Open Liver Resection, Laparoscopic Liver Resection, and Percutaneous Thermal Ablation for Patients with Solitary Small Hepatocellular Carcinoma (≤ 30 mm): Review of the Literature and Proposal for a Therapeutic Strategy

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Keywords

Hepatocellular carcinoma · Open liver resection · Laparoscopic liver resection · Anatomic liver resection · Percutaneous thermal ablation · Percutaneous radiofrequency ablation

Abstract

Background: Patients with a single hepatocellular carcinoma (HCC) ≤ 3 cm and preserved liver function have the highest likelihood to be cured if treated. The most adequate treatment methods are yet a matter that is debated. **Methods:** We reviewed the literature about open anatomic resection (AR), laparoscopic liver resection (LLR), and percutaneous thermal ablation (PTA). **Results:** PTA is effective as resection for HCC < 2 cm, when they are neither subcapsular nor perivascular. PTA in HCC of 2–3 cm is under evaluation. AR

with the removal of the tumor-bearing portal territory is recommended for HCC > 2 cm, except for subcapsular ones. In comparison with open surgery, LLR has better short-term outcomes and non-inferior long-term outcomes. LLR is standardized for superficial limited resections and for left-sided AR. **Conclusions:** According to the available evidences, the following therapeutic proposal can be advanced. Laparoscopic limited resection is the standard for any subcapsular HCC. PTA is the first-line treatment for deep-located HCC < 2 cm, except for those in contact with Glissonean pedicles. Laparoscopic AR is the standard for deep-located HCC of 2–3 cm of the left liver, while open AR is the standard for deep-located HCC of 2–3 cm in the right liver. HCC in contact with Glissonean pedicles should be scheduled for resection (open or laparoscopic) independent of their size. Liver transplantation is reserved to otherwise untreatable patients or as a salvage procedure at recurrence.

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death worldwide [1]. The epidemiology of HCC is changing. Hepatitis C virus (HCV)-related HCC are expected to progressively decrease because of directly acting antiviral agents, while HCC related to nonalcoholic fatty liver disease and metabolic syndrome is expected to increase [2, 3]. The management of patients with HCC must take into account several therapeutic options, including 3 potential radical treatments, that is, liver transplantation, liver resection, and thermal ablation. Patients with a single HCC ≤ 3 cm in size (very early and early HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system) and preserved liver function have the highest likelihood to be cured if treated. The most adequate radical treatment is debated. Liver transplantation is rarely adopted as first-line treatment because of the shortage of donors and of the excellent outcome achieved by resection or ablation that do not preclude a salvage transplantation in case of failure [4–8]. The choice between percutaneous ablation and resection is yet a matter of debate. Several aspects must be balanced including completeness of the procedure, peri-procedural risks, length of hospitalization, and costs. Ablation has minimal invasiveness and morbidity [5], while surgery guarantees the complete removal of the tumor-bearing portal territory where peritumoral micrometastases and microscopic vascular thromboses can be detected [9, 10]. The introduction and diffusion of laparoscopic liver surgery (LLR) complicated matters by reducing the invasiveness of surgery [11]. At the same time, progresses in interstitial treatments, namely, technological improvements and microwave ablations, overcame some limitations of radiofrequency ablations (RFAs) and increased their effectiveness [12, 13].

The present review separately analyzes the 3 commonest therapeutics options adopted for patients with a single HCC ≤ 3 cm and preserved liver function: anatomic open resection, LLR, and percutaneous ablation. The most relevant evidences in the literature are considered, the key issue discussed, and a treatment strategy proposed.

Methods

A systematic search of PubMed, Science Citation Index, and Embase databases was performed for articles published before January 2018 relevant to the radical treatment of early and very early HCC. English language articles were selected using the keywords “hepatocellular carcinoma,” “HCC,” “surgical resection,” “anatomic resec-

tion,” “laparoscopic liver surgery,” “interstitial treatment,” “thermal ablation,” “radiofrequency ablation,” “microwave ablation” to identify all reports that may pertain to the review issue. Manual cross-referencing was performed and relevant references from selected papers were reviewed. Case reports were excluded.

