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ORIGINAL ARTICLE

Selection of treatment modalities for hepatocellular carcinoma at stages T1 and T2: A preliminary analysis based on the Surveillance, Epidemiology, and End Results registry database

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Summary

Purpose: *To explore the selection of treatment modalities for hepatocellular carcinoma (HCC) at stages T1 and/or T2 and to compare the survival of patients treated with surgery alone vs radiation therapy (RT) alone.*

Methods: *Surveillance, Epidemiology, and End Results (SEER) database was used to identify the patients diagnosed with HCC between 2004 and 2013. The tumor-node-metastasis (TNM) stage was established according to the American Joint Committee on Cancer (AJCC) Staging. After age, sex, TNM stage, and tumor extension were matched, the survival was further compared between patients undergoing surgery alone vs RT alone.*

Results: *Of 11967 patients at stages T1 (n=7829) and T2 (n=4138), 10449 (87.31%) underwent surgery alone, 1241 (10.37%) RT alone, and 277 (2.32%) surgery combined with RT. Compared with those treated with RT alone and in combination with surgery, patients treated with surgery alone were younger, with smaller tumor size, higher proportion of females, single lesion, and AJCC stage I/II, and lower proportion of regional and distant lymph nodes, bone, brain, and lung invasion. Among them, 758 pairs (surgery alone and RT alone) at stage T1 and 430 pairs (surgery alone and RT alone) at stage T2 were matched. Regardless of stage T1 or T2, patients undergoing surgery alone had a significantly better cumulative survival than those undergoing RT alone (p<0.001).*

Conclusion: *The treatment selection of HCC was dependent on the age, sex, tumor size, number of lesions, and extrahepatic invasion. Surgery alone should be the preferred treatment modality of HCC at stages T1 and T2.*

Key words: *hepatocellular carcinoma, outcome, radiation, surgery, treatment*

Introduction

Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver malignancies in the United States (US) [1]. HCC is the third leading cause of cancer related mortality worldwide and is the fastest rising cause of cancer related death in the US over the past two decades [2,3].

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HCC is more effectively treated when it is diagnosed at early stage [4]. Hepatic resection (HR) and liver transplantation (LT) are the golden standard curative treatments for resectable HCC [5] and can improve the survival of patients with HCC [6,7]. The reported 5-year overall survival of patients undergoing surgery ranges from 35 to 60% [8,9]. Unfortunately, only fewer than 30% of patients present with early-stage HCC amenable to curative surgery due to organ shortage, underlying liver dysfunction and pathological stage [10]. Additionally, in experienced hands, surgery carries a perioperative mortality of 1.6-10% in optimally selected patients.

Locoregional therapies, such as RT, radiofrequency ablation (RFA), and transarterial embolization (TACE), have been increasingly employed in the multidisciplinary management of unresectable HCC [11-13]. RT is a palliative treatment option [14]. Its drawbacks include low tolerance of whole liver irradiation [15] and risk of radiation-induced liver diseases [16]. However, since the development of three-dimensional conformal RT (3D-CRT), RT can be performed more safely in patients with HCC without severe toxicity. Furthermore, technological developments for precisely targeting HCC lesions by RT, including intensity-modulated RT (IMRT) and stereotactic body RT (SBRT), increase the benefit and reduce the risk [1,17]. Recently, Yuan et al. [18] found that the survival of SBRT was similar to surgery, and RT has been used as a definitive therapy with curative intent in early-stage HCC. Seo et al. [19] also found that the survival of SBRT was nearly identical to RFA in smaller HCC. Especially, if the tumor size was 2-3 cm, SBRT was the preferred treatment option. Thus, RT may be an effective treatment choice for HCC. However, a higher level of clinical evidence is lacking to further establish the comparison of surgery to RT alone or in combination with surgery in the treatment of HCC. Here, the present study aimed to explore the selection of treatment modalities for HCC at stages T1 and/or T2 and to compare the clinical characteristics and outcomes of patients treated with surgery alone *vs* those treated with RT alone or surgery combined with RT in a large cohort of patients with HCC.

