The Optimal Management for Sub-Centimeter Hepatocellular Carcinoma: Curative Treatments or Follow-Up?

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Background: The optimal strategy for dealing with sub-centimeter hepatic nodules has not yet been established. This study aimed to assess whether there was a need to provide curative treatments for sub-centimeter hepatocellular carcinomas (HCCs) to patients at risk for high false positives.

Material/Methods: We identified patients with primary pathologically diagnosed HCC ≤2 cm from 2004 to 2015 in the Surveillance, Epidemiology and End Results (SEER) database. They were divided according to the interventions they received: local ablation, surgical resection, or liver transplantation. In each group, overall survival and cancer-specific survival were used as endpoints to compare the prognoses between patients with sub-centimeter HCC and patients with HCC measuring 1 to 2 cm by Kaplan-Meier. Propensity score matching was performed to reduce bias. We also compared the survival of patients with a primary solitary HCC based on interventions, in the different tumor size groups. Bootstrapping was performed to validate the findings.

Results: Overall, 10.4% of patients (197 out of 1894) had HCCs <1 cm, and 89.6% of patients (1697 out of 1894) had HCCs in the 1 to 2 cm range. There was no significant difference in overall and cancer-specific survival between patients with HCCs <1 cm and those with HCCs in the 1 to 2 cm range, in all treatment groups. After adjusting confounding factors, no significant correlation was found between tumor size and survival time. In patients with HCCs measuring ≤2 cm, overall survival and cancer-specific survival were superior in liver transplantation compared with surgical resection and local ablation. Surgical resection provided better survival than local ablation.

Conclusions: Compared to patients with HCCs measuring 1 to 2 cm, the survival rates of patients with sub-centimeter HCCs was not improved through curative treatments, risking high false positives.

MeSH Keywords: **Carcinoma, Hepatocellular • SEER Program • Survival Analysis**

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Background

Hepatocellular carcinoma (HCC) ranks as the sixth most common cancer and the fourth most lethal malignancy globally, and the 5-year overall survival rate is only 17.8% [1,2]. The Barcelona Clinic Liver Cancer (BCLC) system defines very early-stage (0) HCC as the presence of solitary lesions ≤2 cm in size in patients with preserved liver function and without metastasis. These patients benefit from curative treatments, including resection, transplantation, and ablation, which can achieve a 5-year overall survival rate of approximately 80% [3–5]. This improvement in survival rate gives rise to the widely executed surveillance programs by ultrasound (US) for the population at risk for HCC; these programs have reduced HCC-related mortality by 38% due to their increased applications of radical treatments in the surveillance population [6]. Simultaneously, a notable number of sub-centimeter hepatic nodules have been detected [7]. Although multiphasic contrast-enhanced compute tomography (CT) and magnetic resonance imaging (MRI) have better performance than US in diagnosing HCC, their accuracy is still unsatisfying for detecting these small nodules; even with enhanced MRI, the mean positive predictive value is only 48.3% [8]. Another alternative method is biopsies, which might be able to provide a definitive diagnosis in HCC, but its application in such tiny nodules is limited by tumor track seeding and bleeding. In addition, the false negative rate can reach up to 30% in HCCs ≤2 cm and is likely higher in sub-centimeter HCCs due to sampling errors [9,10].

Until now, no direct comparative research has been conducted to prove what the optimal management strategy is for these solitary, sub-centimeter hepatic nodules that are detected during surveillance imaging with US, follow-up imaging with US, or alternative modalities such as CT and MRI, or immediate biopsy [9]. The BCLC Group, the American Association for the Study of Liver Diseases (AASLD), and the European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC) suggest an augmented follow-up for hepatic nodules smaller than 1 cm [3,9,11]. In contrast, other clinical guidelines on HCC allow the noninvasive diagnosis for sub-centimeter hepatic nodules that show hypervascularity in the arterial phase and washout in the portal or delayed phases, and even propose treatments for these lesions, especially in Asia [12,13]. The reason for such recommendations is that gadoxetic acid-enhanced MRI can improve the accuracy of diagnosing small hepatic nodules through imaging, and approximately 90% of these nodules, which show typical features of malignancy in MRI, can or will be HCCs [14,15]. The major treatment modality for small HCCs in Asia is locoregional therapy, which makes it more reasonable for treating suspicious HCCs, while in western countries, transplantation is more common [12]. However, all the aforementioned guidelines have low level of evidence for their recommendations.

To date, there have been few articles reporting treatment efficiency for primary sub-centimeter HCCs. Only 1 study, which included 63 patients with or without a history of HCC, has reported that recurrence-free survival does not differ significantly between patients who were treated with nodules <1 cm and those with nodules ≥1 cm [16]. To the best of our knowledge, the survival benefits have not been proven for patients with primary sub-centimeter HCCs who received local ablation (LA), surgical resection (SR) or liver transplantation (LT) compared with patients with HCCs that are in the 1 to 2 cm range. In the face of high rates of false positives and an increasing social medical burden, it is essential to evaluate the survival benefits of treating sub-centimeter HCCs, which are quite different from recurrent ones, to determine whether there is a need for immediate treatment for those at risk of high false positives.

The Surveillance, Epidemiology and End Results (SEER) program of the US National Cancer Institute, which covers approximately 30% of the US population, provides a large database of information from patients diagnosed with cancer. By extracting data from the SEER database, we aimed to compare survival rates between patients pathologically diagnosed with primary HCCs <1 cm and HCCs in the 1 to 2 cm range who were treated with LA, SR, or LT and to analyze the optimal strategy for the management of sub-centimeter hepatic nodules, which could provide evidence for recommendations in current guidelines for HCC.