Results

Open Anatomic Resection

Open liver resection has achieved a wide consensus for HCC treatment as long as it provides excellent short-term results with near-zero mortality and low severe morbidity rates [4, 14, 15]. An accurate selection of cirrhotic patients who are candidates to surgery is crucial. The selection process should consider factors such as comorbidities, liver function, and extension of resection to perform [16–19].

HCC has a high propensity to spread along portal pedicles, resulting in segmental tumor deposits and microthrombosis within the tumor-bearing portal tree [9, 10]. On the basis of this trend, a *de principe* anatomic resection (AR) is the only way to guarantee a true and complete resection. In fact, AR is recommended by both the EASL guidelines and the multidisciplinary Italian recommendations about HCC treatment [20, 21]. Nevertheless, this technique is not a standard procedure in surgical practices worldwide. In the literature, there is no conclusive evidence showing the superiority of AR over non-AR. Thus far, no randomized trials have compared the 2 techniques in a specific manner. Several retrospective analyses reported a survival benefit after AR versus non-AR [22–27], but the non-AR group usually included patients with more severe liver disease and, consequently, lower survival expectancy. Recent studies used propensity score matching to overcome this bias. The largest analysis has been published by Shindoh et al. [28] including 209 Child A patients affected by HCC ≤ 5 cm, undergoing non-AR ($n = 153$) or AR ($n = 56$). Baseline characteristics largely differed between groups, confirming the fact the non-AR is usually performed in patients with worse liver function, poorer general conditions, and with subcapsular HCC. However, after a propensity score matching, the authors reported a higher disease-specific survival and lower local recurrence rate in the AR group. Five additional propensity score analyses have been published, 2 of which reported better outcome after AR than after non-AR [29, 30], while 3 reported no differences between groups [31–33]. The results of the most relevant studies comparing AR and non-AR are summarized in Figure 1. While we

Fig. 1. Forest plot of studies analyzing the impact of anatomic resection for HCC on survival. Five studies with a propensity score analysis and one study with a case-control design are included. Hazard ratios (95% CI) are denoted by black boxes (black lines) and the no effect point is denoted by a dotted vertical line. * In the paper of Okamura et al. [32], the recurrence-free survival was considered. AR, anatomic resection.

wait for stronger evidences, some additional considerations are possible. First, a key issue is the size of HCC as has been elucidated by a large Japanese analysis published in 2008 [23]. The authors considered a nationwide database collecting 5,781 HCC patients undergoing liver resection between 1994 and 2001. AR had higher survival than non-AR, but this difference was evident only in the subgroup of patients with an HCC 2–5 cm in size. In larger tumors, other prognostic factors may mask the benefit from AR, while in very early HCC (<2 cm), the risk for tumor spread along portal pedicles is limited. Pathology studies confirmed that microsatellites and thrombosis are extremely rare for very early HCC [34]. Second, superficial HCC are treated by non-AR even in centers regularly performing AR. An adequate non-AR with wide margins is considered oncologically correct worldwide as long as it approximates the harborization of the tumor-bearing portal territory then providing its clearance.

To perform a true AR is technically demanding and may represent per se a further confounding factor in evaluating the impact of this approach. Indeed, anatomical casts and 3D vascular reconstructions demonstrate that liver segments have irregular margins not predictable on the basis of anatomical landmarks [35–38]. Further, an HCC can be nourished by multiple pedicles from different liver segments [35–38]. Then, the delimitation of the segmental area is not obvious. Many reports do not even mention the methods adopted for its disclosure, while others describe incorrect modalities. The intraoperative visualization of the portal territory to remove is mandatory. It cannot rely on the identification at intraoperative ultrasonography (IOUS) of intrahepatic vessels (hepatic