Methods

Data sources

Patient-level data were obtained from the SEER registry (November 2014 submission; version 8.3.4) of the National Cancer Institute. Notably, the SEER database is an authoritative source of information on cancer incidence and survival in the US, which encompasses approximately 30% of the US population. Because SEER database is publicly available, in which patients are de-identified, our study was exempted from the approval of institutional review board.

Patient selection

All patients diagnosed with histologically confirmed HCC at stages T1 and T2 from 2004 to 2013 were eligible. Patients with missing data were excluded from our study. In the SEER database, the International Classification of Diseases for Oncology code ICD-O-3 was employed to identify the histology and behavior of malignancy. The malignant codes for Hist/behav were as follows: 8170/3: HCC, not otherwise specified (NOS); 8171/3: HCC, fibrolamellar; 8172/3: HCC, scirrhous; 8173/3: HCC, spindle cell variant; 8174/3: HCC, clear cell type; 8175/3: HCC, pleomorphic type.

Treatment

In the SEER database, the type of therapy was categorized into surgery alone, RT alone, surgery combined with RT. Noteworthy, "surgery" in the data set was defined as patients undergoing HR and LT. "RT" in the dataset was defined as patients undergoing beam RT, radioactive implants, radioisotopes and combination of beam with implants or isotopes.

Demographic and clinical data

Demographic information included age, race, sex, and diagnosis time. Race was coded as white, black, and others. Diagnosis time was between 2004 and 2013. The major clinical variables were as follows: tumor-node-metastasis (TNM), HCC pathological type, tumor size, tumor extension, American Joint Committee on Cancer (AJCC) stage, grade of differentiation, regional lymph nodes invasion, distant lymph nodes invasion, bone invasion, brain invasion, lung invasion, survival time, follow-up, vital status, and cause of death. It is noteworthy that the data regarding organ invasion was not available before 2010. SEER database also provided the case listings to explain the categories of tumor size, tumor extension, regional nodal disease, and distant metastasis. The TNM stage was established according to the AJCC Cancer Staging Manual (6th edition).

Statistics

Patient characteristics were compared across the treatment groups by using chi-square test for categorical data and Kruskal-Wallis test for continuous data. Survival was measured in months until death or the last recorded follow-up. Survival analysis was performed with the Kaplan-Meier method for the estimation of the survival function and the log-rank test was used to compare the survival of patients according to the treatment modality (surgery alone *vs* RT alone *vs* surgery combined with RT). The variables (sex, age, TNM stage, and tumor extension) were matched to further compare the difference in the survival between patients at stage T1 or T2 undergoing surgery alone *vs* RT alone. Beam RT was the most common type of RT (66.32%) according to SEER database. Additionally, the data regarding beam

RT alone but not other choices of RT can be extracted from the SEER database. Thus, the subgroup analyses in patients undergoing beam RT were further performed. All statistical analyses were performed using the statistical software package SPSS 17.0 for Windows. A p value <0.05 was considered statistically significant.

Results

Overall analyses

We performed overall analyses in all patients regardless of type of RT.

HCC at T1 and T2 stages

A total of 11967 eligible patients were identified at stages T1 and T2 (Table 1). Of them, 10449 (87.31%) underwent surgery alone, 1241 (10.37%) underwent RT alone, and 277 (2.32%) underwent surgery combined with RT; 7829 (65.42%) were at stage T1 and 4138 (34.58%) were at stage T2.

Compared with those treated with RT alone and those treated with surgery combined with RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (25.36%), single lesion (54.46%), and AJCC stage I (64.48%), and lower proportion of regional lymph nodes invasion (2.00%), distant lymph nodes invasion (1.23%), bone invasion (0.15%), brain invasion (0.01%), lung invasion (0.30%), undifferentiated tumor (1.23%), death (42.50%), and death from liver diseases (26.06%) (Table 2).

