–	4 (20%)	9 (45%)
Lai [37]	122	30′	6 (5%)	44 (36%)
Reddy [40]	16	–	2 (12.5%)	–

Table 3 Indications for the laparoscopic approach

Author	Inconspicuous lesions	Superficial lesions	Contiguous viscera	Near hilum	Severe coagulopathy	Ineligibility for HR	Other
Ido [4]	NR	NR	NR	NR	NR	NR	NR
Ito [5]	NR	NR	NR	NR	NR	NR	NR
Goletti [6]	NR	Yes	Yes	Yes	Yes	Yes	NR
Podnos [7]	NR	NR	NR	NR	NR	Yes	NR
Hsieh [8]	NR	NR	NR	Yes	NR	Yes	NR
Ballem [9]	NR	NR	NR	NR	NR	Yes	Tumor size <7 cm Number of lesions <7 Less than 20% of liver volume involved with tumor Absence of biliary dilatation and no or limited extrahepatic disease
Casaccia [10]	Yes	Yes	Yes	NR	NR	Yes	Large tumors (< 5 cm) or multiple lesions Short-term recurrence of HCC
Hirooka [11]	NR	Yes	Yes	NR	NR	NR	NR
Panaro [12]	NR	NR	NR	NR	NR	NR	Neoadjuvant therapy prior to OLT
Tesche [13]	NR	Yes	Yes	NR	NR	Yes	NR
Simo [14]	Yes	Yes	Yes	NR	NR	Yes	NR
Yoon [15]	Yes	Yes	Yes	NR	NR	Yes	Multiple tumors
Seleem [16]	Yes	Yes	Yes	NR	NR	Yes	Patients with additional surgical indication (cholelithiasis, umbilical hernia); patients with HCC ≥ 5 cm
Herbold [17]	Yes	Yes	NR	NR	NR	Yes	Size of the nodule > 2.5 cm Bridge to OLT as therapeutic aim of RFA
Swan [18]	NR	NR	NR	NR	NR	NR	MWA is for patient population should they not qualify for transplantation or if they are anticipated to have a prolonged wait time
Iida [19]	NR	Yes	NR	NR	NR	NR	Maximal size smaller than 3 cm
Jiang [20]	NR	NR	NR	NR	NR	NR	Small HCC in the caudate lobe
Jiang [21]	NR	NR	NR	NR	NR	NR	HCC proximal to the gallbladder
De La Serna [22]	Yes	Yes	Yes	NR	NR	Yes	As bridge therapy in selected patients eligible for OLT as per the Milan Criteria
Murakami [23]	Yes	Yes	NR	NR	NR	Yes	Tumor diameter up to 3 cm number of tumors <3
Tang [24]	Yes	Yes	NR	NR	NR	NR	NR
Baker [25]	NR	NR	NR	NR	NR	NR	Our institution preferentially performs operative MWA in a minimally invasive fashion for patients with HCC
Santambrogio [26]	Yes	Yes	Yes	Yes	Yes	Yes	Short-term recurrence of HCC (<3 months) following percutaneous ethanol injection or RFA or TACE
Gruttadauria [27]	NR	NR	Yes	NR	NR	Yes	Patients judged ineligible for HR or percutaneous approach. The tumors were all <5 cm in diameter, and liver function did not exceed stage B of BCLC
Na [28]	Yes	Yes	Yes	Yes	NR	Yes	Cases with multiple HCC were excluded
Ding [29]	NR	NR	NR	NR	NR	NR	HCC located in the hepatic dome
Eun [30]	Yes	Yes	Yes	NR	NR	Yes	NR
Wang [31]	NR	Yes	Yes	NR	NR	Yes	Patients within Milan criteria Patients beyond Milan criteria but with tumors within 8 cm
Cillo [32]	Yes	Yes	Yes	Yes	Yes	Yes	Patients with BCLC stage D, nodules >5 cm in size, or >6 nodules were excluded