veins and origin of the Glissonean pedicle), since any vascular landmark identifies only a single point of a complex plane separating 2 adjacent segments, which cannot be roughly approximated in this manner, unless the tumor is small and subcapsular. Makuuchi et al. [10] described the “dye injection” technique, which involves segment staining using IOUS-guided injection of dye into the portal branches. This technique requires expertise in IOUS-guided maneuvers and is rarely used in Western countries. Further, the injection technique may fail to identify the area to resect (inadequate staining or multiple pedicles feeding the tumor) in up to 40% of patients [28, 35, 39]. More recently, the injection of indocyanine green into the tumor-bearing portal branch has been proposed to achieve the demarcation of the segment to resect by fluorescence imaging [39, 40]. Even if interesting, this technique conveys the same technical limitation of the one with dye injection, but adding further costs to the procedure. Some alternative techniques have been proposed. First, the radiofrequency-assisted ablation of the tumor-bearing Glissonean pedicle has been suggested [41, 42]. The vascular lesion makes this procedure very effective, but it causes irreversible injuries that are potentially risky and may oblige to extend the resection when pedicles not part of the tumor-bearing portal tree are damaged. Second, the hilar approach was introduced by Takasaki et al. [43]. It relies on a blind dissection that may lead to biliary injury and it is technically demanding for postero-superior segments. In 2004, Torzilli and Makuuchi [44] proposed an alternative procedure based on IOUS, termed “compression technique” [45]. After identification of the tumor-feeding portal pedicle, blunt trans-

Fig. 2. Patient with HCC in segment 7 (S7) and segment 8 dorsal (S8d). IOUS-guided compression of the Glissonean pedicles for S7 and S8d was performed to identify the tumor-bearing portal territory to remove. The compression of the pedicle between the IOUS probe and the surgeon fingertip (F) allowed segmental (S7) and

subsegmental (S8d) demarcation (white arrows; **a**, **b**). The resection areas (S7 and S8d) were marked with the electrocautery (**c**). Anatomical resection of S7 and S8d was performed, the right hepatic vein (RHV) was exposed along the transection plane, and the Glissonean pedicles (P7 and P8d) were sectioned at the origin (**d**).

parenchymal compression is applied between the surgeon's fingertip and the IOUS probe to create vascular occlusion, which results in the discoloration of the downstream portal territory (Fig. 2). Its feasibility and safety have been previously reported [46]. Initially developed for left lateral segments [44], its application is now extended to all the liver segments [46, 47]. The authors have recently analyzed the long-term outcome of compression-guided AR (c-AR; submitted data). c-AR patients were matched on a one-to-two basis with non-AR cases according to both liver function (Child-Pugh class, Model for End-Stage Liver Disease (MELD) score, and underlying cirrhosis) and tumor burden (HCC number and size). Forty-seven c-AR patients were matched with 94 non-AR cases. Patients undergoing c-AR had better 5-year survival (77.4 vs. 60.2%, relative risk = 0.423, $p =$

0.032 at multivariable analysis), lower local recurrence (intra-segmental recurrence, 4 vs. 20%, $p = 0.012$), and better 2-year local recurrence-free survival (94.3 vs. 78.4%, $p = 0.012$). Non-local recurrence-free survival was similar between the groups. The same results were observed in the subgroup of patients with HCC ≤ 3 cm. Short-term outcomes were similar and excellent in both groups (mortality 0%, severe morbidity 6%). c-AR could represent a new standard due to its safety and efficacy and could make the use of AR more widespread.

One further consideration is relevant. Shindoh et al. [28] reported that recurrence after non-AR was often featured by aggressive local recurrence or multinodular tumor spread. These presentations precluded any chance of repeating treatments in many patients. Similar results were observed in the authors series: 28% of non-AR pa-

Fig. 3. Patient with HCC in segment 7 in contact with the RHV (**a**, **b**). Laparoscopic segment 7 resection was performed with section of the RHV (**c**). Adequate margins were achieved (**d**).

tients had repeated radical treatment of recurrence vs. 68% of c-AR patients ($p = 0.0004$) because of more aggressive disease pattern at recurrence in the non-AR group. In the authors' opinion, this aggressive behavior of recurrence after non-AR further underlines the need for AR. In fact, it recalls the features of local failure after incomplete nonsurgical treatments [48, 49]. In cirrhotic patients, the risk of recurrence is very high and it is fundamental to maximize the chance for a repeat treatment or for a salvage transplant whenever needed.

