

# Current treatment strategy for hepatocellular carcinoma

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## ABSTRACT

With the current practice of surveillance programs in high-risk patients, early stage hepatocellular carcinoma (HCC) is commonly diagnosed. This poses great challenge to clinicians, in terms of prognostic estimation, patient stratification to various treatment modalities and patient management during long-term follow-up. This review focuses on the current trends in the management of HCC, with special attention to tumor staging, treatment algorithm, and outcome of various treatment modalities. According to the American Association for the Study of Liver Diseases (AASLD) practice guideline, Barcelona Clinic Liver Cancer (BCLC) staging system has fulfilled the criteria that HCC patients can be stratified into different prognostic subgroups, to which optimal treatments can be offered. Under this management scheme, curative treatments (hepatic resection, liver transplantation, and percutaneous ablation) would be reserved to the subgroup of patients with relatively good prognosis. For patients with advanced malignancy localized to the liver, local ablation or transarterial chemoembolization (TACE) may offer effective symptomatic palliation, and prolongation of patients' survival. For patients with distant metastases, no effective therapy can be offered, and symptomatic palliative care is the best option. Until now, favorable survival outcomes have been reported following hepatic resection, liver transplantation, and local ablation for HCC. Although the therapeutic effect of TACE is less pronounced than curative treatments, randomized controlled studies have proven its survival benefit for HCC patients. A comprehensive treatment algorithm involving these treatment modalities is mandatory to ensure optimal care of patients with HCC.

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The global incidence of hepatocellular carcinoma (HCC) is increasing in recent years. This tumor is the fifth most common solid tumor, and the third leading cause of cancer-related death in the world.<sup>1</sup> In regions where hepatitis B or C viral infection is prevalent, HCC is the leading cause of death in cirrhotic patients. Its clinical relevance and controversies in diagnostic and therapeutic issues have gained much enthusiasm among basic researchers, and clinicians. In particular, surveillance, diagnosis, and treatment strategy are the main targets of current clinical researches. The American Association for the Study of Liver Diseases (AASLD) has recently issued practice guidelines on surveillance, and diagnosis of HCC based on the available evidence.<sup>2</sup> According to this guideline, patients at high risk of developing HCC should be offered a surveillance program, which is performed using ultrasonography at 6-12 months. The algorithm to establish the diagnosis of HCC is based on the size of nodule on surveillance ultrasonography, and it consists of dynamic radiological studies (CT scan, contrast ultrasonography, or MRI), serum alpha fetoprotein assay, and liver biopsy. With these recommendations, the diagnosis of HCC in high-risk patients is clearly defined and it provides a platform, on which clinicians can stratify HCC patients to different treatment modalities in a systemic manner. In the past, the prognosis of patients with HCC was dismal since most of them presented with advance tumor, to which no effective treatment can be offered. Most patients would die within one year, irrespective of treatment.<sup>3</sup> With the current practice of surveillance programs among high risk patients in developed countries, there is an increasing proportion of patients with early HCC, who can benefit from various treatment modalities.<sup>4,5</sup> This review focuses on the current trends in the management of HCC, with special attention to tumor staging, treatment algorithm, and outcome of various treatment modalities.

**Staging systems.** The prediction of prognosis in HCC patients is complex since the majority of underlying have chronic liver disease, which in turn affects the choice of treatment modality. Ideally, any staging system should stratify patients into subgroups of homogeneous prognosis, to which appropriate treatments can be

**Table 1** - Pathologic tumor-node-metastasis (pTNM) staging system.

T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion, or multiple tumors, none >5cm
T3	Multiple tumors >5cm, or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M0	No distant metastasis
M1	Distant metastasis
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage IIIA	T3 N0 M0
Stage IIIB	T4 N0 M0
Stage IIIC	Any T N1 M0
Stage IV	Any T Any N M1

T-Tumor

**Table 2** - Okuda staging system.

<b>Positive features</b>	
	Tumor involving >50% of the liver
	Ascites
	Albumin <3 g/dl
	Bilirubin >3 mg/dl
Stage I	No positive feature
Stage II	1 or 2 positive features
Stage III	3 or 4 positive features

