

Liver Resection Combined with Radiotherapy versus Liver Resection Alone in the Treatment of Hepatocellular Carcinoma: A Population-based Study

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Abstract

Background

Radiotherapy has been used in the treatment of hepatocellular carcinoma (HCC) more widely. However, little research focus on comparing the efficacy of patients with liver resection combined with radiotherapy with that received liver resection alone. The study was conducted to evaluate whether the efficacy of liver resection combined with radiotherapy in the treatment of patients with HCC is better than liver resection alone.

Methods

The study utilized the data from the Surveillance, Epidemiology, and End Results 18 registry (SEER-18). Patients diagnosed with HCC between 2004 and 2015 who received liver resection or the combination of liver resection and radiotherapy were included in the analysis. The propensity score matching model (PSM) was used to reduce selection bias and potential confounding factors.

Results

Before PSM, the median overall survival (mOS) and median cancer-specific survival (mCSS) of patients treated with liver resection alone were longer than in patients treated with the combination of liver resection and radiotherapy ($P < 0.001$). However, there was no statistically significant difference in mOS and mCSS between the groups after PSM ($P > 0.05$). The subgroup analysis after PSM documented that patients with American Joint Committee on Cancer (AJCC) stage I and II who were treated with liver resection and radiotherapy had no longer mOS and mCSS than patients subjected to the combination of liver resection alone ($P = 0.151$ and $P = 0.185$). Similar results were obtained in the subgroup group of patients with a single tumor smaller than 5 cm. Univariate analysis showed that patients undergoing liver resection combined with radiotherapy did not have an increased all-cause mortality risk (HR:1.214, 95%CI: 0.950-1.553; $P = 0.122$) and cancer-specific mortality risk (HR:1.132, 95%CI: 0.848-1.510; $P = 0.401$) when compared to patients treated with liver resection alone after PSM.

Conclusion

The combination of liver resection and radiotherapy does not prolong the survival of HCC patients more than liver resection alone.

Introduction

Hepatocellular carcinoma (HCC) is one of the most malignant cancers and the second most lethal cancer worldwide[1]. In the United States, the number of HCC cases and deaths has increased dramatically in recent decades[2, 3]. The European Association for the Study of the Liver (EASL) guidelines recommend radical treatments, such as liver resection, liver transplantation, and ablation, as the most effective treatment for patients with early HCC[1]. For patients with a single tumor no larger than 3 cm, the efficacy of radiofrequency ablation (RFA) is similar to that of liver resection. However, but for patients with tumors larger than 3 cm, liver resection provides a better outcome than RFA because of the limited range of ablation and the heat sink effect of RFA[4, 5]. Liver resection might inflict more damage to the patients than RFA, limiting its use in patients with a single tumor smaller than 3 cm. However, liver resection might be used more widely in the treatment of HCC. Recent studies documented that patients with intermediate-stage HCC had better overall survival after with liver resection than after transarterial chemoembolization (TACE), which used to be recommended as the first-line treatment for intermediate HCC patients[6–8]. Although liver resection and RFA can both prolong the overall survival of patients with HCC, the 5-years tumor recurrence rate in patients subjected to these therapies remains high, leading to the death of patients in the short term[9, 10]. The combination of liver resection and other treatments might represent a good choice for HCC patients.

Recently, the possibility was raised that radiotherapy might be effective as primary or adjuvant treatment for HCC patients. A retrospective study showed that patients with early HCC who received radiotherapy showed similar local control for small

tumors as patients treated with RFA, but provided an advantage in case of tumors larger than 2 cm[11]. Another study compared the efficacy of stereotactic ablative radiotherapy with liver resection in HCC patients with small tumors and found that both modalities resulted in similar progression-free survival (PFS) and overall survival (OS)[12]. Therefore, in the future, radiotherapy might be used more widely in HCC treatment.

Radiotherapy includes internal radiation therapy and external radiation therapy. Both approaches are used in HCC treatment and ensure adequate efficacy[13, 14]. Typically, radiotherapy is used as an adjuvant treatment for HCC and combined with other treatment protocols. A previous study indicated that radiotherapy combined with TACE prolongs the OS of HCC more than TACE alone[15]. A randomized controlled trial found that the efficacy of radiotherapy combined with liver resection in small HCC tumors that invaded portal vein, defined as advanced HCC, was better than that of liver resection alone[16]. However, whether patients with different stage HCC can get survival benefit from the combined treatment is unknown. Therefore, we compared the efficacy of radiotherapy combined with liver resection and liver resection alone using a population-based cancer registry.

Methods And Materials

This retrospective study was conducted using the Surveillance, Epidemiology, and End Results (SEER 18) database, which covers approximately 28% of the United States population and includes cancer incidence, demographics, the first course of treatment, and mortality from the time of diagnosis.