Material and Methods

Patients and Methods

This study was exempt from informed consent for its retrospect. We extracted patients' information from the SEER database using SEER*Stat software version 8.3.5 (accession number: 13411-Nov2017). All records of the patients with liver site codes C22.0 were retrieved from 2004 to 2015. The inclusion criteria were as follows: 1) tumor size 2 cm; 2) tumor confirmed with International Classification of Disease for Oncology, 3rd Edition (ICD-O-3) histology codes 8170-8175; 3) tumor diagnosed with pathology, and 4) tumor without metastasis. The exclusion criteria included: 1) had other cancer history before; and 2) survived for 0 months. Eventually, 1894 HCC patients with solitary lesions up to 2 cm were included in this research. Of these patients, 486 received LA, 424 underwent SR, and 984 received LT. The primary outcome of this study was overall survival (OS), which was defined as the time from diagnosis to death from any cause. The secondary outcome was cancer-specific survival (CSS), which was defined as the time from diagnosis to death attributed to HCC.

Table 1. Baseline demographic and clinical characteristics.

	Entire group	LA group	SR group	LT group	P value
Variables	n=1894	n=486	n=424	n=984	
Age, year	58.47±9.76	62.57±9.88	59.12±10.87	56.16±8.41	<0.001
Sex					<0.001
Male	1422 (75.1%)	352 (72.4%)	291 (68.6%)	779 (79.2%)	
Female	472 (24.9%)	134 (27.6%)	133 (31.4%)	205 (20.8%)	
Race					<0.001
White	1354 (71.5%)	315 (64.8%)	239 (56.4%)	800 (81.3%)	
Black	195 (10.3%)	52 (10.7%)	49 (11.6%)	94 (9.6%)	
Others/unknown	345 (18.2%)	119 (24.5%)	136 (32.1%)	90 (9.1%)	
Fibrosis score					<0.001
0–4	143 (7.6%)	37 (7.6%)	65 (15.3%)	41 (4.2%)	
5–6	622 (32.8%)	127 (26.1%)	102 (24.1%)	393 (39.9%)	
Unknown	1129 (59.6%)	322 (66.3%)	257 (60.6%)	550 (55.9%)	
AFP level					<0.001
Normal	566 (29.9%)	136 (28.0%)	116 (27.4%)	314 (31.9%)	
Elevated	837 (44.2%)	265 (54.5%)	211 (49.8%)	361 (36.7%)	
Unknown	491 (25.9%)	85 (17.5%)	97 (22.9%)	309 (31.4%)	
Tumor size					<0.001
<1 cm	197 (10.4%)	17 (3.5%)	34 (8.0%)	146 (14.8%)	
1–2 cm	1697 (89.6%)	469 (96.5%)	390 (92.0%)	838 (85.2%)	

AFP – alpha fetoprotein.

Statistical analysis

Chi-squared or Fisher's exact tests were performed to compare the baseline and clinical features in subgroups. A one-to-one propensity score matching (PSM) was constructed to minimize the effect of confounding factors with a caliper of 0.01. OS and CSS were compared between HCCs <1 cm and HCCs in the 1 to 2 cm range in the entire cohort, and in subgroups with different treatment modalities, using Kaplan-Meier analysis and log-rank test, which were also used for comparing the survival of different treatments in each tumor size group. A Cox proportional hazards regression model was built to identify whether tumor size impacted OS and CSS independently. The baseline characteristics were entered as covariates, including age at diagnosis, sex, race, AFP level, and fibrosis score. Furthermore, bootstrapping (re-sampling, n=1000) was performed to validate the findings in current study. Stratified sampling was used, and two-thirds of patients were in the training group while the other one-third ones were validating cohort. Statistical significance was set at a 2-tailed $P<0.05$. All statistical analyses were performed with IBM SPSS 24.0 and R version 3.2.2.

Results

A total of 1894 patients were included in this study, and they all underwent LA, SR, or LT. The baseline demographics and clinical characteristics are shown in Table 1. Among the entire cohort, 10.4% of patients had HCCs <1 cm, while 89.6% of patients had HCCs in the 1 to 2 cm range. The distribution of age at diagnosis and sex was almost equal between the different treatment groups. Approximately 75% of patients were male. In each treatment group, the percentages of patients who were white were obviously higher than those who were black. AFP (alpha-fetoprotein) level and fibrosis score were recorded as categorical variables in the SEER database (normal for code 20 and elevated for code 10; none to moderate cirrhosis for 0–4 scores and severe fibrosis or cirrhosis for 5–6 scores). As shown in Table 1, the SR group contained more patients with 0 to 4 fibrosis scores. In addition, the LT group contained more patients with HCCs <1 cm. For patients with sub-centimeter HCCs, 74.1% received LT. Of the patients with HCCs in the 1 to 2 cm range, only 49.4% received LT and 27.6% received LA. The results of the comparison for demographic and

Table 2. Demographic and clinical characteristics of patients.

