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INTERVENTIONAL

Radiofrequency ablation versus surgical resection of hepatocellular carcinoma: contemporary treatment trends and outcomes from the United States National Cancer Database

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Abstract

Purpose To compare utilization and effectiveness of radiofrequency ablation (RFA) and surgical resection for hepatocellular carcinoma (HCC).

Methods The 2004–2015 United States National Cancer Database was queried for HCC patients treated by RFA and surgical resection. Patients were 1:1 propensity score matched. Duration of hospital stay, unplanned readmission rates, and overall survival (OS) were compared in the matched cohort via multivariable regression models.

Results Eighteen thousand two hundred ninety-six patients were included (RFA, $n = 8211$; surgical resection, $n = 10{,}085$). RFA was more likely in young male whites with high degree of hepatic fibrosis, high bilirubin levels, high INR, and multifocal HCC; resection was more likely in those with private insurance, high income, high cancer grade and stage, and larger HCC. RFA rates varied between 32.3% (East South Central) and 58.5% (New England). Post-treatment outcomes were superior for RFA versus resection regarding duration of hospital stay (median 1 vs. 5d, $p < 0.001$), 30-day unplanned hospital readmission rates (3.1% vs. 4.5%, $p < 0.001$), and 30-/90-day mortality (0% vs. 4.6%/8%, $p < 0.001$). Overall survival was comparable for RFA and resection for severe hepatic fibrosis/cirrhosis (5-year OS 37.3% vs. 39.4%, $p = 0.07$), for patients > 65 years old (5-year OS 21.9% vs. 26.5%, $p = 0.47$), and for HCC < 15 mm (5-year OS 49.7% vs. 52.3%, $p = 0.78$). OS in the full cohort was superior for surgical resection (5-year OS 29.9% vs. 45.7%, $p < 0.01$).

Conclusion RFA for HCC shows substantial variation by geography, socioeconomic factors, liver function, and tumor extent. RFA offers superior post-treatment outcomes versus surgical resection and may be an alternative for older patients with cirrhosis and/or small HCC.

Key Points

- *Duration of hospital stay, unplanned readmissions, and 30-/90-day mortality are lower for RFA versus surgical resection.*
- *RFA and surgical resection show similar survival in severe hepatic fibrosis.*
- *In HCC < 15 mm, RFA and surgical resection yield similar survival.*

Keywords Hepatocellular carcinoma · Ablation technique; operative surgical procedures · Demographic factors · Survival

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Abbreviations

CCI	Charlson comorbidity index
HCC	Hepatocellular carcinoma
INR	International normalized ratio
IQR	Interquartile range
NCDB	National Cancer Database
OS	Overall survival
RFA	Radiofrequency ablation

Introduction

Hepatocellular carcinoma (HCC) is the most common hepatic malignancy and the second most common cause of cancer-associated death worldwide [1, 2]. In the USA, an increasing HCC incidence is reported with 6 annual cases per 100,000 citizens in 2010 [3].

Radiofrequency ablation (RFA) is a minimally invasive local treatment technique that uses heat to induce coagulative necrosis [4]. According to European and US-American guidelines, RFA is recommended for low-stage HCC in surgically ineligible patients [5, 6]. Best RFA results are achieved for single HCC 2–3 cm in diameter, where outcomes can approach those of surgical resection [7]. A potential limitation to liver RFA is vicinity of the HCC to heat-sensitive organs such as the gallbladder, while poor liver function or vessel infiltration might limit surgical approaches [6, 8].

Several randomized controlled clinical trials have recently compared RFA to surgical resection with controversial results: while some studies reported comparable effectiveness regarding overall and recurrence-free survival [9, 10], others showed superior outcomes for surgical resection [11, 12]. To date, large-scale studies comparing RFA and surgical resection on a population level are missing.

The aims of our study were to assess factors associated with utilization of RFA for treatment of HCC and to compare its effectiveness regarding post-treatment outcomes and overall survival to surgical resection using population-level data from the USA. We hypothesized that RFA yields superior perioperative and short-term outcomes versus surgical resection while long-term overall survival might be comparable in patient subgroups.

Material and methods

This study received prior approval by the Yale University Internal Review Board and is Health Insurance Portability and Accountability Act compliant.

The United States-based National Cancer Database (NCDB), jointly sponsored by the American College of Surgeons and the American Cancer Society, was retrospectively queried for HCC diagnosed between 2004 and 2015. The NCDB contains 34 million cancer records from more than 1500 participating institutions. It covers approximately 70% of the annually diagnosed cancer cases in the USA.

From the NCDB, patients with HCC diagnosed via histopathology or radiological imaging were included if treated via RFA or surgical resection, including wedge resection, segmental resection, and hepatic lobectomy. Exclusion criteria were unknown tumor size, age < 18 years, radiation therapy, and unknown survival status and follow-up time. Patients that received liver transplantation after initial RFA or surgical resection were excluded as well.

In the full study cohort, sociodemographic factors (including age, gender, race, education, income, insurance status, and comorbidities), liver status (extent of liver fibrosis, INR, and Bilirubin levels as detailed below), and cancer variables were compared across the treatment approaches. Primary outcomes of interest were unplanned hospital readmission rate within 30 days after RFA or surgical resection, duration of hospital stay and 30-/90-day mortality, and overall survival, defined as time from cancer diagnosis to death from any cause or censoring.

Variables

Only first-line HCC treatments were reported in the NCDB and thus information on consecutive treatments was not provided. The NCDB used American Joint Committee on Cancer 7th edition staging system to stage HCC, considering tumor size and number of tumors as well as its vascular invasion on the "T" domain; absence or presence of lymphnode metastases on the "N" domain; and absence or presence of distant metastases on the "M" domain. The Charlson Deyo Comorbidity Index (CCI) was used to report patients' comorbidities, stratified as CCI 0, CCI 1, CCI 2, and CCI ≥ 3. The extent of hepatic fibrosis was measured according to Ishak and stratified as none to moderate fibrosis (Ishak score 0–4) and severe fibrosis to cirrhosis (Ishak score 5–6) [13]. Bilirubin levels and the international normalized ratio (INR) were measured at time of HCC diagnosis.

Statistical analyses

For descriptive statistics, continuous variables were presented as median with inter-quartile range (IQR) and categorical variables as absolute number and percent. Continuous variables were compared using the Wilcoxon rank sum test and categorical variables using the χ^2 test.

