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Research Letter

Stereotactic Body Radiation Therapy for the Definitive Treatment of Early Stage Kidney Cancer: A Survival Comparison With Surgery, Tumor Ablation, and Observation

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Abstract

Purpose: Partial nephrectomy is the preferred definitive treatment for early stage kidney cancer, with tumor ablative techniques or active surveillance reserved for patients not undergoing surgery. Stereotactic body radiation therapy (SBRT) has emerged as a potential noninvasive alternative for patients with early stage kidney cancer not amenable to surgery, with early reports suggesting excellent rates of local control and limited toxicity.

Methods and Materials: The national cancer database from 2004 to 2014 was queried for patients who received a diagnosis of T1N0M0 kidney cancer. Treatments were categorized as surgery (partial or total nephrectomy), tumor ablation (cryoablation or thermal ablation), SBRT (radiation therapy in 5 fractions or less to a total biological effective dose [BED_{10}] of 72 or more), or observation. A propensity score was generated by multinomial logistic regression. A Cox proportional hazards model was fit to determine association between overall survival and treatment group with propensity score adjustments for patient, demographic, and treatment characteristics.

Results: A total of 165,298 received surgery, 17,196 underwent tumor ablation, 104 underwent SBRT, and 18,241 were observed. Median follow-up was 51 months. On multivariable analysis, surgery, tumor ablation, and SBRT were associated with a decreased risk of death compared with observation, with hazard ratios of 0.25 (95% confidence interval, 0.24-0.26, $P < .001$), 0.36 (0.35-0.38, $P < .001$), and 0.56 (0.39-0.79, $P < .001$), respectively. When stratifying by BED_{10} and compared with observation, hazard ratio for risk of death for patients treated with SBRT to a $BED_{10} \geq 100$ (n = 62) and a $BED_{10} < 100$ (n = 42) was 0.34 (0.19-0.60, $P < .001$) and 0.90 (0.58-1.4, $P = .64$), respectively.

Conclusions: In this population-based cohort, patients undergoing high-dose SBRT ($BED_{10} \geq 100$) for early stage kidney cancer demonstrated longer survival compared with patients undergoing observation. This may be a promising noninvasive treatment option for nonsurgical candidates with prospective efficacy and safety assessments meriting study in future clinical trials.

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Introduction

Partial nephrectomy is the preferred definitive treatment for early stage kidney cancer, with tumor ablative techniques or active surveillance reserved for patients not undergoing surgery.[1] With an increase in the number of incidentally diagnosed kidney cancers and in an increasingly elderly population who may not tolerate invasive procedures,[2,3] stereotactic body radiation therapy (SBRT) has emerged as a potential noninvasive alternative for patients not amenable to surgery, with early reports suggesting excellent rates of local control and limited toxicity.[4–9] This study uses a large national cancer registry to assess patterns of care and survival outcomes in patients with stage I kidney cancer treated with SBRT.

Methods and Materials

The national cancer database was queried from 2004 to 2014 for patients who received a diagnosis of T1N0M0 kidney cancer (7 cm or less with no nodal or distant metastases). Both clinical and pathologic staging was used to determine patient inclusion. Histologic subtypes were limited to clear cell carcinoma, papillary carcinoma, renal cell not otherwise specified (NOS), and carcinoma NOS. Exclusion criteria is listed in Figure 1. Treatments were categorized as surgery (including partial and total nephrectomy), tumor ablation (including cryoablation and thermal ablation), SBRT, or observation. SBRT was defined as radiation therapy in 5 fractions or less to a total biological effective dose (BED_{10}) of 72 or more assuming a tumor α/βvalue of 10. Although there is limited research into the radiobiology of kidney SBRT, studies from non-small cell lung cancer suggest a BED_{10} of approximately 70 corresponds to the lower limit of what may be considered an acceptable tumor control probability.[10–12] Because a BED_{10} of 100 has been shown to be an important cut point for outcomes in multiple other disease sites,[13,14] patients receiving SBRT were dichotomized by those treated to a BED_{10} of <100 or ≥ 100. This project was reviewed by our institutional review board and found to be exempted.