	LA			SR			LT			LT (after PSM)		
	<1 cm	1–2 cm	P value	<1 cm	1–2 cm	P value	<1 cm	1–2 cm	P value	<1 cm	1–2 cm	P value
Variables	n=17	n=469		n=34	n=390		n=146	n=838		n=143	n=143	
Age			0.68			0.47			0.02			0.17
≤60	7 (41.2%)	217 (46.3%)		17 (50.0%)	220 (56.4%)		116 (79.5%)	585 (69.8%)		113 (79.0%)	103 (72.0%)	
>60	10 (58.8%)	252 (53.7%)		17 (50.0%)	170 (43.6%)		30 (20.5%)	253 (30.2%)		33 (21.0%)	40 (28.0%)	
Sex			0.47			0.37			0.31			0.02
Male	11 (64.7%)	341 (72.7%)		21 (61.8%)	270 (69.2%)		111 (76.0%)	668 (79.7%)		109 (76.2%)	91 (63.6%)	
Female	6 (35.3%)	128 (27.3%)		13 (38.2%)	120 (30.8%)		35 (24.0%)	170 (20.3%)		34 (23.8%)	52 (36.4%)	
Race			0.64			0.16			0.02			0.05
White	10 (58.8%)	305 (65.0%)		24 (70.6%)	215 (55.1%)		113 (77.4%)	687 (82.0%)		113 (79.0%)	94 (65.7%)	
Black	3 (17.6%)	49 (10.4%)		4 (11.8%)	45 (11.5%)		23 (15.8%)	71 (8.5%)		20 (14.0%)	25 (17.5%)	
Others	4 (23.5%)	115 (24.5%)		6 (17.6%)	130 (33.3%)		10 (6.8%)	80 (9.5%)		10 (7.0%)	24 (16.8%)	
AFP level			0.82			0.37			<0.001			0.68
Normal	5 (29.4%)	131 (27.9%)		11 (32.4%)	105 (26.9%)		53 (36.3%)	261 (31.1%)		52 (36.4%)	45 (31.5%)	
Elevated	10 (58.8%)	255 (54.4%)		13 (38.2%)	198 (50.8%)		28 (19.2%)	333 (39.7%)		28 (19.6%)	30 (21.0%)	
Unknown	2 (11.8%)	83 (17.7%)		10 (29.4%)	87 (22.3%)		65 (44.5%)	244 (29.1%)		63 (44.1%)	68 (47.8%)	
Fibrosis score			0.68			0.41			0.31			0.08
0–4	1 (5.9%)	36 (7.7%)		6 (17.6%)	59 (15.1%)		5 (3.4%)	36 (4.3%)		5 (3.5%)	6 (4.2%)	
5–6	6 (35.3%)	121 (25.8%)		5 (14.7%)	97 (24.9%)		51 (34.9%)	342 (40.8%)		48 (33.6%)	66 (46.2%)	
Unknown	10 (58.8%)	312 (66.5%)		23 (67.6%)	234 (60.0%)		90 (61.6%)	460 (54.9%)		90 (62.9%)	71 (49.7%)	

AFP – alpha fetoprotein.

clinical characteristics between different tumor sizes in each treatment group are presented in Table 2. Baseline features presented no significant difference between patients with different tumor sizes for the LA and SR subgroups. Though characteristics in the LT group showed significant difference between patients with tumors in different sizes, these confounding variables were balanced after PSM.

The median OS for the entire cohort was 41.5 months. Kaplan-Meier survival analyses were performed according to tumor sizes in each treatment group for both OS and CSS. For the entire group, OS and CSS were significantly different between patients with sub-centimeter HCCs and those with HCCs measuring 1 to 2 cm (P=0.03 and P=0.03 respectively). After adjusting confounding factors including age at diagnosis, sex, race, AFP, fibrosis score, and treatment modality between groups with different tumor sizes, OS and CSS were similar between the 2 groups (P=0.37 and P=0.60 respectively). The survival curves are shown in Figure 1. For OS and CSS, there was no significant difference between HCCs <1 cm and HCCs in the 1 to
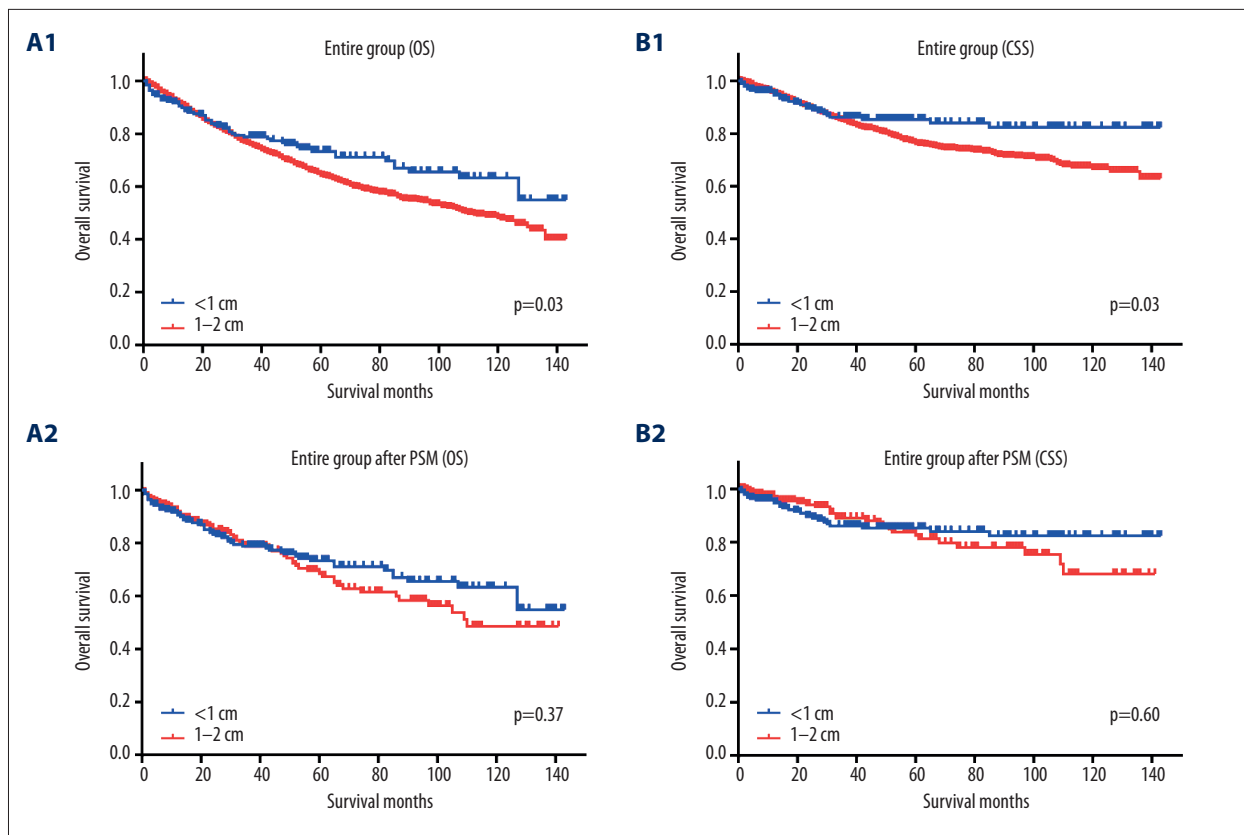
Figure 1. (**A1, A2**) Overall survival (OS) compared between different tumor sizes in the entire group before and after propensity score matching; (**B1, B2**) Cancer-specific survival (CSS) compared between different tumor sizes in the entire group before and after propensity score matching.

