# Percutaneous and Laparoscopic-Assisted Ablation of Hepatocellular Carcinoma

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## 8.1 Introduction

Over the last few decades, percutaneous and laparoscopic ablative techniques have grown as a potentially curative therapeutic option for hepatocellular carcinoma (HCC). Ablation refers to necrosis achieved using chemicals or thermal energy delivered directly to the tumor under image guidance. The seminal technique was percutaneous ethanol injection (PEI). Subsequently, hyper-thermal ablative therapies emerged, including radiofrequency ablation (RFA) and microwave ablation (MWA). Ablation is now considered a valid complement to surgery or even a replacement for resection. It enables sparing of parenchyma, alone or in combination with surgery, and allows treatment of high-risk patients.

## 8.2 Treatment Indications

Beside thermal ablation, potentially curative therapies for HCC include liver resection (LR) and liver transplantation (LT). Owing to the absence of randomized trials comparing the three approaches, when selecting the best option, it is recommended to evaluate the main independent clinical prognostic factors of HCC: tumor burden, vascular invasion, extrahepatic spread, liver function, portal hypertension, and patient conditions (Eastern Cooperative Oncology Group [ECOG] Performance Status) [1]. Both the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases have endorsed the Barcelona

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Clinic Liver Cancer (BCLC) staging system that incorporates all the above-mentioned items [1, 2].

Currently, thermal ablation may be considered as first-line therapy in very early-stage HCC (BCLC 0: single tumor <2 cm, no vascular invasion/satellites, preserved liver function, ECOG-0) and is the best option for patients with early-stage HCC (BCLC A: single tumor >2 cm or three nodules <3 cm, preserved liver function, ECOG-0) who are not candidates for LR. In selected cases, LR leads to the best outcomes (5-year survival of 60–80%) and represents the treatment of choice for patients without cirrhosis, but LR in the cirrhotic liver should be reserved only for patients with solitary tumors, very well-preserved liver function, no portal hypertension or platelet count ≥100,000/mL [3]. Even though an extension of these criteria could be considered, especially after the promising results obtained in experienced centers with LR in patients who did not satisfy the requirements, a consensus has not been reached yet [4]. To address the issue of patients with small tumors and impaired liver function, with respect to the *therapeutic hierarchy* strategy, ablation can be considered the best option for patients affected by both unresectable BCLC A and B HCC [5].

Ablation therapy may serve to treat LT candidates within the Milan criteria to reduce the drop-out risk due to tumor progression while waiting (*bridging*) or to bring patients within validated criteria for LT (*downstaging*) [6]. Indeed, response to bridging and downstaging treatments affects the rate of post-LT tumor recurrence [7].

## 8.3 Ablation Techniques

“Percutaneous” refers to any procedure that delivers chemicals or energy by a guided puncture of the tumor through the abdominal wall of the patient under local anesthesia.

PEI was one of the initial ablative techniques employed for treatment of HCC. Ethanol (95–99.5%) induces coagulative necrosis of the nodule because of cellular dehydration, protein denaturation, and chemical occlusion of small tumor vessels. PEI is performed under ultrasound (US) guidance or in combination with computed tomography (CT). A needle is advanced inside the target lesion and 5–10 mL of agent is injected (several times for tumors >2 cm). PEI is fast and cheaper compared to other techniques [8], but it is characterized by insufficient control of ethanol spread, inhomogeneous distribution within the lesions, and inadequate margin treatment due to heterogeneity within the tumor architecture. Almost complete necrosis can be achieved in HCC ≤ 2 cm treated with PEI [9], but for larger nodules local recurrence is common [10], particularly if compared to thermal ablation techniques.

Heat producing coagulative necrosis of hepatocytes is the mechanism behind RFA and MWA.

RFA produces heat by using high frequency alternating current passed through a circuit including a generator, a monopolar electrode needle advanced into the target lesion, dispersive grounding plates located on the patient's skin, and the tumor, the resistive element. The applied current agitates ions around the tip of the electrode and heat is then conducted deeper into the surrounding tissue. Irreversible cell injury depends on the duration of heat application: the shorter the application the higher the temperatures required [11]. Evidence suggests immediate cell death at temperatures of 60–100 °C or within 5–6 min of heat application >50 °C [12]. Heat allows extension of the necrosis to a safety ring in the peri-tumoral tissue, which might eliminate undetected satellites and might explain the fewer local recurrence compared to PEI. RFA offers increased control over the ablation zone shape, but this is also impacted by increased tissue impedance, which occurs with tissue desiccation and vaporization [11]. This issue has been overcome with the advent of MWA.

