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REVIEW ARTICLE

Small hepatocellular carcinoma: current and future approaches

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Abstract Over 3 decades have passed since the first report of small hepatocellular carcinoma (SHCC), which has been confirmed as one of the most significant prognostic factors. Obviously, it is indeed very important to know when an early SHCC will become more aggressive and lead to worse clinical outcome once it grows beyond a critical size. However, so far, no consensus has been achieved on the size criterion for SHCC among different authors or different clinical practice guidelines that have been used worldwide, although there are currently numerous cutoff values for tumor size used to define SHCC, including 5, 3 and 2 cm in diameter, etc. Herein, based on our current understanding concerning the pathobiological features of SHCC, we briefly review the history of SHCC study, analyze the advantages and limitations of the above criteria for SHCC, and discuss the pathobiological characteristics as well as the clinical significance of SHCC.

Keywords Small hepatocellular carcinoma · Early hepatocellular carcinoma · Guidelines · Pathobiological features · Surgical outcome

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Introduction

The early diagnosis and treatment of cancer have long been established as the basic principle of modern surgical oncology. Macroscopic tumor size has long been considered as an independent prognostic indicator. For example, this concept has been well demonstrated by minute gastric cancer (<5 mm diameter), small gastric cancer (≤1 cm in diameter) and early gastric cancer (submucosal invasion), proposed over 30 years ago. Since that time, the long-term survival for patients with gastric carcinoma who have undergone radical surgery have dramatically improved today [1–4].

Hepatocellular carcinoma (HCC) in men is the third most common solid malignancy and the second most frequent cause of cancer-related deaths in developing countries [5]. Like many other human solid tumors that undergo initiation, promotion and progression, HCC possesses a similar multi-stage evolution model for hepatocarcinogenesis [6–8]. More than 30 years have elapsed since the concept of small HCC (SHCC) was introduced, which greatly improved the early diagnosis and treatment of HCC. However, what defines the characteristics and size of HCC considered to be at an early developmental stage remains a challenging problem, and there is currently no consensus regarding the concept and size criteria for SHCC. We expect that the definition of SHCC should reflect not only the current clinical levels in the diagnosis and treatment of SHCC, but also the understanding levels of the pathobiological features of SHCC. This article is intended to comprehensively review the history of SHCC study and to discuss the advantages and limitations of the current criteria for SHCC and early HCC.

The criterion for SHCC ≤5 cm in diameter

In the mid to late 1970s, the Chinese surgical groups Tang et al. [9] and Wu et al. [10] first put forward the systemic concept of SHCC. This event was a milestone, in due course giving the basic science and clinical research directions for large HCC (LHCC) at the middle-advanced stage to SHCC at the early developmental stage. At that time, an HCC ≤5 cm in diameter was defined as SHCC based on the clinical information that about 70 % of HCC patients who were subclinical without significant symptoms harbored a tumor ≤5 cm in diameter. Similarly, about 70 % of subjects harboring a tumor >5 cm showed obvious clinical symptoms, and patients with a tumor measuring ≤5 cm in diameter survived longer than those with tumors >5 cm in diameter [9, 10]. Since then, the concept that patients at an early stage are those who present with an asymptomatic single HCC <5 cm has been widely accepted even up to today [11–18]. Also, according to the AJCC/UICC 7th edition of TNM classification, the cutoff tumor size is set at 5 cm for T3a HCC staging [19].

However, with the advances in radiographic diagnostic techniques, currently much smaller liver tumors can be easily detected. Therefore, in terms of modern hepatic surgery, using 5 cm as the SHCC criterion seems a bit large when compared with small tumors of the other organs [1–4].

The criterion for SHCC ≤3 cm in diameter

In 1979, the Liver Cancer Pathological Study Group of China proposed a macroscopic classification for HCC in which an HCC ≤3 cm in diameter was first classified as an independent type [20]. In 1986, Ebara et al. [21] reported on 22 Japanese patients with minute HCC less than 3 cm in diameter without special treatment. They found that the serum alpha-fetoprotein levels in these patients were generally low and rarely assisted during diagnosis, but tended to increase when the mass attained a diameter greater than 3 cm. In the following year, Japanese pathologists proposed a gross classification of five subtypes for SHCCs ≤3 cm in diameter [22].

