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TOPIC HIGHLIGHT

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Hepatocellular carcinoma: Defining the place of surgery in an era of organ shortage

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Abstract

Liver resection (LR) and transplantation offer the only potential chance of cure for patients with hepatocellular carcinoma (HCC). Historically, all patients were treated by hepatic resection. With the advent of liver transplantation (LT) patients with HCC were preferentially placed on the waiting list for LT. However, early experience with LT was associated with a high rate of tumour recurrence and poor long-term survival. The increasing scarcity of donor livers resulted in restrictions being placed on tumour size, and an improvement in patient survival. To date there have been no randomised clinical trials comparing LR to LT. We review the evidence supporting LR and/or LT for HCC and discuss the role of neoadjuvant therapy. The decision of whether to resect or transplant remains debatable and is often determined by centre experience, availability of LT and donor organs.

Key words: Hepatocellular carcinoma; Liver transplantation; Liver resection; Adjuvant therapy; Salvage liver transplantation; Radiofrequency ablation; Transarterial chemoembolization

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INTRODUCTION

Liver resection (LR) has been the only potentially curative treatment available for hepatocellular carcinoma (HCC). With the advent of liver transplantation (LT) as a clinical modality patients with HCC were preferentially placed on the waiting list for transplantation[1]. To date, there have been no randomised clinical trials comparing LR to LT in patients with potentially resectable HCC (Child-Pugh A, wedged hepatic venous pressure < 10 mmHg)[2]. The decision of whether to resect or transplant is often determined by centre experience and the availability of LT. Unfortunately, the majority of patients have extensive tumours at presentation and are not candidates for either LT or LR. The use of neoadjuvant therapies to downstage the disease has recently been shown to be effective in a small number of selected cases. The results of newer tumour specific therapies that are currently being developed are awaited and may expand the number of potentially resectable cases. If livers for LT were freely available, a case could be made for transplanting all patients with HCC confined to the liver. However, there are insufficient numbers of grafts to transplant even good risk candidates. Determining which patients should be managed by resection or transplantation remains a subject of much debate.

LIVER RESECTION

For the majority of patients with HCC, eligibility for LR is not only dependant upon anatomical location, but also on the extent of the underlying liver disease[3]. Consequently, only 15%-30% of patients with HCC are candidates for LR at the time of presentation[4]. Although the advantages of LR over LT are not clear-cut, patients with well-preserved liver function (Child-Pugh A) with small solitary (< 5 cm) HCCs should be considered for LR. The presence of hepatic decompensation (Child-Pugh C) is a contraindication to surgical LR, due to the high peri-operative mortality. The more difficult patients

Table 1 Recurrence and survival rates following surgical treatment for hepatocellular carcinoma

Treatment	Author	*n*	Recurrence (%)	5-yr survival (%)
Liver resection				
	Ercolani (2003)[61]	224	54.4	42.0
	Sim (2003)[62]	81	NS	59.0[1]
	Belghiti (2003)[63]	328	NS	37.0
	Bartlett (2007)[59]	53	47.0	42.6
	Nuzzo (2007)[64]	248	46.0	24.0
Deceased donor liver transplantation				
	Mazzaferro (1996) (Milan criteria)[33]	48	8.0	75.4[2]
	Jonas (2001) (Milan criteria)[65]	120	16.0	71.0
	Figueras (2001) (5 cm, localised)[66]	307	21.0	63.0
	Yao (2001) (UCSF criteria)[34]	70	11.4	75.2
	Decaens (2006)[36]			
	Milan criteria	279	NS	60.0
	Beyond Milan, but within UCSF	44	NS	45.6
	Beyond UCSF and Milan criteria	145	NS	34.7
Living donor liver transplantation				
	Todo (2007)[67]			
	Milan criteria	137	1.4	79.4[1]
	Extended criteria	172	22.2	60.0
	Hwang (2005)[68]			
	Milan criteria	173	NS	88.0
	Extended criteria	64	NS	60.0[1]
	Jonas (2007)[69]			
	Milan criteria	8	NS	75.0
	Extended criteria	13	NS	62.0
	Kwon (2007)[70]			
	Extended criteria	139	NS	79.9
	Sugawara (2007)[71]			
	Extended criteria (5 nodules <5cm)	78	10.0	75.0
	Soejima (2007)[40]			
	Milan criteria	16	0.0	100
	Unlimited criteria	44	18.2	74.0[1]
Salvage liver transplantation				
	Belghiti (2003)[55]	18	5.6	61.0
	Schwartz (2006)[19]	18	44.0	NS
	Hwang (2007)[54]	17	NS	NS

NS: Not stated; UCSF: University of California San Francisco. [1]3-year survival; [2]4-year survival.

are those with Child-Pugh B cirrhosis or those with large (> 5 cm) or multiple tumours.

