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Comparative Assessment of the Safety and Effectiveness of Radiofrequency Ablation Among Elderly Medicare Beneficiaries with Hepatocellular Carcinoma

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Abstract

Background—Radiofrequency ablation (RFA) use among patients with hepatocellular carcinoma (HCC) has increased dramatically over the last decade, but assessments outside specialized centers are lacking. This population-based study was intended to evaluate the safety and effectiveness of RFA when used to treat HCC.

Methods—A cohort study of HCC patients (diagnosed 2002–2005) was performed using linked Surveillance, Epidemiology, and End Results—Medicare data. Early (≤ 90 -day) mortality and readmission as well as survival among patients undergoing RFA, resection, or no treatment were compared using multivariate and propensity score adjusted Poisson and Cox regression models.

Results—Of 2,631 patients (mean age 76.2 ± 6.2 years, 65.9% male), 16% underwent RFA (49.6%) or resection (50.4%). Early mortality (13.6 vs 18.7%, $p=0.16$) and readmission (34.5 vs 32.1%, $p=0.60$) rates were similar among RFA and resection patients. One-year survival after RFA and resection was similar (72.2 vs 79.7%, $p=0.18$), but beyond 3-years there was a survival benefit among patients undergoing resection (39.2 vs 58.0%, $p<0.001$). Patients treated with RFA as a sole therapeutic intervention in the first year had a similar hazard of death compared to untreated patients (HR 0.84, 95% CI 0.54–1.33).

Conclusions—In the general community, patients treated with RFA have a similar risk of early adverse events compared to those treated with resection with no clear survival benefit when used as a sole intervention. Although RFA has been described as a safe and effective treatment for HCC at specialized centers, this experience may not extrapolate to the general community and requires further evaluation.

Introduction

In the US, Radiofrequency ablation (RFA) use among patients with hepatocellular carcinoma (HCC) has increased dramatically.¹ While general indications for RFA have been described (three or fewer ≤ 3 cm lesions or a solitary lesion ≤ 5 cm),² little data define patients

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for whom RFA is most appropriate, those who stand to benefit from RFA treatment, and possible reasons to deviate from current indications. Numerous case series report results among many patient subgroups (potentially resectable, cirrhotics, etc.); however, questions regarding generalizability to the general community remain because outcomes from specialized centers may not necessarily translate to community practice. Although RFA is widely perceived as safe and effective based on these studies, this hypothesis has not been rigorously evaluated in a population-based fashion.

The goals of this study were two-fold. First, identify whether RFA can be performed in the general community with a low rate of early adverse events. If so, early adverse event rates after RFA should be lower compared to resection. Second, evaluate whether RFA performed in the general community represents an effective HCC treatment. If so, there should be a survival advantage among patients treated with RFA compared to untreated patients. To address these issues of comparative effectiveness, we performed a population-based assessment of safety and effectiveness among patients with HCC who underwent RFA, resection, or no treatment.

Methods

Data

A cohort study of patients diagnosed with HCC between 2002 and 2005 was conducted using the linked Surveillance, Epidemiology, and End Results (SEER)—Medicare dataset. A comprehensive discussion of the content, quality, and generalizability of SEER-Medicare data has been detailed previously.^{3–5} This study was approved by the University of Washington Institutional Review Board and the National Cancer Institute. The National Cancer Institute reviews all manuscripts submitted for peer-review to ensure confidentiality for all patients and practitioners contained within the database—this manuscript was approved April 22, 2010.