Microwaves are generated by applicators in a range between 915 MHz and 2.45 GHz and transmitted by an antenna to polar water molecules, resulting in tissue heating. They penetrate through biologic materials with high impedance, such as dehydrated or charred tissue. In other terms, MWA can deliver high temperatures for longer time, thus improving ablation efficacy by increasing thermal conduction into the surrounding tissue [11] and allowing faster treatments of larger tumors compared to RFA [13].

The efficacy of percutaneous ablation depends on the imaging-guidance tools, given that precise tumor targeting is essential for achieving complete necrosis. Currently, US, computed tomography (CT), and cone-beam CT are the modalities of choice for guidance and result assessment. Fusion imaging is a novel technique that enables the overlay of multiple imaging and is helpful in small tumors to decrease the risk of missing the target [14].

Hyperthermal ablation techniques have drawbacks. Heat applied near large vessels, typically the hepatic veins, undergoes thermodynamic exchange with the blood stream and ablation efficacy is diminished. MWA is less susceptible to this phenomenon (heat sink effect) than RFA [15]. Both RFA and MWA share similar complications including hemorrhage, hepatic abscess, pneumothorax, bowel perforation, biliary injury, and track seeding. Slow retraction of the electrode/antenna (track ablation) is a technical refinement that may reduce hemorrhage and seeding. In any case, major complication rates are 2–10% and the procedure-related mortality rates are <1% [16].

There are several other percutaneous thermal ablation modalities under investigation, such as laser ablation, cryoablation and irreversible electroporation. Results are promising, but these techniques require higher operator skills and are burdened by severe complications. Therefore, their use is not currently recommended in the routine treatment of HCC, but only as part of clinical trials.

Even though less invasive procedures are preferable in cirrhotic HCC patients, the percutaneous approach has major limitations. Thrombocytopenia and portal hypertension expose patients to an unacceptable risk of peri-operative bleeding. Indirect localization of the tumor requires operator expertise and confidence with image-guidance tools. Moreover, target lesions are often in high-risk locations or too deep to be safely reached from the skin surface. Therefore, to increase the number of patients who could benefit from ablative treatment, laparoscopic ablation has

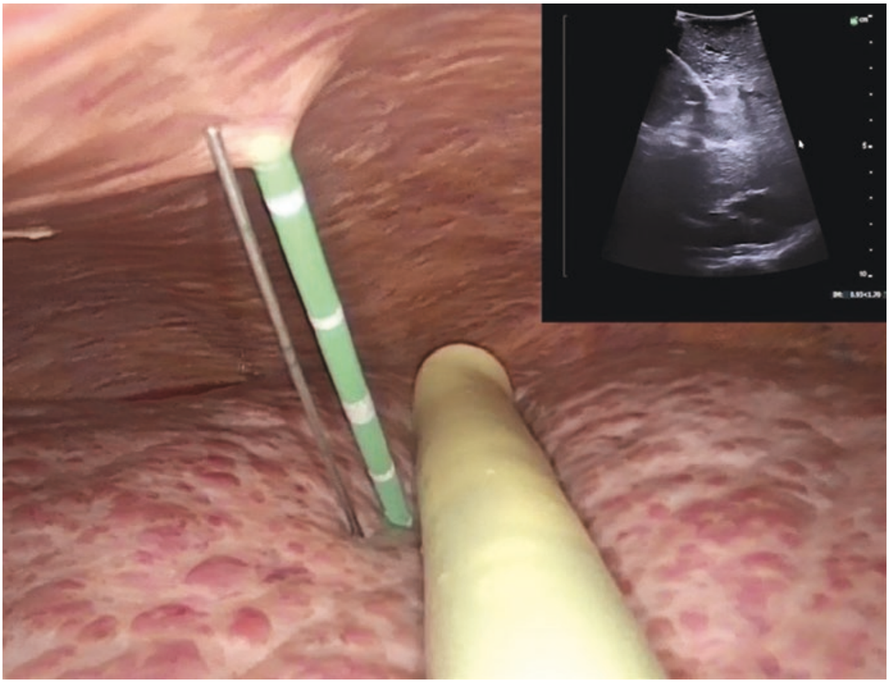

**Fig. 8.1** Laparoscopic microwave ablation (Prof. Cillo's personal experience)

been implemented for RFA and MWA assisted by laparoscopic intraoperative ultrasound (LUS) (Fig. 8.1).

Criteria reaching the highest consensus for a laparoscopic approach are: HCC not visible percutaneously (along the diaphragm) or next to the hilum (risk of biliary thermal injuries), HCC near visceral structures, ineligibility for LR and severe coagulopathy [17–19].

LUS is a major advantage compared to the percutaneous approach since it is considered the most effective tool for detecting liver nodules [18]. Clinical experience supports a single-stage approach with immediate ablation of newly discovered HCC [18, 20].