The study included patients diagnosed with HCC (International Classification of Disease for Oncology, Third Edition (ICD-O-3), histology code 8170/3, 8171/3, 8172/3, 8173/3, 8174/3 and 8175/3, site code C220) between 2004 and 2015. The patients that were younger than 85 years or older than 45 years at the time of diagnosis were excluded. The patients whose exact information (summary stage, AJCC 6th edition stage, whether they received surgical treatment, tumor size, length of survival) was unknown or unclear were excluded. Together, 5187 patients were included in the analysis; among them, 139 patients were treated by a combination of liver resection and radiotherapy, and 5048 patients received liver resection alone (**Figure 1**).

The study was approved by the SEER program managers and the Institutional Review Board.

Variables and outcomes

The characteristics of patients included gender, ethnicity, marital status, age at HCC diagnosis, year of HCC diagnosis, tumor stage according to the AJCC 6th edition, tumor size, number of tumors, administration of chemotherapy. The endpoints of the analysis were overall survival (OS) and cancer-specific survival (CSS). OS was defined as from the time of HCC diagnosis to the death of patients. CSS was defined as from the time of HCC diagnosis to death caused by cancer.

Statistical analysis

The data used in this study was extracted by the SEER*Stat software (version 8.3.6). The characteristics of patients treated with liver resection combined with radiotherapy and treated with liver resection only were compared by Chi-square test or Fisher's exact test before and after propensity score matching (PSM). Kaplan-Meier curves for OS and CSS were plotted and compared using the log-rank test. A univariate and multivariate logistic regression model was used to analyze the predictors for OS and CSS. The predictors with the P-value of less than 0.1 in univariate analysis were included in multivariate analysis. PSM was conducted to reduced confounding factors and selection biases. PSM involved gender, ethnicity, marital status, age at diagnosis, year of diagnosis, summary stage, AJCC stage, tumor size, number of tumors, and administration of chemotherapy. The optimal caliper was set as 0.01, and 568 patients were generated using the 1:4 nearest neighbor approach. The P-value of less than 0.05 was considered statistically significant, and all statistical analyses were two-tailed. SPSS 25.0 (IBM, Chicago, IL, USA) and GraphPad Prism 8.0 (GraphPad Software, San Diego, CA) were used to perform statistical calculations.

Results

Patients

A total of 5187 patients were included in this study before PSM; 3736 were male, and 1451 were female. Among them, 5048 patients were treated with liver resection alone (liver resection alone group), and 139 patients were treated with liver resection combined with radiotherapy (combined treatment group). There was a statistically significant difference in age at diagnosis, tumor stage, AJCC stage, tumor size, ethnicity, and administration of chemotherapy between the two groups before PSM ($P < 0.05$). No statistically significant differences of characteristics between the two groups were present after PSM ($P > 0.05$) (**Table 1**).

Table 1
Baseline characteristics of patients before and after PSM

Characteristics	Before PSM		After PSM	
	Patients (N, %)		Patients (N, %)	
	Liver resection alone (N=5048)	Liver resection combined with radiotherapy (N=139)	p ^a value	p ^b value
Gender			0.430	0.243
Male	3640 (72.1)	96 (69.1)		318 (74.1)
Female	1408 (27.9)	43 (30.9)		111 (25.9)
Age at diagnosis			0.028	0.375
35-44	200 (3.9)	10 (7.2)		16 (3.7)
44-54	722 (14.3)	10 (7.2)		37 (8.6)
55-64	1775 (35.2)	55 (39.6)		178 (41.5)
>64	2351 (46.6)	64 (46)		198 (46.2)
Year of diagnosis			0.124	0.981
2004-2006	919 (18.2)	17 (12.2)		48 (11.2)
2007-2009	1209 (24)	28 (20.2)		86 (20.1)
2010-2012	1369 (27.1)	45 (32.3)		137 (31.9)
2013-2015	1551 (30.7)	49 (35.3)		158 (36.8)
Summary stage			<0.001	0.213
Localized	4047 (80.2)	81 (58.3)		284 (66.2)
Regional	868 (17.2)	43 (30.9)		103 (24)
Distant	133 (2.6)	15 (10.8)		42 (9.8)
AJCC stage			<0.001	0.009
I	2812 (55.7)	45 (32.4)		180 (42)
II	1222 (24.2)	41 (29.5)		111 (25.9)
IIIA	709 (14.1)	25 (18)		80 (18.6)
IIIB	143 (2.8)	12 (8.6)		9 (2.1)
IIIC	66 (1.3)	3 (2.1)		12 (2.8)
IV	96 (1.9)	13 (9.4)		37 (8.6)
Tumor size			0.003	0.677
<3cm	1330 (26.4)	35 (25.2)		95 (22.1)
3-5cm	1345 (26.6)	21 (15.1)		75 (17.5)
>5cm	2373 (47)	83 (59.7)		259 (60.4)
Tumor number			0.562	0.601

