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From minimal to maximal surgery in the treatment of hepatocarcinoma: A review

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Abstract

Hepatocellular carcinoma represents one of the most challenging frontiers in liver surgery. Surgeons have to face a broad spectrum of aspects, from the underlying liver disease to the new surgical techniques. Safe liver resection can be performed in patients with portal hypertension and well-compensated liver function with

a 5-year survival rate of 50%, offering good long-terms results in selected patients. With the advances in laparoscopic surgery, major liver resections can be performed with minimal harm, avoiding the wound and leak complications related to the laparotomies. Studies have shown that oncological margins are the same as in open surgery. In patients submitted to liver resection (either laparoscopic or open) who experience recurrence, re-resection or salvage liver transplantation has been showing to be an alternative approach in well selected cases. The decision making approach to the cirrhotic patient is becoming more complex and should involve hepatologists, liver surgeons, radiologists and oncologists. Better understanding of the different risk factors for recurrence and survival should be aimed in these multidisciplinary discussions. We here in discuss the hot topics related to surgical risk factors regarding the surgical treatment of hepatocellular carcinoma: anatomical resection, margin status, macrovascular tumor invasion, the place of laparoscopy, salvage liver transplantation and liver transplantation.

Key words: Hepatectomy; Liver resection; Cirrhosis; Liver transplantation; Hepatocellular carcinoma; Survival

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Core tip: The decision making approach to the cirrhotic patient with hepatocellular carcinoma (HCC) represents one of the most challenging frontiers in liver surgery and, as a result, should involve a multidisciplinary assessment. Despite the advances in non-surgical therapies, surgery is still the treatment that can offer the best survival. In patients submitted to liver resection who experience recurrence, re-resection or salvage liver transplantation has been shown to be an alternative approach in well-selected cases. We herein discuss some controversial topics regarding the surgical

treatment of HCC: anatomical resection, margin status, macro-vascular invasion, laparoscopic resection, salvage liver transplantation and liver transplantation.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fifth most common malignancy worldwide^[1,2]. In about 90% of cases, it occurs in patients with chronic liver disease^[2,3]. In recent years there has been a clear increase in the number of new cases of HCC due to hepatitis B and C infection^[3,4].

Although focal ablation techniques can treat small HCCs, the only curative therapeutic options available are surgical resection and liver transplantation (LT). Controversial aspects regarding to the surgical treatment of HCC include the extent of resection, whether it should be achieved by laparoscopic or open approach and their impact on subsequent LT. The question of resection or transplantation and the impact of laparoscopic liver resection (LLR) needs to be addressed. We here in discuss the role of laparoscopic (minimal) and open liver resection and LT (maximal) in the treatment of HCC carcinoma in cirrhotic patients.

LIVER RESECTION

Liver resection, a therapeutic alternative that can be performed readily and with lower costs when compared to LT, is a safe procedure with mortality rates in specialized centers lower than 5%^[5]. Survival after liver resection can reach 40%-60% in Eastern and Western series^[6], but recurrence is still a major problem. Recurrence occurs in the liver in around 50%-80% of the cases, being consequence of metastatic spread from the tumor removed or “*de novo*” occurrence due to underlying liver disease^[7-9].

In the context of a rising incidence of HCC and a shortage of cadaveric donors, there is a growing discrepancy between the number of transplant candidates on waiting lists and the organs available for transplantation. This shortage can lead to long waiting times, increasing the risk of tumor progression and waiting list drop out^[10]. Studies comparing resection and transplantation for HCC have often analyzed only those patients who underwent transplantation-ignoring those patients who dropped off the waiting list due to tumor progression. This approach will tend to produce results in favor of transplantation. To be fair, an intention to treat analysis should be

performed^[11].

Resection has the advantages of being readily accessible and cheaper when compared to transplantation and doesn't preclude a future liver transplant in the case of tumor recurrence (salvage LT). Moreover, due to advances in surgical technique (mainly laparoscopic approach), care and patient selection, it has become a safe procedure, with mortality rates in specialized centers lower than 5%^[12,13]. Good long-term results can be achieved (50%-70% 5-year overall survival) in selected patients^[14].

However, resection is followed by high rates of morbidity and mortality in patients with chronic liver disease, being possible only in patients with preserved liver function^[15]. In the context of long transplant waiting lists, some groups specialized in both liver surgery and transplantation have advocated resection for the treatment of solitary HCC in patients with preserved liver function^[14,16].