Laparoscopic Liver Resection

LLR has gained a significant place in liver surgery over the past 20 years. There are no available randomized trials comparing open and laparoscopic surgery for HCC and results arise from case series, comparative studies with propensity score match and meta-analyses. Based on these data, the Morioka Consensus Conference validated minor laparoscopic resections as standard practice and acknowledged short-term advantages without long-term oncologic inferiority [50]. Since the early days of LLR, HCC has been the most common indication [51]. Nowadays, the total rate of LLR has increased to over 40% [52], especially in experienced centers. Similarly, the rate of major LLR has increased to 30% [11]. In a recent review

of the literature, more than 9,000 cases of LLR have been reported [11]. Interestingly, HCC developed on chronic liver disease is the most common indication for malignancy (>50%), while colorectal liver metastasis is the most common indication in an open surgery series. Such findings are evident since the initial reports about LLR [53] and can be explained by the fact that, thanks to the screening program in patients with liver cirrhosis, small solitary HCC can be detected early. Further, liver resection is mainly offered to patients with solitary HCC, while colorectal liver metastases can be multinodular and require multiple resections in different segments.

For small solitary HCC (≤ 3 cm), tumor location may influence the choice of LLR versus open resection. In early series, mostly superficial tumors were considered good candidates for LLR, while lesions located in difficult segments (i.e., 7, 8, and 1) were rarely considered. However, the number of complex anatomical resections are increasingly reported [54]. An example of complex LLR is shown in Figure 3. It is clear that in such difficult locations, the use of the laparoscopic approach is more demanding. The choice must be made on an individual case basis and in view of local expertise.

The main issues in patients with liver cirrhosis undergoing LLR are intraoperative management, the risk

of postoperative liver decompensation, and long-term outcome.

LLR has been shown to be associated with reduced blood loss and transfusion when compared to open liver resection [11, 55, 56]. This finding can be explained by the hemostatic effect of the pneumoperitoneum, better magnification, and the use of new parenchymal transection devices. Meta-analysis of comparative series showed that for the postoperative results, LLR allows reduced pain, complication rate, and hospital stay. The mortality rate was also identical in the 2 groups. For the liver-specific morbidity, laparoscopic approach has shown that it has a decreased rate of ascites development when compared to open surgery as observed by different authors over time [57–62].

Restriction of fluid administration, avoidance of long abdominal incisions with muscles divisions, collateral preservation, and less respiratory impairment seem to have a protective effect on postoperative liver decompensation. Like in open liver surgery, LLR for HCC remains preferable in Child-Pugh class A/Low MELD patients, with no or minimal portal hypertension. However, perioperative advantages of LLR may allow some degree of extension of the indications to Child-Pugh B patients or with portal hypertension [63].

Most importantly, oncologic outcomes of LLR are non-inferior to those of open surgery in case series, comparative studies, and meta-analyses. First, comparative studies have shown that surgical margins were identical in open and laparoscopic surgeries [11]. In terms of long-term outcome, LLR and open liver surgery have comparable results for the overall and disease-free survival [55, 56, 64, 65]. Another advantage of LLR is that it may enhance the possibilities of subsequent liver transplantation for recurrent HCC or decompensation. In a previous study, Laurent et al. [66] showed that liver transplantation after previous LLR was associated with significantly reduced operative time, blood loss, and transfusions as compared to previous open liver resection.

While right and left hepatectomies can be equally performed by open or laparoscopic resection [67], more complex right-sided resections are clearly more demanding by the laparoscopic approach and require advanced expertise. In the case of anterior and posterior sectionectomies, extrahepatic control of the sectional pedicles using the Takasaki technique are increasingly used by the laparoscopic approach, allowing anatomical resection by ischemic delineation [68, 69]. There is a limitation about laparoscopic anatomical segmentectomies. In such cases, the use of preoperative 3D recon-

struction is a significant adjunct to surgical planning. Preoperative planning is even more important for a laparoscopic approach because of inherent technical limitations. Techniques such as dye injection or finger compression are not applicable laparoscopically. Therefore, the identification of segmental anatomical borders must rely on ultrasound and ischemic delineation. In some favorable cases, the Takasaki Glissonean approach may be extended to segments 5, 6, 7, or 8. This gives superficial ischemic demarcation, which, in combination with resection along hepatic veins, allows AR. Care must be taken to avoid biliary injury using this technique. However, in most cases, ultrasound remains the main tool for identification of intrahepatic Glissonean pedicles and hepatic vein locations. For these reasons, mastery in IOUS is needed in order to mark on the liver surface the origin of Glissonean pedicle and the root of hepatic veins. This allows the initiation of the resection following the hepatic veins and to isolate the Glissonean pedicles intraparenchymally [70]. It must be acknowledged that these sophisticated techniques are difficult, not always applicable, and not endorsed by all surgeons. This is also true for open surgery. Therefore, some alleged anatomical resections are in fact intentional, based on theoretical segmental margins.

