Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Assessing the Survival Benefit of Surgery and Various Types of Radiation Therapy for Treatment of Hepatocellular Carcinoma: Evidence from the Surveillance, Epidemiology, and End Results Registries

This article was published in the following Dove Press journal:
Journal of Hepatocellular Carcinoma

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Objective: To evaluate the survival benefit of surgery and radiation for hepatocellular carcinoma (HCC) after adjusting for patient-specific and tumor-specific factors.

Methods: This study analyzed HCC patients who enrolled in the Surveillance, Epidemiology, and End Results (SEER) registry between January 2004 and December 2013. Of the 5552 HCC patients, 4597 received surgery and 955 received radiation. Patients who received radiation were further divided into 3 subgroups: 541 who received beam radiation (BR), 197 who received radioactive implants (RI), and 217 who received radioisotopes (RIT). Propensity score weighting analysis derived from generalized boosted models (GBMs) was performed to ensure well-balanced characteristics in all comparison groups.

Results: Overall survival rates and HCC-specific survival rates were higher in those receiving surgery compared with those receiving radiotherapy. This was confirmed by Cox proportional hazard regression both before and after inverse probability of treatment weighting (IPTW). Before IPTW, the RIT group had a better outcome than the BR group in terms of overall and HCC-specific survival rates, but there was no significant difference between the RI and BR groups. After IPTW, Cox proportional hazard regression demonstrated that both the RIT and RI groups had higher survival rates than the BR group.

Conclusion: In HCC patients, surgery was associated with higher survival rates compared with radiotherapy while adjusting for other factors. Among those who received radiotherapy, RIT and RI granted survival benefits.

Keywords: hepatocellular carcinoma, survival analysis, propensity score, generalized boosted models, inverse probability of treatment weighting, Cox proportional hazard models

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related modality worldwide and the fifth most common malignant neoplasm.[1,2] However, the overall prognosis for patients with HCC is unsatisfactory with a 5-year survival rate of less than 5%, which is further reduced in patients who do not receive any liver-specific therapy.[2] In recent years, many studies have identified locoregional treatment options specifically targeting intrahepatic lesions, including surgical resection, chemotherapy, and radiotherapy, as favorable factors affecting HCC prognosis and long-term survival.[3,4] However, these studies have not taken into account the

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DovePress
http://doi.org/10.2147/JHC.S272813

confounding socio-demographic and clinical predictors on the population level. In addition, there are currently no studies in the literature that specifically investigate the survival benefits of surgery and radiation therapy among HCC patients with adjustment for patient-specific and tumor-specific factors. There is also a lack of data further suggesting which type of radiation treatment is most effective if patients only receive radiation.

The purpose of this retrospective study was to use data from the Surveillance, Epidemiology, and End Results (SEER) registry to evaluate the survival benefits of surgery and radiotherapy in patients with HCC while adjusting for other potential confounding patient-specific and tumor-specific factors. To correct for selection bias and other potential confounders, we adopted the approach of inverse probability of treatment weighting (IPTW)[5–7] as an alternative to conventional survival analysis methods. In addition to analyzing the original SEER sample, this approach created a so-called "pseudo-sample" to estimate a weighted effect on the time-to-event outcomes of both overall survival and HCC-specific survival. In the pseudo-sample, patients from the original sample were assigned a weight derived from the IPTW. An IPTW Kaplan-Meier estimator was used to estimate survival curves, and IPTW Cox proportional hazard models were fit to the SEER data to estimate hazard ratios.[8–10] SEER registry patients who received radiotherapy were further divided into 3 subgroups according to the type of radiation therapy they received: beam radiation, radioactive implants, or radioisotopes. Our study evaluated and compared the survival benefit of each type of radiation therapies among these patients.

Methods

Data

The SEER database, hosted by the National Cancer Institute in the National Institutes of Health, is the largest publicly available cancer dataset in the United States and provides cancer incidence, treatment, and survival data from population-based cancer registries. Specifically, the SEER 9 registry database (1975–2013) was the data source for this study. Patients with pathologically confirmed HCC lesions who enrolled in the registry between 2004 to 2013 were identified by ICD-O-3 histology codes 8170/3-8175/3, combined with the liver site codes C22.0.[9] A total of 18,514 HHC patients were identified, then limited to those who only received surgery or radiation treatment. Exclusion criteria included (i) diagnosis at autopsy; (ii) diagnosis by death certificates only; (iii) surgery not recommended; (iv) age <20 years; (v) T0 stage, or unknown T, N, or M stage; and (vi) radiation therapy other than beam radiation, radioactive implants, or radioisotopes. Finally, a total number of 5552 patients were included in our study, consisting of 4597 who received surgery and 955 who received radiation therapy. Of the 955 patients who received radiation therapy, 541 received beam radiation (BR), 197 received radioactive implants (RI), and 217 received radioisotopes (RIT).

This study was approved by the Ethics Review Board of Weifang Medical University and conformed to the provisions of the Declaration of Helsinki.

Statistical Analysis

Propensity score weighting analysis derived from generalized boosted models (GBMs) has been approved as an effective analysis approach to reduce baseline bias and to compare long-term survival in different groups.[10–13] Therefore, we adopted it as our primary analysis approach to assess and compare the survival rates of HCC patients who received either surgery or radiation treatment. The covariates potentially associated with treatment selection, including age, gender, race, marital status, tumor size, tumor grade, T stage, M stage, N stage, and disease extent condition, were included in the generation of propensity scores. GBMs with these covariates were used to generate a continuous propensity score and estimate the probability that a patient would undergo surgery or radiation; then, propensity score weighting analysis was conducted with these generated propensity scores. The absolute standardized mean difference (ASMD) or the Kolmogorov–Smirnov (KS) statistic was taken as the stopping rule for the complexity of the GBM.[10,14] ASMD values greater than 0.2 were considered to be indicative of moderate imbalance while KS values greater than 0.10 were considered to be indicative of imbalance. The ASMD and the KS distances were used to measure balance between the different groups for each pretreatment covariate.

Baseline characteristics of the different treatment groups were compared and evaluated by the chi-square test or the Mantel-trend test for categorical variables in the original sample. To minimize the impact of selection bias and other potential confounders, a pseudo-sample was created by rigorous adjustment using IPTW of the propensity scores.[15,16] The propensity scores were estimated by the GBMs to predict the probability of a patient undergoing each treatment. The following methods were

employed to estimate overall survival rates: IPTW Kaplan-Meier estimator for estimating survival curves and IPTW Cox proportional hazard models for estimating hazard ratios.[17–19] All significance tests were two-tailed, and P values less than 0.05 were considered statistically significant. All statistical analyses were conducted in the R software environment (version 3.5.0). The GBM propensity score weights were obtained using the Toolkit for Weighting and Analysis of Nonequivalent Groups package.[14] R package "coxphw" was used to conduct IPTW Cox proportional hazard regression.[19,20]

Results

Demographic and Clinical Characteristics of the Original Sample and the Pseudo-Sample at Baseline

Among the 5552 HCC patients included in this study, the median (25% quantile and 75% quantile) follow-up periods were 21.0 (8.0 and 45.0), 26.0 (11.0 and 51.0), and 7.0 (3.0 and 15.0) months in the entire sample, surgery, and radiation groups, respectively. The mean (standard deviation) ages of the entire sample, surgery, and radiation groups were 61.76 (10.78), 63.56 (11.01), and 61.39 (10.69) years, respectively. Among the 955 radiation patients, the median (25% quantile and 75% quantile) follow-up period was 5.0 (2.0 and 12.0), 8.0 (4.0 and 15.0), and 9.0 (5.0 and 20.0) months in the BR, RI, and RIT groups, respectively.

