Chapter 13

Surgical Management of HCC

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Additional information is available at the end of the chapter

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1. Introduction

Hepatocellular cancer (HCC) accounts for approximately 80% of all primary liver cancers. It is the fifth most common cancer worldwide and is the third leading cause of cancer related deaths across the world, with a case fatality rate of 0.93 making it one of the most lethal malignancies [1]. In the majority of cases, HCC develops in the setting of cirrhosis and treatment with curative intent is only possible in a minority of cases. The incidence of HCC continues to rise worldwide, due in part to the rising number of people who have hepatitis C virus (HCV) infection, infection with hepatitis B virus (HBV), (but not to the same degree as HCV) and non-alcoholic fatty liver disease (NAFLD). NAFLD is now the most rapidly rising cause of cirrhosis in the developed world. The outcome from this disease is poor, with a median survival estimated at around 1-year following diagnosis [2]. In keeping with global trends, the incidence and consequent mortality from HCC in the United Kingdom is also increasing, despite greater awareness for the need for surveillance in patients with cirrhosis, and improvements in and access to imaging. This is thought to be secondary to the persistence of alcohol induced liver disease as a significant cause of CLDs [3], the growing incidence of non-alcoholic fatty liver disease (NAFLD) in the UK, immigration to the UK from HBV-endemic countries and the clinical impact of HCV infected individuals, infected before HCV screening of blood products (in the 1990's).

HCC is unique amongst solid cancers in that the outcome from it depends not only on the performance status of the patient and biological behaviour of the tumour, but also on the degree of liver dysfunction. The current treatment options are surgical (liver resection [LR], liver transplant [LT]), ablative (radiofrequency or microwave ablation [RFA/MCT]), non-surgical (trans-arterial chemo-embolisation, selective internal radiation therapy [yttrium90 spheres]) and medical - in particular the use of the targeted kinase inhibitor, Sorafenib. The only curative treatments are the surgical modalities (LR or LT). However these treatments are not suitable for the majority of patients but can achieve the best outcome in carefully selected patients with early tumours or very early tumours. Sometimes LR and LT are complimentary, particularly when LR is considered as a bridge to transplantation. When the liver parenchyma

is normal [5% of the cases in Western countries, and for about 40% in Asia] the treatment of choice is a liver resection (LR) [4]. However most patients also have underlying chronic liver disease and for this group of patients, LT is the treatment of choice as it treats not only the tumour but the underlying chronic liver disease which induces tumourigenesis in the first place. However the relative scarcity of donor organs available for transplantation (NHSBT) and the improved outcomes of LR amongst those with chronic liver disease (CLD) have led to an increased interest in LR for HCC.

For patients with early HCC and CLD who have well-preserved liver function (the vast majority of patients), establishing the best treatment is difficult as there are no well designed randomized controlled trials to guide management. Proposed treatment modalities for individual patients need to take into account not only tumour factors (stage of tumour) but also the degree of underlying chronic liver disease and patient factors (performance status). The Barcelona Clinic Liver Cancer (BCLC) algorithm which incorporates these variables into a decision making process to help choose a specific management option has been found most useful in clinical practice [5].

2. Liver resection as treatment for HCC

2.1. Selection criteria of patients with HCC for Liver Resection (LR)

Clearly extra-hepatic and or distant spread is a contra-indication for LR. This occurs in 60-80% of cases. There is a significant geographical variation in the proportion of patients undergoing surgery with curative intent, varying from 20% in East Asia, through 25-40% in Europe, to 50-70% in Japan. Superior outcomes being related to the implementation of effective screening programs [6].

In addition to the patients overall performance status, the following specific factors need to be considered

1. The Tumour:

a. Stage

b. Size

2. The Liver parenchyma

a. Underlying chronic liver disease (CLD) and portal hypertension (PHT)

b. Quality and volume of the "future functional liver remnant"(FLR)

3. Tumour specific factors

3.1. Staging of HCC

Resection of any cancer is based on pre-operative staging to a large extent. In addition, a proper cancer staging is useful for evaluating prognosis of cancer patients, for tailoring therapy and

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monitoring therapeutic response. Generally prognosis in solid cancers is solely related to stage. However HCC is unique in that cirrhosis underlies the cancer and thus outcome is related too not only tumor but also to the extent of liver parenchymal damage. Therefore any staging for cirrhotic patients with HCC should take into consideration the severity of the liver disease and the extent of the tumour. Numerous staging systems have been described (at least 8), although none has been universally accepted. The variables used in each classification as well as the populations in which they were derived are different. Only 3 – BCLC, CLIP and JIS have been validated in different cohorts of patients [7]- [12]. The BCLC and Cancer of the Liver Italian Program (CLIP) staging systems have been the most popular in Europe and the USA, and the Japan Integrated Staging Score (JIS) in Japan.

The Okuda staging system includes tumour size, serum albumin, bilirubin and ascites [13]. The Child's classification does not discriminate enough for Child's A or B patients in whom resection is being considered in order to prevent postoperative liver de-compensation. The Cancer of the Liver Italian Program (CLIP) is based on the Child–Pugh class, tumour progression, alpha-fetoprotein (AFP) and presence of portal venous thrombosis. CLIP is the most accurate for prognosis [12] especially in patients with advanced HCC and those undergoing loco-regional therapy [14]. Specifically, a CLIP score of less than 2 predicts better response and longer survival [15]. The BCLC system assesses tumour stage, liver function, physical status and cancer-related symptoms, linking these in a widely used treatment algorithm [16], [17] [18]. The BCLC is the only system that links prognosis with treatment recommendations, and is therefore selected in several major trials of HCC therapy.

Conventional methods like TNM (e.g. TNM) exclude the functional status of the liver, which is an important consideration in these patients. However in patients with intermediate or advanced HCC who undergo surgery the AJCC/UICC system is useful [19]– the parameters include tumour size and number, vascular invasion (micro/macro) and degree of fibrosis Ishak grade. The 7th edition [20] has further refined prognostication for the intermediate/advanced stages of the disease and this continues to be where this staging system is useful but does not really improve discrimination for early HCC.

Other tumour factors known to impact on outcomes after LR include size of lesion, satellite nodules, serum AFP, margin status, vascular involvement and UICC stage 3 or 4 disease. These factors therefore need to be considered carefully prior to consideration of hepatectomy for HCC.

Size of lesion: It is unsurprising that the size of the lesion impacts on outcome after LR. Larger lesions indicating increased tumour load with increased risk of vascular invasion, need increased liver mass to be resected and therefore contribute to a lesser future functional liver remanant (FLR) on a background of underlying CLD. Smaller tumour size is a well-accepted as an important independent prognostic indicator for overall survival [22]- [25] but not disease-free survival. From a multi-institutional cohort of 557 patients, tumour size if less than 5 cm resulted in 43% 5-year survival compared to 32% for larger tumours. HR (95% CI) for recurrent disease and death if lesion more than 5 cm was 1.4 (1.1 – 1.9) [26]. In a series of 12,118 patients from Japan, size less than 2 cm was an independent predictor of survival compared to larger tumours (2 cm, 2-5 cm, 5-10 cm and more than 10 cm; 5 year survival 66%, 53%, 37% and 31%

Okuda staging					
	Negative		Positive		Stage
Tumour size	<50% of Liver		>50% of Liver		I: no positive factors
Ascites	Absent		Present		II: 1-2 positive factors
Bilirubin	<51 mmol/L		>51mmol/L		III: 3-4 positive factors
Serum Albumin	>3g/dL		<3g/dL		
Child-Turcotte-Pugh classification					
	1point	2 points		3 points	Class
Encephalopathy	None	Grade 1-2		Grade 3-4	A 5-6 points
Bilirubin	<2	2-3		>3	B 7-9 points
PT/INR	<1.7	1.7-2		>2	C 10-15 points
Ascites	None	Controlled on Rx		Refractory	
Albumin (g/L)					
CLIP – Cancer of the Liver Italian Program					
Points	CTP		Tumour morphology	AFP	PV thrombosis
0	A		Uninodular ≤50% of Liver		No
1	B		Multinodular ≤50% of Liver		Yes
2	C		Massive>50% of Liver		
BCLC – Barcelona caner of Liver Clinic staging					
Stage	Performance status	Tumour stage	PHT	Bilirubin	Classification
A1	0	Single	No	Normal	Very early
A2	0	Single	Yes	Normal	Early
A3	0	Single	Yes	Raised	
A4	0	3 tumours, <3 cm each	Yes	Raised	
B	0				Intermediate
C	1-2	Vascular invasion			Advanced
D	3-4	Any tumour			Terminal
AJCC TNM 7th edition					
Stage	T		N		M
I	T1 solitary tumour, no vascular invasion		N0		M0
II	T2 Solitary tumor with vascular invasion or multiple tumors, none > 5 cm		N0		M0
IIIA	T3a Multiple tumors > 5 cm		N0		M0
IIIB	T3b Single tumor or multiple tumors of any size involving a major branch of the portal or hepatic vein		N0		M0
IIIC	T4 Tumor(s) with direct invasion of adjacent organs other than gallbladder or with visceral peritoneum		N0		M0
IVA	Any T		N1		M0
IVB	Any T		Any N		M1

Table 1. Table of various staging systems [21]

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respectively). In this study on multivariate analysis, tumour size less than 2 cm resulted in a significantly better overall survival. Therefore the Liver Cancer Study Group of Japan (LCSGJ) suggests a tumour cut-off size of 2cm as apposed to the 5 cm suggested by the TNM system [24].