Overall survival was compared using conservative supremum family tests with Gehan-Breslow weights for

Table 1 Baseline characteristics of included patients

	Total $n = 18,296$	RFA $n = 8211$	Surgical resection $n = 10,085$	p value
Age	47.0 (40.0–56.0)	46.0 (40.0–55.0)	49.0 (41.0–57.0)	< 0.0001
Gender				0.0003
Female	5129 (28.0%)	2192 (26.7%)	2937 (29.1%)	
Male	13,167 (72.0%)	6019 (73.3%)	7148 (70.9%)	
Race				< 0.0001
White	12,989 (71.0%)	6135 (74.7%)	6854 (68.0%)	
African American	2571 (14.1%)	1054 (12.8%)	1517 (15.0%)	
Others	2736 (15.0%)	1022 (12.4%)	1714 (17.0%)	
Insurance status				< 0.0001
Govt insurance	377 (2.1%)	224 (2.7%)	153 (1.5%)	
Insurance unknown and no insurance	1071 (5.9%)	456 (5.6%)	615 (6.1%)	
Medicaid	2016 (11.0%)	1092 (13.3%)	924 (9.2%)	
Medicare	8558 (46.8%)	3855 (46.9%)	4703 (46.6%)	
Private insurance	6274 (34.3%)	2584 (31.5%)	3690 (36.6%)	
Median household income for residence area				0.011
< $38,000	3679 (20.1%)	1702 (20.7%)	1977 (19.6%)	
$38,000–$47,999	4191 (22.9%)	1850 (22.5%)	2341 (23.2%)	
$48,000–$62,999	4864 (26.6%)	2244 (27.3%)	2620 (26.0%)	
$63,000+	5291 (28.9%)	2300 (28.0%)	2991 (29.7%)	
Missing	271 (1.5%)	115 (1.4%)	156 (1.5%)	
Education: proportion of residents without high school graduation				0.17
≥=21%	4118 (22.5%)	1858 (22.6%)	2260 (22.4%)	
13–20.9%	4886 (26.7%)	2254 (27.5%)	2632 (26.1%)	
7–12.9%	5355 (29.3%)	2372 (28.9%)	2983 (29.6%)	
< 7	3677 (20.1%)	1619 (19.7%)	2058 (20.4%)	
Missing	260 (1.4%)	108 (1.3%)	152 (1.5%)	
Comorbidities (Charlson score)				< 0.0001
0	8700 (47.6%)	3485 (42.4%)	5215 (51.7%)	
1	5419 (29.6%)	2404 (29.3%)	3015 (29.9%)	
2	2175 (11.9%)	1090 (13.3%)	1085 (10.8%)	
3	2002 (10.9%)	1232 (15.0%)	770 (7.6%)	
Liver fibrosis				< 0.0001
None to moderate fibrosis (Ishak score 0–4)	1921 (10.5%)	371 (4.5%)	1550 (15.4%)	
Severe fibrosis or cirrhosis (Ishak score 5–6)	2906 (15.9%)	1831 (22.3%)	1075 (10.7%)	
No information on liver fibrosis	13,469 (73.6%)	6009 (73.2%)	7460 (74.0%)	
Bilirubin level (mg/dl)				< 0.0001
Median (IQR)	0.9 (0.6–1.5)	1.1 (0.7–1.8)	0.7 (0.5–1.2)	
Missing	10,284 (56.2%)	4266 (52.0%)	6018 (59.7%)	
International normalized ratio (INR)				< 0.0001
Median (IQR)	1.1 (1.0–1.3)	1.2 (1.1–1.3)	1.1 (1.0–1.2)	
Missing	11,424 (62.4%)	4775 (58.2%)	6649 (65.9%)	
Tumor grade				< 0.0001
Grade I	3513 (19.2%)	1448 (17.6%)	2065 (20.5%)	
Grade II	5990 (32.7%)	1258 (15.3%)	4732 (46.9%)	
Grade III	2252 (12.3%)	318 (3.9%)	1934 (19.2%)	
Grade IV	248 (1.4%)	15 (0.2%)	233 (2.3%)	
Grade unknown	6293 (34.4%)	5172 (63.0%)	1121 (11.1%)	
Tumor stage				< 0.0001
Stage I	9608 (52.5%)	4813 (58.6%)	4795 (47.5%)	
Stage II	4463 (24.4%)	1995 (24.3%)	2468 (24.5%)	
Stage III	2273 (12.4%)	492 (6.0%)	1781 (17.7%)	
Stage IV	373 (2.0%)	142 (1.7%)	231 (2.3%)	
Stage unknown	1579 (8.6%)	769 (9.4%)	810 (8.0%)	
Tumor size (mm)	36.0 (25.0–61.0)	28.0 (21.0–39.0)	51.0 (31.0–81.0)	< 0.0001
Number of HCC lesions				< 0.0001
Single lesion	10,341 (56.5%)	4571 (55.7%)	5770 (57.2%)	
Multiple lesions	3702 (20.2%)	1919 (23.4%)	1783 (17.7%)	
Number of lesions not specified	4253 (23.2%)	1721 (21.0%)	2532 (25.1%)	
Chemotherapy				< 0.0001
Chemotherapy	3553 (19.4%)	2347 (28.6%)	1206 (12.0%)	
No chemotherapy	14,743 (80.6%)	5864 (71.4%)	8879 (88.0%)	

Table 1 (continued)

	Total $n = 18,296$	RFA $n = 8211$	Surgical resection $n = 10,085$	p value
Treatment facility type				< 0.0001
Academic/research program	12,090 (66.1%)	5586 (68.0%)	6504 (64.5%)	
Other facility type	6029 (33.0%)	2598 (31.6%)	3431 (34.0%)	
Missing	177 (1.0%)	27 (0.3%)	150 (1.5%)	
Treatment facility location				< 0.0001
East North Central	2722 (14.9%)	1200 (14.6%)	1522 (15.1%)	
East South Central	936 (5.1%)	302 (3.7%)	634 (6.3%)	
Facility location suppressed for age 0–39 years	177 (1.0%)	27 (0.3%)	150 (1.5%)	
Middle Atlantic	3079 (16.8%)	1128 (13.7%)	1951 (19.3%)	
Mountain	575 (3.1%)	280 (3.4%)	295 (2.9%)	
New England	1307 (7.1%)	768 (9.4%)	539 (5.3%)	
Pacific	2976 (16.3%)	1656 (20.2%)	1320 (13.1%)	
South Atlantic	3443 (18.8%)	1473 (17.9%)	1970 (19.5%)	
West North Central	1023 (5.6%)	388 (4.7%)	635 (6.3%)	
West South Central	2058 (11.2%)	989 (12.0%)	1069 (10.6%)	

crossing Kaplan-Meier survival curves [14]. Subgroup analyses depending on patients' age, hepatic fibrosis score, and size of HCC were planned a priori.

