Original Article

Radiofrequency ablation versus surgical resection in elderly patients with early-stage hepatocellular carcinoma in the era of organ shortage

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Abstract

Background/Aims: To compare the survival benefits of surgical resection (SR) with those of radiofrequency ablation (RFA) in elderly patients (≥65 years) with single hepatocellular carcinoma (HCC) ≤5 cm.

Patients and Methods: Using the Surveillance, Epidemiology, and End Results database, a total of 461 patients who underwent SR and 575 patients who underwent RFA were enrolled from 2004 to 2012. Overall survival (OS) and liver-cancer-specific survival (LCSS) comparisons were conducted between the two groups before and after propensity score matching (PSM).

Results: Elderly patients with early-stage HCC had a lower rate of utilization of liver transplantation, and they were more likely to receive SR or RFA as their first-line treatment compared with younger patients ($P < 0.05$). In the whole cohort, the SR group had significantly better OS [RFA, hazard ratio (HR) = 1.680 (1.390, 2.031), $P < 0.001$] and LCSS (RFA, HR = 1.658 (1.327, 2.070), $P < 0.001$) than the RFA group. After PSM, the improved survival in the SR group was further confirmed (all $P < 0.001$). In the subgroup analyses, according to patients' age (65–75, >75 years) and tumor size (≤3.0, 3.1–5.0 cm), the SR group still presented better OS and LCSS than the RFA group (all $P < 0.05$), except for those older than 75 years with tumors ≤3.0 cm (all $P > 0.05$), both before and after PSM.

Conclusion: Treatment strategies for elderly patients (≥65 years) with single HCC ≤5 cm should emphasize SR as the primary therapy, while RFA can be an alternative to SR for those >75 years with single HCC ≤3 cm.

Keywords: Elderly patients, hepatocellular carcinoma, prognosis, radiofrequency ablation, surgical resection

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related death in the world.[1] In the United States, the incidence of HCC has almost tripled since the early 1980s, and it has become the fastest rising cause of cancer-related deaths.[2] In addition, due to the prolongation of human life expectancy, the rising morbidity of chronic liver diseases, and the delaying effect of antiviral therapy on the development of HCC, the incidence of HCC has gradually

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_261_18

How to cite this article: Yu B, Ding Y, Liao X, Wang C, Wang B, Chen X. Radiofrequency ablation versus surgical resection in elderly patients with early-stage hepatocellular carcinoma in the era of organ shortage. Saudi J Gastroenterol 2018;24:317-25.

declined in the American population under the age of 50 years and is expected to reach its highest prevalence among those age ≥65 years by 2030.[3-5] There is no doubt that improving the management of elderly patients with early-stage HCC is becoming a challenging clinical issue in the United States.

Currently, liver transplantation (LT), surgical resection (SR), and radiofrequency ablation (RFA) are the three main optional treatment modalities for early-stage HCC. Considering the current organ shortage, high cost, and strict patient selection criteria, LT is not a viable option for the majority of patients, especially for those older than 65 years, while SR and RFA are often recommended as the initial treatments used for early-stage HCC.[6,7] Along with LT, SR is regarded as a curative treatment for early-stage HCC. However, as a unique group, elderly patients with HCC are generally characterized by age-related deterioration of liver function and higher incidences of comorbidities.[8] Therefore, RFA has been established as the most common alternative treatment for elderly patients with small HCC because of its excellent antitumor effect and its advantage of less invasiveness, lower perioperative risk, and fewer deteriorative effects on liver function than SR.[9] Nevertheless, RFA has a significant drawback of limited ablative margins, which is associated with high risk of marginal recurrence.[10] With advancement of surgical techniques and perioperative management, feasibility, safety, and effectiveness of SR for selected elderly patients with early-stage HCC have been widely identified in the past decade.[11] Hence, for elderly patients with early-stage HCC who are candidates for both SR and RFA, it remains controversial which treatment provides better long-term survival outcomes.[12,13] We therefore compared the survival benefits of SR with those of RFA as the first-line treatment in elderly patients (≥65 years) with single HCC ≤5 cm using Surveillance, Epidemiology, and End Results (SEER), a large population-based database.

