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ORIGINAL ARTICLE

Hepatic resection for large hepatocellular carcinoma in the era of UCSF criteria

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Abstract

Background: Treating patients with hepatocellular carcinoma (HCC) remains a challenge, especially when the disease presents at an advanced stage. The aim of this retrospective study was to determine the efficacy of liver resection in patients who fulfil or exceed University of California San Francisco (UCSF) criteria by assessing longterm outcome.

Methods: Between 2002 and 2008, 59 patients with large HCC (>5 cm) underwent hepatectomy. Thirty-two of these patients fulfilled UCSF criteria for transplantation (group A) and 27 did not (group B). Disease-free survival and overall survival rates were compared between the two groups after resection and were critically evaluated with regard to patient eligibility for transplant.

Results: In all patients major or extended hepatectomies were performed. There was no perioperative mortality. Morbidity consisted of biliary fistula, abscess, pleural effusion and pneumonia and was significantly higher in patient group B. Disease-free survival rates at 1, 3 and 5 years were 66%, 37% and 34% in group A and 56%, 29% and 26% in group B, respectively ($P < 0.01$). Survival rates at 1, 3 and 5 years were 73%, 39% and 35% in group A and 64%, 35% and 29% in group B, respectively ($P = 0.04$). The recurrence rate was higher in group B ($P = 0.002$).

Conclusions: Surgical resection, if feasible, is suggested in patients with large HCC and can be performed with acceptable overall and disease-free survival and morbidity rates. In patients eligible for transplantation, resection may also have a place in the management strategy when waiting list time is prolonged for reasons of organ shortage or when the candidate has low priority as a result of a low MELD (model for end-stage liver disease) score.

Keywords

large HCC, hepatocellular carcinoma, MELD score, liver resection, hepatectomy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide. The rate of HCC occurrence increased from 1.4 per 100 000 in 1980 to 2.4 per 100 000 in 1991–1995.[1] An aetiological association between hepatitis B virus (HBV) infection and the development of HCC has been established and HBV-infected subjects have a relative risk for HCC 200 times greater than that of non-infected individuals.[2] Hepatitis C virus is also proving an important predisposing factor for this malignancy, with incidence rates of 7% at 5 years and 14% at 10 years.[2] The prognosis depends on tumour stage and degree of liver function, which affects the tolerance to invasive treatments. Despite recent advances in diagnostic imaging, HCC frequently presents at an advanced stage as a result of the absence of early symptoms and poorly performed screening.[3]

The use of conventional Milan criteria (single HCC of <5 cm or up to three nodules of <3 cm), has led to careful patient selection,

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resulting in improved outcomes in liver transplantation (LT) in patients with HCC over the last 10 years.[4] The growing experience in and success of LT in the treatment of HCC have raised controversies related to the expansion of the Milan criteria.

Among the proposed expanded criteria, the University of California San Francisco (UCSF) criteria (single tumour nodule ≤6.5 cm, or three or fewer tumours of which the largest is ≤4.5 cm and the sum of the tumour diameters is ≤8 cm) reflect a modest expansion of tumour size limits.[5] The major drawback to LT is the scarcity of donors. Increases in waiting time have resulted in 20% of potential candidates dropping out because outcome on an intention-to-treat basis is jeopardized by the progression of disease.[6]

Liver transplantation is the treatment of choice for patients with early HCC and moderate to severe cirrhosis.[4] By contrast, the optimal treatment for patients with early HCC and preserved liver function seems to be liver resection (LR).[7,8] In this situation transplantation should be considered in cases of unfavourable histological findings,[9,10] or early-stage recurrence of HCC.[11] The treatment of patients with HCC beyond the Milan criteria is more challenging because no firm guidelines exist; a more individualized multimodal strategy consisting of LR, salvage LT and primary LT should be considered.[12]

The aim of this retrospective study was to determine the efficacy of LR, in terms of longterm and disease-free survival, in patients who do and do not fulfil UCSF criteria.