Whilst there is little doubt that the results are superior for small tumours (<5 cm), several studies have indicated that resection for larger tumours (>5 cm) [27], [28] is beneficial. The Memorial Sloan–Kettering Group have analyzed the results of resection in 154 patients (out of total of 412 seen at their institution over a 6 year period) and found that for tumors <5 cm, the overall 5-year survival rate is 57% and the disease-free survival rate is 44%. Even for those with large tumors (>10 cm), the 5-year survival rate was 32%, with disease-free survival rate is only 23% [27]. Therefore they concluded that LR was superior to other forms of treatment for larger tumours and advocated partial hepatectomy as a safe, effective, and potentially curative therapy of choice for HCC >5 cm. For tumors <5 cm, much more relevant is the comparison between LR and ablative options. In a comparative study from China of 1000 small tumours (less than 5 cm) versus 1366 large (more than 5 cm) [28] survival rates after LR at 5 years of 62.7% vs. 37.1% ($p < 0.01$) and at 10 years of 46.3% vs. 29.2% ($p < 0.01$) were seen on univariate analysis. However compared with patients who had large HCC, those with small HCC had a higher percentage of single tumor nodules (82.6% vs. 64.4%), a higher proportion of well encapsulated tumors (73.3% vs. 46.3%), a lower proportion of tumor emboli in the portal vein (4.9% vs. 20.8%) and better differentiation of tumor cells (Edmondson Grade 3–4; 14.9% vs. 20.1%), a higher resection rate (93.6% [1000 of 1068 patients] vs. 55.7% [1366 of 2451 patients]; $P < 0.01$), a higher curative resection rate (80.5% [805 of 1000 patients] vs. 60.7% [829 of 1366 patients]; $p < 0.01$) and a lower operative mortality rate (1.5% [15 of 1000 patients] vs. 3.7% [50 of 1366 patients]; $p < 0.01$). Importantly following multivariate analysis, four independent covariates negatively influenced the survival rate: γ-glutamyl transpeptidase (more than 6IU/mL), presence of cirrhosis, multiple tumors, and emboli in the portal vein. Size of lesion was not an independent predictive factor.

The results of surgery in the so-called giant tumours (>10 cm) which would be exempt from transplantation, are reassuring too; Chen and co-workers [29] reported on 525 patients with tumours >10 cm noting a 2.7% perioperative mortality and a 5-year survival of 16.8%. Yeh and colleagues reported 211 tumours greater than 10 cm in a series of 1196 patients thus representing 17.6% of their patients. They noted resection to be safe and feasible with a reasonable 5-year survival of 16.7% for this cohort although this was significantly lower than the 39.5% documented for tumours less than 10 cm [30]. In a study of 300 patients with tumours >10 cm, the group from MD Anderson reported a 27% 5-year survival [31]. Therefore the value of resecting large and otherwise 'untreatable' tumours was confirmed. It is clear that prognostic indicators such as size can be used as a guide in the decision to operate or not, but cannot be used alone to exclude patients from surgery - such decisions should be based on surgical risk and resectability.

Vascular invasion: Again from the multi-institutional cohorts (vide supra) the presence of vascular invasion appears to be an independent predictor of recurrent disease and death after LR; HR (95% CI) for major vascular invasion – 2.1 (1.4 – 3.3), microvascular invasion – 1.6 (1.2 – 2.1) and 5-year survival with and without macrovascular invasion was 15% versus 41%

respectively [26]. In a cohort of 322 patients undergoing resection for HCC [32] the 5-year survival of those with microscopic venous invasion (n = 140) versus macroscopic venous involvement (n = 50) versus those without any venous invasion (n = 132) was 30.8%, 15% and 50% ($p < 0.05$). Also, larger tumours were associated with higher incidence of venous involvement. Major vascular invasion (macrovascular invasion) into one of the main portal branches or a hepatic vein is associated with a worse prognosis, presumably due to intra-hepatic and systemic dissemination of tumour thrombi. From a multi-institutional study of 102 patients, major portal invasion was associated with 1-, 3- and 5- year survival of 47%, 17% and 10% respectively [31], however in the group which had major vascular involvement but without moderate-severe fibrosis or high nuclear grade 5 year survival was 23% vs 5% and 21% vs 9% respectively. Therefore the MD Anderson data suggests resection in spite of major vascular invasion in the absence of moderate-severe fibrosis in the liver parenchyma and absent high nuclear grade in the tumour. Similarly the incidence of microscopic vascular invasion is increased with tumor size (≤3 cm, 25%; 3.1-5 cm, 40%; 5.1-6.5 cm, 55%; >6.5 cm, 63%) ($p < 0.005$) [33]. Therefore it is clear that tumour size, which can be measured radiologically, is a good surrogate marker for microvascular invasion, which can only be assessed on the resected specimen. It is accepted that larger tumours (especially those more than 7 cm) and certain types of growth patterns (single nodule with extra-nodular growth, contiguous multi-nodular growth patterns) are highly predictive of microvascular invasion (as compared to a single nodular type with clear demarcation) in lesions more than 5 cm in size [34]. However increasing size or number of lesions in the absence of vascular involvement does not impact on survival [26].

3.2. Tumour number, multifocality and satellite nodules

The number of tumours present is another important factor for not only overall survival [35] [31] [36] but for disease-free survival [36]- [39] as well.. The AASLD guidelines recommend LR for a single liver lesion if there is no cirrhosis or significant impairment of liver function [4]. However results from a large multi-institutional cohort study [36] looking at the perioperative and long-term outcomes of 404 patients with single small HCC (<5 cm) as compared to 380 patients with large or multinodular HCC demonstrated overall survival rates were significantly higher in the small HCC group (1 year, 88% vs. 74%; 3 years, 76% vs. 50%; 5 years, 58% vs. 39%; $p < .001$). Among patients with the larger tumours, five independent prognostic factors were identified to be associated with a worse overall survival: namely, symptomatic disease, presence of cirrhosis, multinodular tumor, microvascular tumor invasion, and positive histological margin. Multifocality may be a manifestation of one of 2 differing scenarios: either multiple foci of primary tumour within an at-risk field or the presence of intrahepatic metastases from a primary lesion. It is impossible to determine which scenario is being displayed pre-operatively but the latter carries a significantly worse prognosis.

3.3. Pre-operative Alpha-Fetoprotein (AFP) levels

AFP is a major plasma protein produced by the yolk sac and the liver during fetal development that is thought to be the fetal form of serum albumin. Its levels decrease rapidly after birth and

its functions in the fetus are not clearly known. Its levels are raised in HCC and germ cell tumours. Raised AFP levels have been considered to be a marker of poor prognosis both for overall survival [37] [27], [40] and disease-free survival [30], [37], [41], [42]. The relevance of AFP levels has not been addressed specifically in relation to resection although in one study an AFP level more than 100ng/ml was an independent risk factor [OR (95% CI) 2.56 (1.05 – 6.20)] along with microvascular invasion (OR 4.54 (1.86 – 11.09) in a cohort of small HCC who underwent curative resection [43]. AFP levels are probably a reflection of tumour biology and thus a surrogate marker for size/stage of the tumour.