PATIENTS AND METHODS

Data source and study design

SEER database was used to obtain the relevant data of the patients with a histological diagnosis of HCC [The International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) code: 8170-8175] from 2004 to 2012. The inclusion criteria were as follows: (1) single tumors ≤5.0 cm in diameter; (2) no evidence of major vascular invasion or extrahepatic metastases; (3) age ≥65 years; and (4) cases receiving RFA, SR, or LT as initial treatment. The exclusion criteria were as follows: (1) HCC not as the first malignant primary indicator and (2) cases without complete data of tumor size or survival times.

The analysis in this study included the following demographic variables: sex (male, female), age at diagnosis (65–75, >75 years), and race (white, black, other, unknown). Likewise, cancer characteristics were categorized by grade (I–II, III–IV, unknown), tumor size (≤3.0, 3.1–5.0 cm), alpha fetoprotein (AFP) (negative, positive, unknown), Ishak score (1–4, 5–6, unknown), and microvascular invasion (no, yes, unknown). Treatment characteristics included RFA (code 17), SR (codes 20–60), and LT (code 61). All the variables were defined using specific SEER codes.

The two main endpoints in this study were overall survival (OS) and liver-cancer-specific survival (LCSS). In SEER database, the OS was defined as time until death as a result of any cause, while LCSS was defined as time until death attributed to HCC.

Statistical analysis

The demographic and clinicopathological baseline characteristics were compared within subgroups by Pearson's χ^2 test. Survival analyses for OS and LCSS were performed using Kaplan–Meier method, and the differences between selected groups were compared using log-rank test. Cox proportional hazards model was performed to evaluate the relative risk factors associated with OS or LCSS, and adjusted hazard ratios (aHRs) with 95% confidence intervals (CI) were obtained for each variable. Statistical analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). A two-tailed *P*-value below 0.05 was considered statistically significant.

Propensity score matching

A propensity score matching (PSM) analysis using SPSS 22.0 was performed to control for and minimize the potential bias in this study. For this retrospective analysis, related variables about the age at diagnosis, tumor grade, tumor size, alpha fetoprotein, Ishak score, and microvascular invasion were included in propensity matching analysis. Patients receiving SR or RFA were matched 1:1 based on the propensity score without exceeding match tolerance. Then, the variable balance between the two groups was evaluated by Pearson's χ^2 test. The survival analyses were also performed for matched patients using the same methods mentioned above.

RESULTS

Demographic and clinicopathological baseline characteristics

A total of 461 patients who underwent SR and 575 patients who underwent RFA who met the inclusion and exclusion criteria were extracted from SEER database from 2004 to 2012.

Except for patients' race, sex, and age at diagnosis, notable differences were detected in all relevant clinicopathological variables between the two groups. In contrast to the SR group, the RFA group presented better differentiation, smaller tumor size, a lower probability of microvascular invasion, higher Ishak scores, and a higher proportion of patients with elevated AFP levels (all $P < 0.05$). The major baseline characteristics of this study are shown in Table 1.

Furthermore, with the aim of observing whether the selection of treatments was varied in different age groups, the utilization of the three main treatment modalities for early-stage HCC were compared among the two age groups from 2004 to 2012, using data collected from SEER database with the same inclusion and exclusion criteria mentioned above. The results demonstrated that elderly patients were more likely to undergo SR (40.20% vs 26.36%) or RFA (47.80% vs 36.44%) as their initial treatments, while younger patients had a higher rate of utilization of LT (37.20% vs. 12.00%) ($P < 0.05$) [Figure 1].