1	3953 (78.3)	103 (74.1)	340 (79.3)
2	857 (17)	28 (20.1)	67 (15.6)
3	182 (3.6)	7 (5.1)	18 (4.2)
>3	56 (1.1)	1 (0.7)	4 (0.9)
Ethnicity			0.041 0.225
White	2868 (56.8)	93 (66.9)	295 (68.7)
Black	657 (13)	17 (12.2)	41 (9.6)
Other	1523 (30.2)	29 (20.9)	93 (21.7)
Marital status			0.250 0.325
Married	3180 (63)	79 (56.8)	247 (57.6)
Unmarried	1623 (32.2)	54 (38.9)	149 (34.7)
Other	245 (4.8)	6 (4.3)	33 (7.7)
Chemotherapy			<0.001 0.150
Yes	783 (15.5)	58 (41.7)	150 (35)
No	4265 (84.5)	81 (58.3)	279 (65)
P ^a : Comparison of baseline characteristics between patients with liver resection alone with patients received liver resection combined with radiotherapy before PSM			
P ^b : Comparison of baseline characteristics between patients with liver resection alone with patients received liver resection combined with radiotherapy after PSM			

Survival outcomes

Before PSM, median OS (mOS) and median CSS (mCSS) in the liver resection alone group (mOS: 54 months, 95%CI: 51.1-56.9; mCSS: 65 months, 95%CI: 59.4-70.6) were longer than in the combined treatment group (mOS: 30 months; 95%CI: 23.3-36.7; mCSS: 32 months; 95%CI: 24.1-39.9; P<0.001 for mOS and mCSS) (**Figure 2**). The subgroups analysis showed that patients with AJCC stage I and II in the liver resection alone group had longer mOS and mCSS than patients in the combined treatment group (mOS: 68 months, 95%CI: 63.7-72.3 vs. 33 months, 95%CI: 19.7-46.3; P=0.02; mCSS: 71 months, 95%CI: 64.5-77.5 vs. 32 months, 95%CI: 23.7-42.3; P<0.001) (**Figure 3a-3b**). Patients with a single tumor not than 5 cm group in the liver resection alone group had longer mOS and mCSS than patients in the combined therapy group (mOS: 71 months, 95%CI: 64.5-77.5 vs. 32 months, 95%CI: 20.4-43.6; P=0.023; mCSS: 93 months, 80.2-105.8 vs. 32 months, 95%CI: 20.8-43.2; P=0.006) (**Figure 3c-3d**).

After PSM, the mOS and mCSS in the liver resection alone group (mOS: 39 months; 95%CI: 33.2-44.8; mCSS: 39 months; 95%CI: 32.1-45.9) were slightly longer than in the combined treatment group (mOS: 30 months, 95%CI: 23.3-36.7; mCSS: 32 months; 95%CI: 24.1-39.9), but the difference was not statistically significant (mOS: P=0.118; mCSS: P=0.396) (**Figure 4**). In the subgroup analysis after PSM, for AJCC stage I and II patients, the mOS and mCSS in the liver resection alone group (mOS: 61 months, 95%CI: 47.4-74.6; mCSS: 66 months, 95%CI: 49.6-82.4) were longer than in the combined treatment group (mOS: 33 months, 95%CI: 23.7-42.3; mCSS: 33 months, 95%CI: 19.7-46.3), but the differences did not reach statistical significance (mOS: P=0.151; mCSS: P=0.185) (**Figure 5a-5b**). No significant differences were found in the subgroup with a single tumor smaller than 5 cm; patients in the liver resection alone group had slightly longer mOS and mCSS than patients in the combined

treatment group (mOS: 64 months, 95%CI: 40.1-87.9 vs. 32 months, 95%CI: 20.4,43.6; P=0.479; mCSS: 65 months, 95%CI: 39.6-90.4 vs. 32 months, 95%CI: 20.8-43.2; P=0.452) (**Figure 5c-5d**).

Predictors of overall survival and cancer-specific survival

Before PSM, the univariate and multivariate analysis for OS and CSS of all patients showed that male patients, older patients, the patients diagnosed with the earlier year of HCC, patients with more advanced summary stage and AJCC stage, larger tumor, black patients, and unmarried patients had worse mOS and mCSS (P<0.05) (**Table 3**). Liver resection combined with radiotherapy was an independent factor negatively affecting OS (HR:1.271; 95%CI: 1.091-1.585; P=0.033) but not CSS (HR:1.180; 95%CI: 0.980-1.535; P=0.216).

After PSM, higher AJCC stage and black race were independent predictors of shorter OS. Earlier years of HCC diagnosis, more advanced AJCC stage, and black race were independent predictors of shorter CSS (P<0.05)

