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ORIGINAL ARTICLE

Surgery versus external beam radiation therapy for AJCC stage I hepatocellular carcinoma

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Summary

Purpose: *To compare the survival of American Joint Committee on Cancer (AJCC) stage I hepatocellular carcinoma (HCC) treated with surgery versus external beam radiation therapy (EBRT).*

Methods: *Surveillance, Epidemiology, and End Results (SEER) database was used to identify the patients diagnosed with HCC between 2004 and 2013. Overall survival (OS) and liver-specific survival (LSS) were compared between patients treated with surgery and EBRT. A 1:1 propensity score matching (PSM) analysis was employed by matching age, sex, and race.*

Results: *Among the 1553 patients with HCC ≤2cm, there was no significant difference in OS (p=0.605, before PSM; p=0.891, after PSM) and LSS (p=0.281, before PSM; p=0.346, after PSM) between patients treated with surgery and EBRT. Among the 1752 patients with HCC >2cm and ≤3cm, patients treated with surgery had significantly better OS (p=0.001) than those treated with EBRT, but statistically similar LSS (p=0.072) before PSM; however, there was no significant difference in OS (p=0.139) and LSS (p=0.722) between patients treated with surgery and EBRT after PSM. Additionally, 1157, 723, and 1331 patients had HCC >3cm and ≤4cm, HCC >4cm and ≤5cm, and HCC >5cm, respectively; among them, patients treated with surgery had significantly better OS and LSS than those treated with EBRT regardless of PSM.*

Conclusions: *At the AJCC stage I, the survival after EBRT might be comparable to that after surgery for HCC ≤3cm, but the survival after EBRT was inferior to that after surgery for HCC >3cm.*

Key words: *hepatocellular carcinoma, radiation, surgery, tumor, propensity score matching, survival*

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignances and the second most lethal cancer worldwide [1-4]. Historically, the incidence of HCC in the United States has been significantly lower than in other countries, but in recent decades the number of HCC cases and deaths has increased dramatically [5,6]. Surgery can provide the greatest survival advantage for patients with HCC. The reported 5-year overall survival (OS) of patients undergoing surgery ranges from 35 to

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60% [7-9]. However, many HCC patients are not eligible for surgery due to the presence of underlying comorbidities or advanced tumor stage. Only fewer than 30% of patients present with early-stage HCC amenable to curative surgery [10]. Therefore, non-surgical interventions have been actively explored. External beam radiation therapy (EBRT) is one of the most validated modalities in oncology along with surgery and chemotherapy. The effectiveness of EBRT in the prolongation of survival as well as improvement of loco-regional control has long been recognized in patients with cancer from many sites of the body, including head and neck, central nervous system, thorax and sarcoma. It can be used as a palliative treatment for unresectable tumor lesions and an adjunct treatment before or after surgery. However, the role of EBRT in HCC has been limited due to the low radiation tolerance of the liver. Recently, newer EBRT techniques, such as 3D-conformal RT (3D-CRT), intensity modulated RT (IMRT), and stereotactic body RT (SBRT), have made it possible to improve tumor mapping and deliver high doses of precise radiation [11,12]. So EBRT may be a promising alternative treatment for HCC.

Although research on EBRT for treating HCC has increased recently, there have been few studies comparing survival after EBRT versus surgery [13-15]. In that case, we aimed to compare the outcomes of patients with American Joint Committee on Cancer (AJCC) stage I HCC treated with surgery versus those treated with EBRT.

Methods

Data source

A retrospective cohort study was performed using the SEER registry (November 2014 submission; version 8.3.4) of the National Cancer Institute which encompasses approximately 30% of the US population [16]. Because SEER database is publicly available, in which patients are de-identified, our study was exempted from the approval of institutional review board. Patients with solitary HCC lesions from 2004 to 2013 were identified using ICD-O-3 histology codes 8170/3-8175/3. The malignant codes for Hist/behav were as follows: 8170/3: HCC, not otherwise specified; 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.

Patient selection

Patients with HCC at AJCC stage I and no evidence of metastatic disease who underwent surgery or EBRT were included. Patients with missing data regarding tumor size were excluded. "Surgery" in the data set was defined as patients undergoing hepatic resection (HR) and liver transplantation (LT).

Demographic and clinical data

Demographic information included age, race, and sex. Race was coded as white, black, and others. The major clinical variables were as follows: HCC pathological type, grade of differentiation, survival time, follow-up, vital status, and cause of death.