Table 4 Outcomes of laparoscopic thermoablation for HCC

Author	Follow-up in months (mean)	Complications	Total necrosis	LTP	Survival
Ido [4]	16.8	0%	100%	7%	NR
Ito [5]	NR	43%	NR	28%	NR
Goletti [6]	17	0%	86%	0%	NR
Podnos [7]	7.4	NR	NR	NR	NR
Hsieh [8]	12.5	17.5%	NR	47%	60% (30 months)
Ballem [9]	23 (median)	NR	NR	NR	21% (60 months)
Casaccia [10]	NR	16.6%	90%	21%	NR
Hirooka [11]	NR	0% severe	NR	0%	NR
Panaro [12]	NR	17% 0% severe	82.6%	NR	NR
Tesche [13]	11	10% 2% severe (1 death)	87%	6%	72% (30 months)
Simo [14]	19	14% severe (1 death)	90%	6%	NR
Yoon [15]	33.7	16.8%	NR	NR	86% (60 months)
Seleem [16]	NR	31%	NR	3%	NR
Herbold [17]	36.9	9%	NR	6% (29%)*	26% (60 months)
Swan [18]	11 (median)	28.9% (11.5% severe)	95%	2.9%	52% (30 months)
Iida [19]	NR	3%	NR	20%	74% (60 months)
Jiang [20]	NR	25.9%	NR	NR	63% (60 m.)
Jiang [21]	NR	0%	100%	0%	NR
De La Serna [22]	33 (median)	41% (12% severe)	94%	23%	43% (60 months)
Murakami [23]	NR	17%	NR	0%	NR
Tang [24]	NR	10% (3% severe)	93%	NR	NR
Baker [25]	14.8 (median)	35.6% (5% severe)	96%	8.5%	37% (60 months)
Santambrogio [26]	37.2 (median)	25% (2% severe) (1 death)	93%	15%	34% (60 months)
Gruttadauria [27]	14.1(median)	20%	75%		83% (24 months)
Na [28]	13.7 (median)	5%	95%	6%	NR
Ding [29]	NR	18% (0% severe)	98%	NR	45% (60 months)
Eun [30]	41.3 (median)	NR	100%	2.8%	97% (60 months)
Wang [31]	34 (median)	5.9%	NR	15.7%	28% (36 months)
Cillo [32]	18.4 (median)	30.8% (2% severe) (3 deaths)	NR	23%	36% (60 months)

efficacy, technical success (total necrosis) could be obtained in a single session in more than 90% of all patients and it is in the expected range (90–100%) with similar results obtained by the most important percutaneous series [1, 2, 41, 42]. On the other hand, local tumor progression (LTP) in an TA ablated site is a serious occurrence, with described rates ranging from 3.2 to 26% after RFA in percutaneous series [1, 41, 42], influenced by the tumor size and the difficult location of the nodules. Also for the laparoscopic approach, different indications (see Table 3) should influence the LTP results: in articles published in the last years, the LTP rates in the laparoscopic series ranged from 2.8 to 23%. Many of these studies have suggested that local control of the laparoscope is an advantage during LTA compared with the percutaneous approach. LTP rates shown in the LTA studies represent very good results considering the problematic locations of the HCC tumors submitted to a laparoscopic approach. Some Authors showed that subcapsular tumors and/or tumors contiguous to viscera had an independent statistical association with LTP after percutaneous ablation [22, 43, 44]. In subcapsular tumors, saline injection into the abdominal cavity could be an effective method to widen the extrahepatic space before the RFA procedure reducing the risk of visceral complications [45]. Also, in the study of De La Serna et al. [22], LTP rates are higher for HCC superficially located. However, in other studies the laparoscopic approach obtain higher rates of success for superficial lesions [26, 32], we ascribe the improved LTP rates to the fact that both LUS and direct visualization can become more precise in targeting the lesion, while the increased technical difficulty of placing percutaneously the electrode adequately for a subcapsular tumor, thus leading to incomplete ablation. Also,

for lesions contiguous to viscera, they can safely be mobilized away from the target lesion decreasing the risk of LTP and complications after LTA. On the other hand, also for the laparoscopic approach, the presence of LTP after treatment of deep-sited lesions remains a real problem: larger studies should confirm that this approach could improve LTP and technique effectiveness for deep-sited nodules.

It's mandatory to develop new laparoscopic ultrasound probes or navigation technologies able to simplify electrode insertion into the lesion, thus getting the procedure safer, more effective and reliable, and overcoming the limit of puncturing deep-sited tumors with a totally free-hand technique. Finally, LTA seems to obtain a good rate of total necrosis also in patients with lesions difficult to treat for their position (level 4 of evidence); further studies are needed to elucidate if LTA is able to obtain better results than the percutaneous approach in unselected patients.

Safe treatment of patients at risk of complications

The laparoscopic procedure proved to be feasible and safe with a low rate of serious complications [46–48]. In the majority of these series, severe complications rates (Dindo-Clavien classes superior to 3A and 3B) were 2% or less.

Most common complications after LTA are pulmonary affections (pneumonia and pneumothorax) due to the needle route through the wall chest, and postoperative bleeding from the abdominal wall (trocar access). The advantage of laparoscopic approach over the percutaneous via is the proper bleeding control if early recognize during operation. Moreover, there is so-called "post-ablative syndrome", an early and transient postoperative (within 24–48 h) treatment-related side-effect, including abdominal pain, mild fever, and pleural effusion, generally not requiring any invasive treatment. Quite exceptional complications are bile duct stenosis, liver infarction, and liver abscess or failure. A very few cases of tumor seeding in the puncture route and intraperitoneal dissemination have been described.

Finally, the rate of complications is similar among both approaches (laparoscopic and percutaneous), with a mild advantage for the former especially for what concern bleeding and visceral damage control. (level 4 of evidence).

Conclusion

Laparoscopic thermoablation is an effective and safe curative treatment for HCCs not suitable to liver resection, when percutaneous approach is not feasible (level 4 of evidence).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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