Pathobiologic Characteristics of Small Hepatocellular Carcinoma

2

Wenming Cong, Xinyuan Lu, and Wanyee Lau

2.1 Small HCC Is Not Equivalent to Early HCC

Early diagnosis and treatment of cancer have long been established as basic principles of modern surgical oncology. There is no doubt that a better understanding of the pathobiological features of small hepatocellular carcinoma (SHCC) will provide clinicians with the pathobiological basis to better treat these tumors and to improve long-term survivals of patients. For relatively small HCC, several designations such as "early HCC" and "subclinical HCC" [1] have been proposed. The definitions of these tumors are based mainly upon tumor size, and each definition uses a different size. The concept of SHCC can be traced back to the late 1970s [2, 3], when SHCC was considered as the most significant prognostic factor of long-term survival.

However, no consensus has been reached among researchers or clinicians who designed clinical practice guidelines which have been accepted worldwide on the size criterion for SHCC. As a consequence, a confusing plethora of size standards to define SHCC, including 5 cm [2–4], 4.5 cm [5], 4 cm [6], 3.5 cm [7], 3 cm [8–11], 2.5 cm [12], and 2 cm [13–16] has been used.

According to the database of the Department of Pathology at the Eastern Hepatobiliary Surgery Hospital (EHBH), Shanghai, China, the largest special hepatic surgical hospital in China, 2459 and 3092 liver resections for HCCs were carried out in the years 2007 and 2011, respectively. The resected specimens showed HCCs with a diameter of ≤2 cm and ≤3 cm to account for 9.3 % and 19 %, and 10.3 % and 31.4 %, respectively. These figures were obviously higher than the 2.6 % and 8.7 % reported before 1997 [17]. With the exception of micro or minute HCCs (≤1 cm), which corresponded to carcinoma in situ or very early HCC, our previous studies on pathobiological features of solitary HCCs showed that by dividing HCC into subgroups of 1-cm-diameter increments, there were no significant differences in the clinicopathological features among the subgroups of HCCs, which ranged from 1 to 3 cm (SHCC) or among the subgroups of large HCCs (LHCCs), which ranged over 3 cm. However, if 3 cm was used as a cutoff for SHCC, significant differences were observed between the groups of SHCC and LHCC ($P<0.05$–0.01) [18]. These differences included histological grades I–II versus III–IV, the presence or absence of capsular invasion/portal venous tumor thrombi/satellite nodules, invasive growth patterns, and overall survival and recurrence-free survival. Multivariate Cox regression

W. Cong, MD, PhD (✉) • X. Lu, MD
Department of Pathology, Eastern Hepatobiliary Surgery Hospital, Second Military Medical University, Shanghai, China
e-mail: wmcong@gmail.com

W. Lau, MD, DSc, FACS, FRCS, FRACS(Hon)
The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

M. Chen et al. (eds.), *Radiofrequency Ablation for Small Hepatocellular Carcinoma*,
DOI 10.1007/978-94-017-7258-7_2

analyses showed that tumor size ≤3 cm was an independent prognostic factor of overall and recurrence-free survivals [18, 19]. Similar results were also reported by Pawlik et al. [20].

An early HCC, in general, is a tumor at an early developmental stage characterized by well-differentiation on histology, with noninvasive growth pattern and a more favorable long-term prognosis after curative treatment. The Liver Cancer Study Group of Japan defined early HCC as a well-differentiated HCC with an obscure tumor margin [21]. Early HCC is often detected in cirrhotic livers, and it shows as a hypovascular nodule in the arterial phase of an intravenous contrast enhanced computed tomographic (CT) scan [22].

Although tumor size has been proposed as a criterion to define early HCC, there is still no consensus on the size that should be used. Mazzaferro et al. [23] defined early-stage HCC for transplantation to be a single tumor <5 cm or two to three tumors all <3 cm, with no evidence of extrahepatic tumor (the Milan criteria). Nathan et al. [24] defined early HCC as tumors ≤5 cm and without metastatic disease, nodal metastasis, extrahepatic extension, or major vascular invasion. In the early study of the Barcelona Clinic Liver Cancer (BCLC) group, early HCC was defined as a single tumor ≤5 cm [25, 26]. However, in the recent BCLC classification, very early HCC is defined as well-differentiated tumors ≤2 cm in diameter without any vascular invasion or satellites, and early HCC is defined as HCC ≤2 cm with microscopic vascular invasion/satellites, or 2–5-cm well-differentiated/moderately differentiated HCC without any vascular invasion/satellites, or two or three well-differentiated nodules <3 cm [27, 28]. However, the BCLC group reported that nearly 60 % of their SHCCs, which were less than 2 cm, had moderate to poor differentiation [15], whereas Sakamoto and Hirohashi [29] defined early HCC as a well-differentiated HCC (Edmondson's grade I or grade I with a minor component of grade II), negative for tumor staining on angiographic examination, and regardless of tumor size.

While small HCC is usually defined on tumor size, early HCC is still commonly defined on histopathological grounds. It should be emphasized that a small HCC is not always necessarily equivalent to an early HCC as defined histologically, although most early HCCs are less than 2 cm in its greatest diameter [30]. In the Italian Liver Cancer group (ITA.LI.-CA)'s classification, an early HCC is defined as a solitary HCC smaller than 5 cm because SHCC below 2 cm is rare [16]. In the current revised version of the BCLC system, as released by the American Association for the Study of Liver Diseases, patients diagnosed at an early stage are defined as having single or three nodules below 3 cm each [31, 32]. On the other hand, other scholars defined pathologically early HCC to correspond to carcinoma in situ [33] and clinically early HCC is characterized by a locally curable tumor, which has a favorable long-term survival outcome [34].

Early HCC with its benign behavior is at an early phase in the progression of HCC, while small HCC may already have developed malignant behavior. Although a small HCC is not equivalent to an early "benign" tumor because some aggressive HCC can metastasize when it is still small in size, most researchers agree that with increase in size of a small HCC, there is a gradual change in pathobiological behavior of the tumor. Tumor size has been shown to be the best predictor of tumor behavior [35].

Conceptually, the criteria used to define SHCC are tumor size-based while early HCC are biological behavior-based. A small-size HCC does not absolutely mean a tumor having early biological behavior. Although pathologically, SHCC ≤ 3 cm tends to show relatively benign behavior, a small proportion of SHCC presents with aneuploid DNA content [8, 36, 37] and harbors microvascular invasion [38, 39]. These more malignant features happen even in a minute HCC 0.6 cm in diameter, [18]. As a consequence, SHCC can further be divided into two clinicopathological subtypes: early SHCC and progressive SHCC. In patients with a single tumor, tumor size has no impact on survival in patients with no vascular invasion or microvascular invasion, irrespective of how the tumor size was dichotomized [14]. In HCC ≤ 2 cm, patients who have suspicious features of gross invasive type of tumors on preoperative imaging are at a high risk of having pathological microinvasion. In such patients,

hepatic resection with a wide tumor margin is recommended. Even a SHCC ≤ 3 cm should be surgically resected with reasonable margins. As approximately 80 % of vascular invasion or micrometastatic foci are located within 1 cm of the primary SHCC, it is important to resect or to ablate the tumor with an adequate width of surrounding tissues (of > 1 cm) to prevent recurrence coming from residual tumor cells. Therefore, no matter what therapeutic options are chosen for SHCC, curative treatment with adequate safety margins should always be given.

