Hepatocellular Carcinoma

Current Management and Perspectives for the Future

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Objective: To review the literature on current management of hepatocellular carcinoma (HCC).

Background: Hepatocellular carcinoma represents one of the most common malignancies worldwide with a rising incidence in western countries. There have been substantial advances in the surgical and medical treatment of HCC within the past 2 decades.

Methods: A literature review was performed in the MEDLINE database to identify studies on the management of HCC. On the basis of the available evidence recommendations for practice were graded using the Oxford Centre for Evidence-based Medicine classification.

Results: Advances in surgical technique and perioperative care have established surgical resection and orthotopic liver transplantation (OLT) as primary curative therapy for HCC in noncirrhotic and cirrhotic patients, respectively. Primary resection and salvage OLT may be indicated in cirrhotics with preserved liver function. Selection criteria for OLT remain debated, as slight expansion of the Milan criteria may not worsen prognosis but is limited by organ shortage and prolonged waiting time with less favorable outcome on intention-to-treat analyses. Strategies of neoadjuvant treatment before OLT require evaluation within prospective trials. Transarterial chemoembolization is the primary therapy in patients with inoperable HCC and compensated liver function. Although systemic chemotherapy is not effective in patients with advanced HCC, there is recent evidence that these patients benefit from new molecular targeted therapies. If these agents are also effective in the neoadjuvant and adjuvant setting is currently being investigated. Furthermore, selective intra-arterial radiation therapy represents a promising new approach for treatment of unresectable HCC.

Conclusions: Recent developments in the surgical and medical therapy have significantly improved outcome of patients with operable and advanced HCC. A multidisciplinary approach seems essential to further improve patients' prognosis.

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Hepatocellular carcinoma (HCC) represents the sixth most common malignancy and the third most common cause of cancer-related death worldwide.[1] In the United States and Europe where chronic hepatitis C virus (HCV) infection represents the main risk factor[2] the incidence of HCC has been rising and is expected to further increase in the next 2 to 3 decades.[3] In Asia and Africa chronic hepatitis B virus (HBV) infection is the leading risk factor and might be further enhanced by exposure to Aflatoxin B_1. The majority of HCC patients (95% in the western, 60% in Asian countries) will develop the disease on the ground of preexisting liver cirrhosis. Presence of cirrhosis markedly increases the risk for HCC development. The annual HCC incidence for cirrhotic patients with HBV and HCV infection accounts for 2% to 6.6% and 3% to 5%, respectively.[2,4] Advances in diagnostic tools, surveillance programs, and survival of patients with cirrhosis are likely to further increase the incidence of HCC and the proportion of patients diagnosed at a potentially curative stage of disease. There has been major progress in the understanding of the disease and therapeutic options in the past 2 decades, which substantially altered the clinical management of patients with HCC. In this article, we present current evidence on the management of HCC patients and provide an outlook of further improvements that might be expected in the future. Recommendations were made using the classification by the Oxford Centre for Evidence-based Medicine (Grade of recommendation A–D).[5]

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STAGING OF HCC

Therapy for HCC patients should be based on the patient's prognosis, which in turn is complex to assess, as it depends on the tumor stage, the underlying liver function and the patient's physical condition. Several staging systems have so far been suggested without an overall consensus for any of these (Table 1).[6–9] Although The American Joint Committee on Cancer/Union internationale contre le cancer Tumor-Node-Metastasis staging system (AJCC/UICC TNM) adequately stratifies patients into prognostic groups,[10] it is only applicable to patients undergoing resection or orthotopic liver transplantation (OLT) and does not consider the underlying liver function. In 2009, the seventh edition of the TNM classification of malignant tumors was published.[11] Changes to the previous classification include a subdivision of T3 in T3a and T3b. Furthermore, the UICC stage IV is subdivided in stage IVA (positive regional lymph nodes) and stage IVB (distant metastases). However, the revised TNM classification requires validation. The Okuda and the Cancer of the Liver Italien Program (CLIP) classifications were introduced as clinical staging systems considering tumor features and hepatic function. The Okuda system was developed based on a retrospective analysis of 850 HCC patients[7] and has been found to be rather inaccurate for prognostic stratification of patients, in particular for patients at an early stage of disease.[12] The CLIP scoring system considers several factors related to tumor biology (ie, tumor morphology, AFP level, and portal vein thrombosis). Although it has been validated in a prospective manner,[13] the CLIP scoring system might be inadequate to identify patients at early stages of disease and it is probably rather helpful to identify patients with a poor prognosis. The Japan Integrated Staging score combines the Child-Turcotte-Pugh (CTP) class with the modified TNM stage according to the Liver Cancer Study Group of Japan (LCSGJ) and was developed to overcome this problem.[14] In a multicenter validation including more than 4500 patients the predictive value of the Japan Integrated Staging score was proven to be superior to the CLIP scoring system.[15] The Barcelona Clinic Liver Cancer (BCLC) staging system which was suggested in 1999 as a modification of the Okuda system[6] has been repeatedly validated for prognosis of patients with HCC.[16,17] It involves tumor-related parameters (tumor size, number of nodules, vascular invasion), patients' clinical condition (WHO Performance Status) and liver function (CTP classification). This information forms the framework for categorizing the

TABLE 1. Common HCC Staging Systems

AJCC/UICC tumor-node-metastasis staging system for HCC (7th edition; 2009)

Primary tumor

T_1	Single tumor without vascular invasion
T_2	Single tumor with vascular invasion or multiple tumors none > 5 cm
T_3	T_{3a}: Multiple tumors any >5 cm
T_4	T_{3a}: Tumor of any size involving a major branch of the portal or hepatic vein
	Tumor(s) with direct invasion of adjacent organs, other than the gallbladder, or perforation of visceral peritoneum

Regional lymph nodes*

N0	No
N1	Yes

Distant metastases

M0	No
M1	Yes

Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage IIIA	T_{3a}	N_0	M_0
Stage IIIB	T_{3b}	N_0	M_0
Stage IIIC	T4	N_0	M_0
Stage IVA	Any T	N_1	M_0
Stage IVB	Any T	Any N	M_1

Okuda staging system for HCC

	0 points	1 point
Tumor size	< 50% of liver	> 50% of liver
Ascites	No	Yes
Albumin (g/dL)	>3	<3
Bilirubin (mg/dL)	<3	>3

Stage I: 0 points; Stage II: 1–2 points; Stage III: 3–4 points

Cancer of the Liver Italien Programme staging system of HCC

Points	Cirrhosis	Tumor morphology	Alpha feto protein [ng/dL]	Portal vein thrombosis
0	CTP class A	Single, < 50% of liver	< 400	No
1	CTP class B	Multiple, < 50% of liver	≥ 400	Yes
2	CTP class C	Massive or 50% of liver		

CLIP score (0–6): sum of points for four variables

Barcelona Clinic Liver Cancer staging sytem of HCC

	PS	Tumor stage	Liver function
Stage A1 (very early)	0	Single tumor	No portal hypertension, normal bilirubin level
Stage A2 (early)	0	Single tumor	
Stage A3	0	Single tumor	Portal hypertension, normal bilirubin level
Stage A4	0	≤ 3 tumors, each up to 3 cm	Portal hypertension, elevated bilirubin level
			CTP class A–B
Stage B (intermediate)	0	Large multinodular	CTP class A–B
Stage C (advanced)	1–2	Vascular invasion or extrahepatic spread	CTP class A–B
Stage D (terminal)	3–4	Any tumor stage	CTP class C

Japan Integrated Staging score

	Score			
Variable	0	1	2	3
CTP class	A	B	C	–
TNM stage by LCSGJ	I	II	III	IV

JIS score (0–5): sum of points for the 2 variables

*Regional lymph nodes include hepatic artery, portal vein, hilar, hepatoduodenal ligament, inferior phrenic, caval lymph nodes. A minimum of 3 tumor-free lymph nodes are required for pN0 diagnosis.