Baseline demographic and clinical characteristics of the HCC patients are listed in Table 1. Before IPTW analysis in the original sample, the surgery and radiation groups took significantly different proportions in the categories of all covariates, except for marital status (P = 0.193). However, after IPTW balancing in the pseudo-sample, the two groups took similar proportions (no significant difference was detected in proportions) in the categories of all covariates (Table 1).

Baseline characteristics of the 955 patients in the radiation group are summarized in Table 2. Before IPTW analysis in the original sample, the 3 radiation groups had similar proportions in the categories of age, gender, race, and marital status. However, a significant difference was recognized for tumor size (P = 0.002), tumor grade (P = 0.031), T stage (P < 0.001), N stage (P < 0.001), M stage (P < 0.001), and disease extent condition (P < 0.001). After IPTW balancing in the pseudo-sample, the 3 radiation treatment groups took the similar proportion in the categories of all covariates (Table 2).

Survival in the Original Sample

Figure 1 shows both the unadjusted (without propensity score IPTW) and adjusted (with propensity score IPTW) estimated 5-year Kaplan-Meier overall survival curves and HCC-specific survival curves between the surgery and radiation groups. Table 3 shows the analysis results derived from Cox proportional hazard regression (hazard ratios, their 95% confidence intervals or CIs, and P values) for all-cause mortality and HCC-specific mortality in the original sample; Table 4 displays these results in the pseudo-sample.

In the original sample, the mortality rates were 45.7% in the surgery group (2100 patients died during the study period) and 71.0% in the radiation group (678 patients died). The overall survival rates at the end of the 1st, 3rd, and 5th years were 82.6%, 58.4% and 44.7%, respectively, in the surgery group, and were 37.9%, 15.0%, and 7.7%, respectively, in the radiation group (Figure 1A). Corresponding median survival times were 51 months in the surgery group and 9 months in the radiation group. The results obtained from the Cox proportional hazard regression revealed that the patients who received surgery gained significant benefits in terms of survival rates, compared with the patients who received radiation (all-cause mortality hazard ratio, 0.48; CI, 0.43–0.54). While HCC-specific survival rates at the 1st, 3rd, and 5th years were 88.5%, 71.1%, and 60.6%, respectively, in the surgery group, they were 47.5%, 24.4%, and 15.0%, respectively, in the radiation group (Figure 1B). Corresponding HCC-specific median survival times were 105 months in the surgery group and 11 months in the radiation group. Analysis results from Cox proportional hazard regression revealed that the HCC-specific survival rate in the surgery group was still superior to that in the radiation group (HCC-specific mortality hazard ratio, 0.44; CI 0.38–0.50; P < 0.001).

The following covariates were risk factors for HCC-specific mortality: age 40 to 59 years (versus age 20–39 years; hazard ratio, 1.50; CI, 1.09–2.05; P = 0.012), age 60 to 79 years (versus age 20–39 years; hazard ratio, 1.49; CI, 1.08–2.04; P = 0 0.014), male (versus female; hazard ratio, 1.14; CI, 1.10–1.40; P < 0.001), black race (versus white; hazard ratio, 1.16; CI, 1.01–1.32; P = 0.032), single (never married) social status (versus married social status; hazard ratio, 1.32; CI, 1.16–1.50; P < 0.001), separated social status (versus married social status; hazard ratio, 1.90; CI, 1.34–2.70; P < 0.001), divorced social status (versus married social

Table 1 Baseline Demographic and Clinical Characteristics of Patients Before and After Inverse Probability of Treatment Weighting (IPTW)

Variable	Before IPTW (n=5552)		P value	After IPTW		Minimum P value
	Surgery (n=4597, %)	Radiation (n=955, %)		Surgery (%)	Radiation (%)	
Age group			<0.001			0.078
20–39	106 (2.3)	15 (1.6)		(2.1)	(0.6)	
40–59	2021 (44.0)	359 (37.6)		(43.2)	(42.6)	
60–79	2225 (48.4)	490 (51.3)		(48.9)	(50.7)	
≥80	245 (5.3)	91 (9.5)		(5.7)	(6.1)	
Gender			<0.001			0.163
Female	1125 (24.5)	176 (18.4)		(23.4)	(20.0)	
Male	3472 (75.5)	779 (81.6)		(76.6)	(80.0)	
Race			<0.001			0.371
White	2880 (62.6)	648 (67.9)		(62.8)	(67.2)	
Black	575 (12.5)	166 (17.4)		(14.1)	(14.8)	
Chinese	351 (7.6)	19 (2.0)		(6.7)	(5.4)	
Others	791 (17.2)	122 (12.8)		(16.4)	(12.6)	
Marital status			0.193			0.662
Married/domestic partner	2660 (57.9)	549 (57.5)		(58.9)	(60.5)	
Single (never married)	790 (17.2)	176 (18.4)		(17.2)	(18.2)	
Separated	64 (1.4)	7 (0.7)		(1.2)	(0.7)	
Divorced	552 (12.0)	127 (13.3)		(11.7)	(11.5)	
Widowed	348 (7.6)	69 (7.2)		(7.2)	(5.4)	
Other/unknown	183 (4.0)	27 (2.8)		(3.7)	(3.8)	
Tumor size(cm)			<0.001			0.629
<3.0	1936 (42.1)	157 (16.4)		(37.9)	(34.7)	
3.0–4.9	1289 (28.0)	183 (19.2)		(26.5)	(26.1)	
5.0–10.0	781 (17.0)	296 (31.0)		(19.2)	(22.6)	
>10.0	374 (8.1)	143 (15.0)		(9.4)	(9.4)	
unknown	217 (4.7)	176 (18.4)		(7.1)	(7.2)	
Grade			<0.001			0.060
Grade I	797 (17.3)	88 (9.2)		(15.8)	(14.0)	
Grade II	1458 (31.7)	126 (13.2)		(28.6)	(23.2)	
Grade III	467 (10.2)	68 (7.1)		(9.7)	(9.9)	
Grade IV	39 (0.8)	1 (0.1)		(0.7)	(0.0)	
Unknown grade	1836 (39.9)	672 (70.4)		(45.3)	(52.9)	
T stage			<0.001			0.902
T1	2664 (58.0)	292 (30.6)		(53.2)	(51.9)	
T2	1303 (28.3)	180 (18.8)		(26.8)	(26.2)	
T3	404 (8.8)	316 (33.1)		(13.6)	(14.4)	
T4	94 (2.0)	44 (4.6)		(2.3)	(2.9)	
TX	132 (2.9)	123 (12.9)		(4.1)	(4.5)	
N stage			<0.001			0.849
N0	4325 (94.1)	720 (75.4)		(90.9)	(90.4)	
N1	78 (1.7)	97 (10.2)		(3.0)	(3.4)	
NX	194 (4.2)	138 (14.5)		(6.2)	(6.2)	
M stage			<0.001			0.488
M0	4422 (96.2)	581 (60.8)		(90.8)	(89.3)	
M1	85 (1.8)	346 (36.2)		(7.2)	(8.9)	

(*Continued*)

Table 1 (Continued).