2.2 Pathobiological Characteristics of SHCC

Like many other human solid tumors which undergo initiation, promotion, and progression, HCC possesses a similar multi-stage evolution model in its hepatocarcinogenesis [40–42]. In general, the smaller the tumor, the greater is the chance of radical cure and the longer is the postoperative long-term survival. On the other hand, the more advanced the lesion, the lower is the likelihood that therapy is curative. Also, the smaller the lesion, the closer it lies to the dysplasia/neoplasia boundary, the more difficult it is to be certain on histological analysis whether the lesion is malignant (Edmondson and Steiner's grade I). We herein briefly review the history in the study of SHCC, analyze the advantages and limitations of using different criteria to define SHCC, and discuss the pathobiological characteristics of SHCC and their clinical significance.

2.2.1 The Features of a SHCC ≤ 5 cm

In the mid to late 1970s, Chinese surgeons Dr. Tang ZY et al. [2] and Dr. Wu MC et al. [3] first put forward the concept of SHCC. This has a milestone-like significance to give basic scientists and clinical researchers to direct their research from large HCC (LHCC) at the middle-advanced stage to SHCC at the early developmental stage. At that time, a HCC ≤ 5 cm in diameter was defined as SHCC based on the clinical information that about 70 % of HCC patients who were subclinical (without any symptoms) harbored a tumor ≤ 5 cm in diameter. In contrast, about 70 % of subjects harboring a tumor > 5 cm showed obvious clinical symptoms. Patients with a tumor measuring ≤ 5 cm in diameter survived longer than those with tumors > 5 cm in diameter [2, 3]. Since then, this concept that patients who have an early-stage HCC are those who present with an asymptomatic single HCC ≤ 5 cm has been widely accepted even up to now [14, 20, 24, 25, 43–46]. Also, the AJCC/UICC seventh edition of TNM classification uses a cutoff tumor size of 5 cm in the T3a HCC staging [47].

With advances in radiographic diagnostic techniques, much smaller liver tumors can now be detected. As more studies show improvement in long-term prognosis with treatment of solitary HCCs smaller than 5 cm, using 5 cm as the SHCC criterion in modern hepatic surgery seems too large when compared with the concept of small tumors of other organs [48–51].

2.2.2 The Features of a SHCC ≤ 3 cm

In 1981, the Liver Cancer Pathological Study Group of China proposed a macroscopic classification of HCC, and HCC ≤ 3 cm in diameter was classified as an independent type [52]. In 1986, Ebara et al. [53] reported on 22 Japanese patients with minute HCC of less than 3 cm in diameter who received no special treatment. The serum alpha-fetoprotein levels in these patients were low, and they were rarely useful for diagnosis. However, this tumor marker level tended to increase when the mass had attained a diameter greater than 3 cm. In the following year, the Japanese pathologists proposed a gross classification of five subtypes for SHCC ≤ 3 cm in diameter [54].

We started to compare the relationship between HCC size and DNA ploidy in 1988 to better understand the pathobiological features of SHCC in its early stage [36]. The results showed the majority of HCCs ≤ 3 cm in diameter maintained DNA diploidy. These tumors were characterized by relatively "benign" behaviors, which included a clear tumor margin with or without a complete fibrous capsule, well cell

differentiation, almost no satellites and microvascular invasion, and they were easy to be radically resected resulting in long-term postoperative survival [8, 19, 55]. In comparison, HCCs > 3 cm in diameter mainly showed DNA aneuploidy with obvious malignant behaviors, which included poor cell differentiation, capsular invasion, a high-frequency of satellite nodules and tumor thrombus formation, and a high-risk of residual tumor after radical treatment with relatively poor survival outcomes [8, 19, 55]. As a consequence, we proposed that HCC approaching 3 cm in diameter is reaching an important turning point for critical transformation, with a change from relatively "benign" behaviors to a more aggressive progression. The 3-cm cutoff seems to be the most suitable point to define SHCC [8, 36].

In 1994, Ng et al. [37] reported that DNA ploidy may supplement other predictors in prognostication when HCCs are stratified into small and large tumors at a cutoff point of 5 cm in diameter. Interestingly, a recent study on 12 methylation genes showed that all CpG positions in APC, GSTP1, and CFTR were more highly methylated in small HCCs less than 3 cm than in non-tumorous liver tissues ($p < 0.05$), and RASSF1A, CCND2, and APC were frequently positive (91–100 % of cases examined) in well-differentiated HCCs, small HCCs less than 3 cm, and Stages I and II HCCs [56]. Notably, the three-marker combination of RASSF1A, CCND2, and SPINT2 demonstrated the highest sensitivity and accuracy (89–95 % and 89–97 %), respectively, for all HCCs and early HCCs, and they correctly diagnosed all HCC cases in the early HCC group [56]. Likewise, Llovet et al. [27] found the expressions of GPC3, survivin, and LYVE1 to be significantly increased in dysplastic nodules, early HCC (mean size, 2 ± 0.6 cm, range, 0.9–3 cm) and advanced HCC, and the diagnostic accuracy of this three-gene set was 94 %. These studies suggest that there is a relevant molecular basis for SHCC in its early progression stage.

Histopathologically, when HCCs grow to over 2–3 cm in diameter, the well-differentiated cancerous tissues are completely replaced by moderately differentiated cancer tissues, and it is uncommon to see well-differentiated cancer tissues in tumors larger than 3 cm in diameter [57]. Tumor size larger than 3 cm is also a main risk factor of local recurrence [58], and a wider resection margin is recommended for HCCs more than 3 cm than those less than 3 cm to eradicate all micrometastases aiming to achieve good long-term survivals [59].

Many multi-center studies have reported that the postoperative survival of patients with SHCCs ≤ 3 cm in diameter was significantly better than that of patients with LHCCs > 3 cm in diameter [60–66]. Therefore, a HCC ≤ 3 cm in diameter was named as an SHCC in the first edition of the Barcelona Clinic Liver Cancer (BCLC) staging system in 1999 [4] and in the HCC staging system proposed by the Chinese Society of Liver Cancer in 2001 [67], and it was kept in the 2011 edition (http://www.moh.gov.cn). Also, a consensus-based treatment algorithm for HCC proposed by the Japan Society of Hepatology (JSH), which was revised in 2010 [68], set the cutoff point at ≤ 3 cm.