AJCC/UICC indicates American Joint Committee on Cancer/Union internationale contre le cancer Tumor-Node-Metastasis (TNM) staging system; CTP, Child-Turcotte-Pugh classification; PS, performance status (WHO); LCSGJ, Liver Cancer Study Group of Japan.

disease in a *very early*, *early*, *intermediate*, *advanced*, and *terminal* stage. The BCLC concept directly links the stage of disease to respective treatment strategies and was recently updated because of data on patients with advanced disease[18] (Fig. 1). The prognostic value of these staging systems has been evaluated in several studies with inconsistent results.[16,17,19] Further studies on independent patient sets considering the variable predictive value of staging systems depending on the applied therapy are required to determine the most accurate staging system. However, staging of HCC in scientific reports should already be standardized to enable crosscomparability of the results from different studies. A clinical classification system considering the stage of disease and the underlying liver function such as the BCLC staging system should be used for initial staging. The disease of patients who underwent surgery (ie, resection or OLT) should be categorized additionally using the AJCC/UICC TNM classification. [*Grade of recommendation C*]

CURATIVE TREATMENT

Surgical Resection

If applied in well-selected patients surgical resection is the primary treatment in patients with HCC. Within the last years perioperative mortality could be reduced to less than 5% depending on resection extent and hepatic reserve.[20] The improved outcome is primarily results from advances in surgical and radiologic techniques and perioperative care and more cautious patient selection.

Preoperative Assessment of Liver Function

Because of the potential need for major resections and frequently diseased background livers, posthepatectomy liver failure is a major concern of liver resection in HCC patients. The *Child-Turcotte-Pugh (CTP) score* is the most common measure to assess liver function before hepatic resection, though it was introduced as a predictor of operative risk for cirrhotic patients undergoing surgery for portal hypertension.[21] By staging patients' clinical (presence of ascites and encephalopathy) and laboratory abnormalities (serum albumin, bilirubin, prothrombin time) a score is estimated categorizing patients into 3 grades of liver dysfunction (*CTP class A, B, C*). Although it has been shown that *CTP class B* and *C* patients are poor candidates for liver resection,[22] this score has proven insufficient to stratify the operative risk of patients with compensated cirrhosis (*CTP class A*). In particular in Asian countries further liver function tests are employed preoperatively. Among the various methods available such as the *monoethylglycinexylidide (MEGX) test* and the *galactose elimination capacity (GEC),* the *indocyanine green (ICG) clearance rate* represents the most common one. After injection of 0.5 mg ICG/kg, retention of this organic dye is measured in the peripheral blood at definite time points (usually after 15 minutes; ICG-R15). Indocyanine green is taken up by the hepatocytes and excreted via the bile in an adenosine triphosphate (ATP) dependant manner. It is not metabolized and does not undergo enterohepatic recirculation. Thus, its clearance from systemic circulation is a measure of hepatic blood flow and function. Because of the weakness of the ICG clearance rate to reliably predict perioperative risk in patients with CTP class A cirrhosis, it did not gain general acceptance. However, several studies showed a prognostic relevance of ICG clearance for hepatic resection in cirrhotic patients.[23,24] Using the ICG-R15 in the absence of hyperbilirubinemia and ascites, Imamura et al[25] reported no perioperative mortality in their series of 1056 hepatectomies. In general, a safe major hepatic resection is expected in cirrhotic patients with an ICG-R15 up to 10% to 20%.

The liver remnant volume may vary, particularly in patients with diseased livers because of compensatory hypertrophy. In addition to assessment of hepatic function and liver volume to be resected, volumetric analysis of the future liver remnant (FLR) has been suggested. Advances in imaging techniques enable 3-D modeling of the liver with accurate liver-segmentation and visualization of the arterial and venous supply and biliary drainage (Fig. 2). Liver volumetry is mostly performed using computer-assisted models of contrast-enhanced spiral CT. Several studies have shown an association between the volume of the FLR and hepatic function and postoperative mortality in HCC patients.[26,27]

Recently, the *LiMAx test* together with CT volumetry was suggested to assess function of the FLR, preoperatively.[28] The LiMAx test requires intravenous administration of ^{13}C-methacetin, which is metabolized by the cytochrome P450 1A2 system of the hepatocytes to paracetamol and $^{13}CO_2$. The latter is measured by continuous real-time breath analysis to calculate the $^{13}CO_2/^{12}CO_2$ ratio as an indicator of hepatic function. Despite the promising results of combined volume/function analysis, this approach needs further evaluation and the CTP remains the primary index for preoperative surgical risk evaluation of patients considered for hepatic resection. [*Grade of recommendation B*]

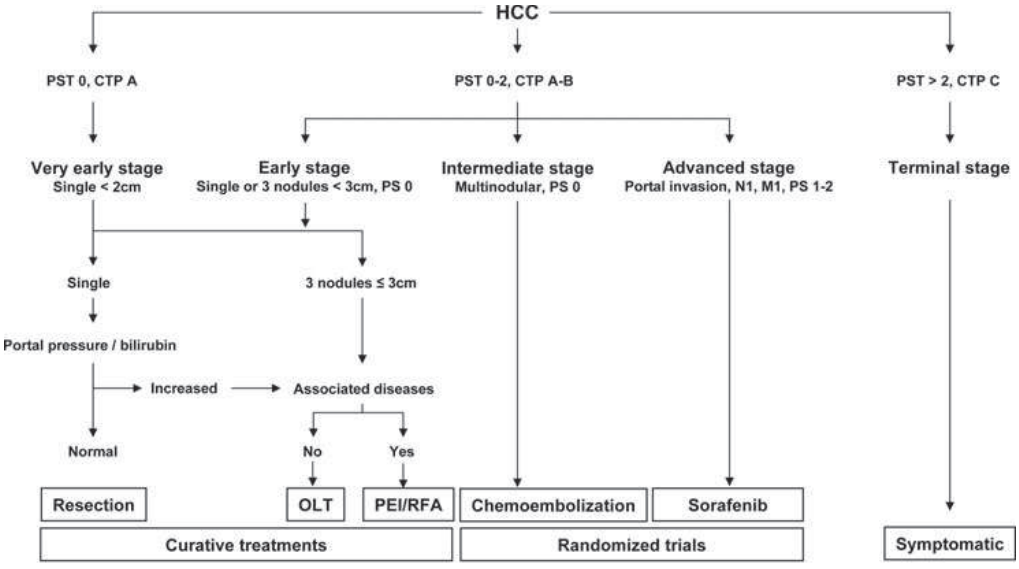

FIGURE 1. Barcelona Clinic Liver Cancer staging system and treatment algorithm.
CTP indicates Child-Turcotte-Pugh; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; PST, WHO performance status; RFA, radiofrequency ablation.

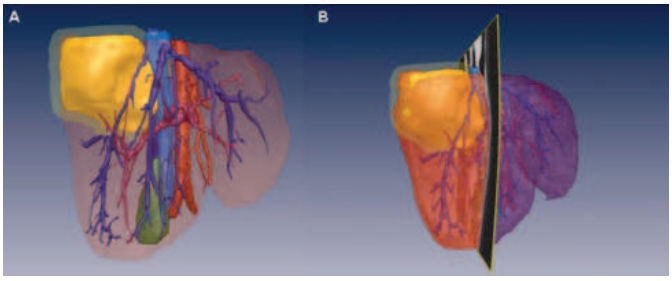

FIGURE 2. Planning of the surgical procedure by 3-dimensional reconstruction of CT scans.
A, Three-dimensional computation from a preoperative CT scan of a patient with HCC. Arteries red, portal vein purple, veins blue, gall bladder green, tumor, and safety margin yellow. B, Anterior 3-dimensional view of a virtually divided liver with calculation of resection and remnant liver volume.

Portal Vein Embolization

On the basis of the idea that an increase in the FLR will reduce the risk of posthepatectomy liver failure, the concept of portal vein embolization (PVE) has been introduced in 1986.[29] By occluding portal branches supplying the tumor-bearing liver segments, PVE causes atrophy of the ipsilateral liver with compensatory hypertrophy of the remaining liver (ie, the FLR). Although liver regeneration is impaired by fibrosis or cirrhosis, PVE may induce clinically sufficient hypertrophy even in these patients. In a nonrandomized trial of 55 patients (28 with HCC) Farges et al[30] demonstrated no positive effect of PVE on the postoperative course of patients with normal livers, whereas it reduced postoperative complications and duration of hospital stay in patients with chronic liver disease. The authors of a meta-analysis including 37 studies with 1088 patients (265 patients with HCC) concluded PVE to be a safe procedure, effective to induce hypertrophy of the liver remnant and to reduce the risk of poshepatectomy liver failure.[31] These data were confirmed in patients with HCC.[32] Portal vein embolization may also be used as dynamic liver function test. The lack of adequate hypertrophy after PVE indicates the inability of the liver to regenerate and should be considered as a contraindication to major liver resection.[30] Currently, PVE is recommended in cirrhotic patients, if a FLR less than 40% of the total liver volume is expected. At eastern institutions PVE has already been suggested for FLR of 40% to 60%, in case ICG-R15 values of 10% to 19% are obtained.[25] Besides these formal criteria potential comorbidities, such as hepatitis and diabetes should be considered when referring patients to liver resection. There are, however, no uniform guidelines incorporating these parameters. [*Grade of recommendation B*]

