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Ablation alone is noninferior to radiotherapy plus ablation in the patients with early-stage hepatocellular carcinoma: a population-based study

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Recently, the efficacy of two low-invasive treatments, ablation, and radiotherapy, has been fully compared for the patients with the early-stage hepatocellular carcinoma (HCC). However, the comparison between radiotherapy plus ablation and ablation alone has been less frequently reported. Data from the Surveillance, Epidemiology, and End Results (SEER) database were searched for early-stage HCC patients treated with ablation plus radiotherapy or ablation alone. The outcome measures were overall survival (OS) and cancer-specific survival (CSS). The propensity score matching (PSM) was used to reduce selection bias. We included 240 and 6619 patients in the radiotherapy plus ablation group and ablation group before the PSM. After PSM, 240 pairs of patients were included. The median OS (mOS) and median CSS (mCSS) of patients receiving ablation alone were longer than that of receiving radiotherapy plus ablation (mOS: 47 vs. 34 months, $P = 0.019$; mCSS: 77 vs. 40 months, $P = 0.018$, after PSM) before and after PSM. The multivariate analysis indicated that radiotherapy plus ablation independent risk factor for OS and CSS before PSM, but the significance disappeared after PSM. The detailed subgroup analyses indicated ablation alone brought more benefit in very early-stage HCC and older patients. In addition, we found different types of radiotherapy might lead to different outcomes when combined with ablation. In conclusion, ablation alone is noninferior to radiotherapy plus ablation in patients with early-stage HCC. The additional radiation prior to ablation may bring survival benefits in the patients with higher tumor stage. However, due to the risk of selection bias in that study, the results should be interpreted cautiously.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related deaths in the world¹, accounting for about 75–85% of the incidence of all liver cancers². For decades, radiotherapy did not play a substantial role in treating liver cancers due to the limited tolerance of the whole liver to radiation and complexity of tumor localization³. However, with the progress of imaging and radiation delivery, radiotherapy was proven to have potential efficacy across all stages of HCC⁴. The American Society for Radiation Oncology recently recommended external beam radiation therapy as the potential first-line treatment in patients with liver-confined HCC who were not suitable for curative therapy. In addition, radiotherapy was also recommended as a bridge treatment to liver transplant or before surgery in carefully selected patients⁵.

For the early-stage HCC, the potentially curative treatments include liver transplantation, partial hepatic resection, and ablation⁶. Ablation treatment mainly included radiofrequency ablation (RFA) which showed similar efficacy compared to surgical resection in patients with tumor size no more than 3 cm⁷. In addition to the similar efficacy, as a minimally invasive approach, ablation treatment could offer fewer complications, better safety and shorter hospital stay^{8,9}. As a non-invasive treatment, the efficacy of radiotherapy mainly including stereotactic body radiation therapy (SBRT) in patients with early-stage HCC attracted more and more attention¹⁰.

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Hong et al. conducted a meta-analysis comparing SBRT vs. RFA in patients with small HCC and they reported that radiotherapy provided a higher local control ratio but a poorer prognosis than RFA¹¹. Given that SBRT could serve as the supplementary therapeutic strategy when the lesion was attached to a vessel or located at subphrenic region, more and more researchers raised the point that these two types of treatment were not rivals but partners for the cure¹². Considering the probability of incomplete RFA, the new strategy based on RFA plus radiotherapy was proposed by many researchers. They found RFA plus radiotherapy was safe and tolerated for patients^{13–15}, meanwhile, patients who received RFA plus radiotherapy may have a lower local disease progression rate and better progression-free survival (PFS)¹⁶.

However, due to the relatively short follow-up periods or relatively small number of included patients in these studies. The aim of our study was to utilize the data from the Surveillance, Epidemiology, and End Results (SEER) database to compare the clinical outcomes of patients with early-stage HCC who received ablation alone and radiotherapy plus ablation. In addition, we investigated the efficacy of different types of radiotherapy plus ablation and the different sequences of radiotherapy plus ablation.

Materials and methods

Patient database

This population-based study was based on the US National Cancer Institute's surveillance, epidemiology, and end results (SEER) database. The population-based data were obtained from Incidence-SEER 17 Regs Research Data (2000–2019) which covered up to 26.5% of the population in the USA. We used SEER*Stat statistical software, version 8.4.0.1 (National Cancer Institute, Bethesda, MD, USA) to collect information regarding demographics and diagnosis information. To be clear, the patients before 2004 have no information about TMN stages, so we selected patients with the year of diagnosis between 2004–2019.

Patient selection

According to the International Classification of Diseases for Oncology, third-edition histology codes, and the World Health Organization lymphoid classification (2008), we limited the patients who were histologically diagnosed with HCC (histology codes 8170/3–8175/3, site code C220.0). The patients with the following features were excluded: (1) patients did not receive the treatment of ablation; (2) patients' tumor stages were unknown/unstaged; (3) patients were not at the stages of TNM I and II; (4) patients with loss of important information (tumor size, survival information, race). Figure 1 showed the flow of individuals through the screening process.

Patient characteristics

For each case, we retrieved the characteristics of patients including age at diagnosis, year of diagnosis, gender, tumor stage (localized or regional), AJCC stage, tumor size, tumor number, race, marital status at diagnosis, the type of ablation, the presence of chemotherapy, survival months, and survival status (including vital status recode and SEER cause-specific death classification).