A 3 cm tumor can be completely ablated with a 10-min application of percutaneous radiofrequency ablation [69], and percutaneous ethanol injection prolongs patient survival with survival rates similar to surgical resection, especially for tumors < 3 cm [70, 71]. Therefore, it is important to diagnose and treat HCC < 3 cm.

2.2.3 The Features of a SHCC ≤ 2 cm

In both the fourth edition (1987) [72] and the fifth edition (1997) [73] of the Tumor-Node-Metastasis (TNM) classification for HCC, ≤ 2 cm was used as the size criterion for T1 HCC as proposed by AJCC/UICC. This approximates to the size of a lesion that could be detected on screening, and this poses some difficulties in diagnosis. However, many scholars reported that these two versions of the TNM classifications were not of prognostic value [45, 74–76]. In the current seventh edition of the TNM system [47], T1 HCC was re-defined as a tumor of any size but without microvascular invasion. Meanwhile, the Liver Cancer Study Group of Japan (LCSGJ)

proposed its own TNM staging using a non-strict 2-cm standard [77]. However, this revision was primarily based on data collected from LCSGJ's data, which were collected from more than 800 institutes through a Japanese nationwide survey during a 6–10-year-period [13].

The concept of a very early stage of HCC or carcinoma in situ for a HCC < 2 cm in size for which a definitive diagnosis is often difficult to establish first appeared in the second edition of the BCLC staging system in 2003 [28]. The BCLC staging system has since become widely accepted in clinical practice, and it is also commonly used in clinical trials on new drugs for HCC. Unfortunately, almost all studies on SHCC ≤ 2 cm which have been reported in medical literature are based on small samples [13, 15, 16, 30, 38, 45, 64, 78–87] or without clearly mentioning the actual sample size [31, 68, 88]. Farinati et al. [16], from the Italian Liver Cancer group (ITA.LI.CA) indicated that their patients with the "very early HCC" of smaller than 2 cm were too few (3 %) to perform an internal validation analysis or to make a definition of this disease stage clinically useful. Therefore, they preferred to use 5 cm as the cutoff point. Although review articles on these classifications have been published, none of these classifications have received universal acceptance.

2.2.4 Pathological Patterns of SHCC

Nakashima et al. [89] divided small HCC of less than 3 cm in diameter into the vaguely nodular type with indistinct margins, the single nodular type, the single nodular type with extranodular growth, and the confluent multinodular type. None of the vaguely nodular type had intrahepatic metastasis or portal vein invasion. The reason why an early HCC shows a vague (indistinct) nodular pattern remains unclear. We speculate that in the early developing stage of SHCC, patients may lack an effective immune response or defense ability, or patients with SHCC have an early/precirrhotic-stage cirrhosis in the noncancerous tissue, which may lead to the absence of a fibrous capsule in early HCC [19].

Histologically, early SHCC usually shows well differentiation with a thin trabecular pattern and lacks prominent cellular and structural atypia. None of the vaguely nodular type showed intrahepatic metastasis or portal vein invasion. Based on histological grading, Sasaki et al. [90] classified SHCC ≤ 3 cm into early HCC, well-differentiated HCC, and moderately or poorly differentiated HCC. The 5-year survival rates of patients in the above three groups were 100 %, 60%, and 27 %, respectively.

SHCC of the vaguely nodular type, which is one of the subtypes derived from the gross classification of HCC of less than 3 cm in diameter, is considered as a macroscopic characteristic of early-stage HCCs by the LCSGJ [54, 80] and the International Consensus Group for Hepatocellular Neoplasia (ICGHN) [38]. However, many SHCCs of the vaguely nodular type as diagnosed by Japanese pathologists tend to be recognized as high-grade dysplastic nodules (HGDN) by Western pathologists [88, 91]. Although pathologic diagnostic criteria for SHCC have been fully described, which include that the lesions should present with intratumoral portal tracts and stromal invasion [38, 88, 92, 93], it is difficult to identify morphological correlates of malignant behavior at the boundary between premalignant and malignant states, because dysplasia and early neoplasia share many common histological features. Many well-differentiated SHCC and HGDN show similar pathological features, such as vaguely nodular appearances, increased cell density, thin trabecular pattern, and unpaired arteries [94]. Individual discrepancy probably exists among even expert hepatopathologists in the histological diagnosis between HGDN and well-differentiated SHCC with a vaguely nodular appearance. For example, "stromal invasion" is considered the most objective and reliable criterion to distinguish a well-differentiated HCC from a HGDN [95]. However, from our experience based on more than 30,000 archived surgical HCC specimens in the database of the Department of Pathology, EHBH, while intranodular portal tracts seem more likely to appear

in dysplastic nodules, stromal invasion into portal tracts or fibrous septa may sometimes but not commonly seen in early SHCC. Any nodule in a cirrhotic liver with a diameter of > 3 cm should be regarded as very suspicious of HCC, because benign nodules of this size is rare [96]. Anyway, diagnosis by hepatopathologists on minute nodules remains a challenge, and this has prompted hepatopathologists to develop new diagnostic tools using immunostaining, gene expression assessment, or molecular classification. In conclusion, early diagnosis and definitive treatment are the keys to achieve good long-term survival outcome.

2.3 Classification of T Staging of HCC According to Size of HCC, How Small Is Small?

The Tumor-Node-Metastasis (TNM) staging system is one of the most widely accepted system for prediction of prognosis [97, 98]. The American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system stratifies the prognosis of hepatocellular carcinoma (HCC) patients by using a TNM classification which considers tumor size and number, vascular invasion, lymph node involvement, and extra-hepatic metastasis. The AJCC/UICC has published the seventh edition of the TNM staging system in 2009 [47]. In the TNM staging system, tumor number, vascular invasion, lymph node involvement, and extrahepatic metastasis are relatively easy to define. However, tumor size in the T staging of HCC changed from 2 cm (AJCC/UICC fifth edition) to 5 cm (AJCC/UICC sixth edition and AJCC/UICC seventh edition). The reason for the change was "All solitary tumors without vascular invasion, regardless of size, are classified as T1 because of similar prognosis." However, our experience suggests that this change is too radical because it did not consider an HCC of 3 cm. We will review the importance of an HCC of 3 cm on prognosis, biological behavior, and its impact on any therapeutic guideline.

2.3.1 Size of HCC on Prognosis

It has been increasingly reported that size of HCC is a prognostic factor. The AJCC first edition cancer staging manual was reported in 1977, the seventh edition was updated in 2009 (Table 2.1). In the first edition, the TNM stage of HCC was not described. In the second edition of the AJCC Cancer Staging system, an early HCC was defined as a tumor size of ≤ 3 cm. Among the third–fifth editions of the AJCC Cancer Staging system, this tumor size was defined as ≤ 2 cm.