Statistical analyses were conducted using R version 3.4.3 and RStudio version 1.1.414 [15, 16]. P values < 0.05 were considered statistically significant. All reported p values are two-sided.

Propensity score matching

Based on their propensity to receive RFA or surgical resection, patients were 1:1 propensity score matched using a nearest neighbor approach with caliper width of 0.01. The overlap assumption (common support) of propensity scores was visually tested after calculation of the propensity scores but before the matching

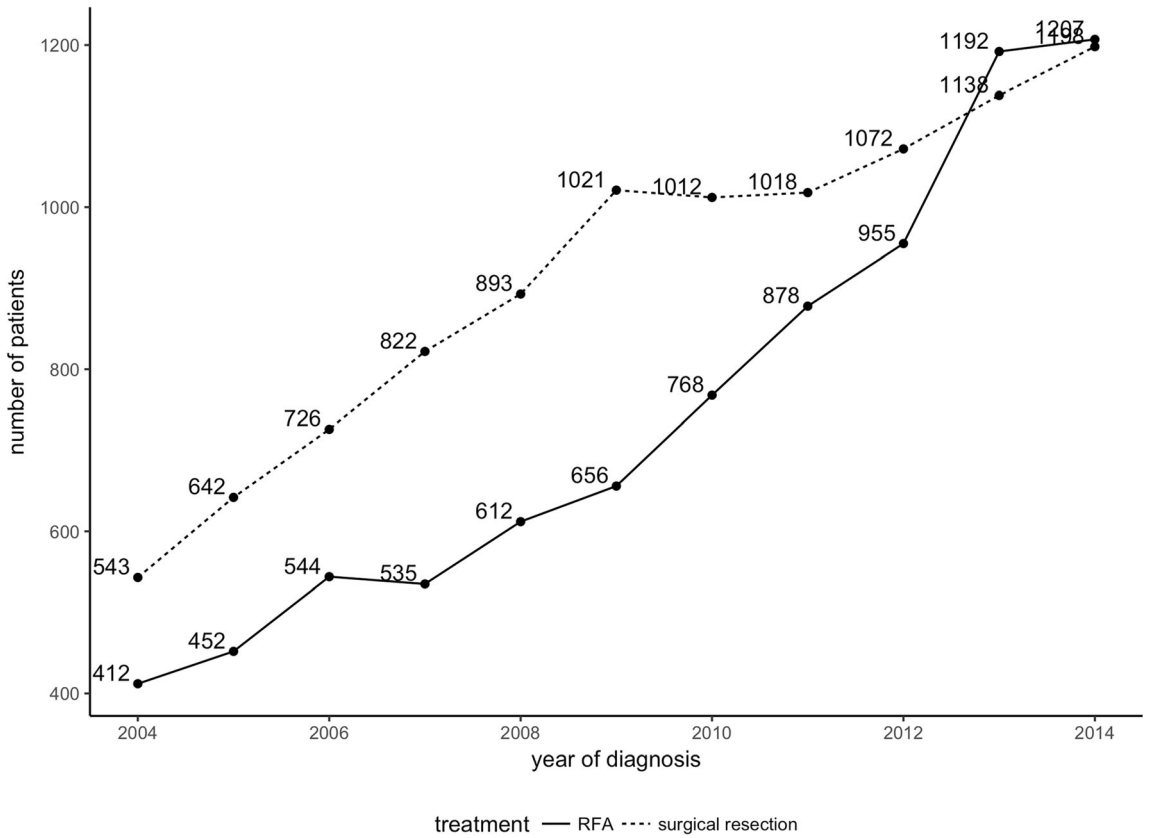

Fig. 1 Absolute number of HCC patients undergoing RFA or surgical resection from 2004 to 2014

procedure. The matching performance was assessed via calculation of the standardized difference among matching variables.

Results

Study cohort

A total of 18,296 patients fulfilled the inclusion criteria. A flow chart of patient inclusion and exclusion is shown in supplemental figure 1. Table 1 summarizes baseline characteristics of the full patient cohort.

Eight thousand two hundred eleven HCC patients (44.9%) were treated with RFA and 10,085 patients (55.1%) were treated with surgical resection. In the surgical subgroup, 6465 patients (64.1%) received segmental or wedge resection and 3620 patients (35.9%) received lobectomy.

Historical and geographical variation in RFA treatment

As shown in Fig. 1, an increasing number of patients received HCC treatment via RFA and surgical resection from 2004 to 2015. While historically more patients were treated with surgical resection, these differences diminished during the study period and in 2013–2014, case numbers for RFA and surgical resection were comparable at approximately 1200 annual cases. Further, HCC treatment showed a high degree of geographical variation: lowest RFA rates were observed in East South Central States (32.3%) and highest in New England States (58.8%), as depicted in Fig. 2. These geographic differences showed no strong correlation with HCC stage, since high proportions of low-stage HCC were evident both in State regions with high and low RFA rates (Fig. 2).