Technical Aspects of Surgical Resection for HCC

Various transection techniques have been developed to reduce blood loss and morbidity of hepatic resection. A meta-analysis of randomized controlled trials (RCT) revealed no advantage of these methods compared to the simple clamp-crushing technique.[33] The surgeon's experience together with the lesion's location should primarily determine the transection method. Further studies are needed to define the optimal transection technique in patients with liver disease. [*Grade of recommendation A*]

The curative resection margin in hepatectomy for HCC has not yet been defined. A narrow resection margin preserves tissue and alleviates the regenerative stimuli that might promote tumor growth, whereas it might fail to remove existing micrometastases. An RCT compared wide (2 cm) to narrow (1 cm) resection margins in HCC patients with a solitary tumor without macrovascular invasion and compensated cirrhosis CTP class A.[34] The authors reported decreased disease recurrence and improved survival for the wide margin group, which they attribute to strict selection criteria. Hence, HCC patients with a macroscopically solitary tumor without vascular invasion benefit from a margin of 2 cm, whereas those beyond these criteria are likely to already having distant micrometastases that cannot be cleared by a wider resection margin. [*Grade of recommendation B*]

Hepatocellular carcinoma has a strong tendency of vascular invasion. Tumor spread occurs primarily via the portal venous system, forming the pathological basis for intrahepatic metastases and early recurrence. Anatomical resections (segmentectomy or subsegmentectomy) include the associated portal branches and potentially remove satellite lesions and microscopically invaded vessels. Several reports favored anatomical resection regarding oncological outcome.[35–37] An analysis of 321 HCC patients with tumors less than 5 cm in diameter revealed a survival benefit of anatomic resection in noncirrhotic patients, whereas limited nonanatomic resection proved superior in cirrhotics.[38] Anatomical resection should thus be intended, if feasible and not contraindicated by the patient's liver function. In the remaining cases other therapies, that is, OLT and ablation, should be considered. [*Grade of recommendation B*]

The anterior approach technique has been introduced for (extended) right hepatectomy for large HCC.[39] The conventional approach requires complete mobilization of the right hepatic lobe for extrahepatic control of the right hepatic vein. In the anterior approach the parenchyma is transected starting from the anterior surface of the liver until the inferior vena cava is exposed and the right hepatic vein can be ligated.[39] Less manipulation of the liver is expected to reduce intraoperative blood loss, tumor cell dissemination and postoperative hepatic dysfunction.[40] In patients with a HCC at least 5 cm the advantage of the anterior approach with respect to perioperative complications and long-term outcome has been shown in a retrospective analysis and a prospective RCT.[41,42] [*Grade of recommendation B*]

The issue of vascular control during hepatectomy is of particular interest in surgery for HCC, as the underlying liver disease possibly increases the susceptibility of the liver to ischemia/reperfusion injury.[43] Intermittent portal triad clamping (ie, alternating periods of ischemia and reperfusion) and ischemic preconditioning (ie, a short period of ischemia and reperfusion followed by a prolonged period of ischemia) are methods to reduce ischemia/reperfusion injury. Transient clamping of the infrahepatic inferior vena cava offers a promising technique to reduce blood loss via the hepatic veins without the disadvantage of ischemia and is currently evaluated in an RCT.[44] A meta-analysis demonstrated hepatic resections to be safe without portal triad clamping, if modern guidelines of liver surgery are adhered to (eg, low central venous pressure).[45] However, if inflow occlusion is required, it should be carried out intermittently or after ischemic preconditioning. One should note that the available RCTs did not specifically evaluate patients with underlying liver disease. For lesions infiltrating the major hepatic veins or those adjacent to the cavohepatic junction combined inflow and outflow control (ie, hepatic vascular exclusion) may be applied with acceptable morbidity.[46] [*Grade of recommendation B*]

There is increasing data that laparoscopic surgery for HCC can be performed safely with lower perioperative morbidity and postoperative ascites, particularly in cirrhotics.[47–49] Furthermore, these studies consistently demonstrated no compromise in surgical margins and long-term outcome after laparoscopic resection of HCC. Recently, the position paper to an international consensus conference on laparoscopic hepatic resection was published.[50] Although the panel agreed that the laparoscopic approach is adequate in the hands of experienced surgeons, it is primarily indicated in patients with single lesions 5 cm or less in the peripheral segments of the liver. [*Grade of recommendation B*]

Selection of HCC Patients for Surgical Resection

In noncirrhotic HCC patients, surgical resection is the preferred curative treatment. These patients are likely to tolerate extended resections with acceptable morbidity. The noncirrhotic residual liver is less likely to develop de-novo HCC and might offer the option of reresection in case of disease recurrence. The 5-year survival after surgical resection of HCC in these patients may exceed 50%[35,51] (Table 2). The majority (>80%) of patient develops HCC in the context of cirrhosis. Cautious selection of cirrhotic candidates for surgical resection may enable moderate long-term outcome that has improved within the past 2 decades.[20,35,52,53] The BCLC staging system restricts hepatectomy to patients with a single HCC nodule less than 2 cm and well-preserved liver function (ie, CTP class A). Moreover, resection is recommended only for patients without clinical evidence of portal hypertension and normal bilirubin levels. In such patients resection is associated with almost no risk of posthepatectomy liver failure and excellent long-term survival.[54,55] However, Torzilli et al. reported acceptable outcomes for patients with BCLC stage B and C disease.[56] In general, tumor-related (ie, number, size and location of lesions, extrahepatic disease, involvement of major vasculature, required resection extent to achieve R0 situation) and patient-dependent factors (ie, physical condition, liver function, comorbidities) and the institution's experience should be considered before hepatectomy. Although extrahepatic disease and invasion of the portal vein trunk, inferior vena cava, and common hepatic artery are contraindications to surgical resection, lesion size, and number per se do not determine resectability. Excellent results were reported in patients who underwent resection for small and single HCC, respectively.[35,53,57] Despite the increased risk of recurrence due to the presence of vascular invasion and intrahepatic tumor cell dissemination in patients with large HCC and multiple lesions, available evidence still justifies hepatectomy in well-selected candidates[35,58,59] (Table 2). In particular, large but solitary HCC may be resected with good prognosis.[59] [*Grade of recommendation B*]

In western institutions, evidence of portal hypertension such as hepatic venous pressure gradient at least 10 mmHg, esophagogastric varices (grade 2 and 3), splenomegaly and thrombocytopenia (platelet count $< 100.000/mm^3$) are used to more precisely assess the perioperative risk.[54,60] Advances in hepatic surgery and perioperative management together with a more aggressive strategy of treating recurrent disease are likely to further extend indications for resection. Using a standardized protocol with preoperative treatment of varices and ascites, resection extent guided by ICG-R15 and aggressive treatment of recurrence, Ishizawa et al[61] reported a 5-year overall survival of 60% in 434 HCC patients with CTP class A, who had multiple tumors and/or portal hypertension. In a smaller study from Japan including 134 cirrhotic patients (CTP class A and B) esophageal varices were not associated with poor perioperative outcome and long-term survival on multivariate analysis.[62] One should note that in this study patients with esophageal varices represented a minority (n = 34) and underwent more limited resections. In an analysis of 241 cirrhotic HCC patients Cucchetti et al[63] reported similar perioperative outcome and survival of patients with and without portal hypertension, if patients had a similar preoperative liver function (assessed by the MELD score) and intraoperative course. Taking the results of these studies together portal hypertension *per se* is not a contraindication to resection in patients with HCC on cirrhosis. On the basis of thorough preoperative work-up surgical resection is generally indicated, if technically feasible and as long as the entire tumor burden can be removed with negative resection margins and sufficient postoperative hepatic function. [*Grade of recommendation B*]

Limitations and Benefits of Surgical Resection

Tumor recurrence is a persisting issue after surgical resection of HCC with and without cirrhosis.[58,64,65] Recurrent disease can result from intrahepatic dissemination of the primary tumor (true recurrence) or by de novo carcinogenesis. Microvascular invasion and satellite nodules are the main predictors of tumor recurrence[55,66,67] suggesting that the most cases are caused by intrahepatic dissemination. This distinction is important owing to the influence on prognosis and therapy. Late recurrence is more likely to result from new tumor development and curative resection, if feasible, might provide outcomes comparable to those of the index hepatectomy.[58,68] Tumor dissemination is more likely within the first 3 years after resection of the primary tumor[65] and mostly presents with multifocal and more aggressive tumors. In this scenario curative treatment is not recommended. Tumor recurrence, however, can to some extent be predicted based on the histological findings of the index hepatectomy specimens (ie, microvascular invasion and satellite lesions). The notion that high-risk patients benefit from being immediately listed for OLT needs to be backed by clinical data.[69]

