

## Surgical management of hepatocellular carcinoma

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restrictive. For early stage tumours, both resection and transplantation offer fairly good survival outcomes (5 years overall survival of around 50%). Selection therefore would depend on the level of hepatic function derangement, organ availability and local expertise. Patients with intermediate stage cancers have limited options, with resection being the only potential for cure. Otherwise, locoregional therapy with transarterial chemoembolization or radiofrequency ablation are viable options. Current issues in resection and transplantation are also briefly discussed such as laparoscopic resection, ablation vs resection, anatomical vs non-anatomical resection, transplantation vs resection, living donor liver transplantation and salvage liver transplantation.

**Key words:** Hepatocellular carcinoma; Liver surgery; Liver resection; Liver transplantation; Laparoscopic liver surgery

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**Core tip:** Surgical management through either resection or transplantation are the only potentially curative treatment for hepatocellular carcinoma. The decision for the management strategy depends on tumour factors, hepatic functional reserve, organ availability, wait time as well as local expertise and resources.

### Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide. Standard potentially curative treatments are either resection or transplantation. The aim of this paper is to provide an overview of the surgical management of HCC, as well as highlight current issues in hepatic resection and transplantation. In summary, due to the relationship between HCC and chronic liver disease, the management of HCC depends both on tumour-related and hepatic function-related considerations. As such, HCC is currently managed largely through non-surgical means as the criteria, in relation to the above considerations, for surgical management is still largely

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is a prevalent cancer. It is estimated, by the World Health Organisation, to affect 782000 people and caused 746000 deaths worldwide in 2012. In fact, it is the second most

common cause of death from cancer worldwide<sup>[1]</sup>. Its incidence is the highest in East and South East Asia, which is related to the prevalence of chronic hepatitis B in these regions. Standard potentially curative treatments for this cancer are either resection or transplantation, although radiofrequency ablation is considered curative therapy in some cases<sup>[2]</sup>. Because of its relationship with liver cirrhosis, the assessment of hepatic function is an important consideration in determining management. It is now well established that liver transplantation is the treatment of choice for early stage HCC in patients with decompensated cirrhosis<sup>[3-5]</sup>.

The aim of this paper is to review the surgical management of hepatocellular carcinoma, as well as highlight current issues in this area.

## SURGICAL RESECTION

Only 10%-37% of patients with HCC are amenable to liver resection at the time of diagnosis<sup>[6-8]</sup>. An Australian study of 235 patients demonstrated that only 17% and 16% of HCC patients were treated with liver resection or transplantation respectively<sup>[9]</sup>. In fact, best supportive treatment was the most common management strategy employed for this cohort. An important aspect of diagnosis in HCC is that there are risk factors which are known to increase the risk of its development. Both the AASLD and EASL-EORTC guidelines recommend 6 monthly surveillance using abdominal ultrasonography in high risk patients, although the definition of which patients are considered high risk varied<sup>[10,11]</sup>. Interestingly, a systematic review of the benefits and harms of HCC screening in patients with chronic liver disease found only poor quality evidence to support the benefits of screening. Of the two randomised controlled trials reviewed, only one demonstrated a survival benefit (ultrasound screening) and one found no difference in all-cause mortality (alpha-feto protein screening)<sup>[12]</sup>.

Improvements in surgical technique and perioperative care have led to a fall in the morbidity and mortality of liver resection over the last two decades. Currently, in high volume centres, the mortality of liver resection is expected to be less than 4%<sup>[13-16]</sup>. There is also evidence to suggest that there is a volume-outcome relationship in hepatic resection surgery<sup>[17]</sup>. Whilst the 5 years overall survival rates of around 50% is now achievable, the recurrence rate remains high which remains an important cause of late deaths<sup>[18,19]</sup>.

The decision for liver resection depends on the assessment of tumour factors, hepatic function and remnant size. With regards to tumour factors, one of the most commonly used staging system in Western countries is the Barcelona Clinic liver Cancer (BCLC) system which classifies patients into early,

