VALUE IN HEALTH 22 (2019) 284–292

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Comparative-Effectiveness Research/HTA

Comparative Effectiveness of Computed Tomography- Versus Ultrasound-Guided Percutaneous Radiofrequency Ablation Among Medicare Patients 65 Years of Age or Older With Hepatocellular Carcinoma

Jinhai Huo, PhD, MD, MSPH [1,], Thomas A. Aloia, MD [2], Ying Xu, PhD [3], Tong Han Chung, PhD, MPH [4], Tommy Sheu, MD, MPH [5], Ya-Chen Tina Shih, PhD [2]*

[1]*Department of Health Services Research, Management and Policy, University of Florida, Gainesville, FL, USA;* [2]*Department of Surgical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [3]*Department of Health Services Research, University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [4]*Healthcare Transformation Initiatives, University of Texas Health Science Center-Houston, Houston, TX, USA;* [5]*Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA*

ABSTRACT

Background: For patients with hepatocellular carcinoma (HCC) not eligible for surgical resection, radiofrequency ablation (RFA) is a promising technique that reduces the risk of disease progression. **Objectives:** To evaluate whether the trend of image guidance for RFA is moving toward the more expensive computed tomography (CT) technology and to determine the clinical benefits of CT guidance over the ultrasound (US) guidance. **Methods:** A cohort of 463 patients was identified from the Surveillance, Epidemiology, and End Results and Medicare–linked database. The temporal trends in use of image guidance were assessed using the Cochrane–Armitage test. The associations between modality of image guidance and survival, complications, and costs were assessed using the Cox regression model, the logistic regression model, and the generalized linear model, respectively. **Results:** The use of CT-guided RFA increased sharply, from 20.7% in 2002 to 75.9% in 2011. Compared with CT-guided RFA, those who received US-guided RFA had comparable risk of periprocedural and delayed postprocedural complications. Stratified analyses by tumor size also showed no statistically significant difference. In adjusted survival analysis, no statistically significant difference was observed in overall and cancer-specific survival. Nevertheless, the cost of CT-guided RFA ($2847) was higher than that of US-guided RFA ($1862). **Conclusions:** Despite its rapid adoption over time, CT-guided RFA incurred higher procedural costs than US-guided RFA but did not significantly improve postprocedural complications and survival. Echoing the American Board of Internal Medicine's Choosing Wisely campaign and the American Society of Clinical Oncology's Value of Cancer Care initiative, findings from our study call for critical evaluation of whether CT-guided RFA provides high-value care for patients with HCC.

Keywords: costs, effectiveness, HCC, imaging, RFA

Introduction

The incidence of hepatocellular carcinoma (HCC) in the United States has increased sharply over the past 2 decades, rising from 3.1 per 100 000 persons in 1992 to 6.7 per 100 000 in 2012, with 31 665 new cases in 2018.[1–4] Among these new cases, 47.6% patients were aged 65 years or older.[5] Although not considered one of the leading cancers in the United States, HCC is among one of the most deadly cancers. The mortality rate of HCC has been rising at a rate of 2.7% per year, whereas the mortality rates of other cancers, such as lung, breast, colorectal, and prostate cancer, have reduced during the same period.[3] The total annual cost of HCC was estimated to be $455 million in the United States in 2009.[6] With steady increase in the incidence of HCC, the economic burden of HCC is expected to grow in the coming decades.

For patients with early-stage resectable HCC, surgical hepatic resection is the recommended treatment. Nevertheless, approximately 80% to 90% of patients with HCC were diagnosed at a stage

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to*: Jinhai Huo, PhD, MD, MSPH, Department of Health Services Research, Management and Policy, University of Florida, 1225 Center Drive, HPNP 3111, P.O. Box 100195, Gainesville, FL 32610.

E-mail: hjh54@ufl.edu

1098-3015/$36.00 - see front matter

https://doi.org/10.1016/j.jval.2018.10.004

at which it is too late to benefit from the potentially curative surgical resection.[7] For those patients, radiofrequency ablation (RFA) offers an alternative treatment option to reduce the risk of the progression. RFA is a local thermal ablative treatment technique that uses high-frequency alternating current to raise the temperature of a tumor, causing tissue desiccation and coagulative necrosis.[8] Several studies have demonstrated the effectiveness of image guidance of RFA in clinical practice and support its use as first-line treatment of unresectable small HCCs.[9–11] There are 3 types of RFA: percutaneous, laparoscopic, and open surgery. The type of RFA received by patients depends on the tumor location, the goal of the treatment, the risk of surgery, and the preference of the surgeon.[12–14] Percutaneous RFA is the least invasive and relies heavily on image guidance during the operation. The ultrasound (US) technique has been used as the guidance technique in evaluating tumor contours and delineating tumor edges for percutaneous RFA treatment. More recently, interventional radiologists have started using computed tomography (CT) guidance to perform RFA.

Although CT-guided RFA has been shown to be a safe and efficacious treatment for patients with unresectable HCC,[15,16] no comparative effectiveness studies to date have demonstrated CT-guided RFA to be superior to US-guided RFA in the United States. If CT- and US-guided RFAs offer similar clinical benefits, then there will be a fast diffusion of the CT-guided RFA because the procedure is nearly twice as expensive as the US-guided procedure. At the quest of promoting high-quality, high-value care, it is important to better understand the comparative effectiveness and costs associated with CT- versus US-guided RFAs as the incidence of HCC continues to rise and therefore the number of image-guided RFAs. The objective of our study was to fill this knowledge gap by examining the utilization pattern of these image-guided procedures among patients with HCC with percutaneous RFA, estimating the associated costs, and comparing overall survival (OS), cancer-specific survival (CSS), and postprocedural complications between CT- and US-guided RFAs. Findings from this study will contribute to the value discussions advocated by the American Board of Internal Medicine's Choosing Wisely campaign and the American Society of Clinical Oncology's Value of Cancer Care Task Force.