Endpoints

The outcome of interest in our study included OS and liver–specific survival (LSS). OS was defined as the time from surgery or EBRT until death as a result of any cause, and LSS was defined as the interval from surgery or EBRT until death as a result of liver disease.

Statistics

All statistical analyses were performed using the statistical software package SPSS 17.0 for windows and StataSE 12.0. Patient characteristics were compared by using Chi-square tests for categorical data and Kruskal-Wallis test for continuous data. P value <0.05 was considered statistically significant. According to the tumor size, the patients were further classified into ≤2cm, >2cm and ≤3cm, >3cm and ≤4cm, >4cm and ≤5cm, and >5cm groups. Statistical analyses were performed among different tumor sizes. 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. The log-rank test was used to compare the survival of patients according to the treatment modality (surgery versus EBRT).

Propensity score matching (PSM) analysis is an emerging statistical method. It firstly calculates the propensity score based on matching variables of every patient, and then pairs case and control groups according to the total propensity score. PSM not only corrects for interference from confounding factors but also reduces overfitting. In the present study, the 1:1 PSM analysis was employed by matching age, sex, and race with the nearest neighbor procedure. The program code used in this study was as follows:

```
ssc install psmatch2;
set seed 10101;
gen x=uniform();
sort x;
psmatch2 Group Sex Age Race HCC pathological type, grade of differentiation, outcome ( Vitalstatus) common ties are n(1) logit;
pstest Sex Age Race,both graph.
```

Results

HCC ≤2cm

A total of 1553 patients were eligible. Among them, 1516 were treated with surgery, and 37 with EBRT. Compared with patients treated with EBRT, patients treated with surgery were significantly younger (59 versus 62 years, P=0.034) (Table 1)

and had a significantly lower proportion of death from liver disease (49.90 versus 91.67%, p=0.016).

There was no significant difference in OS (p=0.605) and LSS (p=0.281) between patients treated with surgery versus EBRT. The median survival time was 29 months (range: 0-119) in the surgery group and 26 months (range: 0-119) in the EBRT group (Figure 1A and C).

After PSM, 23 paired patients were selected. No significant difference in OS (p=0.891) and LSS (p=0.346) was observed between the two groups. The median survival time was 28 months (range: 6-107) in the surgery group and 24 months (range: 2-84) in the EBRT group (Figure 1B and D).

HCC >2cm and ≤3cm

A total of 1752 patients were eligible. Among them, 1705 were treated with surgery, and 47 with EBRT (Table 2). Compared with patients treated with EBRT, patients treated with surgery had a significantly lower proportion of death from liver disease (55.81 versus 80.95%, p=0.021).

Compared with patients treated with EBRT, patients treated with surgery had statistically better OS (p=0.001), but statistically similar LSS (p=0.072). The median survival time was 27 months (range: 0-119) in the surgery group and 17 months (range: 0-114) in the EBRT group (Figure 2A and C).

After PSM, 35 paired patients were selected. No significant difference in OS (p=0.139) and LSS (p=0.722) was observed between the two groups. The median survival time was 24 months (range: 1-81) in the surgery group and 19 months (range: 3-114) in the EBRT group (Figure 2B and D).

HCC >3cm and ≤4cm

A total of 1157 patients were eligible. Among them, 1117 were treated with surgery, and 40