2 cm range in the LA group (*P*=0.95 and *P*=0.32 respectively), which is shown in Figure 2A1 and 2A2. Similar results are presented in Figure 2B1 and 2B2 for the SR group (*P*=0.22 and *P*=0.35 respectively). No significant difference was found for OS and CSS between subgroups of different tumor sizes in the LT group, before or after PSM (*P*=0.54 and *P*=0.33, *P*=0.20 and *P*=0.13, respectively). Kaplan-Meier survival curves for the LT group after PSM are shown in Figure 2C1 and 2C2.

No significant correlation between tumor size and survival was found after adjusting for confounding covariates for OS and CSS in each treatment group, including age at diagnosis, sex, race, AFP level, and fibrosis score (Tables 3, 4). In the LA group, adjusted OS and CSS did not differ significantly between patients with sub-centimeter HCCs and patients with 1 to 2 cm HCCs (hazard ratio [HR] 1.185; 95% confidence interval [CI], 0.555–2.532 and HR 1.700; 95%CI, 0.789–3.661, respectively). Additionally, there was no significant difference in adjusted OS and CSS between patients with different tumor sizes in the SR and LT groups. Detailed information is listed in Tables 3 and 4.

In patients with primary solitary HCCs ≤2 cm in size, LT showed the better survival outcomes in OS and CSS compared with LA

and SR (*P*<0.001). SR provided superior survival than LA in this cohort in terms of OS and CSS (*P*<0.01). Similar results were found in patients with HCCs measuring in 1 to 2 cm. For patients with sub-centimeter HCCs, LT was associated with longer survival than LA and SR. The OS and CSS of LA were not significantly different from those of SR (*P*=0.88 and *P*=0.40 respectively). Detailed results were shown in Figure 3.

To validate the aforementioned findings, bootstrapping was adopted, and the results are shown in Supplement Tables. For OS and CSS, there was no significant difference between different tumor sizes in each surgical modality except for OS in the training cohort of SR and CSS in the validating cohort of LA. Detailed data are presented in Supplementary Tables 1 and 2. To adjust confounding factors, multivariate Cox regression model was performed and the results are shown in Supplementary Tables 3 and 4. No significant difference was found for OS and CSS in all subgroups.
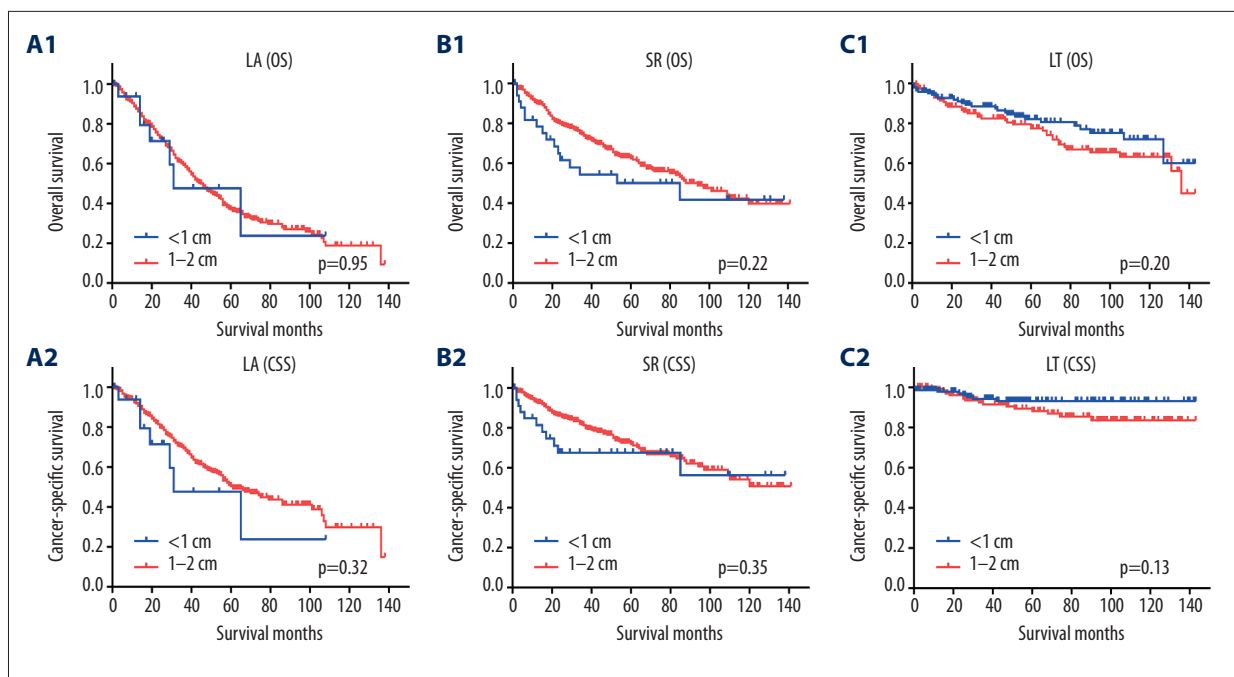
Figure 2. (**A1**) Overall survival (OS) compared between different tumor sizes in local ablation (LA) group. (**A2**) Cancer-specific survival (CSS) compared between different tumor sizes in LA group. (**B1**) OS compared between different tumor sizes in surgical resection (SR) group. (**B2**) CSS compared between different tumor sizes in SR group. (**C1**) OS compared between different tumor sizes in liver transplantation (LT) group. (**C2**) CSS compared between different tumor sizes in LT group.