Materials and methods

Between October 2002 and November 2008, a total of 357 patients with HCC were admitted to the Liver and Pancreatic Surgical Unit at Agia Olga, Konstantopouleio Hospital, Athens. Curative liver resection was performed in 59 cirrhotic patients presenting with large HCC, which was defined as a tumour with diameter ≥5 cm in the pathology report. Cirrhosis was microscopically confirmed in all resected specimens. Non-tumorous liver was analysed using the fibrosis classification scheme proposed by Ishak *et al.*[13]

Based on findings from the pathology report, patients were divided into two groups and data regarding longterm outcome were analysed retrospectively. Group A consisted of those patients who fulfilled UCSF criteria and group B consisted of patients who exceeded UCSF criteria.

Liver function was evaluated by Child–Turcotte–Pugh classification, liver biochemistry and MELD (model for end-stage liver disease) score.

Platelet count was >90 000/ml in all patients.

Portal hypertension was defined by the presence of varices, a platelet count of <100 000/ml or indirect echographic markers (ascites, portal vein diameter ≥13 mm, spleen length >15 cm, maximal and mean velocimetry of portal vein flow [<20 cm/s and <12 cm/s, respectively]). Ascites, encephalopathy, abnormal bilirubin level (>2 mg/dl), previous history of variceal bleeding and portal hypertension were contraindications for liver resection.

Table 1 Staging classification for hepatocellular carcinoma based on American Liver Tumor Study Group criteria

	Modified tumour–node–metastasis (TNM) staging classification
T0	Tumour not found
T1	One nodule < 1.9 cm
T2	One nodule 2.0–5.0 cm
	Two or three nodules, all < 3.0 cm
T3	One nodule > 5.0 cm
	Two or three nodules, at least one > 3.0 cm
T4a	Four or more nodules
T4b	One or more nodules plus gross intrahepatic portal or hepatic vein involvement, as indicated by CT, MRI or ultrasound
N1	Any regional (porta hepatis) nodes involved
M1	Any metastatic disease, including extrahepatic portal or hepatic vein involvement
Stage I	T1
Stage II	T2
Stage III	T3
Stage IV A1	T4a
Stage IV A2	T4b One or more nodules plus gross intrahepatic portal or hepatic
Stage IV B	Any N1, any M1

CT, computed tomography; MRI, magnetic resonance imaging

Hepatocellular carcinoma was diagnosed on the basis of standard clinical and imaging criteria, α-fetoprotein levels (AFP) and biopsy. Routine biopsies were not performed on tumorous or non-tumorous liver tissue.

Preoperative tumour stage was based on two abdominal imaging studies, such as ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). Extrahepatic metastasis was excluded before LR based on chest and abdominal CT or MRI. Tumour contraindications for LR were presence of extrahepatic disease or macroscopic vascular invasion. Patients with diffuse infiltrating HCC were excluded, as were patients with regional lymph node involvement discovered at surgery (stage IV B; Table 1). Liver resection was performed in all patients. When the estimated future liver remnant (FLR) was expected to be < 40% of the total liver volume (TLV) as calculated by three-dimensional CT volumetry, portal vein embolization (PVE) was performed 6–8 weeks before LR to induce hypertrophy of the FLR. CT volumetry was estimated prior to and after PVE for accurate assessment of the functional residual liver volume and occasionally in patients who did not undergo PVE.

Hepatic resection was defined as major if three or more segments were resected and minor if fewer than three segments were resected. Hepatic resection was defined as extended when three liver sectors were resected (trisectorectomy): more than four segments on the right side and more than three segments on the left side. Segment I was included or not in accordance with tumour expansion.

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Resection was performed by the conventional method of hepatic inflow dissection and selective vascular pedicle ligation followed by outflow short hepatic vein ligation in a piggyback fashion. The anterior approach was applied infrequently in our series. Radiofrequency-assisted parenchyma transection was performed in 30 patients and Kelly crushing technique with intermittent portal triad in 29 patients. Radiofrequency-assisted bloodless LR has been described previously.[14,15] Intraoperative ultrasound was performed routinely in patients undergoing hepatectomy. Drains were placed in all cases and remained in place until postoperative day 3 unless bile drainage or serosanguinous fluid >500 cc was noted. The number of tumours, maximal tumour diameter, histological grade based on the modified Edmondson criteria[16] for the degree of tumour differentiation, and the presence or absence of microvascular invasion were recorded. Tumours were staged on the basis of pathological evaluation of the specimen and according to the American Liver Tumor Study Group (ALTSG) modified tumour–node–metastasis (TNM) classification[17] (Table 1). Vascular invasion included microscopic involvement of vessels as well as macroscopic invasion; the latter was defined as the invasion of the branches of the main portal vein (right or left, not including sectoral branches) or of one or more of the three hepatic veins (right, middle or left). Multiple tumours included satellitosis, multifocal tumours and intrahepatic metastasis.[18] Microscopic margins of resection were considered positive if there were tumour cells present at the tested margins (R1).