**Table 3** - Cancer of the Liver Italian Program scoring system.

Scoring system	Score
<b>Child-Pugh stage</b>	
A	0
B	1
C	2
<b>Tumor morphology</b>	
Uninodular and extension ≤50%	0
Multinodular and extension ≤50%	1
Massive or extension >50%	2
<b>Alpha-fetoprotein (ng/ml)</b>	
<400	0
≥400	1
<b>Portal vein thrombosis</b>	
No	0
Yes	1

directed. Thus, prognostic staging systems of HCC patients need to take into account the tumor stage, the underlying liver function, patients' performance status, and treatment efficacy.<sup>6</sup> Although many staging systems of prognostic value were proposed in the past,<sup>7-13</sup> there is no worldwide consensus on the preferred system to be used in clinical practice. Historically, tumor-node-metastasis (TNM)<sup>14</sup> and Okuda staging<sup>3</sup> systems have been widely used to stage HCC. The TNM staging system fashioned by the Union International Contra la Cancrum (UICC) incorporates tumor size, number of tumor nodules, and vascular invasion into its tumor classification<sup>14</sup> (Table 1). Conceivably, it can accurately predict the risk of recurrence after hepatic resection, and shows good correlation between the staging group and patient outcome. In a study of 518 patients with HCC after hepatic resection, there were significant differences in patients' survival between stages I and II, between stages II and IIIA, and between stages II and IIIB.<sup>15</sup> However, the applicability of TNM system is limited since it is based on pathological findings, and liver function is not considered in the system. On the other hand, the Okuda staging system involves variables related to tumor burden and liver function (bilirubin, albumin and ascites)<sup>3</sup> (Table 2). It serves to identify patients with end-stage disease, but it fails to distinguish between patients with early, and advanced stages. Currently, there are 2 widely adopted staging systems, which are derived from a large number of cohort patients, namely, the Cancer of the Liver Italian Program (CLIP) score,<sup>9</sup> and the Barcelona Clinic Liver Cancer (BCLC) staging classification.<sup>6</sup> These 2 staging systems were designed to provide prognostic information for the full spectrum of HCC patients with resectable or unresectable disease.

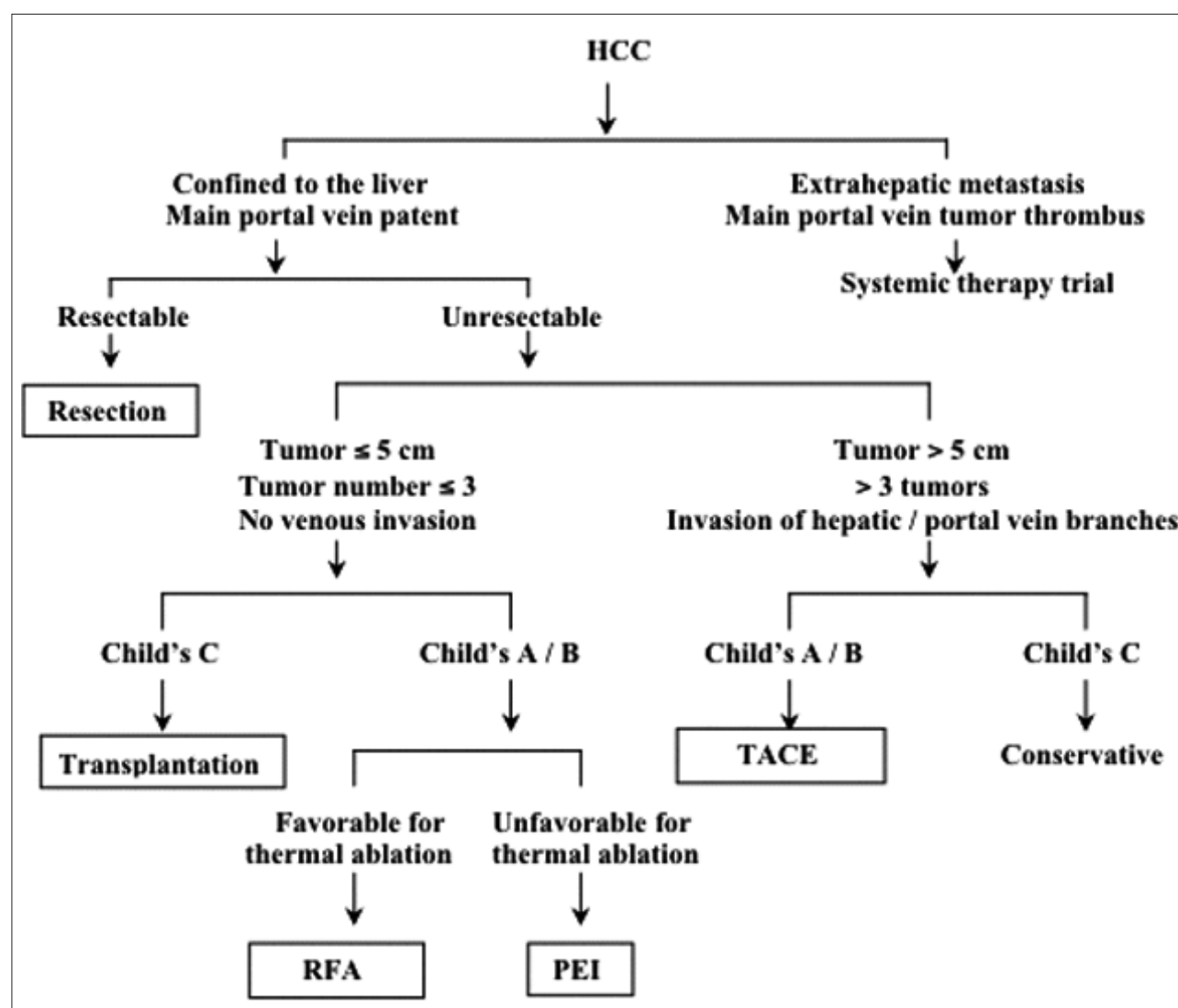
**Cancer of the Liver Italian Program score.** The CLIP score was derived from a retrospective analysis of 435 HCC patients and was published in 1998<sup>9</sup> (Table 3). Unlike the TNM staging system, the CLIP score is composed of several other parameters of prognostic value, including Child-Pugh stage,<sup>16</sup> tumor morphology and extension, serum alpha-fetoprotein level, and presence of portal vein thrombosis. It has been shown that the CLIP score provides accurate prognostic information, and a high predictive power for survival of HCC patients.<sup>9,17,18</sup> The one-year survival rate was 84% for HCC patients with CLIP score of 0, 66% in patients with score one, 45% in patients with score 2, 36% in patients with score 3, 9% in patients with score 4-6. The 5-year survival rate was 65% for HCC patients with CLIP score of 0, 45% in patients with score one, 17% in patients with score 2, 12% in patients with score 3, 0% in patients with score 4-6.