Study Subjects

From SEER records, we identified 10,350 patients with an incident HCC diagnosis. Sequential exclusions were then made for: diagnosed by autopsy/death certificate (n=493); histology inconsistent with HCC (n=1,747 [ICD-O-3 codes other than 8170–8175 were excluded]); age <66 years (n=2,445); second malignancy diagnosed within 6 month prior to or after the HCC diagnosis (n=66); concurrently enrolled in an HMO and/or not continuously fee-for service for one year before and 3 months after diagnosis (n=2,866); underwent one or more additional therapeutic interventions potentially attributable to the HCC diagnosis in the time period between diagnosis and their index procedure or no treatment (n=39); underwent a liver transplant any time after diagnosis (n=63). This gave a final cohort of 2,631 patients. The exclusion of patients younger than 66 years was to enhance the generalizability of our findings since nonelderly patients enrolled in Medicare are either disabled, have end-stage renal disease, or both. Since RFA or hepatic resection can be utilized in the treatment of liver lesions other than HCC, patients with a second malignancy were excluded. Patients not entirely fee-for-service were excluded since concurrent enrollment in another insurance program may lead to incomplete claims ascertainment. To avoid confusing the effectiveness of either resection or RFA with that of other interventions, patients who received additional therapeutic interventions prior to the index procedure were excluded. Patients undergoing transplant could have biased the analysis (since it is the treatment of choice for HCC) and were excluded.

Variables

Demographic and clinical information was available through SEER records. A Klabunde-modified Charlson comorbidity index was calculated from the Physician/Carrier and Outpatient claims files in the year prior to diagnosis.⁶ Included within the Charlson index is a combination of diagnostic and procedural codes characterizing the severity of a patient's liver-associated comorbid condition. Because we were concerned about the possibility of residual confounding, we searched for diagnostic codes (not already included in the Charlson) from the year prior to diagnosis in the Physician/Carrier, Outpatient, and MEDPAR files that might potentially be associated with the severity of a patient's liver-associated comorbidity and/or play a role in treatment decisions: ascites (789.5, 789.51, 789.59), organomegaly (789.1, 789.2), hemorrhoids (455.0, 455.1, 455.2), hepatitis C (070.41, 070.44, 070.51, 070.54, V02.62), hepatitis B (070.20, 070.21, 070.22, 070.23, 070.30, 070.31, 070.32, 070.33, V02.61), portal venous thrombosis/Budd-Chiari (452, 453.0), gastrointestinal bleed (578.0, 578.1, 578.9), thrombocytopenia (287.5), hyperbilirubinemia (782.4, 277.4), and other cirrhotic liver conditions (571.5, 571.8, 571.9). These were then utilized to construct propensity scores for the three treatment groups which were subsequently used to adjust the regression analyses. Indicators of low income and low education were based on the lowest quartile of median income and the proportion without a high-school education within a given zip code, respectively. Healthcare Common Procedure Coding System (HCPCS) in the Physician/Carrier file within 3 months after diagnosis were used to define RFA (47382, 47370, 47380) and resection (47122, 47125, 47120, 47130). HCPCS from the Outpatient file within 3 months after diagnosis were also used to ascertain RFA use.

Analysis

This analysis included three study groups: those treated with resection, RFA, or untreated patients. Untreated patients were defined as those who did not undergo any therapeutic interventions (transplantation, resection, RFA, transarterial chemoembolization, or other forms of ablation) within 3 month after diagnosis. Statistical analyses were performed using STATA 10.1 (StataCorp, College Station, TX). All statistical comparisons were two-sided and p-values were considered significant at the $p < 0.05$ level. Categorical and continuous comparisons were obtained using χ^2 and analysis of variance, respectively. The log-rank test was used to assess differences in survival. Because this study included three comparison groups, propensity scores were calculated using multinomial logistic regression.⁷ Balance of the propensity scores was graphically assessed and the scores were deemed to be equally distributed among the three treatment groups. The propensity scores were subsequently stratified into quintiles. To deal with missing data, regression analyses were repeated using five sets of covariate data obtained through multiple imputation by chained equations.^{8,9}

Ascertainment of death was possible through 2006 for all patients. Overall survival was the primary outcome. Secondary outcomes were early (<90 day) mortality and readmission assessed as binary variables. Time to death, readmission, or censoring was calculated as the lag between index procedure date or diagnosis date (for untreated patients) and outcome. For untreated patients and those who underwent outpatient RFA, "readmission" was defined as an inpatient admission after HCC diagnosis or after the outpatient procedure, respectively. Only patients in whom readmission could be ascertained (due to fee-for-service considerations) were included in the assessment of this outcome.