4. Liver specific factors

4.1. Portal hypertension

It is well known that patients with a normal liver tolerate large hepatectomy without significant risk of liver failure. However, in patients with chronic liver disease the tolerance to liver resection and long-term outcome is reduced in parallel to the degree of liver function impairment and appearance of portal hypertension (PHT) [44]. Hemodynamic studies have shown that the presence of a hepatic vein pressure gradient greater than 10 mmHg is associated with a higher risk of postoperative liver decompensation and of poor long-term outcome after liver resection for HCC [45]. Clinically relevant PHT can also be detected by the presence of esophageal varices or splenomegaly associated with reduced platelet count. Assessment of presence or absence of PHT is an important step in not only risk assessment and outcome prediction, but importantly to ascertain suitability for resectional surgery and the extent of such surgery [46]. Indeed a recent study has suggested that this is an essential part of assessment of these patients for resection [47]. HVPG is an invasive test but some interest and success has recently been demonstrated for measurement of liver stiffness by elastography and its correlation with HVPG [48]. While 5-year survival in patients without PHT exceeds 70%, those patients with such adverse profile present a reduction to 50–60%. If liver disease is decompensated (ascites, jaundice), survival is even further decreased. Presence of PHT higher risk does not translate into absolute contraindication for resection [49], as less extensive resection/ ablation etc. can be considered but the predicted outcome with surgery has to be weighed against other available treatment options in an individual patient.

4.2. Future liver remnant/ Functional Liver Remnant (FLR)

One of the important limiting factors for LR in HCC is the amount of viable liver parenchyma left behind- future liver remnant or more appropriately called functional liver remnant (FLR). In a normal liver, removal of a part of the liver leads to rapid hypertrophy of the remnant to reach the pre-operative liver-body weight ratio. Adequate FLR is not only an adequate volume of liver remnant but also a remnant of adequate function sufficient to meet post-operative physiological demands. Although the removal of up to 75% of the total liver volume is feasible in a young patient (≤40 years of age) with normal hepatic parenchyma, resection must be more conservative in the presence of underlying liver diseases (steatosis, steato-hepatitis, fibrosis,

cirrhosis, cholestasis, chemo-therapy induced liver injury), elderly patients and in the setting of excessive intra-operative blood loss [50]. An adequate FLR is generally considered to be around 25%, 30% and 40% of the pre-operative liver volume in normal [51], steatotic and cirrhotic livers [52] respectively, although it is accepted that volume is a poor correlate of function in livers with chronic disease. Below a certain threshold, a liver remnant cannot sustain metabolic, synthetic and detoxifying functions and liver failure results leading on to the spiral of cholestasis, coagulopathy, sepsis, multiple organ failure and potentially death. Various techniques of assessing the FLR have been described including assessment of volume using axial imaging e.g. triple phase CT Liver, and MR Liver. Dynamic quantitative liver function tests, such as the indocyanine green test and galactose elimination capacity, are more accurate as they measure the elimination process of a substance that is cleared and/or metabolized almost exclusively by the liver. However, these tests only measure global liver function. Nuclear imaging techniques (Tc-galactosyl serum albumin scintigraphy and Tc-mebrofenin hepatobiliary scintigraphy) can measure both total and future remnant liver function and potentially identify patients at risk for post resectional liver failure [53]. A novel technique described has been the utilization of a combination LiMAX test (Liver MAximum capacity) and (triple phase CT, 3-D analysis – MeVIS, CT volumetry and virtual resection) and to successfully predict FLR and postoperative outcome after hepatectomy pre-operatively [54].

Preoperative portal vein embolization of the lobe free of disease may induce compensatory liver growth, allowing resection of larger volumes of tumour bearing liver [55] [56]. Indeed pre-operative selective internal radiotherapy (SIRT/Transarterial radioembolization – TARE) is being used to down-size liver tumors [57] including HCC [58] and increase FLR prior to major hepatectomy.

5. Liver resection for HCC — Technical considerations

Both non-cirrhotic patients and cirrhotics could be subjected to surgical resections as long as liver function was well-preserved and tumor had low burden (ideally single tumor). Usually, best results of surgical approaches are obtained in experienced centers with a perioperative mortality of less than 3% and a 5-year survival rate higher than 50% [6]. The correct selection of candidates is very important for the outcome and all issues discussed above need to be considered. Historically, patients with HCC and cirrhosis had a worse prognosis after LR but those without extrahepatic disease and small tumours had early mortality much lower than that reported for LT. Mortality rate related to LR in non-cirrhotics is approximately 1% [59]. The most common causes of death following LR are postoperative haemorrhage, liver failure and sepsis, even in well-compensated Child's A or B cirrhotics. Extended left and right hepatectomy are well documented in cirrhotic patients with low complication rates, ensuring a sufficient remnant hepatic function. The improvements of surgical techniques (e.g. Pringle's manoeuvre, anterior approach, low CVP anaesthesia), a better Knowledge of Couinaud's segmental anatomy, the development of ultrasonic dissectors and vascular staplers have contributed to reduce postoperative morbidities, including bleeding complications. Therefore LR for HCC should be an important treatment modality in the current era.

5.1. The anterior approach and the hanging manoeuvre

During right hepatic resection for hepatocellular carcinoma (HCC), complete mobilization of the right lobe of liver with the right hepatic vein controlled outside the liver before parenchymal transection had been advised by most surgeons in an effort to reduce blood loss. However, this can be difficult, when resection for large HCC is being performed. The size of the tumor may limit access to the posterior aspect of the right lobe of liver and the anterior surface of the inferior vena cava, where the right hepatic vein and many caval branches are present. Injudicious mobilization and forceful retraction of the liver may cause profuse bleeding from avulsion of the hepatic vein and caval branches, prolonged ischemia of the liver remnant from rotation of the hepatoduodenal ligament iatrogenic tumor rupture, and scatter of tumoural cells into peripheral blood. Alternatively, the anterior approach can be used in the more difficult cases of right hepatic resection for HCC. The technique implies initial completion of parenchymal transection before the right lobe is mobilized. Briefly following laparotomy, intra-operative ultrasonography and hilar dissection to control the right hepatic artery and portal vein, mobilization of the tumor and the right lobe of liver is not performed as in the conventional approach. The plane of parenchymal transection, depending on the extent of hepatic resection, is marked on the Glisson capsule with the help of intraoperative ultrasonography and transection carried out from the anterior surface of the liver down to the right side of liver hilum and down to the anterior surface of the inferior vena cava. The right hepatic vein is then isolated, clamped, divided, and sutured outside the liver parenchyma. When the specimen is completely disconnected from the inferior vena cava, the right hepatic lobe is mobilized from the right abdominal cavity by dividing the triangular ligament and other posterior attachments [25], [60]. This technique pioneered from Hong Kong demonstrated significantly fewer intraoperative haemorrhages and blood transfusions, a lower hospital death rate, a lower incidence of pulmonary metastases, and a better median disease-free survival and median overall cumulative survival in n=54 patients as compared to patients who underwent conventional approach n=106 to major liver resection for HCC more than 5 cm in size [25]. A randomized controlled study from the same institute reported better operative (lower blood loss, lower transfusion requirements, lower plasma albumin mRNA levels) and survival outcomes [lower in-hospital mortality 91/60 vs. 6/60), overall survival but not disease free survival] from anterior approach compared with the conventional approach [61]. However the anterior approach can potentially be dangerous" because "torrential bleeding can occur at the deeper plane of parenchymal transection" and "without prior mobilization of the right liver and the tumor, and control of the right hepatic vein, bleeding can be substantial and difficult to control. Therefore the anterior approach can be an effective alternative when difficulty is encountered during liver mobilization utilizing the conventional technique [62].

5.2. Anatomic (AR) vs. Non-Anatomic Resections (NAR)

Microportal invasion and intrahepatic metastasis were considered to be the most important factors leading to recurrence and were associated with poor prognosis [26], [63], [64]. Therefore anatomic resection [65] (AR), which is the systematic removal of a hepatic segment/s bearing the tumour/s. Theoretically, this procedure may be effective in eradicating intrahepatic

metastasis of HCC, leading to more favorable results in HCC patients. Although some authors have reported that AR may prevent hepatic recurrence and prolong survival [7–9], others have failed to detect survival benefits of AR [10–12]. Thus, the superiority of AR compared to non-anatomic resection (NAR) remains controversial. A recent metaanalysis of 16 nonrandomized studies involving 2,917 patients (AR n=1,577 vs NAR n= 1,340) reported that AR was characterized by better survival and lower local recurrence rates than NAR for the treatment of HCC [66]. Patients in the AR group had lower prevalence of cirrhosis and hepatitis virus infection, better liver function, and larger tumor size compared with patients in the NAR group. AR provided a better 5-year overall survival than NAR (OR, 1.63; 95% CI, 1.15-2.32). Local recurrence (OR, 0.28; 95% CI, 0.16-0.50) and early (≤2 years) recurrence (OR, 0.55; 95 CI, 0.34-0.89) were all significantly lower in the AR group. AR improved disease-free survival significantly at 3 years (OR, 2.09; 95% CI, 1.52-2.88) and 5 years (OR, 2.24; 95% CI, 1.85-2.72). There were no differences regarding postoperative morbidity, mortality, and length of hospital stay between two groups. However another metaanalysis reported on nine comparative studies comprising 1,503 patients (833 AR and 670 NAR) [67]. In the combined results, disease-free survival was significantly higher in the AR group than in the NAR group (OR 1.78, 95% CI 1.22-2.59, P = 0.003; heterogeneity P = 0.08). Given the heterogeneity in the studies the authors cautioned against acceptance of the results. Presence of cirrhosis is a well-established risk factor not only for both hepatocellular carcinoma occurrence but also for recurrence after hepatic resection [2, 4, 5] in comparison to chronic hepatitis without cirrhosis. Since most of cirrhotic patients were submitted to NAR to save the liver parenchyma as much as possible to avoid postoperative liver failure, the end result of Zhou et al. is a natural consequence of this fundamental bias of the study population therefore the jury regarding the superiority of AR for HCC is still out [68].