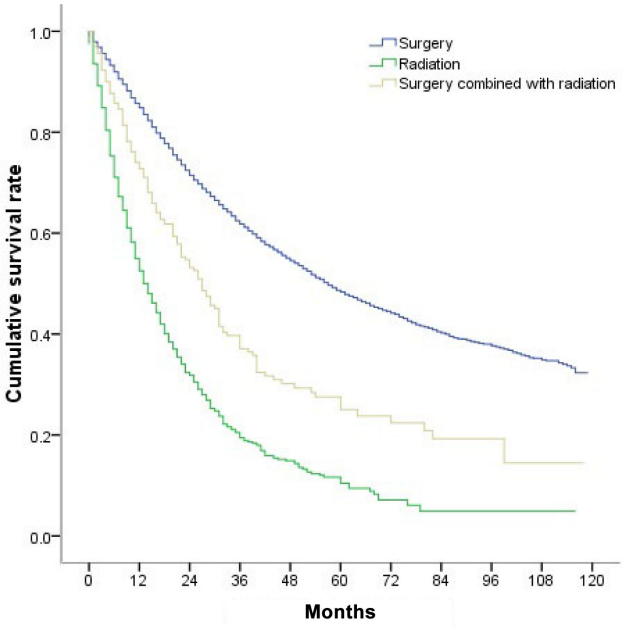

Figure 1. Difference in the cumulative survival of patients with HCC at stages T1 and T2 according to the treatment modality (p<0.001).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001; Figure 1). The median survival time was 27 months (range 0-119) in the surgery alone group, 9 months (range 0-116) in the RT alone group and 17 months (range 0-118) in the surgery combined with RT group.

HCC at T1 stage

Among the stage T1 patients, 6865 were treated with surgery alone, 789 with RT alone, and 175 with surgery combined with RT.

Compared with patients treated with RT alone and those treated with surgery combined with RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (26.51%), single lesion (82.88%), and AJCC stage I (97.95%), and lower proportion of regional lymph nodes invasion (1.72%), distant lymph nodes invasion (1.10%), bone invasion (0.13%), brain invasion (0.03%), lung invasion (0.31%), undifferentiated tumor (1.21%), death (40.73%), and death from liver diseases (24.24%).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001; Figure 2A). The median survival time was 27 months (range 0-119) in the surgery alone group, 9 months (range 0-116) in the RT alone group and 17 months (range 0-118) in the surgery combined with RT group. After sex, age, TNM stage and tumor extension were well-matched between them, 758 patients who underwent surgery alone and 758 patients who underwent RT alone were selected. Patients treated with surgery alone had a significantly better cumulative survival than those treated with RT alone (p<0.001; Figure 2B). The median survival time was 82 months (range 0-119) in the surgery alone group and 9 months (range 0-116) in the RT alone group.

HCC at T2 stage

Among T2 stage patients, 3584 were treated with surgery alone, 452 with RT alone, and 102 with surgery combined with RT.

Compared with patients treated with RT alone and those treated with surgery combined with RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (23.16%), single lesion (0.03%), undifferentiated tumor (1.25%), and AJCC stage II (96.99%), and lower proportion of regional lymph nodes invasion (2.53%), distant lymphnodes invasion (1.46%), bone invasion (0.21%), brain invasion (0.00%), lung invasion (0.42%), death (45.90%), and death from liver diseases (29.55%).