Associations between overall survival and treatment were evaluated using Cox proportional hazard regression. The proportional hazard assumption was assessed using Schoenfeld residuals and extended (stratified) models were utilized if this assumption was not satisfied. Because early mortality and readmission were common in this cohort, the use of logistic

regression would likely have overestimated the association between treatment and outcome. Thus, Poisson regression was used to calculate adjusted risk ratios.^{10–12} Analyses were also evaluated in subgroups who were continuously fee-for-service for 6 months post diagnosis and those who were continuously fee-for-service for 1 year post diagnosis. These subgroups allowed evaluation of survival among patients not receiving other potentially therapeutic interventions (other than additional RFA sessions for those in the RFA group) after their index procedure—the intent being to capture only the effect of RFA or resection. All regression analyses used robust standard errors and covariate adjustments for age quartile at the time of diagnosis, sex, race, marital status, extent of disease (local, regional, distant), Charlson score, prior malignancy, tumor size (≤ 2 cm, 2.1–5cm, or > 5 cm), > 1 lesion, propensity score quintile, as well as clustering at the regional level.

Results

There were 2,631 patients with a diagnosis of HCC (average age 76.1 ± 6.1 years, with 65.9% being male, and 67.9% white). Most patients (84.2%) were untreated, while 7.8% underwent RFA and 7.9% resection. Among treated patients, 39.7% had tumors > 5 cm and 41.7% had more than one lesion. Most patients had some burden of comorbid illness, with 68.5% having a Charlson score ≥ 1 . Table 1 summarizes demographic and clinical patient characteristics stratified by treatment. Among patients treated with RFA, 17% had tumors > 5 cm and 44.7% had more than one lesion. Table 2 describes the liver-related comorbid conditions used to generate the propensity scores and the distribution of these conditions across the three treatment groups.

Safety Assessment

Thirty-day and 90-day mortality rates for the cohort were 1.5% and 21.6%, respectively. Although the rate of 30-day (5.3 vs 10.1%, $p=0.08$) and 90-day mortality (13.6 vs 18.7%, $p=0.16$) after RFA was lower than resection, neither comparison achieved statistical significance. Compared to untreated patients (0.5% and 22.6%; 30-day and 90-day mortality, respectively), RFA treated patients had higher 30-day ($p<0.001$) and lower 90-day mortality ($p=0.005$), while resected patients had higher 30-day ($p<0.001$) but similar 90-day mortality. Table 3 describes adjusted risk ratios associated with treatment and safety outcomes. Comparing resection and RFA, there were no identifiable differences in the risk of either early mortality or readmission.

Effectiveness Assessment

Overall survival rates at 1-, 3-, and 5-years for the cohort were 44.5%, 21.9%, and 17.4%, respectively. There was no difference in survival at one year between patients who underwent RFA and resection (72.2% vs 79.7%, $p=0.18$). However, at 3-years (39.2 vs 58.0%, $p<0.001$) and 5-years (34.8 vs 50.2%, $p<0.001$), survival after resection was significantly higher. Figure 1 demonstrates the association between treatment and risk of death. As compared to no treatment, RFA was associated with a lower hazard of death (HR 0.65, 95% CI 0.50–0.85). Patients treated only with RFA (either as a single session [HR 0.85, 95% CI 0.53–1.36] or in multiple sessions [HR 0.88, 95% CI 0.59–1.31]) who received no other therapeutic interventions within one year of diagnosis did not have a lower hazard of death compared to untreated patients. Receipt of resection, relative to RFA or no treatment, was associated with a 50–75% decreased hazard of death among all subgroups.

Sensitivity Analyses

Sensitivity analyses were conducted to evaluate whether the results of the effectiveness assessment were robust to varying assumptions. Because these analyses did not vary greatly from our initial analysis, only a brief summary is provided. Since there was a high

proportion of missing data for important clinical variables (in particular tumor size, number of lesions, and stage), a case-complete analysis was performed. The results were virtually identical (for both point estimates and inference) to those obtained using the imputed data. A second analysis excluding patients with metastatic disease again demonstrated similar results with one notable difference—the subgroup of patients receiving only a single RFA session within 6 months of diagnosis no longer had a significantly lower risk of death compared to no treatment.