**Barcelona Clinic Liver Cancer staging classification.** The BCLC staging system was proposed in 1999,

**Table 4 -** Barcelona Clinic Liver Cancer (BCLC) staging classification.

Stages	Performance status	Tumor stage	Liver function
<i>Stage A: Early HCC</i>			
A1	0	Single, ≤5cm	No portal hypertension and normal bilirubin level
A2	0	Single, ≤5cm	Portal hypertension, normal bilirubin level
A3	0	Single, ≤5cm	Portal hypertension and abnormal bilirubin level
A4	0	≤3 tumors, all <3cm	Child-Pugh A-B
Stage B: Intermediate HCC	0	Single, >5cm or >3 tumors, >3cm	Child-Pugh A-B
Stage C: Advanced HCC	1-2	Vascular invasion or extrahepatic spread	Child-Pugh A-B
Stage D: Terminal HCC	3-4	Any	Child-Pugh C

HCC-hepatocellular carcinoma



**Figure 1 -** Treatment algorithm for patients with hepatocellular carcinoma (HCC), radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) and transarterial chemoembolization (TACE).

with the aim of defining prognosis, and treatment strategies in patients with resectable or transplantable disease, or those undergoing locoregional therapies<sup>6</sup> (Table 4). This system stratifies HCC patients into 4 risk groups, proposing different strategies for each group. Stage A HCC patients (early stage) are suitable for curative treatment modalities, including hepatic resection, liver transplantation, and local ablation therapies, such as percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA). Stages B and C HCC patients (intermediate and advanced stages) should qualify for palliative treatment such as transarterial chemoembolization (TACE) or some new agents in the setting of clinical trials. Lastly, stage D HCC patients (terminal stage) should only receive symptomatic treatment because of their extremely grim prognosis despite any interventions. The overall survival rates at 1, 3, and 5 years in patients with stage A HCC were 85%, 62%, and 51%. Within this group, the 3-year survival rate dropped to 35% if patients developed unresolved portal hypertension as indicated by a preoperative hepatic venous pressure gradient of 10 mm Hg or more. For patients with stages B and C HCC, the overall survival rates at 1, 3, and 5 years were 54%, 28%, and 7%. Patients with stage D HCC had the poorest survival of only 10% at one and 0% at 5 years. The main advantage of one BCLC staging system is that it links tumor staging with appropriate treatment modalities, and the life expectancy in each subgroup can be estimated according to the response to various treatments. In 2 recent studies by Marrero et al,<sup>19</sup> and Grieco et al,<sup>20</sup> this staging system has been shown to be superior compared with other staging systems, and was cross-validated in the United States and Italian patients.