The natural history of HCC has been studied in small series 20-30 years ago. Those patients with a solitary small (< 3 cm) tumour have good three-year survival irrespective of treatment modality. Of those that undergo LR approximately 70% will develop intrahepatic tumour recurrence within 5 years of resection[5]. This represents either tumour that was present, but not detected at the time of LR (synchronous), or a new tumour that has arisen in the diseased liver remnant (metachronous). The results of LR for HCC in some recent publications are summarised in Table 1.

A number of different clinico-pathological staging systems have been proposed to help predict survival outcomes for patients with HCC to assist clinicians in deciding whether patients are suitable for LR. The Barcelona Clinic Liver Cancer (BCLC) group stratifies patients with HCC into 4 categories (early, intermediate, advanced and terminal) and recommends different treatment options for each category[6]. Accordingly, LR is only indicated in patients with early stage HCC, that is; a single nodule ⩽ 5 cm or up to 3 nodules ⩽ 3 cm; Okuda stage 1 or 2[7]; Child-Pugh A or B[8]; Performance score of 0[9]; with no portal hypertension and a normal serum bilirubin level. The role of LR for BCLC group intermediate-stage HCC (single nodule > 5 cm or multinodular tumours) in the presence of preserved liver function (Okuda stage 1 or 2; Child-Pugh A; Performance score 0-2) remains controversial. Patients with large (> 5 cm) HCCs are not suitable for ablative therapies and are excluded from LT if the Milan criteria are used for patient selection. These patients are often deemed too high-risk to undergo LR due to the extent of the resection. The American Association for Study of Liver Diseases (AASLD)[10] and the European Association for Study of Liver (EASL)[11] guidelines state that LR is contraindicated for tumours > 5 cm due to the high incidence of vascular invasion and the associated poor prognosis. However, a number of centres have reported acceptable outcomes for patients with resected HCC greater than 5 cm or even 10 cm. A multicentre study of 300 patients with HCC > 10 cm reported a 5-year overall survival rate of 26.9%[12]. Poon *et al* reported a 5-year actual survival rate of 20.6% for 58 patients resected for tumours > 10 cm[13].

Much of the improvement in patient outcome following LR has been due to the adoption of a multidisciplinary approach to managing these patients with stringent preoperative evaluation of hepatic function and liver manipulation by selective portal vein or hepatic artery embolization. This has been borne out by nationally representative data which has shown inpatient mortality to be 40% less in high-volume hospitals compared to low-volume hospitals (odds ratio 0.60; $P = 0.02$)[14]. Supporting the concept that patients requiring hepatectomy, particularly in the presence of chronic liver disease, should be managed in high-volume centres.

Multi-focal HCC is associated with a poor outcome, due to the high rate of recurrence and is considered a relative contraindication to LR. A recent audit of LR in 380 patients with large and multifocal HCC and small (< 5 cm) single nodules ($n = 404$), revealed similar peri-operative morbidity and mortality rates between the two groups, but the three-year survival that was significantly better for small solitary HCC (76% *vs* 50%)[15]. Despite this the authors stated that survival of patients with multifocal HCC after LR was better than that achieved with trans-arterial chemoembolization (TACE), and suggested that if functional reserve was acceptable they should be considered for LR provided all identifiable tumour is able to be resected[15].

Patients with early Child-Pugh B cirrhosis without evidence of significant portal hypertension should be considered for minor LRs. The difficulty is objectively assessing liver function and the extent of LR likely to be tolerated. The indocyanine green (ICG) clearance test[16,17] has been well validated and the Model of End Stage Liver Disease (MELD) also appears to predict peri-operative mortality following LR. A MELD score of $\geqslant 9$ had a peri-operative mortality rate of 29%, whilst a score of < 9 had no mortality[18]. However, no technique has been shown to be superior to that of the judgement of an experienced clinician.