As an exploratory analysis, the clinical characteristics of the small number of patients (n=18) who survived at least 3 years after treatment with RFA were evaluated. Compared to RFA treated patients surviving less than 3 years, their clinical characteristics suggested they may have been a lower surgical risk group, had favorable tumor biology, and/or signs of social support: Charlson score of ≤ 1 (78 vs 63%); no prior malignancies (89 vs 72%); tumor size ≤ 5 cm (86 vs 78%); married (78 vs 66%). The majority of these patients also had favorable economic characteristics (all had higher levels of education and only 22% were low income).

Discussion

In this population-based evaluation, we observed three important findings that should prompt further studies to clarify the role for RFA as a treatment for HCC patients in the general community. First, when compared to patients undergoing resection, the risk of early adverse events was not significantly lower among RFA treated patients. Second, when RFA was used as the only therapeutic intervention (either in single or multiple sessions) in the first year after diagnosis, there was no obvious survival benefit over no treatment. Finally, RFA may be associated with some survival benefit for certain patient subgroups who as yet have not been well-characterized.

In a prior population-based analysis, our group identified a several-fold increase in RFA utilization over the last decade with a large proportion of the patients treated with RFA having a dominant lesion >5 cm or multiple lesions at diagnosis.¹ Although general indications for RFA use exist and may vary between institutions, current data suggest RFA may be less effective for patients with lesions >5 cm and/or those with more than one lesion because of a high local recurrence rate.¹³ This either suggests indications for RFA are not widely known or expanded indications are being applied in the absence of data to support such practice. Alternatively, patient demand for new therapeutic technologies, low associated cost for clinicians to learn to apply the technology, marketing/promotion by device manufacturers, and perceived benefits to stakeholders have been identified as important drivers of adoption of new surgical innovations¹⁴—RFA satisfies each of these four conditions.

Complications and inpatient mortality rates after hepatic resection have been reported to be 40–50%^{15, 16} and 5–6%,^{17–19} respectively. By comparison, numerous studies have reported low rates of complications (1.8–10%)^{20–26} and peri-operative death ($\leq 1\%$)^{23, 25–28} after RFA. In this cohort, we found a higher rate of early mortality than previously reported. Also, risk of early death and readmission after RFA was not different compared to resection. This suggests RFA may not be as safe as has been widely reported. Because prior studies were from Asia, Europe, and/or referral centers in the US, outcomes from these centers may not be indicative of care provided in the community at large. By comparison, SEER-Medicare data are considered representative of care provided in the general community and across varied practice settings.³ Alternatively, our results may simply represent RFA use among poorly selected and/or high risk patients.

Two recent randomized trials have compared RFA to resection among patients within Milan criteria. The first demonstrated no significant difference in either overall or disease-free survival.²⁹ There were, however, numerous issues pertaining to the study design and methods making interpretation of the results challenging (e.g.: inconsistency between the sample size calculation [based on recurrence] and the reported endpoints [survival]; the authors concluding equivalence between RFA and resection even though a non-inferiority design was not employed [underpowering the study to assess equivalence]). In the second trial, the authors found significantly better overall and recurrence-free survival as well as lower recurrence rates among resection patients.³⁰ Our prior and current work suggest a notable proportion of US patients treated with RFA fall outside Milan criteria; therefore, the generalizability of the results from this study must be considered. In our current study, RFA treated patients not receiving any other form of intervention within one year of diagnosis did not have a significantly lower risk of death relative to no treatment. The sample size in these subgroups was relatively small (96 patients received a single RFA session and 126 patients underwent one or more RFA sessions), therefore the analyses may have been underpowered to detect a survival benefit. However, our study also included a similar number of patients who underwent only resection (n=139) which clearly demonstrated a benefit relative to both RFA and no treatment.

We expected to see a survival advantage attributable to RFA when compared to no treatment. The fact that we did not observe this either suggests RFA as a solitary intervention may not be as effective as previously described or more likely indicates poor patient selection (for example, when used outside of current indications or among patients who are at high surgical risk). Poor patient selection may have been due (at least in part) to the fact patients for whom RFA treatment is most appropriate have, as yet, not been well-defined. To explore this issue of selection, we evaluated the available characteristics of patients surviving at least 3 years and found they generally had favorable socioeconomic and clinical characteristics—highlighting the importance of patient selection in determining the effectiveness of RFA as an HCC treatment. While there may be a desire to offer RFA to any HCC patient not a candidate for resection or transplantation, improved survival may only occur among carefully selected surgical candidates.