Propensity score matching

Propensity score matching (PSM) analysis was used to reduce the selection bias due to baseline characteristics between the two groups. The variables including age at diagnosis, year of diagnosis, gender, tumor stage, AJCC stage, tumor size, tumor number, race, marital status at diagnosis, the type of ablation, and the presence of chemotherapy were used to perform PSM. One-to-one matching without replacement was applied, and the caliper value was 0.02.

Statistical analysis

Age at diagnosis, year of diagnosis, and tumor size were converted from continuous variables into groups and analyzed as categorical variables. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test. SEER cause-specific death classification (CSS) and overall survival (OS) curves between the radiotherapy plus ablation group and ablation group were made by the Kaplan–Meier method and the log-rank test was conducted to determine statistical significance. In addition, the log-rank Mantel-Cox test was applied for pairwise comparisons of survival data. Cox regression analysis was used for univariate analysis, in which variables with *P* value less than 0.05 in univariate analysis were added to multivariate analysis. All statistical analyses were conducted using SPSS 24.0 (IBM, Corp, NY, USA). *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 6859 patients with HCC were included in the study, with 240 and 6619 patients in the radiotherapy plus ablation group and ablation group before the PSM, respectively (Table 1). The age at diagnosis in the radiotherapy plus ablation group was older than that in the ablation group (*P* = 0.033). The years of diagnosis in the ablation group were earlier than that in the radiotherapy plus ablation group (*P* < 0.001). The patients who underwent radiotherapy plus ablation tended to have higher AJCC stage, larger tumor size, and more tumor numbers than whom received ablation treatment alone. Meanwhile, more patients in the ablation group also received the treatment of chemotherapy (69.90% vs. 32.08%, *P* < 0.001). In addition, the variable ethnicity between the two groups was unbalanced (*P* = 0.002) before the PSM. After the PSM, the *P*-values for all variables after were more than 0.1, which suggested that PSM effectively minimized the selection bias and imbalance between the two groups.

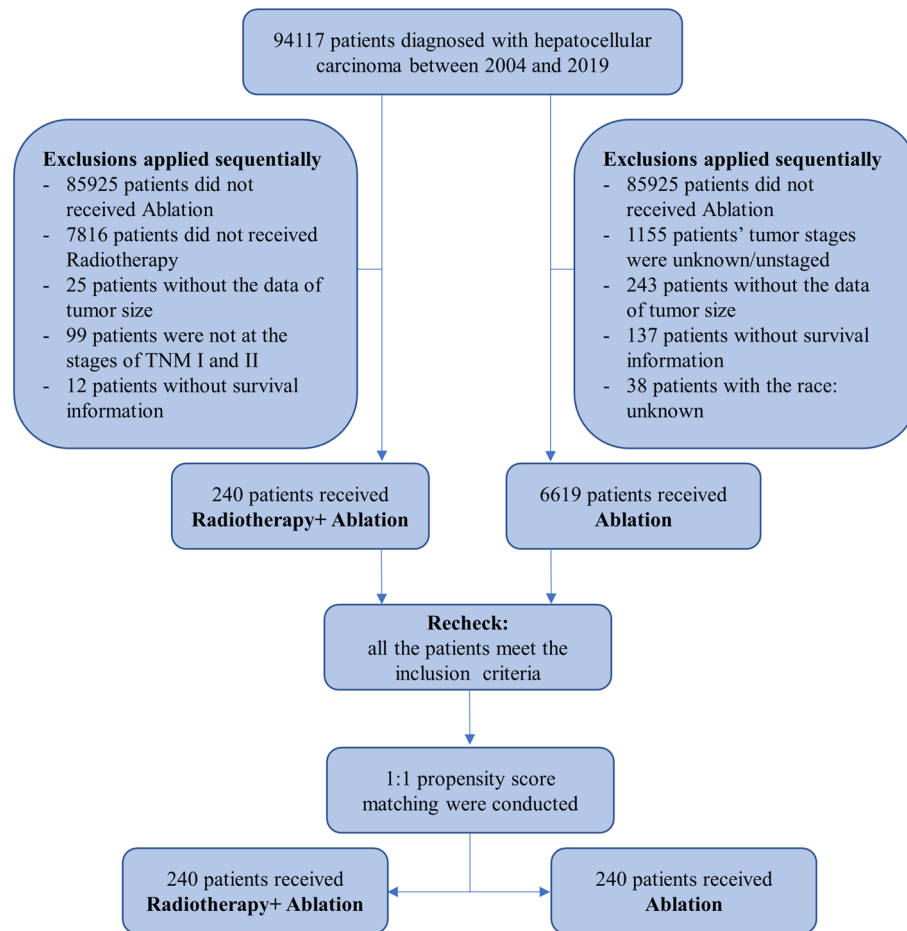


Figure 1. Flow chart of the patients included in the study.

Survival outcomes before and after PSM

Before the PSM, the median OS (mOS) in the ablation group was longer than mOS in the radiotherapy plus ablation group (47 vs. 34 months, $P=0.001$, Fig. 2A). Similarly, the median CSS (mCSS) in the ablation group was longer than mCSS in the radiotherapy plus ablation group (69 vs. 40 months, $P<0.001$, Fig. 2B). After the PSM, the mOS in the ablation group was still longer than that in the radiotherapy plus ablation group (47 vs. 34 months, $P=0.019$, Fig. 2C), meanwhile, the mCSS achieved a similar result (77 vs. 40 months, $P=0.018$, Fig. 2D).