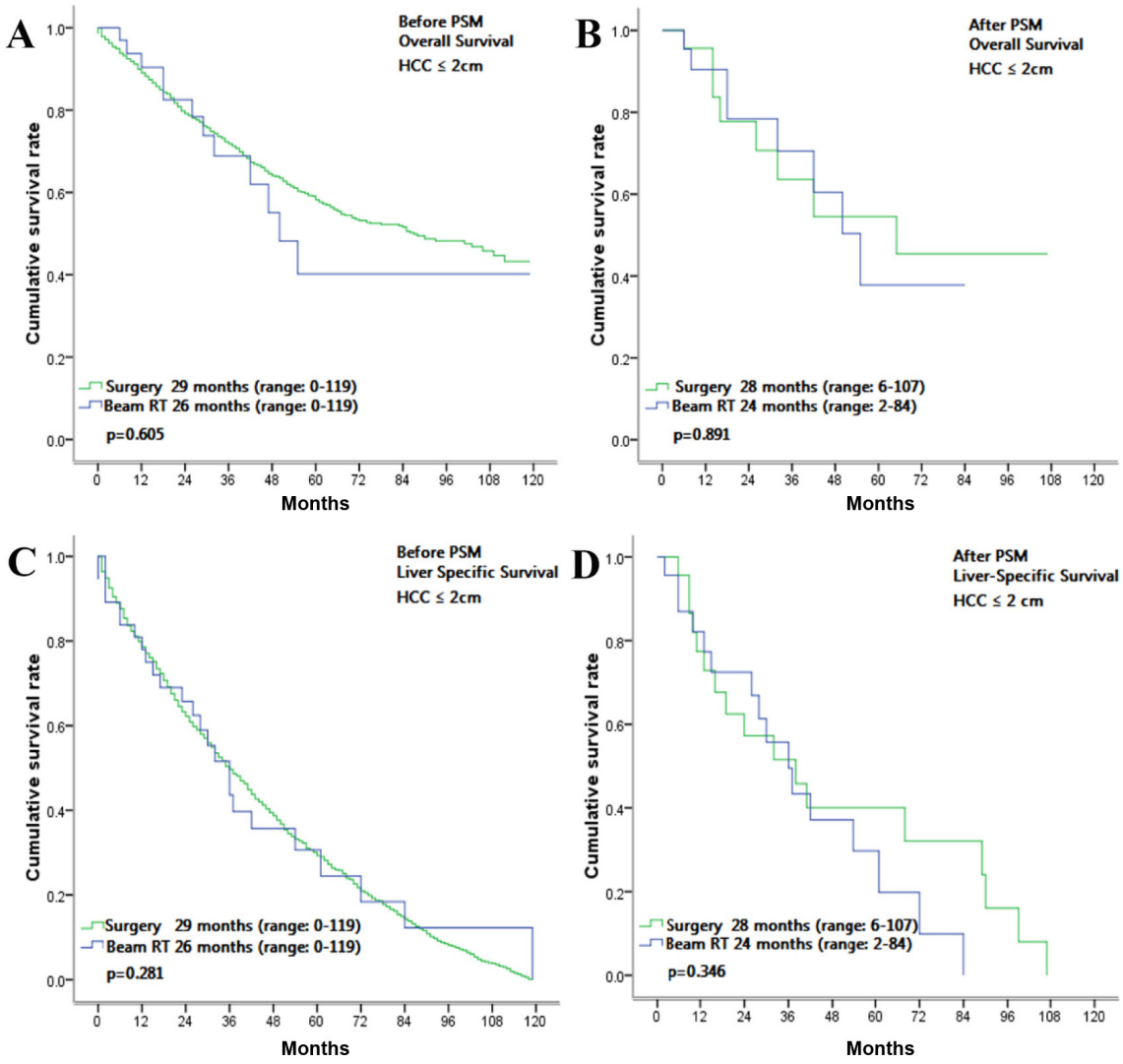

Figure 1. Difference in the overall and liver-specific survival of patients with ≤2cm HCC at AJCC stage I undergoing surgery versus those undergoing EBRT. **A:** overall survival before PSM; **B:** overall survival after PSM; **C:** liver-specific survival before PSM; **D:** liver-specific survival after PSM.

with EBRT. Compared with patients treated with EBRT, patients treated with surgery were significantly younger (62 versus 68 years, p=0.005) (Table 3) and had a significantly lower proportion of death from any cause (43.42 versus 60.00%, p=0.038).

Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p<0.001) and LSS (p<0.001). The median survival time was 27 months (range: 0-118) in the surgery group and 12 months (range: 1-71) in the EBRT group.

After PSM, 31 paired patients were selected. Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p=0.012) and LSS (p=0.003). The median survival time was 24 months (range: 0-85) in the surgery group and 9 months (range: 1-38) in the EBRT group.

HCC >4cm and ≤5cm

A total of 723 patients were eligible. Among them, 690 were treated with surgery, and 33 with EBRT. Compared with patients treated with EBRT, patients treated with surgery were significantly younger (63 versus 72 years, p<0.001) (Table 4).

Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p<0.001) and LSS (p<0.001). The median survival time was 25 months (range: 0-119) in the surgery group and 13 months (range: 0-49) in the EBRT group.

After PSM, 21 paired patients were selected. Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p=0.027) and LSS (p=0.028). The median survival time was 25 months (range: 0-101) in the surgery group and 8 months (range: 0-41) in the EBRT group.