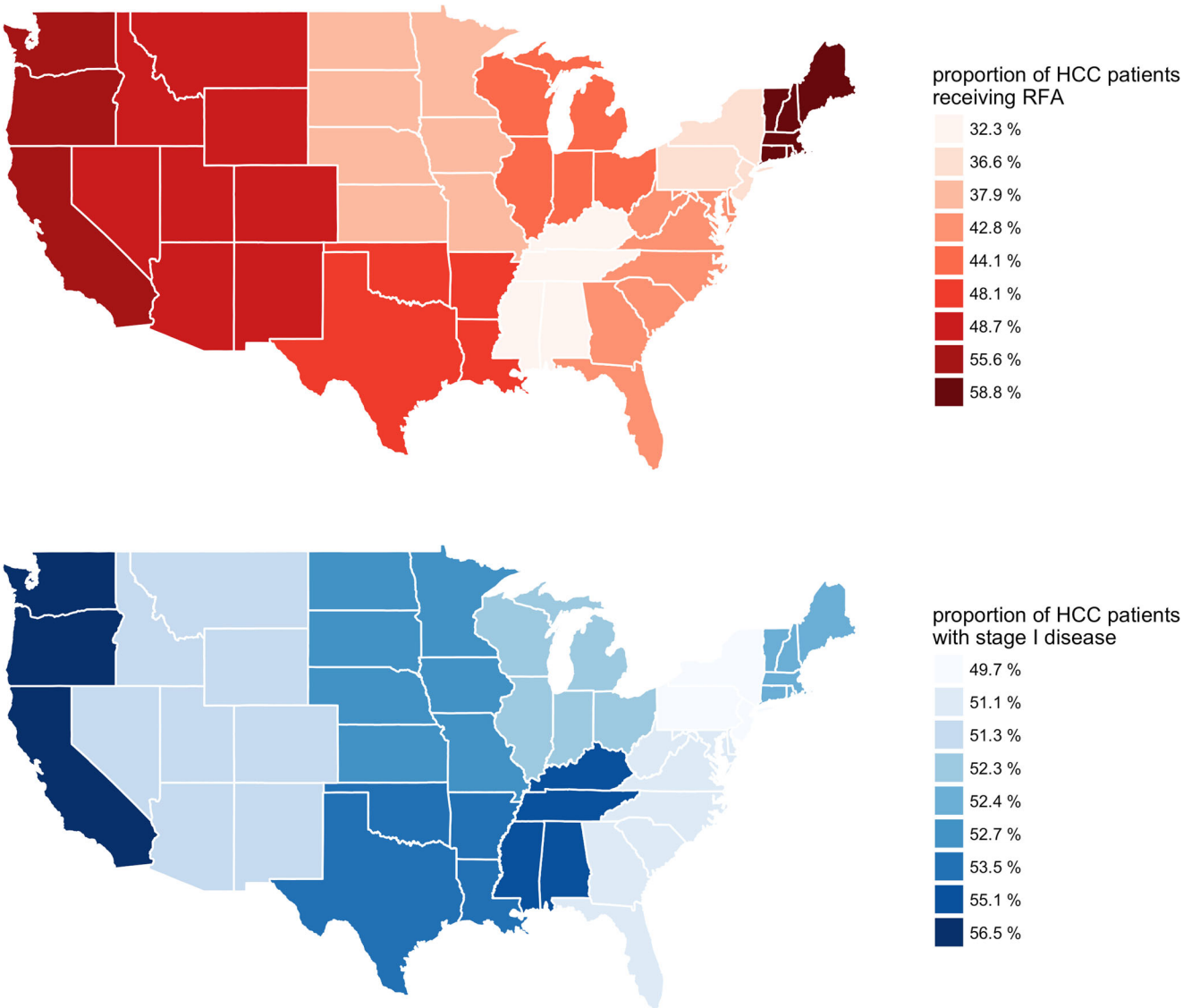

Fig. 2 Geographic maps of the US depicting proportion of HCC patients receiving RFA and those with stage I HCC

HCC treatment allocation:influence of socioeconomic factors, liver function and cancer variables

As shown in Table 1, a higher likelihood of RFA treatment was evident for younger male white patients, while patients with private insurance and high income were more likely to receive surgical resection ($p < 0.001$, respectively).

A higher likelihood of RFA was seen for comorbid patients with severe liver fibrosis (Ishak score 5–6), high bilirubin levels, high INR, and multifocal HCC ($p < 0.001$, respectively): severe liver fibrosis was evident in 22.3% of RFA patients versus 10.7% of surgical resection patients ($p < 0.001$); median bilirubin levels were 1.1 mg/dl in RFA and 0.7 mg/dl in surgical resection patients ($p < 0.001$); median INR was 1.2 in RFA and 1.1 in surgical resection patients ($p < 0.001$); and multifocal HCC was diagnosed in 23.4% of RFA patients versus 17.7% of surgical resection patients ($p < 0.001$).

Figure 3 depicts higher RFA rates for patients with severe hepatic fibrosis and cirrhosis, while surgical resection numbers were higher for patients with none to moderate hepatic fibrosis. These discrepancies further increased from 2004 to 2014.

RFA treatment was more likely for low-grade, low-stage, and smaller HCC receiving concurrent chemotherapy, compared to surgical resection ($p < 0.001$, respectively): median HCC diameter was 28 mm in RFA patients and 51 mm in patients undergoing surgical resection ($p < 0.001$). Most RFA were performed for single lesions < 50 mm in diameter ($n = 4181$, 50.9%; median size 26 mm, IQR 20–33 mm), followed by multiple lesions < 30 mm in diameter ($n = 990$, 12.1%; median size 23 mm, IQR 19–26 mm). Another 929 RFAs were performed for multiple lesions > 30 mm (11.3%; median size 41 mm, IQR 35–52 mm) and 390 for single lesions > 50 mm (4.8%; median size 61 mm, IQR 53–71 mm). In 1721 cases, there was no information on the number of HCC lesions.

RFA treatment also showed variation according to facility type with higher RFA rates in academic or research centers, and according to US state region as mentioned above.

Propensity score matching

Patients receiving RFA and surgical resection were 1:1 matched based on their respective propensity for RFA treatment, considering the following variables as predictors: age, gender, race, insurance, comorbidities, fibrosis score, extent of HCC, cancer stage, grade and size, administration of chemotherapy, and treatment facility type. Bilirubin levels and INR were not included as these variables were only available for a subset of patients. Visual assessment of the propensity scores prior to matching revealed an adequate common support.

The 1:1 matched patient cohort comprised 3422 patients treated via RFA and 3422 patients treated via surgical resection. Potential confounding variables were well balanced between both treatment groups with standardized mean differences < 0.1 except for tumor size, which was slightly smaller for patients undergoing RFA (Table 2).