Next, we conducted detailed subgroup analyses by forest plot according to the baseline characteristics of patients before and after PSM, the hazard ratios with 95% confidence intervals (CI) for the OS and CSS were shown in Figs. 3 and 4. Before the PSM, of note, we found that ablation alone was a favorable factor for OS and CSS in patients with earlier tumor stage (with tumor stage localized, with AJCC stage I, with tumor size no more than 3 cm, with single tumor), meanwhile, for patients with higher tumor stage, ablation alone tended to achieve similar efficacy compared with radiotherapy plus ablation (Fig. 3). After the PSM, we still found that ablation alone was a favorable factor for OS and CSS in patients with tumor stage localized (OS: HR = 0.715, 95%CI: 0.530–0.964, $P=0.028$; CSS: HR = 0.646, 95%CI: 0.461–0.904, $P=0.011$), patients with AJCC stage I (OS: HR = 0.622, 95%CI: 0.440–0.880, $P=0.007$; CSS: HR = 0.589, 95%CI: 0.398–0.872, $P=0.008$), patients with tumor size no more than 3 cm (OS: HR = 0.475, 95%CI: 0.311–0.725, $P=0.001$; CSS: HR = 0.517, 95%CI: 0.320–0.833, $P=0.007$), patients with single tumor (OS: HR = 0.629, 95%CI: 0.458–0.864, $P=0.004$; CSS: HR = 0.613, 95%CI: 0.431–0.872, $P=0.007$, Fig. 4).

Cox regression analysis

Before the PSM, the univariable cox regression analysis indicated that the ablation alone was a favorable factor for OS (HR = 0.728, 95%CI: 0.603–0.878, $P=0.001$) and CSS (HR = 0.653, 95%CI: 0.529–0.806, $P<0.001$). To avoid over-fitting, the multivariable cox regression model contained only variables that had P -values <0.05 in the univariable cox regression analysis. Similarly, multivariable analysis showed that ablation alone was a favorable factor for OS (HR = 0.811, 95%CI: 0.670–0.982, $P=0.031$) and CSS (HR = 0.726, 95%CI: 0.587–0.898, $P=0.003$, Table S1–S2).

After the PSM, the univariable cox regression analysis still showed that the ablation alone was a favorable factor for OS (HR = 0.727, 95%CI: 0.556–0.951, $P=0.020$) and CSS (HR = 0.698, 95%CI: 0.516–0.945, $P=0.020$).

Characteristics	Before matching			After matching		
	Radiotherapy + Ablation (n = 240)	Ablation (n = 6619)	P value	Radiotherapy + Ablation (n = 240)	Ablation (n = 240)	P value
Age at diagnosis			0.033			0.171
≥ 65	129 (53.75%)	3095 (46.76%)		129 (53.75%)	114 (47.50%)	
< 65	111 (46.25%)	3524 (53.24%)		111 (46.25%)	126 (52.50%)	
Gender			0.079			0.494
Male	189 (78.75%)	4877 (73.68%)		189 (78.75%)	195 (81.25%)	
Female	51 (21.25%)	1742 (26.32%)		51 (21.25%)	45 (18.75%)	
Years of diagnosis			< 0.001			0.105
2004–2009	23 (9.58%)	1495 (22.59%)		23 (9.58%)	30 (12.50%)	
2010–2015	71 (29.58%)	2719 (41.08%)		71 (29.58%)	87 (36.25%)	
2016–2019	146 (60.84%)	2405 (36.33%)		146 (60.84%)	123 (51.25%)	
Tumor stage			< 0.001			0.74
Localized	181 (75.42%)	5822 (87.96%)		181 (75.42%)	197 (82.08%)	
Regional	59 (24.58%)	797 (12.04%)		59 (24.58%)	43 (14.92%)	
AJCC stage			< 0.001			0.113
I	136 (56.67%)	4833 (73.01%)		136 (56.67%)	153 (63.75%)	
II	104 (43.33%)	1786 (26.99%)		104 (43.33%)	87 (36.25%)	
Tumor size (cm)			< 0.001			0.649
No more than 3	114 (47.50%)	4113 (62.14%)		114 (47.50%)	123 (51.25%)	
3–5	104 (43.33%)	2196 (33.18%)		104 (43.33%)	99 (41.25%)	
Larger than 5	22 (9.17%)	310 (4.68%)		22 (9.17%)	18 (7.50%)	
Tumor number			< 0.001			0.977
1	179 (74.58%)	5688 (85.93%)		179 (74.58%)	180 (75.00%)	
2	49 (20.42%)	796 (12.03%)		49 (20.42%)	49 (20.42%)	
≥ 3	12 (5.00%)	135 (2.04%)		12 (5.00%)	11 (4.58%)	
Ethnicity			0.002			0.472
White	185 (77.08%)	4613 (69.90%)		185 (77.08%)	191 (79.58%)	
Black	28 (11.67%)	647 (9.77%)		28 (11.67%)	20 (8.33%)	
Other	27 (11.25%)	1359 (20.53%)		27 (11.25%)	29 (12.09%)	
Marital status			0.750			0.967
Married	128 (53.33%)	3598 (54.36%)		128 (53.33%)	127 (52.92%)	
Unmarried	100 (41.67%)	2754 (41.61%)		100 (41.67%)	102 (42.50%)	
Unknown	12 (5.00%)	267 (4.03%)		12 (5.00%)	11 (4.58%)	
Chemotherapy			< 0.001			0.371
Yes	77 (32.08%)	4627 (69.90%)		77 (32.08%)	68 (28.33%)	
No	163 (67.92%)	1992 (30.10%)		163 (67.92%)	172 (71.67%)	
Ablation			0.489			0.566
RFA	223 (92.92%)	6173 (93.26%)		223 (92.92%)	219 (91.25%)	
Cryoablation	2 (0.83%)	127 (1.92%)		2 (0.83%)	5 (2.08%)	
Laser ablation	2 (0.83%)	43 (0.65%)		2 (0.83%)	4 (1.67%)	
Alcohol ablation	13 (5.42%)	276 (4.17%)		13 (5.42%)	12 (5.00%)	