Variable	Before IPTW (n=5552)		P value	After IPTW		Minimum P value
	Surgery (n=4597, %)	Radiation (n=955, %)		Surgery (%)	Radiation (%)	
MX	90 (2.0)	28 (2.9)		(2.0)	(1.8)	
Disease extent condition			<0.001			0.433
Localized	3594 (78.2)	311 (32.6)		(70.9)	(67.9)	
Regional	824 (17.9)	279 (29.2)		(19.8)	(21.6)	
Distant	108 (2.3)	350 (36.6)		(7.7)	(9.3)	
Unstaged	71 (1.5)	15 (1.6)		(1.6)	(1.2)	

status; hazard ratio, 1.32; CI, 1.14–1.53; P < 0.001), widowed social status (versus married social status; hazard ratio, 1.51; CI, 1.26–1.83; P < 0.001), tumor size level 3.0 to 4.9 cm (versus <3.0 cm; hazard ratio, 1.47; CI, 1.29–1.69; P < 0.001), tumor size level 5.0 to 10.0 cm (versus <3.0cm; hazard ratio, 1.57; CI, 1.35–1.83; P < 0.001), tumor size level >10.0 cm (versus <3.0cm; hazard ratio, 2.26; CI, 1.90–2.69; P < 0.001), grade III (versus grade I; hazard ratio, 1.78; CI, 1.47–2.16; P < 0.001), T2 (versus T1; hazard ratio, 1.14; CI, 1.01–1.29; P =0.039), T3 (versus T1; hazard ratio, 1.70; CI, 1.44–2.00; P < 0.001), M1 (versus M0; hazard ratio, 1.63; CI, 1.06–2.50; P = 0.026), regional disease extent (versus localized status; hazard ratio, 1.41; CI, 1.24–1.62; P < 0.001), and distant disease extent (versus localized status; hazard ratio, 1.91; CI, 1.24–2.96; P = 0 0.003).

Survival in the Pseudo-Sample

After IPTW, the patients in the pseudo-sample were well-balanced across the surgery and radiation groups (Table 1). The overall survival rates in the surgery group at the 1st, 3rd, and 5th years were 78.2%, 53.4%, and 40.0%, respectively, and were 56.0%, 28.0%, and 15.8%, respectively, in the radiation group (Figure 1A). Corresponding median survival times were 43 months in the surgery group and 17 months in the radiation group. Analysis results obtained from the IPTW Cox proportional hazard regression demonstrated that the surgery group was superior to the radiation group in terms of all-cause mortality rates in the pseudo-sample (Figure 1B, Table 4). The HCC-specific survival rates at the 1st, 3rd, and 5th years were 84.2%, 65.7%, and 55.1%, respectively, in the surgery group, and were 65.9%, 38.2%, and 26.0%, respectively, in the radiation group. Corresponding HCC-specific median survival times were 83 months in the surgery group and 24 months in the radiation group. The IPTW Cox proportional hazard regression showed a significant difference in HCC-specific mortality rates between the two groups (Table 4).

We discovered that the following covariates were risk factors for HCC-specific mortality: age 40–59 years (hazard ratio, 1.53; CI, 1.06–2.21; P = 0.024), single (never married) social status (versus married social status; hazard ratio, 1.35; CI, 1.05–1.73; P = 0.021), separated social status (versus married social status; hazard ratio, 1.74; CI, 1.03–2.94; P = 0.039), divorced social status (versus married social status; hazard ratio, 1.32; CI, 1.05–1.65; P = 0.018), widowed social status (versus married social status; hazard ratio, 1.48; CI, 1.14–1.92; P= 0.003), grade III (versus grade I; hazard ratio, 1.81; CI, 1.18–2.76; P = 0.006), T3 (versus T1; hazard ratio, 1.70; CI, 1.29–2.24; P < 0.001), and T4 (versus T1; hazard ratio, 2.13; CI, 1.05–4.32; P = 0.035). In addition, tumor size level was significantly associated with an increased HCC-specific mortality (Table 4).

Survival in the 3 Radiation Subgroups

Figure 2 shows both the unadjusted (without propensity score IPTW) and adjusted (with propensity score IPTW) estimated 5-year Kaplan-Meier HCC-specific survival curves among the 3 radiation groups. Table 5 shows the analysis results derived from Cox proportional hazard regression (hazard ratios, their 95% CIs and P values) for all-cause mortality and HCC-specific mortality in the 3 original radiation subgroups; Table 6 displays these results in the pseudo-sample subgroups.

In the 3 original sample radiation subgroups, the mortality rates were 81.1% in the BR group (439 patients died during the study period), 59.9% in the RI group (118 patients died), and 55.8.0% in the RIT group (121 patients died). The overall survival rates at the end of the 1st, 3rd, and 5th years were 27.9%, 10.4%, and 3.5%, respectively, in the BR group; 46.0%, 14.8%, and 4.9%, respectively, in

Table 2 Clinical Characteristics of Radiation Patients Before and After Inverse Probability of Treatment Weighting (IPTW)

Variable	Before IPTW (n = 955)				After IPTW			
	BR (n = 541, %)	RI (n = 197, %)	RIT (n = 217, %)	P value	BR (%)	RI (%)	RIT (%)	Minimum P value
Age				0.413				0.384
20–39	11 (2.0)	2 (1.0)	2 (0.9)		(1.6)	(1.5)	(1.0)	
40–59	210 (38.8)	64 (32.5)	85 (39.2)		(37.5)	(33.9)	(33.2)	
60–79	265 (49.0)	112 (56.9)	113 (52.1)		(51.8)	(56.8)	(59.7)	
≥80	55 (10.2)	19 (9.6)	17 (7.8)		(9.2)	(7.8)	(6.0)	
Gender				0.338				0.161
Female	91 (16.8)	41 (20.8)	44 (20.3)		(18.8)	(21.8)	(15.3)	
Male	450 (83.2)	156 (79.2)	173 (79.3)		(81.2)	(78.2)	(84.7)	
Race				0.151				0.118
White	362 (66.9)	139 (70.6)	147 (67.7)		(69.8)	(71.4)	(78.1)	
Black	95 (17.6)	36 (18.3)	35 (16.1)		(16.7)	(15.7)	(11.5)	
Chinese	9 (1.7)	1 (0.5)	9 (4.1)		(1.3)	(1.0)	(1.5)	
Others	75 (13.9)	21 (10.7)	26 (12.0)		(12.2)	(11.9)	(8.9)	
Marital status				0.378				0.513
Married/domestic partner	298 (55.1)	114 (57.9)	137 (63.1)		(58.6)	(63.0)	(67.1)	
Single (never married)	109 (20.1)	36 (18.3)	31 (14.3)		(18.3)	(16.2)	(16.9)	
Separated	5 (0.9)	1 (0.5)	1 (0.5)		(0.8)	(0.3)	(0.3)	
Divorced	73 (13.5)	22 (11.2)	32 (14.7)		(12.8)	(11.6)	(9.9)	
Widowed	39 (7.2)	16 (8.1)	14 (6.5)		(7.3)	(7.2)	(4.6)	
Other/unknown	17 (3.1)	8 (4.1)	2 (0.9)		(2.2)	(1.6)	(1.1)	
Tumor size (cm)				0.002				0.857
<3	89 (16.5)	34 (17.3)	34 (15.7)		(16.2)	(16.5)	(14.2)	
3–4.9	94 (17.4)	40 (20.3)	49 (22.6)		(19.4)	(19.4)	(22.5)	
5–10	150 (27.7)	68 (34.5)	78 (35.9)		(30.8)	(30.0)	(34.8)	
>10	81 (15.0)	29 (14.7)	33 (15.2)		(15.1)	(15.3)	(13.7)	
Unknown	127 (23.5)	26 (13.2)	23 (10.6)		(18.5)	(18.7)	(14.9)	
Grade				0.031				0.872
Grade I	37 (6.8)	26 (13.2)	25 (11.5)		(8.2)	(9.9)	(10.1)	
Grade II	65 (12.0)	30 (15.2)	31 (14.3)		(13.1)	(13.1)	(12.9)	
Grade III/IV	47 (8.7)	10 (5.1)	12 (5.5)		(7.4)	(6.8)	(9.5)	
Unknown Grade	392 (72.5)	131 (66.5)	149 (68.7)		(71.4)	(70.1)	(67.5)	
T stage				<0.001				0.476
T1	183 (33.8)	50 (25.4)	59 (27.2)		(30.4)	(27.4)	(24.5)	
T2	76 (14.0)	45 (22.8)	59 (27.2)		(17.9)	(18.8)	(17.5)	
T3	154 (28.5)	82 (41.6)	80 (36.9)		(33.9)	(37.5)	(43.6)	
T4	30 (5.5)	7 (3.6)	7 (3.2)		(4.6)	(3.8)	(2.9)	
TX (99)	98 (18.1)	13 (6.6)	12 (5.5)		(13.2)	(12.5)	(11.5)	
N stage				<0.001				0.866
N0	368 (68.0)	170 (86.3)	182 (83.9)		(75.1)	(77.6)	(73.1)	
N1	64 (11.8)	16 (8.1)	17 (7.8)		(10.2)	(9.8)	(11.6)	
NX	109 (20.1)	11 (5.6)	18 (8.3)		(14.6)	(12.7)	(15.3)	
M stage				<0.001				0.314
M0	210 (38.8)	171 (86.8)	200 (92.2)		(59.0)	(68.2)	(66.7)	
M1	320 (59.1)	18 (9.1)	8 (3.7)		(38.2)	(28.6)	(30.3)	
MX	11 (2.0)	8 (4.1)	9 (4.1)		(2.8)	(3.2)	(3.0)	
Disease extent condition				<0.001				0.345
Localized	132 (24.4)	85 (43.1)	94 (43.3)		(31.8)	(37.1)	(33.7)	