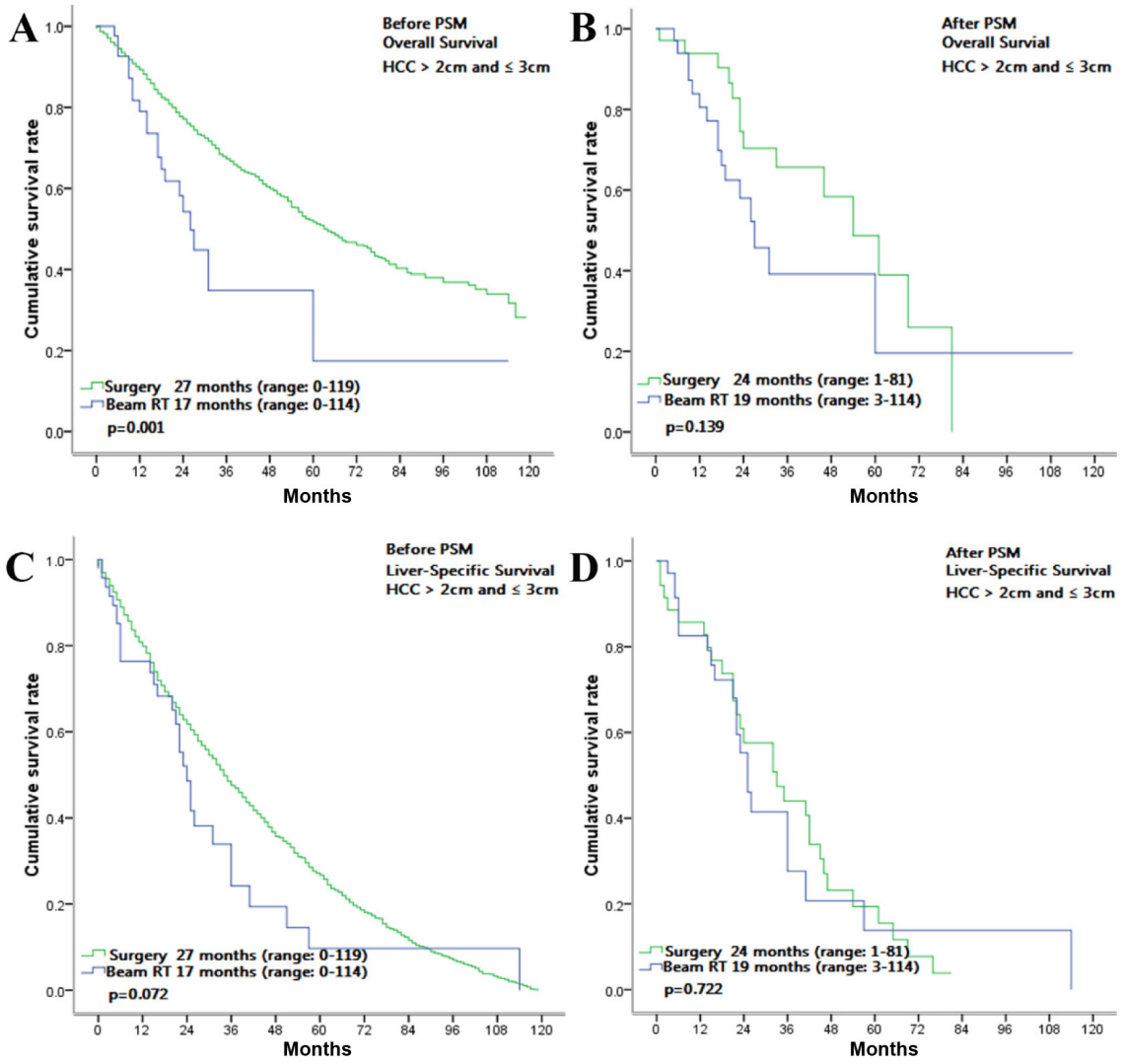

Figure 2. Difference in the overall and liver-specific survival of patients with >2cm and ≤3cm HCC at AJCC stage I undergoing surgery versus those undergoing EBRT. **A:** overall survival before PSM; **B:** overall survival after PSM; **C:** liver-specific survival before PSM; **D:** liver-specific survival after PSM.