All patients were followed after surgery and underwent CT scans of the chest and abdomen every 3 months for the first 2 years and every 6 months thereafter. In addition, AFP level was measured every 3 months. Additional imaging techniques (MRI, bone scintigraphy) were performed if recurrent HCC was suspected. Recurrence of HCC was categorized according to localization, either as extrahepatic recurrence or recurrence in the liver only. Treatment of recurrent HCC included radiofrequency ablation (RFA), transarterial chemoebolization (TACE) or both, and targeted chemotherapy (sorafenib). Patients with hepatic recurrence only after LR were considered for repeat hepatectomy or salvage LT if HCC recurred at an early stage (ALTSG stages I and II).

Statistical analysis

Chi-square test or Fisher's test, where appropriate, were used for univariate comparisons. Survival was determined using the Kaplan–Meier method and comparisons were made with log-rank statistics. Multivariate logistic regression and the Cox model with determination of the hazard ratio were applied to evaluate the risk associated with prognostic variables. Differences were considered significant at $P = 0.05$.

Results

Tumour pathology is summarized in Table 2. Median AFP was 760 ng/ml (range 540–1000 ng/ml). A total of 38 patients had a MELD score <9 and 21 patients presented with MELD scores of 9–11. Microvascular invasion and the mean number of tumour nodules were significantly greater in patients exceeding UCSF criteria. The presence of satellitosis and degree of differentiation were similar in the treatment groups.

Extended hepatectomies were performed more frequently when patients exceeded UCSF criteria (Table 2).

No perioperative mortality was documented. Morbidity consisted of biliary fistula, peri-hepatic abscess, pleural effusion and pneumonia (Table 3). The complication rate was higher in the group of patients exceeding UCSF criteria.

Median follow-up was 29 months (range 1–60 months) for the entire cohort, 33 months (range 1–60 months) for patients within the UCSF criteria (group A) and 27 months (range 1–60 months) for patients exceeding UCSF criteria (group B). Cumulative 1-, 3- and 5-year disease-free survival rates were 66%, 37% and 34%, respectively, in group A, significantly higher than in group B, where 1-, 3- and 5-year disease-free survival rates were 56%, 29% and 26%, respectively (Table 4). Overall survival rates at 1, 3 and 5 years were 73%, 39% and 35%, respectively, for patients in group A. Overall survival rates at 1, 3 and 5 years in group B were significantly lower, at 64%, 35% and 29%, respectively (Table 4).

Death was caused by recurrence and tumour dissemination.

Recurrence was significantly greater in patients who exceeded UCSF criteria (Table 4). The remnant liver was the most common site of recurrence. Radiofrequency was the most commonly used treatment for recurrent HCC, followed by TACE and targeted chemotherapy (sorafenib). Repeated hepatic resection was not feasible in this cohort because of low functional reserve and advanced disease. Some patients were listed for salvage LT but were not transplanted because of tumour progression during the waiting time.

The association of various clinicopathological factors with survival was evaluated. Among the most influential on univariate analysis were tumour grade, tumour size and number of lesions. Of little or no influence were age, gender, aetiology of liver disease, Child classification, MELD score, AFP level, preoperative treatment, microvascular invasion, satellitosis and tumour distribution. On multivariate analysis, only tumour size and grade remained independent predictors of adverse longterm outcome.

Discussion

Treatment of HCC remains very challenging because a delicate balance must be maintained between radical tumour excision and maximal parenchymal preservation. Orthotopic liver transplantation (OLT) theoretically seems to be superior to resection in cirrhotic patients because it provides complete tumour excision and simultaneous treatment of the underlying liver pathology.