It has also been shown that in patients within the Milan criteria, the long-term outcome of those listed for LT (intention to treat analysis) was similar when compared to patients who underwent resection^[17]. A recent meta-analysis including studies using case controlled and intention to treat analysis showed that resection and transplantation lead to similar 5-year overall survival (OR = 0.84, 95%CI: 0.48-1.48, $P = 0.45$)^[18].

Laparoscopic vs open liver resection

LLR is now considered the gold standard by many specialized hepatobiliary teams for the treatment of selected cases of benign and malignant liver tumors. Its feasibility and safety are reproducible by teams all over the world^[19]. Recent series of laparoscopic resection of HCC have shown excellent short and long terms results^[16,20-29]. A recent meta-analysis showed that LLR resulted in to shorter hospital stay, decreased blood loss, and lower rates of postoperative morbidity (specially ascites and pulmonary complications) when compared to open liver resection^[12,16,21,22].

Despite selection bias in the laparoscopic group, rates of positive margins after LLR were lower than or similar to those after open approach^[30]. An increase in peritoneal carcinomatosis and port site recurrence does not seem to have been a major issue^[18]. Finally, in all studies comparing laparoscopic and open LR for HCC, there was no significant difference in recurrence free and overall survival, suggesting that LLR does not compromise oncological principles.

Anatomical vs non-anatomical resections

LR for HCC can be either anatomical (lobectomy, segmentectomy) or non-anatomical (wedge resection, subsegmental resection). In HCC, intrahepatic metastasis occurs mainly through the portal tract, and may be present before surgery. It has been proposed that the intrahepatic spread of hepatic tumors follows the pattern of step-by-step intrahepatic dissemination^[31]. With small

tumors and early metastases, satellite nodules usually lie in the same segment of the main tumor. The anatomical approach is particularly important for the purpose of reducing postoperative intrahepatic tumor recurrence rates.

Anatomical resection, when possible, should be performed^[32]. A recent study using meta-regression analysis indicated that the 5-year overall survival and disease-free survival are significantly better with anatomical resection^[33]. Recent paper including 543 patients treated with HCC addressing this issue concluded that anatomical resection can lead to a lower recurrence rate in patients presenting tumors with unfavorable features (poorly differentiated and with vascular invasion), suggesting that the higher the invasiveness of the tumor, the greater the need for the removal of the entire liver functional unit^[34].

On the other hand, when dealing with cirrhotic patients, leaving sufficient residual liver volume is critical. For small liver HCCs, non-anatomical resection can be carried out without impact on the overall survival^[35]. The rationale for this approach is that it may lead to a decrease in the rate of postoperative liver failure and that for small lesions, the risk of local satellites or local portal venous invasion is lower than for lesions more than 5 cm in diameter^[36].

Margin status

The optimal resection margin for HCC remains controversial. In a randomized trial comparing a wide 2 cm margin with a margin aiming for 1 cm, improved recurrence-free and overall survival were observed in the wide margin group. However, it is accepted that a 1 cm surgical margin is adequate for the majority of patients with HCC^[37]. On the other hand, other authors found that a minimal resection margin (surgical margin less than 1 mm) did not negatively affect postoperative recurrence-free survival^[37]. In a recent meta-analysis, Zhou *et al.*^[38] showed no differences in surgical margins when comparing the open with the LLR group.

Surgeons who are less familiar with liver surgery may be inclined to perform less radical resections. This may represent a lost opportunity for some patients who may have had better long-term prognoses with more radical surgery. In order to minimize the risk of local recurrence and maximize the overall survival chance, a surgical strategy that supports the preference for anatomical and adequate resection with free margins should be adopted whenever possible.

Repeated liver resection

Although not properly addressed in a prospective trial, repeated hepatic resection in patients with solitary liver recurrence resulted in better survival than palliative treatment (37%-86% in 5 years)^[39]. The resectability rate varies and depends on the extent of primary resection and the functional status of the remnant liver^[40] and even repeated laparoscopic resection can be carried out in selected patients^[41]. Poor prognostic factors associated

with repeated liver resection for HCC are: vascular invasion in the primary surgery, short recurrence interval, tumor size, gender, estimated blood loss^[39,40,42].