Table 3. HRs for tumor size after adjusting confounding factors (OS).

Surgical modality	HR	95% CI	P value
LA			
<1 cm *vs.* 1–2 cm	1.185	0.555–2.532	0.661
SR			
<1 cm *vs.* 1–2 cm	1.285	0.757–2.184	0.353
LT			
<1 cm *vs.* 1–2 cm	0.755	0.463–1.233	0.262

LA – local ablation; SR – surgical resection; LT – liver transplantation; HR – hazard ratio; CI – confidence interval.

Table 4. HRs for tumor size after adjusting confounding factors (CSS).

Surgical modality	HR	95% CI	P value
LA			
<1 cm *vs.* 1–2 cm	1.700	0.789–3.661	0.175
SR			
<1 cm *vs.* 1–2 cm	1.209	0.638–2.292	0.560
LT			
<1 cm *vs.* 1–2 cm	0.546	0.229–1.306	0.174

LA – local ablation; SR – surgical resection; LT – liver transplantation; HR – hazard ratio; CI – confidence interval.
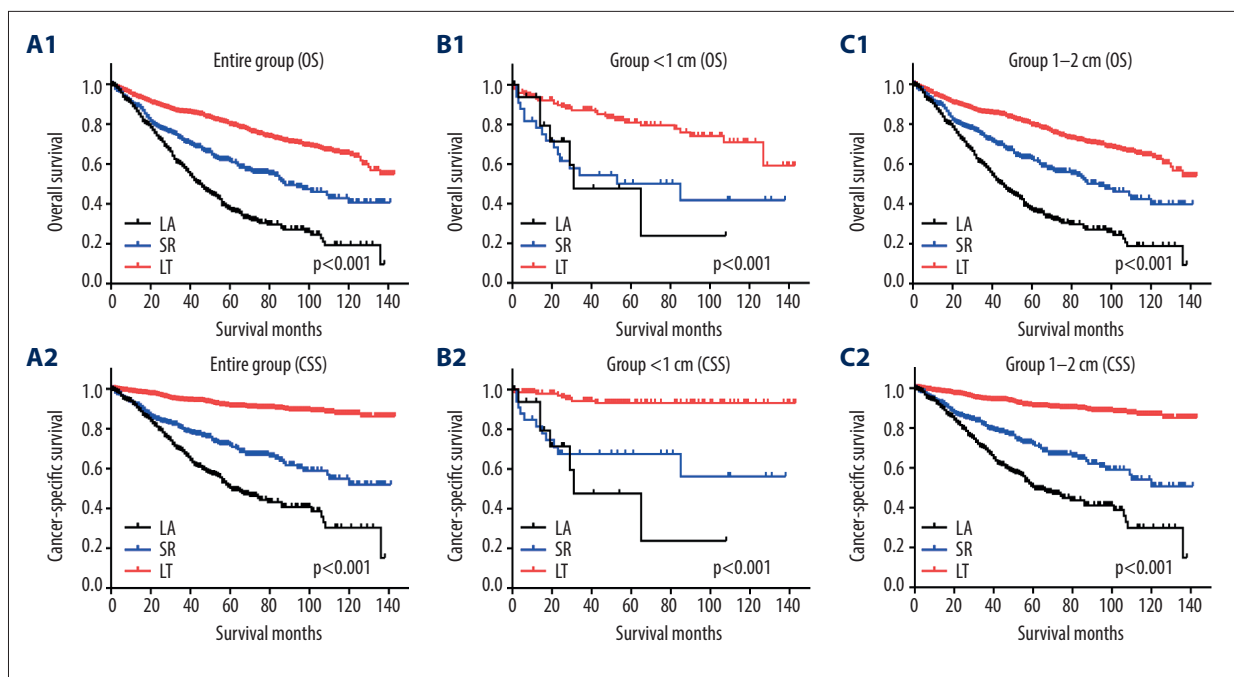
Figure 3. (**A1**) Overall survival (OS) of different treatments (LA, local ablation; SR, surgical resection; LT, liver transplantation) for entire cohort. (**A2**) Cancer-specific survival (CSS) of different treatments for entire cohort. (**B1**) OS of different treatments for group with sub-centimeter HCCs. (**B2**) CSS of different treatments for group with sub-centimeter HCCs. (**C1**) OS of different treatments for group with HCCs in 1 to 2 cm size. (**C2**) CSS of different treatments for group with HCCs in 1 to 2 cm size.

Discussion

Currently, favorable survival in patients with primary solitary HCCs ≤2 cm has been reported in many studies [4,17,18]. The BCLC and the eighth edition of the American Joint Committee on Cancer (AJCC) staging systems have adopted a critical size cutoff for HCC at 2 cm because the development of micro-metastasis increases sharply beyond this threshold [11,19–21]. All of these factors motivate regular surveillance in the population at risk for HCC to diagnose malignancies below the size of 2 cm, thus an increasing number of sub-centimeter hepatic lesions has been detected [3].