5.3. Laparoscopic liver resection for HCC

Laparoscopic liver resection (LLR) was first reported in the early nineties as a novel procedure and initially adopted for non-anatomical liver wedge resection for peripheral benign tumors [69]. With increasing advances in instrumentation and techniques, LLR has been established as a safe and feasible option for both benign and malignant liver lesions. A world review of laparoscopic liver resection (2804 patients, 127 published papers, both malignant and benign tumours) demonstrated that the procedure in experienced hands carries an acceptable morbidity and mortality for both minor and major hepatectomy [70]. Intuitively it does appear that for patients with a solitary HCC <5 cm in the periphery of the liver i.e. segments 2, 3, 4b, 5, and 6, compensated liver disease in the absence of significant portal hypertension, LLR has an important role. A number of advantages have been recognized when comparing LLR vs LR from case-matched analyses [71], [72] and case series - including reductions in postoperative pain, less blood loss, lower blood transfusion requirements, less operative morbidity [71], and shorter length of hospitalization [71] with similar long-term outcomes [71] especially for cirrhotic patients [72]. However to date there are no randomized trials comparing these 2 modes of surgery.

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At least 3 different meta-analyses [73] [74], [75] have been published in the last 20 months comparing available evidence for and against LLR vs LR for HCC. All 3 analyses concluded that LLR results in less blood loss, decreased rate of intraoperative transfusion and shorter lengths of hospital stay with no adverse impact long-term oncologic outcomes or increased risk of tumor recurrence. In fact for tumours in the periphery of the liver, resection can be performed with reduced mortality and morbidity and equivalent oncologic outcomes, disease-free survival, and overall survival when compared with similarly selected cirrhotic patients undergoing open resection [76].

Importantly, because HCC recurrence remains high in the cirrhotic liver, treatment following surgical resection mandates routine surveillance and further treatment of the recurrence either by locoregional therapy, re-resection, or transplantation as appropriate - the latter two of which are facilitated by an initial laparoscopic resection [76], [77].

6. Long-term outcome after liver resection for HCC

The majority of patients presenting with hepatocellular cancer are inoperable, largely due to extent of disease and poor liver function. The overall resection rate is <40% with a long term survival – of no more than 15%, due largely to the high post op mortality rate, intra-hepatic recurrence, distant metastases, progressive liver disease and the lifelong risk of hepatitis – although the new treatment options now available may reduce the risk in the long term.

Reviewing survival after resection for HCC in 17 series reported since 2000, each of which included more than 100 patients Takayama [78] et al. reported median survival rates of 80% (range 63 – 97%) at 1-year, 70% (34 – 78%) at 3 years and 50% (17–69%) at 5 years. Such wide ranges of survival rates are attributed mainly to differences in the HCC stage among the studies, but the survival rate is obviously much better for early-stage HCCs [79].

There is a large variation in the mortality rate following resection due to differences in definitions thus making inter-series comparisons difficult, this being further complicated by the mix of cirrhotic and non-cirrhotic patients, and various distributions of Child-Pugh status. Irrespective of the presence or absence of cirrhosis, the median perioperative mortality rate either 30 day or in-hospital mortality was a median of 4.7% with a range from 0 to 21.1%, with lower rates seen in series with larger volumes irrespective of underlying liver disease [80].

HCC frequently recurs after curative liver resection. The post- operative 5-year recurrence rate is 77–100%, and median survival after recurrence is 7–28 months [81]. Nonetheless, the long-term survival after hepatectomy remains unsatisfactory because of the high incidence of recurrence. Intrahepatic recurrences are the most common and are seen in up to 36.8–78% of patients [82]. About 80% of recurrent tumors develop exclusively within the liver, and only 20% of such tumors are resectable. As a treatment option, repeat liver resection has plays an important role in selected patients, yielding results similar to those after primary resection, with a 5-year survival rate of about 50%. Japanese authors have proposed that repeat resection is indicated for the treatment of recurrence in patients with a single HCC at the first resection,

a disease-free interval longer than 1 year and recurrent HCC with no portal invasion [78]. In patients who met these criteria, the 5-year survival rate was 86% after the second resection [83].

Predictors of poor outcomes in HCC are common to all therapeutic approaches and include more than three tumors, a tumor size larger than 5 cm, portal vein invasion, intrahepatic metastases, absence of a tumor pseudocapsule, advanced TNM stage (III or IV), Hepatitis C viral infection [84] and a Child – Pugh class of C [85]. The most important factors appear to be vascular invasion and liver function [86].

7. Liver resection prior to liver transplantation (Salvage liver transplantation)

Resection can be used as a treatment for HCC prior to LT in three different settings. First, resection can be used as a primary therapy, and LT reserved as a ''salvage'' therapy for patients who develop recurrence or liver failure. Second, resection can be used as an initial therapy to select patients who might get benefit from LT, according to detailed pathological examination of the tumor and the surrounding liver parenchyma. Third, resection can be used as a ''bridge'' therapy for patients who have already been enlisted for LT. Salvage LT has been performed for recurrent HCC or deterioration of liver function after primary liver resection.

Resection as the first-line treatment for patients with small HCC with preserved liver function, followed by salvage transplantation only for recurrence or liver failure is an attractive option. Initial resection, which should be preferably an anatomic resection, gives rapid access to an effective therapy, without the need for a donor, and offers 5-year survival rates exceeding 50% with a good quality of life [87]. The main obstacle to this strategy is the risk of ''loss of chance of cure'' in case of rapid and extensive recurrence not amendable to salvage LT. At the time of recurrence, salvage LT is only applicable/gives best results in patients with a tumor within the Milan criteria.

Another justification for resection prior to transplantation is that it helps refine the selection process, giving access to detailed pathological examination of the tumor and the surrounding liver parenchyma. Important prognostic information can be obtained, including differentiation, presence of satellite nodules, and the presence of microvascular and capsular invasions. As a result, resection may help avoid transplantation in patients with tumors apparently within the Milan criteria but with histological features of especially poor prognosis. In contrast, resection may help decide on transplantation in patients with tumors slightly outside the Milan criteria but with histological features of good prognosis.

Resection can also be used as a ''bridge'' therapy in patients already enlisted for LT. TACE and radiofrequency ablation, which are the mainstays of ''bridge'' therapies, can be challenged by resection, which provides the best control of the tumour, allowing accurate histological assessment of both the tumour and the underlying liver status. Although limited resection appears to be sufficient in this setting, it is associated with increased risk and is only appropriate for patients with peripheral tumours and Child A cirrhosis. The subsequent LT

may be made more difficult. The use of laparoscopic or transthoracic approaches for peripheral tumours may further contribute to expand this strategy by minimizing technical difficulties during the transplant procedure (vide supra). An important consideration is that significant adhesions and anatomical distortion exist in the abdomen following LR, although LLR seems to have a benefit to facilitate later LT by reducing these (vide supra). Although it has been claimed that prior LR neither increases operative morbidity nor impairs survival following cadaveric LT [88], this strategy is by no means universally acceptable [89]. This is due to LT after liver resection being associated with a higher operative mortality, an increased risk of recurrence, and a poorer outcome than primary LT [89]. In addition, liver resection as a bridge to LT impairs the patient transplantability and the chance of long-term survival of cirrhotic patients with HCC [89]. Indeed a recent comparative analysis of prognostic factors for HCC recurrence in a Western and an Eastern HCC patient cohort revealed on multi-variate analysis that that our independent risk factors for post-LT HCC recurrence: micro- vascular invasion (odds ratio, OR = 4.88; p = 0.001), poor tumour grading (OR = 6.86; p = 0.002), diameter of the largest tumour (OR = 4.72; p = 0.05), and previous liver resection (LR) (OR = 3.34; p = 0.04) [90]. It is therefore suggested that primary LT should therefore remain the ideal choice of treatment of a cirrhotic patient with HCC, even when the tumour is resectable. The salvage LT strategy should therefore be restricted to those patients with favourable oncological factors, thereby excluding patients with poor tumour grading, vascular invasion, diameter >3 cm and presence of satellite nodules at pathological examination, as recently suggested by the Belghiti group [91].