Table 1. Characteristics of patients with HCC at stages T1 and T2

Characteristics	*Patients, n*	*Patients, n*(%)	Median (range)
Sex	11967		
Female		2975 (24.86)	
Male		8992 (75.14)	
Age (years), mean±SD	11967	61.84±11.10	61 (0-100)
Race	11945		
White		7945 (66.51)	
Black		1248 (10.45)	
Others		2752 (23.04)	
TNM stage	11967		
T1		7829 (65.42)	
T2		4138 (34.58)	
HCC pathological type	11967		
HCC, NOS		11741 (98.12)	
HCC, fibrolamellar		64 (0.53)	
HCC, scirrhous		23 (0.19)	
HCC, spindle cell variant		3 (0.03)	
HCC, clear cell type		129 (1.08)	
HCC, pleomorphic type		7 (0.05)	
Tumor size, cm	11524		
≤2		2515 (21.82)	
>2 and ≤3		3109 (26.98)	
>3 and ≤4		2140 (18.57)	
>4 and ≤5		1488 (12.91)	
>5		2272 (19.72)	
Tumor extension	11967		
Confined to liver, NOS		1240 (10.36)	
Stated as T1 with no other information on extension		26 (0.22)	
Stated as T2 with no other information on extension		70 (0.58)	
Single lesion		6307 (52.70)	
Single lesion with intrahepatic vascular invasion		1072 (8.96)	
Single lesion with extension to gallbladder		72 (0.61)	
Single lesion with intrahepatic vascular invasion with extension to gallbladder		42 (0.35)	
Multiple nodules		2813 (23.51)	
Multiple nodules with intrahepatic vascular invasion		309 (2.58)	
Multiple nodules with extension to gallbladder		16 (0.13)	
AJCC stage	11637		
I		7201 (61.88)	
II		3766 (32.36)	
III		155 (1.33)	
IV		515 (4.43)	
Grade of differentiation	7045		
Well differentiated; Grade I		2318 (32.91)	
Moderately differentiated; Grade II		3526 (50.05)	
Poorly differentiated; Grade III		1112 (15.78)	
Undifferentiated; anaplastic; Grade IV		89 (1.26)	

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Characteristics	*Patients, n*	*Patients, n*(%)	Median (range)
Regional lymph nodes invasion	11674	291 (2.49)	
Distant lymph nodes invasion	11853	515 (4.34)	
Bone invasion	5531	155 (2.80)	
Brain invasion	5531	13 (0.24)	
Lung invasion	5528	50 (0.90)	
Treatment	11967		
Surgery alone		10449 (87.31)	
RT alone		1241 (10.37)	
Surgery combined with RT		277 (2.32)	
Diagnosis, year	11967		
2004-2008		5229 (43.69)	
2009-2013		6738 (56.31)	

HCC: hepatocellular carcinoma, RT: radiation therapy, TNM: tumor-node-metastasis, AJCC: American Joint Committee on Cancer, NOS: not otherwise specified, SD: standard deviation