A propensity score was generated by multinomial logistic regression, and a Cox proportional hazard model was fit to determine association between treatment group

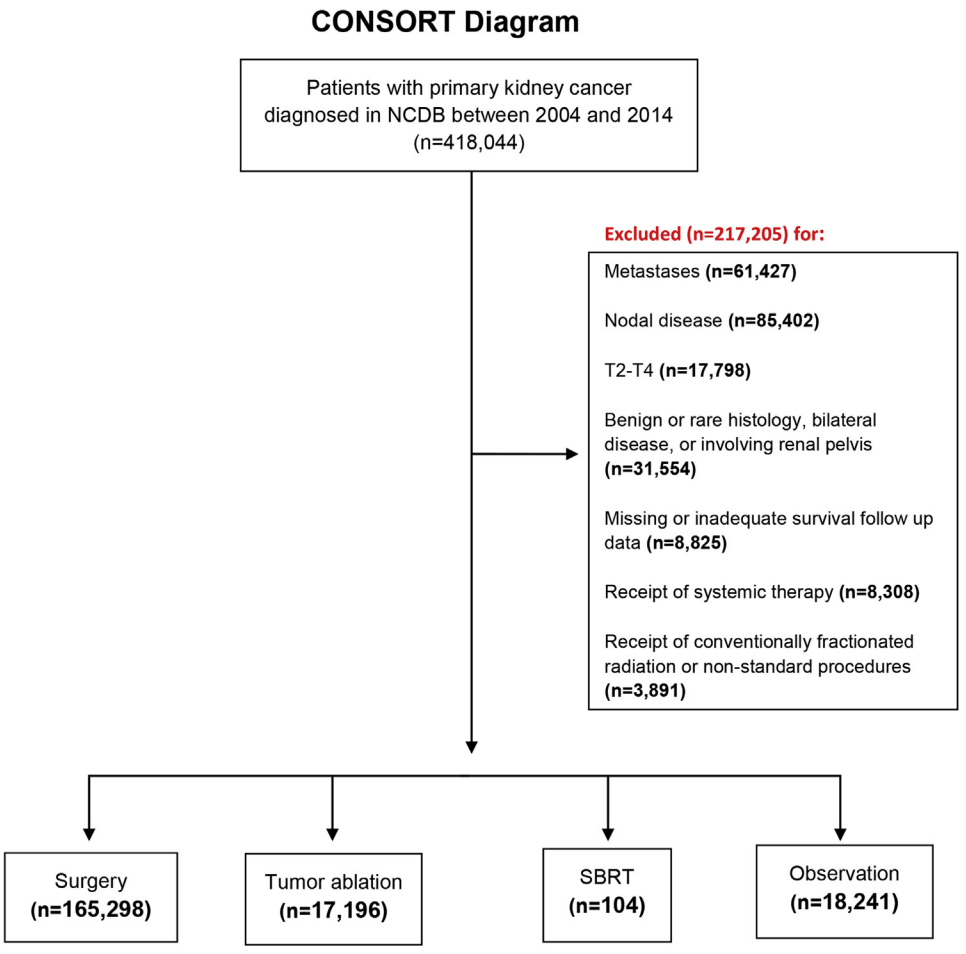

Figure 1 Consort diagram displaying. *Abbreviations*: NCDB = National Cancer Database; SBRT = stereotactic body radiation.