(*Continued*)

Table 2 (Continued).

Variable	Before IPTW (n = 955)				After IPTW			
	BR (n = 541, %)	RI (n = 197, %)	RIT (n = 217, %)	P value	BR (%)	RI (%)	RIT (%)	Minimum P value
Regional	78 (14.4)	91 (46.2)	110 (50.7)		(28.1)	(33.0)	(33.5)	
Distant	323 (59.7)	17 (8.6)	10 (4.6)		(38.6)	(28.7)	(31.3)	
Unstaged	8 (1.5)	4 (2.0)	3 (1.4)		(1.5)	(1.3)	(1.6)	

Abbreviations: BR, beam radiation; RI, radioactive implants; RIT, radioisotopes.

the RI group; and 52.6%, 25.8%, and 12.0%, respectively, in the RIT group. Corresponding median survival times were 6.11, and 14 months in the BR, RI, and RIT groups, respectively. The results obtained from the Cox proportional hazard regression revealed that the patients who received RIT gained significant benefits in terms of survival rates, compared with the patients who received BR (all-cause mortality hazard ratio, 0.68; CI 0.54–0.87; P=0.002); however, there were no significant superior benefits among patients who received RI compared with those who received BR (all-cause mortality hazard ratio, 0.86; CI 0.68–1.08; P=0.191). The HCC-specific survival rates at the 1st, 3rd, and 5th years were 36.6%, 17.5%, and 10.2%, respectively, in the BR group; 58.3%, 26.7%, and 10.7%, respectively, in the RI group; and 61.1%, 38.4%, and 35.6%, respectively, in the RIT group (Figure 2A). Corresponding HCC-specific median survival times were 8.17, and 23 months in the BR, RI, and RIT groups, respectively. Analysis results from Cox proportional hazard regression revealed that the HCC-specific survival rate in the RIT group was still superior to that in the BR group (HCC-specific mortality hazard ratio, 0.69; CI 0.52–0.91; P = 0.008), and there were no significant benefits to HCC-specific survival rate in the RI group compared with the BR group (HCC-specific mortality hazard ratio, 0.85; CI 0.65–1.11; P = 0.227).

The following covariates were risk factors for HCC-specific mortality: tumor size level 3.0 to 4.9 cm (versus <3.0 cm; hazard ratio, 1.68; CI, 1.19–2.37; P = 0.003), tumor size level 5.0 to 10.0 cm (versus <3.0cm; hazard ratio, 1.69; CI, 1.19–2.39; P = 0.003), tumor size level >10.0 cm (versus <3.0cm; hazard ratio, 1.95; CI, 1.31–2.90; P =0.001), grade III (versus grade I; hazard ratio, 1.58; CI, 1.03–2.45; P = 0.038), T3 (versus T1; hazard ratio, 1.56; CI, 1.18–2.06; P = 0.002), and distant disease extent (versus localized status; hazard ratio, 3.28; CI, 1.35–7.95; P = 0.009).

After IPTW, the patients in the pseudo-sample were well-balanced across the 3 radiation groups (Table 2). Analysis results obtained from the IPTW Cox proportional hazard regression demonstrated that the RI and RIT groups were both superior to the BR group in terms of all-cause mortality rates in the pseudo-sample (Table 6). HCC-specific survival rates at the 1st, 3rd, and 5th years were 42.8%, 22.4%, and 7.8%, respectively, in the BR group; 47.5%, 21.6%, and 12.0%, respectively, in the RI group; and 52.9%, 33.5%, and 31.4%, respectively, in the RIT group. Corresponding HCC-specific median survival times were 10, 12, and 17 months in the BR, RI, and RIT groups, respectively. The IPTW Cox proportional hazard regression showed that the RIT and RI groups both outperformed the BR group in terms of HCC-specific mortality rates in the pseudo-sample (Figure 2B, Table 6).

We also discovered that the following covariates were risk factors for HCC-specific mortality: male (versus female; hazard ratio, 1.37; CI, 1.15–1.64; P =0.001), tumor size level 3.0 to 4.9 cm (versus <3.0 cm; hazard ratio, 1.83; CI, 1.46–2.29; P < 0.001), tumor size level 5.0 to 10.0 cm (versus <3.0cm; hazard ratio, 1.40; CI, 1.11–1.77; P = 0.004), tumor size level >10.0 cm (versus <3.0cm; hazard ratio, 1.97; CI, 1.52–2.56; P < 0.001), T2 (versus T1; hazard ratio, 1.31; CI, 1.10–1.65; P = 0.004), T3 (versus T1; hazard ratio, 2.19; CI, 1.81–2.64; P < 0.001), N1 (versus N0; hazard ratio, 0.62; CI, 0.50–0.77; P < 0.001), and distant disease extent (versus localized status; hazard ratio, 2.12; CI, 1.21–3.72; P = 0 0.008). The male risk factor was not identified in the unadjusted Cox proportional hazard regression.

Discussion

Surgical resection and liver transplantation are the main curative treatments for HCC. Unfortunately, only 20% to 30% of HCC patients, mostly diagnosed by regular screening, may benefit from these therapies.[21,22] While surgical resection remains the primary treatment approach to HCC, it is not always feasible due to patient comorbidities or tumor characteristics. In this circumstance, radiotherapy becomes an alternative. Tumor location is a factor