8. Liver transplantation for HCC

Liver transplantation (LT) is the treatment of choice for Child B and C patients with HCC but LT is limited by the lack of donor organs (demand exceeds availability) and the therapy cannot be given immediately (at least in the cadaveric LT setting)! One of the consequences of this shortage is that access to transplantation is usually restricted by rules that take into account need, transplant benefit, utility and distributive justice.

Liver transplantation for HCC before 1995 yielded disappointing results; 2-year survivals were 30% or less [92], [93], 3-year survival 3-year survival rates of 21% to 47% and the recurrence rates were high after transplantation (29% to 54%) [94]. These results were due to a bias toward performing transplantation for patients with unrespectable tumours. Through the 1980s and early 1990s, hepatic resection remained the treatment of choice for patients with early HCC and enough hepatic reserve to tolerate resection. Therefore, transplantation was often left to those with unresectable tumours (large, multiple, or both). The disappointing results called into question the value of transplantation for HCC [95]. However, within the total cohort of HCC patients who underwent transplantation, centers also reported on subgroups with early-stage disease that did well [96], [97]. Specifically, it was known that patients who had undergone transplantation and were found to have incidental small HCCs on histological examination of the explanted liver had excellent disease-free survival [98], [99].

In the current era the benchmark for LT in HCC is the Milan criteria. Following years of unrestricted use of LT for HCC with survival post LT being dismal (vide supra), the Milan criteria were introduced [100]. This prospective study included single tumours up to 5 cm or up to 3 tumours each not more than 3 cm and after four years their actuarial survival rate was 75%, the rate of recurrence-free survival was 83% and recurrence was seen in 8%. These results have been duplicated other in large cohorts [101] [102]. The Milan criteria have been widely implemented - the TNM staging system was modified such that T2 corresponds to the Milan criteria, UNOS has adopted these changes into their policy on recipient prioritization for liver transplantation and the BCLC staging system has incorporated the Milan Criteria into tis algorithm.

9. Assessment of candidates for LT

Staging of HCC patients (Table 1) should not only assess the tumour in the liver but also take into account the background liver disease and their performance status [103]. This will improve the accuracy of prognostication and enable selection of specific treatment alternatives.

Despite significant technological advances in cross-sectional imaging techniques (ultrasonography, CT, and MRI), standard imaging methods can underestimate or overestimate the extent of HCC in up to 25% of cases, compared with pathological findings of the explanted liver [104]. Conclusive imaging features rely on the presence of arterial enhancement followed by washout on portal venous or delayed imaging [105]. Dynamic CT or MRI, including unenhanced, arterial, portal venous, and delayed phases, provide improved sensitivity and specificity as compared with standard techniques of the past. Currently, there is no data showing the superiority of either MRI or CT. Dynamic ultrasonography has improved the accuracy of ultra sonography, but is less useful than CT or MRI because of the inability to reliably acquire images of the entire liver during a particular contrast phase. The American Association for the Study of Liver Disease (AASLD) has proposed an algorithm for diagnosis of HCC based on availability of state-of-the-art CT or MRI [106]. Bone scintigraphy has been used for evaluating bone metastases; however, the technique is poor in terms of cost-effectiveness when used routinely. There is insufficient data to propose [18] F-fluorodeoxyglucose (FDG)-PET for staging HCC before liver transplantation although PET scans using other isotopes (carbon-11, Fluorine-18 choline) have been utilized in staging HCC [107].

10. UK guidelines

The criteria first published in 2003 [108] for selection to the transplant list for cases with HCC has recently been revised. The current UK guidelines from May 2008 [109] (UK Guidelines for the management of suspected hepatocellular carcinoma (HCC) in adults) advise the following:

1. Radiological assessment should include both multidetecor (MD) CT and MRI, with size assessed by the widest dimensions of the neoplasm on either modality.

2. A lesion (for the purposes of counting numbers) will require to be identified as an arterialised focal abnormality with portal phase washout on MDCT or Gd enhanced MR. Other lesions are considered indeterminate.
3. Tumour rupture and an AFP > 10,000 IU/l are absolute contraindications to transplantation, as are extrahepatic spread and macroscopic vascular invasion.
4. The following are criteria for listing for transplantation; standard Milan criteria or the new UK criteria, which include: up to 5 lesions all < 3 cm single lesion > 5 cm < 7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%; no extrahepatic spread; no new nodule formation) over a 6 month period. Locoregional +/- chemotherapy may be given during that time. Their waiting list place may be considered from the time of their first staging scan.
5. Locoregional therapy should be considered for all transplant list cases.
6. Cases outwith current proposed selection criteria will not be selectable on to the transplant list after their tumour has been downsized by surgical or loco-regional treatments.

When utilising staging systems; clinical based systems are probably of greater use rather than the TNM (pathological classification) or the upto-7 criteria [110] (which relies on micro-vascular invasion) given that clinical decisions can be made more appropriately and prognostic information can be provided in counselling patients for such treatment. This is where the BCLC treatment algorithm becomes useful and indeed has been validated in cohorts outside of spain for this purpose. The International consensus report [103] recommended the use of BCLC staging system when considering treatment options (Evidence level 2b Strong recommendation) and the TNM system to assess prognosis after transplantation (Evidence level 2b Strong recommendation).

11. Role of tumour biopsy

A tissue diagnosis of a suspicious liver lesion would be an ideal guide to appropriate treatment in the setting of equivocal imaging and serology. Increasing advances in imaging (scanning machines and techniques) resulting in better discrimination of hypervascular lesions into HCC or other tumours has resulted in a decreasing need for pre-listing biopsy of tumours suspected of being HCC. The accuracy of cross-sectional imaging in diagnosing small malignant liver tumours (less than 2 cm), especially in the cirrhotic liver, however, remains problematic with sensitivities for MRI detection of such lesions being 13–67% and approaching 100% for lesions more than 3 cm [111] [112] [113]. Therefore the European Association for the Study of the Liver (EASL) permitted needle biopsy of lesions ranging from 10 to 20 mm in diameter in patients with cirrhosis [114] this has however been updated in 2012. Tumour biopsy is not required in cirrhotic patients considered for liver transplantation who have high-quality dynamic CT or MRI findings typical for HCC and a lesion larger than 1 cm according to current AASLD guidelines [106]; and for patients with lesions smaller or equal to 10 mm or atypical findings, non-invasive imaging does not allow an accurate diagnosis, and should not be used to

make a decision for or against transplantation. These recommendations were incorporated into the 2012 International consensus conference report [103] and EASL endorses these guidelines [115].

A systematic review [116] of 8 studies (none were RCT) revealed a needle track risk of seeding of 2.7% (CI 1.8 – 4) overall or 0.9% per year with a median time of about 17 (IQR 7- 48) months. However whether this risk does impact on treatment delivery and outcome from it is open to question [117]. In addition tumour biopsy has other limitations: The specificity of liver biopsy is close to 100%, but sensitivity varies depending on location of the tumour, needle size (86–90% with an 18 gauge cutting needle, 67% with 21–22 gauge needle), and tumour size (>90% for nodules >1 cm *vs* 83% for nodules <1 cm) [103] [118], [119]. A positive tumour biopsy is clinically relevant to rule in a diagnosis of HCC, but a negative biopsy is less useful. It is however clear that in the presence of unequivocal evidence i.e. AFP levels greater than 400 ng/L and imaging characteristics in a patient with known cirrhosis, there is no need for tumour biopsy according to the UNOS recommendations.

The recently updated European clinical practice guidelines for the management of HCC [115], referred to above, highlight the importance of preventive strategies and implementation of surveillance in those at risk. Surveillance with either USS or a combination of USS with serum alpha-fetoprotein is widely adopted with the intention of detecting early tumours in patients fit enough for surgical treatment. The diagnostic criteria for HCC as referred to in the consensus document are summarised in Table 2.

Size of nodule	Cirrhotic patient only
Nodule <1cm	4 month recall
Nodule 1-2cm	Non-invasive criteria i.e. typical features on one imaging technique, or biopsy
Nodule >2cm	Non-invasive criteria, with biopsy if atypical radiological features or uncertainty.