The aim of LR is to achieve local control of the index tumour, accepting that new or unrecognised tumours may subsequently appear. Thirty-nine percent of patients with a solitary HCC < 5 cm on preoperative cross sectional imaging are found after LT to have other lesions on histologic examination of the explanted liver[19]. Although preoperative imaging has improved, less than one third of HCCs < 1 cm can be identified using either contrast enhanced computer tomography (CT) or magnetic resonance imaging (MRI)[19]. This suggests that progression of established disease present at the time of LR accounts for a significant proportion of tumour recurrences post resection.

Parenchymal preservation is important in preserving hepatic function and reducing the risk of small for size syndrome[3]. However, HCC has a propensity for vascular invasion resulting in intrahepatic metastases. Anatomical (segmental) LR, results in resection of a greater volume of liver parenchyma, leads to the *en bloc* resection of the primary tumour and all the potentially tumour-bearing portal tributaries. In support of this, anatomical resection for solitary HCC has been shown to be associated with a lower rate of disease recurrence and improved overall survival[20-22]. In a retrospective study of 321 patients who underwent curative LR for solitary HCC < 5 cm, patients with preserved synthetic function (Liver damage group A) that underwent anatomical LR had improved overall and recurrence free 5-year survival compared to those treated by non-anatomical LR (87% *vs* 76%, $P = 0.02$ and 63% *vs* 35%, $P < 0.01$, respectively)[21]. Similarly, a recent retrospective analysis of 158 consecutive patients undergoing either anatomical ($n = 95$) or non-anatomical ($n = 63$) LR for HCC, demonstrated improved disease-free and long-term survival after anatomical LR, despite having larger tumours and higher prevalence of vascular invasion[22]. However, anatomical LR cannot always be performed due to limited hepatic reserve. The only option in these patients is a more limited (non-anatomical) LR or local ablative therapy. Patients with moderately impaired (Liver damage group B) synthetic function who underwent non-anatomical LR had significantly better 5-year overall and recurrence free survival compared to those treated by anatomical LR (72% *vs* 48%, $P < 0.01$ and 43% *vs* 28%, $P = 0.01$, respectively)[21]. Although the reason for this dichotomy remains speculative, it is possible that non-anatomical LR is associated with less physiological stress, which is better tolerated by patients with limited hepatic reserve.

More recently ablative therapies, such as radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), have been shown to offer similar outcomes to LR for small tumours (< 4 cm) without the associated operative morbidity. In a randomised controlled trial comparing PEI and RFA for HCCs < 3 cm, 4-year local recurrence and survival rates were 1.7% and 74%, respectively[23]. This was achieved despite a 63% incidence of disease recurrence elsewhere within the liver. Outcome appears to be operator dependent, both in terms of patient selection and technique, with rates of complete ablation varying from 20% to 96%. In a trial comparing PEI with RFA in HCCs $\leqslant$ 4 cm, RFA achieved initial complete ablation in 96% of lesions[24]. Looking at explant pathology, Lu *et al* reported complete necrosis in 83% of HCCs < 3 cm[25]. The higher failure rate of RFA compared to LR in larger lesions may be due to the presence of vascular invasion, which is present in 10%-15% and 46%-50% of 2 cm and 3-4 cm HCCs, respectively[26]. LR has the advantage of removing unrecognised regional metastases contained within the resected specimen and is supported by the finding of less intrahepatic recurrence after anatomical compared to non-anatomical LR[20].

INCREASING RESECTABILITY

Attempts to improve resectability include down staging the primary tumour and reducing the extent of surgery or increasing the size of the future liver remnant. Several techniques have been used to 'down-size' the tumour or to increase the size of the future liver remnant. Pre-operative portal vein embolization allows extensive resections to be performed by decreasing the likelihood

of post-operative liver insufficiency. This is achieved by embolizing the lobe of liver that is to be resected 6 wk prior to surgery, inducing hypertrophy in the future liver remnant. An increase of 40% to 60% in the size of the non-embolized liver is observed in non-cirrhotic livers.