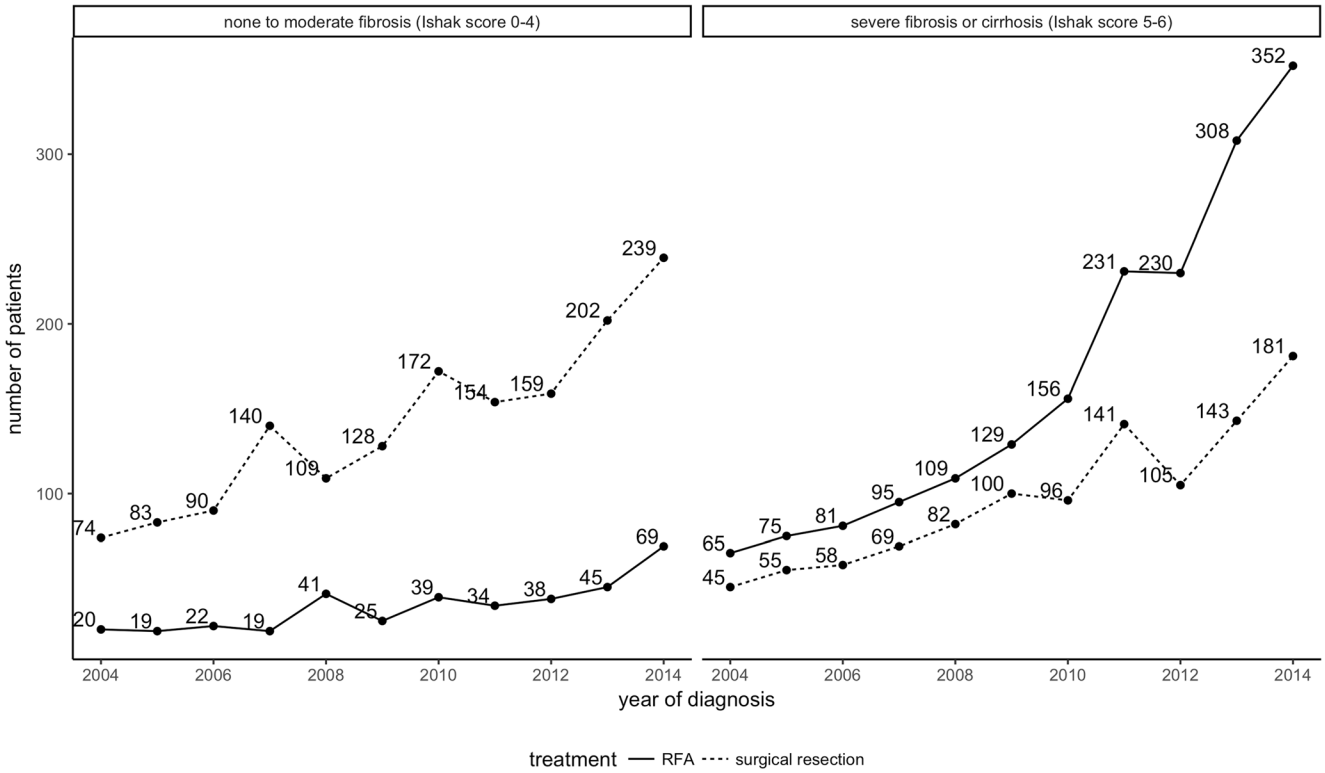

Fig. 3 RFA and surgical resection stratified by degree of hepatic fibrosis

Table 2 Characteristics of 1:1 matched patients

	RFA $n = 3422$	Surgical resection $n = 3422$
Age	47.0 (40.0–56.0)	48.0 (41.0–56.0)
Gender		
Female	897 (26.2%)	917 (26.8%)
Male	2525 (73.8%)	2505 (73.2%)
Race		
White	2478 (72.4%)	2481 (72.5%)
African American	506 (14.8%)	495 (14.5%)
Others	438 (12.8%)	446 (13.0%)
Insurance status		
Govt insurance	76 (2.2%)	71 (2.1%)
Insurance unknown and no insurance	172 (5.0%)	190 (5.6%)
Medicaid	389 (11.4%)	379 (11.1%)
Medicare	1680 (49.1%)	1689 (49.4%)
Private insurance	1105 (32.3%)	1093 (31.9%)
Comorbidities [Charlson score]		
0	1495 (43.7%)	1500 (43.8%)
1	1049 (30.7%)	1049 (30.7%)
2	450 (13.2%)	454 (13.3%)
3	428 (12.5%)	419 (12.2%)
Liver fibrosis		
None to moderate fibrosis (Ishak score 0–4)	252 (7.4%)	247 (7.2%)
Severe fibrosis or cirrhosis (Ishak score 5–6)	625 (18.3%)	593 (17.3%)
No information on liver fibrosis	2545 (74.4%)	2582 (75.5%)
Tumor grade		
Grade I	1057 (30.9%)	1065 (31.1%)
Grade II	1136 (33.2%)	1155 (33.8%)
Grade III	297 (8.7%)	310 (9.1%)
Grade IV	12 (0.4%)	14 (0.4%)
Grade unknown	920 (26.9%)	878 (25.7%)
Tumor size [mm]	31.0 (23.0–45.0)	34.0 (23.0–49.0)
Tumor stage		
Stage I	1949 (57.0%)	1993 (58.2%)
Stage II	771 (22.5%)	723 (21.1%)
Stage III	310 (9.1%)	319 (9.3%)
Stage IV	61 (1.8%)	59 (1.7%)
Stage unknown	331 (9.7%)	328 (9.6%)
Number of HCC lesions		
Single lesion	1944 (56.8%)	1983 (57.9%)
Multiple lesions	723 (21.1%)	679 (19.8%)
Number of lesions not specified	755 (22.1%)	760 (22.2%)
Chemotherapy		
Chemotherapy	666 (19.5%)	562 (16.4%)
No chemotherapy	2756 (80.5%)	2860 (83.6%)
Treatment facility type		
Academic/research program	2196 (64.2%)	2170 (63.4%)
Other facility type	1226 (35.8%)	1252 (36.6%)
30-day unplanned hospital readmission		
No unplanned readmission	3324 (97.1%)	3270 (95.6%)
Unplanned readmission	98 (2.9%)	152 (4.4%)
Duration of hospital stay		
Median (IQR)	1.0 (0.0–2.0)	5.0 (4.0–8.0)
Missing	529 (15.5%)	316 (9.2%)

Duration of hospital stay and unplanned readmissions

In the 1:1 matched cohort, the duration of hospital stay was shorter after RFA (median 1 day, IQR 0–2 days) compared to surgical resection (median 5 days, IQR 4–8 days, $p < 0.01$). Further, the unplanned hospital readmission rate after RFA was lower ($n = 98$, 2.9%) compared to surgical resection ($n = 152$, 4.4%, $p < 0.01$).

Survival analyses

In the full study cohort, 5-year overall survival increased for RFA and surgical resection from 2004 to 2014, after adjustment for potential confounders (Table 3). In the 1:1 matched cohort, median follow-up was 57.9 months (IQR 35.5–87.9 months). Overall survival was higher after RFA than surgical resection during the first 6 months and lower thereafter, as shown in Fig. 4. The 30- and 90-day mortality rates were superior for RFA where no patient died, compared to surgical resection with 156 deaths (4.6%) at 30 days and 275 deaths (8%) at 90 days ($p < 0.01$, respectively). However, long-term overall survival was superior for patients undergoing surgical resection with 5-year survival rates of 45.6% versus 30.7% for RFA. These differences were further supported by statistical comparisons for crossing Kaplan-Meier curves (overall survival difference $p < 0.01$).