**Treatment algorithm.** In general, treatment modalities of HCC can be divided into curative, and palliative. Curative treatments include hepatic resection, liver transplantation, and local ablation therapies, of which PEI and RFA are commonly practiced. Complete tumor eradication is expected from these treatments, and hence patients' survival can be improved accordingly. On the other hand, palliative treatments are not aimed to cure the disease, but to prolong patients' survival by achieving reasonable tumor control. These treatments involve TACE, transarterial irradiation, and systemic therapies. As stated previously, HCC patients should be stratified by disease stages, in which an optimal treatment modality is indicated. According to AASLD practice guidelines,<sup>2</sup> the BCLC management scheme has fulfilled these criteria and can be applied to the majority of patients evaluated for HCC. One potential drawback of the BCLC management scheme is that TACE is advocated in patients with intermediate

stage HCC. In many patients with intermediate stage HCC with preserved liver function, the tumor is still resectable. In a cohort study of 380 patients with BCLC intermediate stage HCC undergoing hepatic resection, an overall survival rate of 39% can be achieved with low mortality (2.7%) and morbidity (23%) rates.<sup>21</sup> Hence, large and multiple HCC can be safely treated by an aggressive surgical approach, and a favorable survival outcome is expected. From the authors' experience, large tumor size, and multiple tumor nodules are not absolute contraindications for hepatic resection. Rather, the resectability of HCC depends on patients' liver function, volume of liver remnant, presence of main portal vein tumor thrombus, and any extrahepatic disease.

The value of indocyanine green (ICG) clearance test in the preoperative assessment of liver function has been emphasized in several studies.<sup>22-24</sup> In a study from the authors' institution, ICG clearance test was found to be the most powerful predictor of hospital mortality after hepatic resection when compared with other tests, including the amino-acid clearance test and the aminopyrine breath test.<sup>23</sup> The authors have previously demonstrated that perioperative outcomes after major hepatic resection in patients with an ICG retention at 15 minutes (ICGR-15) higher than 14% were comparable to those with an ICGR-15 below 14%, with the median ICGR-15 value in the former group being 17.4%.<sup>25</sup> Furthermore, a more recent study has shown that extended hepatectomy is safe in selected patients with ICGR-15 up to 20%.<sup>26</sup> Another contributing factor affecting outcome of major hepatectomy is the volume of functional liver remnant. Computerised Tomography volumetry has been shown to be helpful in selecting patients for major hepatic resection.<sup>27</sup> It has been shown that a small remnant liver volume was associated with worse postoperative liver function, and a higher major complication rate after extended hepatectomy.<sup>28</sup> The safety limit for the remnant liver volume in patients undergoing major hepatectomy ranges from 25-40% in different studies.<sup>27-29</sup> From the authors' experience, the tumor is considered resectable if the following conditions are fulfilled: 1) Tumor nodules are confined to liver segments which can be technically resected. 2) Child-Pugh class A<sup>16</sup> and ICGR-15 of less than 20% in case of major hepatic resection, defined as resection of 3 or more liver segments according to Couinaud's classification.<sup>30</sup> 3) Child-Pugh class B<sup>16</sup> in case of minor hepatic resection, defined as resection of less than 3 Couinaud's segments. 3) The volume of liver remnant is at least 30% of estimated standard liver volume, derived by Urata et al.<sup>31</sup> 4) There is no main portal vein tumor thrombus, and extrahepatic metastasis. In the authors' center, the following treatment algorithm