TACE as a down-staging procedure in irresectable tumors has been shown to result in necrosis in 40%-100% of tumors with a three-year survival rate of 77%[26]. There is no clear evidence currently that chemoembolization is more effective than embolization alone[27]; however, combination of local ablative therapy with systemic chemotherapy or biological agents appears to increase resection rates in patients with compensated liver disease.

ADJUVANT TREATMENT FOLLOWING LIVER RESECTION

Several strategies have been employed in an attempt to reduce tumour recurrence following LR for HCC, including systemic chemotherapy, regional chemotherapy and internal radiotherapy. Intra-arterial 131-iodine labelled lipiodol has been shown to increase disease-free and overall survival in randomised controlled trials[27]. These findings have subsequently been confirmed in a retrospective analysis, where the 3-year disease-free survival rates were 68.4% and 41.5% in those that did and did not receive 131-iodine labelled lipiodol, respectively[28]. A large randomised study is awaited to confirm these results. More recently, menatetrenone, a vitamin K2 analogue with known anti-proliferative effects against hepatoma cell lines, reduced tumour recurrence and improved patient survival in patients with HCC following LR or local ablative therapy[29]. Sorafenib (Nexavar, Bayer Pharmaceuticals Corporation), an oral multi-kinase inhibitor, has been shown in a phase Ⅲ placebo-controlled randomised trial to improve overall survival by 44% in patients with stage IV HCC (Hazard Ratio = 0.69, $P = 0.0006$)[30]. Whether this will translate into an improvement in survival in patients following LR or ablation remains to be tested.

LIVER TRANSPLANTATION

LT is theoretically the best option for treating HCC as it allows for both radical resection of the primary tumour and treatment of the underlying liver disease, thus eliminating the risk of developing new HCCs and progression to end-stage liver failure. For many patients LR is not feasible because of tumour size, anatomical location or poor liver function, and LT is the only surgical option.

Early experience with LT for HCC was associated with a high rate of tumour recurrence and poor long-term survival[31]. Improving results for LT and the increasing scarcity donor grafts resulted in restrictions on tumour size as a 20%-40% survival at 5-years was deemed unacceptable. Bismuth[32] proposed and Mazzaferro[33] popularised the Milan criteria (single HCC $\leqslant$ 5 cm or up to 3 nodules $\leqslant$ 3 cm in diameter) for LT in patients with HCC to restrict access and to improve long-term outcome[33]. In many centres this has become the 'gold-standard' in determining eligibility for LT; however, some consider these criteria as too restrictive. Yao *et al* analyzed the outcome of 70 patients with HCC undergoing LT and found that patients with a single lesion $\leqslant$ 6.5 cm, 2 to 3 nodules with the largest $\leqslant$ 4.5 cm or a total tumor diameter $\leqslant$ 8 cm had a 75% 5-year survival[34]. Patients exceeding these University of California at San Francisco (UCSF) criteria, however, had a 1-year survival rate of 50% following LT[34]. Onaca *et al*, in an analysis of 1206 patients that underwent LT, found that patients with 2-4 tumours $\leqslant$ 5 cm or a solitary HCC $\leqslant$ 6 cm had tumour free survival similar to those that were within the Milan criteria[35]. Despite these encouraging reports adopting expanded criteria, a recent a retrospective study found that patients meeting the Milan criteria pre-transplant had a 5-year survival rate of 60% compared to 45% for those exceeding the Milan criteria, but meeting the UCSF criteria[36]. Although the difference was not statistically different, such a clinical difference warrants further examination. The results from a multicenter audit being undertaken by the 'Mazzaferro' group looking at the preoperative number and size of tumours and outcome is awaited[37].