The number of studies on sub-centimeter HCCs have been increasing in recent years, with most of them focused on the diagnostic performance of imaging technology and how to improve the accuracy [8,22–24]. In our study, we extracted information from patients in the SEER database who were pathologically diagnosed with primary solitary HCCs <1 cm and those with HCCs measuring 1 to 2 cm and received LA, SR or LT. The survival time was compared between patients with HCCs <1 cm and those with HCCs in the 1 to 2 cm range. No significant difference was found in OS and CSS between the 2 groups after receiving curative treatments, which implied that the survival time could not be improved by treating HCCs in the sub-centimeter stage compared with those treated in the 1 to 2 cm stage, even if the nodules displayed typical imaging features

of HCC, including hypervascularity in the arterial phase and washout in the portal or delayed phases. A close follow-up approach for sub-centimeter nodules is more reasonable, which could definitely decrease the false diagnosis and social medical burden and satisfyingly control these small lesions to within 2 cm in size [3,9,11].

During treatments for hepatic nodules less than 1 cm in size, technical difficulties exist, such as trouble in precisely colocalizing the lesions [25,26]. Actually, there exists a more urgent need to decrease the high rate of false positives from imaging diagnoses of sub-centimeter HCCs, and many studies have focused on the accuracy of imaging diagnosis for sub-centimeter HCCs. According to Yu et al., the positive predictive value of gadoxetic acid-enhanced MRI for HCCs ≤1 cm was only 48.3% [8]. The positive predictive value could be increased to 81.3% when lesions conformed to both major and ancillary hallmarks of HCC, including typical hypervascularity in the arterial phase, washout in delayed or portal phases, moderately high signal intensity on both T2W and DW imaging, and low signal in hepatobiliary phase, but the results needed to be further validated [27].

Woo et al. reported that recurrence-free survival does not differ significantly between early treatment and watchful waiting for sub-centimeter hypervascular nodules with usual imaging features of HCC on MRI [16]. The mean size of nodules

at treatment in their research was 7.4 mm for the early treatment group and 11.2 mm for the watchful waiting group. However, this research included patients with a history of HCC and those with primary HCCs. For sub-centimeter hepatic nodules occurring in patients with HCC history, a more aggressive strategy should be adopted since recurrence is a significant factor for poor survival after curative treatments for HCC [28]. Rapid tumor growth and separation exist in recurrent sub-centimeter HCCs, and a wait-and-see strategy might miss the opportunity for locoregional therapy in recurrent tumors [14,29]. Considering the high possibility of recurrence in HCC and how it can cause great anxiety in patients, contrast-enhanced MRI should be utilized in this group. It has been reported that for sub-centimeter nodules showing both major and ancillary features of HCC, 89.9% of them could progress into HCC within 12 months [14].

Based on our results, since the survival time after common treatments showed no significant difference between patients with HCCs <1 cm and those with HCCs measuring 1 to 2 cm, it is crucial to make a strict, scientific plan to follow and control lesions until they are larger than 1 cm when they can be diagnosed by imaging according to current guidelines [3,9,11]. If patients insist on a biopsy for definitive diagnosis and the first biopsy is negative, a repeated biopsy might be unnecessary when lesions are still smaller than 1 cm [3]. An approach of closely following the lesion is more reasonable and cost-effective. But if sub-centimeter hepatic nodules are pathologically confirmed to be HCC by biopsy, immediate treatments are suggested to reduce patient anxiety and medical cost for follow-up.

For patients with primary sub-centimeter hepatic nodules and a cirrhosis background, an interval of 3 to 4 months is usually recommended for follow-up [3,9]. However, a more precise protocol of surveillance should be made for high risk-stratification patients. Sub-centimeter nodules showing hypervascularity are usually more rapidly progressed, so a more intense follow-up plan should be adopted, such as every 1 or 2 months [30]. Studies have shown that the growth rate of early-stage HCC is also associated with initial tumor diameter, type of etiology, and antivirus treatment [31,32]. Future research should be devoted to determining a better follow-up guideline for sub-centimeter hepatic nodules based on individual situations. An optimal interval time for following up is important since short-interval follow-ups can decrease the cost-effectiveness of the approach, while long-interval follow-up can increase the risk of delaying HCC diagnosis. Except optimal follow-up time, personalized treatment protocol ought to be made for patients with primary small HCCs.

The survival time of LA was significantly different from that of SR for patients with HCCs ≤2 cm in size, which was different

from the results by Kutlu et al. [33]. The LA performed in their study was limited in radiofrequency ablation while our research also included other ablation modalities such as percutaneous ethanol injection. Variable modalities can cause survival difference [34]. All patients in our research were pathologically diagnosed, which was not demanded in the Kutlus et al. study. For small HCCs, imaging diagnosis can cause false positives [24]. The selected bias in retrospective studies should not be overlooked, such as worse liver function in patients with LA, so well-designed prospective randomized controlled trails are urged to provide high level evidence. Though LA has been recommended as the first-line treatment for patients with early HCCs who are not suitable for resection, whether the effectiveness of LA is comparable to SR is still controversial [9]. One systematic review with trial sequential analysis has demonstrated that randomized controlled trials to date still do not prove the treatment efficiency of LA for small HCCs [35].

Although LT could achieve better survival than LA and SR for patients with sub-centimeter HCCs, these small lesions might be detected occasionally after LT, but not by routine screening. Considering donor shortage and high medical cost of LT, its cost effectiveness should be rigorously evaluated [36]. In our current study, LA and SR achieved similar survival in patients with sub-centimeter HCCs. Compared with SR, LA is a minimal invasive modality with less deterioration of liver function, thus, LA would be a more feasible treatment for sub-centimeter HCCs if treatment was demanded [37].