Vascular invasion

Vascular invasion is a well-defined prognostic factor for overall and disease free survival in patients with HCC either submitted to resection or transplantation^[43,44]. Macrovascular invasion is considered a formal contraindication to resection and invariably patients with macrovascular invasion submitted to LT suffer from recurrence. As proposed by the barcelona clinic liver cancer, patients with macrovascular invasion are sent for palliative treatment (Sorafenib) or best supportive care^[43,44]. Overall survival for patients with portal vein invasion or hepatic vein invasion is 2.7 mo and 5 mo, respectively. The overall survival for patients treated with Sorafenib is 6 mo^[43-45].

Although not universally accepted, liver resection for HCC with macrovascular invasion may be an option in highly selected patients, in whom a survival of around 10% in 5 year can be offered. Equivalent survival is not achievable with other forms of treatment. In recent surgical series including HCC patients with macrovascular invasion, the postoperative mortality and morbidity ranges from 3.4% to 7.7% and from 30.8% to 37.1%, respectively^[46]. In a multicentric study on 102 HCC patients with macrovascular invasion treated by surgical resection, Pawlik *et al.*^[47] reported a 5-year survival rate of 10%.

Chok *et al.*^[46] described the following three approaches for patients with portal vein thrombus based on the extension of the tumor thrombosis: group 1, HCC with ipsilateral portal vein tumor thrombus resected in a hepatectomy; group 2, HCC with portal vein tumor thrombus extending to or beyond the portal vein bifurcation, treated by en bloc resection followed by portal vein reconstruction; group 3, portal vein tumor thrombosis extending to or beyond the portal vein bifurcation, treated by thrombectomy. The short and long-term results were similar among the three groups with a 5-year overall survival rate of 11.2%, 12.5% and 14.3%, respectively^[46].

After HCC resection, the hepatic remnant is the most common site of tumor recurrence ranging from 68% to 91% of patients so a close follow up strategy should be adopted^[48]. While macroscopic vascular invasion can be detected at imaging, microscopic vascular invasion is impossible to visualize before operation. The presence of microvascular invasion can only be confirmed by histological examination of resected specimen.

LT

LT has become a standard procedure adopted worldwide in the treatment of end stage liver disease with remarkable good results, even for malignancy (1 year overall survival of > 80% and 5-year around 70%)^[49]. LT

has the advantage of removing the previous and potential carcinogenic diseased liver but has the disadvantage of organ allocation.

LT vs liver resection

The choice between LT and resection (LR) is controversial and there are no controlled trials comparing these modalities. Although some can argue that resection is cost effective when compared with LT^[50], only LT has the advantage of simultaneously treating the tumor and the underlying liver disease^[51]. To achieve good results with transplantation, it is only offered to patients with liver only disease fulfilling strict criteria^[51-53]. There is considerable variation around the world in what criteria are used to assess transplant eligibility^[52-55].

For many patients with cirrhosis and HCC, the ideal treatment is transplantation-treating the underlying liver condition and at the same time removing the tumor. This also reduces the “*de novo*” formation of cancer. It is crucial to be selective in choosing patients with HCC for transplantation, with many criteria in use around the world. Most criteria use radiological parameters such as tumor size and number as a surrogate marker for biological behavior^[52,54-60].

Unfortunately many patients are delisted for transplantation due to progression of the underlying liver disease or tumor progression (beyond the accepted criteria). When comparing survival between LT and LR, many studies have commenced at the time of the transplant and fail to include analysis of the patients removed from the waiting list due to tumor progression (*i.e.*, not an intention to treat analysis). For optimal evaluation of the treatment effect of LT, the waiting time on the list should be included.

Llovet *et al.*^[45] found a dropout probability of 23%. This resulted in a reduction of 2-year overall survival from 84% to 54%. Waitlist time can serve as a selection period for patients with the best prognosis, because only patients with stable disease undergo transplantation. This might explain the higher recurrence-free survival after LT than in resected patients who did not undergo this selection process. Another reason for better overall survival in different studies might be that LT represents a cure for the underlying cirrhosis, which is the main risk factor for development of HCC. The recurrence rate is higher after LR than orthotopic liver transplant. Given the shortage of deceased donor organs, transplantation for resectable HCC may be considered by some groups an inappropriate use of a precious resource if LR alone in selected cases could achieve a similar overall survival, and together with salvage LT may cure recurrence^[18].

For patients with HCC beyond transplant criteria, the Barcelona Clinic Liver Cancer (BCLC) system recommends palliative treatment^[61]. Although this system is widely accepted, if followed strictly there are patients who may be denied a curative liver resection and treated with palliative intent with trans-arterial chemoembolization. Many studies criticizing this policy have shown 5-year overall survival

of 50% even in patients with large HCC or in patients with multiple nodules^[62].