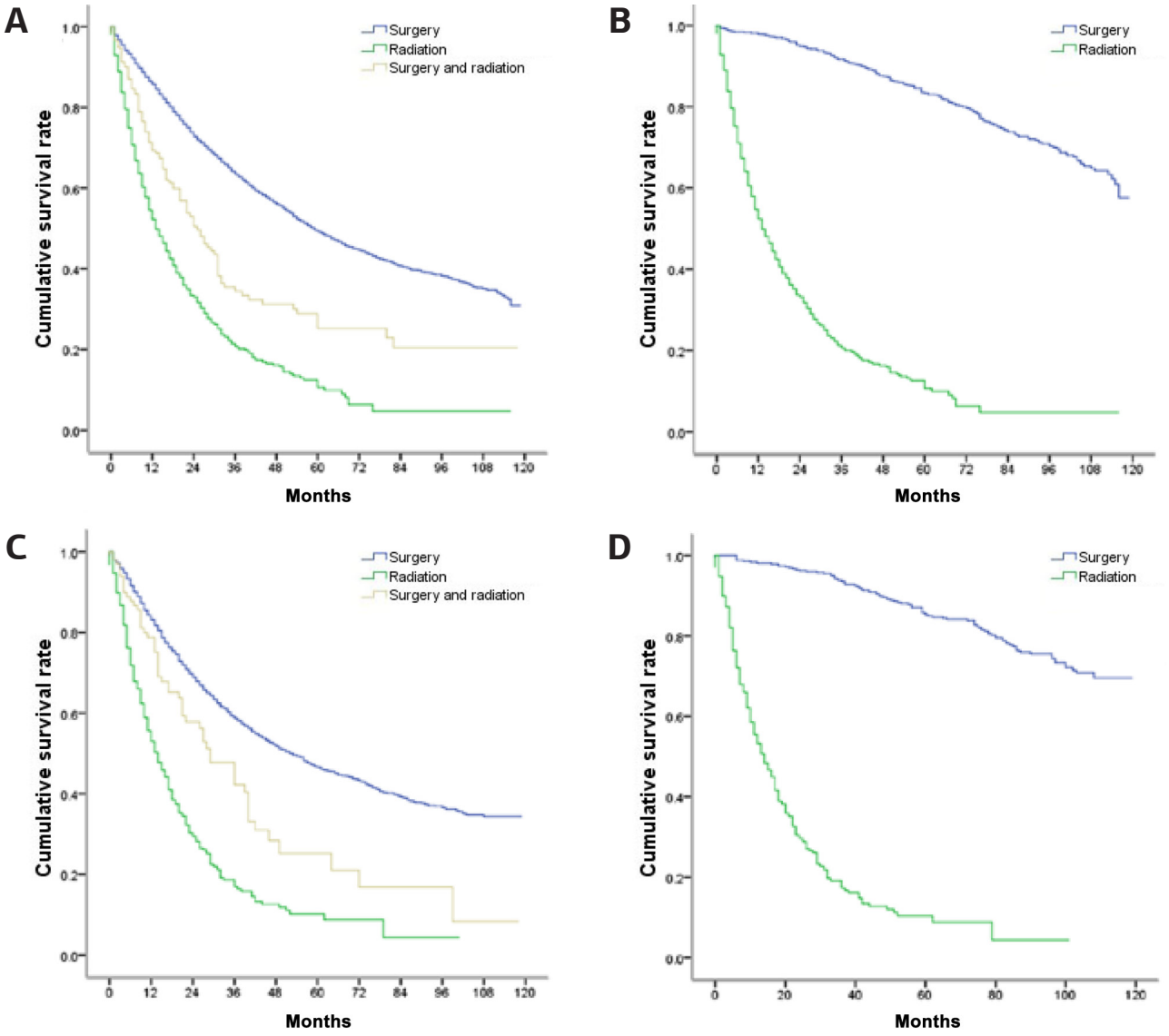

Figure 2. Difference in the cumulative survival of patients with HCC at stage T1 or T2 according to the treatment modality. **A:** HCC patients at stage T1. **B:** Well-matched HCC patients at stage T1. **C:** HCC patients at stage T2. **D:** Well-matched HCC patients at stage T2 ($p<0.001$).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001; Figure 2C). The median survival time was 27 months (range 0-119) in the surgery alone group, 9 months (range 0-101) in the RT alone group and 17 months (range 0-118) in the surgery combined with RT group. After sex, age, TNM stage and tumor extension were well-matched between them, 430 patients who underwent surgery alone and 430 patients who underwent RT alone were selected. Patients treated with surgery alone had a significantly better cumulative survival than those treated with RT alone (p<0.001; Figure 2D). The median survival time was 27 months (range 0-119) in the surgery alone group and 9 months (range 0-101) in the RT alone group.

Subgroup analyses

We performed subgroups analyses in patients undergoing beam RT.

HCC at T1 and T2 stages

In this subgroup analysis, a total of 11272 eligible patients were selected. 7434 (65.95%) had stage T1 and 3838 (34.05%) had stage T2 disease.

Compared with those treated with beam RT alone and those treated with surgery combined with beam RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (25.36%), single lesion (54.46%), and AJCC stage I (64.48%), and lower proportion of regional lymph nodes invasion (2.00%), distant lymph nodes invasion (1.23%), bone invasion (0.15%), brain invasion (0.01%), lung invasion (0.30%), undifferentiated tumor (1.23%), death (42.50%), and death from liver diseases (26.06%).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001). The median survival time was 27 months (range 0-119) in the surgery alone group, 8 months (range 0-114) in the beam RT alone group and 16 months (range 0-118) in the surgery combined with beam RT group.

HCC at T1 stage

Among T1 stage patients, 6865 were treated with surgery alone, 469 with beam RT alone, and 100 with surgery combined with beam RT.

Compared with patients treated with beam RT alone and those treated with surgery combined with beam RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (26.51%), single lesion (82.88%), and AJCC stage I (97.95%), and lower proportion of regional lymph nodes invasion (1.72%), distant lymph nodes invasion (1.10%), bone invasion (0.13%), brain invasion (0.03%), lung invasion (0.31%), undifferentiated tumor (1.21%), death (40.73%), and death from liver diseases (24.24%).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001). The median survival time was 27 months (range 0-119) in the surgery alone group, 8 months (range 0-119) in the beam RT alone group and 16 months (range 0-118) in the surgery combined with beam RT group. After sex, age, TNM stage and tumor extension were well-matched between them, 335 patients who underwent surgery alone and 335 patients who underwent beam RT alone were selected. Patients treated with surgery alone had a significantly better cumulative survival than those treated with beam RT alone (p<0.001). The median survival time was 93 months (range 7-119) in the surgery alone group and 9 months (range 0-114) in the beam RT alone group.