From the sixth edition of the AJCC Cancer Staging system, the tumor size was defined as ≤ 5 cm. It was described in the sixth edition that "All solitary tumors without vascular invasion, regardless of size, are classified as T1 because of similar prognosis" [99]. However, our two large cohort studies revealed that the cumulative survival rates were significantly different among groups of patients with HCC ≤ 2 cm, 3 cm, and 5 cm [8, 18]. In addition, our published data also supported that patients with HCC above or below 3 cm had significantly different survival rates [18]. The updated BCLC also considered HCC of 3 cm to be the main factor in choice of any potentially curative option such as curative liver resection, ablation, or transplantation [100].

2.3.2 Size of HCC Versus Pathological Features

Nakashima et al. [89], Sasaki et al. [90], and our data proposed that the prognosis is related to tumor size, pathologic stage, growth pattern, gross feature, histological feature, clinical stage, and biological stage [101].

2.3.3 Size of HCC Versus Biological Behavior

Our study proposed that an HCC approaching 3 cm in diameter is reaching an important turning point for critical transformation, which

Table 2.1 Illustration of TNM stages of HCC

Edition	Publication year	Effective year	T-stage
1	1977	1978	None
2	1983	1984	T1 Small solitary tumor (<3 cm) confined to one lobe
			T2 Large tumor (>3 cm) confined to one lobe, T2a: single tumor nodule, T2b: multiple tumor nodule (any size)
			T3 Tumor involving both major lobes, T3a: single tumor nodule (with direct extension), T3b: multiple tumor nodules
			T4 Tumor invading adjacent organs
3	1988	1989	T1 Solitary tumor 2 cm or less in greatest dimension without vascular invasion
			T2 Solitary tumor 2 cm or less in greatest dimension with vascular invasion, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension without vascular invasion, or solitary tumor more than 2 cm in greatest dimension without vascular invasion
			T3 Solitary tumor more than 2 cm in greatest dimension with vascular, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension, with vascular invasion, or multiple tumors limited to one lobe, any more than 2 cm in greatest dimension, with or without vascular invasion
			T4 Multiple tumors in more than one lobe, or tumors involving a major branch of portal or hepatic veins
4	1992	1993	T1 Solitary tumor 2 cm or less in greatest dimension without vascular invasion
			T2 Solitary tumor 2 cm or less in greatest dimension with vascular invasion, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension without vascular invasion, or solitary tumor more than 2 cm in greatest dimension without vascular invasion
			T3 Solitary tumor more than 2 cm in greatest dimension with vascular, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension, with vascular invasion, or multiple tumors limited to one lobe, any more than 2 cm in greatest dimension, with or without vascular invasion
			T4 Multiple tumors in more than one lobe, or tumors involving a major branch of portal or hepatic veins
5	1997	1998	T1 Solitary tumor 2 cm or less in greatest dimension without vascular invasion
			T2 Solitary tumor 2 cm or less in greatest dimension with vascular invasion, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension without vascular invasion, or solitary tumor more than 2 cm in greatest dimension without vascular invasion
			T3 Solitary tumor more than 2 cm in greatest dimension with vascular, or multiple tumors limited to one lobe, none more than 2 cm in greatest dimension, with vascular invasion, or multiple tumors limited to one lobe, any more than 2 cm in greatest dimension, with or without vascular invasion
			T4 Multiple tumors in more than one lobe or tumors involves a major branch of portal or hepatic veins or invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum
6	2002	2003	T1 Solitary tumor without vascular invasion
			T2 Solitary tumor with vascular invasion, or multiple tumors, none >5 cm
			T3 Multiple tumors, any >5 cm (T3a), or tumors involving major branch of portal or hepatic veins
			T4 Tumors with direct invasion of adjacent organs other than the gallbladder, or with perforation of visceral peritoneum
7	2009	2010	T1 Single tumor without vascular invasionc
			T2 Single tumor with vascular invasion, or multiple tumors, none >5 cm
			T3 Multiple tumors, any >5 cm (T3a), or tumors involving major branch of portal or hepatic veins (T3b)
			T4 Tumors with direct invasion of adjacent organs other than the gallbladder, or perforation of visceral peritoneum

changes from a relatively "benign" behavior to a more aggressive progression.[8, 18, 19, 36, 55]. This 3-cm cutoff seems to be the best point to define SHCC [8]. Other scholars have also found the relationship between tumor size and DNA ploidy [37] .

The tumor size definition in the T stage of the seventh edition of the AJCC might need to be re-evaluated by a large scale, multi-center prognostic analysis on biological stage, clinical stage, and other pathological observations. The size of HCC of 3 cm might have to be re-considered as an important factor.

2.4 Can SHCC Be Cured by RFA Basing on Its Pathological Characteristics?

Buscarini et al. in 1992 and Rossi et al. in 1993 first reported that radiofrequency ablation (RFA) is an easy-to-operate and minimally invasive technique that provides an effective local treatment. Subsequently, Shiina et al. [102] reported in cases with a small number (<3 nodules) of small size (<3 cm in diameter) hepatocellular carcinomas (HCC), RFA was superior to the conventional HCC treatments of percutaneous ethanol injection therapy and surgical resection in terms of recurrence, complications, and survival rates. However, some tumors remain difficult to treat with RFA because these tumors cannot be visualized or are adjacent to intestinal loops or main bile ducts, which might be damaged by the treatment.

RFA can be performed percutaneously, laparoscopically, or during laparotomy and can replace surgical resection in selected patients with SHCC. However, long-term results are difficult to ascertain, because the majority of reports evaluated success in terms of tumor necrosis and few data are available on overall and disease-free survivals of patients. In this book chapter, we primarily focus on the effectiveness of RFA on SHCC based on its pathological characteristics. We also discuss protocols and new developments in ablation techniques.