Methods

Database and Patient Selection Criteria

We used the Surveillance, Epidemiology, and End Results (SEER) database linked with Medicare claims.[17] The SEER registries, supported by the National Cancer Institute, consist of 18 geographic areas covering approximately 30% of the US population. The Medicare program contains healthcare claims and payments for inpatient, outpatient, and physician services for 97% of US citizens aged 65 years or older. Protected health information has been de-identified in these data sets, and no information could be linked to individual patients.

Patients in the database were included in our study if they were at least 66 years old and diagnosed with HCC (*International Classification of Diseases for Oncology, 3rd edition* [ICD-O-3] histology codes: 8170, 8171, 8173, 8174, and 8175) between January 2002 and December 2011. The exclusion criteria were as follows: (1) a cancer diagnosis that was not pathologically confirmed or was based on a death certificate or autopsy; (2) cancer classified as late-stage (tumors had spread to regional lymph nodes); (3) no continuous Part A and Part B insurance coverage 12 months before cancer diagnosis through 12 months after delivery of RFA or until death, whichever occurred first; and (4) health maintenance organization enrollment during the same period, because medical claims for these patients were incomplete (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.004).

Patient Characteristics

Patient sociodemographic information, including age at cancer diagnosis, year of cancer diagnosis, race/ethnicity, marital status, and US census region, was extracted from the SEER database. Because some racial groups had a value less than 11 in subgroup analysis, as per the Data Use Agreement of SEER–Medicare, we suppressed the race variable for 2 categories (non-Hispanic white and all others) to protect the patient's identity. Marital status was classified as single, married, or other. The 4 census regions were West, Northeast, Midwest, and South.

The clinical variables included tumor size, comorbidity, and use of chemotherapy. According to the "principle of locoregional therapy" in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology—Hepatobiliary Cancers and in consultation with the clinical collaborator, tumor size was classified into 4 categories on the basis of the largest dimension of the liver tumor: less than 3 cm, 3 to 5 cm, more than 5 cm, and unknown.[18] To calculate the comorbidity before cancer diagnosis, the Klabunde-adapted version of the Charlson comorbidity index was used.[19,20] This algorithm generated a continuous score for each patient; we categorized patients into 3 groups by their comorbidity score: 0, 1, and 2 or more. Information on the use of chemotherapy from 6 months before RFA through 9 months after RFA was extracted from the Medicare claims using both *ICD* (*Ninth Revision*) procedure codes and level II Healthcare Common Procedure Coding System: Current Procedural Terminology (CPT) codes. By using a previously validated algorithm,[21,22] we also constructed a claims-based indicator of poor performance status. Patients were classified into 2 groups: restricted (if canes, wheelchairs, commodes, home oxygen, and related hospital beds were claimed) and normal (if no indicator of poor performance status exists).

Identification of Image Guidance

Receipt of image guidance of RFA was determined using Medicare claims data for the 30 days before to the 30 days after the date of percutaneous RFA delivery (Healthcare Common Procedure Coding System 47382). Two image guidance techniques identified using CPT codes were US (codes 76490 and 76940) and CT (codes 76362 and 77013). If a patient underwent both types of image guidance during the study period, the patient was assigned to the CT-guided RFA because although these patients may benefit from the advanced CT technology clinically, they also incur higher costs.

Cost Analysis

The procedure costs of CT- and US-guided RFA were estimated using the CPT code–based Medicare reimbursement rates for the image guidance and RFA delivery. We also estimated the healthcare costs associated with postprocedural complications using all inpatient, outpatient, and carrier claims within 1 year after the date of treatment. The costs of postprocedural complication were determined by adding up all costs occurring on days when a diagnosis indicating postprocedural complication occurred. The bootstrap simulation with 500 replications was used to estimate the mean of costs, SD, and the 95% confidence interval (CI). All reported costs were adjusted and normalized to 2017 US dollars using the medical care component of the Consumer Price Index.[23]

Postprocedural Complications

As per previous studies, 1-year postprocedural complications for patients with HCC included ascites, pulmonary complications,

Table 1 – Patients demographic and clinical characteristics.