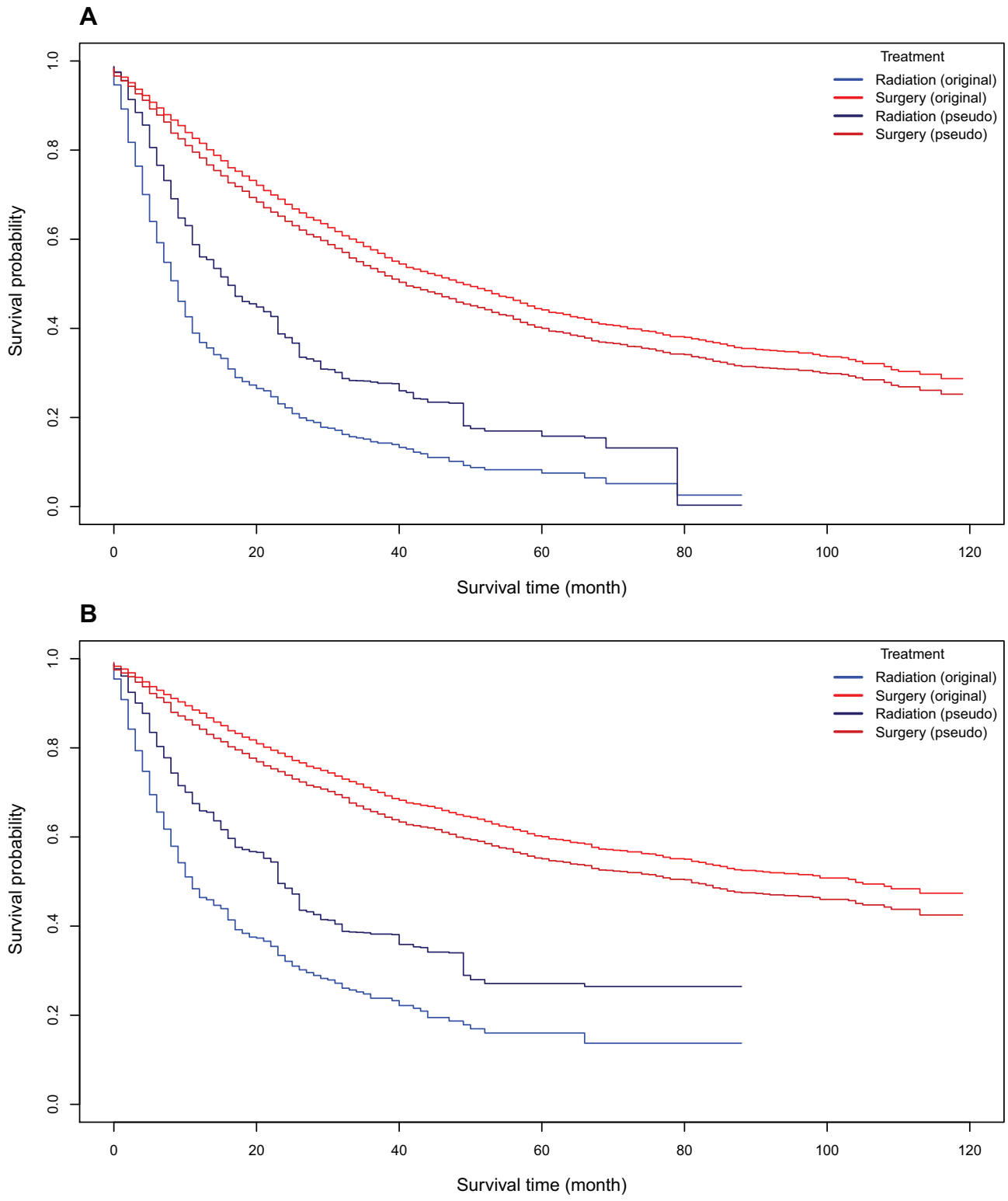

Figure 1 Overall and HCC-specific Kaplan-Meier survival curves for the original and pseudo samples. Panel (**A**) Overall Kaplan–Meier survival curves for the original and pseudo samples. Panel (**B**) HCC-specific Kaplan–Meier survival curves in the original and pseudo samples.

restricting the success of other treatment therapies, such as ablation, but less so for radiotherapy, suggesting that radiation may provide a unique therapeutic opportunity.[23] While radiotherapy has emerged as an alternative treatment plan, however, debate still exists on which type of radiation therapy is superior.

Table 3 Hazard Ratios, Confidence Internals, and P values Obtained from Cox Proportional Hazard Models for All-Cause Mortality and HCC-Specific Mortality in the Original Sample

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment				
Radiation	Reference		Reference	
Surgery	0.48 (0.43–0.54)	< 0.001	0.44 (0.38–0.50)	< 0.001
Age				
20–39	Reference		Reference	
40–59	1.72 (1.28–2.29)	< 0.001	1.50 (1.09–2.05)	0.012
60–79	2.00 (1.50–2.69)	< 0.001	1.49 (1.08–2.04)	0.014
≥80	2.71 (1.97–3.74)	< 0.001	1.40 (0.96–2.03)	0.080
Gender				
Female	Reference		Reference	
Male	1.21 (1.10–1.33)	< 0.001	1.24 (1.10–1.40)	< 0.001
Race				
White	Reference		Reference	
Black	1.21 (1.09–1.35)	< 0.001	1.16 (1.01–1.32)	0.032
Chinese	0.65 (0.54–0.78)	< 0.001	0.87 (0.72–1.06)	0.174
Others	0.97 (0.87–1.07)	0.531	0.99 (0.86–1.12)	0.834
Marital status				
Married/domestic partner	Reference		Reference	
Single (never married)	1.27 (1.15–1.42)	< 0.001	1.32 (1.16–1.50)	< 0.001
Separated	1.58 (1.17–2.15)	0.003	1.90 (1.34–2.70)	< 0.001
Divorced	1.33 (1.18–1.50)	< 0.001	1.32 (1.14–1.53)	< 0.001
Widowed	1.44 (1.24–1.67)	< 0.001	1.51 (1.26–1.83)	< 0.001
Other/unknown	0.98 (0.80–1.20)	0.841	0.97 (0.75–1.26)	0.846
Tumor size (cm)				
<3.0	Reference		Reference	
3.0–4.9	1.42 (1.28–1.57)	< 0.001	1.47 (1.29–1.67)	< 0.001
5.0–10.0	1.49 (1.32–1.68)	< 0.001	1.57 (1.35–1.83)	0.000
>10.0	1.90 (1.64–2.19)	< 0.001	2.26 (1.90–2.69)	<0.001
Unknown	1.79 (1.50–2.14)	< 0.001	1.91 (1.54–2.38)	< 0.001
Grade				
Grade I	Reference		Reference	
Grade II	1.00 (0.88–1.13)	0.963	1.15 (0.98–1.36)	0.084
Grade III	1.41 (1.21–1.65)	< 0.001	1.78 (1.47–2.16)	< 0.001
Grade IV	1.12 (0.73–1.72)	0.606	1.30 (0.77–2.22)	0.329
Unknown grade	1.26 (1.12–1.42)	< 0.001	1.49 (1.27–1.73)	< 0.001
T stage				
T1	Reference		Reference	
T2	1.12 (1.01–1.24)	0.027	1.14 (1.01–1.29)	0.039
T3	1.50 (1.31–1.72)	< 0.001	1.70 (1.44–2.00)	< 0.001
T4	1.37 (1.07–1.75)	0.012	1.32 (0.99–1.77)	0.056
TX	1.11 (0.88–1.41)	0.387	1.19 (0.90–1.57)	0.222
N stage				
N0	Reference		Reference	
N1	1.04 (0.86–1.26)	0.694	1.18 (0.95–1.45)	0.127

(*Continued*)

Table 3 (Continued).

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
NX	1.30 (1.11–1.53)	0.001	1.39 (1.15–1.67)	0.001
M stage				
M0	Reference		Reference	
M1	1.68 (1.16–2.43)	0.006	1.63 (1.06–2.50)	0.026
MX	1.15 (0.87–1.52)	0.327	1.22 (0.88–1.70)	0.228
Disease extent condition				
Localized	Reference		Reference	
Regional	1.35 (1.21–1.51)	< 0.001	1.41 (1.24–1.62)	< 0.001
Distant	1.72 (1.18–2.49)	0.005	1.91 (1.24–2.96)	0.003
Unstaged	0.90 (0.63–1.30)	0.583	0.78 (0.50–1.21)	0.266

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, 95% confidence interval.