HCC at T2 stage

Among the patients at stage T2, 3584 were treated with surgery alone, 202 with beam RT alone, and 52 with surgery combined with beam RT.

Compared with patients treated with beam RT alone and those treated with surgery combined with beam RT, patients treated with surgery alone were significantly younger and had smaller tumor size, higher proportion of females (23.16%), single lesion (0.03%), undifferentiated tumor (1.25%), and AJCC stage II (96.99%), and lower proportion of regional lymph nodes invasion (2.53%), distant lymph nodes invasion (1.46%), death (45.90%), and death from liver diseases (29.55%).

Patients treated with surgery alone had a significantly better cumulative survival (p<0.001). The median survival time was 27 months (range 0-119) in the surgery alone group, 8 months (range 0-101) in the beam RT alone group and 15 months (range 0-118) in the surgery combined with beam RT group.

After sex, age, TNM stage and tumor extension were well-matched between them, 178 patients who underwent surgery alone and 178 patients who underwent beam RT alone were selected. Patients treated with surgery alone had a significantly better cumulative survival than those treated with beam RT alone (p<0.001). The median survival time was 96 months (range 0-119) in the surgery alone group and 7 months (range 0-101) in the beam RT alone group.

Table 2. Selection of treatment modalities for HCC at stages T1 and T2

Variables	*Surgery alone (n=10449)*			*RT alone (n=1241)*			*Surgery combined with RT (n=277)*			*p value*
	Patients, n	Patients, n (%)	Median (range)	Patients, n	Patients, n (%)	Median (range)	Patients, n	Patients, n (%)	Median (range)	
Sex	10449			1241			277			0.004
Female		2650 (25.36)			264 (21.27)			61 (22.02)		
Male		7799 (74.64)			977 (78.73)			216 (77.98)		
Age (years)	10449	61.41±11.04	61 (0-100)	1241	65.24±11.00	64 (17-92)	277	62.64±11.23	62 (14-95)	<0.001
Race	10428			1240			277			<0.001
White		7036 (67.47)			909 (73.30)			0 (0.00)		
Black		1082 (10.38)			166 (13.39)			0 (0.00)		
Others		2310 (22.15)			165 (13.31)			277 (100.00)		
TNM stage	10449			1241			277			0.242
T1		6865 (65.70)			789 (63.58)			175 (63.18)		
T2		3584 (34.30)			452 (36.42)			102 (36.82)		
HCC pathological type	10449			1241			277			0.094
HCC, NOS		10245 (98.05)			1226 (98.80)			270 (97.48)		
HCC, fibrolamellar		58 (0.55)			3 (0.24)			3 (1.08)		
HCC, scirrhous		18 (0.17)			5 (0.40)			0 (0.00)		
HCC, spindle cell variant		3 (0.03)			0 (0.00)			0 (0.00)		
HCC, clear cell type		119 (1.14)			7 (0.56)			3 (1.08)		
HCC, pleomorphic type		6 (0.06)			0 (0.00)			1 (0.36)		
Tumor size, cm	10144			1120			260			<0.001
≤2		2374 (23.40)			107 (9.55)			34 (13.08)		
>2 and ≤3		2808 (27.68)			234 (20.89)			67 (25.77)		
>3 and ≤4		1890 (18.64)			200 (17.86)			50 (19.23)		
>4 and ≤5		1242 (12.24)			217 (19.38)			29 (11.15)		
Tumor extension	10449			1241			277			<0.001
Confined to liver, NOS		960 (9.19)			245 (19.74)			35 (12.65)		
Stated as T1 with no other information on extension		19 (0.18)			7 (0.56)			0 (0.00)		
Stated as T2 with no other information on extension		51 (0.49)			16 (1.29)			3 (1.08)		
Single lesion		5691 (54.46)			483 (38.93)			133 (48.01)		
Single lesion with intrahepatic vascular invasion		977 (9.35)			71 (5.72)			24 (8.66)		
Single lesion with extension to gallbladder		56 (0.54)			13 (1.05)			3 (1.08)		
Single lesion with intrahepatic vascular invasion with extension to gallbladder		33 (0.31)			8 (0.65)			1 (0.36)		
Multiple nodules		2392 (22.89)			353 (28.44)			68 (24.55)		
Multiple nodules with intrahepatic vascular invasion		259 (2.48)			40 (3.22)			10 (3.61)		
Multiple nodules with extension to gallbladder		11 (0.11)			5 (0.40)			0 (0.00)		