Ruzzenente *et al.*^[63] conducted a study on 464 HCC patients from a multi-institutional database and found that patients with fewer than three nodules who underwent LR had a higher survival rate than those who were treated with local therapies [including percutaneous ablation and transarterial chemo-embolization (TACE)] with median survival of 58 and 20 mo ($P < 0.01$), respectively. These findings were confirmed by a subsequent randomised controlled trial. In patients with HCC meeting Milan Criteria, the authors reported a 5-year survival rate after liver resection and radiofrequency ablation of 69% and 45% ($P = 0.042$), respectively^[64].

A Japanese national survey reported that liver resection has an advantage over local ablative therapies because it can prevent recurrence in individuals with fewer than three HCC nodules that are ≤ 3 cm^[65]. Liver resection also appears to provide better long-term survival than percutaneous ablation in patients with less than 3 HCC nodules that are > 3 cm.

In selected patients with multinodular BCLC B (more than 3 nodules) HCC and preserved liver function, LR yielded better long-term results than TACE with 5-year survival rates of 36%-37% and 11%-14%, respectively^[62].

Salvage LT

The major drawback of LR is a recurrence rate of about 40% in the first year^[66]. Despite this, most authors have shown that those patients can be referred for salvage LT^[67-70]. With this strategy, HCC patients who had undergone liver resection with pathological parameters at higher risk of recurrence (*i.e.*, microvascular invasion, satellite nodules) could enter the waiting list for LT directly without waiting for evidence of HCC liver recurrence^[71]. On the other hand, Fuks *et al.*^[72] have shown in 329 transplantable patients enrolled in an intention to treat study that the presence of ≥ 3 poor prognostic factors (from a list of microscopic vascular invasion, presence of satellite nodules, tumor size > 3 cm, poor tumoral differentiation, and existence of cirrhosis) should warrant LT before recurrence. This strategy seemed to save 26 grafts that would otherwise have been used unnecessarily. However only 28% of patients included in intention-to-treat analysis and only 39% of patients with recurrence could receive ST, suggesting that tissue analysis should be used as selection criteria for salvage LT^[72]. Whether this policy is clinically effective and would further improve the long-term outcomes of resected patients remains to be evaluated in prospective trials.

Belghiti *et al.*^[73] showed that patients submitted to salvage transplantation have the same long-term results as those submitted to transplantation as the primary treatment. Indeed, Cherqui *et al.*^[74] have shown that 77% of patients with recurrent HCC following LLR were transplantable (within Milan criteria). The same group found that the morbidity of salvage LT for HCC was lower following LLR, than open LR^[75-77]. Some surgeons

argue that adhesion formation and previous hilar manipulation associated with LR can make subsequent LT difficult or even impossible. However, strategies such as Glissonian approach and the use of Pringle maneuver and intraparenchymal access to liver pedicles to avoid hilar manipulation can be employed in order to decrease the morbidity of repeat liver surgery. The use of anti-adhesive products (Seprafilm®) although proved to facilitate bowel surgery^[78] have not been addressed in a randomized trial for liver surgery.

The impact of laparoscopic liver resection *vs* open resection on subsequent LT has not yet been analysed in prospective trials. Theoretical advantages of minimal dissection are less adhesions, minimal manipulation in liver hilum and decreased blood loss^[79-81].

CONCLUSION

The main endpoint in the surgical treatment of HCC is to resect the tumor and at the same time preserve remnant liver function. This should be performed with refined techniques and respecting the oncological principals of any cancer surgery. Liver resection and LT are the only curative treatment of HCC. Meanwhile, there are some strategies to increase resectability or to downstage the tumor, such as portal vein embolization, TACE or radiofrequency ablation/percutaneous ethanol injection. Laparoscopic liver resection has gained acceptance and decreases post-operative complications (less ascites and wound related problems). Surgeons can improve disease-free survival by preventing recurrence adopting many strategies, such as > 1 cm surgical margin, anatomical resection encompassing portal area of tumor, using an anterior approach to minimize the risk of tumor cell dissemination, minimizing intraoperative blood loss. Repeat resection is an option in some suitable cases that can be used in the armamentarium of liver surgeons. Salvage transplantation should be offered in non aggressive tumors that recur after liver resection and may improve survival rates. Future clinical research should reveal the optimal combination of therapies in properly selected patients.

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