Comparison of survival outcomes between RFA and SR groups

The median follow-up time was 40.0 months [interquartile range (IQR), 25.0–64.0 months] in the SR group and 32.0 months (IQR, 18.0–52.0 months) in the

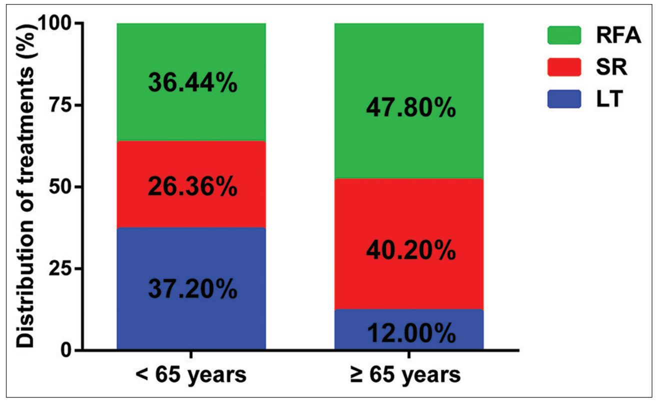

Figure 1: Therapy utilization of patients with early-stage HCC stratified by age. LT: Liver transplantation; SR: Surgical resection; RFA: Radiofrequency ablation

Table 1: Patient and tumor characteristics (before and after propensity score matching)

Variables	Before matching			After matching		
	SR (*n*=461), *n* (%)	RFA (*n*=575), *n* (%)	*P**	SR (*n*=259), *n* (%)	RFA (*n*=259), *n* (%)	*P**
Median follow-up (months) (IQR)	40.0 (25.0-64.0)	32.0 (18.0-52.0)		47.0 (24.0-74.0)	34.0 (18.0-52.0)	
Age at diagnosis (years), range	65-91	65-91		65-91	65-89	
65-75	340 (73.8)	409 (71.1)	0.349	199 (76.8)	200 (77.2)	0.917
>75	121 (26.2)	166 (28.9)		60 (23.2)	59 (22.8)	
Race						
White	259 (56.2)	340 (59.1)	0.598	140 (54.0)	162 (62.5)	0.166
Black	40 (8.7)	42 (7.3)		23 (8.9)	18 (7.0)	
Other	161 (34.9)	190 (33.1)		96 (37.1)	78 (30.1)	
Unknown	1 (0.2)	3 (0.5)		0	1 (0.4)	
Sex						
Female	303 (65.7)	357 (62.1)	0.226	176 (68.0)	174 (67.2)	0.851
Male	158 (34.3)	218 (37.9)		83 (32.0)	85 (32.8)	
Grade						
I-II	332 (72.0)	221 (38.4)	**<0.001**	184 (71.0)	187 (72.2)	0.478
III-IV	83 (18.0)	28 (4.9)		31 (12.0)	23 (8.9)	
Unknown	46 (10.0)	326 (56.7)		44 (17.0)	49 (18.9)	
Tumor size (cm)						
≤3.0	209 (45.3)	364 (63.3)	**<0.001**	149 (57.5)	145 (56.0)	0.723
3.1-5.0	252 (54.7)	211 (36.7)		110 (42.5)	114 (44.0)	
AFP						
Negative	139 (30.1)	153 (26.6)	**<0.001**	84 (32.4)	84 (32.4)	0.900
Positive	189 (41.0)	305 (53.1)		121 (46.7)	117 (45.2)	
Unknown	133 (28.9)	117 (20.3)		54 (20.9)	58 (22.4)	
Ishak score						
1-4	78 (16.9)	43 (7.5)	**<0.001**	24 (9.3)	25 (9.7)	0.985
5-6	79 (17.1)	140 (24.3)		48 (18.5)	47 (18.1)	
Unknown	304 (66.0)	392 (68.2)		187 (72.2)	187 (72.2)	
Microvascular invasion						
No	387 (83.9)	549 (95.5)	**<0.001**	245 (94.6)	246 (95.0)	0.843
Yes	74 (16.1)	26 (4.5)		14 (5.4)	13 (5.0)	
Status						
Alive	221 (47.9)	188 (32.7)	**<0.001**	112 (43.2)	82 (31.7)	**0.006**
Dead	240 (52.1)	387 (67.3)		147 (56.8)	177 (68.3)	
Liver cancer	179 (38.8)	286 (49.7)		107 (41.3)	136 (52.5)	
Other	61 (13.3)	101 (17.6)		40 (15.5)	41 (15.8)	

**P*-values calculated by Pearson's Chi-squared testing; statistically significant values are given in bold, $P<0.05$. SR: Surgical resection; RFA: Radiofrequency ablation; IQR: Interquartile range; AFP: Alpha fetoprotein