Beginning in 1988, we compared the relationship between HCC size and DNA ploidy to better understand the pathobiological features of SHCC in its early stage. The results showed that the majority of HCCs ≤3 cm in diameter maintained DNA diploidy and were characterized by relatively benign behavior, including clear margins with or without a complete fibrous capsule, good cell differentiation, almost no satellites and microvascular invasion, and being easily radically resected for long-term postoperative survival, etc. Comparatively, HCCs >3 cm in diameter mainly showed DNA aneuploidy and obvious malignant behaviors, including poor cell differentiation, capsule invasion, high frequency of satellite nodules and tumor thrombus formation, high-risk residual tumor cells after radical treatment and relatively poor outcomes. Accordingly, we proposed that an HCC of nearly 3 cm in diameter may reach an important turning point for the critical transformation, changing from relatively benign behavior to a more aggressive progression, and the 3 cm cutoff seems to be the best definition for SHCC [23, 24].

In 1994, Ng et al. [25] reported that DNA ploidy may supplement other prognostication predictors when HCCs are stratified into small and large tumors of 5 cm in diameter. Interestingly, a recent study of 12 methylation genes showed that RASSF1A, CCND2 and SPINT2 were similarly methylated in all SHCCs ≤3 cm (nearly 100 % specificity) [26]. Likewise, Llovet et al. [27] found the expressions of GPC3, survivin and LYVE1 were significantly increased in dysplastic nodules, early HCC (mean size, 2 ± 0.6 cm, range 0.9–3 cm) and advanced HCC in turn, and the diagnostic accuracy of this three-gene set was 94 %. The above studies suggest 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 will be 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 [28]. Tumor size larger than 3 cm is also found to be the main risk factor for local recurrence [29], and a larger resection margin is always needed for HCCs of more than 3 cm than for those less than 3 cm in order to eradicate all micrometastases and achieve long-term survival [30].

Many multi-center studies have reported that the postoperative survival rate of patients with SHCCs ≤3 cm in diameter was significantly better than that of patients with LHCCs >3 cm in diameter [31–37]. Therefore, an HCC ≤3 cm in diameter was named SHCC in the first edition of the Barcelona Clinic Liver Cancer (BCLC) staging system in 1999 [38] and in the HCC staging system proposed by the Chinese Society of Liver Cancer, which was developed in 2001 [39] and preserved the definition in the 2011 edition (http://www.moh.gov.cn). Also, a consensus-based treatment algorithm proposed by the Japan Society of Hepatology (JSH), revised in 2010, was set to ≤3 cm for HCC [40].

On the other hand, it was found that a 3-cm tumor can be completely ablated with a 10-min application of percutaneous radiofrequency ablation [41], and percutaneous ethanol injection prolongs patient survival with rates similar to those with surgical resection, especially for tumors <3 cm [42, 43]. Therefore, at present, significantly increasing the ratio of SHCC <3 cm in patients who receive radical treatment poses an urgent and practical issue in hepatic surgery.

The criterion for SHCC ≤2 cm in diameter

In both the 4th (1987) [44] and the 5th editions (1997) [45] of TNM (tumor node metastasis) classification for HCC, ≤2 cm was used as the size criterion for T1 HCC as proposed by the AJCC/UICC. However, many scholars reported that these two versions of TNM classification were not of prognostic value [16, 46–48]. In the current 7th edition TNM system [19], T1 HCC has been re-defined as any size without microvascular invasion. Meanwhile, the Liver Cancer Study Group of Japan (LCSGJ) proposed their own TNM stage using a non-strict 2-cm standard [49].

The concept of very early stage HCC for HCC <2 cm in diameter first appeared in the 2nd edition of the BCLC staging system in 2003 [50]. 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- to 10-year period [51]. Roughly speaking, in terms of an individual hepatic center, almost all studies on SHCC ≤2 cm reported in the literature so far were based on a small sample (Table 1) [16, 35, 51–65] or did not clearly mention the sample size [40, 66, 67]. Farinati et al. [61], from the Italian Liver Cancer group (ITA.LI.CA), indicated that their patients with so-called very early HCCs smaller than 2 cm were too few (3 %) to perform an internal validation analysis and to make a definition of this disease stage clinically useful. Therefore, they preferred to use 5 cm as the cutoff point. The main currently used staging systems that contain the tumor size of HCC are listed in Table 2.