Table 2
Predictors for OS and CSS of patients before PSM

Characteristics	Predictors for OS				Predictors for CSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value						
Gender								
Male	Reference		Reference		Reference		Reference	
Female	0.846 (0.776,0.923)	<0.001	0.773 (0.708,0.844)	<0.001	0.845 (0.759,0.940)	0.002	0.770 (0.690,0.859)	<0.001
Age at diagnosis								
35-44	Reference		Reference		Reference		Reference	
44-54	1.157 (0.930,1.440)	0.191	1.173 (0.941,1.462)	0.156	1.146 (0.902,1.458)	0.265	1.201 (0.942,1.530)	0.140
55-64	1.051 (0.855,1.292)	0.635	1.078 (0.875,1.329)	0.482	0.981 (0.781,1.231)	0.874	1.072 (0.850,1.351)	0.558
>64	1.321 (1.079,1.618)	0.007	1.407 (1.147,1.727)	0.001	1.242 (0.992,1.554)	0.059	1.445 (1.151,1.815)	0.002
Year of diagnosis								
2004-2006	Reference		Reference		Reference		Reference	
2007-2009	0.947 (0.855,1.049)	0.298	0.928 (0.837,1.028)	0.154	0.905 (0.799,1.025)	0.117	0.873 (0.769,0.990)	0.035
2010-2012	0.816 (0.733,0.908)	<0.001	0.819 (0.735,0.913)	<0.001	0.763 (0.670,0.870)	<0.001	0.764 (0.669,0.873)	<0.001
2013-2015	0.690 (0.607,0.784)	<0.001	0.715 (0.628,0.814)	<0.001	0.580 (0.496,0.678)	<0.001	0.589 (0.502,0.691)	<0.001
Summary stage								
Localized	Reference		Reference		Reference		Reference	
Regional	2.132 (1.949,2.332)	<0.001	1.415 (1.258,1.593)	<0.001	2.292 (2.058,2.551)	<0.001	1.449 (1.258,1.669)	<0.001
Distant	2.980 (2.479,3.582)	<0.001	1.635 (1.081,2.474)	0.020	3.661 (2.982,4.496)	<0.001	1.836 (1.153,2.923)	0.010
AJCC stage								
I	Reference		Reference		Reference		Reference	
II	1.452 (1.322,1.595)	<0.001	1.384 (1.258,1.523)	<0.001	1.562 (1.389,1.757)	<0.001	1.506 (1.337,1.697)	<0.001
IIIA	2.532 (2.284,2.806)	<0.001	1.855 (1.626,2.116)	<0.001	2.841 (2.512,3.213)	<0.001	1.954 (1.670,2.287)	<0.001
IIIB	2.962 (2.458,3.569)	<0.001	1.977 (1.545,2.529)	<0.001	3.235 (2.595,4.032)	<0.001	2.013 (1.491,2.719)	<0.001
IIIC	3.089	<0.001	1.911	<0.001	3.918	<0.001	2.261	<0.001

	(2.362,4.040)		(1.424,2.564)		(2.898,5.296)		(1.621,3.155)	
IV	3.493 (2.808,4.344)	<0.001	1.998 (1.252,3.189)	0.004	4.555 (3.556,5.835)	<0.001	2.412 (1.424,4.085)	0.001
Tumor size								
<3cm	Reference		Reference		Reference		Reference	
3-5cm	1.191 (1.064,1.333)	0.002	1.111 (0.991,1.244)	0.071	1.258 (1.089,1.453)	0.002	1.178 (1.019,1.362)	0.027
>5cm	1.694 (1.538,1.866)	<0.001	1.254 (1.128,1.393)	<0.001	1.917 (1.697,2.164)	<0.001	1.378 (1.207,1.574)	<0.001
Tumor number								
1	Reference				Reference		Reference	
2	0.970 (0.878,1.072)	0.547			0.617 (0.499,0.763)	<0.001	0.6161 (0.497,0.762)	<0.001
3	0.800 (0.650,0.984)	0.035			0.188 (0.060,0.582)	0.004	0.175 (0.056,0.544)	0.003
>3	0.895 (0.631,1.269)	0.534			NA	0.854	NA	0.820
Ethnicity								
White	Reference		Reference		Reference		Reference	
Black	1.217 (1.090,1.360)	<0.001	1.228 (1.097,1.376)	<0.001	1.195 (1.045,1.367)	0.009	1.181 (1.029,1.356)	0.018
Other	0.762 (0.697,0.833)	<0.001	0.784 (0.715,0.858)	<0.001	0.771 (0.692,0.858)	<0.001	0.758 (0.679,0.846)	<0.001
Marital status								
Married	Reference		Reference		Reference		Reference	
Unmarried	1.237 (1.141,1.340)	<0.001	1.227 (1.128,1.334)	<0.001	1.190 (1.077,1.314)	0.001	1.186 (1.069,1.317)	0.001
other	0.895 (0.741,1.083)	0.254	0.951 (0.785,1.151)	0.606	0.942 (0.752,1.179)	0.599	0.972 (0.775,1.219)	0.807
Chemotherapy								
Yes	Reference		Reference		Reference		Reference	
No	0.842 (0.765,0.928)	0.001	1.005 (0.908,1.112)	0.925	0.780 (0.697,0.873)	<0.001	0.997 (0.887,1.122)	0.965
Treatment								
Liver resection alone	Reference		Reference		Reference		Reference	
Liver resection combined with radiotherapy	1.632 (1.316,2.023)	<0.001	1.271 (1.019,1.585)	0.033	1.669 (1.295,2.151)	<0.001	1.180 (0.980,1.535)	0.216