Characteristic	Study sample						Propensity score–matched sample					
	Total	US-guided		CT-guided		P value	Total	US-guided		CT-guided		P value
		n	%	n	%			n	%	n	%	
Year						<.001						.912
2002-2003	64	45	70.3	19	29.7		35	20	57.1	15	42.9	
2004-2005	86	35	40.7	51	59.3		49	24	49.0	25	51.0	
2006-2007	95	36	37.9	59	62.1		64	30	46.9	34	53.1	
2008-2009	109	29	26.6	80	73.4		54	27	50.0	27	50.0	
2010-2011	109	26	23.9	83	76.2		52	26	50.0	26	50.0	
Age group						.009						.325
66-69	122	49	40.2	73	59.8		62	35	56.5	27	43.6	
70-74	148	66	44.6	82	55.4		83	43	51.8	40	48.2	
>75	193	56	29.02	137	70.9		109	49	45.0	60	55.1	
Sex												.797
Male	284	105	37.0	179	63.0	.983	154	76	49.4	78	50.7	
Female	179	66	36.9	113	63.1		100	51	51.0	49	49.0	
Race/ethnicity						.842						.799
Non-Hispanic white	268	100	37.3	168	62.7		104	53	51.0	51	49.0	
Nonwhite	195	71	36.4	124	63.6		150	74	49.3	76	50.7	
Marital status						.847						.793
Single	82	29	35.4	53	64.6		45	22	48.9	23	51.1	
Married	290	110	37.9	180	62.1		151	78	51.7	73	48.3	
Other	91	32	35.2	59	64.8		58	27	46.6	31	53.5	
Geographic region						.292						.883
West	262	94	35.9	168	64.1		136	71	52.2	65	47.8	
Northeast	109	46	42.2	63	57.8		69	32	46.4	37	53.6	
Midwest	27	12	44.4	15	55.6		16	–*	–	–	–	
South	65	19	29.2	46	70.8		33	–	–	–	–	
Tumor size						<.001						.919
<3 cm	145	57	39.3	88	60.7		84	43	51.2	41	48.8	
3-5 cm	111	57	51.4	54	48.7		69	32	46.4	37	53.6	
>5 cm	60	19	31.7	41	68.3		35	18	51.4	17	48.6	
Unknown	147	38	25.9	109	74.2		66	34	51.5	32	48.5	
Charlson comorbidity score						.145						.907
0	119	52	43.7	67	56.3		75	39	52.0	36	48.0	
1	135	43	31.9	92	68.2		60	30	50.0	30	50.0	
>2	209	76	36.4	133	63.6		119	58	48.7	61	51.3	
Chemotherapy						.269						.896
No	302	118	38.9	185	61.1		163	81	49.7	82	50.3	
Yes	161	53	33.1	107	66.9		91	46	50.6	45	49.5	
Performance status						.939						.765
Normal	361	133	36.8	228	63.2		196	99	50.5	97	49.5	
Restricted	102	38	37.3	64	62.8		58	28	48.3	30	51.7	

CT indicates computed tomography; SEER, Surveillance, Epidemiology, and End Results; US, ultrasound.
* These numbers had to be suppressed because the Data Use Agreement with the National Cancer Institute on the SEER–Medicare data does not allow the reporting of any values <11 anywhere in the article.

abdominal bleeding, abdominal infections, hepatic vascular damage, and biliary tract damage.[24–26] To obtain more information on the timing of complication occurrence, complications were classified into 2 periods: periprocedural (occurring within 30 days after RFA) and delayed (occurring more than 30 days after RFA through the end of the first year after the procedure).[12] The delayed complications could also include the persisted/recurred periprocedural complications that occurred after the initial 30 days after ablation. Periprocedural and delayed complications were identified using *ICD-9* diagnosis codes (see Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.004) and analyzed separately.

OS and CSS

The survival duration was estimated from the date of HCC diagnosis to death owing to HCC or other causes. CSS was determined using the SEER site recode cause-of-death variable. The liver site (*ICD-O-3* site C220) was coded as 21071 in the SEER data set.

Statistical Analysis

We compared the use of modality of image-guided RFA in patients with HCC stratified by the patients' demographic and clinical variables with Pearson χ^2 tests, and tested temporal trends in the use of modality of image-guided RFA using the Cochran–Armitage

trend test. Multivariable generalized linear regression was used to identify the predictors of use of CT- versus US-guided RFA. The Cox proportional hazards model was used to assess the relationship between the uses of different modalities of image-guided RFA and OS as well as CSS. Schoenfeld residuals were plotted to test the proportional hazard assumption in the Cox model. Kaplan-Meier estimates were conducted to illustrate the rates of OS and CSS, with log-rank tests to examine the homogeneity of survival curves over 2 groups. To determine the effects of image guidance on postprocedural complications, we used the Pearson χ^2 test to evaluate the differences in frequency of periprocedural and delayed complications stratified according to use of US- and CT-guided RFA. We further conducted a subsidiary analysis by stratifying the study cohort into 4 subgroups according to the tumor size. Multivariable logistic regression models were used to determine adjusted odds ratio for use of modality of image-guided RFA. The variables in the univariate analysis that had a *P* value of less than .200 or were clinically meaningful were included in the final models. We assessed the goodness of fit using the Hosmer and Lemeshow test. In the cost analysis, we used the Mann-Whitney test to estimate the differences in the procedural costs of US- and CT-guided RFA. To control for imbalance in confounding variables, we conducted 1:1 propensity score matching between US- and CT-guided RFA patients with the following matching factors: year of cancer diagnosis, age group, race, marital status, census region, tumor size, Charlson comorbidity score, use of chemotherapy, and performance status.[27,28]

All statistical analyses were conducted using the SAS software program, version 9.4 (SAS Institute, Cary, NC). The criterion for statistical significance was a *P* value of less than .050. Our study was exempted by the University of Texas MD Anderson Cancer Center Institutional Review Board. All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patient Characteristics

For our study, we identified a total of 463 patients with HCC who were at least 66 years old. Their demographic and clinical characteristics stratified by the use of US- and CT-guided RFA are presented in Table 1. The use of CT-guided RFA was significantly more likely in patients who received RFA in later years, who were at an older age, were nonwhite, and had a large tumor size.

Trends in Image Guidance and Costs

Temporal trends in the use of image guidance of RFA are shown in Figure 1. We observed a significant increase in the use of CT-guided RFA over the study period, going from 20.7% in 2002 to 75.9% in 2011, whereas the use of US-guided RFA decreased from 79.3% to 24.1% (both $P_{trend} < .0001$). Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.004 lists covariates associated with receipt of CT-guided RFA in our multivariable generalized linear regression model. After controlling for patients' demographic characteristics and clinical variables, the year of HCC diagnosis is the single most significant predictor associated with increased relative risk of receipt of CT-guided RFA (relative risk > 2.6; *P*<.050 for all years after 2003 in reduced model). In our cost analysis, the estimated procedure costs were $2847 for CT-guided RFA and $1862 for US-guided RFA (Table 3).