RFA group. Kaplan–Meier analysis revealed that patients receiving SR had better prognosis than those receiving RFA in terms of OS ($P < 0.001$) and LCSS ($P < 0.001$). The 1-, 3-, and 5-year OS rates were 88.0%, 68.6%, and 54.0% for the SR group and 84.4%, 53.6%, and 32.5% for the RFA group, respectively. The 1-, 3-, and 5-year LCSS rates were 90.5%, 75.4%, and 63.7% for the SR group and 88.2%, 61.7%, and 43.5% for the RFA group, respectively [Figure 2a and b]. In addition, a multivariate analysis was performed to evaluate the prognostic factors of OS and LCSS. In the multivariate model, age, tumor size, AFP, and treatment were significantly associated with OS, while tumor size, AFP, microvascular invasion, and treatment were associated with LCSS. All the independent risk factors and their HR with 95% CI are listed in Table 2. After adjusting those prognostic values, the SR group still had better long-term survival than the RFA group both in terms of OS (RFA, aHR = 1.680 (1.390, 2.031), $P < 0.001$) and LCSS (RFA, aHR = 1.658 (1.327, 2.070), $P < 0.001$).

Considering tumor heterogeneity and sample capacity disparity between the two surgical groups, PSM analysis was conducted to control for and reduce the potential selection bias. A total of 518 patients were selected after PSM, with a 1:1 ratio between the SR group and the RFA group. Table 1 outlines the balanced characteristics after PSM (all $P > 0.05$). Then, the OS and LCSS were compared between the two groups, and the outcomes were consistent with the original survival comparisons before PSM. The 1-, 3-, and 5-year OS rates were 86.5%, 68.3%, and 54.7% for the SR group and 82.1%, 53.9%, and 31.6% for the RFA group, respectively ($P < 0.001$). The 1-, 3-, and 5-year LCSS rates were 90.7%, 75.9%, and 65.6% for the SR group and 85.7%, 60.8%, and 41.7% for the RFA group, respectively ($P < 0.001$) [Figure 2c and d]. Multivariate analysis also showed that the RFA group was associated with poorer OS (RFA, aHR = 1.595 (1.276, 1.994), $P < 0.001$) and LCSS (RFA, aHR = 1.691 (1.305, 2.191), $P < 0.001$) than the SR group. All the independent risk factors and their HR with 95% CI are listed in Table 3.

Subgroup analysis of surgical effects

To further investigate the effects of different treatments on survival, subgroup analysis was performed based on patients' age and tumor size, which were identified as independent risk factors associated with OS or LCSS in this study. Cox's regression model was separately used to estimate aHR with 95% CI in each subgroup. In age group A (65–75 years), the SR group was associated with better OS and LCSS than the RFA group regardless of tumor size (all $P < 0.05$). However, in age group B (>75 years), there was no significant difference