Table 3
Predictors for OS and CSS of patients after PSM

Characteristics	Predictors for OS				Predictors for CSS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR	P value		P value		P value		P value
Gender								
Male	Reference				Reference			
Female	0.866 (0.680,1.104)	0.246			0.828 (0.613,1.119)	0.219		
Age at diagnosis								
35-44	Reference				Reference			
44-54	0.836 (0.450,1.552)	0.570			0.881 (0.453,1.714)	0.710		
55-64	0.947 (0.563,1.594)	0.838			0.985 (0.562,1.727)	0.959		
>64	1.051 (0.628,1.759)	0.850			1.054 (0.603,1.842)	0.853		
Year of diagnosis								
2004-2006	Reference				Reference		Reference	
2007-2009	0.776 (0.548,1.098)	0.152			0.669 (0.436,1.026)	0.066	0.584 (0.375,0.910)	0.017
2010-2012	0.760 (0.547,1.057)	0.103			0.700 (0.464,1.054)	0.087	0.538 (0.347,0.835)	0.006
2013-2015	0.704 (0.492,1.005)	0.053			0.628 (0.406,0.974)	0.038	0.539 (0.342,0.847)	0.007
Summary stage								
Localized	Reference		Reference		Reference		Reference	
Regional	2.081 (1.640,2.642)	<0.001	1.444 (1.020,2.043)	0.038	1.887 (1.427,2.497)	<0.001	1.276 (0.841,1.935)	0.251
Distant	2.242 (1.601,3.141)	<0.001	1.442 (0.563,3.696)	0.446	2.436 (1.668,3.558)	<0.001	1.361 (0.420,4.414)	0.608
AJCC stage								
I	Reference		Reference		Reference		Reference	
II	1.150 (0.862,1.534)	0.343	1.062 (0.790,1.428)	0.689	1.059 (0.755,1.486)	0.740	0.963 (0.680,1.365)	0.834
IIIA	2.194 (1.637,2.941)	<0.001	1.583 (1.055,2.375)	0.027	2.064 (1.465,2.907)	<0.001	1.723 (1.067,2.782)	0.026
IIIB	3.428 (2.141,5.490)	<0.001	2.331 (1.241,4.381)	0.009	2.983 (1.682,5.292)	<0.001	2.340 (1.052,5.206)	0.037

IIIC	2.384 (1.310,4.336)	0.004	1.474 (0.735,2.959)	0.275	2.276 (1.095,4.730)	0.028	1.622 (0.690,3.811)	0.268
IV	2.240 (1.528,3.282)	<0.001	1.525 (0.556,4.188)	0.413	2.472 (1.609,3.799)	<0.001	1.844 (0.530,6.416)	0.336
Tumor size								
<3cm	Reference		Reference		Reference		Reference	
3-5cm	1.539 (1.067,2.221)	0.021	1.326 (0.910,1.933)	0.142	1.439 (0.935,2.215)	0.098	1.415 (0.893,2.241)	0.139
>5cm	1.698 (1.283,2.247)	<0.001	1.221 (0.891,1.674)	0.214	1.650 (1.192,2.283)	0.003	1.167 (0.802,1.699)	0.420
Tumor number								
1	Reference			Reference		Reference		
2	0.866 (0.643,1.166)	0.343			0.560 (0.287,1.090)	0.088	0.675 (0.343,1.330)	0.256
3	0.812 (0.474,1.391)	0.449			NA	NA	NA	NA
>3	1.340 (0.498,3.601)	0.562			NA	NA	NA	NA
Ethnicity								
White	Reference		Reference		Reference		Reference	
Black	1.620 (1.172,2.240)	0.004	1.694 (1.217,2.357)	0.002	1.701 (1.144,2.527)	0.009	1.571 (1.028,2.401)	0.037
Other	0.825 (0.625,1.087)	0.171	0.812 (0.612,1.079)	0.151	0.761 (0.555,1.042)	0.088	0.676 (0.482,0.949)	0.023
Marital status								
Married	Reference				Reference			
Unmarried	1.087 (0.864,1.366)	0.477			0.963 (0.734,1.265)	0.787		
other	0.902 (0.569,1.430)	0.661			0.947 (0.580,1.545)	0.826		
Chemotherapy								
Yes	Reference				Reference			
No	0.882 (0.709,1.097)	0.260			0.895 (0.694,1.154)	0.393		
Treatment								
Liver resection alone	Reference				Reference			
Liver resection combined with radiotherapy	1.214 (0.950,1.553)	0.122			1.132 (0.848,1.510)	0.401		

Discussion

Published guidelines do not recommend radiotherapy as the standard treatment for any stage HCC, which limited its usage for this type of tumor¹. Several decades ago, external radiotherapy was not recommended to treat patients with HCC because the radiation could not be precisely positioned according to tumor location, size, and shape, which might lead to the damage of normal liver tissue and surrounding vital organs, and liver failure. However, modern imaging techniques, including the emergent internal radiotherapy and stereotactic body radiotherapy (SBRT), as well as the progress in understanding the tolerance of liver parenchyma to radiation, led to the wide use of radiotherapy in the treatment of HCC as an adjuvant therapy[17, 18].