These results must be interpreted in the context of several limitations. First, we were unable to ascertain intent or indication for RFA use. If RFAs were performed with curative intent (among potentially resectable patients), the lack of an obvious survival benefit relative to no treatment is not reassuring of RFA's effectiveness. Alternatively, it is possible none of the RFAs were intended as a stand-alone therapy. However, even when patients who underwent multiple RFA sessions were considered, risk of death was not different as compared to no treatment. While some RFAs may have been intended as a bridge to transplantation, the mean age of this cohort (well over 70 years) makes transplantation an unlikely anticipated endpoint.

Other limitations include restriction of our study to elderly, Medicare beneficiaries with full, fee-for-service coverage which could affect the generalizability of our results to broader patient populations. Although we controlled for comorbid illness using the Charlson score and the presence of additional liver-related comorbid conditions using propensity score adjustment, our results still likely suffer from residual confounding by indication. Since procedural ascertainment was based on HCPCS, our study included a relatively small sample of patients treated with RFA (because a CPT code for RFA was not created until 2002) potentially resulting in Type II error for some parts of the analysis (for example, to identify a statistically significant difference in 30 and 90-day mortality of the observed magnitude with 80% power, 524 and 855 [respectively] patients in each treatment group would have been needed). Some patients may have been misclassified in terms of the

readmission outcome—data on the indication for readmission are not provided and it is not possible to ascertain whether a readmission was planned. Finally, SEER-Medicare data do not contain information on tumor location, variables quantifying surgical risk (e.g.: cardiovascular status, pre- and post-operative lab data, family involvement, as well as other pertinent surgical and anesthetic factors), or other clinical variables impacting surgical decision-making. Such information would have been helpful to understand therapeutic intent allowing a more accurate comparison of RFA and resections performed for the same purpose or to provide more adequate risk-adjustment.

In this population-based evaluation, we were unable to identify an early safety benefit for RFA (compared to resection) or an obvious survival benefit when used as a lone therapeutic intervention (compared to no treatment). We did however identify a higher than anticipated rate of early mortality and readmission which should be factored into any informed consent discussion between a patient and his or her provider. The results of this work suggest a need for more data to inform RFA use in the US and highlight the importance of patient selection. Future work should attempt to identify patients for whom RFA use is most appropriate, better define the impact of liver reserve and/or burden of comorbid illness on RFA outcomes, and evaluate outcomes based on institutional/provider experience—all of which will be important for defining its role as a management option for patients with HCC.

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(a)

b)

(c)

Figure 1.

a–c Multivariate analysis of therapeutic effectiveness comparing: (a) resection to no treatment (reference no treatment); (b) resection to RFA (reference RFA); (c) RFA to no treatment (reference no treatment).

†These subgroups did not undergo any other potentially therapeutic procedures within 6 months or 1 year of diagnosis, respectively. Similarly, untreated patients received no therapeutic interventions over this same time period.

‡These subgroups did not undergo any other potentially therapeutic procedures (except additional RFA sessions for those in the RFA group) within 6 months or 1 year of diagnosis,

respectively. Similarly, untreated patients received no therapeutic interventions over this same time period.