Table 4 Hazard Ratios, Confidence Internals, and P values Obtained from Cox Proportional Hazard Models for All-Cause Mortality and HCC-Specific Mortality in the Pseudo-Sample

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment				
Radiation	Reference		Reference	
Surgery	0.42 (0.36–0.49)	< 0.001	0.38 (0.31–0.46)	< 0.001
Age				
20–39	Reference		Reference	
40–59	1.69 (1.22–2.35)	0.002	1.53 (1.06–2.21)	0.024
60–79	1.73 (1.24–2.41)	0.001	1.29 (0.89–1.88)	0.175
≥80	2.01 (1.38–2.92)	< 0.001	0.96 (0.60–1.51)	0.846
Gender				
Female	Reference		Reference	
Male	1.27 (1.08–1.50)	0.005	1.23 (0.99–1.51)	0.062
Race				
White	Reference			
Black	1.10 (0.91–1.32)	0.322	0.92 (0.71–1.21)	0.564
Chinese	0.71 (0.44–1.15)	0.164	0.96 (0.57–1.64)	0.890
Others	0.83 (0.67–1.01)	0.063	0.79 (0.62–1.02)	0.066
Marital status				
Married/domestic partner	Reference		Reference	
Single (never married)	1.26 (1.04–1.52)	0.018	1.35 (1.05–1.73)	0.021
Separated	1.36 (0.81–2.29)	0.248	1.74 (1.03–2.94)	0.039
Divorced	1.26 (1.05–1.52)	0.015	1.32 (1.05–1.65)	0.018
Widowed	1.42 (1.17–1.74)	0.001	1.48 (1.14–1.92)	0.003
Other/unknown	1.16 (0.81–1.66)	0.408	0.73 (0.46–1.17)	0.190
Tumor size (cm)				
<3.0	Reference		Reference	
3.0–4.9	1.67 (1.38–2.02)	< 0.001	1.75 (1.34–2.29)	< 0.001

(*Continued*)

Table 4 (Continued).

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
5.0–10.0	1.81 (1.44–2.28)	< 0.001	1.86 (1.36–2.56)	< 0.001
>10.0	2.17 (1.62–2.91)	< 0.001	2.54 (1.77–3.66)	< 0.001
Unknown	2.33 (1.72–3.16)	< 0.001	2.55 (1.71–3.80)	< 0.001
Grade				
Grade I	Reference		Reference	
Grade II	0.90 (0.69–1.18)	0.437	1.14 (0.78–1.68)	0.492
Grade III	1.49 (1.09–2.05)	0.012	1.81 (1.18–2.76)	0.006
Grade IV	1.00 (0.54–1.85)	0.997	1.20 (0.58–2.46)	0.628
Unknown grade	1.12 (0.87–1.42)	0.380	1.34 (0.95–1.91)	0.099
T stage				
T1	Reference		Reference	
T2	1.17 (0.97–1.41)	0.101	1.14 (0.87–1.49)	0.348
T3	1.50 (1.20–1.88)	< 0.001	1.70 (1.29–2.24)	< 0.001
T4	2.03 (1.10–3.73)	0.023	2.13 (1.05–4.32)	0.035
TX	0.92 (0.64–1.33)	0.655	0.93 (0.60–1.42)	0.722
N stage				
N0	Reference		Reference	
N1	0.75 (0.55–1.02)	0.068	0.82 (0.59–1.15)	0.250
NX	1.28 (0.97–1.69)	0.087	1.44 (1.04–2.01)	0.029
M stage				
M0	Reference		Reference	
M1	1.93 (1.04–3.58)	0.038	1.98 (0.96–4.06)	0.063
MX	0.93 (0.58–1.50)	0.760	0.93 (0.54–1.60)	0.781
Disease extent condition				
Localized	Reference		Reference	
Regional	1.23 (1.03–1.48)	0.024	1.22 (0.97–1.53)	0.097
Distant	1.33 (0.69–2.56)	0.392	1.42 (0.67–3.04)	0.363
Unstaged	0.89 (0.52–1.52)	0.664	0.72 (0.38–1.36)	0.305

Abbreviations: HCC, hepatocellular carcinoma; HR: hazard ratio; CI: 95% confidence interval.

In this study, a SEER registry sample of 5552 HCC patients was identified for the purpose of comparing overall survival and HCC-specific survival rates between patients who received surgery and patients who received radiotherapy. Of these 5552 patients, 82.8% received surgery, 9.7% received BR, 3.9% received RIT, and 3.5% received RI. Prior to IPTW, survival rates in the surgery group were superior to the radiation groups in both overall survival rate and HCC-specific survival rate. Cox proportional hazard regression both before and after IPTW confirmed that surgery was associated with higher survival rates compared with radiotherapy. Among the patients who received radiotherapy, those who received RIT or RI had better survival outcomes than those who received BR. Despite the obvious benefits from surgery that have been reported previously,[24,25] other studies using SEER registry data have found that nearly 50% of HCC patients who met Milan criteria[26] for transplantation received only supportive care, and there was an apparent underutilization of surgical therapy in patients with HCC.[27,28] In addition, Komatsu et al[29] reported that particle radiotherapy is potentially preferable in HCC patients with stage IIIB inferior vena cava tumor thrombus and at least equal in efficiency to liver resection in those with stage IV disease.

For patients receiving radiation treatment, our study demonstrated a lower overall survival rate at the end of the 1st year (37.9%) than that reported in a previous study by Rim et al.[30] McIntosh et al[31] analyzed 20 patients with