Our research was the first to compare the survival of patients with primary pathologically diagnosed HCCs <1 cm and those measuring 1 to 2 cm after curative treatments. Undeniably, there are several limitations in our study, including its retrospective nature. First, although we had a relatively large sample size of 1894 patients, detailed information such as serum albumin and etiology of the HCCs could not be obtained, which could influence the prognosis. Second, the lack of data for recurrence-free survival might affect the preciseness of our comparison. Recurrence-free survival is more sensitive than OS and CSS because salvage treatments could cause bias in OS and CSS. Third, because the SEER database only covers approximately 30% of the population in the United States, whether our results are generalizable to other populations remains unknown. Though our results lack external validation, bootstrapping was performed to validate our findings. Considering rare pathologically diagnosed sub-centimeter HCCs, worldwide multi-centric cooperation may be needed to obtain sufficient cases. Randomized clinical trials may be difficult for this group of patients because of its relatively small proportion in the general population.

Conclusions

The results of our study suggest that there was no significant difference in survival for patients with primary HCCs <1 cm and those with HCCs in the 1 to 2 cm range, regardless if the patient received LA, SR, or LT treatments. Compared with immediate curative treatments for sub-centimeter HCCs in patients at risk of high over-diagnosis, a more detailed and individual follow-up protocol might provide more beneficial.

Acknowledgements

Conflict of interest

None.

Supplementary Tables

Supplementary Table 1. Validation for OS after bootstrap.

Surgery modality	Training cohort			Validating cohort		
	Tumor size	No. patients	P value	Tumor size	No. patients	P value
LA	<1 cm	10	0.387	<1 cm	7	0.116
	1–2 cm	308		1–2 cm	161	
SR	<1 cm	26	0.046	<1 cm	8	0.510
	1–2 cm	246		1–2 cm	144	
LT	<1 cm	95	0.825	<1 cm	51	0.164
	1–2 cm	577		1–2 cm	261	

LA – local ablation; SR – surgical resection; LT – liver transplantation.

Supplementary Table 2. Validation for CSS after bootstrap.

Surgery modality	Training cohort			Validating cohort		
	Tumor size	No. patients	P value	Tumor size	No. patients	P value
LA	<1 cm	10	0.817	<1 cm	7	0.031
	1–2 cm	308		1–2 cm	161	
SR	<1 cm	26	0.136	<1 cm	8	0.825
	1–2 cm	246		1–2 cm	144	
LT	<1 cm	95	0.407	<1 cm	51	0.684
	1–2 cm	577		1–2 cm	261	

LA – local ablation; SR – surgical resection; LT – liver transplantation.

Supplementary Table 3. HRs for tumor size after adjusting confounding factors (OS).

Surgical modality	Training cohort			Validating cohort		
	HR	95% CI	P value	HR	95% CI	P value
LA						
<1 cm *vs.* 1–2 cm	1.403	0.443–4.448	0.565	0.402	0.145–1.119	0.081
SR						
<1 cm *vs.* 1–2 cm	0.628	0.353–1.120	0.115	1.202	0.279–5.173	0.805
LT						
<1 cm *vs.* 1–2 cm	0.912	0.596–1.397	0.672	1.916	0.763–4.808	0.166

LA – local ablation; SR – surgical resection; LT – liver transplantation; HR – hazard ratio; CI – confidence interval.

Supplementary Table 4. HRs for tumor size after adjusting confounding factors (CSS).

Surgical modality	Training cohort			Validating cohort		
	HR	95% CI	P value	HR	95% CI	P value
LA						
<1 cm *vs.* 1–2 cm	0.921	0.287–2.952	0.889	0.392	0.140–1.094	0.074
SR						
<1 cm *vs.* 1–2 cm	0.588	0.290–1.193	0.141	0.847	0.193–3.723	0.826
LT						
<1 cm *vs.* 1–2 cm	1.426	0.613–3.318	0.410	1.447	0.328–6.391	0.626

LA – local ablation; SR – surgical resection; LT – liver transplantation; HR – hazard ratio; CI – confidence interval.

References:

1. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018; GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin, 2018; 68; 394–424

2. Wong LL, Reyes RJ, Kwee SA et al: Pitfalls in surveillance for hepatocellular carcinoma; How successful is it in the real world? Clin Mol Hepatol, 2017; 23: 239–48

3. European Association for the Study of the Liver, European Association for the Study of the Liver: EASL Clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol, 2018; 69: 182–236

4. 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: 82–89

5. Roayaie S, Obeidat K, Sposito C et al: Resection of hepatocellular cancer </=2 cm: Results from two western centers. Hepatology, 2013; 57: 1426–35

6. Mittal S, Kanwal F, Ying J et al: Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: A United States cohort. J Hepatol, 2016; 65: 1148–54

7. Park MJ, Kim YK, Lee MW et al: Small hepatocellular carcinomas: improved sensitivity by combining gadoxetic acid-enhanced and diffusion-weighted MR imaging patterns. Radiology, 2012; 264: 761–70

8. Yu MH, Kim JH, Yoon JH et al: Small (</=1-cm) hepatocellular carcinoma: Diagnostic performance and imaging features at gadoxetic acid-enhanced MR imaging. Radiology, 2014; 271: 748–60