Based on the database of the Department of Pathology at the Eastern Hepatobiliary Surgery Hospital (EHBH), Shanghai, China, which is the largest special hepatic surgical hospital in China, 2,459 and 3,092 surgical resections of HCCs were performed in 2007 and 2011, respectively. Among them, HCCs with a diameter of ≤2 cm and ≤3 cm accounted for 9.3 and 19 %, and 10.3 and 31.4 %, respectively, which were obviously higher than that of 2.6 and 8.7 % before 1997 [69, 70]. Our previous studies on the pathobiological features of solitary HCCs, which were divided into groups by 1-cm-diameter increments, demonstrated that with the exception of micro or minute HCC (≤1 cm), which is considered to correspond to carcinoma in situ, or very early HCC, almost no differences in clinicopathological features existed among HCCs ranging from 1 to 3 cm (SHCC) or among LHCCs over 3 cm. But if 3 cm was used as the cutoff size for SHCC, significant differences were observed between SHCC and LHCC ($p < 0.05$–0.01). Multivariate Cox regression analyses showed that tumor size ≤3 cm was one of the independent prognostic factors for both overall survival and recurrence-free survival [70, 71]. Similar results were also reported by Pawlik et al. [12]. A schematic diagram thought to be involved in tumor growth from micro HCC to LHCC is summarized in Fig. 1.

Table 1 Information about studies on ≤2-cm SHCCs in the literature

Years	Authors	SHCC/total	Survey periods	5-year survival	No. of units
1987	Kondo et al. [52]	15/–	10 years	–	2
1992	Nagao et al. [53]	23/–	10 years	61 %	1
1995	Nakashima et al. [54]	27/–	8 years	–	1
1998	Takayama et al. [55]	80/1,172	10 years	93–54 %	2
2000	Arii et al. [51]	1,318[a]/8,010	8 years	71.5 %	≈800 (LCSGJ)
2002	Vauthey et al. [15]	57/591	18 years	59–50 %	4
2004	Ikai et al. [56]	2,320/12,118	10 years	–	≈800 (LCSGJ)
2005	Wu et al. [36]	45/–	17 years	Median: 138 months	1
2006	Ando et al. [57]	91[a]/574	6 years	55.2 %	1
2007	Minagawa et al. [58]	2,767/63,736	7 years	70 %	829 (LCSGJ)
2008	Forner et al. [59]	60[a]/89[a]	4 years	–	2
2008	Livraghi et al. [60]	218/– (RFA)	11 years	68.5 %	5
2009	Farinati et al. [61]	65[a]/1,834[a]	18 years	Median: 60 months	10 (ITA.LI.CA)
2009	International Consensus Group for Hepatocellular Neoplasia (ICGHN) [62]	23/– (in 2002)[b] + 22/– (in 2004)[b]	–	–	3 ?
2010	Takayama et al [63]	1,235/– (surgery)	4 years	2-year: 94 %	≈800(LCSGJ)
2011	Di Tommaso et al [64]	47/86 (biopsy)	5 years	–	2
2012	Yamashita et al [65]	149/–	16 years	67–87 %	2

[a] Some patients were pathologically confirmed

[b] Small hepatic nodular lesions, including low- and high-grade dysplastic nodules and HCCs

Table 2 Current staging systems referring to the tumor size of HCC in the literature

Years	Staging system	Acronym	Score/stage	Tumor size
2001	Chinese Society of Liver Cancer	CSLC [39]	Ia	≤3 cm, vessel/satellites (−)
			Ib	≤5 cm, vessel/satellites (−)
			IIa	≤10 cm, vessel/satellites (−)
			IIb	>10 cm, vessel/satellites (−)
2003	Barcelona Clinic Liver Cancer	BCLC [50]	Very early HCC	1 HCC, <2 cm
			Early HCC	1 HCC or 3 nodules, <3 cm
2003	International Hepato-Pancreato-Biliary Association	IHPBA [68]	T1	≤2 cm
2006	Llovet JM, et al.	BCLC Group [27]	Very early HCC	≤2 cm, vessel/satellites (−)
			Early HCC	≤2 cm, vessel/satellites (+), or 2- to 5-cm, well/mode-diff., vessel/satellites (−), or 2-3 nodules, ≤3 cm, well-diff.
2007	The Liver Cancer Study Group of Japan	LCSGJ [58]	T1 (Small/early)	≤2 cm, vessel (−)
2009	American Joint Committee on Cancer	AJCC/TNM-7 [19]	T1	Any size, microvessel (−)
			T2	Any size, microvessel (+)
			T3a	Multiple tumors >5 cm
			T3b	Any size, major vessel (+)
2009	International Consensus Group for Hepatocellular Neoplasia	ICGHN [62]	Early HCC	< or >2 cm, vaguely nodular, well-diff.
2010	Japan Society of Hepatology	JSH [40]	Early HCC (Small HCC)	≤3 cm, vaguely nodular, well-diff.