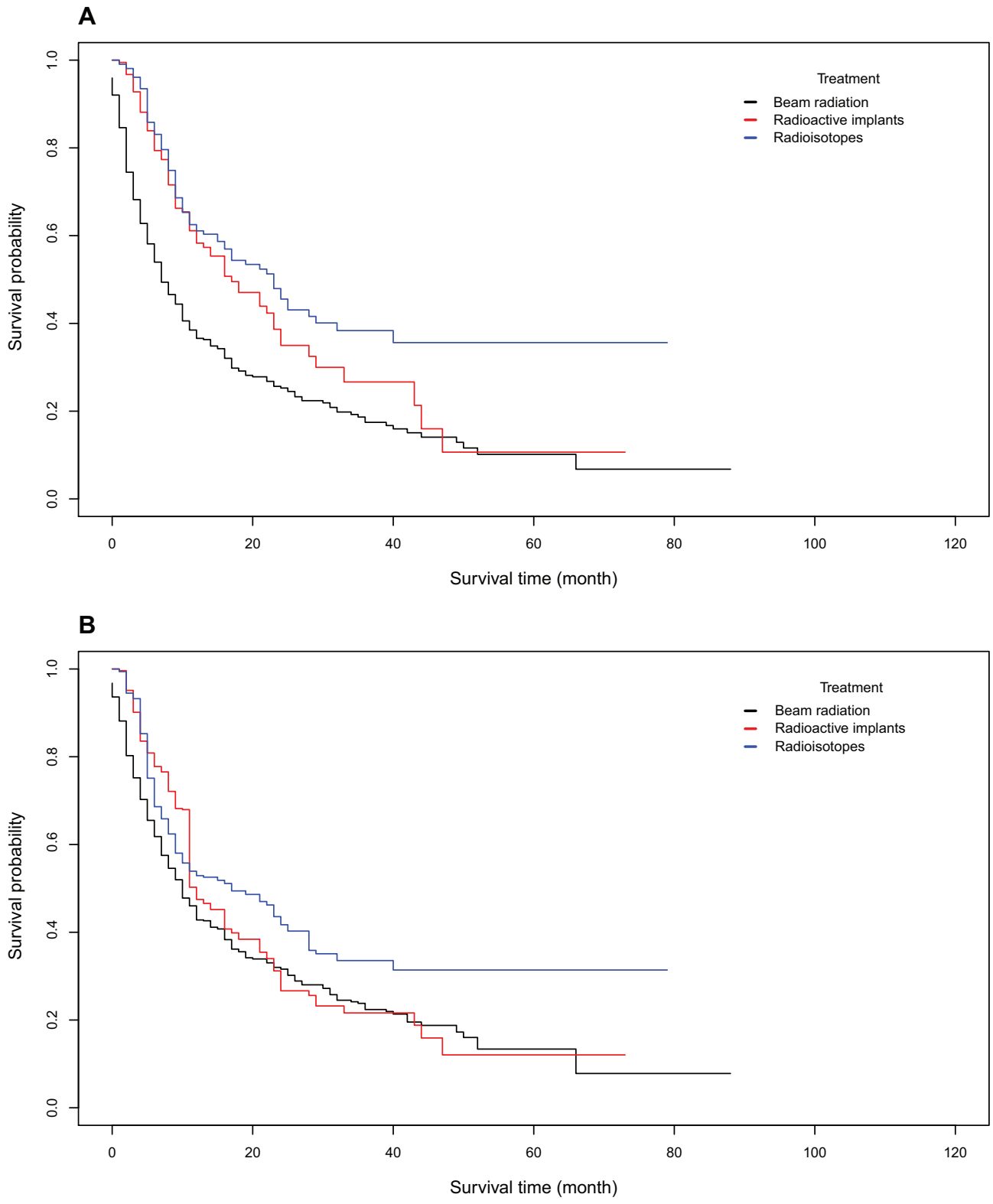

Figure 2 HCC-specific Kaplan-Meier survival curves for the 3 radiation groups in the original and pseudo samples. Panel (**A**) HCC-specific Kaplan–Meier survival curves for the 3 radiation groups in the original sample. Panel (**B**) HCC-specific Kaplan–Meier survival curves for the 3 radiation groups in the pseudo sample.

Table 5 Hazard Ratios, Confidence Internals, and P values Obtained from Cox Proportional Hazard Models for All-Cause Mortality and HCC-Specific Mortality in the Original Radiation Sample

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment				
BR	Reference		Reference	
RI	0.86 (0.68–1.08)	0.191	0.85 (0.65–1.11)	0.227
RIT	0.68 (0.54–0.87)	0.002	0.69 (0.52–0.91)	0.008
Age				
20–39	Reference		Reference	
40–59	1.34 (0.72–2.50)	0.358	1.23 (0.64–2.38)	0.539
60–79	1.10 (0.59–2.06)	0.767	0.88 (0.45–1.71)	0.707
≥80	1.09 (0.55–2.16)	0.816	0.68 (0.32–1.46)	0.322
Gender				
Female	Reference		Reference	
Male	1.11 (0.89–1.38)	0.374	1.15 (0.89–1.50)	0.280
Race				
White	Reference		Reference	
Black	1.20 (0.97–1.49)	0.095	1.04 (0.81–1.33)	0.762
Chinese	0.86 (0.49–1.53)	0.617	1.09 (0.60–1.99)	0.773
Others	1.03 (0.81–1.32)	0.803	0.93 (0.70–1.24)	0.634
Marital status				
Married/domestic partner	Reference		Reference	
Single (never married)	0.92 (0.74–1.14)	0.448	0.90 (0.71–1.15)	0.413
Separated	1.61 (0.65–4.03)	0.306	2.25 (0.89–5.68)	0.086
Divorced	1.12 (0.85–1.48)	0.424	1.19 (0.88–1.62)	0.261
Widowed	1.16 (0.81–1.67)	0.426	1.17 (0.76–1.80)	0.485
Other/unknown	0.97 (0.60–1.56)	0.886	0.69 (0.36–1.31)	0.254
Tumor size (cm)				
<3.0	Reference		Reference	
3.0–4.9	1.70 (1.27–2.28)	< 0.001	1.68 (1.19–2.37)	0.003
5.0–10.0	1.78 (1.32–2.41)	< 0.001	1.69 (1.19–2.39)	0.003
>10.0	2.10 (1.49–2.95)	< 0.001	1.95 (1.31–2.90)	0.001
Unknown	2.47 (1.74–3.50)	< 0.001	2.30 (1.54–3.43)	< 0.001
Grade				
Grade I	Reference		Reference	
Grade II	0.78 (0.56–1.08)	0.136	0.98 (0.66–1.45)	0.907
Grade III	1.31 (0.90–1.90)	0.154	1.58 (1.03–2.45)	0.038
Grade IV	1.33 (0.17–10.23)	0.783	1.99 (0.25–15.67)	0.515
Unknown grade	0.95 (0.72–1.25)	0.698	1.08 (0.77–1.53)	0.647
T stage				
T1	Reference		Reference	
T2	1.23 (0.96–1.59)	0.106	1.16 (0.86–1.57	0.338
T3	1.43 (1.12–1.82)	0.004	1.56 (1.18–2.06)	0.002
T4	0.76 (0.50–1.15)	0.198	0.79 (0.49–1.27)	0.332
TX	0.86 (0.62–1.20)	0.371	0.90 (0.62–1.30)	0.565
N stage				
N0	Reference		Reference	

(*Continued*)

Table 5 (Continued).

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
N1	1.06 (0.82–1.38)	0.644	1.12 (0.84–1.49)	0.444
NX	1.43 (1.13–1.82)	0.003	1.47 (1.13–1.91)	0.004
M stage				
M0	Reference		Reference	
M1	0.94 (0.42–2.10)	0.880	0.82 (0.35–1.95)	0.661
MX	0.98 (0.58–1.66)	0.954	0.99 (0.54–1.80)	0.965
Disease extent condition				
Localized	Reference		Reference	
Regional	1.17 (0.91–1.50)	0.212	1.12 (0.83–1.49)	0.464
Distant	2.69 (1.18–6.12)	0.018	3.28 (1.35–7.95)	0.009
Unstaged	0.80 (0.37–1.74)	0.568	0.81 (0.33–1.98)	0.641

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, 95% confidence interval; BR, beam radiation; RI, radioactive implants; RIT, radioisotopes.

unresectable HCC who underwent helical tomotherapy-based intensity-modulated radiation therapy (IMRT) and reported 1-year overall survival rates of 73% and 11% for patients with Child-Pugh classification A and B disease, respectively. In another study conducted by Lo et al,[32] 53 patients with unresectable HCC and a median tumor size of 4.3 cm who received stereotactic body radiotherapy presented with a median overall survival rate of 20 months. When compared with our results, the higher survival rates in these studies may be explained by the fact that the SEER registry data utilized in our study represented a mixture of various radiation treatments.

Analysis results from the pseudo-sample generated from our IPTW approach validated our findings in the original sample. However, the weighted 5-year survival rate of 40% in the surgery group was below the range of the 5-year survival rates of 62.1% to 91.5% reported in previous studies.[1,33–38] In the radiation group, the overall weighted survival rate at the end of the 5th year was only 15.8%, which was below the range of the 5-year survival rates of 66% to 85.9% reported in previous studies.[1] As many studies have shown, the variability of overall survival rates among patients who receive radiation may be accounted for by the subtypes and dose employed during radiotherapy. Jang et al[39] demonstrated that a 2-year overall survival rate for patients who received radiation dosages of <45, 45–54, and >54 Gray were 71%, 64%, and 30%, respectively.