Table 1. Characteristics of patients with HCC ≤2cm at AJCC stage I undergoing surgery or beam RT

Variables	*Before PSM*							*After PSM*						
	Surgery (n=1516)			*Beam RT (n=37)*			*P value*	*Surgery (n=23)*			*Beam RT (n=23)*			*P value*
	No. Pts Available	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*		*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	
Sex, n (%)	1516			37			0.625	23			23			1.000
Female/Male		424 (27.97)/ 1092 (72.03)			9 (24.32)/ 28 (75.68)				9 (39.13)/ 14 (60.87)			9 (39.13)/ 14 (60.87)		
Age (years)	1516	60.00±10.00	59 (1-90)	37	63.89±10.40	62 (45-86)	0.034	23	66.30±10.36	66 (47-84)	23	66.30±10.36	66 (47-84)	1.000
Race, n (%)	1510			36			0.378	23			23			1.000
White		1082 (71.66)			25 (69.44)				15 (65.22)			15 (65.22)		
Black		151 (10.00)			6 (16.67)				3 (13.04)			3 (13.04)		
Others		277 (18.34)			5 (13.89)				5 (21.74)			5 (21.74)		
HCC pathological type, n (%)	1516			37			0.945	23			23			1.000
HCC, NOS		1489 (98.21)			37 (100.00)				23 (100.00)			23 (100.00)		
HCC, fibrolamellar		6 (0.40)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, acirrhous		6 (0.40)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, spindle cell variant		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, clear cell type		15 (0.99)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, pleomorphic type		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
Grade of differentiation, n (%)	848			5			0.869	12			1			0.705
Well differentiated; I		393 (46.34)			2 (40.00)				4 (33.33)			0 (0.00)		
Moderately differentiated; II		382 (45.05)			3 (60.00)				5 (41.67)			1 (100.00)		
Poorly differentiated; III		69 (8.14)			0 (0.00)				3 (25.00)			0 (0.00)		
Undifferentiated; IV		4 (0.47)			0 (0.00)				0 (0.00)			0 (0.00)		

HCC: hepatocellular carcinoma, RT: radiation therapy, AJCC: American Joint Committee on Cancer, PSM: propensity score matching, NOS: not otherwise specified.

Table 2. Characteristics of patients with HCC >2cm and ≤3cm at AJCC stage I undergoing surgery or beam RT

Variables	*Before PSM*							*After PSM*						
	Surgery (n=1705)			*Beam RT (n=47)*			*P value*	*Surgery (n=35)*			*Beam RT (n=35)*			*P value*
	No. Pts Available	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*		*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	
Sex, n (%)	1705			47			0.398	35			35			0.799
Female/Male		450 (31.43)/ 1255 (68.57)			15 (34.29)/ 32 (65.71)				11 (31.43)/ 24 (68.57)			12 (34.29)/ 23 (65.71)		
Age (years)	1705	61.92±9.56	61 (21-91)	47	64.11±11.77	63 (41-89)	0.271	35	64.86±11.81	66 (43-89)	35	66.57±11.90	68 (44-89)	0.569
Race, n (%)	1701			47			0.198	35			35			0.788
White		1135 (77.14)			37 (78.72)				27 (77.14)			25 (71.43)		
Black		174 (11.43)			4 (8.51)				4 (11.43)			4 (11.43)		
Others		392 (11.43)			6 (12.77)				4 (11.43)			6 (17.14)		
HCC pathological type, n (%)	1705			47			0.880	35			35			1.000
HCC, NOS		1681 (98.59)			47 (100.00)				35 (100.00)			35 (100.00)		
HCC, fibrolamellar		2 (0.12)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, acirrhous		1 (0.06)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, spindle cell variant		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, clear cell type		21 (1.23)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, pleomorphic type		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
Grade of differentiation, n (%)	966			9			0.409	22			8			0.109
Well differentiated; I		355 (36.75)			5 (55.56)				8 (36.36)			5 (62.50)		
Moderately differentiated; II		480 (49.69)			2 (22.22)				12 (54.55)			1 (12.50)		
Poorly differentiated; III		124 (12.84)			2 (22.22)				2 (9.09)			2 (25.00)		
Undifferentiated; IV		7 (0.72)			0 (0.00)				0 (0.00)			0 (0.00)		

HCC: hepatocellular carcinoma, RT: radiation therapy, AJCC: American Joint Committee on Cancer, PSM: propensity score matching, NOS: not otherwise specified.