The ideal test of the benefit of any treatment is a randomized prospective trial, but such studies are limited for patients with HCC.[19] The existing treatment strategies have been based on theoretical analyses and several cohort investigations.[20–22] Access

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Table 2 Clinical and pathological characteristics of patients undergoing liver resection for large hepatocellular carcinoma

	Liver resection		*P*-value
	Fulfilling UCSF criteria	Exceeding UCSF criteria	
Patients, *n*	32	27	
Mean age, years (range)	63 (49–73)	65 (52–72)	0.1
Aetiology			
Hepatitis B	16 (50%)	13 (48%)	0.3
Hepatitis C	10 (31%)	5 (19%)	
Other	6 (19%)	9 (33%)	
CTP score, mean (range)	5 (5–6)	6 (5–6)	0.2
MELD score, mean (range)	8 (7–14)	9 (8–14)	0.1
Tumour size, cm, mean (range)	6 (2–6.5)	9 (6.5–12)	0.008
Solitary	28	19	0.07
Nodules, *n*, mean	2	3	0.04
Microvascular invasion, *n*	20 (62%)	21 (78%)	0.03
Satellitosis, *n*	10 (31%)	8 (30%)	0.1
Lobectomy, *n*	23	9	<0.01
Extended hepatectomy (trisectorectomy), *n*	9	18	0.02
Tumour-free resection margin ≥1 cm	29	18	0.03
Differentiation			
Good, *n*	19	12	
Moderate, *n*	13	10	0.08
Poor, *n*	7	5	
ALTSG staging			
III, *n*	36	22	
IV A1, *n*	3	3	0.04
IV A2, *n*	0	2	
Median follow-up	33 months	27 months	

UCSF, University of California San Francisco; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; ALTSG, American Liver Tumor Study Group

Table 3 Complications after liver resection for large hepatocellular carcinoma

	Liver resection		*P*-value
	Fulfilling UCSF criteria	Exceeding UCSF criteria	
Patients, *n*	32	27	
Biliary fistula	2 (6.2%)	2 (7.4%)	0.04
Perihepatic abscess	1 (3.1%)	2 (7.4%)	0.004
Pleural effusion	10 (31.2%)	10 (37%)	0.04
Pneumonia	2 (6.2%)	3 (11%)	0.002

UCSF, University of California San Francisco

to treatment options is a serious parameter and must be incorporated into decision making, given the limited availability of organs for OLT. In our study, 'large HCC' was defined as HCC > 5 cm, and these ranged from 5 cm to 12 cm.

Despite the theoretical advantage, satisfactory results after OLT have been confirmed only for patients fulfilling the Milan[4] or UCSF criteria.[5] Numerous retrospective studies from the 1990s have demonstrated that the outcome after OLT for HCCs exceeding UCSF criteria is poor in relative terms, with 5-year survival rates of <20–30%.[23–25]

However, acceptable outcomes after resection of HCC exceeding UCSF criteria have been reported by a number of centres. A multicentre study of 300 patients with HCC > 10 cm reported a 5-year overall survival rate of 26.9%.[26] Poon *et al.* reported a 5-year actual survival rate of 20.6% for 58 patients resected for tumours > 10 cm.[27] Our 5-year survival rate after LR in patients exceeding UCSF criteria was 29%. We were able to undertake major or extended resections in patients with HCCs that exceeded UCSF criteria. In this setting, our preference was to consider only patients with a MELD score < 9, normal bilirubin and no signs of ascites or encephalopathy. As we previously reported, in agreement with other reports in the literature, a MELD score > 9 is associated strongly with higher postoperative morbidity.[28,29]

Recurrence after resection for large HCC exceeding UCSF transplantation criteria has been reported to be as high as 82% within 3 years of resection.[11,12,30,31] Higher recurrence rates in large

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Table 4 Longterm results after resection of large hepatocellular carcinoma

	Liver resection		*P*-value
	Fulfilling UCSF criteria	Exceeding UCSF criteria	
Patients, *n*	32	27	
Median follow-up, months	33	27	
1-, 3-, 5-year disease-free survival, %	66, 37, 34	56, 29, 26	<0.01
1-, 3-, 5-year survival, %	73, 39, 35	64, 35, 29	0.04
Total recurrence	22/32 (69%)	20/27 (74%)	0.002
Hepatic only	14/32 (44%)	12/27 (44%)	0.004
Extrahepatic	7/32 (22%)	8/27 (30%)	

UCSF, University of California San Francisco

tumours have been found to be related to a higher incidence of satellite lesions and micro- and macrovascular invasion. In our cohort, the recurrence rate for patients exceeding UCSF criteria was 73% within 5 years of resection.