Table 1. The baseline characteristics of patients before and after PSM. AJCC American Joint Committee on Cancer; RFA Radiofrequency ablation.

However, in the multivariable cox regression model, ablation alone was not an independent favorable factor for OS (HR = 0.779, 95%CI: 0.594–1.022, $P = 0.071$) and CSS (HR = 0.759, 95%CI: 0.559–1.030, $P = 0.077$, Tables 2, 3), although a modest trend was present.

Types and sequences of radiotherapy analysis

The types and sequences of radiotherapy's detailed information in radiotherapy plus ablation group (240 included patients) was listed in Table S3. We observed the types of radiotherapy may provide different survival outcomes when combine with ablation. The mOS in the patients with the radiotherapy type “Radiation, NOS method or source not specified” were significantly longer than patients with the radiotherapy type “Beam radiation” (79 vs. 30 months, $P = 0.002$, Fig. 5A) and type “Radioisotopes” (79 vs. 31 months, $P = 0.013$). The CSS achieved similar results (Fig. 5B), and it indicated that “Beam radiation” and “Radioisotopes” may impair the survival benefit brought by ablation (Table S3).

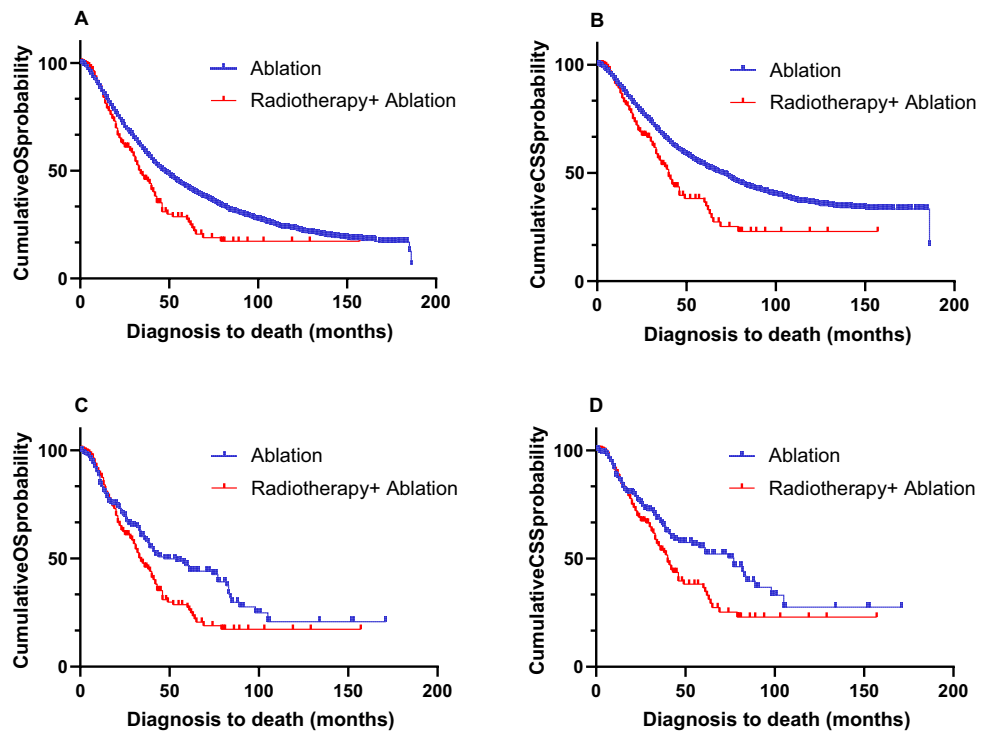


Figure 2. (A) Kaplan–Meier curve of OS before PSM; (B) Kaplan–Meier curve of CSS before PSM; (C) Kaplan–Meier curve of OS after PSM; (D) Kaplan–Meier curve of CSS after PSM.