Vascular invasion has been shown to be predictive of tumour recurrence and poor long-term survival in patients with HCC[38]. Vascular invasion is more common in large HCCs; however a significant proportion of tumours > 5 cm do not have histological evidence of vascular invasion[38]. Using size as a surrogate marker of biological behaviour may, therefore, result in patients with large well-differentiated HCC, who would potentially benefit from LT being excluded, and include small poorly differentiated tumours that are at high risk of recurrence[34]. An alternative method of assessing the risk of tumour recurrence is undertaking preoperative percutaneous biopsies, which places the patient at potential risk of local and hematogenous recurrence. Studies have demonstrated that percutaneous biopsy impairs the chance of curative resection. A retrospective review of 85 HCCs resected over 12 years found that preoperative biopsy resulted in the 5-year disease-free survival rate falling from 52% to 24%[38]. A recent review estimated the risk of needle tract seeding as being less than 2%, but acknowledged that biopsy carries a risk of hematogenous dissemination, but considered the degree of risk as speculative[39]. Further studies are needed to evaluate using histological criteria from biopsy for patients with tumours exceeding standard criteria. It is likely histological and other molecular analyses of tissue samples will increasingly be used preoperatively to characterise the biological behaviour of HCC.

As a consequence of donor shortage, live donor LT (LDLT) has become increasingly utilized for patients with end-stage liver disease. Despite the initial enthusiasm, the number of LRLT performed in the United States has fallen since 2002 as a consequence of

the realisation of donor risk and the implementation of the MELD system for organ allocation, which gave greater priority to patients with HCC. Out of necessity the number of LDLT undertaken in Asian countries, where cadaveric donation is not routinely available, has increased dramatically over the last decade.

For patients with early HCC for whom a suitable donor is available, LDLT offers a number of benefits. It can be performed in a timely manner eliminating the risk of waiting list dropout due to disease progression. LDLT does not rely upon cadaveric donation that is dependent upon equitable allocation for all patients with end-stage liver disease. Consequently, there have been a number of studies looking at LDLT using extended criteria, where the size and number is lesions is not limited[40,41]. The largest study reviewed 125 patients that underwent LDLT, 55 of which had tumours that exceeded Milan criteria[41]. Patients that exceeded Milan criteria, but had $\leqslant$ 10 tumours, all of which were $\leqslant$ 5 cm in diameter, had a 5-year recurrence rate similar to those that were within the Milan criteria (7.3% and 9.7%, respectively; $P = 0.89$). Multivariate analysis also demonstrated a preoperative des-gama-carboxy prothrombin (PIVKA-Ⅱ; protein induced by vitamin K antagonist-Ⅱ) value of > 400 mAU/mL as strongly associated with disease recurrence, and a level of < 400 mAU/mL be included in the selection criteria[41]. Similarly, Soejima *et al* reported on 60 patients that underwent LDLT for HCC, and found that there were no recurrences in those that were within the Milan Criteria. Multivariate analysis identified only tumour diameter of > 5 cm and PIVKA-Ⅱ of > 300 mAU/mL as strongly associated with disease recurrence[40]. Although these studies are small and have short follow-up, they suggest that expansion of the current tumour size and number with the use of preoperative PIVKA-Ⅱ, may be associated with acceptable outcomes in patients undergoing LDLT.

LOCAL ABLATIVE THERAPIES AS A BRIDGE TO LIVER TRANSPLANTATION

RFA and TACE have been used by many centres to downstage and/or prevent disease progression in patients with HCC. Currently there are no prospective randomised trials evaluating the effect of these therapies prior to LT.

RFA is operator dependent, both in terms of patient selection and technique, with rates of complete ablation varying from 20% to 96%[25]. Most studies have demonstrated a reduction in the dropout rate compared to historical controls. A study of 60 consecutive HCCs in 50 patients on the waiting list for LT treated by percutaneous and laparoscopic RFA demonstrated a 0% dropout rate and a 8% morbidity at a mean time to LT of 9.5 mo[42]. This compares favourably to an historical dropout rate of 10%-30% with waiting times of 6-12 mo[43]. More recently, a study of 52 patients treated by preoperative RFA reported a dropout rate of 5.7% at a mean of 12.7 mo with no evidence of tumour recurrence post-transplant[44]. Although there remains a potential risk for needle track dissemination and its efficacy has not been demonstrated in large HCC, RFA should be considered in patients on the waiting list with small (< 3 cm) solitary tumours and reasonable synthetic function (Child-Pugh A, and selected B).