Liver transplantation is considered by many authors to be the treatment of choice for cirrhotic patients fulfilling the Milan criteria.[4] The Milan group showed that 10-year overall survival surpassed 70% in 300 liver transplants for HCC that fulfilled the Milan criteria.[4] Such good results have been confirmed worldwide.[32,33] Liver resection is not considered as the first treatment option in this group of patients, but it is the only potentially curative method when no graft is available within a reasonable interval of time or when the patient's access to transplantation is limited. Resection for such tumours has shown favourable outcomes regarding 5-year survival (76–87%), but the recurrence rate was high, reaching 65–70% at 5 years after resection.[34,35]

In describing their UCSF criteria, Yao *et al.*[5] expanded the transplantation norm for treating HCC. This group of patients in whom HCC exceeds Milan criteria represent the most difficult category of patients regarding the treatment plan. Yao *et al.* reported a 5 year survival rate > 70% after transplantation with the new extended criteria.[36] A recent multicentre retrospective analysis reported that 5-year survival was > 50% after OLT in patients with extended criteria.[35] However, at least three transplant experiences from Europe and the USA have underlined the limitations of the applicability of the UCSF criteria in the pre-transplant setting, particularly as most of the patients who adhered to the UCSF criteria also fulfilled the Milan criteria.[37,38] Although the UCSF criteria have been independently validated in several studies, the population of patients who adhere to the UCSF, but not the Milan, criteria is often negligible and estimated to represent < 10% of the total transplanted population.[39,40] Such a limitation was evidenced by a multicentre study from France, in which 39 of 461 patients (8.7%) had explanted tumours beyond the Milan but within the UCSF criteria.[37] Although the 5-year survival rate of 67% for patients meeting UCSF criteria was equivalent to that of the 183 patients meeting Milan criteria (and significantly better than the 34% 5-year survival rate of 238 patients exceeding both sets of criteria), the 44 patients meeting UCSF but exceeding Milan criteria at pre-transplant staging had a 5-year survival rate of only 48%. This can be compared with the 60% rate observed in the 272 patients who fulfilled the Milan criteria and the 37% rate in 121 patients whose symptoms fell outwith both sets of criteria.

It should be remembered that although transplantation criteria have been expanded, patients with well-preserved liver function and with HCC beyond Milan criteria are unlikely to receive a liver from a deceased individual in a timely manner, given the current organ allocation system in the USA.[41] Using an arbitrary index rate or snapshot, Shiffman *et al.*[42] showed that only 1.6% of patients on the liver waiting list with MELD scores of < 11 (like our cohort of patients in the LR group) underwent LT within 90 days of the snapshot. Only 6% of patients with MELD scores of 11–20 received a liver transplant within 90 days of the snapshot. With increasing waiting times for OLT, patients with HCC face the prospect of their disease progressing beyond the limits fixed by transplant criteria while they wait for a suitable donor. Overall, 5-year survival rate decreases by 10–20% (from 81–58% to 62–47%) for waiting times of 6–12 months, and dropout rates range from 10% to 30%.[6]

There are no firm guidelines regarding the optimal treatment (OLT or LR) for tumours that fall between the Milan and UCSF criteria. The decision depends not only on the expected outcome, which seems to favour OLT, but on graft availability and method applicability as well. Lower 5-year survival and higher 5-year recurrence rates for LR (35% and 70%, respectively) compared with OLT (53% and 35%, respectively) have been reported.[10,11,23,35] The 5-year disease-free survival and overall survival rates after LR in patients fulfilling UCSF criteria were 34% and 35%, respectively, in our cohort. Yao *et al.* reported that tumour recurrence was 11.4% after OLT in patients who fulfilled UCSF criteria.[5] In the same cohort, Kaplan–Meier survival rates at 1 and 5 years were 91.3% and 72.4%, respectively, for patients with pT1 or pT2 HCC, and 82.4% and 74.1%, respectively, for pT3 tumours.[5]

Undertaking LR for patients fulfilling UCSF criteria with a long waiting time allows us to evaluate disease aggressiveness based on histology and to perform OLT for recurrence. In the medium-

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term, overall survival for patients undergoing LR with early-stage HCC has been shown to be comparable with that of primary OLT although recurrence is higher in the resected group.