Several recent studies documented that HCC patients receiving radiotherapy combined with other treatments had longer survival than those treated with radiotherapy alone[19–21]. A meta-analysis that compared the efficacy of TACE combined with radiotherapy with TACE alone treatment in patients with portal vein tumor thrombus (PVTT) demonstrated that the combined treatment yielded a higher objective response rate (ORR) and better survival benefits than the TACE alone treatment[22]. Wei and coworkers conducted a randomized clinical trial to compare the efficacy of hepatectomy combined with neoadjuvant radiotherapy with that of hepatectomy alone in patients with resectable HCC and portal vein tumor thrombus. The trial demonstrated that the 6, 12, 18, and 24 months OS and disease-free survival was significantly higher in the combined treatment group ($P < 0.001$)[16]. The present investigation compared the efficacy of the combination of liver resection and radiotherapy as the treatment for HCC with liver resection alone. Before PSM, the mOS and mCSS in the liver resection alone group were longer than in the combined treatment group ($P < 0.05$). However, the results documented that patients subjected to the combined treatment did not have better OS and CSS than patients treated with liver resection alone, after PSM.

Liver resection is recommended as the first-line treatment for early HCC by the EASL guideline, and it can increase the 1-, 3-, and 5-years survival¹. However, liver resection can result in significant damage. Patients with HCC often present poor liver function and physical condition due to cirrhosis, which is one of the main reasons why liver resection is not widely used in HCC treatment. Although liver damage induced by radiotherapy has been markedly reduced, radiation-induced hepatotoxicity might trigger more extensive liver injury when combined with liver resection, leading to the death of patients due to liver failure[23].

A recent study by Lewandowski and collaborators concluded that radiotherapy could extend the survival of patients with early HCC. The results indicated that 90% of patients showed tumor response according to the EASL criteria, of which 59% showed a complete response with a median time to progression of 2.4 years and mOS of 6.7 years[24]. Another analysis utilizing PSM compared the efficacy of radiotherapy and RFA in HCC patients with no more than three tumors, 3 cm or smaller in size. The results showed that the 3-year local recurrence rate in the radiotherapy group was lower than in the RFA group ($P < 0.01$), and the 3-year survival rate in the radiotherapy group was similar as in the with RFA group ($P = 0.86$). These findings indicate that in comparison with RFA, radiotherapy ensures superior local control and comparable OS[25]. However, in the current study, mOS and mCSS of patients with AJCC stage I and II and with single tumor not larger than 5 cm, was comparable between the liver resection alone group and the combined treatment group. These results support the conclusion that radiotherapy may not provide additional survival benefits in HCC patients who received liver resection.

Although the mOS and mCSS in the liver resection alone group were longer than in the combined treatment group, in multivariate logistic regression analysis, the combination of liver resection and radiotherapy was an independent factor negatively affecting OS ($P = 0.033$), but not CSS ($P = 0.216$) before PSM. After PSM, the combined treatment did not predict the outcomes of patients.

Some limitations of the current study should be acknowledged. First, this research was designed as a retrospective analysis, and the selection bias was inevitable. However, the bias was reduced by employing the PSM model. Second, this study was population-based, liver function and physical condition of the patients were not consistently from the SEER data, and these factors might affect the patient outcomes. However, in contrast to previously published research, the present study included a large number of subjects, which strengthens the reliability of the results. Future randomized clinical trials are needed to confirm the results reported here.

Conclusions

Radiotherapy might provide more survival benefits for HCC patients who had received or will undergo liver resection, regardless of the stage of the disease.

Abbreviations

HCC Hepatocellular carcinoma

SEER Surveillance, Epidemiology, and End Results

PSM Propensity score matching

OS Overall survival

CSS Cancer-specific survival

AJCC American Joint Committee on Cancer

EASL European Association for the Study of the Liver

RFA Radiofrequency ablation

TACE Transarterial chemoembolization

Declarations

Ethics approval and consent to participate

This study does not need to be reviewed by the ethics committee because the data used in the study were from SEER database and the written informed consent was exempted. However, the data was permitted to be used in the study by the SEER database management department (12577-Nov2019).

Consent for publication

All authors approve the manuscript for publication.

Availability of data and materials

The data used in this study can be got from the SEER database. (<https://seer.cancer.gov/data/>)

Competing interests

The authors declared that there was no competing interests existing.

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Authors' contributions

Chuansheng Zheng and Fan Yang designed the work. Lei Chen acquired the data from the SEER database. Lei Chen and Xiaopeng Guo, and Shi Chen analyzed the data. Lei Chen, Shi Chen, Yanqiao Ren, and Tao Sun wrote the manuscript. Chuansheng Zheng, Fan Yang, and Xiaopeng Guo reviewed the manuscript. All authors approved the version to be published.