The treatment strategy for recurrent disease is indeed controversial. Repeat hepatectomy may provide 5-year survival of up to 50%, but is usually associated with high incidence of rerecurrence.[70] Second and third hepatectomy for recurrent HCC may be equally safe and effective as the primary resection and may enable better results compared to the strategy of no repeat resection[71] Favorable long-term results have also been shown for local ablative treatment of HCC recurrence.[72,73] Liang et al[74] compared radiofrequency ablation (RFA) to repeat hepatectomy in patients who developed limited

TABLE 2. Long-Term Outcome of Patients with Hepatocellular Carcinoma Stratified for Prognostic Variables and Treatment Modality

Treatment	Prognostic Parameter	Variables	5-year OS [%]	5-year DFS %
Resection	Cirrhosis	HCC with cirrhosis	23–48	22–36
		HCC without cirrhosis	44–58	24–45
	Tumor size	HCC ≤ 3 cm	55–78	30–51
		HCC ≤ 5 cm	41–67	21–44
		HCC > 5 cm	29–56	22–23
	Number of nodules	Single	35–68	19–46
		Multiple	21–58	6–25
Transplantation	Milan criteria		59–83	62–92
	UCSF criteria		50–78	43–93

DFS indicates disease-free survival; OS, overall survival.

disease recurrence of up to 3 lesions with the largest up to 5 cm in diameter after hepatectomy for HCC. Both treatments yielded a comparable 5-year survival of 30.7% for hepatectomy and 39.9% for RFA. The Hong Kong group published their results for treating transplantable recurrent HCC after surgical resection with either salvage transplantation or nontransplant therapies such as second resection, RFA or transarterial chemoembolization (TACE). Although the direct comparison of both strategies did not show a significant difference in patients' long-term outcome, salvage transplantation provided better results in patients with stage II disease and early intrahepatic recurrence.[75] Secondary (salvage) transplantation might serve as a viable strategy for selected patients with recurrence restricted to the liver after previous resection. In patients with cirrhosis and compensated liver function resection before OLT might indeed be indicated from various perspectives:

Resection as primary therapy. Because of the organ shortage, hepatic resection might serve as primary therapy for HCC on cirrhosis with acceptable survival rates in selected patients (Table 2). The question whether to choose primary OLT or primary resection and salvage OLT for patients with small HCC on cirrhosis remains a matter of debate. Patients' outcome should be evaluated on an intention-to-treat (ITT) basis including patients with tumor progression while on the waiting list for primary OLT and those with recurrence after initial resection that exceeds transplant criteria. In their ITT analysis of 98 and 195 HCC patients who underwent primary resection and salvage OLT and primary OLT, Adam et al[76] demonstrated unfavorable 5-year overall (50% vs 61%; $P = 0.05$) and disease-free survival (18% vs 58%; $P < 0.0001$) for the group of patients who underwent initial resection. Remarkably, secondary OLT was associated with significantly higher operative mortality. Further studies, however, reported comparable overall survival of patients with early HCC treated with primary OLT or primary resection followed by salvage OLT in case of recurrence.[77–85] One should note that disease-free survival is reduced in patients undergoing primary resection (Table 3). Cherqui et al[86] reported their results on 67 patients with compensated cirrhosis and HCC meeting the Milan criteria who underwent primary resection. These authors showed excellent 5-year overall survival of 72% in the ITT population including 16 patients who underwent salvage OLT. In this study, a significant proportion of patients underwent laparoscopic liver resection (55%) and there was no mortality in patients who underwent salvage OLT. Despite the lack of controlled trials, the available evidence suggests the concept of primary resection and salvage OLT as an effective treatment in selected patients with early HCC on compensated cirrhosis. [*Grade of recommendation B*]

Liver resection as a bridge treatment to OLT. Although TACE is the most commonly applied treatment to prevent tumor progression in HCC patients listed for OLT, incomplete tumor necrosis may promote tumor progression.[87,88] Therefore, resection with complete tumor removal might be favorable in patients with small HCC on CTP class A cirrhosis. However, further investigation is needed due to the potential morbidity of resection. Furthermore, the outcome of patients undergoing OLT after resection of disease exceeding the Milan criteria needs to be evaluated.[89] [*Grade of recommendation D*]

Liver resection for patient selection. Liver resection with pathological analysis of the specimen allows clinicians to identify patients at high risk for recurrence (eg, microvascular invasion, satellite lesions). These patients may probably benefit from being listed for OLT immediately after resection, whereas patients with favorable tumor features might be followed-up and listed for salvage OLT in case of recurrence. This strategy may help to select patients with very unfavorable tumor features who are not eligible for OLT and those with disease beyond selection criteria with low-risk tumor biology who might still benefit from OLT. The promising preliminary results of this approach need validation in prospective studies using standardized treatment protocols.[69] [*Grade of recommendation C*]

Neoadjuvant and Adjuvant Therapy

Transarterial (chemo-)embolization is the most thoroughly investigated neoadjuvant treatment. The results of 3 RCTs do not support routine use of preoperative transarterial (chemo-) embolization before hepatic resection.[90–92] [*Grade of recommendation A*] However, sequential TACE and PVE might improve perioperative and long-term outcomes before major hepatic resection for HCC.[93]

There is currently no strong evidence supporting adjuvant therapy to reduce the risk of recurrence after curative therapy. Several trials including a small RCT of 60 patients that suggested a benefit of adjuvant capecitabine lack statistical power.[94] Further studies on adjuvant systemic chemotherapy, intra-arterial chemotherapy or the combination of both did not reveal a benefit on patients' long-term outcome.[95–98] Adoptive immunotherapy significantly improved recurrence-free survival in a trial of 150 patients. However, there was no significant difference in overall survival between both study groups.[99] In an RCT a significantly higher disease-free and overall survival at 3 years was reported for adjuvant intra-arterial treatment with ^{131}Iodine-labeled lipiodol.[100] Although this trial was prematurely closed after enrolment of 43 patients, the long-term results confirmed the survival advantage, though the effect became nonsignificant after a period of 8 years.[101] This result may reflect the effectiveness of the treatment against preexisting microscopic lesions, whereas it failed to prevent de novo carcinogenesis. However, as a false negative result (type II error) cannot be ruled out, these results together with the results from nonrandomized trials necessitate a well-designed confirmatory RCT before adjuvant therapy with intra-arterial ^{131}I-lipiodol can be recommended.

Although the earlier therapies address the issue of true recurrence from residual tumor cells, therapies also targeting the underlying liver disease have been employed to prevent recurrence originating from *de novo* tumors. An RCT of 89 patients revealed adjuvant administration of oral acyclic acid to significantly prevent true tumor recurrence.[102] In patients with HCC and viral hepatitis adjuvant interferon has been proposed because of its combined antitumor (antiproliferative and antiangiogneic) and antiviral actions. A meta-analysis revealed a significant benefit of adjuvant interferon regarding recurrence-free survival.[103] The results require cautious interpretation as the benefits of adjuvant interferon on late recurrence and survival remain unclear and the effectiveness of adjuvant interferon in HBV versus HCV-related HCC was not explored. Finally, the sample size of the individual studies and the pooled analysis was rather small. These data do not justify adjuvant interferon therapy as standard of care but warrant further investigation of interferon in a pegylated form and in combination with other agents such as ribavirin.[104] [*Grade of recommendation B*] Future trials on adjuvant therapy of HCC should evaluate individual therapies tailored to patients' risk profile (ie, high risk of true recurrence versus de novo tumor development; patients with HBC or HCV-related HCC) to identify subsets of patients that will most likely benefit from specific therapies.

Liver Transplantation

In the absence of metastases and macroscopic vascular invasion, OLT is the best available curative treatment of HCC on cirrhosis, as it removes the tumor burden and effectively treats the underlying liver disease, which limits patients' prognosis and serves for de novo carcinogenesis. In the early 1990s OLT was reserved for HCC patients with contraindications to resection due to insufficient hepatic reserve and/or tumor size and number. The 5-year survival of 15% to 40% was significantly worse than those of OLT for benign diseases and prompted the definition of stricter selection criteria.