OS and CSS

Among 345 (74.5%) patients who died within the study period, 215 patients (62.3%) died of liver cancer. In comparison, 85 patients (49.7%) who received US-guided RFA and 130 patients (44.5%) who received CT-guided RFA have died of liver cancer (*P*=.290). The median OS and CSS durations were equivalent between patients who received CT-guided RFA and those who received US-guided RFA (OS: 28 months [95% CI 25-31 months] for CT-guided RFA and 27 months [95% CI 24-32 months] for US-guided RFA [*P*=.180]; CSS: 43 months [95% CI 36-57 months] for CT-guided RFA and 44 months [95% CI 32-60 months] for US-guided RFA [*P*=.930]) (Fig. 2). In covariates-adjusted Cox hazard regression model with US-guided RFA as the reference, the hazard ratio of OS was 1.22 (95% CI 0.96-1.56; *P*=.120) for patients with CT-guided RFA and the hazard ratio of CSS was 1.11 (95% CI 0.81-1.51; *P*=.520) for those with CT-guided RFA (Table 2). In the propensity score matching analysis, there were no statistically significant differences between CT- and US-guided RFA on both OS and CSS (*P*>.400).

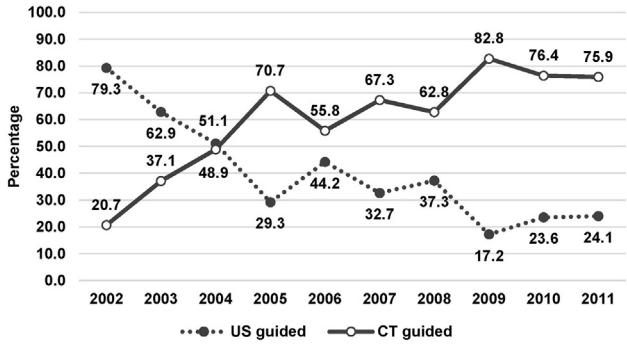

Fig. 1 – Temporal trends in image guidance utilization (2002-2011). The solid line represents the use of CT-guided RFA, and the dotted line represents the use of US-guided RFA from the year 2002 to 2011. CT indicates computed tomography; RFA, radiofrequency ablation; US, ultrasound.

Periprocedural Complications and Costs

In our univariate analysis of associations between use of image guidance and periprocedural and delayed complications (see Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.004), the risk of periprocedural biliary tract damage in patients who received US-guided RFA was 2.3% higher than in those who received CT-guided RFA (*P*=.020). Nevertheless, except periprocedural biliary tract damage, there was no statistically significant reduction on risk of the other 5 measures of periprocedural complications (ascites, pulmonary complications, abdominal bleeding, abdominal infections, and hepatic vascular damage), and there was also no reduction on risk found for all 6 measures of delayed complications. This finding on the similar risk of periprocedural and delayed complications between US- and CT-guided RFA was consistent in our subsidiary analysis where the cohorts were stratified on the basis of the tumor size (see Appendix Figure 1 in Supplemental Materials). These findings were also supported by the propensity score matching analysis (see Appendix Figure 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.10.004). In our multivariable logistic regression models controlling for patients' demographic and clinical covariates, patients who received CT-guided RFA had insignificant difference in the risk of periprocedural complications and delayed complications than did patients who received US-guided RFA (Fig. 3). The costs of periprocedural complications are similar for patients who underwent US- and CT-guided RFA: $16 134 (95% CI $12 316-$19 953) versus

Table 2 – Hazard ratios of image-guided RFA in patients with HCC.

Characteristic	OS				CSS			
	HR	95% CI		P value	HR	95% CI		P value
Image guidance								
US-guided	1.00				1.00			
CT-guided	1.22	0.95	1.56	.115	1.11	0.81	1.51	.520
Year								
2002	1.00				1.00			
2003	1.04	0.58	1.88	.892	0.81	0.42	1.53	.510
2004	1.68	0.97	2.92	.065	1.44	0.80	2.60	.221
2005	1.16	0.64	2.10	.618	1.19	0.64	2.23	.588
2006	1.10	0.61	1.97	.751	0.71	0.36	1.38	.311
2007	0.80	0.45	1.42	.448	0.52	0.28	0.99	.047
2008	0.94	0.53	1.64	.819	0.50	0.26	0.97	.041
2009	1.19	0.67	2.11	.558	0.69	0.35	1.37	.289
2010	0.64	0.34	1.20	.163	0.28	0.13	0.59	.001
2011	0.64	0.33	1.25	.189	0.15	0.06	0.39	<.001
Age group (y)								
66-69	1.00				1.00			
70-74	1.19	0.87	1.62	.275	1.26	0.85	1.87	.241
>75	1.34	1.00	1.79	.051	1.42	0.98	2.05	.061
Sex								
Male	1.00				1.00			
Female	1.06	0.83	1.34	.641	1.12	0.83	1.52	.461
Race/ethnicity								
Nonwhite	1.00				1.00			
Non-Hispanic white	1.25	0.97	1.61	.079	1.22	0.89	1.68	.210
Marital status								
Single	1.00				1.00			
Married	0.74	0.55	1.00	.050	0.69	0.47	1.03	.068
Other	0.81	0.56	1.17	.260	0.77	0.48	1.25	.298
Geographic region								
West	1.00				1.00			
Northeast	1.06	0.78	1.43	.717	0.97	0.66	1.42	.860
Midwest	1.41	0.88	2.25	.150	1.04	0.55	1.98	.908
South	1.50	1.08	2.10	.017	1.41	0.93	2.14	.109
Tumor size (cm)								
<3	1.00				1.00			
3-5	1.34	0.99	1.81	.056	1.35	0.93	1.96	.113
>5	2.13	1.48	3.07	<.001	2.47	1.59	3.86	<.001
Unknown	1.82	1.17	2.83	.008	2.27	1.34	3.85	.002
Charlson comorbidity score								
0	1.00				1.00			
1	1.11	0.81	1.52	.510	1.16	0.79	1.71	.453
>2	1.55	1.15	2.08	.004	1.55	1.07	2.25	.022
Chemotherapy								
No	1.00				1.00			
Yes	0.93	0.73	1.18	.550	1.03	0.76	1.39	.861
Performance status								
Normal	1.00				1.00			
Restricted	1.37	1.06	1.77	.018	1.02	0.72	1.44	.924

CI indicates confidence interval; CSS, cancer-specific survival; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; OS, overall survival; US, ultrasound.