intermediate, advanced and terminal stages<sup>[20]</sup>. This system is utilised by both the American Association for the Study of Liver Disease and the European Association for the Study of Liver guidelines on the management of HCC<sup>[21,22]</sup>. According to this system, the surgical treatment of HCC is limited to the early stage cancers, that is, those which satisfy the Milan Criteria (a single HCC  $\leq$  5 cm in diameter or up to 3 HCCs  $\leq$  3 cm in diameter<sup>[5]</sup>) and have good hepatic function (Child-Pugh class A in the absence of portal hypertension) and performance status. However, such a criteria for resection is considered restrictive, for size and number of tumours is not a contraindication for resection provided there is adequate hepatic reserve and that the tumour is resectable. Certainly, long term disease-free survival is possible in these patients<sup>[23]</sup>. Tumour size and number are not the most important factors influencing survival<sup>[9,19]</sup>. In fact, for those patients with HCCs who do not satisfy the Milan Criteria, the only hope of cure is through hepatic resection. Ng *et al.*<sup>[24]</sup> demonstrated that large or multinodular HCC could be safely resected, with a five-year overall survival of 39% and disease-free survival of 26% being achievable. In general, tumours which are extensively multifocal and bilateral, involve the main portal vein or inferior vena cava are considered contraindicated for surgery.

Hepatic function can be classified using a variety of measures. The simplest and most commonly used is the Child-Pugh Score<sup>[25]</sup>. Resection is really only considered in patients with Child A cirrhosis and early Child B cirrhosis. In the former, up to 50% resection may be considered, whilst in the latter, up to 25% resection may be performed. On the other hand, in patients with entirely normal hepatic function with no history of cirrhosis could tolerate the resection of up to 75% of liver parenchyma<sup>[26]</sup>. In Asian countries, the use of ICG clearance at 15 min is also prevalent, with a cut-off of greater than 20% precluding major liver resection<sup>[27,28]</sup>. Model of End-Stage Liver Disease (MELD) score is an alternative score used to classify patients into risk groups. A MELD score of  $<$  9 is associated with minimal perioperative mortality<sup>[29,30]</sup>. In addition to hepatic function, the other aspect which precludes hepatic resection is significant portal hypertension. This can be objectively measured using a transhepatic caval approach (hepatic vein pressure gradient). This is a measure of the pressure difference between the wedged hepatic venous pressure (an estimation of portal venous pressure) and the free hepatic venous pressure (inferior vena caval pressure). A pressure gradient of greater than 10 mmHg is associated with poorer outcomes post resection<sup>[31]</sup>. Other indicators of clinically relevant portal hypertension include splenomegaly, oesophageal varices and thrombocytopaenia.

Given the relevance of liver function on the permitted resection size, the size of the liver remnant is important. This can be measured using CT volumetry<sup>[32]</sup>. If adequate future liver remnant is not achievable, then portal vein embolization (PVE) should be considered. The aim of PVE is to induce compensatory hypertrophy in the non-embolised side. Generally, this is performed by the percutaneous transhepatic approach. A recent meta-analysis has demonstrated that PVE is safe and effective in inducing liver hypertrophy and preventing liver failure<sup>[33]</sup>. It has also been shown to increase resectability<sup>[34,35]</sup>.

It should be noted that the recurrence rate after hepatic resection is high. In a systematic review and meta-analysis of resection vs transplantation, the 5 year disease-free survival rate of resection varied from 18%-51% compared to 54%-84% for transplanted patients<sup>[18]</sup>. In patients with intermediate and advanced stage HCC (multiple tumours or macrovascular invasion), 5 year disease free survival range from 0%-31%<sup>[36]</sup>. Follow-up for recurrence is therefore mandatory and recurrence should be managed using a multimodal approach including re-resection, TACE and ablative therapy.

## CURRENT ISSUES IN HEPATIC RESECTION

### **Laparoscopic liver resection**

With the advent of minimally invasive surgery, there is increasing uptake of the laparoscopic techniques for liver resection. Initially, the experience of laparoscopic liver resection was restricted to benign pathologies, and peripheral lesions/left lateral sectionectomy, although now major resections are being conducted laparoscopically<sup>[37]</sup>. There have been several systematic reviews with meta-analyses on this topic. The most recent and the largest, a meta-analysis of 32 studies by Rao *et al*<sup>[37]</sup>, found that laparoscopic hepatic resection was associated with significantly lower blood transfusion requirements, blood loss and length of stay but longer operating time. The overall complication rate was significantly lower (OR = 0.35,  $P < 0.001$ ) in the laparoscopic group. Whilst overall survival was not different between the two groups, the rate of positive resection margins were found to be lower in the laparoscopic group. Note however, that the vast majority of studies were retrospective studies, with no randomised controlled trials, and therefore there may be significant selection bias. Unsurprisingly, these findings echo those of an earlier meta-analysis of 26 studies<sup>[38]</sup>. However, in relation to oncological outcomes, this meta-analysis analysed HCC outcomes separately to other malignant diseases and found that there was a significant trend for improved overall survival (OR: 1.5 - 1.0-2.2;  $P = 0.049$ ) in the