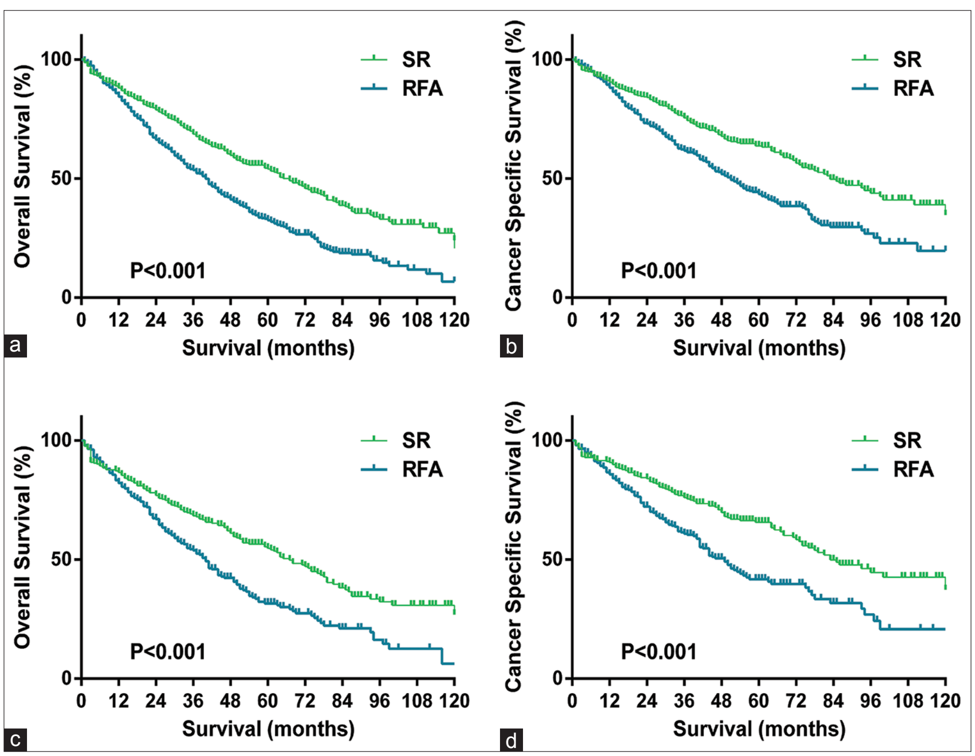

Figure 2: Kaplan–Meier curves of OS and LCSS stratified by treatment before and after PSM. (a) OS comparison before PSM. (b) LCSS comparison before PSM. (c) OS comparison after PSM. (d) LCSS comparison after PSM. OS: Overall survival; SR: Surgical resection; RFA: Radiofrequency ablation; PSM: Propensity score matching; LCSS: Liver cancer-specific survival

Table 2: Cox proportional hazards regression model analyses of overall survival and liver-cancer-specific survival before propensity score matching

Variables	OS		LCSS	
	aHR (95% CI)	*P**	aHR (95% CI)	*P**
Age at diagnosis, years				
65–75	Reference		Reference	
>75	1.304 (1.094-1.553)	**0.003**	1.121 (0.910-1.381)	0.284
Race				
White	Reference		Reference	
Black	1.197 (0.909-1.576)	0.201	1.077 (0.774-1.499)	0.659
Other	0.554 (0.460-0.666)	**<0.001**	0.546 (0.441-0.676)	**<0.001**
Unknown	0.250 (0.035-1.806)	0.169	0.355 (0.049-2.580)	0.306
Sex				
Female	Reference		Reference	
Male	1.007 (0.853-1.190)	0.932	1.113 (0.920–1.348)	0.271
Grade				
I–II	Reference		Reference	
III–IV	1.226 (0.932-1.613)	0.146	1.396 (1.028-1.896)	**0.033**
Unknown	1.065 (0.884-1.284)	0.507	1.159 (0.932-1.442)	0.186
Tumor size (cm)				
≤3.0	Reference		Reference	
3.1–5.0	1.277 (1.085-1.503)	**0.003**	1.293 (1.070-1.563)	**0.008**
AFP				
Negative	Reference		Reference	
Positive	1.465 (1.201-1.786)	**<0.001**	1.462 (1.159-1.845)	**0.001**
Unknown	1.273 (1.019-1.590)	**0.033**	1.355 (1.047-1.753)	**0.021**
Ishak score				
1–4	Reference		Reference	
5–6	1.241 (0.908-1.698)	0.176	1.423 (0.978-2.071)	0.065
Unknown	1.260 (0.960-1.655)	0.096	1.418 (1.018-1.973)	**0.039**
Microvascular invasion				
No	Reference		Reference	
Yes	1.279 (0.979-1.670)	0.071	1.555 (1.166-2.073)	**0.003**
Treatment				
SR	Reference		Reference	
RFA	1.680 (1.390-2.031)	**<0.001**	1.658 (1.327-2.070)	**<0.001**

**P*-values calculated by log-rank testing; statistically significant values are given in bold, $P<0.05$. SR: Surgical resection; RFA: Radiofrequency ablation; AFP: Alpha fetoprotein; CI: Confidence interval; OS: Overall survival; LCSS: Liver-cancer-specific survival; aHR: Adjusted hazard ratio (adjusted for age at diagnosis, race, sex, grade, tumor size, AFP, Ishak score, microvascular invasion, treatment)

between the SR group and RFA group in terms of OS or LCSS when the tumors measured less than 3.0 cm (all $P > 0.05$), while the SR group presented better OS and LCSS than the RFA group when the tumors were larger than 3.0 cm (all $P < 0.05$). The results of subgroup analyses after PSM were consistent with the original survival comparisons before PSM [Figure 3].