TABLE 3. Recent Studies Comparing Long-Term Outcome of Patients with HCC Treated Primarily With Resection (and salvage transplantation) or Primary Liver Transplantation

First Author	Year	Primary Therapy	Sample Size	5-year OS Rate	5-year DFS Rate	Study Period	ITT Analysis
Lee[85]	2010	Transplantation	78	68%	75%*	1997–2007	Yes
		Resection	130	52%	50%		
Facciuto[84#]	2009	Transplantation	119	62%	—	1997–2007	Yes
		Resection	60	61%	—		
Del Gaudio[83]	2008	Transplantation	147	58%	54%	1996–2005	Yes
		Resection	80	66%	41%		
Shah[82]	2007	Transplantation	140	64%	78%*	1995–2005	Yes
		Resection	121	56%	60%		
Poon[81]	2007	Transplantation	85	44%	—	1995–2004	Yes
		Resection	228	60%	—		
Margarit[80]	2005	Transplantation	36	50%	64%*	1988–2002	Yes
		Resection	37	78%	39%		
Bigourdan[79]	2003	Transplantation	17	71%	80%*	1991–1999	Yes
		Resection	20	36%	40%*		
Adam[79]	2003	Transplantation	195	61%*	58%*	1984–2000	Yes
		Resection	98	50%	18%		
Belghiti[77]	2003	Transplantation	70	—	59%	1991–2001	No
		Resection	18	—	61%		
Figueras[78]	2000	Transplantation	85	60%	60%*	1990–1999	Yes
		Resection	35	51%	31%		

*Significant difference as reported in the original study; #4-year survival rates are reported for patient meeting the Milan criteria.
DFS indicates disease-free survival; ITT, Intention-to-treat analysis; OS, overall survival.

Selection Criteria of HCC Patients for Liver Transplantation

In a retrospective analysis of 48 patients Mazzaferro et al[105] reported an actuarial 4-year overall survival rate of 75% and a recurrence-free survival rate of 83%, if OLT was restricted to patients who had a single tumor of up to 5 cm or up to 3 tumors each 3 cm or less in diameter with no evidence of macrovascular invasion or extrahepatic disease. These results served as the basis for the so-called Milan criteria, which have been adopted by the United Network for Organ Sharing (UNOS) as selection criteria for HCC patients. Numerous subsequent reports confirmed these results and established OLT as therapy for HCC patients with cirrhosis[106–108] (Table 2). The excellent outcomes have in turn raised the question, whether selection criteria for HCC patients should be expanded. In their study Mazzaferro et al[105] could already show a 50% 4-year survival of patients whose disease extended their proposed criteria. Yao et al[107] from the University of California San Francisco (UCSF) provided further evidence that the Milan criteria can be expanded. Their study of 70 patients revealed no adverse impact on survival, if selection was broadened to a solitary tumor of up to 6.5 cm or 3 tumors or less with diameters of up to 4.5 cm, and a maximum total tumor size of 8 cm (5-year overall survival rate 75%). Although these data were obtained for tumor variables at explantation, prospective validation of the UCSF criteria based on preoperative imaging yielded similar results.[109] The largest analysis including 467 HCC patients revealed similar outcome of patients meeting the Milan and UCSF criteria both when assessing preoperative imaging and explant pathology, whereas a worse long-term survival was noticed for patients beyond the UCSF criteria.[110] The Milan and UCSF criteria can currently be recommended for selection of HCC patients for OLT. [*Grade of recommendation B*]

Optimal criteria for selection of HCC patients for OLT remain a matter of debate. Adherence to restrictive criteria is dictated by 3 major reasons: (1) lack of donor organs, (2) increased risk of recurrence, (3) increased rates of tumor progression, if patients with advanced disease will be listed. The limited number of available donors is the main restricting factor for OLT and contributes to prolonged waiting time. Prolonged waiting times are associated with increased drop out rates mainly due to tumor progression beyond current selection criteria. Expansion of selection criteria might increase the need for donor organs and by this is likely to further lengthen waiting periods, increase drop out rates and impair outcome on ITT analysis.

Expanded liver donor criteria (*rescue allocation*) address the lack of organs. A study on 45 cases of OLT with *rescue organs* that were rejected by other centers owing to medical and/or logistical reasons showed a 2-year recipient overall survival of 84.4%.[111] This study included 8 patients with HCC who all fulfilled the Milan criteria and were all alive at the end of the study period. A further retrospective study showed no significant difference in recurrence between recipients of standard and extended donor criteria allografts, despite more advanced disease in the latter group.[112] These results should prompt further prospective studies using extended donor criteria for patients with HCC.

At present, living donor liver transplantation (LDLT) and neoadjuvant therapy represent the 2 major strategies to address the lack of donor organs and prolonged waiting periods.

Living Donor Liver Transplantation

Initial results of Living donor liver transplantation (LDLT) for HCC have been promising with 3-year survival rates of 62% to 73%[113,114] (Table 2). The Hong Kong group reported a 5-year survival of 72% for recipients with HCC within the Milan criteria.[114] These authors observed higher recurrence rates after LDLT possibly due to proliferative stimuli of the regenerating liver graft. This finding is supported by Fisher et al[115] who reported higher recurrence rates at

3 years in the LDLT patients, whereas Soejima reported recurrence-free survival of 100% and 74% in patients within and beyond the Milan criteria, respectively.[116] LDLT may offer transplantation to patients beyond the Milan criteria. A study of 56 HCC patients treated with LDLT showed that 15 of the 20 patients who did not meet the Milan criteria had a median recurrence-free survival of 12 months. As those who developed disease recurrence survived for a median of 20 months the authors suggested to apply different selection criteria for LDLT.[117] A recent study of 25 HCC patients exceeding the UCSF criteria confirmed poor recurrence-free and moderate overall survival.[118] However, as a complex procedure it requires an experienced team and is still associated with donor morbidity of up to 40% and mortality of up to 0.5% raising ethical considerations.[119] Most studies reported on Asian populations, which are known to primarily develop HCC due to chronic HBV infection. Although recurrence of hepatitis C has been reported to be more severe in living donor than in cadaveric OLT, data on hepatitis C patients are scarce. Long-term data on overall and recurrence-free survival after LDLT are lacking for either type of underlying hepatitis. In selected cases surgical resection may improve outcome of isolated intrahepatic recurrence after LDLT.[120] Also the issue of primary graft nonfunction (PNF) after LDLT, in particular in patients beyond the Milan criteria is unsolved. Although in some cases LDLT might be justified in patients with advanced disease, selection of patients and management of those with severe complications require further discussion.

Treatment Before Liver Transplantation

Although TACE causes marked tumor necrosis with good local tumor control, its advantage as a bridging tool preventing drop outs of patients listed for OLT remains unclear, as available data are derived from case series and cohort studies and their results are rather inconsistent.[121–123] A positive response to TACE has been shown to be associated with a prolonged 5-year survival of 71% as compared to 49%, if no neoadjuvant TACE was performed and 29% in case of treatment failure with TACE.[121] A study of 96 HCC patients with a median of 5 TACE sessions before OLT confirmed a 5-year survival of 80% in 50 transplanted patients with 34 of them initially exceeding the Milan criteria. Progression-free TACE but not the Milan criteria was identified as predictor for disease recurrence suggesting treatment response as selection criterion for OLT.[124] These results are supported by studies applying a downstaging protocol for patients who initially presented with disease outside the Milan criteria.[125] Chapman et al[123] enrolled patients with a single HCC 8 cm or less or 2 HCCs 5 cm or less or up to 5 HCCs with a maximum diameter 4 cm or less and a total tumor diameter 12 cm or less were in a study using TACE, RFA, percutaneous ethanol injection (PEI) or hepatic resection for downstaging. The authors reported comparable survival of OLT in patients who initially met the Milan criteria and those who met the Milan criteria after successful downstaging. In a further study patients with stable, progressive, or untreatable disease were prioritized for OLT with comparable survival as patients who had a complete or partial response.[126] Multimodal therapy consisting of TACE before OLT and systemic chemotherapy during and after surgery might be of benefit in patients with large tumors.[127] Although some authors suggest Sorafenib as a bridging therapy due to its impact on disease progression,[128] further data from randomized trials are required to evaluate this indication.[129] However, as long as there are no controlled trials the potential benefits of bridging patients to OLT and OLT after successful downstaging remain controversial. [*Grade of recommendation C*]