We compared the survival outcomes of patients with different sequences of radiotherapy. The result indicated that the mOS (32.0 vs. 47.0 months, $P=0.009$, Fig. 5C) and mCSS (40.0 vs. 77.0 months, $P=0.012$, Table S3, Fig. 5D) patients with “Radiation after ablation” were significantly shorter than patients who received ablation alone. “Radiation after ablation” means that radiation can be used as salvage therapy after a local recurrence. We found that patients with “Radiation after ablation” tended to have higher tumor stage at baseline compared to patients in the ablation alone group (regional: 26.1% vs 17.9%, $P=0.060$, Table S4). The mOS (32.0 vs. 47.0 months, $P=0.335$, Fig. 5C) and mCSS (39.0 vs. 77.0 months, $P=0.309$, Fig. 5D) were similar in patients with “Radiation prior to ablation” and ablation alone group. The patients with “Radiation prior to ablation” have higher AJCC stage at baseline compared to patients in the ablation alone group (AJCC stage II: 49.4% vs 36.2%, $P=0.033$, Table S5).

Discussion

As the technique of radiotherapy evolves, the role of radiotherapy in the treatment of hepatocellular cancer has been explored. Previous studies have demonstrated the safety of SBRT plus ablation in early and even intermediate-stage HCC^{13–15}, therefore, we analyzed data from the publicly accessible SEER database to compare the efficacy of radiotherapy plus ablation and ablation alone in early-stage HCC.

Similar to surgical procedures¹⁷, radiotherapy given before ablation may help remove cancer cells that cannot be seen with Computed Tomography or Ultrasound, and convert tumors beyond indications for ablation into ablation-able tumors by shrinking the tumor. Meanwhile, due to the large size, irregular shape, and “heat sink effect” of the tumor⁸, radiotherapy given after ablation may help kill the residual HCC cells. However, we here yield a result less compatible with these hypotheses: we observed that ablation alone was noninferior to radiotherapy plus ablation in the patients with early-stage HCC from the perspective of overall outcomes, and ablation alone may gain more benefits in special subgroups. Combined with the results of subgroup analyses (Fig. 4), we found that ablation alone may bring more survival benefits to patients at very early-stage HCC with smaller tumor size and single tumor. One explanation could be that ablation alone was enough to kill most tumor cells in very early-stage HCC, additional radiotherapy may cause the unnecessary death of normal hepatocytes which may lead to potential radiation-induced liver injury (RILI). In addition, older age has been associated with higher rates of toxicity from radiotherapy¹⁸ and this could explain why we found that patients older than 65 were more likely to benefit from ablation alone.

The liver is a crucial organ and plays the most important role in various physiological functions such as bile acid circulation, glucose metabolism, lipid metabolism, protein metabolism and, immunity^{19,20}. As a radiosensitive organ, hepatic toxicity from radiation therapy has been extensively reported²¹. The RILI can lead to the injury of hepatocytes and Kupffer cells, sinusoidal obstruction syndrome, and perivenular fibrosis²². The severity of RILI depends on the means of radiotherapy, the total exposure dose, the dose rate, and the physical area of exposure¹⁹. Therefore, we investigated the impact of different types and sequences of radiotherapy on survival