laparoscopic group. Another meta-analysis restricted only to studies evaluating laparoscopic resection for patients with HCC has demonstrated similar findings - lesser blood loss and blood transfusion requirements, lesser overall morbidity, cirrhotic decompensation and shorter length of stay<sup>[39]</sup>. However, no differences in oncological outcomes (margins and survival) were found. Whilst the above studies point to potential advantages of performing laparoscopic hepatic resection, the major weakness of this systematic review is that the majority of studies included only patients who underwent minor hepatic resections. Their findings therefore may not be applicable to major laparoscopic hepatic resections. The efficacy of major liver resections is still under evaluation although early reports would suggest that they are comparable to the open procedure in terms of short and long term outcomes. For instance, Martin *et al*<sup>[40]</sup> compared 90 laparoscopic hepatectomies (left or right) to case-matched open hepatectomies and found lesser blood loss, lesser use of Pringle manoeuvre, lesser operative time, and lesser incidence of any type of complication. At present there exist only a few case series on robotic major hepatic resections-so while it is possible, the limited experience makes any conclusion about its comparative efficacy and risks difficult to make at the present time<sup>[41]</sup>.

Whilst the above results are encouraging, these should be interpreted with caution as there is likely significant publication and selection biases in the above studies. Also, laparoscopic liver resection has a learning curve, both for the surgeon and the institution<sup>[42]</sup>. Results in centres where such expertise is available may not be generalizable to other centres. For instance, Viganò *et al*<sup>[43]</sup> demonstrated over the course of a 12 year period, operative time, pedicle clamping, blood loss, morbidity and hospital stay all decreased<sup>[43]</sup>. They estimated the learning curve for minor laparoscopic liver resection is 60 based upon cumulative sum analysis on conversion rates. The same group reviewed the major hepatectomies performed laparoscopically at 6 experienced centres around the world and found similar improvements in operative time, conversion rate, blood loss and pedicle clamping<sup>[42]</sup>. A larger study of 365 patients over a 14 year period estimated the learning curve for laparoscopic liver surgery to be in the order of 30-40 cases<sup>[44]</sup>.

### **Ablation vs resection**

The alternative to resection in early HCC (satisfying Milan criteria) is ablation, either percutaneous ethanol injection (PEI), radiofrequency (RFA) or microwave ablation. In theory, ablation could treat a tumour of up to 5 cm in diameter - a size which correlates with the Milan criteria. Indeed, the European Association for the Study of the Liver

(EASL) and the European Organisation for Research and Treatment of Cancer (EORTC) guidelines suggest that ablation with either radiofrequency ablation or percutaneous ethanol injection is recommended as standard of care for patients with BCLC stage 0 or A who are unsuitable for surgery<sup>[11]</sup>. A recent meta-analysis analysing outcomes from three randomised controlled trials and 25 non randomised studies has suggested little difference in survival or recurrence early after intervention but at 5 years, significantly different survival began to be observed. This appeared to be more pronounced in larger tumours than smaller ones and more in the non-randomised studies than the randomised trials. Consistently however, the complication rate and length of stay favoured RFA<sup>[45]</sup>. Another recent systematic review which pooled the findings of 6 randomised controlled trials and 4 cohort studies comparing RFA/PEI to resection came to the same conclusion - that early outcomes (survival and recurrence) were equivalent (at one-year) but the differences became more pronounced with longer duration of follow-up. This seemed to apply even for small cancers (tumour size  $\leq 3$  cm). Complication rates however significantly favoured ablative therapy<sup>[46]</sup>. Therefore one can conclude that in appropriately selected patients, surgical resection is the preferred management even for small cancers although ablative treatment had the advantage of lower morbidity.

#### **Anatomical vs non-anatomical resection**

The debate surrounding anatomical vs non-anatomical resection remain a controversial one. In theory, hepatocellular carcinomas recurrence is strongly related to microvascular tumour emboli, therefore, resection of the vascular territory of the tumour makes oncological sense<sup>[47]</sup>. On the other hand, HCC often occurs in cirrhotic livers and the preservation of hepatic parenchyma to prevent postoperative liver failure suggests a non-anatomical approach. Indeed, numerous studies have been performed to elucidate the benefits of either approach, but none in a randomised fashion<sup>[48]</sup>. Two meta-analysis of these non-randomised studies favoured anatomical resection although only one found statistically significant difference between the two groups in terms of both overall and disease-free survival<sup>[49,50]</sup>. To further complicate one's understanding of this debate, a meta-regression performed by Cucchetti *et al*<sup>[48]</sup> demonstrated that much of the heterogeneity of overall and disease-free survival results arose from the presence or absence of cirrhosis as a covariate. That is, non-anatomical resection had poorer outcomes because of the higher prevalence of cirrhosis in that group<sup>[48]</sup>. Hence, only a randomised trial whereby the baseline characteristics are randomised can we make any final conclusions regarding this ongoing debate. An