Percutaneous Ablation

Image-guided percutaneous ethanol injection (PEI) was the first interventional procedure clinically employed to ablate small HCC [71], but PEI has been progressively replaced by RFA. In the very early and early stage HCC, several randomized controlled trials demonstrated the superiority of RFA versus PEI, with complete response rates of 95–96% for RFA vs. 82–86% for PEI, 2-year local recurrence rates of 2–18 vs. 11–33%, and 3-year survival rates of 74–81 vs. 55–73% [72, 73]. This superiority has been mostly attributed to the capability of RFA to ablate a rim of perilesional non-tumoral tissue where microsatellite nodules are frequently located [34]. Nowadays, PEI has a very limited role for the treatment of tiny (≤ 10 mm) HCC, mostly located in anatomical areas at risk for ablation (adjacent to gallbladder, main bile ducts, or bowel loops).

For the last 25 years, RFA has been increasingly employed for the treatment of small HCC in patients with chronic liver disease and nowadays can be offered as first-line curative treatment when patients are not candidates for liver transplantation [74, 75], and additionally as bridge treatment for patients who are on the waiting list for liver transplantation. Case series and cohort studies

Fig. 4. Patient with 3.0 cm HCC in segment 8, following previous transarterial chemoembolizations for multiple small HCCs in HCV-related cirrhosis (**a**). After percutaneous ablation with high-power microwaves (Amica, HS, Hospital Service, Aprilia, Italy) delivering 60 W for 8 min, 24-h post-ablation CT scan shows a wide (5.8 × 2.9 × 4.4 cm) area of necrosis (**b**). Using a new software (Ablation-fit™, R.A.W. Endosight, Milan, Italy), pre- and post-ablation CT scans are co-registered and overlapped, showing on single slices (**c**) and on 3D acquisition (**d**) that both the pre-ablation tumor volume (in orange-yellow color) and the 5-mm ablative margin (in green color) are entirely embedded in the volume of necrosis (in blue color).

have demonstrated that RFA may reduce the dropout rate of HCC patients on the waiting list for liver transplantation to 0–25% [76].

The results of RFA can be influenced by tumor location (central vs. peripheral, distance from gallbladder, main bile ducts, bowel loops), patient's body habitus (lean vs. overweight), and presence of portal hypertension [77, 78]. Nodules in the 2-cm size range that are neither subcapsular nor perivascular are the ideal target for RFA. In such nodules, RFA is considered the standard technique at most institutions, with the complete response rate approaching 97% and 5-year survival rates of 65–68% [5]. In one of the largest studies ever published on RFA of very early and early HCC based on a 10-year consecutive case series, complete tumor ablation was achieved for 2,964 (99.4%) of 2,982 treatments performed for the 1,170 primary HCC patients. With a median follow-up of 38.2 months, 5- and 10-year survival rates were 60% (95% CI 57–64) and 27% (95% CI 22–35) respectively. Multivariable analysis demonstrated that age, HCV infection, Child-Pugh class, tumor size, tumor number, serum des-gamma-carboxy-prothrombin level, and serum lectin-reactive alpha-fetoprotein level were significantly

related to survival. The 5- and 10-year local tumor progression rates were both 3.2% (95% CI 2.1–4.3) [79]. Recent reports on long-term outcomes of patients treated with ablation have shown that in patients with Child-Pugh class A cirrhosis and early stage HCC, 5-year survival rates are as high as 51–64% and may reach 76% in patients who meet the BCLC criteria for surgical resection [80, 81]. In general, at first HCC diagnosis, ablation is recommended when surgical options are precluded or severely challenging, while for relapses after surgery, which occur in as many as 50–60% of patients with HCV-related cirrhosis during their lifetime, ablation is the first-line treatment when nodules are in suitable and safe location for percutaneous targeting.