Table 1 Patient and tumor characteristics

	Treatment								*P* value
	Surgery		Tumor ablation		SBRT		Observation		
	165,298	(%)	17,196	(%)	104	(%)	18,241	(%)	
Age (y)									<.001
Median	61		69		75		74		
18-49	33,312	20.2%	1165	6.8%	1	1.0%	1122	6.2%	
50-64	67,870	41.1%	4860	28.3%	24	23.1%	3902	21.4%	
>64	64,116	38.8%	11,171	65.0%	79	76.0%	13,217	72.5%	
Race									<.001
White	122,024	73.8%	13,230	76.9%	75	72.1%	12,972	71.1%	
Black	18,671	11.3%	1765	10.3%	15	14.4%	2749	15.1%	
Hispanic	20,055	12.1%	1828	10.6%	10	9.6%	2069	11.3%	
Other	4548	2.8%	373	2.2%	4	3.8%	451	2.5%	
Sex									<.001
Female	65,644	39.7%	6411	37.3%	37	35.6%	7655	42.0%	
Male	99,654	60.3%	10,785	62.7%	67	64.4%	10,586	58.0%	
Year of diagnosis									<.001
2004	11,597	7.0%	436	2.5%	0	0.0%	1034	5.7%	
2005	12,400	7.5%	735	4.3%	0	0.0%	1247	6.8%	
2006	13,488	8.2%	1161	6.8%	1	1.0%	1319	7.2%	
2007	14,394	8.7%	1416	8.2%	5	4.8%	1469	8.1%	
2008	14,753	8.9%	1762	10.2%	11	10.6%	1554	8.5%	
2009	15,600	9.4%	1905	11.1%	9	8.7%	1630	8.9%	
2010	15,190	9.2%	1917	11.1%	18	17.3%	1716	9.4%	
2011	16,202	9.8%	1864	10.8%	14	13.5%	1786	9.8%	
2012	16,991	10.3%	1928	11.2%	12	11.5%	1939	10.6%	
2013	17,183	10.4%	1964	11.4%	21	20.2%	2330	12.8%	
2014	17,500	10.6%	2108	12.3%	13	12.5%	2217	12.2%	
Charlson-Deyo comorbidity score									<.001
0	115,165	69.7%	11,551	67.2%	83	79.8%	12,178	66.8%	
1	37,410	22.6%	4029	23.4%	18	17.3%	3685	20.2%	
2	9387	5.7%	1182	6.9%	2	1.9%	1555	8.5%	
3	3336	2.0%	434	2.5%	1	1.0%	823	4.5%	
Tumor stage									<.001
T1a	110,014	66.6%	15,188	88.3%	63	60.6%	11,837	64.9%	
T1b	55,284	33.4%	2008	11.7%	41	39.4%	6404	35.1%	
Tumor size (mm)									<.001
Median	34.9		26.5		35.8		32.7		
0-25	57,245	34.6%	9397	54.6%	29	27.9%	8294	45.5%	
26-50	81,524	49.3%	7527	43.8%	65	62.5%	7807	42.8%	
51-70	26,529	16.0%	272	1.6%	10	9.6%	2,140	11.7%	
Laterality									<.001
Left	79,987	48.4%	8407	48.9%	46	44.2%	8771	48.1%	
Right	85,080	51.5%	8775	51.0%	58	55.8%	9285	50.9%	
Unknown	231	0.1%	14	0.1%	0	0.0%	185	1.0%	
Histology									<.001
Clear cell carcinoma	92,157	55.8%	6779	39.4%	37	35.6%	2693	14.8%	
Papillary carcinoma	26,457	16.0%	2465	14.3%	13	12.5%	1088	6.0%	
Renal cell carcinoma NOS	46,382	28.1%	7545	43.9%	47	45.2%	12,792	70.1%	
Carcinoma NOS	302	0.2%	407	2.4%	7	6.7%	1668	9.1%	
Tumor grade									<.001
1	23,580	14.3%	2685	15.6%	11	10.6%	954	5.2%	
2	84,040	50.8%	4330	25.2%	23	22.1%	1545	8.5%	
3	30,161	18.2%	612	3.6%	0	0.0%	360	2.0%	
4	2623	1.6%	35	0.2%	0	0.0%	50	0.3%	
Unknown	24,894	15.1%	9534	55.4%	70	67.3%	15,332	84.1%	

(*continued on next page*)

Table 1 (*continued*)