Perspectives of Patient Selection for Transplantation

Liver allocation follows a scoring system (MELD, Model for End-Stage Liver Disease) originally developed by the United Network for Organ Sharing Priority (UNOS) to prioritize patients with the highest short-term mortality risk. As it solely consisted of biochemical variables (ie, bilirubin, creatinine, INR), the MELD score would fail to assess the risk of disease progression and drop-out in patients with malignant disease and compensated liver function. Hepatocellular carcinoma patients eligible for OLT therefore receive additional points according to their tumor size and number with 10% point increase for every 3 months on the list. It has remained controversial, whether pre-OLT staging should include further diagnostic criteria. The Milan and the UCSF criteria solely rely on radiological findings, that is, the number and size of detectable lesions. Unfortunately, inaccuracy of radiological imaging remains a problem, particularly in cirrhosis. A cohort study including 789 transplant patients revealed accuracy of radiological imaging to be as low as 44% with the actual pathologic stage being as frequently over- as underestimated.[130] Furthermore, imaging does not detect vascular invasion as the underlying pathological condition for metastatic spread and tumor recurrence. Although tumor size is a risk factor for recurrence, it is a surrogate parameter for vascular invasion and poor differentiation.[131] This might explain why up to 20% of patients who meet restricted selection criteria develop recurrent disease[108,132] and others develop a large tumor without vascular invasion. Moreover, the kind of microvascular invasion may be of clinical relevance. A recent study revealed invasion of a vessel with a muscular wall and invasion of a vessel that is more than 1 cm from the tumor as specific features of microvascular invasion that are associated with poor prognosis.[133] Liver biopsy to assess tumor biology as part of the pre-OLT work-up might reduce the proportion of patients with recurrence and help to identify those who benefit from OLT though they do not meet the selection criteria. Cillo et al[106] excluded patients with poorly differentiated tumors, which reduced post-OLT recurrence to fewer than 10%. One should note that the accuracy of preoperative core biopsy to assess tumor differentiation is controversial.[134,135] In a retrospective multicenter study, the outcome of 1556 patients who underwent OLT for HCC (1112 patients beyond Milan criteria) was analyzed.[136] Although 5-year overall survival was 73.3% and 53.6% for patients within and beyond the Milan criteria, a 5-year overall survival of 71.2% was achieved in patients without microvascular invasion who met the up to 7 criteria (7 as the sum of the size of the largest tumor [in cm] and the number of tumors). Patients with more than 3 lesions of limited diameter might still experience good survival after OLT.[137,138] In a study analyzing the Scientific Registry of Transplant Recipients (SRTR) database of 6478 patients who received a primary OLT for HCC the Milan criteria were found to be too restrictive.[139] The authors suggested a new selection score consisting of AFP level less than 400 ng/mL and total tumor volume (TTV) less than 115 cm^3 that accurately predicted outcome and should be validated in prospective studies.

Genotype analysis can potentially further improve prediction of tumor recurrence.[140,141] The fractional allelic loss rate (FAL) of a group of 9 microsatellite markers, which are located close to or within known tumor suppressor genes has been reported to have a higher predictive value of tumor recurrence than vascular invasion.[142] Fractional allelic loss rate is calculated by division of the number of mutated microsatellites by the total number of included microsatellite markers. Schwartz et al[143] showed that microsatellite analyses may help to predict recurrence, particularly in disease beyond the Milan criteria. Apparently, assessment of tumor biology requires liver biopsy, which bears a 0% to 3.4% risk of tumor-tract seeding.[106,144,145] In almost all cases tumor seeding can be cured by local excision with no impact on survival.[146] In addition, marking of the needle track during biopsy and subsequent excision at OLT can possibly prevent tumor seeding.[147] In any case, the risks and benefits of incorporating tumor biology into selection criteria of HCC patients for OLT need to be evaluated within further trials.

Immunosuppression After Liver Transplantation for HCC

Immunosuppression after OLT for HCC is a subject of raising interest. The calcineurin inhibitors (CNI) cyclosporin and tacrolimus currently form the main components of immunosuppression, though their use in HCC patients is under debate owing to their potentially tumor-promoting action.[148] Because of its antiproliferative effects the mTOR inhibitor Sirolimus has been suggested for immunosuppression of HCC patients. In addition to data demonstrating antitumor activity of Sirolimus,[149] favorable effects on oncological outcome of HCC patients with acceptable toxicity and rejection rates were reported.[150] Although these data have been confirmed recently,[151] effectiveness and safety of Sirolimus-based immunosuppression in HCC patients is currently investigated a in multicenter RCT.[152]

Percutaneous Local Ablation

Patients not eligible for resection or OLT due to their medical condition might be candidates for local ablative therapies, which are commonly performed percutaneously under ultrasound guidance. The effectiveness of local ablative therapies depends on the degree of cirrhosis and the number and size of lesions, which should thus guide patient selection. The most frequent local therapies are PEI and RFA. Percutaneous ethanol injection is tolerated well, inexpensive and causes complete necrosis rates of 90% to 100% for tumors 2 cm or less. The necrosis rate rapidly declines to 50% for tumors of 3 cm to 5 cm in diameter.[153,154] Destruction of tumor cells by RFA results from local hyperthermia (ie, coagulative necrosis) induced by a single or multiple electrodes. Radiofrequency ablation leads to more complete tumor necrosis with increasing tumor size and requires fewer sessions compared to PEI.[155–159] As the degree of necrosis depends on the achieved temperature, RFA is less effective for tumors adjacent to major vessels. Moreover, RFA may increase the risk for peritoneal seeding in subcapsular tumors. Five RCT have so far compared outcome of patients with early HCC after PEI versus RFA therapy[155–159] (Table 4). Three trials and a meta-analysis reported a benefit of RFA regarding overall survival.[156–158,160] Four RCTs favored RFA compared to PEI regarding recurrence-free survival suggesting better local tumor control.[155–157] In contrast to previous reports, the RCT do not confirm a relevant difference in complications and thus favor RFA for treatment of patients with HCC less than 4 cm not eligible for surgery. [*Grade of recommendation A*] Moreover, RFA can be repeated successfully in cirrhotic patients with intrahepatic recurrence.[161]

Percutaneous local ablation in patients eligible for resection remains controversial. A nationwide analysis of more than 17.000 HCC patients revealed a lower 2-year recurrence rate after hepatectomy compared to percutaneous ablation (with no difference in overall survival).[162] An analysis of 235 patients with HCC and CTP class A or B cirrhosis, demonstrated RFA to be safe and effective for up to 3 lesions at least 5 cm.[163] Tumor size was a predictor of local recurrence but did not affect survival because of treatment of recurrent tumors with additional RFA sessions. Overall survival of patients who underwent RFA for disease meeting BCLC criteria for operable tumors was similar to that of patients undergoing hepatic resection (3- and 5-year survival rates: 82% and 76%). A Markov model analysis recently suggested that RFA followed by resection in case of initial local failure enabled almost identical overall survival to primary resection in patients with compensated cirrhosis and very early HCC (<2 cm).[164] Although 3 RCT on early HCC showed similar oncological outcome after surgical resection and local ablation,[165–167] a recent RCT including 234 patients meeting the Milan criteria favored resection compared to RFA with respect to overall and recurrence-free survival.[168] However, methodological issues of these trials that were, moreover, performed exclusively in Asian populations do not allow final conclusions on the value of local ablation as first-line treatment of early HCC. Further trials considering the stage and etiology of disease and patients' liver function are warranted. [*Grade of recommendation B*] For multifocal HCC a combined treatment of resection and RFA was suggested in patients with preserved liver function. Choi et al[169] reported a 5-year overall survival rate of 55% in 53 patients with no procedure-related deaths. The combination of hepatectomy and RFA may be a viable option for patients who are not eligible for OLT. [*Grade of recommendation C*]

NONCURATIVE TREATMENT

Transarterial Embolization and Chemoembolization

Along with growing size HCC lesions increasingly derive their blood supply from the hepatic artery, which forms the rationale for selective catheterization and obstruction of the tumor's feeding arterial vessel (transarterial embolization, TAE). Before embolization chemotherapeutic agents (eg, doxorubicin, mitomycin, cisplatin) can be injected as a suspension with lipoidol to retain the injected agents in the tumor (transarterial chemoembolization, TACE). The results of an RCT challenge the need for embolization after transarterial

TABLE 4. Characterstics of Randomized Controlled Trials Comparing Radiofrequency Ablation to Percutaneous Ethanol Injection for the Treatment of Hepatocellular Carcinoma

		Sample Size			CTP Class A/B		Complete Necrosis Rate (%)		
First Author	Year	RFA	PEI	Tumors	RFA	PEI	RFA	PEI	3-year OS Rate
Lencioni[155]	2003	52	50	Milan criteria	45/7	35/15	91	82	RFA: 98% PEI: 88%
Lin[156]	2004	52	52	1–3 lesions ≤4 cm	41/11	39/12	96	88	RFA: 74% PEI: 48%
Lin[157]	2005	62	62	1–3 lesions ≤3 cm	46/16	47/15	96	88	RFA: 74% PEI: 51%
Shiina[158]	2005	118	114	Milan criteria	85/33	85/29	100	100	RFA: 81% PEI: 67%
Brunello[159]	2008	70	69	1–3 lesions ≤3 cm	56/44	56/44	95	65	RFA: 63% PEI: 59%