Table 3. Characteristics of patients with HCC >3cm and ≤4cm at AJCC stage I undergoing surgery or beam RT

Variables	*Before PSM*							*After PSM*						
	Surgery (n=1117)			*Beam RT (n=40)*			*P value*	*Surgery (n=31)*			*Beam RT (n=31)*			*P value*
	No. Pts Available	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*		*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	
Sex, n (%)	1117			40			0.415	31			31			0.776
Female/Male		298 (26.68)/ 819 (73.32)			13 (32.50)/ 27 (67.50)				8 (25.81)/ 23 (74.19)			9 (29.03)/ 22 (70.97)		
Age (years)	1117	62.53±10.70	62 (2-99)	40	67.93±11.34	68 (47-85)	0.005	31	67.52±10.52	67 (47-84)	31	67.39±11.07	67 (47-85)	0.989
Race, n (%)	1117			40			0.001	31			31			1.000
White		696 (62.31)			30 (75.00)				24 (77.42)			24 (77.42)		
Black		125 (11.19)			9 (22.50)				6 (19.35)			6 (19.35)		
Others		296 (26.50)			1 (2.50)				1 (3.23)			1 (3.23)		
HCC pathological type, n (%)	1117			40			<0.001	31			31			0.207
HCC, NOS		1097 (98.21)			37 (92.50)				31 (100.00)			28 (90.32)		
HCC, fibrolamellar		4 (0.36)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, acirrhous		2 (0.18)			2 (5.00)				0 (0.00)			2 (6.45)		
HCC, spindle cell variant		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, clear cell type		14 (1.25)			1 (2.50)				0 (0.00)			1 (3.23)		
HCC, pleomorphic type		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
Grade of differentiation, n (%)	702			12			0.120	19			9			0.013
Well differentiated; I		248 (35.33)			8 (66.66)				5 (26.32)			6 (66.67)		
Moderately differentiated; II		337 (48.01)			2 (16.67)				12 (63.15)			2 (22.22)		
Poorly differentiated; III		108 (15.38)			2 (16.67)				2 (10.53)			1 (11.11)		
Undifferentiated; IV		9 (1.28)			0 (0.00)				0 (0.00)			0 (0.00)		

CC: hepatocellular carcinoma, RT: radiation therapy, AJCC: American Joint Committee on Cancer, PSM: propensity score matching, NOS: not otherwise specified.

Table 4. Characteristics of patients with HCC >4cm and ≤5cm at AJCC stage I undergoing surgery or beam RT

Variables	*Before PSM*							*After PSM*						
	Surgery (n=690)			*Beam RT (n=33)*			*P value*	*Surgery (n=21)*			*Beam RT (n=21)*			*P value*
	No. Pts Available	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*		*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	
Sex, n (%)	690			33			0.674	21			21			1.000
Female/Male		166 (24.06)/ 524 (75.94)			9 (27.27)/ 24 (72.73)				6 (28.57)/ 15 (71.43)			6 (28.57)/ 15 (71.43)		
Age (years)	690	63.41±11.46	63 (17-91)	33	71.52±11.86	72 (48-90)	<0.001	21	68.43±12.12	69 (48-87)	21	69.67±12.13	70 (48-87)	0.705
Race, n (%)	689			33			0.026	21			21			0.835
White		454 (65.90)			29 (87.88)				19 (90.48)			18 (85.72)		
Black		61 (8.85)			2 (6.06)				1 (4.76)			1 (4.76)		
Others		174 (25.25)			2 (6.06)				1 (4.76)			2 (9.52)		
HCC pathological type, n (%)	690			33			0.889	21			21			0.599
HCC, NOS		674 (97.68)			32 (96.97)				19 (90.48)			20 (95.24)		
HCC, fibrolamellar		4 (0.58)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, acirrhous		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, spindle cell variant		0 (0.00)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, clear cell type		11 (1.60)			1 (3.03)				1 (4.76)			1 (4.76)		
HCC, pleomorphic type		1 (0.14)			0 (0.00)				1 (4.76)			0 (0.00)		
Grade of differentiation, n (%)	453			18			0.031	14			11			0.031
Well differentiated; I		150 (33.12)			8 (44.45)				6 (42.86)			5 (45.46)		
Moderately differentiated; II		240 (52.98)			6 (33.33)				7 (50.00)			3 (27.27)		
Poorly differentiated; III		59 (13.02)			4 (22.22)				0 (0.00)			3 (27.27)		
Undifferentiated; IV		4 (0.88)			0 (0.00)				1 (7.14)			0 (0.00)		

HCC: hepatocellular carcinoma, RT: radiation therapy, AJCC: American Joint Committee on Cancer, PSM: propensity score matching, NOS: not otherwise specified.