$17 457 (95% CI $11 488-$23 426) (*P*=.700), and the finding is consistent in the propensity score–matched cohort (Table 3).

Discussion

In this retrospective cohort study, we observed a significant increase in the use of CT-guided RFA over the 10-year study period among patients with HCC. Nevertheless, compared with the use of US-guided RFA, the use of CT guidance did not appear to be associated with better clinical benefits, as quantified by the OS, CSS, as well as periprocedural and delayed complications. Considering the higher costs of CT-guided RFAs, the similarity in clinical benefits between these 2 image guidance procedures begs the question whether CT-guided RFA represents high-value cancer care for patients with unresectable HCC.

Table 3 – Cost estimates ($) of CT- and US-guided RFAs as well as the costs of postprocedural complications.

Study sample	Mean ± SD	95% CI	P value
Cost of RFAs			<.001
CT-guided RFAs	2 847 ± 1 690	2 652-3 041	
US-guided RFAs	1 862 ± 1 352	1 657-2 065	
Cost of postprocedural complications			.700
CT-guided RFAs	16 134 ± 33 152	12 316-19 953	
US-guided RFAs	17 457 ± 39 541	11 488-23 426	
Propensity score–matched cohort			
Cost of RFAs			<.001
CT-guided RFAs	2 671 ± 1 586	2 488-2 853	
US-guided RFAs	1 746 ± 1 268	1 554-1 937	
Cost of postprocedural complications			.713
CT-guided RFAs	15 135 ± 31 099	11 553-18 717	
US-guided RFAs	16 376 ± 37 093	10 777-21 976	

CI indicates confidence interval; CT, computed tomography; HCC, hepatocellular carcinoma; HR, hazard ratio; RFA, radiofrequency ablation; US, ultrasound.

The sharp increase in the use of CT-guided RFA is consistent with the national trend of the dramatically increasing supply of CT facilities.[29,30] Although financial incentive from providers might have escalated the adoption of CT-guided RFAs, another plausible explanation is the concern over inferior image quality of US-guided procedures because of difficulty in visualizing small tumors and macronodular cirrhosis and high dependence on operator experience and the patient's liver status.[31] It is not clear whether the trend of increasing use of CT guidance will continue because the need for experienced radiologists and anesthesiologists may slow down the rate of replacing US guidance with CT guidance in community practice.

In our analysis, the periprocedural and delayed complication rates were statistically indistinguishable between patients with CT- and US-guided RFA. Among the 6 types of complications examined, CT-guided RFA was only marginally superior to US-guided RFA on the risk of periprocedural biliary tract damage in the univariate analysis. No benefits on risk reduction were found across the subgroups stratified by the tumor size (<3 cm, 3-5 cm, and >5 cm). Furthermore, all odds ratios of complications from multivariate analyses were not statistically significant between CT- and US-guided RFA. The noninferior performance of US-guided RFA compared with CT-guided RFA was also found on the OS and CSS. It is worth noticing that the overall postprocedural complication rates reported in our study were higher than those reported in clinical trials or single-institution studies published in the literature. The rate of any short-term and long-term complications in our study was 25.2% and 53.2%, respectively, for US-guided RFA, whereas the rate reported from an Italian multicenter trial of US-guided RFA was 2.2% for major complications and 4.7% for minor complications[32] and about 4.8% in a Taiwanese trial.[33] In a US-based study, Curley et al[34] reported the complication rate after RFA to be 12.7%, which was similar to the rate reported in a study conducted at a tertiary referral cancer center by Amersi et al.[35] A higher complication rate (~14.3%) after US-guided RFA was found in an Italian trial of 139 patients.[36] The relatively high complication rates in our study likely reflected the older age of patients in our SEER–Medicare analysis because participants of clinical trials tended to be younger and healthier.

The financial implication of replacing US-guided imaging procedures with CT-guided procedures calls for the development of clinical criteria to identify patients who will truly benefit from CT procedures because widespread, nondiscretionary use of CT-guided RFA would increase the economic burden of cancer care for patients with HCC and the overall healthcare expenditures without apparent clinical benefit. Concerns over the unsustainable increase in the cost of cancer care and affordability motivated the collaboration between the American Board of Internal Medicine's Choosing Wisely campaign and the American Society of Clinical Oncology's Value of Cancer Care to publish 2 "top five" lists of low oncology care.[37,38] Both lists called out overutilization of advanced imaging technology. The findings of similar clinical benefits (in terms of survival and postprocedural complications) between CT- and US-guided RFA from our observational study warranted further investigation into the value of CT-guided RFA in the care of patients with unresectable HCCs. As the number of patients with HCC continues to grow each year in the United States and worldwide, a practice pattern that switches from US- to CT-guided RFA could impose substantial financial burden on the healthcare system.