A number of cohort studies have evaluated the efficacy of TACE, alone or in combination with systemic chemotherapy prior to LT[45,46]. The results are conflicting, and a recent meta-analysis of TACE as a bridge to LT found that there was insufficient evidence to support the use of neoadjuvant TACE prior to LT as it did not improve long-term survival, allow for the expansion of selection criteria or reduce the dropout rates on the waiting list[47]. TACE has been proposed as a method of selecting patients with favourable tumour biology. In a study of 96 consecutive patients with HCC, 62 of whom exceeded Milan criteria, tumour recurrence was influenced by the response to pre-transplant TACE. Patients who had a sustained response to TACE pre-transplant ($n = 39$) had a 5-year tumour free recurrence rate of 94.5%, whereas patients who had disease progression had a tumour free recurrence rate of 35.4% ($P = 0.0017$)[48]. Similarly, in a smaller study there were only 2 recurrences in 19 patients with tumours > 3 cm that had decreased the sum of two diameters by > 50% following pre-transplant TACE[49].

The current practice guidelines from the American Association for the Study of Liver Diseases (AASLD) state that local ablation, RFA and TACE, are safe and effective in patients who are not suitable for LR, or as a bridge to LT if the waiting list time exceeds 6 mo[10].

SALVAGE LIVER TRANSPLANTATION

Salvage LT has been promoted as a way of managing patients with HCC in an era of organ shortage. LR is performed as the primary procedure, keeping LT in reserve for those who develop further intrahepatic tumours or decompensation. The strategy offers a number of potential benefits. With increasing waiting times for LT patients with HCC face the prospect of disease progression beyond transplant criteria whilst waiting for a suitable donor. Overall, 5 year survival decreases by 10%-20% (from 81%-58% to 62%-47%) for waiting times of 6-12 mo, and dropout rates range from 10%-30%[43]. Undertaking LR in the first instance allows one to observe the natural history of the disease and allow those patients with aggressive disease to declare extrahepatic disease, thus avoiding inappropriate LT and eliminating the risk of disease progression beyond transplant criteria while on the waiting list. In addition, the potential exists to reduce the number of patients requiring LT. In the medium term, disease-free survival for patients undergoing LR with early stage HCC has been shown to be comparable to that of primary LT. LR also allows for histological analysis of the tumour and those with poor prognostic criteria, such as macroscopic vascular invasion or poor differentiation, should be excluded from LT due to the high likelihood

of tumour recurrence, while resected patients who had solitary well-differentiated tumours without vascular invasion can be managed by surveillance and offered LT only if there is tumour recurrence or hepatic decompensation.

Salvage LT for HCC relies upon the principal that patients that have tumour recurrence following LR are still amenable to LT. Tanaka *et al* found that 8% of patients who underwent LR within the Milan criteria had tumour recurrence that exceeded Milan criteria[50]. Conversely, only 22% of patients undergoing LR for tumours outside the Milan criteria develop post-resection recurrence that is within Milan criteria[50]. Multivariate analysis identified size of the primary tumour and degree of differentiation as risk factors for recurrence exceeding Milan criteria[50]. Others have identified the presence of portal vein invasion in the resected liver specimen as the most important predictor of tumour recurrence[51]. A number of molecular indices have been examined to try to predict tumour recurrence. A high level of telomerase activity is reported as an independent predictor for tumour recurrence[52]. However, no marker has been confirmed to predict the risk of tumour recurrence reliably.

Salvage LT appears to have higher morbidity and mortality and an increased incidence of tumour recurrence compared to primary LT[53]. Of 18 patients that under went salvage LT at Mount Sinai following LR, 2 died peri-operatively (11%), and 7 subsequently developed tumour recurrence (44%)[19]. Similarly, of 17 patients that underwent salvage LDLT, bleeding complications were more common, and the peri-operative mortality rate (5.9%) was significantly higher than after primary LT[54]. In contrast, Belghiti *et al* reported that LR prior to LT did not significantly increase the operative difficulty of the procedure[55]. Furthermore, they did not find any difference in disease-free or overall survival between primary and salvage LT. Patients who underwent salvage LT had a mean 20 mo disease-free interval before listing for LT[55]. The long-term outcome of these strategies is awaited.