Table 5. Characteristics of patients with HCC >5cm at AJCC stage I undergoing surgery or beam RT

Variables	*Before PSM*							*After PSM*						
	Surgery (n=1279)			*Beam RT (n=52)*			*P value*	*Surgery (n=34)*			*Beam RT (n=34)*			*P value*
	No. Pts Available	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*		*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	*No. Pts Available*	*Mean±SD or Frequency (percentage)*	*Median (Range)*	
Sex, n (%)	1279			52			0.560	34			34			1.000
Female/Male		323 (25.25)/ 956 (74.75)			15 (28.85)/ 37 (71.15)				10 (29.41)/ 24 (70.59)			10 (29.41)/ 24 (70.59)		
Age (years)	1279	63.36±13.40	64 (7-94)	52	71.92±10.63	74 (42-90)	<0.001	34	71.27±9.88	72 (53-86)	34	71.41±10.47	72 (53-90)	0.946
Race, n (%)	1278			52			0.054	34			34			0.483
White		806 (63.07)			38 (73.08)				26 (76.47)			24 (70.58)		
Black		139 (10.88)			8 (15.38)				2 (5.88)			5 (14.71)		
Others		333 (26.05)			6 (11.54)				6 (17.65)			5 (14.71)		
HCC pathological type, n (%)	1278			52			0.959	34			34			0.314
HCC, NOS		1228 (96.09)			51 (98.08)				34 (100.00)			33 (97.06)		
HCC, fibrolamellar		19 (1.49)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, acirrhous		2 (0.16)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, spindle cell variant		1 (0.01)			0 (0.00)				0 (0.00)			0 (0.00)		
HCC, clear cell type		26 (2.02)			1 (1.92)				0 (0.00)			1 (2.94)		
HCC, pleomorphic type		3 (0.23)			0 (0.00)				0 (0.00)			0 (0.00)		
Grade of differentiation, n (%)	971			22			0.755	28			17			0.251
Well differentiated; I		313 (32.23)			6 (27.27)				10 (35.71)			4 (23.53)		
Moderately differentiated; II		477 (49.13)			11 (50.00)				10 (35.71)			9 (52.94)		
Poorly differentiated; III		159 (16.37)			5 (22.73)				7 (25.00)			4 (23.53)		
Undifferentiated; IV		22 (2.27)				0 (0.00)					1 (3.58)	0 (0.00)		

HCC: hepatocellular carcinoma, RT: radiation therapy, AJCC: American Joint Committee on Cancer, PSM: propensity score matching, NOS: not otherwise specified.

HCC >5cm

A total of 1331 patients were eligible. Among them, 1279 were treated with surgery, and 52 were treated with EBRT. Compared with patients treated with EBRT, patients treated with surgery were significantly younger (64 versus 74 years, p<0.001) (Table 5) and had significantly lower proportions of death from any cause (46.95 versus 67.31%, p=0.004) and death from liver disease (66.83 versus 74.29%, p=0.009).

Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p<0.001) and LSS (p<0.001). The median survival time was 26 months (range: 0-119) in the surgery group and 9 months (range: 0-63) in the EBRT group.

After PSM, 34 paired patients were selected. Compared with patients treated with EBRT, patients treated with surgery had significantly better OS (p=0.003) and LSS (p=0.025). The median survival time was 27 months (range: 0-83) in the surgery group and 11 months (range: 0-40) in the EBRT group.

Discussion

Our study demonstrated the following major findings: 1) in both patients with HCC ≤2cm and HCC >2cm and ≤3cm, the survival after EBRT was comparable to that after surgery; 2) in patients with HCC >3cm and ≤4cm, HCC >4cm and ≤5cm, and HCC >5cm, the survival after EBRT was inferior to that after surgery; and 3) patients treated with surgery might be younger.