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Figures

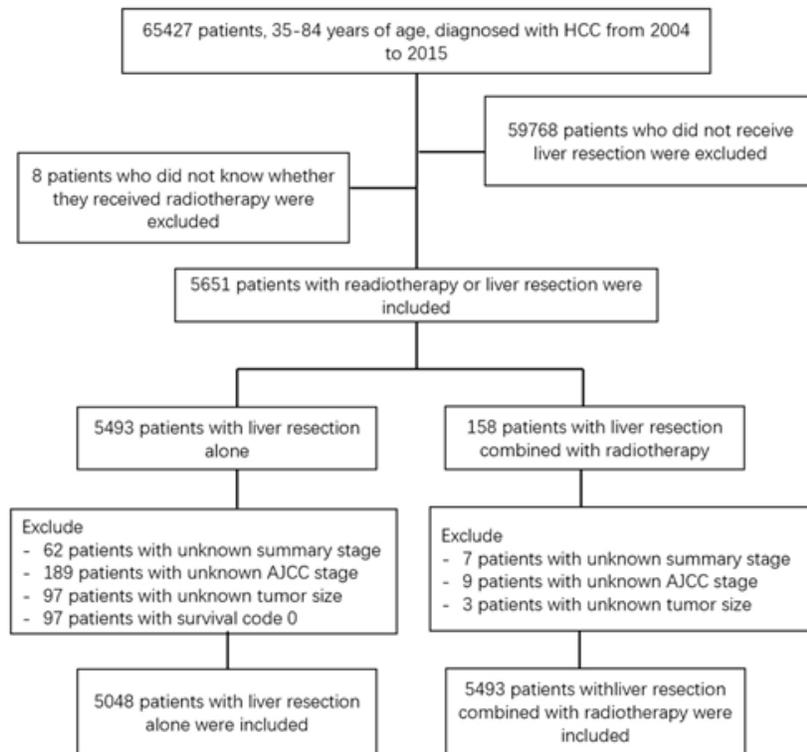


Figure 1

Flowchart of patients selection

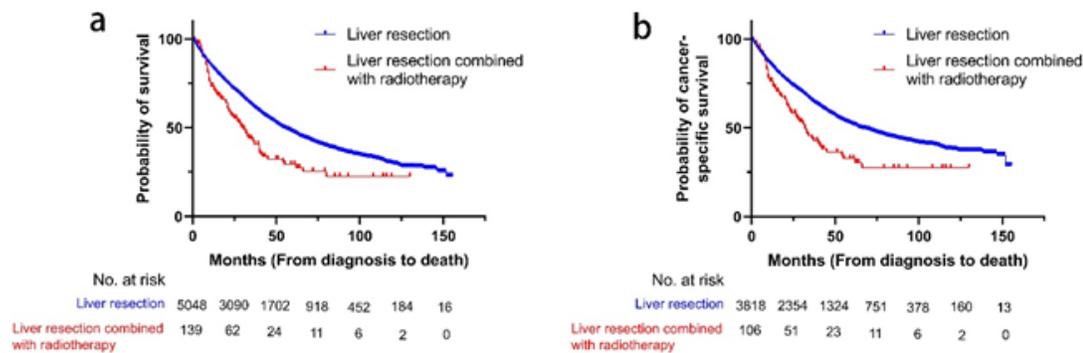


Figure 2

Kaplan-Meier curve of OS and CSS of all patients before PSM. (a) Kaplan-Meier curve of OS; (b) Kaplan-Meier curve of CSS

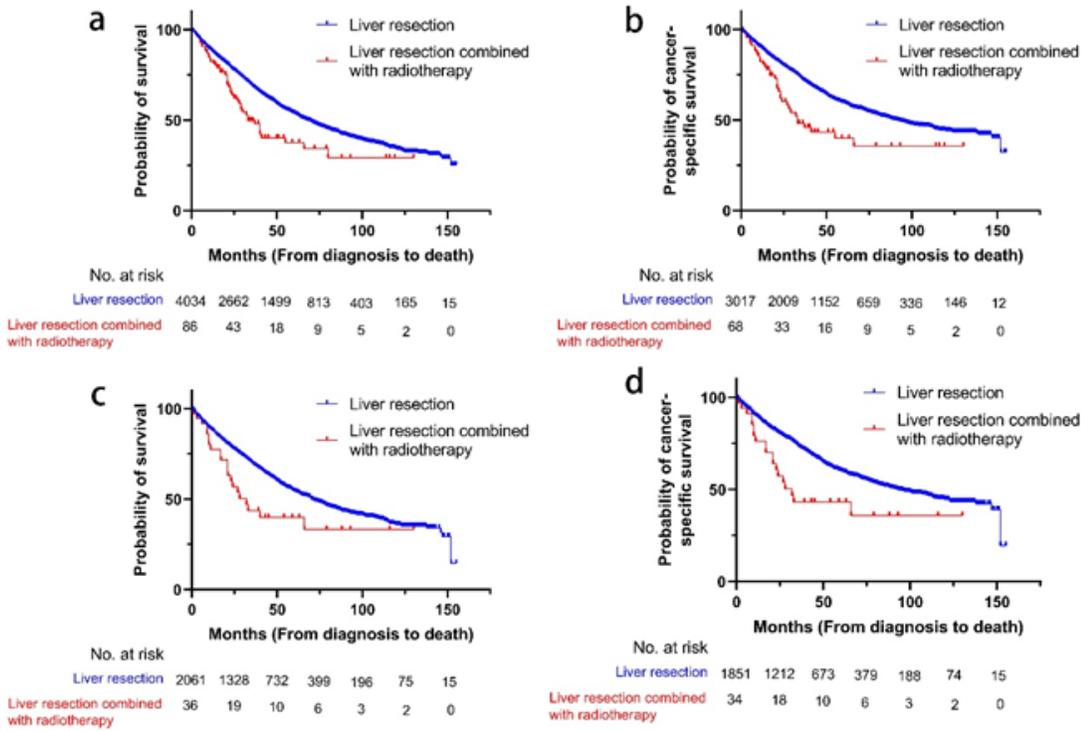


Figure 3

Kaplan-Meier curve of OS and CSS of patients in the subgroups before PSM. (a-b) Kaplan-Meier curve of OS and CSS of patients with AJCC stage I and II; (c-d) Kaplan-Meier curve of OS and CSS of patients with single tumor no more than 5 cm