	Treatment								*P* value
	Surgery		Tumor ablation		SBRT		Observation		
	165,298	(%)	17,196	(%)	104	(%)	18,241	(%)	
Academic treatment facility									<.001
Yes	65,410	39.6%	7362	42.8%	49	47.1%	6593	36.1%	
No	90,197	54.6%	9560	55.6%	54	51.9%	11,346	62.2%	
Unknown	9691	5.9%	274	1.6%	1	1.0%	302	1.7%	

Abbreviations: NOS = not otherwise specified; SBRT = stereotactic body radiation therapy.

and overall survival (OS) with propensity score adjustments for patient, demographic, and treatment characteristics, including age at diagnosis, race, sex, year of diagnosis, Charlson-Deyo comorbidity score, tumor size, laterality, histology, grade, insurance plan, rurality, median income, education, academic hospital, and distance traveled for treatment. The proportional hazard assumption was visually checked. To reduce lead time bias, patients were excluded if they died or were lost to follow-up before 2.67 months from diagnosis, corresponding to the time in which 90% of subjects had started definitive treatment. Approximately 3.5% of all patients (1.9% of surgery patients, 1.3% of tumor ablation patients, no SBRT patients, and 16.8% of observation patients) were excluded from analysis by this follow-up time constraint.

Results

A total of 200,839 patients were included, of whom 165,298 received surgery (median follow-up 57 months), 17,196 underwent tumor ablation (median follow-up 50

Table 2 Patient and tumor characteristics by radiation dose

	SBRT dose				*P* value
	BED <100		BED≥100		
	42	(%)	62	(%)	
Age (y)					.47
Median	75		73		
Charlson-Deyo comorbidity score					.83
0	33	78.6%	50	80.7%	
1	8	19.1%	10	16.1%	
2	1	2.4%	1	1.6%	
3	0	0.0%	1	1.6%	
Tumor stage					.32
T1a	23	54.8%	40	64.5%	
T1b	19	45.2%	22	35.5%	
Tumor size (mm)					.06
Median	39.2		33.5		
Laterality					.57
Left	20	47.6%	26	41.9%	
Right	22	52.4%	36	58.1%	
Histology					.16
Clear cell carcinoma	20	47.6%	17	27.4%	
Papillary carcinoma	3	7.1%	10	16.1%	
Renal cell carcinoma NOS	17	40.5%	30	48.4%	
Carcinoma NOS	2	4.8%	5	8.1%	
Most common fractionation (fx) schemes					N/A
40 Gy in 5 fx	13	31.0%			
39 Gy in 3 fx	9	21.4%			
36 Gy in 3 fx	9	21.4%			
48 Gy in 3 fx			29	46.8%	
45 Gy in 3 fx			9	14.5%	
50 Gy in 5 fx			8	12.9%	

Abbreviations: BED = biological effective dose; NOS = not otherwise specified; SBRT = stereotactic body radiation therapy.

months), 104 underwent SBRT (median follow-up 37 months), and 18,241 were observed (median follow-up 19 months; Table 1). The most common fractionation schemes for patients receiving SBRT were 40 Gy in 5 fractionation for the BED_{10} <100 cohort (42 patients) and 48 Gy in 3 fractionation for the BED_{10} ≥100 cohort (62 patients; Table 2).

At a median follow-up of 51 months, 40,489 patients (20.2%) had died with 5-year OS estimate shown in Table 3 and Figure 2. On multivariable analysis with propensity score adjustment, patients undergoing surgery, tumor ablation, and SBRT were associated with a decreased risk of death compared with patients undergoing observation, with a hazard ratio (HR) of 0.25 (95% confidence interval [CI] 0.24-0.26, $P < .001$), 0.36 (0.35-0.38, $P < .001$), and 0.56 (0.39-0.79, $P < .001$), respectively. Compared with observation, HR for risk of death for SBRT patients treated to a BED_{10} <100 and a BED_{10} ≥100 was 0.90 (0.58-1.4, $P = .64$) and 0.34 (0.19-0.60, $P < .001$), respectively (Table 4). A sensitivity analysis using Cox regression with propensity score adjustment stratified into quintiles provided similar results (Table 5).