The concept of early HCC

No consensus has been achieved concerning the relationship between tumor size and early HCC. Nathan et al. [17] defined early HCC as tumors ≤5 cm without metastatic disease, nodal metastasis, extrahepatic extension or major vascular invasion, whereas Sakamoto and Hirohashi [72] 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, regardless of tumor size. In an early study of the BCLC group, a single tumor ≤5 cm was used for the definition of early HCC [14, 73]. In the recent BCLC classification, very early HCC is defined as well-differentiated tumors ≤2 cm in diameter without vascular invasion or satellites, and early HCC is defined as HCC ≤2 cm with microscopic vascular invasion/satellites or 2- to 5-cm well-/moderately differentiated HCC without vascular invasion/satellites or two or three well-differentiated nodules <3 cm [27, 50]. However, the BCLC group reported that their nearly 60 % of SHCCs less than 2 cm were moderately to poorly differentiated [59]. In the ITA.LI.CA's classification, early HCC is defined as a single node HCC smaller than 5 cm, because SHCC ≤2 cm is so rare [61]. In the current revised version of the BCLC system, released by the American Association for the Study of Liver Diseases, patients diagnosed at the early stage are defined as having single or three nodules ≤3 cm [67, 74], whereas other scholars found that pathologically early HCC corresponds to carcinoma in situ [75] and clinically early HCC is characterized as locally curable and has a favorable long-term outcome [76].

Basically, SHCC is a tumor size-based criterion, and early HCC is a biological behavior-based concept. A small-size HCC really does not absolutely mean that it harbors early biological behavior. Although pathologically SHCC ≤3 cm tends to show relatively benign behavior, a small proportion of SHCCs may present aneuploid DNA content [23–25] and harbor microvascular invasion [62, 77], even in a minute HCC 0.6 cm in diameter [70]. So, for hepatic surgeons, even SHCC ≤3 cm should be carefully surgically resected with reasonable margins and watched carefully for the long-term outcome.

Pathological features of SHCC

Nakashima et al. [78] divided small HCCs less than 3 cm in diameter into the vaguely nodular type with indistinct margins, single nodular type, single nodular type with