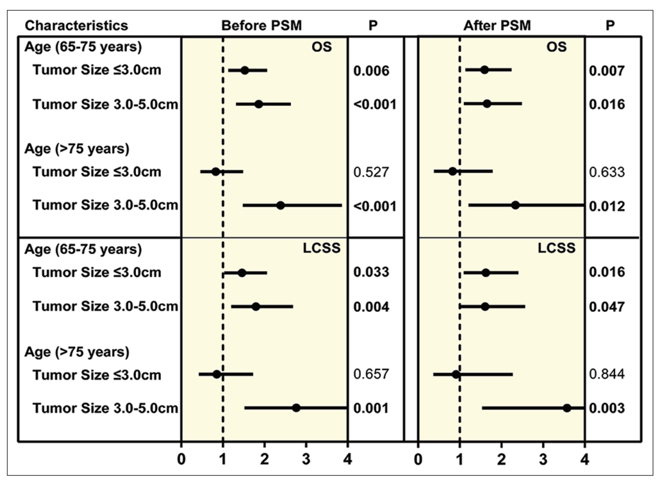

Figure 3: Multivariate Cox proportional hazard regression model of OS and LCSS comparing SR with RFA stratified by patient's age and tumor size before and after PSM. OS: Overall survival; SR: Surgical resection; RFA: Radiofrequency ablation; PSM: Propensity score matching; LCSS: Liver cancer-specific survival

DISCUSSION

An aging society means that the number of elderly patients with cancer is also predicted to increase in the future.[5] It is estimated that the incidence of HCC will increase by approximately 59% by 2030, more than 50% of which will be accounted for by those ≥65 years old.[4] It cannot be denied that elderly patients (≥65 years) with HCC deserve more attention. With prolongation of life expectancy, advanced surgical techniques, and better perioperative management, active treatments have currently been recommended as a rational approach to early-stage HCC in the elderly patients.[9,11,14-16] LT is a superior curative therapy in terms of long-term survival for early-stage HCC compared with SR or RFA, including selected elderly

Table 3: Cox proportional hazards regression model analyses of overall survival and liver-cancer-specific survival after propensity score matching

Variables	OS		LCSS	
	aHR (95% CI)	*P**	aHR (95% CI)	*P**
Age at diagnosis, years				
65-75	Reference		Reference	
>75	1.223 (1.057-1.475)	**0.008**	1.009 (0.732-1.390)	0.958
Race				
White	Reference		Reference	
Black	1.300 (0.885-1.908)	0.181	1.073 (0.672-1.714)	0.767
Other	0.546 (0.420-0.709)	**<0.001**	0.517 (0.383-0.699)	**<0.001**
Unknown	1.427 (0.196-10.403)	0.726	1.615 (0.220-11.866)	0.637
Sex				
Female	Reference		Reference	
Male	1.212 (0.958–1.534)	0.109	1.186 (0.915-1.537)	0.198
Grade				
I-II	Reference		Reference	
III-IV	1.226 (0.846-1.775)	0.282	1.417 (0.938-2.142)	0.098
Unknown	0.858 (0.622-1.182)	0.349	1.081 (0.762-1.534)	0.664
Tumor size (cm)				
≤3.0	Reference		Reference	
3.1-5.0	1.215 (1.080-1.445)	**0.012**	1.246 (1.107-1.537)	**0.007**
AFP				
Negative	Reference		Reference	
Positive	1.539 (1.176-2.014)	**0.002**	1.661 (1.213-2.274)	**0.005**
Unknown	1.334 (0.980-1.815)	0.067	1.386 (0.965-1.989)	0.077
Ishak score				
1-4	Reference		Reference	
5-6	1.176 (0.743-1.860)	0.488	1.462 (0.852-2.507)	0.168
Unknown	1.046 (0.698-1.567)	0.828	1.207 (0.745-1.957)	0.444
Microvascular invasion				
No	Reference		Reference	
Yes	1.387 (0.827-2.326)	0.215	1.604 (0.931-2.761)	0.088
Treatment				
SR	Reference		Reference	
RFA	1.595 (1.276-1.994)	**<0.001**	1.691 (1.305-2.191)	**<0.001**