Table 2. Table for Diagnosis of HCC

Non-invasive criteria can only be applied to cirrhotic patients and should be based on triple or 4-phase CT scan or dynamic contrast enhanced MRI. The typical radiological hallmark of HCC is a hypervascular lesion relative to non-tumour liver in the arterial phase of a scan, with subsequent washout in venous or delayed phases. If features are suboptimal on one imaging modality, especially for small lesions, a second imaging technique (i.e. MRI + CT, not contrast enhanced USS) is recommended. In pathological diagnosis, in addition to assessment by an expert liver histopathologist, immunostaining for glypican-3, glutamine synthase are recommended to differentiate high grade dysplastic nodules from early HCC. In non-cirrhotic patients with a suspicious liver nodule (s), biopsy of non-tumour and tumour liver should be performed to confirm the diagnosis in patients who are candidates for treatment.

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12. MELD prioritization points

Following publication of the Milan criteria, the suitability of certain patients with HCC for LT led to an increasing number of patients being put forward for this procedure during the 1990s and early 2000s. Increasing demand and shortage of available organs led to long waiting times and stage progression for these patients with HCC whilst on the W/L leading them becoming unsuitable for Tx; in Spain the wait time increased from 62 to 162 days [44] and in the USA 25% of HCC patients dropped off the list every year [120]. When the MELD-based prioritization system for liver transplantation replaced the Child-Pugh system in February 2002, patients with HCC were given prioritization points as the MELD was not affected by the presence of HCC. Earlier under the CTP system patients with T2 or lower HCC were moved into a higher-priority group (status 2B), but waiting time within the group remained a significant factor and that was perceived as a significant injustice to HCC patients. Under the MELD prioritization the system initially gave additional points (up to 24 for T1 HCC and 29 for patients with T2 HCC) with extra points being added every 90 days spent on the waiting list - to represent a 10% increase in mortality. Although the average waiting time decreased from 2.28 years before the MELD system to 0.69 years under MELD, and >85% of HCC patients waited less than 90 days for transplantation and Tx for HCC tripled it went too far. Non-HCC patients with MELD scores of 24 to 29 had a higher chance of dying or dropping off the list because they often had more significant hepatic decompensation than HCC patients with MELD plus points. Also, the increase in transplantations for HCC had an adverse effect on organ allocation [121]. Fourteen percent of transplants performed for HCC had no HCC on explant histology in the first 8 months of MELD system [122]. This pre-transplantation false-positive diagnosis occurred more often for small, single lesions (e.g., T1). Moreover, data from the pre-MELD era indicated that patients with T1 lesions had less than a 10% risk of dropout in the first year listed. Conversely, patients with T2 lesions were responsible for much of the poor intention-to-treat outcomes under the old system [123]. Because of these data, the assigned MELD scores for patients with HCC were decreased to 20 and 24 for T1 and T2 lesions, respectively, in April 2003. Therefore the assigned MELD scores for patients with HCC were decreased to 20 and 24 for T1 and T2 lesions, respectively, in April 2003. This change decreased the proportion of transplantations performed for HCC from 21% to 14% [122]. Before MELD, the rate was 8%. More recently, the score upgrade for T1 lesions (20 points) was eliminated, so that now only patients with T2 lesions may receive a score upgrade (initially 24 points and now 22 points). The effects of these changes are not yet known.

Expansion of Milan criteria: Proponents of expanding the current criteria are driven by the increasing number of HCC patients in need of treatment and the observation that some patients with tumour burdens exceeding the Milan criteria do have long, disease-free survival after transplantation. Several studies have reported a good outcome for some patients transplanted outside these conventional criteria and the nature of these criteria has been challenged for being too strict, because they exclude specific subgroups with meaningful, although lower, chances to benefit from transplantation. Furthermore, some patients might be excluded from transplantation as a result of the improvement in the accuracy of imaging

techniques that enable the identification of very small lesions (<1 cm), which were undetectable a decade ago. Most of the studies on patients exceeding Milan criteria, however, are retrospective, with only a small number of patients, disease of variable severity, and short follow-up [124] [6], [125] [126].

In the context of shortage of available grafts, decisions have to take into account the collective benefit of all potential liver recipients, in addition to the benefit for the individual patient. Even though a survival opportunity considerably lower than that achieved in non-HCC patients might be considered worth the risk of surgery for some patients with HCC, the negative effects on others on the donor list must be taken into consideration. The international consensus group [103] recommended that liver transplantation should be reserved for HCC patients who have a predicted 5-year survival comparable to non-HCC patients.

Milan criteria	**5-year survival**
Single tumour ≤ 5cm	85%
Not more than 3 tumours, largest ≤ 3 cm	
UCSF	
Single lesion ≤ 6.5 cm	80%
Multiple lesions ≤ 3 cm	
Largest tumour diameter if multiple ≤ 4.5 cm	
Total tumour diameter if multiple ≤ 8 cm	
UK criteria	
Single lesion lesion > 5 cm < 7 cm diameter where there has been no evidence of tumour progression (volume increase by <20%; no extrahepatic spread; no new nodule formation) over a 6 month period.	
If multiple, up to 5 lesions all < 3 cm	
Metro-ticket (up-to 7 criteria)	
Single tumour 7 cm	71%
Multiple tumours seven as the sum of the size of the largest tumour [in cm] and the number of tumours	

* All survival figures depend on absence of vascular invasion. The metroticket model can predict for 3- and 5-year survival with and without vascular invasion (http://www.hcc-olt-metroticket.org/calculator/)

Table 3. Liver Transplantation criteria for HCC

The UCSF group found that patients who had undergone transplantation with single tumours up to 6.5 cm or no more than 3 tumours with maximum sum of diameters up to 8 cm and no tumour larger than 4.5 cm had acceptable disease-free survival, similar to that of patients who met Milan criteria [126]. This data was based on explant histology sizing and not on pretrans-

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plantation imaging. A follow-up study on a larger number of patients confirmed an acceptable 5-year disease-free survival of 88.5%, compared with 93.8% for those who met Milan criteria [123]. These findings have been subsequently prospectively validated based on pre-operative imaging too [127]. Numerous other expansions of Milan have been proposed including single lesions - 6 cm or up to 3 tumours, but none more than 5 cm where recurrence-free survival was 70% at 3 years [128], and the Up-to-seven criteria (Metroticket prognostication model - hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours with or without vascular invasion) where a 5-year overall survival of 71 2% (64 3–77 0) was seen [110]. But these have not been validated prospectively. Therefore the international consensus group [103] recommended only modest expansion of the Milan criteria (in line with UCSF recommendations) but emphasised that this should occur on the background of an individual centres waiting list of non-HCC patients, waiting list mortality and the loco-regional scarcity/abundance of donor organs.

13. Role of downstaging

An attractive strategy to improve the results of liver transplantation for expanded criteria HCC is downstaging to within Milan criteria using loco-regional therapy. The goal of downstaging using therapy, as alcohol injection, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial radioembolisation/selective internal radiotherapy (TARE/SIRT), or liver resection, is to decrease the tumour size and number in patients initially presenting with tumours that do not meet locally acceptable criteria for liver transplantation.

Theoretically, a downstaged tumour may carry a reduced risk of posttransplant recurrence comparable to that of one initially within the Milan criteria. More importantly, downstaging may allow selection of tumours with more favourable biology that respond well to treatment and also do well after liver transplant.

Two prospective studies showed that survival after liver transplantation in patients with large tumour burden successfully treated by downstaging was similar to survival in patients who initially met the criteria for transplantation. Pinna et al. compared the outcome of patients down-staged from outside Milan (n=48) to those within Milan (n=129) and reported similar LT rates (67 vs 68%), 1- and 3-year survival rates (71% vs 80% and 71% vs 78% respectively) between the 2 groups with no significant difference in actuarial intention to treat survival between the 2 groups (56.3% vs 62.8%) [129]. Forty-three patients were downstaged to meet the Milan criteria with a combination of liver resection, local ablation or TACE. Ten patients dropped out before transplantation due to liver failure (n = 2) or tumour progression (n = 8) and 32 underwent liver transplantation. The rate of dropout due to cancer progression was, as expected, higher in the downstaging group (27.1% vs. 11.6%) with more advanced HCC and the dropout should be regarded as a part of the selection process in order to achieve an acceptable posttransplant outcome in these patients. The authors rightly stated in the discussion, 'we clinically selected the HCCs with a more favourable biology'. Interestingly in this series nearly 70% of the patients in this series of expanded criteria recipients had serum

alphafetoprotein < 30 ng/mL. Serum alphafetoprotein has been found to be an important prognostic indicator for patients with HCC after liver transplantation and the incorporation of serum alphafetoprotein into a scoring system [130] as selection criteria can help to identify the high-risk, high-volume HCC for exclusion and the low-risk, low-volume HCC [131] for LT after down-staging. It is likely that downstaging may simply provide another mode of selection but its advantage over more simple selection criteria such as tumour size and number, histologic features or serum alphafetoprotein remains to be confirmed by further studies.