Current treatment options for early HCC consist of LT, HR, and radiofrequency ablation (RFA) [17,18]. Theoretically, the best treatment is LT [19,20], which offers the potential to eliminate the entire tumor-bearing and cirrhotic liver. However, the limited availability of suitable living donors, high cost, as well as an increased waiting period, have raised the demand for other alternatives of early HCC, such as HR and RFA. HR has been accepted as the first choice of treatment for HCC at many centers. Nevertheless, the presence of cirrhosis limits the feasibility of surgery and increases the risk of postoperative liver failure. RFA, a promising ablation technique, is recommended as the primary treatment option for patients with early HCC who are not suitable for HR or LT [20]. However, it may induce deep thermal injury in hepatic tissue while sparing the normal parenchyma. Although HR had some advantages in the survival and recurrence regardless of tumor size [21, 22], some studies suggested that RFA be as effective as HR in the treatment of solitary and small HCC [23].

Recently, EBRT has been used as a definitive therapy with curative intent for early-stage HCC [24]. Yuan et al. [13] found that the 1-, 2-, and 3-year local tumor control rates after SBRT were 92.9%, 90.0%, and 67.7%, respectively. The adverse effects of SBRT were milder than those of HR. The 1-, 2-, and 3-year OS rates were also similar between them (HR: 88.5%, 73.1%, and 69.2%; SBRT: 72.7%, 66.7%, and 57.1%). Seo et al. also found that the OS of SBRT was nearly identical to RFA in HCC ≤3cm, and the predicted life expectancy was 6.452 and 6.371 years in the RFA and SBRT groups, respectively. Especially, if the tumor size is 2-3 cm, SBRT is the preferred treatment option [25]. In addition, Su et al. found that the local effect of SBRT was similar to that of HR in patients with small primary HCC with 1 or 2 nodules and Child-Pugh A cirrhosis. PSM analysis demonstrated that 1-, 3-, and 5-year OS of HCC patients undergoing SBRT were better than those of HCC patients undergoing HR (100%, 91.8%, and 74.3% versus 96.7%, 89.3%, and 69.2%) [15]. Similarly, our study further confirmed that the survival after surgery was comparable to that after EBRT in patients with HCC ≤3cm. EBRT can minimize the irradiation of surrounding healthy tissue and allow for dose escalation and ultimately better local tumor control with a relatively lower incidence of complications. Thus, it should be considered as a potential alternative choice for small tumors [26].

Large HCC lesions may have more aggressive biological behaviors than small lesions. Curative HR seems to yield better outcomes than non-surgical treatments for large HCC [27]. Our study suggested that the survival after surgery was superior to that after EBRT in patients with HCC >3cm. Indeed, EBRT for large HCC remains challenging due to the potential of proximity to critical organ, limited liver volume, and relatively poor liver functional status.

There are several limitations in our study. First, SEER database does not provide the 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. Second, in the SEER database, only surgery and RT are the recorded therapeutic modalities of HCC, but TACE or RFA are not included. Third, the type of EBRT (e.g., 3D-CRT, IMRT, or SBRT) is unavailable in the SEER database, while there is a growing evidence for the usefulness of SBRT in the management of patients with HCC [28-31]. Fourth, the detailed information regarding RT technique, such as treatment plan, imaging guidance, immobilization, simulation and target delineation, dose constraints for normal liver, tumor dose and frac-

tions, is lacking in the SEER database. Fifth, in the SEER database, only the AJCC Cancer Staging system (based on the 6th edition) is employed for tumor staging. Sixth, as well-known, a wide difference in the number of experimental versus control cohorts on PSM will lead to wasted cases and PSM paradox. Thus, we should acknowledge the fact that 1516 patients are attributed to surgery group but only 37 patients are attributed to EBRT group in the subgroup analysis of HCC<2 cm, which will preclude from our precise estimates of treatment effects.

In summary, RT may be an effective treatment choice for HCC ≤3cm. Efficacy of EBRT in combination with other non-surgical treatments are worth of further research.

Authors' contributions

Bing Han: reviewed the literature, collected the data, performed the statistical analysis, interpreted the data, and drafted the manuscript. Lichun Shao: performed the statistical analysis, interpreted the data, and gave critical comments. Chuan Li, Ying Xu, Yufu Tang and Lei Han: gave critical comments. Xingshun Qi: conceived the work, performed the statistical analysis, interpreted the data, and drafted the manuscript. All authors have made an intellectual contribution to the manuscript and approved the submission.

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Conflict of interests

The authors declare no conflict of interests.

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