Survival subgroup analyses

For the subgroup of patients with severe hepatic fibrosis and cirrhosis, RFA and surgical resection showed comparable overall survival with 2/5-year survival rates of 84.4%/37.3% and 85.4%/39.4% (Fig. 5). Overall survival differences showed no statistically significant differences ($p = 0.07$).

Further, overall survival was comparable for patients > 65 years old (2/5-year OS 74.3%/26.4% vs. 78%/26.4%, survival difference $p = 0.74$, Fig. 6) and those with HCC of less than 15 mm diameter (2/5-year OS 91%/49.2% vs. 86.4%/54.6%, survival difference $p = 0.23$, supplemental figure 2).

Further survival subgroup analyses were performed according to number and diameter of HCC, stratifying for (i) patients with single HCC < 50 mm diameter or multiple HCC < 30 mm diameter and (ii) patients with single HCC > 50 mm diameter or multiple HCC > 30 mm diameter. In both subgroups, results were comparable to the full cohort, showing a short-term overall survival benefit for RFA, while long-term overall survival was superior for surgical resection (supplemental figures 3–4).

Table 3 Adjusted 5-year overall survival rates by RFA and surgical resection, showing increasing treatment effectiveness from 2004 to 2014

	RFA: adjusted 5-year OS (%)	Surgical resection: adjusted 5-year OS (%)
2004–2006	21.8	37.2
2007–2010	26.7	45.7
2011–2014	36.2	54.0

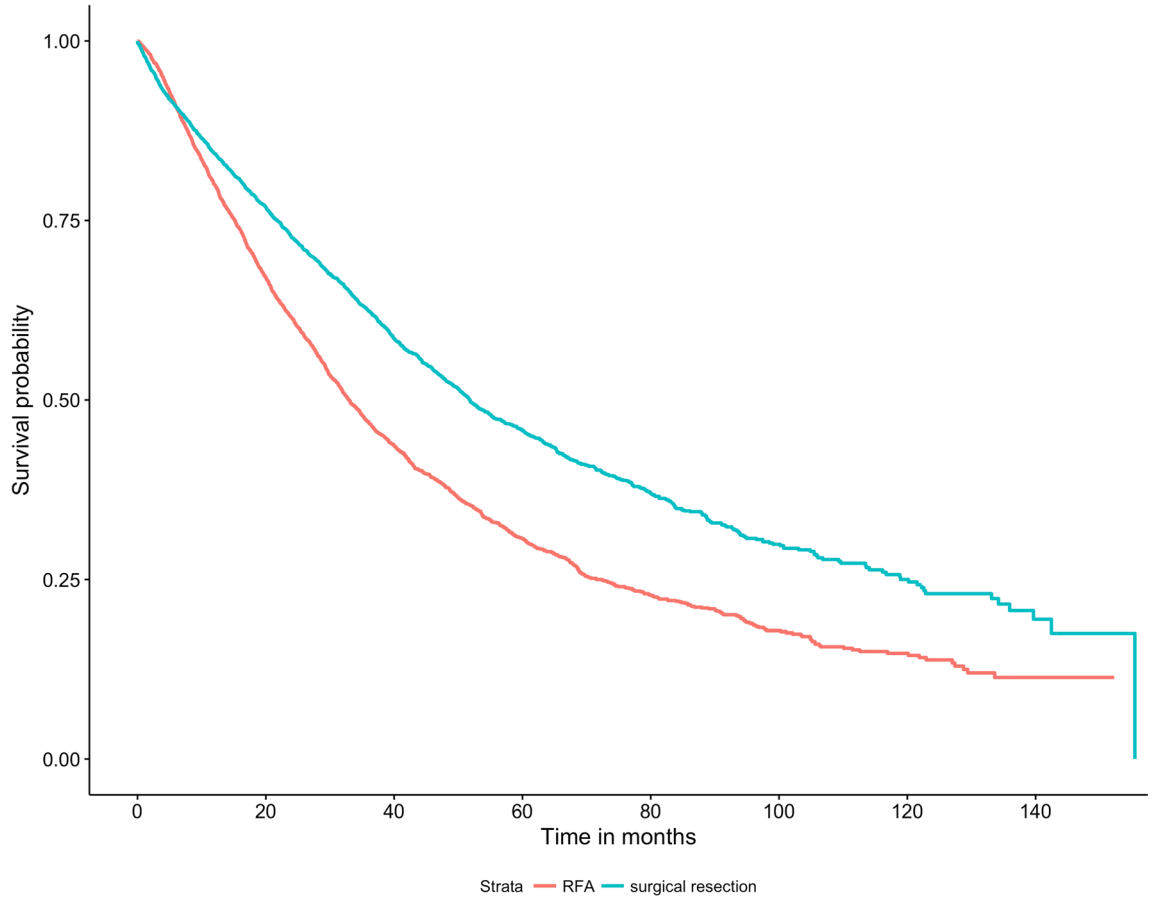

Fig. 4 Overall survival in the 1:1 matched cohort showing crossing Kaplan-Meier curves at approximately 6 months with superior post-treatment outcomes for RFA versus surgical resection (30-/90-day mortality rates: 0%/0% vs. 4.6%/8%, $p < 0.01$). Long-term overall survival was superior for surgical resection (overall survival difference $p < 0.01$)

Discussion

HCC treatment via RFA is currently recommended for low-stage disease in surgically ineligible patients [5, 6]. Still, recent trials have compared the effectiveness of RFA to surgical resection with conflicting results [9–12].

Using the large-scale National Cancer Database, we compared current HCC treatment trends and assessed perioperative as well as long-term outcomes for RFA and surgical resection.

HCC treatment allocation showed substantial historical and geographical variation and was correlated with socioeconomic factors, liver function, and cancer staging. During the study period, RFA and surgical resection rates increased, which could be attributed to an increasing HCC incidence, broadening of treatment indications for both modalities, and to an increase in participating NCDB centers. Historically, lower RFA rates increased during the study period and were comparable to surgical resection in 2013–2014, probably reflecting the growing body of evidence on RFA effectiveness [10, 17–20].