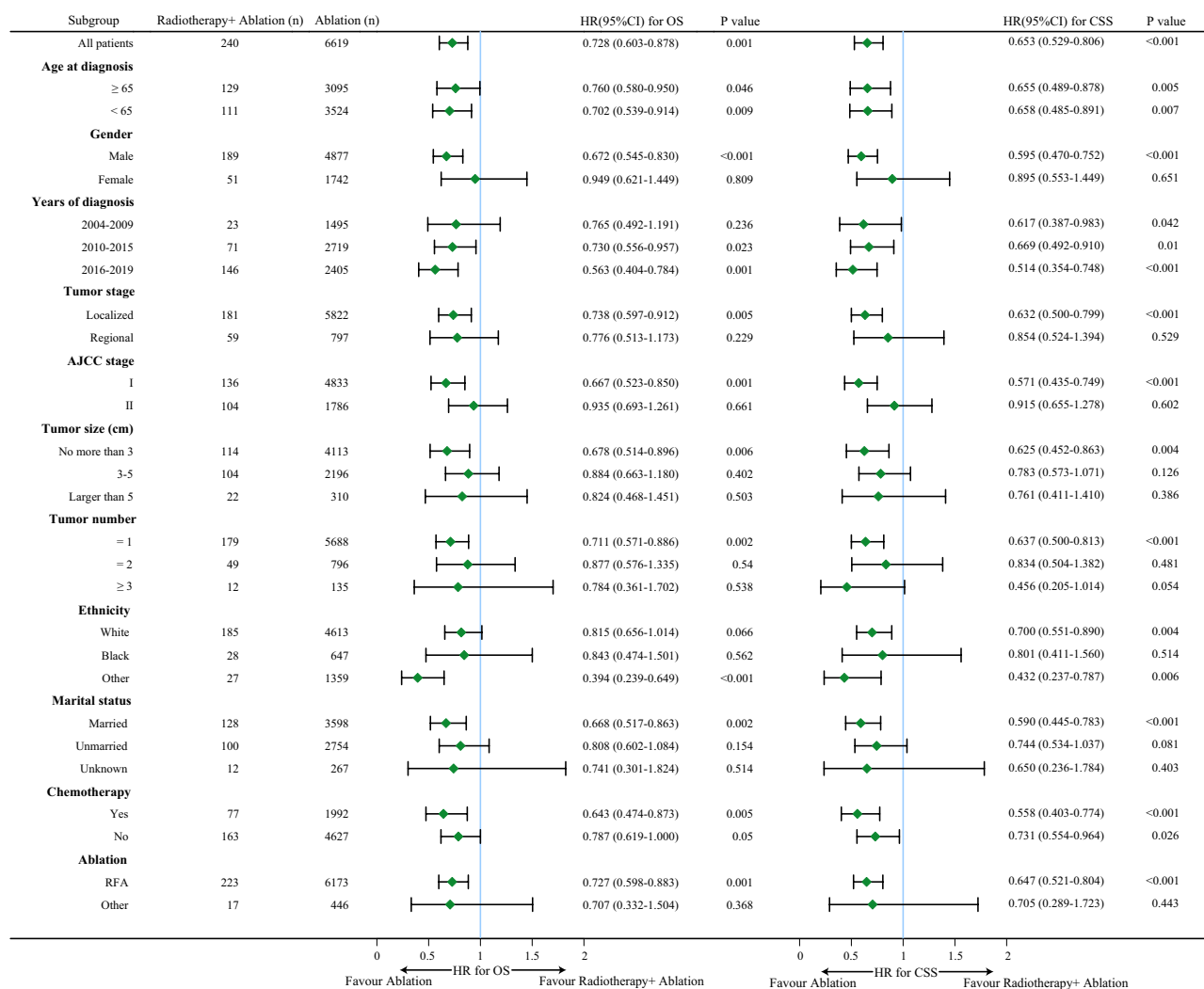


Figure 3. Forest plot of subgroup analysis before PSM.

outcomes. The results indicated that the different sequences of radiotherapy achieved similar results, and they both tended to be inferior to ablation alone (Fig. 5B). Notably, although the SEER database did not give the SBRT a special code number, many studies regarded “beam radiation” as SBRT therapy^{23–25}. If we based on this hypothesis, we found that SBRT plus ablation might get the worst outcomes from the curves (Fig. 5A). However, a retrospective study reported that the safety and efficacy of SBRT plus ablation were similar to ablation alone in HCC patients at the stage of 0-B1¹³, therefore, we speculated that “beam radiation” may include other kinds of radiation therapy whose efficacy are worse than SBRT. Moreover, we needed to cleared that part of patients treated with combination therapy might use radiotherapy as a salvage treatment which might lead to selection bias in the population between two groups. Notably, when we compared the survival outcomes of patients with different sequences of radiotherapy, the patients with “Radiation after ablation” or “Radiation prior to ablation” tend to have higher tumor stage. Therefore, this additional radiotherapy may represent an imbalance in the population, either as salvage treatment after ablation or as treatment before ablation to reduce tumor burden. More specifically, this additional radiotherapy after ablation in the higher risk population did not bring additional survival benefits, while radiation prior to ablation bring additional early-stage survival benefits in the patients with higher AJCC stage (Fig. 5D).

The treatment of HCC has placed a severe economic burden on health care systems and each patient²⁶. Parikh et al. reported that RFA and SBRT for early-stage hepatocellular carcinoma showed similar survival, 90-day hospitalization, or costs²⁷ using the SEER-Medicare linked database. An earlier Markov modeling study reported that SBRT is the preferred salvage therapy for local progression after RFA in inoperable HCC from the point of cost-effectiveness. However, different from this study, we included patients with real and longer follow-up time (instead of model-simulated survival curves)²⁸. Meanwhile, RFA has been reported to be less expensive compared with selective internal radiation therapy (SIRT)²⁹. It is conceivable that no matter what type or sequence of radiotherapy is, the cost of radiotherapy plus ablation will be much higher than that of ablation alone. Consequently, ablation alone is still the better choice especially for patients with very early-stage HCC according to the results presented here.