**P*-values calculated by log-rank testing; statistically significant values are given in bold, $P<0.05$. SR: Surgical resection; RFA: Radiofrequency ablation; AFP: Alpha fetoprotein; CI: Confidence interval; OS: Overall survival; LCSS: Liver-cancer-specific survival; aHR: Adjusted hazard ratio (adjusted for age at diagnosis, race, sex, grade, tumor size, AFP, Ishak score, microvascular invasion, treatment)

patients.[10,15,16] Nevertheless, due to organ shortage, LT is not a viable option on a large scale, and age greater than 65 years is currently a relative contraindication for LT.[6,7] In this study, we observed a significant treatment selection bias (the proportions of LT, SR, and RFA, 37.20%, 26.36%, and 36.44% versus 12.0%, 40.20%, and 47.80%, respectively) between the younger and elderly groups from 2004 to 2012 in the United States. The elderly patients were more likely to receive SR or RFA as their first-line treatment for early-stage HCC. Several retrospective studies have separately compared the survival benefits of SR or RFA between selected elderly patients and younger patients, in which the safety and effectiveness of SR or RFA for elderly patients with small HCC have been widely confirmed.[9,11] It is generally recognized that both SR and RFA are able to effectively modify the natural history of early-stage HCC in elderly patients who have adequate liver functional reserves.[17-20] Unfortunately, it still remains controversial which treatment provides better survival outcomes in this age group. From this perspective, it is worthwhile to identify the better therapeutic option, SR or RFA, for elderly patients with early-stage HCC in the era of organ shortage.

Although numerous studies have been conducted to compare the efficacy of SR and RFA for patients with HCC conforming to Milan criteria, the conclusions continue to be an ongoing debate at present,[21,22] and very few studies have exclusively compared the survival benefits of SR with those of RFA in elderly patients. To the best of our knowledge, there are only two high-quality studies concerning this issue. In a retrospective study, Peng *et al.* reported that there was no obvious difference between RFA (n = 89) and SR (n = 91) groups in terms of OS (1-, 3-, and 5-year OS, 93.2%, 71.1%, and 55.2% versus 88.8%, 62.8%, and 51.9%, respectively, $P > 0.05$) for elderly patients (>65 years) with HCC meeting Milan criteria; besides, RFA was found to be more effective than SR for elderly patients with HCC ≤3.0 cm (1-, 3-, and 5-years OS, 94.2%, 82.6%, and 67.5% versus 90.1%, 65.0%, and 55.1%, respectively, $P < 0.05$).[13] In contrast, Bauschke *et al.* demonstrated that SR (n = 63) resulted in significantly better long-term survival rates than RFA (*n* = 64) in elderly patients (≥70 years) with early-stage HCC ($P < 0.05$).[12] The controversy between the two studies is obvious, as are their limitations, such as small sample size, selection bias, lack of histological diagnosis, or subgroup analyses. Therefore, this large population-based retrospective study was conducted using PSM analysis to compare the different survival outcomes of SR (*n* = 461) and RFA (*n* = 575) in elderly patients (≥65 years) with single HCC ≤5 cm. In line with the study by Bauschke *et al*., the results of this study demonstrated that SR resulted in significantly better OS and LCSS than RFA for the cohort of patients in this study, both before and after PSM (all $P < 0.05$).