CTP indicates Child-Turcotte-Pugh; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

chemotherapy.[170] However, TACE represents an effective treatment option for well-selected patients with unresectable, *intermediate stage* HCC. Despite objective response rates of up to 60% only 2% of patients are expected to develop a complete response.[171] Transarterial chemoembolization may be effective in tumors more than 10 cm in diameter. Because of potential necrosis to peritumorous liver parenchyma, main portal vein thrombosis (PVT) is considered a contraindication for TACE. For the same reason treatment with TACE should not be chosen for patients with an increased risk of liver failure (eg, tumor load >30%) or decompensated liver function.[172] Further contraindications include infiltration of adjacent organs, severe contrast agent allergy and severe coagulopathy. Finally, patients with extrahepatic disease are unlikely to benefit from TACE. However, TACE may be safe and effective in patients with main PVT who have preserved liver function and sufficient collateral blood flow.[173] Side effects may result from the injected agents (that is nausea, vomiting, alopecia, bone marrow depression, renal failure) or obstruction of the hepatic artery (ie, postembolization syndrome with right upper quadrant pain, nausea, fever) and are usually self-limited. Serious complications requiring additional therapy occur in less than 10% of patients and include liver failure, cholecystitis, and hepatic abscess formation. In 2003, a seminal meta-analysis revealed a significant 2-year survival benefit for the TACE compared to conservative or suboptimal therapies without proven antitumoral activity.[174] These results are in line with a prospective cohort study on 8510 patients with unresectable HCC from Japan.[175] Transarterial chemoembolization remains the reference treatment option for patients with unresectable HCC to which new therapies should be compared. [*Grade of recommendation A*]

Selective Intra-Arterial Radiation Therapy

Selective intra-arterial radiotherapy (SIRT), also known as radioembolization, is a minimally invasive procedure using radioactive microspheres to deliver tumoricidal radiation doses internally. External beam therapy has the risk of radiation induced liver disease (RILD), which can result from exposure to 40 Gy.[176] Radiation induced liver disease is a syndrome of anicteric hepatomegaly, ascites, and increased liver enzymes weeks to months after therapy due to pathological sequelae of radiation injury to normal liver tissue.[177] Much higher doses can be delivered cumulatively through SIRT without clinical manifestation of RILD.

Contraindications and Complications

There are 2 absolute contraindications to SIRT: (1) a ^{99m}Tc scan that demonstrates more than 30 Gy would be delivered to the lungs with a single infusion or up to 50 Gy with multiple infusions due to hepatopulmonary shunting; (2) delivery of microspheres to the gastrointestinal tract as shown by the pretreatment hepatic angiogram that cannot be avoided with current catheter techniques. The most common complication of SIRT is a postembolic syndrome that manifests as fatigue, abdominal pain, and fever. Other complications include cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, pneumonitis, and RILD. Most toxicities can be avoided by proper planning, delivery, and dosimetry.

Outcomes With Radioembolization

The role of SIRT for palliative treatment of unresectable HCC is evolving. There have been no RCTs comparing the efficacy of SIRT to other established first line therapies for inoperable HCC (eg, TACE). Recently, an analysis of 291 HCC patients who were treated with SIRT at various stages of disease was published.[178] The authors reported response rates of 42% and 57% based on WHO and EASL criteria. Selective intra-arterial radiotherapy offered a survival benefit in CTP class A patients independently of PVT, whereas only CTP class B patients without PVT obtained a survival benefit. Although these results together with previous data[179] demonstrate SIRT to be safe in patients with PVT, survival benefits may be limited to patients with PVT who have preserved liver function. Further studies confirmed the effectiveness of SIRT in advanced HCC[180] and, moreover, reported no difference and an advantage of SIRT compared to TACE regarding time-to-progression and toxicity, respectively.[181,182]

Selective intra-arterial radiotherapy may be useful to downstage patients to undergo resection, ablation, or OLT. In an analysis comparing TACE to SIRT for downstaging of HCC, higher partial response rates (61% vs 37%; $P = 0.07$) and successful downstaging (58% vs. 31%; $P = 0.02$) was achieved in the SIRT group.[183] Further studies confirmed the ability of SIRT to reduce the size of targeted lesions.[184,185]

Although SIRT seems safe and effective in selected HCC patients, level I evidence is lacking favoring SIRT for palliative treatment of advanced HCC and treatment before OLT. Furthermore, benefits of SIRT in combination with other therapies such as systemic targeted agents and as (neo)adjuvant therapy after curative treatment require further evaluation. At present SIRT can be recommended as palliative therapy for advanced HCC, though treatment should preferably be delivered in the setting of clinical trials. [*Grade of recommendation B*]

External Beam Radiation Therapy

Because of the low tolerance of the liver to radiation therapy (RT), the role of external beam RT in the management of HCC has traditionally been limited. Whole liver RT of 28 Gy to 35 Gy over 3 weeks carries a 5% risk of RILD.[186] As new RT delivery technologies have evolved the role of external beam RT for advanced HCC needs to be redefined and treatment within clinical trials is recommended.

Conformal Radiation Therapy

Improved imaging techniques that better define the tumor such as tumor immobilization, organ tracking to control for breathing, 3-D planning techniques and increased knowledge of the liver's partial volume tolerance to radiation have allowed delivery of increased doses. Ben-Josef et al[187] treated 128 patients with irresectable hepatic malignancies (35 patients with HCC) using conformal hyperfractionated RT with simultaneous hepatic arterial infusion of fluorodeoxyuridine as radiosentisizer. Overall, 38 patients (30%) had grade 3 to 4 toxicity with 5 cases of RILD (4%). A survival benefit was shown for a dose of at least 75 Gy (23.9 months) versus at least 75 Gy (14.9 months) ($P < 0.01$). Other studies using conformal RT support this dose effect.[188,189] [*Grade of recommendation C*]

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) has been developed to deliver highly conformal radiation in high-doses to target volumes. By employing immobilization and accurate localization, potent doses can be delivered with minimal exposure to surrounding normal tissues due to a very rapid drop-off of dose beyond the target volume.[190] These doses are typically delivered in fewer than 10 fractions. A prospective study, in which 6 fraction SBRT was given in escalating doses (24 Gy to 54 Gy) was conducted on 31 CTP class A patients with small and large HCC unable to receive standard therapies. Portal vein thrombosis was present in 53% of these patients. Although liver function declined in 5 patients, there was no case of RILD or dose-limiting toxicity.[191] The ability of SBRT to provide local control without serious toxic side effects has also been demonstrated in smaller studies.[192,193] [*Grade of recommendation C*]

Proton and Heavy Ion Radiotherapy

Proton and heavy ion RT have also been studied in HCC. These positively charged particles are heavier than electrons and have a unique dose distribution. The protons are delivered in rapidly increasing doses, which deposits them at the end of the range of the beam within the patient at a depth that is determined by the particular beam energy. These properties favor them for deep tumors with maximal sparing of the normal tissue. The proton dose is reported in GyE (Cobalt gray equivalents), which is translated into equivalent photon dose in Gy. Twenty-four CTP class A or B patients with HCC tumors ranging from 2.1 to 8.5 cm were prospectively studied using carbon ion RT (49.5 to 79.5 GyE in 15 fractions).[194] The treatment was tolerated well other than grade 3-skin toxicity, and 5-year survival was 25%. A phase II trial showed a 2-year survival of 55% in 34 patients with unresectable HCC who received proton therapy (63 GyE in 15 fractions). Remarkably, 6 patients underwent OLT 6 to 16 months later.[195] The outcomes with proton and heavy-ion RT for HCC are among the best after RT. Unfortunately access to this modality is limited. [*Grade of recommendation C*]

Because of new radiation techniques and fractionation schedules RT is used more safely and effectively in the palliative treatment of HCC. Patients with CTP class B, patients with large tumors and HBV carriers are at increased risk for toxicity. Excellent local control has been seen with small tumors fewer than 5 cm, if sufficient doses are delivered. Randomized controlled trials are needed to support these findings before any of the various modalities of external beam RT can be included in standard treatment algorithms of HCC. As the experience with heavy ion RT demonstrates that if high enough doses of RT can be delivered, HCC can potentially be controlled, further evaluation of this treatment as a component within potentially curative treatment regimens for HCC patients should be considered.