9. Heimbach JK, Kulik LM, Finn RS et al: AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology, 2018; 67: 358–80

10. Stigliano R, Marelli L, Yu D et al: Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev, 2007; 33: 437–47

11. Bruix J, Reig M, Sherman M: Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology, 2016; 150(4): 835–53

12. Korean Society of Abdominal Radiology: Diagnosis of hepatocellular carcinoma with gadoxetic acid-enhanced MRI: 2016 consensus recommendations of the Korean Society of Abdominal Radiology. Korean J Radiol, 2017; 18: 427–43

13. Kudo M, Matsui O, Izumi N et al: Surveillance and diagnostic algorithm for hepatocellular carcinoma proposed by the Liver Cancer Study Group of Japan: 2014 update. Oncology, 2014; 87(Suppl. 1): 7–21

14. Song KD, Kim SH, Lim HK et al: Subcentimeter hypervascular nodule with typical imaging findings of hepatocellular carcinoma in patients with history of hepatocellular carcinoma: Natural course on serial gadoxetic acid-enhanced MRI and diffusion-weighted imaging. Eur Radiol, 2015; 25: 2789–96

15. Kim JE, Kim SH, Lee SJ, Rhim H: Hypervascular hepatocellular carcinoma 1 cm or smaller in patients with chronic liver disease: Characterization with gadoxetic acid-enhanced MRI that includes diffusion-weighted imaging. Am J Roentgenol, 2011; 196: W758–65

16. Woo JH, Song KD, Kim SH: Subcentimeter hypervascular nodules with typical imaging findings of hepatocellular carcinoma on gadoxetic acid-enhanced MRI: Outcomes of early treatment and watchful waiting. Eur Radiol, 2017; 27: 4406–14

17. 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: 1224–29

18. Todo S, Furukawa H: Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. Ann Surg, 2004; 240: 451–59; discussion 459–61

19. Chun YS, Pawlik TM, Vauthey JN: 8th Edition of the AJCC Cancer Staging Manual; Pancreas and Hepatobiliary Cancers. Ann Surg Oncol, 2018; 25: 845–47

20. Cucchetti A, Piscaglia F, Cescon M et al: Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol, 2013; 59: 300–7

21. Roskams T: Anatomic pathology of hepatocellular carcinoma impact on prognosis and response to therapy. Clin Liver Dis, 2011; 15: 245–59, vii-x

22. Choi YR, Chung JW, Yu MH et al: Diagnostic accuracy of contrast-enhanced dynamic CT for small hypervascular hepatocellular carcinoma and assessment of dynamic enhancement patterns: Results of two-year follow-up using cone-beam CT hepatic arteriography. PLoS One, 2018; 13: e0203940

23. Kim JE, Kim SH, Lee SJ, Rhim H: Hypervascular hepatocellular carcinoma 1 cm or smaller in patients with chronic liver disease: Characterization with gadoxetic acid-enhanced MRI that includes diffusion-weighted imaging. Am J Roentgenol, 2011; 196: W758–65

24. Lee YJ, Lee JM, Lee JS et al: Hepatocellular carcinoma: diagnostic performance of multidetector CT and MR imaging – a systematic review and meta-analysis. Radiology, 2015; 275: 97–109

25. Lee MW, Kim YJ, Park HS et al: Targeted sonography for small hepatocellular carcinoma discovered by CT or MRI: factors affecting sonographic detection. Am J Roentgenol, 2010; 194: W396–400

26. Kim PN, Choi D, Rhim H et al: Planning ultrasound for percutaneous radiofrequency ablation to treat small (</=3 cm) hepatocellular carcinomas detected on computed tomography or magnetic resonance imaging: A multicenter prospective study to assess factors affecting ultrasound visibility. J Vasc Interv Radiol, 2012; 23: 627–34

27. Park CJ, An C, Park S et al: Management of subcentimetre arterially enhancing and hepatobiliary hypointense lesions on gadoxetic acid-enhanced MRI in patients at risk for HCC. Eur Radiol, 2018; 28: 1476–84

28. de Lope CR, Tremosini S, Forner A et al: Management of HCC. J Hepatol, 2012; 56(Suppl. 1): S75–87

29. Lee MW, Lim HK: Management of sub-centimeter recurrent hepatocellular carcinoma after curative treatment: Current status and future. World J Gastroenterol, 2018; 24: 5215–22

30. International Consensus Group for Hepatocellular Neoplasia: Pathologic diagnosis of early hepatocellular carcinoma: A report of the international consensus group for hepatocellular neoplasia. Hepatology, 2009; 49: 658–64

31. An C, Choi YA, Choi D et al: Growth rate of early-stage hepatocellular carcinoma in patients with chronic liver disease. Clin Mol Hepatol, 2015; 21: 279–86

32. Taouli B, Goh JS, Lu Y et al: Growth rate of hepatocellular carcinoma: Evaluation with serial computed tomography or magnetic resonance imaging. J Comput Assist Tomogr, 2005; 29: 425–29

33. Kutlu OC, Chan JA, Aloia TA et al: Comparative effectiveness of first-line radiofrequency ablation versus surgical resection and transplantation for patients with early hepatocellular carcinoma. Cancer, 2017; 123: 1817–27

34. Luo W, Zhang Y, He G et al: Effects of radiofrequency ablation versus other ablating techniques on hepatocellular carcinomas: A systematic review and meta-analysis. World J Surg Oncol, 2017; 15: 126

35. Xu XL, Liu XD, Liang M, Luo BM: Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: Systematic review of randomized controlled trials with meta-analysis and trial sequential analysis. Radiology, 2018; 287: 461–72

36. Akoad ME, Pomfret EA: Surgical resection and liver transplantation for hepatocellular carcinoma. Clin Liver Dis, 2015; 19: 381–99

37. Rhim H, Lim HK, Choi D: Current status of radiofrequency ablation of hepatocellular carcinoma. World J Gastrointest Surg, 2010; 2: 128–36