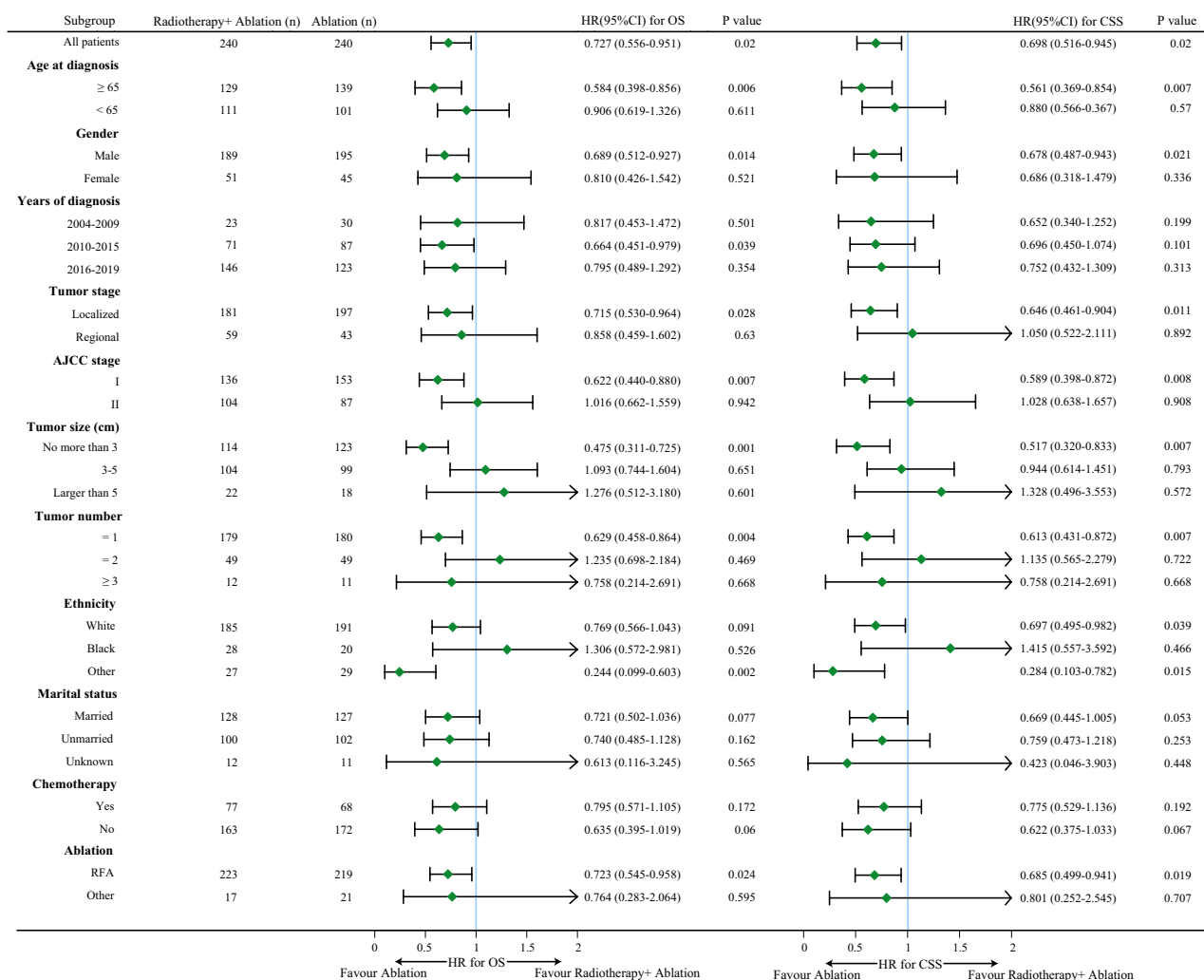


Figure 4. Forest plot of subgroup analysis after PSM.

The treatment decision to combine radiotherapy and ablation should be individualized. From a clinical practice perspective, tumors close to blood vessels or located in subphrenic area jeopardized local control of RFA¹². The SBRT and SIRT were unaffected by the position of tumor, therefore, radiotherapy may still help improve local control of treatment. However, when tumor was far from a blood vessel or located in a non-subphrenic region, the clinician should consider with care whether additional radiotherapy could bring more survival benefits or not.

Our study has limitations. As with other SEER-based studies, the SEER database does not provide specific information about the type, dose, and timing of radiotherapy. Similarly, we did not get information about the postoperative complications and liver functions which were important to evaluate the safety of radiotherapy plus ablation. Like other retrospective studies, selection bias and confounding factors could have affected the results, but PSM, multivariate Cox regression models, and detailed subgroup analyses may help reduce these. Despite these statistical managements, this conclusion should be interpreted with caution.

Conclusions

Ablation alone is noninferior to radiotherapy plus ablation in patients with early-stage HCC. The additional radiation prior to ablation may bring survival benefits in the patients with higher tumor stage. However, due to the risk of selection bias in that study, the results should be interpreted cautiously.

Characteristics	Univariable analysis for OS		Multivariate analysis for OS	
	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis				
≥ 65	Reference			
< 65	1.093 (0.836, 1.429)	0.513		
Gender				
Male	Reference			
Female	0.774 (0.547, 1.095)	0.148		
Years of diagnosis				
2004–2009	Reference			
2010–2015	0.711 (0.500, 1.012)	0.058		
2016–2019	0.796 (0.534, 1.185)	0.261		
Tumor stage				
Localized	Reference		Reference	
Regional	1.421 (1.011, 1.998)	0.043	1.342 (0.951, 1.893)	0.094
AJCC stage				
I	Reference			
II	1.260 (0.957, 1.658)	0.099		
Tumor size (cm)				
No more than 3	Reference		Reference	
3–5	1.812 (1.365, 2.406)	< 0.001	1.746 (1.313, 2.323)	< 0.001
Larger than 5	2.476 (1.531, 4.004)	< 0.001	2.392 (1.473, 3.887)	< 0.001
Tumor number				
1	Reference			
2	1.343 (0.973, 1.853)	0.073		
≥ 3	1.584 (0.858, 2.923)	0.142		
Ethnicity				
White	Reference			
Black	1.139 (0.736, 1.762)	0.558		
Other	0.875 (0.578, 1.323)	0.526		
Marital status				
Married	Reference			
Unmarried	0.956 (0.726, 1.259)	0.749		
Unknown	0.788 (0.367, 1.690)	0.540		
Chemotherapy				
Yes	Reference			
No	0.842 (0.635, 1.116)	0.231		
Treatment				
Radiotherapy + Ablation	Reference		Reference	
Ablation	0.727 (0.556, 0.951)	0.020	0.779 (0.594, 1.022)	0.071

Table 2. Univariable and multivariable cox regression analysis for OS after PSM. OS Overall Survival; AJCC American Joint Committee on Cancer; RFA Radiofrequency ablation.