In our original radiation subgroups, prior to IPTW, the RIT group was superior to the BR group in terms of overall survival rate and HCC-specific survival rate, but there was no significant difference between the RI and BR groups. In the radiation pseudo-sample, both the RIT and RI groups outperformed the BR group in overall survival. Similar results were discovered in HCC-specific survival rates between these groups. Our study demonstrated a median overall survival time of 6 months in the BR group, which was shorter than the overall survival times reported in some other studies.[40–43] The median overall survival time of the RIT group in our study was 14 months, which was longer than that reported by Mercedes et al[44] but shorter than that reported by Kulik et al.[45]

Our investigation confirms that propensity score IPTW is an efficient and helpful method of creating balanced groups to assess the effects of different therapies, although there are still some limitations in this study. Our study shows that surgery is significantly associated with improved overall and HCC-specific survival rates among SEER patients with HCC. However, selection of HCC treatments may largely depend on patients' clinical characteristics, and therefore clinicians should not choose one treatment over another for an HCC patient based on the conclusions drawn from this study. The decision of treatment of HCC is a selection-procedure by clinicians according to the Clinical Practice Guidelines for HCC.[46,47] Another limitation of our study is that our data from the SEER registry did not include any critical details on surgery and radiation therapy, consequently restricting our clinical investigation. For instance, when a patient received surgery as the HCC treatment, the SEER registry did not record whether the surgical procedure was partial

Table 6 Hazard Ratios, Confidence Internals, and P values Obtained from Cox Proportional Hazard Models for All-Cause Mortality and HCC-Specific Mortality in the Radiation Pseudo-Sample

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
Treatment				
BR	Reference		Reference	
RI	0.80 (0.71–0.90)	< 0.001	0.84 (0.73 −0.96)	0.010
RIT	0.79 (0.70–0.90)	< 0.001	0.83 (0.72 −0.96)	0.010
Age				
20–39	Reference		Reference	
40–59	1.99 (1.22–3.24)	0.005	1.49 (0.90 −2.45)	0.119
60–79	1.33 (0.81–2.17)	0.257	0.89 (0.53 −1.47)	0.639
≥80	1.40 (0.82–2.38)	0.216	0.82 (0.47 −1.45)	0.501
Gender				
Female	Reference		Reference	
Male	1.20 (1.03–1.39)	0.016	1.37 (1.15 −1.64)	0.001
Race				
White	Reference		Reference	
Black	1.14 (0.98–1.33)	0.079	1.04 (0.87 −1.24)	0.646
Chinese	0.87 (0.53–1.44)	0.597	1.08 (0.64 −1.83)	0.765
Others	1.15 (0.97–1.36)	0.107	1.09 (0.89 −1.32)	0.406
Marital status				
Married/domestic partner	Reference		Reference	
Single (never married)	0.90 (0.78–1.04)	0.167	0.91 (0.77 −1.08)	0.281
Separated	1.34 (0.66–2.73)	0.414	1.78 (0.87 −3.65)	0.113
Divorced	1.10 (0.91–1.33)	0.341	1.21 (0.98 −1.51)	0.077
Widowed	1.16 (0.91–1.47)	0.220	1.06 (0.79 −1.42)	0.697
Other/unknown	1.22 (0.82–1.80)	0.327	0.69 (0.38 −1.25)	0.223
Tumor size (cm)				
<3.0	Reference		Reference	
3.0–4.9	1.88 (1.54–2.28)	< 0.001	1.83 (1.46 −2.29)	< 0.001
5.0–10.0	1.65 (1.35–2.01)	< 0.001	1.40 (1.11 −1.77)	0.004
>10.0	2.31 (1.84–2.90)	< 0.001	1.97 (1.52 −2.56)	< 0.001
Unknown	2.58 (2.02–3.29)	< 0.001	2.26 (1.71 −2.99)	< 0.001
Grade				
Grade I	Reference		Reference	
Grade II	0.73 (0.59–0.90)	0.004	1.00 (0.78 −1.28)	0.971
Grade III	1.07 (0.84–1.36)	0.605	1.28 (0.96 −1.70)	0.089
Grade IV	1.81 (0.45–7.30)	0.407	4.12 (1.00 −17.01)	0.050
Unknown grade	0.90 (0.76–1.07)	0.247	1.02 (0.82 −1.27)	0.840
T stage				
T1	Reference		Reference	
T2	1.27 (1.07–1.50)	0.006	1.34 (1.10 −1.65)	0.004
T3	1.70 (1.44–2.00)	< 0.001	2.19 (1.81 −2.64)	< 0.001
T4	0.94 (0.69–1.28)	0.699	1.13 (0.79 −1.61)	0.518
TX	1.01 (0.79–1.30)	0.916	1.01 (0.76 −1.36)	0.929
N stage				
N0	Reference		Reference	

(*Continued*)

Table 6 (Continued).

Variable	All-Cause Mortality		HCC–Specific Mortality	
	HR (95% CI)	P value	HR (95% CI)	P value
N1	0.79 (0.66–0.95)	0.012	0.62 (0.50 −0.77)	< 0.001
NX	1.31 (1.10–1.55)	0.002	1.45 (1.20 −1.74)	< 0.001
M stage				
M0	Reference		Reference	
M1	1.70 (1.04–2.79)	0.035	1.57 (0.91 −2.71)	0.108
MX	1.15 (0.83–1.59)	0.396	1.04 (0.72 −1.52)	0.818
Disease extent condition				
Localized	Reference		Reference	
Regional	1.17 (1.00–1.36)	0.049	1.07 (0.89 −1.28)	0.468
Distant	1.65 (0.99–2.73)	0.053	2.12 (1.21 −3.72)	0.008
Unstaged	0.76 (0.45–1.28)	0.301	0.89 (0.49 −1.63)	0.705

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; CI, 95% confidence interval; BR, beam radiation; RI, radioactive implants; RIT, radioisotopes.

hepatectomy, transplant, wedge resection, or lobectomy. Likewise, when a patient received radiotherapy, the SEER registry did not record radiation dose or other details regarding the radiotherapy. Lastly, the data analysis method of propensity score balancing was invented to mimic randomization by creating a pseudo-sample in which the subjects in two or more treatment groups are comparable. However, this method relies on the assumption of "strong ignorability," which requires that there be no unmeasured confounders. In our study, due to the limitations inherited from the SEER registry, there must be some covariates that were not measured on HCC patients. Therefore, our analysis of the surgery and radiotherapy groups was not to derive causality but to confirm a population-level association.

Conclusion

This study demonstrated that SEER registry HCC patients who received surgery as their HCC treatment had a better survival rate compared with those who received radiotherapy. We evaluated both overall survival and HCC-specific survival rates, before and after propensity score weighting. This study also discovered that among patients who received radiotherapy, those who received RIT and RI outperformed those who received BR in terms of overall survival and HCC-specific survival rates after IPTW.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of this research work. Dr. Fuyan Shi, Chen Wang, Dr. Yujia Kong made equal contribution to this research article. Dr. Bo Zhang and Dr. Suzhen Wang are co-senior authors of this research article.

Funding

Dr. Fuyan Shi's research was partially supported by the National Natural Science Foundation of China (No. 81803337), the Shandong Provincial Youth Innovation Team Development Plan of Colleges and Universities (No.2019-6-156, Lu-Jiao), the Shandong Provincial Government Fund for Overseas Study (No. 27, 2019, Lu-Jiao), the Shandong Science and Technology Development Plan Project (No. 2015 WS0067), and the Weifang Medical University Doctoral Foundation Project (No. 2017BSQD51). Liping Yang's research was partially supported by the Shaanxi Key Industry Innovation Chain (No. 2016KTZDSF02-07-01). Dr. Suzhen Wang's research was partially supported by the National Natural Science Foundation of China (No. 81872719), the National Bureau of Statistics Foundation Project (No. 2018LY79), the Natural Science Foundation of Shandong Province (No. 2019MH034), and the Poverty Alleviation Fund project of Weifang Medical University (No. FP1801001).

Disclosure

The authors declare that they have no conflict of interests.

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