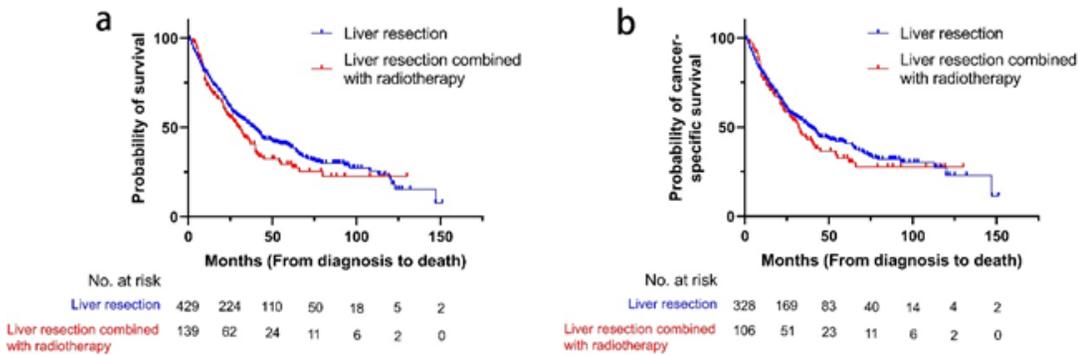


Figure 4

Kaplan-Meier curve of OS and CSS of all patients after PSM. (a) Kaplan-Meier curve of OS; (b) Kaplan-Meier curve of CSS

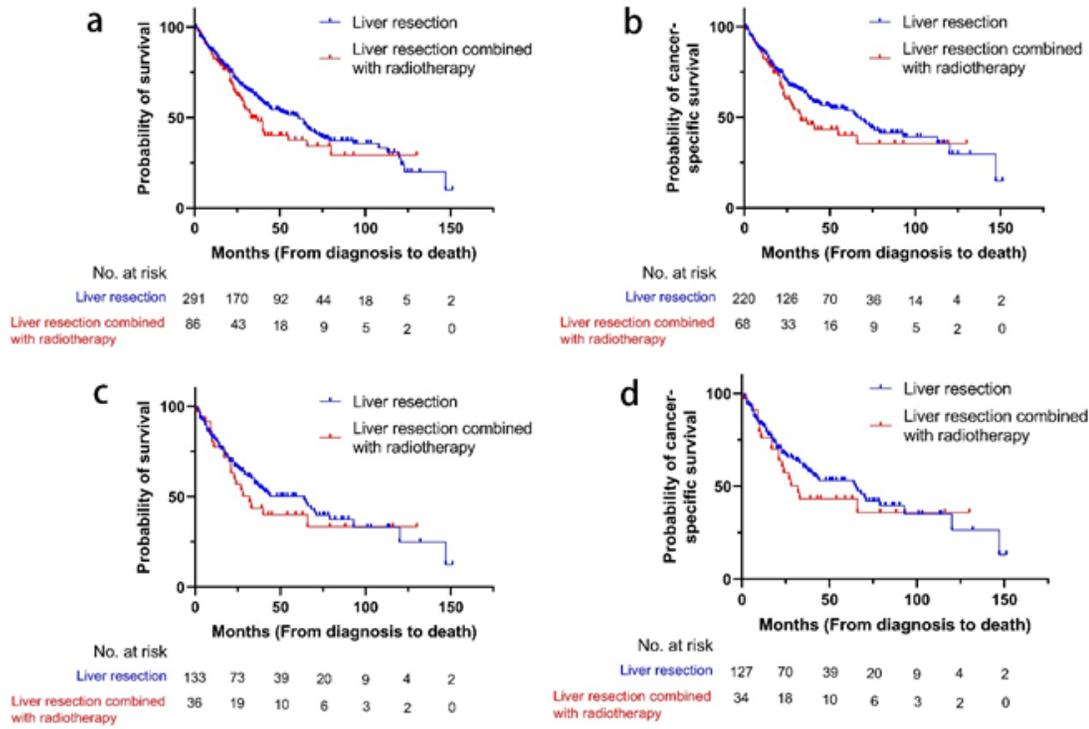


Figure 5

Kaplan-Meier curve of OS and CSS of patients in the subgroups after PSM. (a-b) Kaplan-Meier curve of OS and CSS of patients with AJCC stage I and II; (c-d) Kaplan-Meier curve of OS and CSS of patients with single tumor no more than 5 cm