The results in this study can be readily explained by the following. First, with advanced surgical techniques and better perioperative management, SR (open or laparoscopic) can be tolerated as well as RFA in majority of elderly patients with similar postoperative comorbidities, and laparoscopic resection has been suggested to be considered as an option in selected elderly patients who are deemed poor candidates for open hepatectomy.[11,23] Besides, significant advantages of SR over RFA are mainly attributable to the removal of potential venous tumor thrombi and complete eradication of the primary tumor with clean resection margins by SR,[24] while RFA is restricted by the limitation of ablation volume and non-histological confirmation of the ablative margin.[10,25,26] Previous studies have reported that RFA is unable to produce a sufficiently high temperature in all areas of tumor if the nodule is larger than 4 cm in diameter and that the maximum tumor size under optimal conditions is 3 cm to achieve a 1-cm ablative margin.[10,25] Imperfect tumor removal may result in a higher risk of recurrence and worse survival.[21] In addition, RFA is technically infeasible for tumors in certain locations, such as those close to major bile ducts and large vessels, which are associated with higher operative risk and incomplete tumor removal.[26] Open or laparoscopic resection might be the better choice in those situations. Furthermore, one interesting study indicated that SR could provide better middle-term (24 months) quality of life after treatment than RFA, including physical, functional, emotional, and social well-being.[27] Improved middle-term quality of life after treatment may contribute to prolongation of patients' long-term survival.

The long-term survival of elderly patients, a unique group, is inevitably affected by age-related life expectancy, with 19.3 years at age 65 years, 12.2 years at age 75 years, and 6.6 years at age 85 years in the United States.[28,29] In addition, tumor size has been widely identified as an independent risk factor for OS and LCSS, and the controversy about optimal therapy mainly focused on single tumors ≤3.0 cm in diameter.[21,22,30] These factors should be given special consideration when selecting an appropriate treatment for elderly patients. In this study, subgroup analysis according to patient's age (65–75, >75 years) and tumor size (≤3.0, 3.1–5.0 cm) revealed that SR group still had better OS and LCSS than the RFA group, except for those older than 75 years with tumors ≤3.0 cm. Based on the above evidence, it is not surprising that SR results in better local control of the tumor and a longer survival period than RFA for single tumors measuring 3–5 cm in diameter regardless of the patient's age. For tumors ≤3 cm, the different results in the two age groups might be explained by inherent features of very elderly patients (>75 years) and the comparable efficacy of RFA to SR for selected patients. Apart from the influence of life expectancy, elderly patients with HCC are generally characterized by age-related deterioration of liver function and higher incidences of comorbidities, which are related to higher perioperative risk.[8,31] Considering these characteristics, the advantages of RFA over SR, such as minimal invasiveness, less blood loss, lower perioperative risk, and fewer deteriorative effects on liver function, must not be overlooked.[13,24,32] In addition, tumor diameter ≤3 cm is deemed as a favorable prognostic factor for both OS and LCSS, and several studies have proved that RFA can provide comparable survival rates to SR for selected patients with HCC with single tumors ≤3 cm in diameter, if a patient's performance status, tumor location, and underlying liver function are considered.[30,32-34] These reasons may partly explain why RFA can be a viable alternative to SR for those older than 75 years with tumor ≤3.0 cm.

There are some limitations of this study. First, the information of postoperative adjuvant therapy (such as adjuvant antiviral therapy and treatments for local recurrence) is not available in SEER database. Besides, the propensity matching values do not include Child–Pugh score, performance status, and patient comorbidities, which are critical prognostic factors for HCC. Furthermore, interest in microwave ablation (MWA) has increased in recent years due to its potential physical advantages, which have been facilitated by modern high-powered devices.[35] It was reported that MWA could be as effective as RFA for single HCC less than 3 cm, and MWA showed better tumor inactivation ability over RFA for 3.0–5.0 cm tumors and tumors adjacent to vessels and gallbladder.[36] It is a pity that SEER database does not include patients with HCC who underwent MWA, and hence survival benefits of SR versus those of MWA in elderly patients with early-stage HCC are warranted to be further compared in a future study.

CONCLUSION

In summary, this study provides further evidence supporting SR over RFA for elderly patients (≥65 years) with single HCC tumors ≤5 cm, in terms of long-term survival. However, RFA can be an alternative to SR for very elderly patients (>75 years) with single HCC tumor ≤3 cm. Given the limitations of SEER database, further high-quality studies are needed to validate these findings.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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