Discussion

In this analysis, we show that SBRT for primary kidney cancer is an uncommon treatment in the United States despite an increasing number of diagnosed patients, emerging evidence for the safety and efficacy of the treatment, and recent technical improvements in radiation delivery.[2–6] We demonstrate that this is a recently adopted treatment, with no reported cases of primary kidney SBRT in 2004 or 2005 and only one case in 2006. Moreover, we show that patients treated with SBRT, and in particular, those with a BED_{10} ≥100, demonstrated an improved OS at 5 years compared with those who were observed, even after adjusting for patient and tumor characteristics. This outcome may in part reflect patient selection based on clinical factors not available or measured in covariates. For example, the median size of tumors in the higher BED cohort was 33.5 mm compared with 39.2 mm in the lower BED group, which suggests that BED may in part be a surrogate for tumor size. Still, the improved survival in patients treated with SBRT to a BED_{10} ≥100 versus BED_{10} <100 persisted after propensity-adjustments and generates the hypothesis that radiation treatment, particularly at highly ablative doses, may have the potential to significantly alter the disease course in treated patients. This analysis supports prior single center studies that generally explored SBRT for primary kidney cancer with highly ablative doses[4–6] and ongoing prospective clinical trials.[15]

For patients who are not ideal candidates for surgical resection, potential options include tumor ablation with cryotherapy or radiofrequency ablation, SBRT, or observation. SBRT may be an attractive treatment option for many patients for several reasons. First, SBRT is able to treat tumors larger than 4 cm or tumors located near the renal pelvis, criteria which are generally unsuitable for interventional radiology–guided tumor ablation.[16,17] In this analysis, nearly 40% of SBRT tumors were >4 cm, compared with just 12% of ablated tumors. Second, SBRT is a noninvasive treatment with no associated anesthesia risk or prolonged recovery time. Third, SBRT is convenient for the patient, with treatment generally completed in 5 days or less or, in many cases, in a single day.

Limitations include the small number of patients treated with SBRT compared with other cohorts and the potential for confounding factors. Without information on cancer specific mortality or cause of death, and in a disease where overall outcomes are expected to be favorable,[18] it is unclear whether the observed differences are related to differences in treatment or patient selection. Our findings of improved OS in patients treated with BED_{10} ≥100 compared with <100 are surprising because the risk of distant metastases and cancer-specific death in patients with T1N0M0 kidney cancer is relatively low.[19–22] Indeed, prior single institutional studies of kidney SBRT demonstrated very low rates of local failure.[4–6] Even if higher BED_{10} leads to improved local control, it is unclear if this

Table 3 Unadjusted 5-year overall survival estimates by treatment group

	Patients N	Events N	5-year estimated OS	(95% CI)	*P* value
All	200,839	40,489	0.82	(0.81, 0.82)	
Surgery	165,298	26,768	0.86	(0.86, 0.86)	<.001
Tumor ablation	17,196	4180	0.77	(0.76, 0.77)	
SBRT, BED <100	42	20	0.42	(0.25, 0.59)	
SBRT, BED ≥100	62	12	0.73	(0.56, 0.84)	
Observation	18,241	9509	0.43	(0.42, 0.43)	

Abbreviations: BED = biological effective dose; SBRT = stereotactic body radiation therapy.