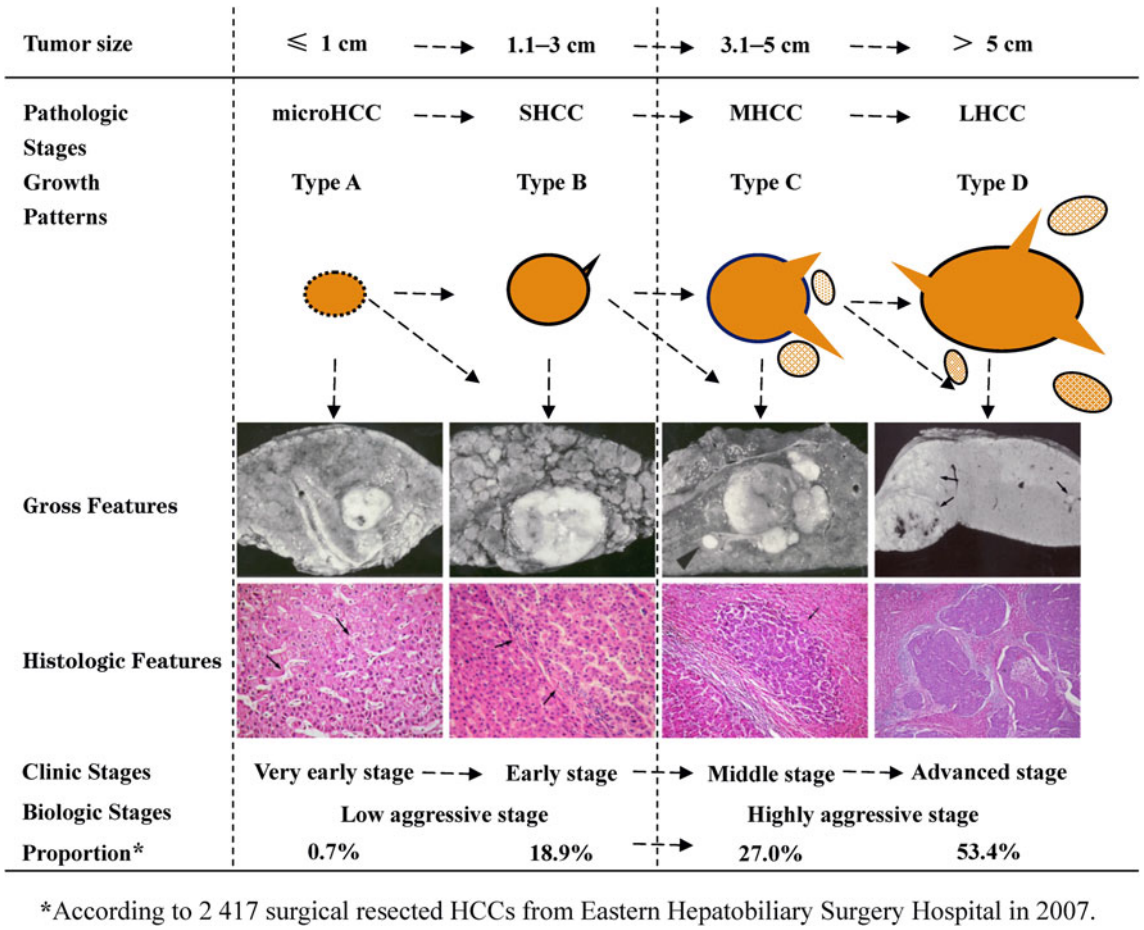

Fig. 1 Schematic representation of tumor growing types from micro HCC to LHCC. *Type A* Vaguely nodular type with indistinct margin: the tumor shows a transitional margin between well-differentiated cancer cells and surrounding hepatocyte plates. *Type B* Single nodular type: the tumor frequently presents a complete fibrous capsule with a distinct margin, and occasionally cancer cells may invade the capsule. *Type C* Single nodular type with extracapsular growth: a few tumor foci grow outside close to the capsule. *Type D* Multinodular type: multiple tumor nodules are scattered in the liver tissues. However, as illustrated by the *vertical* and *diagonal dotted lines*, each of these consecutive stages is not distinct because of tumor heterogeneity. (Reprinted from our previous study [70])

extranodular growth and confluent multinodular type. None of the vaguely nodular type showed intrahepatic metastasis or portal vein invasion. Based on histological grading, Sasaki et al. [79] classified SHCCs ≤3 cm into early, well-differentiated, and moderately or poorly differentiated HCC. The 5-year survival rates of the patients in the above three groups were 100, 60 and 27 %, respectively.

SHCC of vaguely nodular type, which is one of the subtypes derived from the gross classification of HCCs less than 3 cm in diameter, is widely considered to be a macroscopic characteristic of early stage HCCs by LCSGJ [22, 54] and the International Consensus Group for Hepatocellular Neoplasia (ICGHN) [62]. However, many SHCCs of vaguely nodular type diagnosed by Japanese pathologists tend to be recognized as high-grade dysplastic nodules by Western pathologists [66, 80], although pathological diagnostic criteria for SHCC have been fully described elsewhere, including the lesions presenting intratumoral portal tracts and stromal invasion [62, 66, 81, 82]. As an empirical discipline, individual discrepancy probably always exists among hepatopathologists in the histological diagnosis for dysplastic nodules and SHCC with a vaguely nodular appearance. For example, from our experience based on more than 30,000 archived surgical HCC specimens in the database of the Department of Pathology, EHBH, intranodular portal tracts seem more likely to appear in dysplastic nodules, and stromal invasion into the portal tracts or fibrous septa may sometimes but not commonly be seen in early SHCC. Hence, it is important to promote academic exchange among hepatopathologists worldwide.

Surveillance approach for SHCC

HCC surveillance is a common practice for patients with hepatitis B/hepatitis C-related liver cirrhosis. Consequently,

several Western and Eastern guidelines for HCC management recommend offering surveillance to high-risk populations [39, 40, 67, 74]. Although consensus on these guidelines is somewhat different between the East and the West, mainly concerning tumor marker measurements (especially serum α-fetoprotein, AFP), surveillance in high-risk patients with combined ultrasonography and/or serum AFP in 6- or 12-month intervals has been recommended for early detection of HCC and has been shown to be effective, especially in the Asian-Pacific region [40, 83, 84].

Conclusions

SHCC is a key step in HCC development and progression, and it has been emphasized as an effective approach to helping SHCC patients survive longer. Besides morphology, other factors that may influence the biological behavior of SHCC include molecular alterations required for metastasis and vascular invasion. More consideration should be given to conducting multidisciplinary collaborative research to design a more preferable pathological and clinical staging system based on the pathobiological characteristics of early SHCC.

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