When there is a lack of definitive evidence on the superiority of CT-guided RFA over US-guided RFA, the concept of "less is more" deserves careful consideration in the treatment of unresectable HCCs.[39]

Our study had several limitations. First, clinical outcomes evaluated in our study were limited to those that could be measured in claims linked to cancer registry; therefore, we were not able to examine the technical effectiveness of image guidance of RFA, such as the complete ablation of macroscopic tumors after RFA, and local tumor progression. Second, we did not find any patients who used magnetic resonance guidance in our study cohort because of unavailability of the most recent data on this new technology. Compared with CT and US guidance, magnetic resonance guidance has demonstrated better efficacy at supporting RFA,[40] but is also far costlier than the CT- or US-guided procedure. Future research should investigate the cost effectiveness of these 3 imaging guidance technologies for patients with unresectable HCCs who received RFAs. Third, many clinical variables that could potentially affect the selection of the type of RFA or health outcomes, such as tumor location, grading of toxicities, and the Child–Pugh score, were not captured in the SEER–Medicare data. Besides tumor size and comorbidity, tumor location is another important clinical factor that has an impact on periprocedural complications. The procedure conducted near the hilum of the liver is complex because of the vascular structures and high risk of biliary stricture or fistula formation.[41] The risk of perforation is also high when the procedure was for lesions near the liver capsule or in proximity to a hollow intra-abdominal viscus.[32,42] Another unmeasured clinical confounder is physician's experience. RFA is a highly skill-dependent procedure, and

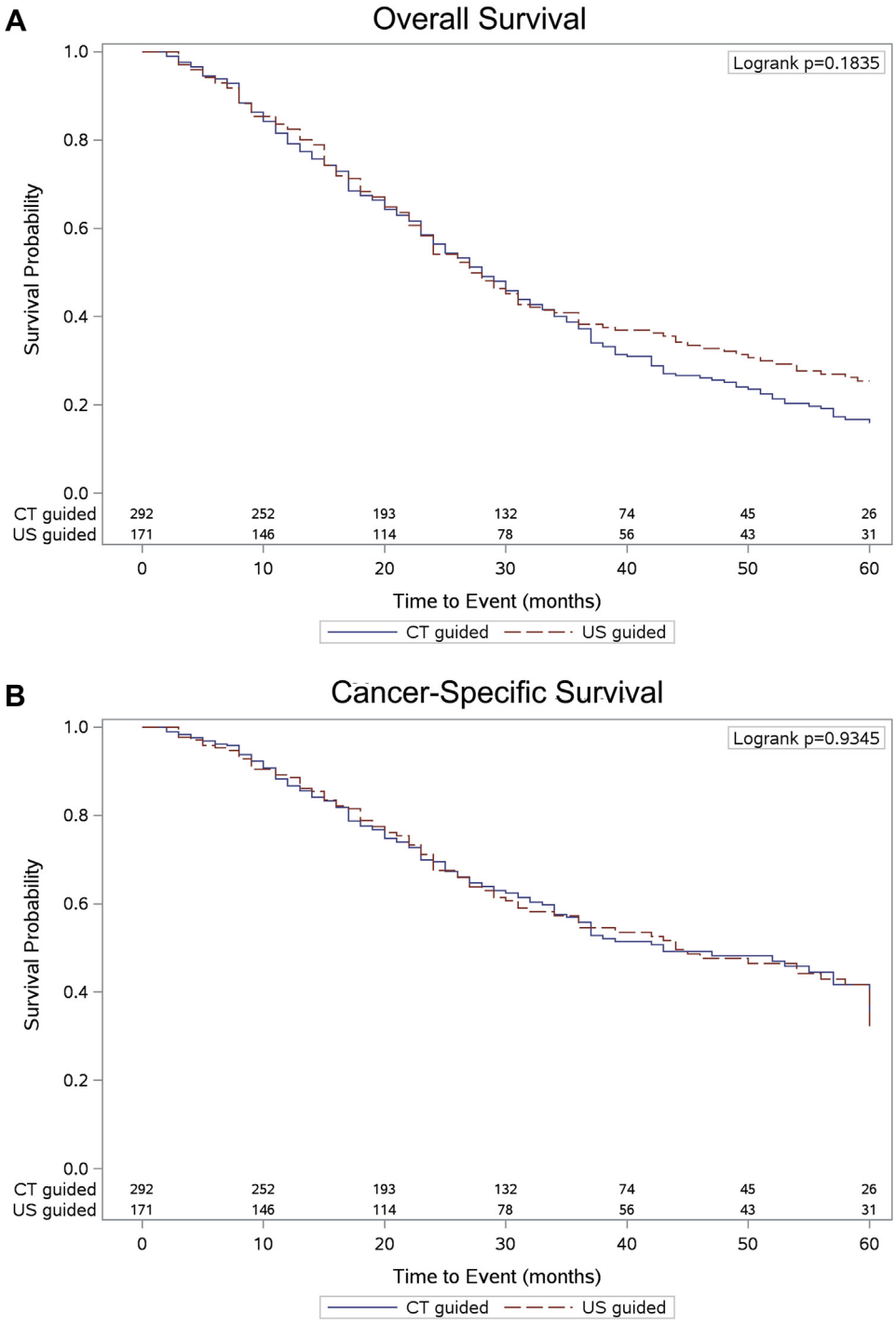

Fig. 2 – (A) OS and (B) CSS of patients undergoing RFA. CSS indicates cancer-specific survival; CT, computed tomography; OS, overall survival; RFA, radiofrequency ablation; US, ultrasound.

physician's experience in this procedure is an independent prognostic factor.[43] Patients who were operated by experienced physicians may have a lower risk of complications than those operated by less experienced physicians. Nevertheless, because of the limitation of the database, we were not able to measure the physician's experience. Fourth, minor toxicities that do not require medical intervention were not captured in the claims database. Fifth, this study is limited to the Medicare population aged 65 years and older, and therefore the study findings may not be generalizable to younger populations. Sixth, the SEER–Medicare data do not collect information on patient quality of life and patient satisfaction after treatment; future studies that compare these patient-reported outcomes are needed. Finally, although the Medicare claims data included payment to clinician consultations, they do not collect information to allow the comparison of physician training costs between CT- and US-guided RFA.