In another prospective study [132], 43/61 (70.5%) patients were downstaged (TACE and RFA) to UNOS criteria (vide supra) and after 3-months of progression free interval, 35(57.4%) underwent LT. Treatment failure was observed in 18 patients (29.5%), primarily due to tumour progression. In the explant of 35 patients who underwent LT, 13 had complete tumour necrosis, 17 met T2 criteria, and five exceeded T2 criteria and none demonstrated microvascular invasion or poorly differentiated disease. The Kaplan-Meier intention-to-treat survival at 1 and 4 years after down staging were 87.5% and 69.3%, respectively. The 1-year and 4-year post transplantation survival rates were 96.2% and 92.1%, respectively. No patient had HCC recurrence after a median post transplantation follow-up of 25 months. The only factor predicting treatment failure was pre-treatment alpha-fetoprotein >1,000 ng/mL. The main thrust of this study appears to suggest that using response to locoregional therapy to select transplant recipients provides an attractive alternative to simply expanding the existing criteria.

14. Managing patients on wait-list for LT

One of the consequences of waiting for transplantation is that during this time, the disease may change or in other words allow the true biological nature of the neoplasm to be expressed thereby aiding improved selection of patients for LT. Also the waiting time in which the disease can evolve allows treatment strategies, which can be implemented to influence its course. The seminal article of the BCLC study group [44] which compared the intention- to-treat (ITT) outcomes of resection and transplantation for HCC, identified that the concept of dropout on the waiting list was crucial, and it has become the equivalent of the risk of pretransplant mortality addressed by the Model for End-Stage Liver Disease (MELD) priority system for non-HCC patients. Therefore managing patients involves minimizing the drop-out rate and successfully "bridging" patients to a LT.

The term "bridging" is for strategies that are implemented in patients who already qualify for LT according to the accepted selection criteria so that they can wait until a graft is available. A bridging strategy can be effective because (1) it allows candidates to wait for a longer time or more candidates to wait for the same time (or both) or (2) it improves the results of transplantation by excluding patients whose disease will recur or by stopping the progression of a tumour before extrahepatic spread has occurred. The word "down-staging" refers to the reduction of the clinical stage of a disease from any initial stage (e.g., from T2 to T1), down-staging in the context of LT for HCC is used for strategies allowing the transplantation of patients who at first do not qualify for OLT because their tumours are outside the accepted

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criteria (T3 or higher). Down-staging strategies may use the same neoadjuvant treatments that are used in bridging strategies.

Therefore the aims of managing patients whilst on a wait-list i.e. bridging strategies are

1. For patients to remain good candidates until a graft is available.
2. For the transplant program and society to exclude poor candidates even though on entry they fulfilled restrictive selection criteria.
3. To improve the results after transplantation.
4. To be compatible with a treatment other than transplantation in the case of dropout.
5. To have an optimal cost and complication/effectiveness ratio.

Managing patients while they are waiting for a liver graft to become available involves monitoring not only the tumour but also the background liver disease. With increases in waiting times for liver transplantation, it is common practice to monitor patients with HCC to ensure that they remain within the acceptability criteria for liver transplantation. Both imaging and measurement of AFP levels are commonly utilised. There is no agreement about specific timing or optimum imaging methods (dynamic CT, dynamic MRI, or contrast-enhanced ultrasonography). In our Unit a 3-month interval between surveillance scans whilst on the wait-list is adopted.

Locoregional therapies represent bridging strategies for patients on the waiting list, because they can decrease tumour-related dropout rates and the incidence of recurrences after liver transplantation, above all for patients that have to wait 6 months or longer [133]. There is, however, no evidence that bridging strategies could be helpful in patients with United Network for Organ Sharing (UNOS) T1 tumours (<2 cm). Bridging strategies might be appropriate for patients with UNOS T2 lesions (one nodule 2–5 cm or three or fewer nodules each ≤3 cm) who are likely to wait 6 months or longer. Therefore a recent consensus conference [103] (clavien PA Lancet Oncol 2012) concluded that in patients with UNOS T2 (one nodule 2–5 cm or three or fewer nodules each ≤3 cm) HCC (Milan criteria) and a likely waiting time of longer than 6 months, locoregional therapy may be appropriate. However no one particular type of treatment was found superior although pathologically RFA was found to cause more tumour necrosis [133]. They also recommended that patients found to have progressed beyond criteria acceptable for listing for liver transplantation should be placed on hold and considered for downstaging, if this was not appropriate/not effective, they should be removed from the waiting list. Liver resection before transplantation in patients with well preserved liver function, and newer strategies such as a combination of TACE with RFA and use of 90-yttrium radioembolisation or targeted therapies, have shown some benefits in preliminary studies.

Two well-documented cohort studies - Rochester (54 patients) [134] and Innsbruck (116 patients) [135] have confirmed that TACE allows long waiting times [median 211 days (range 28-1099 days) in the Rochester study; median 274 days (range 36-1037 days) in the Innsbruck study] with relatively low total dropout rates (9% and 14%, respectively). Recurrences were rare in both studies and were not higher than what would be expected for T2 patients.

However a multicenter case-control study compared matched patients with TACE (100) and without TACE (100) and the survival rates 5 years after OLT were similar (59.3% versus 59.4%) [136]. Nevertheless, there were fewer recurrences in the TACE group (13 versus 23) but more non–tumour-related deaths (15 patients versus 7 patients). Therefore TACE may allow patients to wait longer than would otherwise be possible, and is not associated with more recurrences (which may in fact be less frequent). If the option of TACE is chosen, it should be pursued (if needed with multiple treatments) until the best possible effect on tumour necrosis is obtained [133].

RFA was not at first sight an appealing treatment in pretransplant patients because of the risk of local spread, and there were early reports of RFA in which seeding was frequent. Experience with the technique and a well-conducted cohort study have shown that seeding and recurrence are rare when patients and contraindications are selected carefully (i.e., subcapsular tumours and direct nodule puncture) [137]. Other confirmatory studies have shown that the technique can be used safely in pretransplant patients and that the percutaneous route is as safe as the laparoscopic approach and less cumbersome [138], [139]. In pathological studies, the results for RFA appear to be superior to those for TACE [140] [141] and RFA appears to be associated with less tumour progression [142]. Therefore RFA appears to be safe and can be used as a bridging strategy if this is indicated. Its ability to reduce dropout rates and its effects on post-transplant results need to be proven in a prospective, comparative study. In some anatomical situations – subcapsular lesions and very large lesions (more than 5-6 cm in diameter) optimal treatment is difficult to achieve with RFA, however this can be overcome with use of probes which can cause larger burns and those designed for use on the surface of the liver.

Although resection appears to be safe before transplantation (in terms of operative results and long- term outcomes) and to have a place in decision analysis when the waiting time is longer than 1 year, resection is very rarely used at the moment as a bridging strategy. This is further discussed in the salvage transplantation section.

Radioembolization with yttrium-90 represents 5% to 10% of bridging LRT procedures in the OPTN registry, but data on its impact are scanty. In a study that reported the correlation between radiological and pathological findings in patients with HCC who underwent radioembolization with yttrium-90 microspheres before transplantation, all target lesions demonstrated some degree of histological necrosis, and 23 of 38 (61%) showed complete pathological necrosis [143]. A recent study retrospectively analyzed transarterial radioembolization (TARE) and TACE in similar patients (122 and 123, respectively); 44 TARE patients and 46 TACE patients were at stage T2 [144]. Although there was no survival benefit for TARE, the time to disease progression and the AFP responses were significantly more favourable with TARE, and this suggests that this treatment could be a promising modality before LT but current data are too scanty to recommend the use of TARE for this, but this technique may be an appropriate one to use and should be the object of further investigation.

Conformal radiotherapy (CRT) is known as a feasible and efficient therapeutic option for HCC patients who are ineligible for a curative treatment (i.e., surgical resection or transplantation). However, minimal data exists for the use of CRT as a bridging option for patients on the waiting list and although CRT may be a safe and potent local bridging therapy for patients with

advanced HCC who are on the waiting list for LT [145]. Further studies are warranted to compare the effectiveness of CRT and other local therapeutic options in this setting.