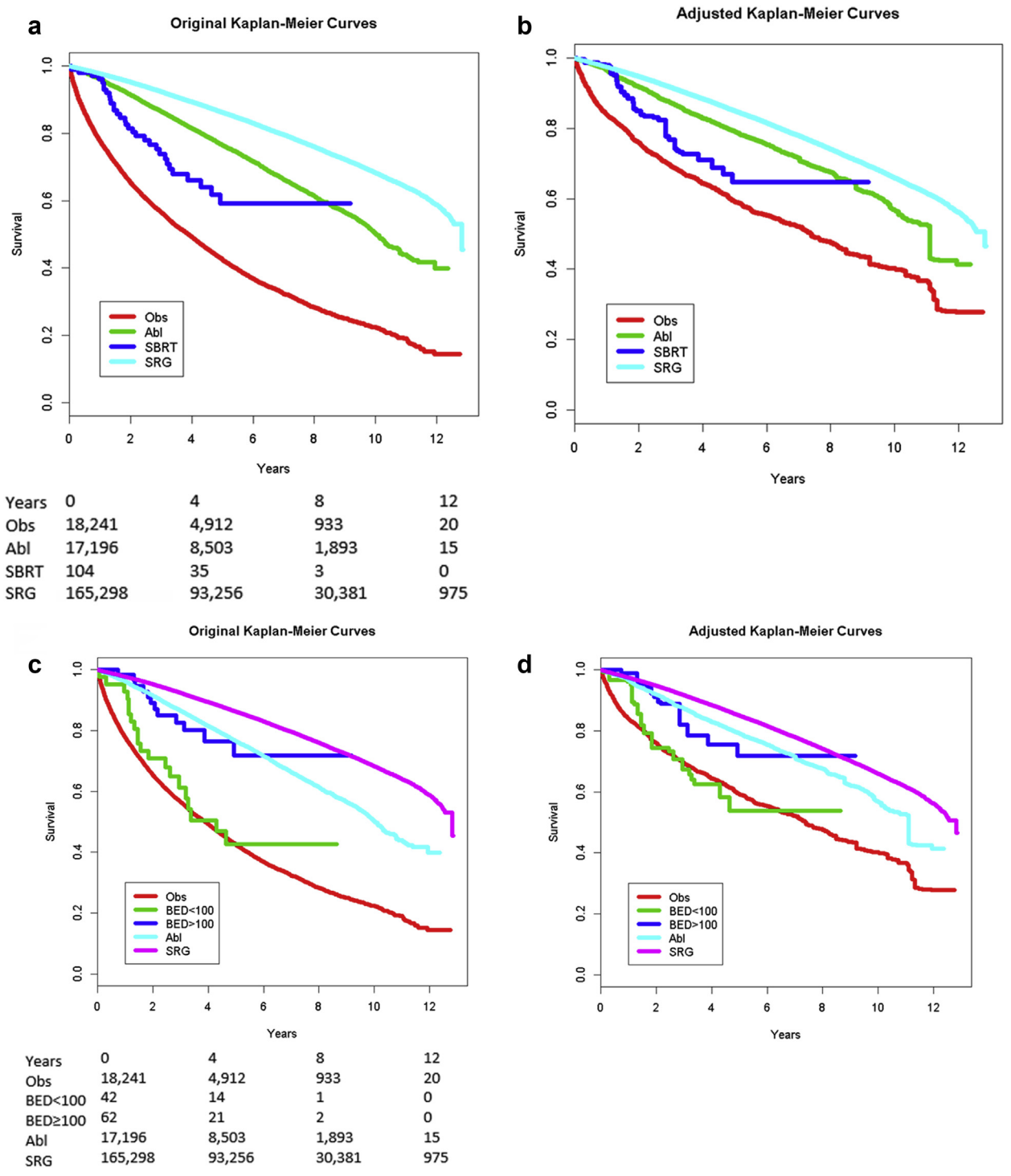

Figure 2 Kaplan-Meier survival curves of overall survival by treatment groups with SBRT cohorts combined (a and b) or separated by BED_{10} (c and d). *Abbreviations*: Abl = tumor ablation; Obs = observation; SBRT = stereotactic body radiation therapy; SRG = surgery.

would drive a survival benefit in this population during this period of follow-up.