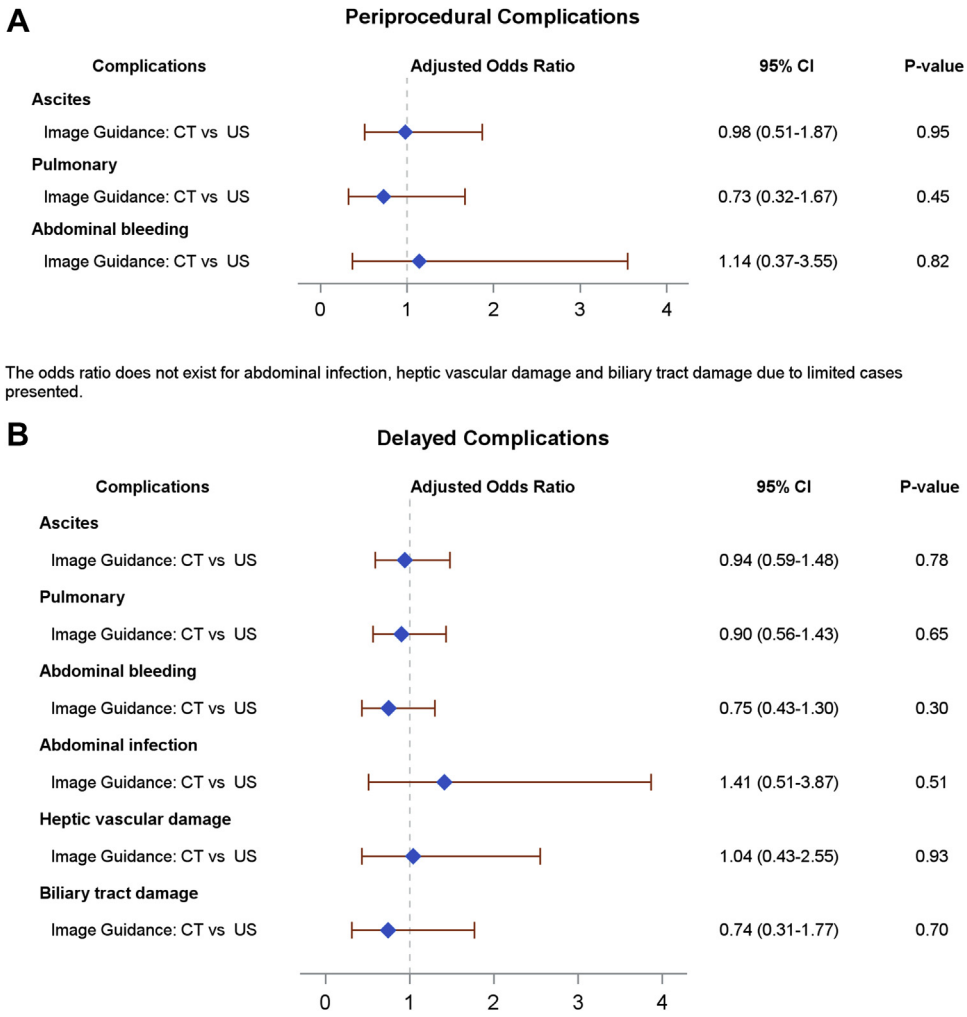

Fig. 3 – Adjusted odds ratios of use of image guidance in predicting postoperative complications: (A) the association of image guidance and periprocedural complications and (B) the association of image guidance and delayed complications. CI indicates confidence interval; CT, computed tomography; US, ultrasound.

Conclusions

Our study found that despite its rapid adoption over time, CT-guided RFA incurred higher procedural costs than US-guided RFA but did not significantly improve postprocedural complications and survival. Echoing the American Board of Internal Medicine's Choosing Wisely campaign and the American Society of Clinical Oncology's Value of Cancer Care initiative, findings from our study call for critical evaluation of whether CT-guided RFA provides high-value care for patients with HCC.

Acknowledgments

We acknowledge our use of the linked SEER–Medicare database in this study. The interpretation and reporting of the data are the sole responsibilities of the authors. We also acknowledge the efforts of the Applied Research Program of the National Cancer Institute; the Office of Research, Development and Information of the Centers for Medicare & Medicaid Services; Information Management Services, Inc; and the SEER Program registries in the creation of the SEER–Medicare database. We acknowledge the National Cancer Institute (Shih; R01 CA207216, CCSG P30 CA016672). We also acknowledge Donald Norwood at the University of Texas MD Anderson Cancer Center.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2018.10.004.

REFERENCES

1. Altekruse SF, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. J Clin Oncol 2009;27(9):1485–91.
2. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: Where are we? Where do we go? Hepatology 2014;60(5):1767–75.
3. American Cancer Society. Cancer Facts & Figures 2018. Atlanta, GA: American Cancer Society; 2018.