In recent years, further advancements in the fields of technology of image guidance and type of energy delivered are leading to significant improvements of the outcome of thermal ablations (Fig. 4). The routine use of ultrasound contrast agents (microbubbles) immediately at the end of the procedure, when ablations are performed in ultrasound rooms, enables the assessment of the amount and location of the necrosis achieved and, if needed, to guide retreatments of partially ablated tumors

in the same interventional session [82, 83]. Real-time fusion of ultrasound and the imaging modality which best depicts the single target lesion (CT; MRI; positron emission tomography-CT) actually allows to reach and precisely ablate almost any target anywhere in the liver [12, 84]. In addition, specific software enabling to spatially co-register and overlap pre- and post-ablation CT or MRI scans are currently being introduced in clinical practice, enabling the achievement of extremely precise assessment of the volumes of necrosis compared to the original tumors and, moreover, of the thickness and regularity of ablative margins in 3D [85].

In the field of ablative methods, RFA still has the largest diffusion worldwide, but high-power microwaves (MWs) technology, recently introduced in the clinical practice, is able to overcome some specific limitations of radiofrequency. Thanks to the inherent properties of electromagnetic radiation and the broader fields of power density, MWs facilitate the process of reaching much higher temperatures and, accordingly, larger, more uniform, rounded, and regularly demarcated volumes of necrosis in a shorter time. MWs are not susceptible of increasing impedance from ablated tissue, and are not completely dependent on hydrated tissues, both of which are important limitations for radiofrequency. In addition, with MWs, the heat sink effect, which occurs when radiofrequency is used, is minimized or completely lacking, thus allowing the possibility of adequately ablating portions of tumors even adjacent to large blood vessels. Consequently, microwave ablation (MWA) is enabling significant increase of the rate of complete ablation achieved with RFA in HCC larger than 3 cm and/or multiple and will likely lead to “raise the bar” of HCC routinely treatable, provided the location is suitable and safe [13, 86, 87]. The main advantage of MWA versus RFA is the capability to routinely achieve 5–10 mm thick and regular perilesional ablative margin, which has been demonstrated to be the most important determinant for the achievement of complete local control of ablated tumors [88]. Two recent meta-analyses concluded that both RFA and MWA are equally effective and safe, but MWA is more effective in preventing local tumor progression when treating larger tumors [89, 90].

Irreversible electroporation (IRE) is a nascent non-thermal ablation modality which, by applying short pulses of very high-voltage direct current energy, leads to the destabilization of the electrical potential across cell membranes, resulting in the rupture of cell membranes and tissue death via apoptosis, while fully preserving the periblastic zone architecture including blood vessels and

bile ducts because their higher content of collagenous/elastic fibrous tissue acts as a barrier preventing the flow of electrical current. Contrary to RFA and MWA, CT-guided IRE is usually performed under general anesthesia with muscular blockade and pulsed timed to the cardiac cycle to prevent arrhythmias [91]. For HCC, the main utility of IRE may lie in treating nodules adjacent to the gallbladder and bile ducts, not suitable for resection, ablation, or radiotherapy. No long-term survival data on HCC treated with IRE are currently available. In small series, local recurrence-free survival rates of 90 and 50% at 6 and 12 months, respectively, and local recurrence rates of 9.7% for HCC <5 cm and 64.7% for HCC >5 cm have been reported [92, 93].