interesting addition to the debate comes from the development of preoperative 3D simulation, which facilitates subsegmental and segmental anatomical resection, potentially allowing anatomical resection to be performed in patients who have limited hepatic reserve and allowing for a quality indicator of success or otherwise of anatomical resection<sup>[51]</sup>.

## **LIVER TRANSPLANTATION**

The first successful liver transplantation in humans was performed in 1967<sup>[52]</sup>. The attraction of using liver resection to manage HCC is that not only is the HCC treated with maximal resection margins, the underlying liver disease (and hence, premalignant field change) is also treated. In a landmark paper by Mazzaferro *et al*<sup>[5]</sup>, the Milan criteria were established in 1996. Mazzaferro *et al*<sup>[5]</sup> described that patients operated within this criteria had excellent outcomes post liver transplantation which were comparable to those of patients operated on for non-cancer indications. The overall and recurrence-free survival rates at 4 years were 85% and 92% respectively<sup>[5]</sup>. This criteria was subsequently expanded by the University of California San Francisco (UCSF) group who nonetheless demonstrated equivalent excellent outcomes - 5 year survival of 72%<sup>[53]</sup>. These results have been validated in the Australian/New Zealand cohort by Chen *et al*<sup>[54]</sup>, who demonstrated a 5 year survival rate of 74% and 73% in those satisfying the Milan and UCSF criteria respectively<sup>[54]</sup>. Those outside Milan or UCSF criteria were found to have significantly poorer outcomes. On the other hand, the use of UCSF criteria as preoperative selection criteria was found by a French group to have resulted in a 5 year survival of less than 50% despite a short waiting time<sup>[55]</sup>.

Other complications of transplantation include rejection as well as complications from immunosuppression may limit the long term survival of transplant recipients<sup>[56]</sup>. The major limitation of liver transplantation in the treatment of HCC is the limited availability of donor livers. These patients with HCC also compete with non-cancer patients for transplants. As a result, strict listing criteria are used, such as mentioned above, to limit transplantation to those patients whose outcomes are comparable to those who do not have HCC. In the context of donor shortage, it is often accepted that transplanted patients should have 5 year survival rates of at least 50%. Unfortunately, whilst outcomes of transplantation are good, the potentially significant period on the waiting list may lead to dropout due to disease progression. This could be as high as 25%-38% in 12 mo, although it is highly variable<sup>[55,57,58]</sup>. In fact, studies included in a recent systematic review reported median time to transplantation varying from 30 to 231 d<sup>[18]</sup>.

## CURRENT ISSUES IN LIVER TRANSPLANTATION

### ***Liver resection vs liver transplantation***

The question of whether liver transplantation or liver resection is more efficacious in the treatment of HCC depend very much on the clinical scenario. For instance, for the patient with early HCC with inadequate hepatic reserve for resection, transplantation may be the only potentially curative option. On the other hand, a patient with a large HCC but with preserved hepatic function would only have resection as the curative option. The controversial case is of patients with early HCC with well compensated cirrhosis. In this case, not only are the outcomes of resection and transplantation important, the availability of donor livers, and therefore the dropout rate is highly relevant. Analysis of survival on an intention-to-treat basis would be more reflective of the relative efficacy of each treatment strategy in the real world. There have been some recent meta-analyses conducted to evaluate the question of relative efficacy. Rahman *et al.*<sup>[18]</sup> in 2012 looked at nine studies comparing liver resection and transplantation for early stage HCC<sup>[18]</sup>. The key finding was that all these studies were retrospective and only a few reported intention-to-treat survival data for the transplantation group. Five-year overall survival ranged from 40%-70% for resection and 52%-81% for transplantation. Pooling of data from studies which conducted intention-to-treat survival analysis demonstrated no significant difference in survival between the two treatment strategies at 5 years. Another meta-analysis on an intention-to-treat basis also found no significant difference between the outcomes of the two groups<sup>[59]</sup>. The other key finding highlighted by these two systematic reviews is the lack of prospective/randomised or even simply well-matched studies in the literature. Certainly, as yet there are no randomised controlled trials to guide treatment<sup>[60]</sup>.