4. White DL, Thrift AP, Kanwal F, et al. Incidence of hepatocellular carcinoma in all 50 United States, from 2000 through 2012. Gastroenterology 2017;152(4):812–820.e5.
5. National Cancer Institute. Cancer Stat Facts: Liver and Intrahepatic Bile Duct Cancer. Rockville, MD: National Cancer Institute; 2018.
6. Lang K, Danchenko N, Gondek K, et al. The burden of illness associated with hepatocellular carcinoma in the United States. J Hepatol 2009;50(1):89–99.
7. Machi J, Uchida S, Sumida K, et al. Ultrasound-guided radiofrequency thermal ablation of liver tumors: percutaneous, laparoscopic, and open surgical approaches. J Gastrointest Surg 2001;5(5):477–89.
8. Curley SA. Radiofrequency ablation of malignant liver tumors. Oncologist 2001;6(1):14–23.
9. Abi-Jaoudeh N, Kruecker J, Kadoury S, et al. Multimodality image fusion–guided procedures: technique, accuracy, and applications. Cardiovasc Intervent Radiol 2012;35(5):986–98.
10. Wood BJ, Kruecker J, Abi-Jaoudeh N, et al. Navigation systems for ablation. J Vasc Interv Radiol 2010;21(8):S257–63.
11. Lau WY, Lai ECH. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. Ann Surg 2009;249(1):20–5.
12. Goldberg SN, Grassi CJ, Cardella JF, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria. J Vasc Interv Radiol 2009;20(7):S377–90.
13. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update. Radiology 2014;25(11):1706–8.
14. Solomon SB, Silverman SG. Imaging in interventional oncology. Radiology 2010;257(3):624–40.
15. Nakai M, Sato M, Sahara S, et al. Radiofrequency ablation assisted by real-time virtual sonography and CT for hepatocellular carcinoma undetectable by conventional sonography. Cardiovasc Intervent Radiol 2008;32(1):62–9.
16. Park BJ, Byun JH, Jin YH, et al. CT-guided radiofrequency ablation for hepatocellular carcinomas that were undetectable at US: therapeutic effectiveness and safety. J Vasc Interv Radiol 2009;20(4):490–9.
17. Warren JL, Klabunde CN, Schrag D, et al. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. Med Care 2002;40(8):IV3–18.
18. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatobiliary Cancers, Version 1.2018. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2018.
19. Klabunde CN, Potosky AL, Legler JM, et al. Development of a comorbidity index using physician claims data. J Clin Epidemiol 2000;53(12):1258–67.
20. Charlson ME, Sax FL, MacKenzie CR, et al. Assessing illness severity: Does clinical judgment work? J Chronic Dis 1986;39(6):439–52.
21. Davidoff AJ, Zuckerman IH, Pandya N, et al. A novel approach to improve health status measurement in observational claims-based studies of cancer treatment and outcomes. J Geriatr Oncol 2013;4(2):157–65.
22. Davidoff AJ, Tang M, Seal B, et al. Chemotherapy and survival benefit in elderly patients with advanced non–small-cell lung cancer. J Clin Oncol 2010;28(13):2191–7.
23. US Bureau of Labor Statistics. Measuring Price Change for Medical Care in the CPI. Consumer Price Index. Washington, DC: Division of Consumer Prices and Price Indexes, US Bureau of Labor Statistics; 2015.
24. Lahat E, Eshkenazy R, Zendel A, et al. Complications after percutaneous ablation of liver tumors: a systematic review. Hepatobiliary Surg Nutr 2014;3(5):317–23.
25. Lencioni RA, Allgaier H-P, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228(1):235–40.
26. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol 2010;28(3):493–508.
27. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Paper presented at: Proceedings of the Twenty-Sixth Annual SAS Users Group International Conference. Cary, NC: SAS Institute Inc; 2001.
28. Rubin DB. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127(8):757–63.
29. Smith-Bindman R, Miglioretti DL, Larson EB. Rising use of diagnostic medical imaging in a large integrated health system: the use of imaging has skyrocketed in the past decade, but no one patient population or medical condition is responsible. Health Aff (Millwood) 2008;27(6):1491–502.
30. Smith-Bindman R, Miglioretti DL, Johnson E, et al. Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010. JAMA 2012;307(22):2400–9.
31. Kim J-E, Kim Y-S, Rhim H, et al. Outcomes of patients with hepatocellular carcinoma referred for percutaneous radiofrequency ablation at a tertiary center: analysis focused on the feasibility with the use of ultrasonography guidance. Eur J Radiol 2011;79(2):e80–4.
32. Livraghi T, Solbiati L, Meloni MF, et al. Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226(2):441–51.
33. Lin S-M, Lin C-J, Lin C-C, et al. Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005;54(8):1151–6.
34. Curley SA, Izzo F, Ellis LM, et al. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. Ann Surg 2000;232(3):381–91.
35. Amersi FF, McElrath-Garza A, Ahmad A, et al. Long-term survival after radiofrequency ablation of complex unresectable liver tumors. Arch Surg 2006;141(6):581–8.
36. Brunello F, Veltri A, Carucci P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial. Scand J Gastroenterol 2008;43(6):727–35.
37. Schnipper LE, Lyman GH, Blayney DW, et al. American Society of Clinical Oncology 2013 top five list in oncology. J Clin Oncol 2013;31(34):4362–70.
38. Schnipper LE, Smith TJ, Raghavan D, et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol 2012;30(14):1715–24.
39. Grady D, Redberg RF. Less is more: how less health care can result in better health. Arch Intern Med 2010;170(9):749–50.
40. Clasen S, Rempp H, Hoffmann R, et al. Image-guided radiofrequency ablation of hepatocellular carcinoma (HCC): Is MR guidance more effective than CT guidance? Eur J Radiol 2014;83(1):111–6.
41. Curley SA, Izzo F. Radiofrequency ablation of primary and metastatic hepatic malignancies. Int J Clin Oncol 2002;7(2):72–81.
42. Buscarini E, Buscarini L. Radiofrequency thermal ablation with expandable needle of focal liver malignancies: complication report. Eur Radiol 2004;14(1):31–7.
43. Lee L-H, Hwang J-I, Cheng Y-C, et al. Comparable outcomes of ultrasound versus computed tomography in the guidance of radiofrequency ablation for hepatocellular carcinoma. PLoS One 2017;12(1):e0169655.