Comparative Studies between Ablation and Surgery

In recent years, several trials compared the performances of RFA with those of resection. RFA has lower morbidity rates and leads to shorter hospitalization and lower costs [80, 94–97]. Four randomized trials did not show a superiority of resection over RFA in terms of overall and progression-free survival [95–98]. Similar data were reported by some propensity score analyses [99, 100]. However, these data are not conclusive because of some methodology limitations. In fact, large retrospective series [101–104], propensity score analyses [105–112], one randomized trial [80], and 2 recent meta-analyses [94, 113] demonstrated superiority of surgery over RFA in terms of local disease control, even for 2–3 cm HCC. One multicentre Italian study collected 544 patients with single HCC ≤ 3 cm and compensated cirrhosis [104]. Patients undergoing RFA ($n = 298$) had similar survival to patients undergoing surgery ($n = 246$), but the local recurrence rate after RFA largely exceeded the local recurrence rate after surgery (20 vs. <1%). Recently, a paper from Li et al. [114] compared the short- and long-term outcomes of patients with small HCC treated by open or laparoscopic resection or MWA. Short-term outcomes were improved by LLR and MWA, but disease-free survival was decreased in the local ablation group. In the meta-analysis conducted by Xu et al. [113], RFA and resection had similar overall survival at 1 and 3 years, whereas RFA resulted in decreased overall survival compared with resection at 5 years. More trials are needed to control random errors and to reach conclusive evidences, but until date, resection is preferable to ablation for HCC of 2–3 cm. Conversely all the authors agree that surgery and RFA are equivalent for very early-stage HCC (<2 cm) in terms of both local control rate and overall survival [5, 103, 115]. One exception should be considered.

Table 1. Most relevant studies comparing liver resection and ablation for HCC patients

Author	Year	Inclusion criteria	Study design	LR vs. RFA, n	Morbidity, %		Hospital stay, days		3-year OS, %		3-year RFS, %	
					LR	RFA	LR	RFA	LR	RFA	LR	RFA
Chen et al. [95]	2006	Single ≤50 mm	Randomized	90 vs. 90	55.6*	4.2*	19.7*	9.2*	73.4	71.4	51.6	64.1
Lu et al. [98]	2006	Milan criteria	Randomized	54 vs. 51	11.1	7.8	19.2*	5.2*	86.4	87.1	82.4	51.3
Huang et al. [80]	2010	Milan criteria	Randomized	115 vs. 115	27.8*	4.3*	15.4*	6.9*	92.2*	69.6*	60.9*	46.1*
Feng et al. [96]	2012	Single ≤50 mm	Randomized	84 vs. 84	21.4*	9.5*	14.8*	7.3*	74.8	67.2	61.1	49.6
Fang et al. [97]	2014	Single ≤30 mm	Randomized	60 vs. 60	27.5*	5.0*	11.8*	4.3*	77.5	82.5	41.3	55.4
Wang et al. [107]	2012	1–3 ≤30 mm	Propensity score	52 vs. 52	–	–	–	–	98	82.8	62.1	46.4*
Kang et al. [99]	2015	Single ≤30 mm	Propensity score	99 vs. 99	–	–	–	–	92.7	95.7	67.1	53.3
Kim et al. [106]	2016	Single ≤30 mm	Propensity score	152 vs. 152	–	–	–	–	61 months	69 months	42 months*	39 months*
Santambrogio et al. [105] [†]	2016	Single ≤30 mm	Propensity score	76 vs. 76	–	–	–	–	86*	64*	60*	33*
Miura et al. [110]	2015	Single ≤30 mm	Propensity score	871 vs. 871	–	–	–	–	66*	52*	–	–
He et al. [111]	2016	Milan criteria	Propensity score	150 vs. 109	27	24	11.4*	5.1*	78.5*	69.7*	65.0*	37.0*
Ito et al. [108] [‡]	2016	1–3 ≤30 mm	Propensity score	27 vs. 27	15	0	12.6*	7.6*	–	–	100* [‡]	61.4* [‡]
Liu et al. [109]	2016	Single ≤20 mm	Propensity score	79 vs. 79	–	–	–	–	97*	83*	65*	36*
Lee et al. [112] [‡]	2018	Single ≤30 mm	Propensity score	62 vs. 62	–	–	–	–	98.4*	91.9*	68.7*	41.2*
Takayasu et al. [100]	2018	Single ≤20 mm	Propensity score	146 vs. 439	–	–	–	–	94	90	64	59
Hasegawa et al. [103]	2013	1–3 ≤30 mm	Retrospective	5,364 vs. 5,548	–	–	–	–	85.3*	81.0*	56.7*	42.8*

Bold values are values with a statistically significant difference between LR and RFA groups. * $p < 0.05$; [†] Laparoscopic ablation or laparoscopic resection; [‡] Laparoscopic liver resection; [‡] Local recurrence-free survival; [‡] Perivascular HCC.