EFFECT OF IMMUNOSUPPRESSION ON TUMOUR RECURRENCE

Calcineurin inhibitors, cyclosporine and tacrolimus, are currently the mainstay of immunosuppression in LT recipients. Sirolimus, a novel immunosuppressive drug that inhibits the mammalian target of rapamycin has been shown *in vitro* to allow for the maintenance of tumour immunosurveillance, and may theoretically offer survival benefit in patients transplanted for HCC. In a study of 70 patients transplanted for HCC receiving *de novo* sirolimus and low dose calcineurin inhibitor for 6-12 mo and either a short course (3 mo) or no steroids, tumour free survival at a median of 49 mo was comparable to that achieved with conventional immunosuppression[56]. However, 50% of patients had at least one episode of rejection and 34% developed an incisional hernia. A better understanding of tumour biology and particularly the role of immunosuppression and tumour growth will provide further improvement in the treatment of HCC.

DIRECT COMPARISONS: RESECTION VERSUS TRANSPLANTATION

The oncological advantage of LT compared to LR has not been universally demonstrated. For large tumours LR is not often possible and LT is the only potential treatment modality. Numerous retrospective studies from the 1990s have demonstrated that the results of LT for large HCCs are poor in relative terms, with 5-year survival rates of < 20%-30%[31,57,58]. In contrast the best therapeutic modality for small tumours (< 5 cm) is debatable. A retrospective analysis of 102 patients treated by LT (n = 50) and LR (n = 52) showed no difference in 3-year survival or recurrence rate for tumours < 5 cm[57]. In contrast, Bismuth found that LT was superior to LR for small (< 3 cm) tumours[32]. The 3-year survival rate for patients with tumours < 3 cm with 1 to 2 nodules was 83% and 41% for LT and LR, respectively[32]. The difference could be attributed to lower peri-operative mortality and tumour recurrence in the LT recipients. The operative mortality for LR for HCC varies from 0.5% and 21.5% and reflects the incidence of hepatic insufficiency-associated with underlying liver disease[59]. In addition, the rate of 'recurrent' disease is significantly higher after LR compared to LT with a 3-year recurrence-free survival rate of 83% and 18%, respectively[32]. Taken together, it is apparent that in the presence of chronic liver disease, LT offers the greatest chance of long-term survival for patients with small (< 5 cm) tumours. In the present climate of donor organ scarcity it is difficult to justify LT for large and/or advanced HCC.

CONCLUSION

Currently, in the absence of large randomised clinical trials, the treatment strategy for patients with HCC remains a matter of choice depending upon the interpretation of retrospective studies, anecdotal evidence, unit experience, and availability of therapeutic options.

To date, we have relied upon radiological criteria as a surrogate marker of tumour behaviour. What is needed is an accurate predictor of the biological behaviour of the tumour at the time of presentation. The molecular analysis of tumour biopsies has yet to deliver, and is associated with a risk of needle track recurrence. Less invasive markers that can accurately predict the risk of tumour recurrence are needed to help stratify patients for appropriate therapy.

One of the confounding factors in comparing the outcome of different treatment modalities for HCC is the lack of a uniform staging system. A large multicentre trial examining the commonly used staging systems, found that the American Joint Committee

on Cancer/Union Internationale Contre le Cancer AJCC/UICC (sixth edition) staging system provides the best stratification of prognosis following LR or LT[60]. Adoption of a uniform staging system by all centres would help to provide a better comparison of therapeutic modalities in the future.

Although there is no consensus as to the best treatment for patients with HCC, it is apparent that LR appears to be the most appropriate treatment for patients with small (< 5 cm) solitary HCC with well-preserved synthetic function (Child-Pugh A) and normal portal pressures (hepatic vein wedge pressure < 10 mmHg). On account of the high rate of complete ablation that can be achieved in small tumours (< 3 cm), with a similar rate of local control compared to LR, it is hard to justify LR for patients with HCCs < 3 cm, especially if they have significant co-morbidities. Given the scarcity of donor organs and the lack of prospective data demonstrating an acceptable outcome in extending the current criteria, LT should be reserved for early stage HCC (solitary < 5 cm; ⩽ 3 lesions 3 cm) that cannot be treated by LR. Medical treatments currently have limited efficacy, and their role, as a surgical adjuvant to LR and LT is yet to be determined.

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