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Variables	*Surgery alone (n=10449)*			*RT alone (n=1241)*			*Surgery combined with RT (n=277)*			*p value*
	Patients, n	Patients, n (%)	Median (range)	Patients, n	Patients, n (%)	Median (range)	Patients, n	Patients, n (%)	Median (range)	
AJCC stage	10182			1189			266			<0.001
I		6565 (64.48)			516 (43.40)			120 (45.11)		
II		3377 (33.17)			307 (25.82)			82 (30.83)		
III		113 (1.11)			33 (2.78)			9 (3.38)		
IV		127 (1.24)			333 (28.00)			55 (20.68)		
Grade of differentiation	6526			385			134			<0.001
Well differentiated; Grade I		2131 (32.65)			145 (37.66)			42 (31.34)		
Moderately differentiated; Grade II		3322 (50.90)			152 (39.48)			52 (38.81)		
Poorly differentiated; Grade III		993 (15.22)			82 (21.30)			37 (27.61)		
Undifferentiated; anaplastic; Grade IV		80 (1.23)			6 (1.56)			3 (2.24)		
Regional lymph nodes invasion	10264	205 (2.00)		1148	70 (6.10)		262	16 (6.11)		<0.001
Distant lymph nodes invasion	10358	127 (1.23)		1225	333 (27.18)		270	55 (20.37)		<0.001
Bone invasion	4612	7 (0.15)		780	128 (16.41)		139	20 (14.39)		<0.001
Brain invasion	4612	1 (0.02)		780	10 (1.28)		139	2 (1.44)		<0.001
Lung invasion	4610	14 (0.30)		779	34 (4.36)		139	2 (1.44)		<0.001
Survival time (months)	10449	35.51±29.67	27 (0-119)	1241	13.99±14.96	9 (0-116)	277	24.01±23.09	17 (0-118)	<0.001
Incomplete follow-up	10449	543 (5.20)		1241	59 (4.75)		277	19 (6.86)		0.359
Death	10449	4441 (42.50)		1241	806 (64.95)		277	159 (54.40)		<0.001
Cause of death	4441			806			159			<0.001
Death from liver disease		2723 (61.32)			606 (75.19)			122 (76.73)		
Death from other cause		1718 (38.68)			200 (24.81)			37 (23.27)		

HCC: hepatocellular carcinoma, RT: radiation therapy, TNM: tumor-node-metastasis, AJCC: American Joint Committee on Cancer, NOS: not otherwise specified

Discussion

Currently, several treatment options for HCC are available, and the ideal treatment option is determined based on the burden of tumor and the severity of liver dysfunction [21,22]. The Barcelona Clinic Liver Cancer (BCLC) stage is the most commonly used classification system for staging HCC and guiding the treatment [23]. At very early and early stages of HCC according to the BCLC stage, surgery is the main treatment option [24]. Recently, several large scale studies suggested that hepatic resection might be appropriate in HCC cases beyond the BCLC stage A [25]. Unfortunately, SEER database cannot provide data regarding BCLC stage, but TNM stage. The TNM stage is only based on tumor characteristics and invasion extent. Although it does not account for the underlying hepatic function, TNM stage has been validated to predict post-surgical outcomes in HCC patients treated with hepatic resection or transplantation [26]. We found that a majority of HCC patients at stages T1 and/or T2 underwent surgery. Features of patients who preferred to select surgery as a main treatment option of HCC included younger age and smaller tumor size, female gender, single lesion, and more AJCC stage I/II, and less regional lymph nodes, distant lymph nodes, bone, brain, and lung invasion.