Systemic Therapies

The potential of systemic chemotherapy to prolong survival of patients with unresectable HCC has been evaluated for several protocols.[196–198] Although anthracyclines are considered the most effective agents and single-agent doxorubicin regimens have been widely used; response rates of chemotherapy are low (< 20%) with no survival advantage. For reasons of toxicity, particularly in patients with underlying liver disease, systemic chemotherapy is neither recommended as first-line therapy nor as control treatment within clinical trials. [*Grade of recommendation A*] Expression of sex hormone receptors on HCC cells suggested tumor growth to be in part dependent on hormone stimulation. The promising initial data with the antiestrogen tamoxifen were disproved by a meta-analysis of 7 RCT[174] and a subsequent RCT of 420 patients.[199] [*Grade of recommendation A*] The known antimitotic effect of somatostatin and the expression of its receptors in HCC formed the rationale to treat patients with somatostatin (analogues). Encouraging effects[200] were not reproduced in larger RCT.[201,202] A survival benefit of somatostatin in advanced HCC with overexpression of its receptors requires further evaluation.[203] A phase III study comparing the combination of tamoxifen and the somatostatin analog octreotid to tamoxifen alone did not favor combined therapy in advanced HCC.[204] [*Grade of recommendation B*] First studies on interferon in patients with inoperable HCC demonstrated prolonged survival compared to doxorubicin and no antitumor therapy, respectively.[205,206] A subsequent RCT could not reproduce these data.[207] The combined treatment with systemic chemotherapy interferon did not improve survival either.[208] [*Grade of recommendation B*]

The disappointing results of conventional systemic therapies together with the growing understanding of the tumor's biology prompted the development of further therapies against molecular targets. These agents are applied either alone or in combination with systemic chemotherapy. Bevacizumab (Avastin), a recombinant, humanized monoclonal antibody against VEGF has been tested within 2 phase II trials of patients with advanced HCC. Zhu et al[209] evaluated efficacy and safety of bevacizumab in combination with gemcitabine and oxaliplatin (GEMOX-B) and reported objective response rates of 20% and a median progression-free survival of 5.3 months. Siegel et al[210] examined bevacizumab as single agent in patients with advanced HCC. In this phase II trial 13% of patients had objective responses the median progression-free survival was 6.9 months. The monoconal antibody cetuximab (Erbitux) targets the epidermal growth factor receptor (EGFR). Although a phase II study of cetuximab as a single agent in the treatment of advanced HCC failed to show antitumoral activity,[211] a further phase II trial of cetuximab in combination with gemcitabine and oxaliplatin showed response rates of 20%.[212] Erlotinib, a small molecule with specific receptor tyrosine kinase inhibitory effects against EGFR has been tested as a single agent in phase II trials showing modest disease-control.[213,214] A recent phase II trial on 40 patients with advanced HCC showed that 62% of patients who received bevacizumab and erlotinib achieved a 16-week progression-free survival with limited toxicity.[215] A confirmatory phase III trial is required to assess a potential survival benefit by this combined treatment.

Sorafinib (Nexavar) is an oral multikinase inhibitor with activity against raf-kinase, VEGF receptor-2/3 (VEGFR-2/3) and platelet-derived growth factor receptor beta (PDGFR-β) tyrosine kinases, thereby blocking cell proliferation and neoangiogenesis.[216] A multicenter, phase III trial on sorafinib as a single agent in patients with advanced HCC was stopped prematurely. The analysis of 602 patients demonstrated longer median overall survival [10.7 months vs 7.9 months; hazard ratio 0.69; 95% confidence interval (CI), 0.55–0.87] and median time to progression (5.5 months vs 2.8 months; HR = 0.58; 95% CI, 0.45–0.74) for the treatment group.[217] This study for the first time showed a systemic therapy to provide a survival advantage in advanced HCC. A further phase III trial confirmed these results in patients from the Asia-Pacific region.[218] Sorafinib received FDA and EMEA approval for treatment of HCC and should be considered as control treatment within future trials. [*Grade of recommendation A*] In line with these data combined therapy with sorafinib and doxorubicin was shown to be superior compared to doxorubicin alone.[219] Subsequent trials should assess application of sorafinib in combination with other molecular therapies or systemic chemotherapeutic compounds for treatment of advanced HCC.[220] Moreover, one might hypothesize that this drug might also improve outcome within neoadjuvant or adjuvant protocols of patients undergoing potentially curative therapy. Three phase II trials assessed clinical activity of the multitargeted tyrosine kinase inhibitor sunitinib in patients with advanced HCC.[221–223] Although antitumor activity was comparable to that observed in phase II trials on sorafenib,[224] there is evidence of higher (dose-dependent) toxicity of sunitinib.[221] However, efficacy and safety of both agents is currently compared within an ongoing phase III trial.

Perspectives in the Management of Hepatocellular Carcinoma

Although surgical therapy forms the cornerstone of curative treatment of HCC, patients should be treated within a multidisciplinary setting. Figure 3 summarizes the treatment algorithm of HCC at the University of Heidelberg. Advances in surgical management have enabled surgery in patients with more advanced tumors and underlying liver disease. Posthepatectomy liver failure remains a major concern and may be prevented by cautious patient selection and PVE. Failure of the liver to respond to PVE can be considered as biologic marker of insufficient functional capacity and these patients

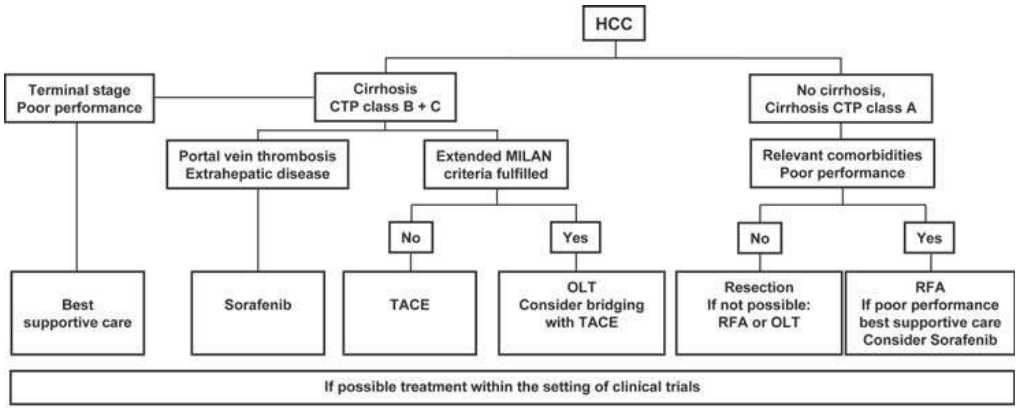

FIGURE 3. Treatment algorithm of HCC at the University of Heidelberg.
CTP indicates Child-Turcotte-Pugh classification; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization. RFA is indicated for lesions with a maximum diameter of 3.5 cm (multifocal tumors) or 5 cm (single tumor) and a maximum number of 3 lesions per lobe. Extended Milan criteria: single lesion $\leq$ 6 cm or 2–3 lesions $<$ 3 cm.

are at increased risk of liver failure. The increasing experience with surgical therapy in HCC shows a survival benefit in selected patients with unfavorable tumor characteristics and has further established the indication for surgery. However, local ablative therapy might provide adequate treatment of early HCC. The selection of patients for curative treatment modalities remains controversial and requires further evaluation within prospective studies. Although introduction of well-defined selection criteria have improved long-term outcome of HCC patients undergoing OLT, the Milan criteria seem too restrictive. Besides careful expansion of the current radiological criteria, the strategy of involving histological and/or molecular markers, and response to neoadjuvant therapy are promising concepts to optimize patient selection. At present TACE and systemic sorafenib are accepted for treatment of intermediate and advanced HCC, respectively. Furthermore, innovative therapies such as SIRT may offer effective treatment in these patients. Molecular targeted therapy and in particular the promising initial experience with sorafenib opens a broad field of potential applications in HCC including adjuvant and neoadjuvant therapy. It is subject of current and future investigation to identify patients who benefit from molecular targeted therapy and invasive treatments. It should, however, be noted that despite increasing efforts to better understand and treat the disease, current recommendations for patients with HCC are based on a limited number of well-designed RCT, in particular in the field of surgical therapy. Randomized controlled trials should not only evaluate new surgical, interventional, and systemic therapies and their combinations within a multidisciplinary setting, but also assess the clinical value of biological markers to identify responders to specific therapies. Accomplishing these trials and achieving more individualized treatment remain major challenges to continue the progress that has already been made in the management of HCC.

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