is adopted for the management of HCC patients (Figure 1). In the absence of main portal vein tumor thrombus and extrahepatic metastasis, the resectability of tumor is evaluated according to the above criteria. Patients with resectable HCC will be subjected to hepatic resection, whereas patients with unresectable HCC will be stratified according to tumor size, number of tumors, and presence of tumor invasion to hepatic or portal vein branches. For patients with early HCC (single tumor <5cm or up to 3 tumor nodules, each <3cm, and absence of tumor invasion to hepatic or portal vein branches), RFA or PEI is indicated in patients preserved liver function (Child-Pugh class A or B),<sup>16</sup> while liver transplantation is considered in patients with decompensated cirrhosis (Child-Pugh class C).<sup>16</sup> If a long waiting time (>6 months) of liver transplantation is expected, percutaneous treatments (RFA or PEI) or TACE are recommended prior to liver transplantation for tumor control. For patients with unresectable advanced HCC (single tumor >5cm or >3 tumor nodules, and presence of tumor invasion to hepatic or portal vein branches), TACE will be offered to patients with preserved liver function (Child-Pugh class A or B).<sup>16</sup> However, only symptomatic treatment can be given in this group if the liver function is poor (Child-Pugh class C).<sup>16</sup> Finally, patients who present with a more advanced tumor (presence of main portal tumor thrombus or extrahepatic metastases) would be enrolled into current drug trials testing new systemic agents against HCC. The design of such drug trials is in the form of the comparison of therapeutic intervention versus placebo, or the best supportive care as currently practiced.

**Treatment outcome. Hepatic resection.** Hepatic resection can effectively eliminate the cancer, but it is limited by its inability to eliminate the remaining portions of the liver carrying the risk of malignant transformation. Furthermore, only HCC patients with preserved liver function benefit from hepatic resection. The overall resectability rate of HCC patients is less than 20% in most studies. Nevertheless, favorable results of hepatic resection have been obtained in selected groups of HCC patients. Large series of liver resection for HCC patients have reported 3 and 5-year survival rates between 38-65% and 33-50%.<sup>32-38</sup> In the past decade, major advances have led to improvement of the long-term survival results after hepatectomy. Early diagnosis at the asymptomatic phase of disease and a more accurate staging system has allowed identification of patients with early stage HCC. Meanwhile, more accurate evaluation of the underlying liver function has identified those patients with compensated liver function who can tolerate hepatic resection safely. Apart from Child-Pugh classification,<sup>16</sup> ICG retention test and

hepatic vein catheterization to assess the degree of portal hypertension are commonly used to elucidate patients' liver function and severity of cirrhosis preoperatively. Moreover, technical refinements for liver transection and the use of intraoperative ultrasonography allow precise anatomical resection of liver tumor in a relatively bloodless manner. Despite these favorable survival results, the cumulative 5-year recurrence rate was in the range of 75-100% from most series, thus contributing to a low disease-free survival.<sup>39-45</sup> Microvascular invasion, poor histological differentiation, and presence of satellite nodules predict occurrence of recurrence.<sup>46</sup> The majority of recurrence occurs in the liver remnant, and aggressive treatment of recurrence by re-resection, local ablation or TACE is indicated in order to prolong patients' survival.

**Liver transplantation.** Orthotopic liver transplantation is theoretically the best treatment for HCC patients as it involves the widest possible resection margins for cancer, removes the remnant liver at risk of malignant change, and restores hepatic function. This is a particularly good treatment option for patients with early HCC, and hence a low metastatic potential, but advanced Child-Pugh class C<sup>16</sup> cirrhosis. In such patients, other effective treatments cannot be offered because of poor liver function, and prognosis is dismal, and determined by the cirrhosis rather than HCC without further treatment. However, the scarcity of liver grafts has made this treatment modality less effective and available to HCC patients, when compared with hepatic resection. Milan criteria<sup>47</sup> (solitary tumor <5cm or ≤3 tumor nodules, each <3cm) are the most widely used criteria for inclusion of HCC patients for liver transplantation, based on which, the 4-year survival rate of up to 75% could be achieved, with a recurrence rate lower than 15%. Vascular invasion has been postulated to be a major predictor of recurrence and survival.<sup>48</sup> Nonetheless, the overall survival benefit of liver transplantation has been limited by the long waiting time for liver grafts for HCC patients. An intention-to-treat analysis has revealed a decrease in survival from 84-54% when the mean waiting time increased from 62-162 days.<sup>35</sup> Adjuvant treatments given while patients are on the waiting list are used in most centers to prevent tumor progression. These include percutaneous ablation, and TACE. Recently, live donor liver transplantation is emerging as a solution to eliminate the limiting factor of long waiting time for liver grafts, and is theoretically a more preferred choice for HCC patients. However, the potential risk of donor hepatectomy (0.3-0.5% mortality) and relatively higher recipients' complication (20-40%) need to be considered in offering such treatment.<sup>49</sup> Theoretically, live donor liver grafts are often small-for-size. The subsequent acute phase injury, regeneration and the

resulting tumor angiogenesis might increase the chance of tumor recurrence ultimately.<sup>50</sup> Whether this has any clinical impact on the long-term survival of patients with live donor liver transplantation has not yet been clarified.