Liu et al. found that surgical resection was associated with improved survival, even after controlling for age, tumor size, race, sex, and geographical region [27]. Meta-analyses also showed a superior survival in patients undergoing surgery [6,7,28,29]. Similarly, our study demonstrated that patients undergoing surgery had a significantly longer survival time than patients undergoing RT alone or in combination with surgery at stages T1 and/or T2.

RT, a key locoregional therapeutic modality in oncology [14], is minimally invasive and effective

for local control of HCC and vascular invasion, relieving the pain from bone and adrenal metastases, and improving the quality of life, especially in patients with HCC combined with portal vein tumor thrombus (PVTT) [30,31]. HCC patients with PVTT undergoing palliative RT have an objective response rate of 40-60% and the responders have a median overall survival time of 15-20 months [32]. SBRT is also considered as a bridge to liver transplantation for HCC [33]. Recently, Su et al. found that the local effect of SBRT was similar to that of liver resection in patients with small primary HCC with 1 or 2 nodules and Child-Pugh A cirrhosis. Propensity-score matching analysis demonstrated that 1-, 3-, and 5-year overall survival rates of HCC patients undergoing SBRT were better than those of HCC patients undergoing resection (100, 91.8, and 74.3% *vs* 96.7, 89.3, and 69.2%), but no significant difference was observed. Notably, in this analysis, the median survival time of HCC patients undergoing SBRT should be beyond 5 years [34]. By contrast, our study found that HCC patients undergoing RT alone had a significantly shorter median survival time than those undergoing surgery (median survival time 9 *vs* 27 months). The results remained in the well-matched analysis (median survival time of surgery and RT alone at stage T1:9 *vs* 82 months). This might be primarily because a majority of the studied patients undergoing RT alone had lymph node, brain, lung, and/or bone metastases.

In the SEER database, RT consists of beam RT, radioactive implants, radioisotopes, and combination of beam with implants or isotopes. Our study found that beam RT accounts for 66.32% of RT and should be the most common type of RT. Beam RT can take a more precise irradiation application to the tumor [35,36]. A recent retrospective analysis demonstrated that the median survival period from the first beam RT was 61 months and the 2- and 5-year overall survival rates were 87.5 and 49.4%, respectively [37]. However, our subgroup analyses found that the median survival time of patients undergoing beam RT alone was 8 months regardless of stage T1 and T2. By comparison, surgery alone has a marked survival benefit over beam RT alone or in combination with surgery. After matching, this difference becomes more significant.

Surgery combined with RT includes RT prior to surgery, RT after surgery, RT before and after surgery, and intraoperative RT, which improves the overall survival and recurrence-free survival of HCC [38-40]. Preoperative RT could result in PVTT necrosis, as PVTT would cause HCC cells to be disseminated [38]. Postoperative RT aimed to irradiate micro-lesions caused by tumor thrombus or HCC itself [39]. Besides, intraoperative RT mainly allowed to administer precisely into the target volume a cancericidal dose and to prevent essential side effects [41]. In this study, only 277 patients (2.32%) underwent surgery combined with RT, because this combination was restricted to palliative treatment.

In conclusion, we comprehensively analyzed the treatment selection of HCC in the US. However, this study should be interpreted in light of several limitations. SEER database does not provide data regarding performance status, Child-Pugh score, and comorbidity (e.g., coronary artery disease, chronic obstructive pulmonary disease, or renal failure), which are significantly associated with patients' outcomes. In addition, the database provides data regarding surgery and RT as the potential therapeutic modality of HCC, but lacks data on systemic chemotherapy, TACE, RFA, or percutaneous ethanol injection. Therefore, we just conducted a preliminary analysis on the treatment selection and prognosis of HCC. In the future, it may be necessary to combine SEER dataset with the Medicare billing dataset to deeply analyze the distribution in the treatment selection of HCC.

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Conflict of interests

The authors declare no conflict of interests.

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