

Minimally Invasive Approach for Multiple Hepatocellular Carcinoma

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Contributor: Gianluca Cassese , Ho-Seong Han , Jai Young Cho , Hae-Won Lee , Boram Lee , Roberto Ivan Troisi

The best therapy for patients with multiple hepatocellular carcinoma (HCC) within the Milan Criteria is liver transplantation (LT). Unluckily, LT cannot be offered to all the patients. For the intermediate staged multiple HCC trans-arterial chemoembolization (TACE) still remains the treatment of choice. However, a growing body of evidence is showing better outcomes after surgery than TACE. Trans-arterial radioembolization and stereotaxic body radiation therapy can also play an important role in this setting. Furthermore, the role of minimally invasive liver surgery (MILS) for patients with multiple HCC is still debated.

multiple hepatocellular carcinoma

multinodular hepatocellular carcinoma

laparoscopic liver resection

1. Introduction

Hepatocellular carcinoma (HCC), with an estimated incidence of around 900,000 cases per year, accounts for the seventh most common cancer worldwide and the third leading cause of cancer-related death ^[1]. HCC prognosis is related to the stage of diagnosis, reaching 5-yr overall survival rates (OS) of 50–70% at early stages due to technical and technological advances as well as improvements in perioperative management ^[2]. However, recurrence still represents a major issue, with a rate of 70% after liver resection (LR) and 20% after liver transplantation (LT) ^[3].

Surgery represents the cornerstone treatment for HCC. LT is the best therapeutic option, aiming to treat both HCC and underlying chronic liver disease, including liver cirrhosis. Nonetheless, owing to the organ shortage, there is a long waiting time carrying a high risk of dropout for tumor progression ^[4]. Accordingly, both LR and thermal ablations (TA) are actually considered the first-line strategy for well-compensated HCC patients according to all Western guidelines. LT is essentially reserved for patients who are not candidates for LR due to impaired liver function or for patients with negative prognostic factors on specimen examination after a previous resection ^{[5][6]}.

Among the different risk factors of HCC recurrence, an important role is played by the number of tumors. Indeed, the tumor number is an important parameter within all selection criteria for LT. Classically, the Milan criteria are the most widely used transplant criteria, and they restrict the applicability of LT to patients with fewer than three nodules, all smaller than 3 cm ^[7]. Similar restrictions are indicated by the University of California San Francisco criteria (UCSF) as well as the up-to-seven criteria that are even more rigid ^{[8][9]}. Thus, the therapeutic management

of patients with multiple HCC who do not meet such criteria is still debated; the same applies to HCC patients who meet the criteria but with little possibility of receiving an organ in the short time. According to the most recent European recommendations, LR is indicated for very early and early stages of the Barcelona Clinic Liver Cancer staging system (BCLC 0/A), while TA is recommended in cases of bi- or tri-focal tumors ≤ 3 cm, if LT is not feasible [10]. For more than three nodules, patients are staged as BCLC-B, and they are recommended to undergo trans-arterial chemoembolization (TACE). However, the latest guidelines from the National Comprehensive Cancer Network (NCCN) recommend LR also in cases of multiple HCCs [11]. Furthermore, Asian guidelines also suggest LR for multinodular HCC [12].

In this scenario, the laparoscopic approach has widely spread in liver surgery, becoming the standard of care in referral tertiary centers [13][14]. However, there are some challenging situations in which the role of laparoscopic liver resection (LLR) is still debated, and the resection of multiple HCC is definitely one of them [15].

2. Minimally Invasive Approach for Multiple Hepatocellular Carcinoma

The role of minimally invasive liver surgery (MILS) in multinodular HCCs is an important open issue. All the available literature comes from third-level referral centers. In 2012, one group published the first experience on LLR for multiple HCC [16]. Among 260 patients, the outcomes of LLR or LLR + TA were compared between patients with single tumors vs. multiple tumors. The two cohorts had comparable clinical and pathologic characteristics, except for a higher rate of previous TACE in the multiple HCC group. No significant differences were found in the rate of intraoperative transfusion, length of postoperative hospital stay, mean operative time, or postoperative complications. Obviously, laparoscopic TA was more commonly used for multiple HCCs. No significant difference in OS was found after a median follow-up of 33.7 months, but disease-free survival (DFS) was lower in the group with a single lesion.

A further propensity-score matching (PSM) study enrolling 150 patients reported similar complication rates, as well as OS ($p = 0.502$) and DFS ($p = 0.887$) between LLR and open liver resection (OLR) for multinodular HCC, with a significantly shorter length of hospital stay after LLR (median, 7 vs. 8 days, respectively, $p = 0.014$) [17].

LLR for multinodular HCC should be safe and feasible. However, some precautions are essential to reaching adequate oncologic outcomes, such as a high expertise in ultrasonography-guided parenchymal dissection with intraoperative ICG-guided fluorescence that can further help detect HCC nodules and guide difficult parenchymal dissection, while 3D-high definition scopes could represent an additional supportive visual tool [18][19]. Further technological research is supposed to help surgeons in this scenario, such as the application of 3-D preoperative modeling and virtual realities, which could also be beneficial in this context [20].

Finally, an interesting recent PSM study compared LLR and OLR for BCLC-B patients with resectable multiple HCC, showing better perioperative outcomes for the minimally invasive approach in selected patients [21]. In particular, median estimated blood loss (200 vs. 350 mL, $p = 0.005$) was lower after LLR, with similar complication

rates ($p = 0.035$), OS ($p = 0.827$), and DFS ($p = 0.694$). The mean operation time was shorter after OLR (237.5 vs. 210 min, $p = 0.024$). Interestingly, the rate of postoperative ascites was 0% after LLR in the BCLB-B patients vs. 11.3% after OLR ($p = 0.06$).

In conclusion, in high volume referral centers, LLR (\pm TA) should be considered in cases of multinodular HCCs suitable for LR, because of the potential advantages over OLR, particularly in the subset of Child-B cirrhotic patients [22]. A personalized strategy, with the combination of LLR and TA, should always be proposed to overcome some technical issues about deep and posterior lesions while maintaining the advantages of a minimally invasive approach [23]. More robust studies are needed to support clinical practice.

The Role of Robotic Liver Resection

Although robotic surgery is rapidly expanding in minimally invasive liver surgery, there are still concerns about long-term outcomes, especially for complex procedures such as multiple resections [24]. In such cases, the robotic platform can provide useful tools for the visualization of the multiple lesions, such as high-definition ICG-fluorescence thanks to the *firefly* system, as well as the 3D navigation integration *tylepro* program [25].

There are still no studies in the literature focusing specifically on the robotic approach for multiple liver tumors, including HCC. However, the most recent series include resection of multiple HCC in their population and show very encouraging results [26]. Indeed, robotic liver resection (RLR) can ideally overcome some limitations of LLR, such as the lack of flexibility of the operating instruments, due to the ability to articulate the instruments because of the 360° of freedom for the surgeon's wrist and a magnified high-definition vision, as well as to considerable ergonomic advantages [27][28]. Recently, a meta-analysis including 487 RLR concluded for lower bleeding rates after RLR at the expense of a longer operation time [29].

Therefore, some advantages could be cautiously hypothesized for multiple HCC, but more evidence is required. Furthermore, the expensive costs and the organizational and logistic aspects are still important drawbacks for the further expansion of the indications of RLR.

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