**Local ablation therapy.** Local ablation therapy has been practiced widely for unresectable HCC. It has the advantage of effective tumor destruction and preservation of maximal non-tumorous liver tissue at the same time. Among different local ablation therapies, PEI and RFA are the most popular techniques with associated impressive prognosis. The PEI induces tumor necrosis by cellular dehydration, protein denaturation, and thrombosis of small vessels. It can be performed as an outpatient procedure under local anesthesia, with ultrasound or CT guidance. Histopathologic studies have shown that PEI can induce complete tumor necrosis in 90-100% of patients with HCC <2cm, 70% of patients with HCC of 3cm in diameter, and 50% of patients with HCC of 5cm in diameter.<sup>51</sup> The reported 5-year survival rates after PEI in patients with HCC <5cm was in the range of 28-71%.<sup>32,51-54</sup> Some adverse prognostic factors that influence the efficacy of PEI include liver function status, tumor size, pretreatment AFP level and multiple tumor nodules. The RFA has gained much enthusiasm in modern management of unresectable malignant liver tumors. As a form of thermal ablation treatment, it relies on the interaction of high frequency alternating current (460-480 kHz) with living tissue to generate heat energy through ionic vibration. At lethal temperatures above 60°C, there is instantaneous protein coagulation with irreversible damage of key intracellular enzymes, which contributes to coagulative necrosis of the target lesion. In recent years, there are new models of RF electrodes (multitined expandable electrodes, internally cooled electrodes, perfusion electrodes, and bipolar electrodes), that can produce larger coagulation necrosis to extend the limit of ablation volume for liver tumors. The complete ablation rate of RFA for HCC approaches 100% in many series,<sup>55-59</sup> while the local recurrence at the RFA treatment site ranges from 5.7-39%.<sup>58,60-68</sup> The range of the reporter 3-year survival rate of RFA for HCC was 45-71%. The of the reporter 5-year survival rate of RFA for HCC was 33-55%.<sup>69-75</sup>

**Transarterial chemoembolization.** The TACE is a regional therapy widely used for unresectable HCC since the 1980s. During the procedure, iodized poppyseed oil (Lipiodol) and chemotherapeutic agents (doxorubicin, cisplatin, or mitomycin C) are administered through the feeding artery of the tumor, followed by arterial embolization with gelatin sponge particles. The long-term survival benefit of TACE for HCC patients has been demonstrated by 2 recent randomized controlled

studies, which suggested a beneficial effect of TACE (3-year survival rate of 26-29%) compared with conservative management.<sup>76,77</sup> A meta-analysis of all the randomized clinical trials available in the literature has shown that TACE provided short-term (2-year) survival benefit (odds ratio=0.42) as compared with control.<sup>78</sup>

**Systemic treatment.** The HCC is relatively resistant to systemic chemotherapeutic agents. Doxorubicin is the most commonly used agent, but the overall response rate is low (<20%) with poor median survival of patients (-4 months).<sup>79</sup> Immunotherapy using high dose recombinant interferon-alpha<sup>2</sup> has been shown to be superior than systemic doxorubicin in some studies.<sup>80,81</sup> However, flu-like symptoms and significant toxicities is associated with high drug dosage. Somatostatin receptors have been identified in HCC, and hence octreotide, a somatostatin analogue, is potentially effective for tumor clearance by exerting a suppressive effect on cell growth. While a small randomized trial,<sup>82</sup> showed some survival benefit with the use of octreotide, another randomized trial from our group<sup>83</sup> did not show any difference in survival compared with conservative management. The role of octreotide for patients with advanced HCC needs to be further clarified by large-scale randomized study.

**Summary.** The HCC remains a major health problem with poor prognosis worldwide. Because of the advances in imaging techniques, more frequent diagnosis of HCC has been made, especially in the asymptomatic phase. A wide range of treatment modalities is available for HCC patients, depending on the stage of the disease as well as the liver function state. Stratification of HCC patients according to the different prognostic subgroups to the optimal treatment modality is important. With this management scheme, curative treatments would be reserved to the subgroup of patients with relatively good prognosis. For patients with advanced malignancy localized to the liver, local ablation, or TACE may offer effective symptomatic palliation, and prolongation of patients' survival. For patients with distant metastases, currently no effective therapy can be offered and symptomatic palliative care or participation in new drug trials is the best option.

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