The majority of cases in the NCDB followed international guidelines, such as the Barcelona Clinic liver cancer group, recommending RFA for single HCC < 50 mm diameter of multiple HCC < 30 mm diameter [5, 6, 21]. Still, a relevant number of NCDB cases deviated from these recommendations, with 929 RFAs performed for multiple HCC > 30 mm diameter and 390 RFAs for single HCC > 50 mm diameter. Since treatment decisions were not detailed in the NCDB, one could only hypothesize that these treatment approaches were tailored by multidisciplinary teams to optimize individual patient care. Further, utilization of RFA demonstrated substantial geographical variation across the USA that is not fully explained by HCC stage differences: East South Central States RFA rates were 32.3% and 55.1% of patients stage I HCC, while New England States RFA rates were 58.8% and 52.1% of patients had stage I HCC. Geographic variations in RFA rates might coincide with factors that were not captured by the NCDB, such as clinical performance and portal venous pressure [5, 6]. Considering the benefit of RFA in selected patient populations as detailed in the results section, these differences could reflect preferential referral and treatment patterns that health policy makers and physicians should be aware of.

Further, RFA was more likely for comorbid patients, those with impaired liver function, low HCC stage, grade and smaller

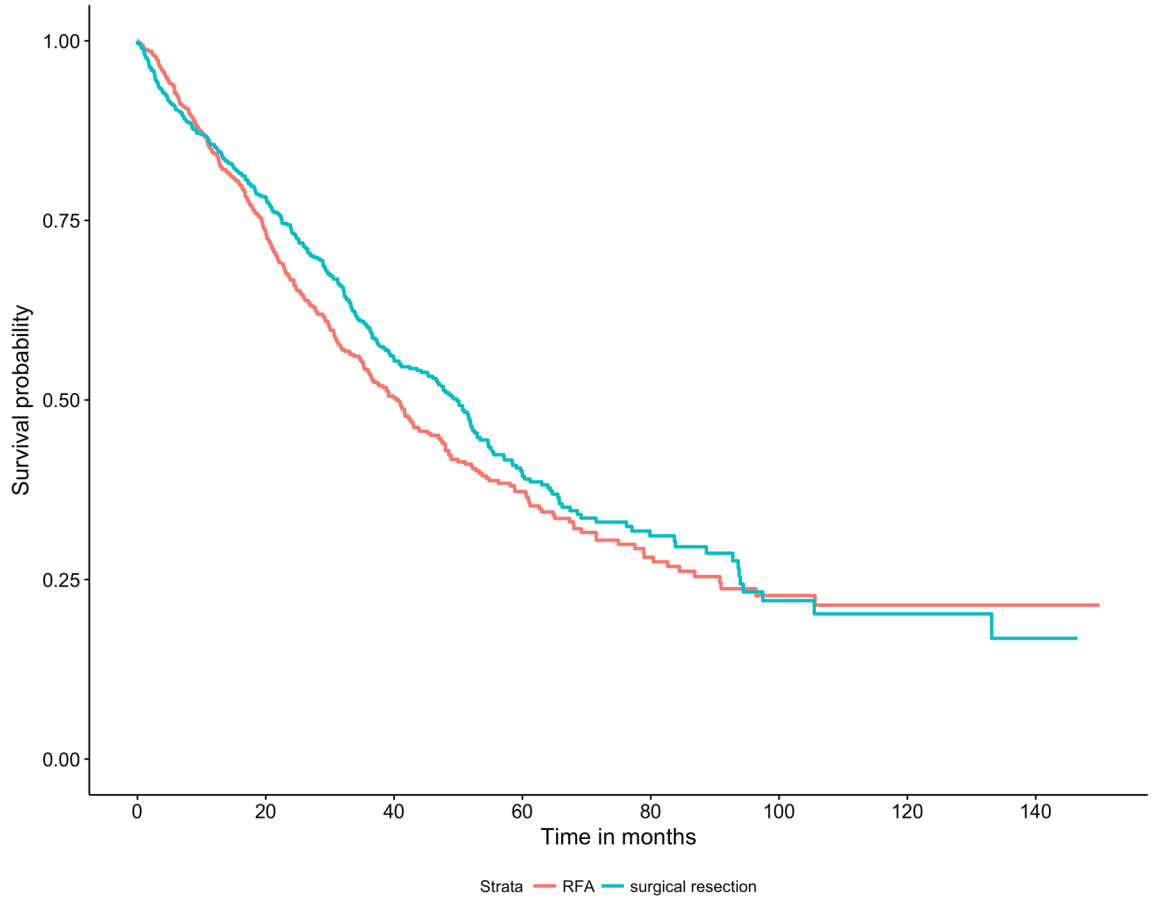

Fig. 5 Overall survival for the subgroup of patients with severe hepatic fibrosis and cirrhosis, showing comparable outcomes for RFA and surgical resection (overall survival difference $p = 0.07$)

diameter. This treatment allocation closely follows recommendations of international guidelines on RFA for HCC [5, 6].

Our study showed superior post-treatment outcomes for RFA compared to surgical resection. After propensity score matching, the duration of hospital stay was 5-fold shorter for RFA and unplanned hospital readmission rates within 30 days significantly lower than for surgical resection. Furthermore, no RFA patients died within the first 30–90 days after intervention, whereas mortality rates in the surgical resection subgroup reached 8% at 90 days. These results highlight that RFA is well tolerable for HCC treatment and associated with low post-treatment morbidity and mortality. Our findings are supported by several studies reporting RFA complications within 30 days in 1.8–3.5% and short-term mortality below 1% in smaller cohorts undergoing RFA for very-early stage HCC, but also those HCC in high-risk locations [20, 22–24]. Further, our study supports earlier publications on smaller patient cohorts reporting shorter duration of hospital stay for HCC patients undergoing RFA versus surgery [25].

Our study demonstrated comparable overall survival for RFA and surgical resection in subgroups of HCC patients with severe hepatic fibrosis/cirrhosis, those > 65 years of age and with cancers < 15 mm diameter. Age-dependent differences in RFA effectiveness have to be emphasized in light of higher RFA utilization in younger patients, as detailed above. Beyond these selected cohorts, overall survival was superior for surgical resection. These results confirm earlier prospective randomized controlled clinical trials that reported comparable outcomes of RFA and surgical resection, although these studies limited analyses to single or < 2 HCCs less than 4–5 cm in diameter [9, 10]. Chen et al reported 2-year OS rates of 82.1–82.3% in 161 Child-Pugh A patients with singular HCC < 5 cm diameter [9] and Feng et al 76.6–87.6% in 168 Child-Pugh A/B patients up to 2 HCC nodules < 4 cm diameter [10]. Their results are comparable to ours with 2-year OS rates of 74.3–91% depending on patient subgroups. Further, our results are supported by a recent meta-analysis demonstrating comparable survival for patients with Child-Pugh A cirrhosis and HCC < 3 cm diameter [26]. Our results support the rationale behind current treatment algorithms on RFA utilization proposed for example by the Barcelona Clinic Liver Cancer group or the European Association for Study of the Liver [6, 21].