Characteristics	Univariable analysis for CSS		Multivariate analysis for CSS	
	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis				
≥ 65	Reference			
< 65	0.974 (0.720, 1.317)	0.863		
Gender				
Male	Reference			
Female	0.684 (0.456, 1.027)	0.067		
Years of diagnosis				
2004–2009	Reference			
2010–2015	0.709 (0.478, 1.051)	0.087		
2016–2019	0.799 (0.510, 1.252)	0.328		
Tumor stage				
Localized	Reference			
Regional	1.431 (0.974, 2.102)	0.068		
AJCC stage				
I	Reference			
II	1.304 (0.958, 1.774)	0.092		
Tumor size (cm)				
No more than 3	Reference		Reference	
3–5	1.872 (1.359, 2.580)	<0.001	1.820 (1.320, 2.511)	<0.001
Larger than 5	2.789 (1.650, 4.715)	<0.001	2.513 (1.477, 4.274)	0.001
Tumor number				
1	Reference			
2	1.119 (0.762, 1.644)	0.565		
≥ 3	1.960 (1.057, 3.637)	0.033		
Ethnicity				
White	Reference			
Black	1.118 (0.683, 1.829)	0.658		
Other	0.839 (0.524, 1.343)	0.464		
Marital status				
Married	Reference			
Unmarried	0.955 (0.701, 1.300)	0.769		
Unknown	0.717 (0.291, 1.766)	0.470		
Chemotherapy				
Yes	Reference		Reference	
No	0.718 (0.526, 0.979)	0.036	0.770 (0.563, 1.052)	0.100
Treatment				
Radiotherapy + Ablation	Reference		Reference	
Ablation	0.698 (0.516, 0.945)	0.020	0.759 (0.559, 1.030)	0.077

Table 3. Univariable and multivariable Cox regression analysis for CSS after PSM. CSS Cancer-Specific Survival; AJCC American Joint Committee on Cancer; RFA Radiofrequency ablation.

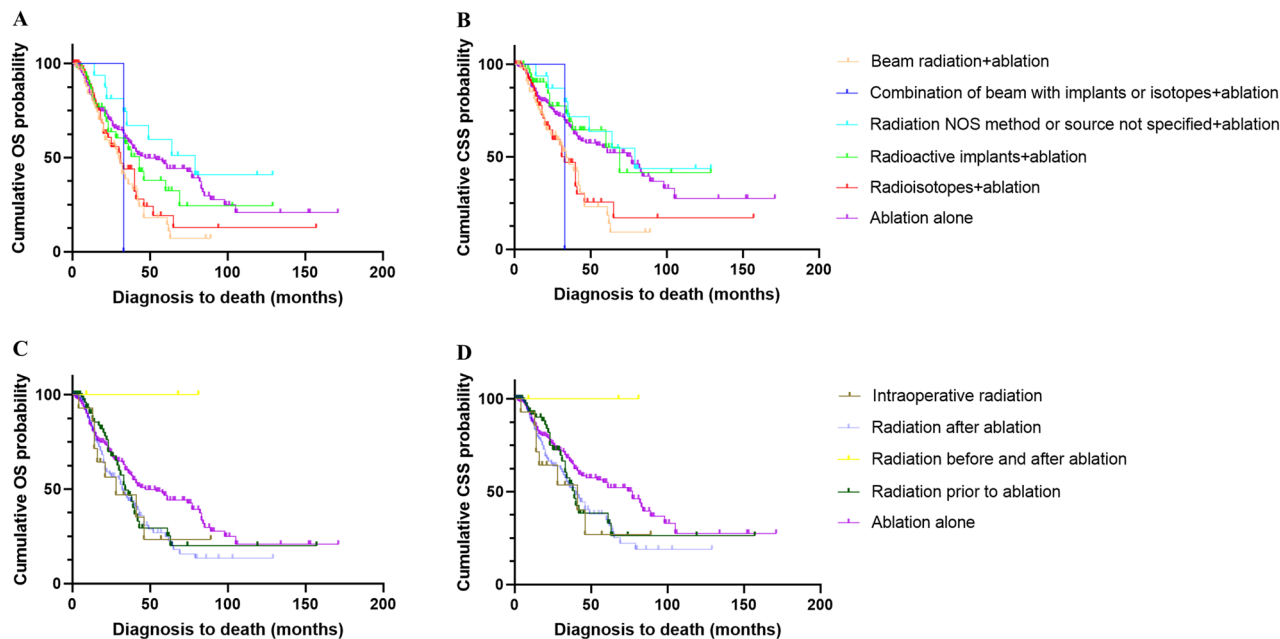


Figure 5. (A) Kaplan–Meier curve of OS in patients with different types of radiotherapy; (B) Kaplan–Meier curve of CSS in patients with different types of radiotherapy; (C) Kaplan–Meier curve of OS in patients with different sequences of radiotherapy; (D) Kaplan–Meier curve of CSS in patients with different sequences of radiotherapy.

Data availability

Raw data used in analyses is available in supplementary materials and SEER database (<http://seer.cancer.gov/seerstat>).

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Conception and design: Y.G., L.Y., C.Z.; Administrative support: C.Z.; Collection of data: Y.G., H.C. and L.C.; Data analysis and interpretation: R.Q., T.S. and F.W.; Manuscript writing: Y.G., H.C., J.W.; Final approval of manuscript: All authors; Accountable for all aspects of the work: All authors.

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