* $p < 0.05$, § $p < 0.001$

Table 1

Demographic and clinical characteristics of HCC cohort

Demographics	Untreated (n=2,216)	REB (n=206)	Resection (n=209)	p-value
Mean Age $\pm$ SD, years	76.2 $\pm$ 6.2	74.7 $\pm$ 5.7	75.7 $\pm$ 5.8	0.002
Age, years (%)				0.03
	≤ 70	18.1	24.3	19.6
	71–75	27.0	29.6	27.8
	76–80	27.7	30.1	29.2
	> 80	27.2	16.0	23.4
Male sex (%)	66.6	63.1	61.2	0.20
Race (%)				0.04
	White	67.8	60.2	76.1
	Black	8.2	9.2 [†]	
	*Other	24.0	30.6	23.9
Low Income (%)	25.5	20.4	22.0	0.17
Low Education (%)	4.4	< 5.3	< 5.3	0.75
	Missing	4.3	< 5.3	
Married (%)	56.3	65.5	65.1	0.02
	Missing	3.5	< 5.3	
Geography (%)				0.29
	West	53.2	50.5	52.2
	East	20.9	26.2	19.6
	Midwest	12.1	9.2	10.1
	South	13.9	14.1	18.2
Residence (%)				0.24
	Metropolitan	89.2	92.7	86.6
Clinical Characteristics				
Comorbidity index (%)				0.001
	0	30.8	29.6	40.7
	1	29.4	35.4	33.0

Demographics	Untreated (n=2,216)	RFA (n=206)	Resection (n=209)	p-value
2	15.7	15.5	13.9	
≥3	24.1	19.4	12.4	
Prior Malignancy (%)	19.4	26.2	23.9	0.03
RFA approach (%)				n/a
<i>Percutaneous</i>	-	42.0	-	
<i>Laparoscopic</i>	-	22.7	-	
<i>Open</i>	-	35.3	-	
Tumor size (%)				<0.001
≤3cm	11.7	31.6	19.1	
3.1–5cm	16.3	32.0	25.6	
>5cm	38.3	17.0	55.3	
Missing	33.7	19.4	‡	
>1 lesion (%)	55.3	44.7	34.0	<0.001
Missing	17.5	7.8	<5.3	
SEER historical stage (%)				<0.001
<i>Localized</i>	44.0	71.4	76.9	
<i>Regional</i>	25.3	15.5	17.7	
<i>Metastatic</i>	14.9	5.8	5.4	
Missing	15.9	7.3	‡	

Use of SEER-Medicare data does not permit description of results where the value is <11 patients. Therefore, cell percentages less than a given value indicate 10 or fewer patients.

* For untreated patients, <1% were missing data on race.

‡ Proportion of resection patients who were black was <5.3% (exact proportion cannot be shown because cell value is fewer than 11 patients). Proportion of resection white and other patients is calculated excluding black patients.

‡ Indicates a cell value <5.3% (fewer than 11 patients). Remaining proportions were calculated excluding those with a missing value.

Table 2

Liver Associated Comorbid Conditions Used in Propensity Score

	Overall	Untreated	RFA	Resection
	n (%)			
Ascites	1,267 (48)	1,073 (48)	112 (54)	82 (39)
Organomegaly	839 (32)	681 (31)	77 (37)	81 (39)
Hemorrhoids	324 (12)	261 (12)	36 (18)	27 (13)
Hepatitis C	894 (34)	717 (32)	115 (56)	62 (30)
Hepatitis B	420 (16)	318 (14)	57 (28)	45 (22)
Portal Vein Thrombosis	192 (7)	165 (8)	16 (8)	11 (5)
GI bleed	894 (34)	765 (35)	69 (34)	60 (29)
Thrombocytopenia	443 (17)	360 (16)	51 (25)	32 (15)
Hyperbilirubinemia	295 (11)	247 (11)	26 (13)	22 (11)
Cirrhotic Liver	1,541 (59)	1,269 (57)	168 (82)	104 (50)

Table 3

Adjusted Risk Ratios of Mortality and Readmission Associated with Treatment (95% CI)

	Untreated	RFA	Resection	[†] Resection vs RFA
Mortality				
30-day	1.0	[§] 14.44 (5.42–38.45)	[§] 27.06 (13.31–55.01)	1.87 (0.80–4.40)
90-day	1.0	0.80 (0.59–1.09)	0.94 (0.63–1.42)	1.18 (0.99–1.40)
Readmission				
30-day	1.0	0.84 (0.58–1.22)	[*] 0.79 (0.63–0.96)	0.93 (0.67–1.27)
90-day	1.0	[*] 0.67 (0.50–0.90)	[*] 0.70 (0.57–0.86)	1.04 (0.69–1.57)

^{*} p<0.05,[§] p<0.001[†] RFA patients are the reference group.