Those patients with poor prognostic criteria, such as evidenced by macroscopic vascular invasion or poor differentiation, should be excluded from possible future OLT because of the high likelihood of tumour recurrence. By contrast, resected patients with solitary well-differentiated tumours without vascular invasion can be managed by surveillance and offered OLT only if there is tumour recurrence or hepatic decompensation. Salvage OLT for HCC relies upon the principle that patients who have tumour recurrence following LR are still amenable to OLT. Tanaka *et al.* found that 8% of patients who underwent LR for HCC within the Milan criteria had tumour recurrence that exceeded Milan criteria.[43] Conversely, only 22% of patients undergoing LR for tumours outside the Milan criteria developed post-resection recurrence that fell within the Milan criteria.[43] In our group of patients, salvage transplantation was not performed because of tumour dissemination. Multivariate analysis identified size of the primary tumour and degree of differentiation as risk factors for recurrence in patients exceeding Milan criteria.[43] Others have identified the presence of portal vein invasion in the resected liver specimen as the most important predictor of tumour recurrence.[44] A number of molecular indices have been examined in attempts to predict tumour recurrence. A high level of telomerase activity is reported as an independent predictor for tumour recurrence.[45] However, no marker has been confirmed to predict the risk of tumour recurrence reliably.

Salvage OLT appears to have higher morbidity and mortality and an increased incidence of tumour recurrence compared with primary OLT.[46] Of 18 patients who underwent salvage OLT following LR, at Mount Sinai Hospital in New York, two (11%) died perioperatively and seven (44%) subsequently developed tumour recurrence.[47] Similarly, in 17 patients who underwent salvage living donor LT (LDLT), bleeding complications were more common and the perioperative mortality rate (5.9%) was significantly higher than after primary OLT.[48] By contrast, Belghiti *et al.* reported that LR prior to OLT did not significantly increase the operative difficulty of the procedure.[10] Furthermore, they did not find any difference in disease-free or overall survival between primary and salvage OLT. Patients who underwent salvage OLT had a mean 20-month disease-free interval before listing for OLT.[10] The longterm outcomes of these therapies are awaited.

The most commonly used treatment for recurrent HCC in our study was RFA with or without TACE. In non-resectable recurrent HCC these are the most commonly used approaches to treatment.[49,50]

Overall and disease-free survival were significantly lower in patients exceeding UCSF criteria after resection in our study. This was to be expected because more extended resections were performed. In addition, we know that larger tumours are related to higher incidences of micro- or macrovascular invasion, a higher incidence of satellitosis, more advanced tumour grade and more aggressive tumour behaviour.[51]

The operative mortality of LR for HCC varies from 0.5% to 21.5% and reflects the incidence of hepatic insufficiency associated with underlying liver disease.[52] We experienced no perioperative mortality in either of our two patient groups. In addition, the rate of 'recurrent' disease has been shown to be significantly higher after LR compared with OLT, with 3-year recurrence-free survival rates of 83% and 18%, respectively.[53] The 3-year disease-free survival rates after LR were 37% and 29% for patients who met and those who exceeded the UCSF criteria, respectively, in our cohort.

It is apparent that in the presence of chronic liver disease, OLT offers the greatest chance of longterm survival for patients with small (<5 cm) tumours. Liver resection can be performed for such tumours when the patient has no access to transplantation, but he or she must be very closely followed because of the increased risk of recurrence. Patients with HCC that fall between the Milan and UCSF criteria seem to have a better outcome after OLT.[36] In the present climate of donor organ scarcity, given that not all patients can be referred to transplant centres, LR can be considered as a valuable option in this group of patients. Liver resection, if feasible, is potentially curative and gives the patient the chance of instant tumour excision and pathological analysis of the tumour. These data regarding the tumour may be useful when salvage transplantation is considered for the treatment of possible future recurrence. For patients with resectable tumours, which exceed UCSF criteria, LR, if feasible, is the treatment of choice.

Conflicts of interest

None declared.

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