Superior overall survival for surgical resection in the full study cohort might be attributable to residual confounding: the NCDB does not provide information on HCC etiology, viral status, or the patients' clinical performance, and data on bilirubin and INR were only available for a subset of patients. It is

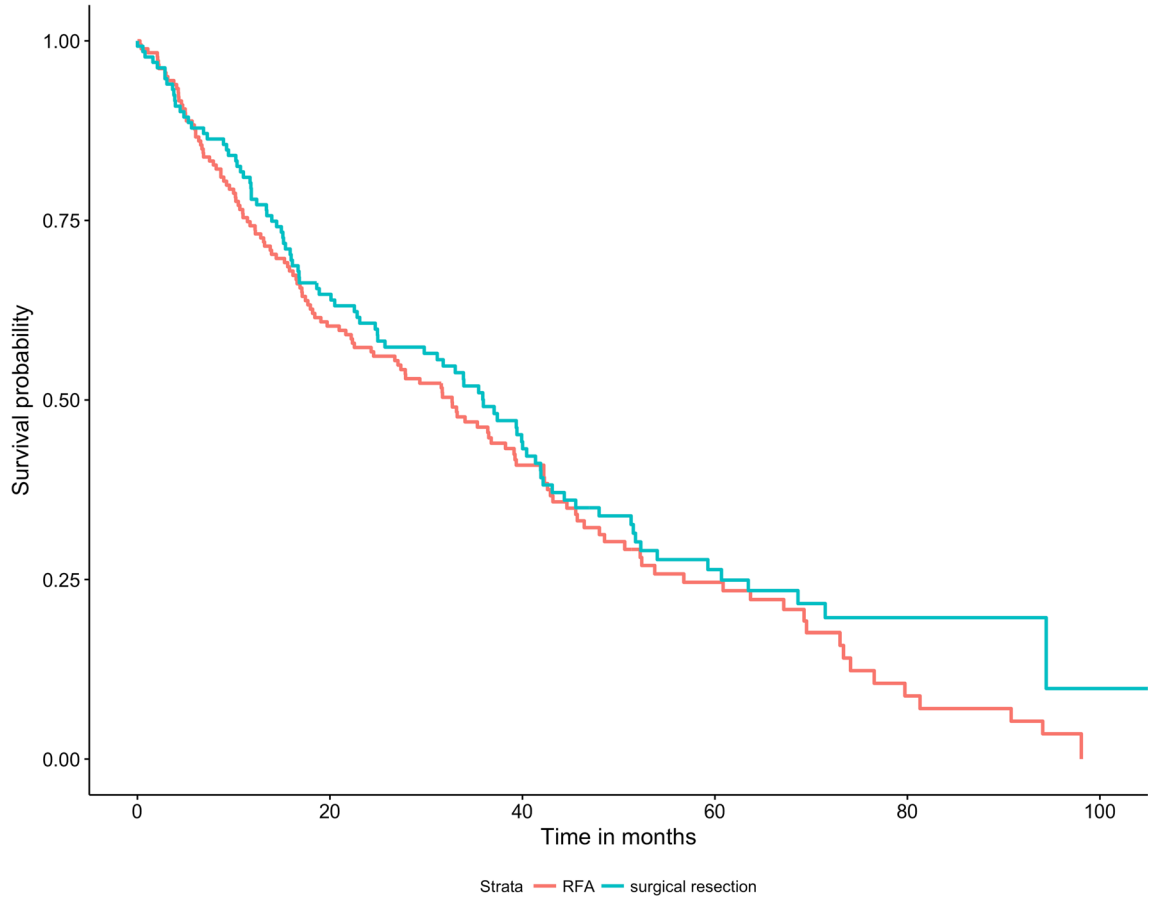

Fig. 6 Overall survival for patients age > 65 years old in the matched cohort showing comparable survival for those receiving RFA and surgical resection (overall survival difference $p = 0.74$)

possible that an unequal distribution of these known confounders in the RFA and surgical resection subgroup contributes in part to the observed benefit of surgical resection [27, 28].

For both RFA and surgical resection, improving survival rates were observed during the study period with lover survival rates for patients treated from 2004 to 2006 compared to 2011–2014, after adjustment for confounders. Notably, 5-year OS rates for RFA almost increased 2-fold comparing HCC treated in 2004–2006 (21.8%) to 2011–2014 (36.2%). Technical advancements and growing procedural experience might explain these increases in RFA effectiveness, although improvements in systemic therapy schemes might contribute as well.

Our study is inherently limited by its data source: the NCDB does not allow for the calculation of the Barcelona Clinic Liver Cancer stage or Child-Pugh score, lacking information on patients' clinical performance status, albumin levels, ascites, and hepatic encephalopathy [29]. Furthermore, laboratory results were only available for a subset of patients which could bias our results. In the general, the NCDB only provides information on first-line treatments: repeated RFA interventions and their complications are not detailed, as well as missing information on potential time to liver transplantation in cases of bridging therapy. Whether treatment decisions were reached by institutional multidisciplinary tumor boards was not highlighted in the database. Further, the NCDB exclusively reports any-cause mortality and lacks data on disease recurrence, which is a crucial endpoint for assessment of thermal ablation techniques. Also, no details on patients cause of death are provided, which limits analyses of cancer-specific survival. Finally, there are concerns about generalizability as the NCDB only covers patients presenting at participating institutions, which may yield a selection bias [30]. Potentially, patients with complications presented at non-participating institutions, and thus our results on hospital readmission rates might be biased.

Still, a wide range of potential confounders were accounted for with propensity score matching and to the best of our knowledge, our study is the largest to date comparing RFA and surgical resection for HCC.

Conclusion

In conclusion, HCC treatment via RFA shows substantial variation depending on US geography, socioeconomic factors, liver function, and tumor extent. RFA offers superior post-treatment outcomes versus surgical resection with short duration of

hospital stay, low unplanned readmission, and 30-/90-day mortality rates. Although a survival benefit for surgical resection was seen in general population, survival rates for RFA were comparable in subgroups of older patients, those with cirrhosis and small HCC. Given its superior tolerability, RFA should thus be considered a treatment alternative to surgical resection in selected subpopulations.

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Ethical approval The study was received prior approval by the Yale University internal review board.

Methodology
• observational

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