2.4.1 Development of RFA in SHCC Therapy

RFA is a physical thermal ablation technique which induces thermal injury to tissues through electromagnetic energy deposition. The temperature can reach to 90–120 °C by agitation resulting in frictional heat around the electrode. This leads to immediate tissue death and thermal coagulation necrosis [103]. There are three stages of development of RFA in clinical treatment of SHCC. In the first stage (during the early 1990s), only a single and solid-center needle electrode was used, and a very small diameter of ablative region of about 1.6 cm was achieved. It was not widely adopted in clinical practice because of the limited ablative region and lack of experience in its application. It the second stage (the mid-1990s), a multiple electrode, the LeVeen electrode, and an internally cooled needle electrode were developed, which led to an increase in diameter of the ablative region to 3.5–5.0 cm. These developments made very significant improvement in the therapeutic effectiveness, and RFA gradually becomes widely used in the treatment of SHCC and other tumors. As a result, RFA gradually replaced other forms of ablative therapies and became the focus of attention. In the last stage, a new generation of electrode was invented, which integrated two-different mechanisms: a combined cluster needle electrode and a saline enhanced electrode. New electrodes used clinically for SHCC now include the expandable LeVeen (Boston Scientific Corp., Natick, MA, USA) and the monopolar Cool-tip (Covidien, Boulder, CO, USA). The LeVeen needle contains an array with diameters of 20, 30, 35, or 40 mm, and the Cool-tip needle includes a 10-mm and a 20-mm non-insulated tip, respectively. The selection of needle electrodes depends on tumor size. The selection of needle electrodes should also take into consideration the condition of the surrounding hepatic tissues to ensure a sufficient ablative margin. Masayoshi et al. [104] proposed a solution in the selection of an electrode, which can produce a wider area of ablation than what is normally required.

Over the past two decades, radiofrequency ablation (RFA) has evolved into an important therapeutic tool for treatment of SHCC. In 1996, Rossi et al. [105] first reported the long-term survival rates of RFA for SHCC. Thirty-nine patients with SHCC ≤ 3.0 cm in diameter were enrolled for RFA therapy. The overall 1-, 3-, and 5-year survival rates were 97 %, 68%, and 40 %, respectively. RFA has gradually been accepted in the treatment of SHCC, although for some clinicians, the preferred treatment for SHCC is still surgical resection and liver transplantation. RFA has significant advantages over surgery which include the following: (1) it is minimally invasive procedure and it has a high efficacy. It only takes about 10 min to ablate a tumor ≤ 3.0 cm completely. The wound is small, and the recovery is rapid; (2) it has only a relatively small impact on liver function and quality of life; (3) it is safe. A study which included 2320 patients with 3530 HCC tumors reported that the mortality after RFA was 0.3 % [106]; (4) it has a very low rate of complication; (5) it is cost-effective and has easy operability, the procedure can be done in a day clinic; and (6) the necrotic tumor tissues after treatment can become a source of autogenous vaccine, which enhances the immune response to cancer.

2.4.2 Pathological Characteristics and Other Factors Which Impact on Prognosis of RFA for SHCC

RFA offers a new option of curative treatment for SHCC. The initial results are encouraging, and it can be used in patients when surgical resection or liver transplantation is contraindicated because of poor general condition of patients. In most studies, the initial complete tumor response rates for small HCCs ≤ 3 cm following RFA have been reported to be 90–95 %. The estimated 3- and 5-year overall and disease-free survival rates were 67.0 % and 40.1 % and 68.0 and 38.0 %, respectively. The local tumor progression rates were 10–20 %. There are factors which affect good outcomes of RFA. There is no controversy that the patient's own body mass index (BMI), which reflects technical difficulty in carrying out RFA, is significantly associated with results of RFA therapy for SHCC. Other factors include the following:

1. Tumor location and methods of RFA: when compared to surgical resection, percutaneous RFA is more likely to result in residual tumors, especially when the lesions are located at some specific sites of the liver, e.g., underneath the liver capsule, adjacent to the gallbladder, or under the diaphragm. Laparoscopic approach appears to be the safest and most effective method to treat small tumors on the liver surface and offers the additional advantages of laparoscopic ultrasound, which provides a good resolution to show the number and location of liver tumors. Although more invasive, open RFA can be performed and the direction of puncture of the RF needle can be better selected than the laparoscopic approach, especially for lesions located close to the gallbladder or in contact with the diaphragm.
2. Tumor size: in a report coming from Japan, 183 patients with a solitary HCC of 3 cm or less were treated either with hepatic resection (HR) (n = 101) or RFA (n = 82) as a first-line treatment. There were no significant differences between the two groups for HCC of 2 cm or less. In patients treated with RFA, a tumor size of more than 2 cm was the only independent prognostic factor of a worse disease-free survival (risk ratio = 1.832, $P = 0.039$) [107].
3. Serum albumin: Peng et al. reported that in 224 patients with a solitary HCC ≤ 5 cm and with a liver background of Child-Pugh class A treated with RFA between November 1999 and June 2007, the overall 5-, 7-, 10-year survival rates were 59.8 %, 55.2 %, 33.9 %, respectively. The median overall survival was 76.1 months. Complete ablation was achieved in 216 patients (96.4 %). Serum albumin was the only factor which significantly impacted recurrence-free and tumor-free survivals ($P = 0.008$, 0.002, respectively) [108].
4. Serum alpha fetoprotein (AFP) and age: in a study from South Korea, 570 patients with

674 early-stage HCCs were treated with percutaneous RFA. The primary technique effectiveness rate was 96.7 %. The cumulative survival rates at 1, 2, 3, 4, and 5 years were 95.2 %, 82.9 %, 69.5 %, 60.8 %, and 58.0 %, respectively. Patients with Child-Pugh class A cirrhosis, younger age (≤58 years), or low AFP level (≤100 microg/L) demonstrated better survival results (P < 0.05). The Child-Pugh class, age, and AFP level before RFA were significant prognostic predictors of long-term survival [109].

5. Endothelial cell-specific molecule 1 (ESM-1): in a study which included 150 patients with early HCC treated with RFA, ESM-1 expression by HCC stromal endothelial cells was observed in 58 patients (40 %) and it was associated with higher serum AFP levels, larger tumors, and more frequent expression of EpCAM (a surrogate marker of activation of Wnt-ß-catenin pathway). The two independent predictive factors of overall recurrence were serum AFP (HR 1.11, p = 0.045) and ESM-1 expression (HR 1.56 [1.004; 2.43], p = 0.048). Thus, ESM-1 expression was an independent predictive factor of early recurrence (HR 1.81 [1.02; 3.21], p = 0.042) [110].
6. High serum hyaluronic acid and HBV viral load have been reported to be the main prognostic factors of local recurrence after complete radiofrequency ablation of hepatitis-B-related small HCC [111].
7. Age: a multivariate analysis on patients with HCV-related SHCC who were treated with RFA showed age of 75 years or more [relative hazard (RH) 1.61, p = 0.019] and a serum albumin level of less than 3.5 g/dL (RH 1.61, p = 0.016), which were significant factors of a decrease in overall survival. Furthermore, a serum albumin level of less than 3.5 g/dL (RH 1.50, p = 0.003) was the only significant factor of decrease in recurrence-free survival [112].
8. Neutrophil-to-lymphocyte ratio (NLR): an elevated preoperative NLR has been reported to be a prognostic factor for SHCC patients after RFA treatment. Multivariate analysis showed that the postoperative change in NLR, but not the preoperative NLR, was an independent prognostic factor of both overall survival (P < 0.001, HR = 2.39, 95%CI 1.53–3.72) and recurrence-free survival (*P* = 0.003, HR = 1.69, 95%CI 1.87–8.24). The postoperative change in NLR was an independent prognostic factor, and patients with a decrease in NLR had better survival than those with an increase in NLR [113] .