### ***Living donor liver transplantation***

With the limitation of the availability of cadaveric liver transplants, there is increasing interest in the use of living donor liver transplant (LDLT). Clearly this requires the donation of a liver graft from a donor - a procedure not without its risks. The risk of mortality is estimated to be 0.1% for donor left hepatectomy and 0.5% for donor right hepatectomy; with a morbidity rate of up to 20%<sup>[61,62]</sup>. This risk to the donor, without direct beneficial effects to the person also brings about an ethical dilemma to transplant surgeons and physicians alike - "first do no harm". However, the advantage of LDLT is that as the liver is obtained outside the usual donor pool, this strategy expands the number of organs available for transplantation. As a result, the criteria

for liver transplantation can often be extended beyond the usual Milan or UCSF criteria. The Kyoto criteria ( $\leq 10$  tumours, less than 5 cm, PIVKA-II  $\leq 400$ ) and "up-to-seven" criteria are examples of extended transplant criteria which have been used in the context of living donor transplants<sup>[63,64]</sup>. Using a decision analytical model taking into account the risk of dropout while waiting (4% per month), the expected survival of the recipient (70% at five years) and the risk for the donor (0.3% to 0.5% mortality), Sarasin *et al.*<sup>[65]</sup> demonstrated that patients with HCC waiting more than seven months for a deceased donor liver would benefit from LDLT. Early reports have suggested a higher recurrence rate in LDLT as compared to Deceased donor liver transplantation (DDLT), however, this is hypothesised to be due to the "fast-tracking" of LDLT which therefore allowed transplantation of patients with more aggressive HCC<sup>[61]</sup>. Two recent meta-analysis of LDLT vs DDLT were reported. These found overall survival rates to be similar between the two groups. One of these, by Grant *et al.*<sup>[66]</sup> found LDLTs to be associated with decreased disease-free survival rates. On the other hand, Liang *et al.*<sup>[67]</sup> performed a subgroup analysis of patients within the Milan criteria and found similar survival outcomes between the two groups.

### ***Bridging therapy and salvage liver transplantation***

Out of the need to minimise dropout during waiting, strategies such as bridging therapy or resection with salvage transplantation has been developed. Bridging therapies such as RFA or TACE are frequently used. Whilst bridging therapy does seem to be useful in decreasing dropout rate whilst awaiting transplant, its role in improving survival after transplantation has not been established<sup>[68]</sup>. An alternative strategy to primary transplantation is primary resection followed by salvage transplantation. The advantage to this is to minimise the need for organs and to use resection as the ultimate bridging therapy to prevent progression whilst waiting for transplantation. A recent systematic review of 16 studies found that of those 7 studies which reported salvage transplant rates, the median rate of salvage transplantation was 41% after a median time to recurrence of 21 mo<sup>[69]</sup>. Whilst a meta-analysis was not performed, they found a median 5 year survival to be 67%. Interestingly, half of studies reported a mortality rate of higher than 5% and two studies reported mortality rates of greater than 10%<sup>[70,71]</sup>. A meta-analysis by Zhu *et al.*<sup>[72]</sup> analysed 14 studies, of which 10 overlapped with Chan's systematic review. Zhu *et al.*<sup>[72]</sup> found that compared to primary liver transplantation, salvage liver transplantation was associated with longer operative time, greater blood loss but failed to find a significant difference in postoperative mortality. With regards to long term survival, primary liver transplant was found to have

better five-year disease free survival but not overall survival<sup>[72]</sup>. These results would suggest that salvage liver transplant is a viable strategy in appropriately resourced transplant centres.

## CONCLUSION

HCC is currently largely managed through non-surgical means as the tumour-related and hepatic function considerations for surgical management is still largely restrictive. For those who have tumours eligible for surgical therapy from the tumour point of view (early stage tumours), those with good hepatic function and significant functional liver remnant would be candidates for either resection or transplantation depending on local resources. Those with poor hepatic function may be placed on the liver transplant list, with or without bridging therapy. Patients with intermediate stage cancers have limited options, with resection being the only potential for cure. Otherwise, regional therapy with TACE or RFA are viable options. With further development of surgical techniques, including salvage liver transplantation, the indications for surgical management of HCC may continue to expand. With this, the outcomes of HCC may further improve.

Surgical therapy is the only curative hope for patients with HCC. The selection of patients for transplantation and resection will depend on local resources, but both have potentially good outcomes in appropriately selected patients.

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