Laparoscopy allows direct visualization of the liver, enhancing the ability to treat HCC located at the dome, peripherally, or in proximity to other organs. In the latter scenario, laparoscopy permits active protection of surrounding structures, reducing the risk of visceral injuries. Moreover, visualization of the entry point of the applicator allows bleeding source control. Severe complications rates are reported to be about 2% [17]. Common complications are pneumonia, pneumothorax, and bleeding from the trocar access. Tumor seeding, peritoneal dissemination, biliary strictures, arterial thrombosis, and liver abscess are reported less frequently.

While remaining minimally invasive, laparoscopic ablation is more flexible compared to the percutaneous approach [18, 19, 21] and, for HCC in difficult locations, it improves success rates [18, 19].

## 8.4 Oncological Outcomes

Although PEI has been largely replaced by thermoablation, it may still be applied in selected cases or to target part of a tumor located near structures at risk for thermal injury. Metanalyses comparing PEI to RFA have demonstrated the superiority of the latter in terms of overall survival (OS) and recurrence-free survival (RFS). The 3-year survival rate of patients treated with PEI was 48–67%, while for those treated with RFA it was 63–81%. Local tumor recurrence (LTR) was significantly less frequent with RFA [8, 22].

In the absence of randomized trials comparing RFA to surgery in compensated cirrhotic patients with very early HCC, Cho et al. created a Markov model to simulate a randomized trial comparing LR, percutaneous RFA monotherapy and percutaneous RFA monotherapy followed by LR in the case of local residual disease. The expected values for OS were 7.6, 7.4, and 7.6 years, respectively, while the expected 5-year OS rates were 62.5%, 60.3%, and 62.3% [23]. For unresectable candidates, the combination of RFA and transarterial chemoembolization (TACE) has shown benefit in terms of OS and RFS compared to monotherapy with RFA (OS: HR = 0.62; 95% CI 0.49–0.78, $p < 0.001$; RFS: HR = 0.55; 95% CI 0.40–0.76, $p < 0.001$) or TACE alone (2-year OS: 91.1% vs. 60.6%, $p = 0.004$; 2-year LTR: 48.1% vs. 78.2%, $p < 0.001$) [24, 25]. In cases of single HCC < 3 cm, when tumor recurs after RFA, LT should be considered [26].

As for MWA vs. RFA, Cui et al. have recently found no significant difference in 3- and 5-year OS, in 3-year RFS, in 1-year LTR, in technical efficacy, or in major complications. MWA is compared to LR only in two non-randomized studies showing similar 3-year OS (MWA 70–87.7% vs. LR 72–93.6%), but higher LTR (MWA 10.3–16.2% vs. LR 2.8–4.9%) [27].

Laparoscopic ablation achieves total necrosis of the tumor in a single session in more than 90% of the cases, comparable with the expected range of success of percutaneous ablation. Local tumor progression, when looking at the experience gained in the era of laparoscopy, is 2.8–23% [17]. In the earliest years, median OS for patients undergoing laparoscopic RFA for unresectable HCC was 26 months, while RFS was 14 months [28]. More recent analyses in high-volume centers, offering laparoscopic ablation for HCC unsuitable for LR or LT, report 1-, 3-, and 5-year OS of 88%, 55%, and 34%, respectively [18]. A retrospective analysis of 815 laparoscopic MWA on 674 patients treated in the authors' center, one of the most experienced in this field, has reported 1-, 3-, and 5-year OS of 81.9%, 54.9%, and 35.9%, respectively [19]. The updated data are listed in Table 8.1.

In conclusion, laparoscopic thermoablation has been shown to be a safe and effective curative treatment for HCC in those patients at risk of complications or unsuccessful therapy through a percutaneous access.

**Table 8.1** Laparoscopic microwave ablations (MWA) performed at Padua University Hospital 2014–2021 (unpublished data)

| | | |
|---|---|---|
| No. of patients | 1273 | |
| No. of laparoscopic MWA | 1796 | |
| Child-Pugh score | | |
| • A | 762 | (59.9%) |
| • B | 260 | (20.4%) |
| • C | 24 | (1.9%) |
| • Missing | 227 | (17.8%) |
| Milan-out[a] | 248 | (19.5%) |
| Postoperative complications | | |
| • Fever | 54 | (4.2%) |
| • Nausea/vomiting | 4 | (0.3%) |
| • Ascites | 110 | (8.6%) |
| • Liver failure[b] | 60 | (4.7%) |
| • Hemoperitoneum | 1 | (0.1%) |
| • Pleural effusion | 10 | (0.8%) |
| • Pneumothorax | 5 | (0.4%) |
| Overall survival | | |
| • 1-year | 87% (95% CI 85–90) | |
| • 3-year | 60% (95% CI 56–63) | |
| • 5-year | 45% (95% CI 41–49) | |

[a]Exceeding the Milan criteria for liver transplantation
[b]According to 50–50 criteria

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