Conclusion

In conclusion, RFA is safe and effective for treating SHCC, with the advantages of having less complication, easy operation, and rapid recovery. There is no difference in disease-free survival and overall survival, and RFA and surgical resection in patients with SHCC are safe and effective. However, the pathological characteristics of SHCC with more aggressive behavior such as DNA aneuploidy, microvascular invasion, microscopic satellites, poor differentiation, capsular invasion, tumor location as well as macroscopic growth patterns, can influence the long-term treatment results for both RFA and surgical resection.

References

1. Tang ZY. Subclinical hepatocellular carcinoma: Historical aspects and general consideration. In: Tang ZY, editor. Subclinical hepatocellular carcinoma. Berlin: Springer; 1985. p. 1–11.
2. Zhaoyou T, Yeqin Y, Zhiying L, et al. Small hepatocellular carcinoma: clinical analysis of 30 cases. Chin Med J (Engl). 1979;92(7):455–62.
3. Wu MC, Chen H, Zhang XH, et al. Primary hepatic carcinoma resection over 18 years. Chin Med J (Engl). 1980;93(10):723–8.
4. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–38.
5. Okuda K, Nakashima T, Obata H, et al. Clinicopathological studies of minute hepatocellular carcinoma. Analysis of 20 cases, including 4 with hepatic resection. Gastroenterology. 1977;73(1):109–15.
6. Kanematsu T, Sonoda T, Takenaka K, et al. The value of ultrasound in the diagnosis and treatment of small hepatocellular carcinoma. Br J Surg. 1985;72(1):23–5.
7. Kondo Y, Niwa Y, Akikusa B, et al. A histopathologic study of early hepatocellular carcinoma. Cancer. 1983;52(4):687–92.

8. Cong WM, Wu MC. The biopathologic characteristics of DNA content of hepatocellular carcinomas. Cancer. 1990;66(3):498–501.
9. Libbrecht L, Severi T, Cassiman D, et al. Glypican-3 expression distinguishes small hepatocellular carcinomas from cirrhosis, dysplastic nodules, and focal nodular hyperplasia-like nodules. Am J Surg Pathol. 2006;30(11):1405–11.
10. Aishima S, Nishihara Y, Kuroda Y, et al. Histologic characteristics and prognostic significance in small hepatocellular carcinoma with biliary differentiation: subdivision and comparison with ordinary hepatocellular carcinoma. Am J Surg Pathol. 2007;31(5):783–91.
11. Okuwaki Y, Nakazawa T, Shibuya A, et al. Intrahepatic distant recurrence after radiofrequency ablation for a single small hepatocellular carcinoma: risk factors and patterns. J Gastroenterol. 2008;43(1):71–8.
12. Kudo M. Atypical large well-differentiated hepatocellular carcinoma with benign nature: a new clinical entity. Intervirology. 2004;47(3-5):227–37.
13. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. Hepatology. 2000;32(6):1224–9.
14. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol. 2002;20(6):1527–36.
15. Forner A, Vilana R, Ayuso C, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology. 2008;47(1):97–104.
16. Farinati F, Sergio A, Baldan A, et al. Early and very early hepatocellular carcinoma: when and how much do staging and choice of treatment really matter? A multi-center study. BMC Cancer. 2009;9:33.
17. Cong W, Wu M, Wang Y, et al. Primary liver tumors in China. Oncol Rep. 1997;4(3):649–52.
18. Lu XY, Xi T, Lau WY, et al. Pathobiological features of small hepatocellular carcinoma: correlation between tumor size and biological behavior. J Cancer Res Clin Oncol. 2011;137(4):567–75.
19. Cong WM. Clinicopathologic features of small hepatocellular carcinoma – an analysis of ninety-three cases. Zhonghua Zhong Liu Za Zhi. 1993;15(5):372–4.
20. Pawlik TM, Delman KA, Vauthey JN, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. Liver Transpl. 2005;11(9):1086–92.
21. LCSGO. Classification of primary liver cancer. Tokyo: Kanehara Press Co; 1997.
22. Matsui O, Kadoya M, Kameyama T, et al. Benign and malignant nodules in cirrhotic livers: distinction based on blood supply. Radiology. 1991;178(2):493–7.
23. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9.
24. Nathan H, Hyder O, Mayo SC, et al. Surgical therapy for early hepatocellular carcinoma in the modern era: a 10-year SEER-medicare analysis. Ann Surg. 2013;258(6):1022–7.
25. Llovet JM, Bruix J, Fuster J, et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. Hepatology. 1998;27(6):1572–7.
26. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology. 1999;30(6):1434–40.
27. Llovet JM, Chen Y, Wurmbach E, et al. A molecular signature to discriminate dysplastic nodules from early hepatocellular carcinoma in HCV cirrhosis. Gastroenterology. 2006;131(6):1758–67.
28. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907–17.
29. Sakamoto M, Hirohashi S. Natural history and prognosis of adenomatous hyperplasia and early hepatocellular carcinoma: multi-institutional analysis of 53 nodules followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or percutaneous ethanol injection. Jpn J Clin Oncol. 1998;28(10):604–8.
30. Takayama T, Makuuchi M, Hirohashi S, et al. Early hepatocellular carcinoma as an entity with a high rate of surgical cure. Hepatology. 1998;28(5):1241–6.
31. Bruix J, Sherman M. Practice Guidelines Committee AaFTSOLD. Management of hepatocellular carcinoma. Hepatology. 2005;42(5):1208–36.
32. Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
33. Sakamoto M. Pathology of early hepatocellular carcinoma. Hepatol Res. 2007;37 Suppl 2:S135–8.
34. Sakamoto M. Early HCC: diagnosis and molecular markers. J Gastroenterol. 2009;44 Suppl 19:108–11.
35. Kim SJ, Lee KK, Kim DG. Tumor size predicts the biological behavior and influence of operative modalities in hepatocellular carcinoma. Hepatogastroenterology. 2010;57(97):121–6.
36. Cong Wm WM. Significance of clinicopathology in quantitative measurement of DNA content in hepatocellular carcinoma. J Med Coll PLA. 1988;3:153–6.
37. Ng IO, Lai EC, Ho JC, et al. Flow cytometric analysis of DNA ploidy in hepatocellular carcinoma. Am J Clin Pathol. 1994;102(1):80–6.
38. Kojiro M, Wanless IR, Alves V, et al. International Consensus Group for Hepatocellular Neoplasiathe International Consensus Group for Hepatocellular N. Pathologic diagnosis of early hepatocellular carcinoma: a report of the international consensus