It is important to emphasize that proof that bridging treatments does not result in more recurrences and worse outcomes after transplantation is not yet available (the above quoted studies may have a strong selection bias in the allocation of patients to treatment and no-treatment arms). Therefore a RCT with a no-treatment arm is the suggestion from a recent consensus conference [133] but the ethical and logistical problems in implementing such a trial can be substantial.

15. Role of LDLT

Living-donor liver transplantation (LDLT) using the right or left hemiliver of a healthy donor is the best therapeutic strategy for liver transplantation in some countries, especially in Asia, because of limited availability of deceased-donor organs. LDLT has also been used in other countries with well established programmes for organ donation from brain dead or non-heart-beating donors for organ shortage, long waiting times associated with deaths on the waiting list, drop-out due to medical reasons, or progression of tumours beyond acceptable criteria.

The main issue in LDLT is donor safety, because of the risk of complications or death, even if small. The concept of double equipoise was proposed to describe the balance between the recipient's survival benefit with LDLT and the risk of a complication or death of a healthy donor [146]. The physicians might discuss probable risks and benefits with their patients and meet the test of equipoise.

Six studies compared deceased-donor liver transplantation (DDLT) and LDLT for HCC, including a report from a multicentre US consortium of LDLT centres [147] [148] [149] [150]-[152]. No convincing difference in outcome could be identified according to type of graft, although a higher risk of recurrence was noted in fast-tracked patients, since a short delay between diagnosis and liver transplantation might not allow enough time for the biological behaviour of the tumour to manifest. Therefore the recent consensus conference [103] suggested a period of observation (e.g., 3 months) when offering LDLT in recipients with HCC although it is not included in their recommendations. They did recommend that LDLT is acceptable for HCC patients who have an expected 5-year survival similar to comparably staged patients receiving a deceased-donor liver. However a more recent meta-analysis of 12 studies which provided information on disease free survival on a total of n=633 LDLT and n=1232 DDLT concluded lower disease free survival for LDLT [153]. This result could no doubt occur due to reporting bias but the fact that the boundaries of criteria for LDLT are more relaxed as compared to DDLT. Most centres would transplant HCC without macrovascular invasion and absence of extra-hepatic disease in the setting of LDLT whilst the same tumour load would not be considered for DDLT and this practice has been cautioned against [154].

16. Post-LT management

The role of immunosuppression in HCC patients after liver transplantation is still controversial, because experimental models would have shown oncogenic properties of immunosuppressive drugs. Currently, most programmes are careful to balance the inherent risks of rejection and tumour recurrence. However, there are no RCTs that have shown that lowering immunosuppression reduces the risk of HCC recurrence after liver transplantation. One class of immunosuppressive drugs, the mTOR inhibitors, might be useful for patients with HCC who receive a liver transplantation, since experimental studies have shown that this drug has strong immunosuppressive effects with concomitant anti-neoplastic properties [155]. Uncontrolled pilot trials and retrospective analyses have suggested that sirolimus, an mTOR inhibitor, was associated with lower tumour recurrence and improved survival after liver transplantation [156], [157], these results have not been confirmed in an RCT. At present, therefore, the type or dose of immunosuppression therapy influencing the incidence of HCC recurrence or its prognosis are still much debated [103].

There is also no evidence to support the use of adjuvant treatment to decrease risk of post LT recurrence [103]. Numerous uncontrolled studies and 4 RCTs (n=213) [158]- [162] do suggest some benefit but the variety of drugs used and the varied inclusion criteria and end-points make interpretation difficult. Sorafenib (multitargeted tyrosine-kinase inhibitor) and Licartin [159] (131I-radiolabelled murine monoclonal antibody that specifically binds HCC cells) show some promise but are not recommended for adjuvant use after transplantation at present.

The main problem after liver transplantation for HCC is the risk of tumour recurrence, which occurs in 8–20% of recipients. HCC recurrence occurs usually during the first 2 years after liver transplantation, and is associated with a median survival of less than 1 year (IQR 7–18 months) from the time of diagnosis [163]. The routine use of imaging and α-fetoprotein monitoring has allowed earlier detection of recurrence, with a likelihood of cure with ablation therapies in up to a third of cases [164]. However no particular protocol for surveillance has been proven and individual centres like ours tailor their imaging frequency based on AFP levels.

The treatment of HCC recurrence after liver transplantation is much debated. Retransplantation is not appropriate since during most recurrences there is often systemic dissemination of tumour cells [165]. Locoregional therapy for HCC recurrence, including liver resection [166], radiofrequency ablation, or TACE, has been successfully used in selected patients with limited disease, and might be considered when technically feasible. Sorafenib has been used after liver transplantation recurrence, sometimes in conjunction with mTOR inhibitors with success and with limited side-effects [167].

17. Concluding statements

The best results for liver resection are obtained in patients with small solitary tumours. While multifocal disease may not impede resection as regards technical feasibility, most of the data

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suggests that long-term survival even in the absence of portal hypertension is poor with a high rate of disease recurrence [44]. This is the major drawback of surgical resection (as well as of ablation) and is due to two mechanisms. The most frequent is cell dissemination prior to treatment. This gives rise to metastatic nests and its incidence is higher in tumours exhibiting microscopic vascular invasion and/or satellites [168]. More than 80% of the patients with this profile will suffer recurrence within the first two years of follow-up and their prognosis is negatively affected. The second mechanism for recurrence is related to the oncogenic capacity of the background liver parenchyma which is diseased that can give rise to metachronous tumours [168]. They are more prevalent after the two years of follow- up and their potential to be successfully treated is higher as compared with early recurrence that is usually multifocal. Since the prevalence of vascular invasion/satellites increases along with tumour size, it is clear that the larger the tumour, the higher the risk of these and of recurrence. However, there are some infrequent patients with large solitary HCC in whom the expansive tumour growth has not been associated with development of additional tumour sites. Hence, if after proper staging of a large HCC there is no proven dissemination, surgery should not be contraindicated, but physicians and patients should be aware of the statistics showing that the likelihood of microscopic vascular invasion (and hence, early recurrence after surgery) parallels tumour size. Indeed, intraoperative ultrasound may disclose additional tumour sites not detected preoperatively and abort the proposed resection. Careful evaluation of the non-tumoural liver parenchyma to be resected and of the expected remaining volume is mandatory prior to operation.

Interestingly, the risk of HCC recurrence after transplantation is less than after resection or ablation even if stratifying for the same pathology risk profile. Hence, with similar survival and less recurrence, it would appear reasonable to consider transplantation as the first option as it would solve HCC and the underlying oncogenic liver. This consideration has to be tempered by the fact that liver transplantation is not a simple procedure. Morbidity and death rate in the early and intermediate follow-up period are higher than after resection surgery in optimal candidates. Also, while recurrence of hepatitis B and alcoholic liver disease may be prevented, the status in patients infected with hepatitis C virus is not so encouraging [169] [170]. Effective viral eradication is not common in cirrhotics (the underlying disease in most HCC), treatment pre and post-transplantation may have severe side effects, reinfection of the graft is the rule and the long-term outcome is significantly impaired as compared to the other populations. All these facts have maintained surgical resection as the first line surgical option in patients with optimal profile as defined by solitary HCC in a liver without clinically relevant portal hypertension. Operative risk is very low and analysis of the resected tumour will allow the classification of the tumor as at low risk for recurrence (no vascular invasion or satellites) or as at high risk because of adverse pathology profile [171]. If this is the case recurrence will impair prognosis and if the patient had been transplanted the risk and survival would have been significantly better. Based on this, the recommendation in these high-risk patients is to propose transplantation because of high risk of recurrence and not delay the decision to the appearance of recurrence as at that time multifocality will be the rule and transplantation will be contraindicated. By contrast, if the resected tumour does not have an invasive phenotype, the patient can avoid liver transplantation and the associated risks, while being under strict

surveillance. Recurrence will likely correspond to a metachronous tumour and benefit again of the same decision making process for treatment allocation [5].

Because of the lack of donor livers for transplantation, strict selection criteria were introduced in order to achieve acceptable outcomes. Since the introduction of these Milan criteria in 1993, LT for HCC has been associated with an overall 70% 5-year survival. Although the Milan criteria have been criticised in recent years for being too restrictive, recent data has shown them to have stood the 'test of time' and are as relevant today as they were 20 years ago. Therefore any expansion of these criteria such as the UCSF or 'Metro-ticket' criteria must be critically assessed.

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