Lee et al. [112] analyzed patients with very early HCC in contact with major intrahepatic vessels. They reported that thermal ablation was inferior to resection in perivascular HCC (3-year overall survival 92 vs. 98%; 3-year recurrence-free survival 41 vs. 69%). This inferiority was evident only for HCC in contact with Glissonean pedicles and not in those in contact with the hepatic veins. Resection should be the preferred option in such patients despite the small tumor size. The details and the results of the most relevant studies comparing resection and thermal ablation are summarized in Table 1.

Proposal for a Therapeutic Strategy

No evidence-based recommendations can be drawn as long as the literature does not provide conclusive comparisons among different therapeutic options. Nevertheless, some major considerations are possible based on the available clinical studies. Percutaneous ablation, mainly RFA, has proved to be as effective as surgical resection for the treatment of very early HCC (<2 cm), when they are neither subcapsular nor perivascular (Glissonean pedicles) [5, 103, 112, 115]. In HCC of 2–3 cm in size, the results of percutaneous ablation are still under evaluation, and until date, surgery is preferable [80, 94, 101–113]. LLR has reached an excellent safety and reproducibility profile for superficial limited resections of all the liver segments and for left-sided AR [11]. As compared with open surgery, LLR is superior in terms of short-term outcomes and not inferior in terms of long-term outcome [11, 55, 56]. LLR can even expand indication to resection in some selected Child-Pugh B patients [63]. However, some more complex procedures, specifically right-sided ARs, are not yet fully standardized with a laparoscopic approach. Open surgery can provide a proper AR even in more complex disease presentation with a low-risk profile, provided an adequate patient selection [4, 14, 15, 28, 46]. Liver transplantation remains a solution for both the underlying liver cirrhosis and the neoplasm but should be considered upfront only in otherwise untreatable patients (tumor location or compromised liver function) [6–8]. In the patients amenable to resection or ablation, transplantation should be considered a salvage procedure in case of recurrence [6–8].

According to these considerations, the following therapeutic strategy is proposed. Percutaneous ablation is the first-line treatment for any very early HCC (<2 cm), except for those subcapsular and in contact with Glissonean pedicles. Open AR is the standard for deep-located HCC of 2–3 cm provided liver function is adequate, and for very early deep-located HCC not ap-

Fig. 5. Proposal for a therapeutic strategy in patients with HCC ≤ 3 cm and preserved liver function. AR, anatomic resection; Lap, laparoscopic; RFA, radiofrequency ablation; MWA, microwave ablation.

Table 2. Proposal for therapeutic strategy according to HCC size and tumor location

Tumor location			First-line treatment	
			HCC ≤ 20 mm	HCC 21–30 mm
Left liver	Subcapsular		Laparoscopic limited resection	
	Intraparenchymal	In contact with Glissonean pedicle	Laparoscopic/open anatomic resection	
		Not in contact with Glissonean pedicle	Thermal ablation	Laparoscopic/open anatomic resection
Right liver	Subcapsular		Laparoscopic limited liver resection	
	Intraparenchymal	In contact with Glissonean pedicle	Open anatomic resection Laparoscopy in expert centers	
		Not in contact with Glissonean pedicle	Thermal ablation	Open anatomic resection Laparoscopy in expert centers

proachable with an adequate safety by thermal ablation, as those in contact with Glissonean pedicles. LLR is the standard for any subcapsular solitary small HCC, given the approximation of non-AR to AR for such tumor presentation. For segments 2, 3, and 4 inferior, laparoscopic AR should be the suitable approach. Although difficult locations and complex right-sided resections remain in majority of cases performed by open surgery, such resections are increasingly reported laparoscopically by expert surgeons. Surgeons who are expert in both open and

laparoscopic surgery, must improve their surgical technique. The evolution of devices and surgical standardization will improve the quality of such resections in the future. Figure 5 and Table 2 summarize the proposed therapeutic strategy.

Disclosure Statement

The authors declare that they have nothing to disclose.

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