group for hepatocellular neoplasia. Hepatology. 2009;49(2):658–64.
39. Llovet JM, Fuster J, Bruix J, et al. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl. 2004;10(2 Suppl 1):S115–20.
40. Tsuda H, Hirohashi S, Shimosato Y, et al. Clonal origin of atypical adenomatous hyperplasia of the liver and clonal identity with hepatocellular carcinoma. Gastroenterology. 1988;95(6):1664–6.
41. Takayama T, Makuuchi M, Hirohashi S, et al. Malignant transformation of adenomatous hyperplasia to hepatocellular carcinoma. Lancet. 1990;336(8724):1150–3.
42. Sakamoto M, Hirohashi S, Shimosato Y. Early stages of multistep hepatocarcinogenesis: adenomatous hyperplasia and early hepatocellular carcinoma. Hum Pathol. 1991;22(2):172–8.
43. Liver Cancer Study Group of Japan. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. Ann Surg. 1990;211(3):277–87.
44. Livraghi T, Bolondi L, Buscarini L, et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: a retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. J Hepatol. 1995;22(5):522–6.
45. Ryder SD, British Society of Group. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut. 2003;52(3):1–8.
46. Forner A, Hessheimer AJ, Isabel Real M, et al. Treatment of hepatocellular carcinoma. Crit Rev Oncol Hematol. 2006;60(2):89–98.
47. Edge SB, Byrd DR, Carducci MA. American Joint Committee on Cancer (AJCC) Cancer staging manual. New York: Springer; 2009.
48. Kunavisarut T, Kak I, Macmillan C, et al. Immunohistochemical analysis based Ep-ICD subcellular localization index (ESLI) is a novel marker for metastatic papillary thyroid microcarcinoma. BMC Cancer. 2012;12:523.
49. Edge SB, Byrd DR, Compton CC. AJCC Cancer staging manual. New York: Springer; 2010. p. 347–76.
50. Laudano MA, Klafter FE, Katz M, et al. Pathological tumour diameter predicts risk of conventional subtype in small renal cortical tumours. BJU Int. 2008;102(10):1385–8.
51. Saito H, Osaki T, Murakami D, et al. Macroscopic tumor size as a simple prognostic indicator in patients with gastric cancer. Am J Surg. 2006;192(3):296–300.
52. Zy T. Primary liver cancer. Shanghai: Shanghai Scientific & Technical Publishers; 1981.
53. Ebara M, Ohto M, Shinagawa T, et al. Natural history of minute hepatocellular carcinoma smaller than three centimeters complicating cirrhosis. A study in 22 patients. Gastroenterology. 1986;90(2):289–98.
54. Kanai T, Hirohashi S, Upton MP, et al. Pathology of small hepatocellular carcinoma. A proposal for a new gross classification. Cancer. 1987;60(4):810–9.
55. Cong WM. Clinical studies on pathobiological characteristics of early hepatocellular carcinoma. Zhonghua Wai Ke Za Zhi. 1991;29(6):341–4, 396.
56. Moribe T, Iizuka N, Miura T, et al. Methylation of multiple genes as molecular markers for diagnosis of a small, well-differentiated hepatocellular carcinoma. Int J Cancer. 2009;125(2):388–97.
57. Kojiro M. 'Nodule-in-nodule' appearance in hepatocellular carcinoma: its significance as a morphologic marker of dedifferentiation. Intervirology. 2004;47(3–5):179–83.
58. Lam VW, Ng KK, Chok KS, et al. Incomplete ablation after radiofrequency ablation of hepatocellular carcinoma: analysis of risk factors and prognostic factors. Ann Surg Oncol. 2008;15(3):782–90.
59. Ueno S, Kubo F, Sakoda M, et al. Efficacy of anatomic resection vs nonanatomic resection for small nodular hepatocellular carcinoma based on gross classification. J Hepatobiliary Pancreat Surg. 2008;15(5):493–500.
60. Vilana R, Bruix J, Bru C, et al. Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. Hepatology. 1992;16(2):353–7.
61. Kojiro M, Nakashima O. Histopathologic evaluation of hepatocellular carcinoma with special reference to small early stage tumors. Semin Liver Dis. 1999;19(3):287–96.
62. Shimada M, Rikimaru T, Hamatsu T, et al. The role of macroscopic classification in nodular-type hepatocellular carcinoma. Am J Surg. 2001;182(2):177–82.
63. Hu RH, Lee PH, Chang YC, et al. Prognostic factors for hepatocellular carcinoma < or = 3 cm in diameter. Hepatogastroenterology. 2003;50(54):2043–8.
64. Shimozawa N, Hanazaki K. Longterm prognosis after hepatic resection for small hepatocellular carcinoma. J Am Coll Surg. 2004;198(3):356–65.
65. Wu FS, Zhao WH, Liang TB, et al. Survival factors after resection of small hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2005;4(3):379–84.
66. Marelli L, Grasso A, Pleguezuelo M, et al. Tumour size and differentiation in predicting recurrence of hepatocellular carcinoma after liver transplantation: external validation of a new prognostic score. Ann Surg Oncol. 2008;15(12):3503–11.
67. Cancer CSOL. Clinical diagnosis and staging of primary liver cancer. Chin J Hepatol. 2001;9:324.
68. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis. 2011;29(3):339–64.
69. Tiong L, Maddern GJ. Systematic review and meta-analysis of survival and disease recurrence after radiofrequency ablation for hepatocellular carcinoma. Br J Surg. 2011;98(9):1210–24.
70. Cabrera R, Nelson DR. Review article: the management of hepatocellular carcinoma. Aliment Pharmacol Ther. 2010;31(4):461–76.

71. Memon K, Kulik L, Lewandowski RJ, et al. Radiographic response to locoregional therapy in hepatocellular carcinoma predicts patient survival times. Gastroenterology. 2011;141(2):526–35, 535 e521-522.
72. Hermanek P, Sobin LH. TNM classification of malignant tumours. Berlin: Springer; 1987.
73. Sobin LH, Wittekind C. TNM classification of malignant tumours. New York: Wiley-Liss; 1997.
74. Izumi R, Shimizu K, Ii T, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. Gastroenterology. 1994;106(3): 720–7.
75. Staudacher C, Chiappa A, Biella F, et al. Validation of the modified TNM-Izumi classification for hepatocellular carcinoma. Tumori. 2000;86(1):8–11.
76. Chiappa A, Zbar AP, Podda M, et al. Prognostic value of the modified TNM (Izumi) classification of hepatocellular carcinoma in 53 cirrhotic patients undergoing resection. Hepatogastroenterology. 2001;48(37):229–34.
77. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol. 2003;38(3):207–15.
78. Kondo F, Hirooka N, Wada K, et al. Morphological clues for the diagnosis of small hepatocellular carcinomas. Virchows Arch A Pathol Anat Histopathol. 1987;411(1):15–21.
79. Nagao T, Nagashima I, Inoue S, et al. Hepatic resection for minute hepatocellular carcinoma. Surg Today. 1992;22(2):110–4.
80. Nakashima O, Sugihara S, Kage M, et al. Pathomorphologic characteristics of small hepatocellular carcinoma: a special reference to small hepatocellular carcinoma with indistinct margins. Hepatology. 1995;22(1):101–5.
81. Ikai I, Arii S, Kojiro M, et al. Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer. 2004;101(4):796–802.
82. Ando E, Kuromatsu R, Tanaka M, et al. Surveillance program for early detection of hepatocellular carcinoma in Japan: results of specialized department of liver disease. J Clin Gastroenterol. 2006;40(10):942–8.
83. Minagawa M, Ikai I, Matsuyama Y, et al. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg. 2007;245(6):909–22.
84. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology. 2008;47(1):82–9.
85. Takayama T, Makuuchi M, Hasegawa K. Single HCC smaller than 2 cm: surgery or ablation?: surgeon's perspective. J Hepatobiliary Pancreat Sci. 2010;17(4):422–4.
86. Di Tommaso L, Destro A, Fabbris V, et al. Diagnostic accuracy of clathrin heavy chain staining in a marker panel for the diagnosis of small hepatocellular carcinoma. Hepatology. 2011;53(5):1549–57.
87. Yamashita Y, Tsuijita E, Takeishi K, et al. Predictors for microinvasion of small hepatocellular carcinoma </= 2 cm. Ann Surg Oncol. 2012;19(6):2027–34.
88. Kojiro M. Focus on dysplastic nodules and early hepatocellular carcinoma: an Eastern point of view. Liver Transpl. 2004;10(2 Suppl 1):S3–8.
89. Nakashima Y, Nakashima O, Tanaka M, et al. Portal vein invasion and intrahepatic micrometastasis in small hepatocellular carcinoma by gross type. Hepatol Res. 2003;26(2):142–7.
90. Sasaki Y, Imaoka S, Ishiguro S, et al. Clinical features of small hepatocellular carcinomas as assessed by histologic grades. Surgery. 1996;119(3):252–60.
91. Desmet VJ. East-West pathology agreement on precancerous liver lesions and early hepatocellular carcinoma. Hepatology. 2009;49(2):355–7.
92. Kondo F. Histological features of early hepatocellular carcinomas and their developmental process: for daily practical clinical application : Hepatocellular carcinoma. Hepatol Int. 2009;3(1):283–93.
93. Park YN. Update on precursor and early lesions of hepatocellular carcinomas. Arch Pathol Lab Med. 2011;135(6):704–15.
94. Di Tommaso L, Sangiovanni A, Borzio M, et al. Advanced precancerous lesions in the liver. Best Pract Res Clin Gastroenterol. 2013;27(2):269–84.
95. Kojiro M. Diagnostic discrepancy of early hepatocellular carcinoma between Japan and West. Hepatol Res. 2007;37 Suppl 2:S121–4.
96. Bolondi L, Gaiani S, Celli N, et al. Characterization of small nodules in cirrhosis by assessment of vascularity: the problem of hypovascular hepatocellular carcinoma. Hepatology. 2005;42(1):27–34.
97. Henderson JM, Sherman M, Tavill A, et al. AHPBA/AJCC consensus conference on staging of hepatocellular carcinoma: consensus statement. HPB (Oxford). 2003;5(4):243–50.
98. Lu W, Dong J, Huang Z, et al. Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP TNM and CUPI. J Gastroenterol Hepatol. 2008;23(12):1874–8.
99. Greene F, Fleming I, Fritz A, et al. AJCC cancer staging manual. Chicago: Springer, 2010. p 435.
100. Forner A, Reig ME, De Lope CR, et al. Current strategy for staging and treatment: the BCLC update and future prospects. Semin Liver Dis. 2010;30(1): 61–74.
101. Cong WM, Wu MC. Small hepatocellular carcinoma-current and future approaches. Hepatol Int. 2013;7(3):805–12.
102. Shiina S, Teratani T, Obi S, et al. Nonsurgical treatment of hepatocellular carcinoma: from percutaneous ethanol injection therapy and percutaneous microwave coagulation therapy to radiofrequency ablation. Oncology. 2002;62 Suppl 1:64–8.

103. Lencioni R, Crocetti L, Cioni D, et al. Percutaneous radiofrequency ablation of hepatic colorectal metastases: technique, indications, results, and new promises. Invest Radiol. 2004;39(11):689–97.
104. Masayoshi T, Wakui N, Sumino Y. Use of radiofrequency ablation in the treatment of hepatocellular carcinoma: Experience of ablation protocols. Exp Ther Med. 2012;4(6):959–61.
105. Rossi S, Di Stasi M, Buscarini E, et al. Percutaneous RF interstitial thermal ablation in the treatment of hepatic cancer. AJR Am J Roentgenol. 1996;167(3):759–68.
106. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radiofrequency ablation: complications encountered in a multicenter study. Radiology. 2003;226(2):441–51.
107. Imai K, Beppu T, Chikamoto A, et al. Comparison between hepatic resection and radiofrequency ablation as first-line treatment for solitary small-sized hepatocellular carcinoma of 3 cm or less. Hepatol Res. 2013;43(8):853–64.
108. Peng ZW, Zhang YJ, Chen MS, et al. Radiofrequency ablation as first-line treatment for small solitary hepatocellular carcinoma: long-term results. Eur J Surg Oncol. 2010;36(11):1054–60.
109. Choi D, Lim HK, Rhim H, et al. Percutaneous radiofrequency ablation for early-stage hepatocellular carcinoma as a first-line treatment: long-term results and prognostic factors in a large single-institution series. Eur Radiol. 2007;17(3):684–92.
110. Ziol M, Sutton A, Calderaro J, et al. ESM-1 expression in stromal cells is predictive of recurrence after radiofrequency ablation in early hepatocellular carcinoma. J Hepatol. 2013;59(6):1264–70.
111. Xia F, Lai EC, Lau WY, et al. High serum hyaluronic acid and HBV viral load are main prognostic factors of local recurrence after complete radiofrequency ablation of hepatitis B-related small hepatocellular carcinoma. Ann Surg Oncol. 2012;19(4):1284–91.
112. Toshikuni N, Takuma Y, Goto T, et al. Prognostic factors in hepatitis C patients with a single small hepatocellular carcinoma after radiofrequency ablation. Hepatogastroenterology. 2012;59(120):2361–6.
113. Dan J, Zhang Y, Peng Z, et al. Postoperative neutrophil-to-lymphocyte ratio change predicts survival of patients with small hepatocellular carcinoma undergoing radiofrequency ablation. PLoS One. 2013;8(3), e58184.