Other limitations include the potential for discrepancies between staging technique between treatment cohorts (ie, patients treated with SBRT are staged only clinically, compared with those undergoing surgery who are staged pathologically). In addition, this analysis grouped together patients treated with both total and partial nephrectomy, although these are distinct treatments with likely distinct outcomes. Furthermore, we excluded any patients who received systemic therapy as a component of initial treatment, which may erroneously

Table 4 Cox proportional hazards regression for overall survival with propensity score adjustments*

	HR	(95% CI)	*P* value
Treatment			
Observation	1		
Surgery	0.25	(0.24, 0.26)	<.001
Tumor ablation	0.36	(0.35, 0.38)	<.001
SBRT	0.56	(0.39, 0.79)	<.001
BED <100	0.9	(0.58, 1.4)	.64
BED ≥100	0.34	(0.19, 0.6)	<.001
Age (y)			
18-49	1		
50-64	1.75	(1.66, 1.84)	<.001
>64	2.85	(2.71, 2.99)	<.001
Race			
White	1		
Black	0.99	(0.96, 1.02)	.5
Hispanic	0.88	(0.85, 0.91)	<.001
Other	0.8	(0.74, 0.86)	<.001
Sex			
Female	1		
Male	1.16	(1.13, 1.18)	<.001
Year of diagnosis			
2004-2009	1		
2010-2012	0.89	(0.87, 0.91)	<.001
2013-2014	0.88	(0.85, 0.92)	<.001
Charlson- Comorbidity Score			
0	1		
1	1.38	(1.35, 1.41)	<.001
2	1.97	(1.91, 2.04)	<.001
3	2.56	(2.45, 2.68)	<.001
Tumor size			
0-25 mm	1		
26-50 mm	1.21	(1.19, 1.24)	<.001
51-70 mm	1.56	(1.52, 1.61)	<.001
Laterality			
Left	1		
Right	0.98	(0.96, 1.00)	.09
Histology			
Clear cell carcinoma	1		
Papillary carcinoma	1.01	(0.98, 1.04)	.67
Renal cell carcinoma NOS	1.13	(1.11, 1.16)	<.001
Carcinoma NOS	1.33	(1.25, 1.42)	<.001
Grade			
1	1		
2	1.05	(1.01, 1.08)	.007
3, 4	1.27	1.23-1.33	<.001

Abbreviations: BED = biological effective dose; OS = not otherwise specified; SBRT = stereotactic body radiation therapy.

* Models additionally adjusted for age at diagnosis, race, sex, year of diagnosis, Charlson-Deyo comorbidity score, tumor size, laterality, histology, grade, insurance plan, rurality, median income, education, academic hospital, distance traveled for treatment and propensity score.

exclude patients receiving planned adjuvant systemic therapy after surgery, tumor ablation, or SBRT. Additionally, patients with less than 2.67 months of follow-up were excluded in an attempt to reduce lead time bias.

Table 5 Cox proportional hazards regression for overall survival by propensity score stratification in quintiles*

	HR	(95% CI)	*P* value
Treatment			
Observation	1		
Surgery	0.20	(0.19, 0.20)	<.001
Tumor ablation	0.32	(0.31, 0.33)	<.001
SBRT	0.52	(0.37, 0.74)	<.001
BED <100	0.85	(0.55, 1.32)	.64
BED ≥100	0.32	(0.18, 0.56)	<.001

Abbreviations: BED = biological effective dose; CI = confidence interval; HR = hazard ratio; NOS = not otherwise specified; SBRT = stereotactic body radiation therapy.

* Models additionally adjusted for age at diagnosis, race, sex, year of diagnosis, Charlson-Deyo comorbidity score, tumor size, laterality, histology, grade, insurance plan, rurality, median income, education, academic hospital, distance traveled for treatment and propensity score.

Although such exclusion criteria may limit capture of perioperative or treatment-related mortality, perioperative mortality after nephrectomy or partial nephrectomy is low.[23] Finally, this study does not include cases treated in the past several years given the nature of national cancer database reporting and the lag between treatment and data collection and distribution.

Conclusions

SBRT for early stage kidney cancer may be a promising noninvasive treatment option for nonsurgical patients. Despite the small number of patients treated with SBRT and potential for unmeasured confounding factors, a national registry study such as this may be the only current viable way to compare outcomes after SBRT in early stage kidney cancer given its extremely limited utilization at present. The efficacy and safety of this approach is being evaluated in ongoing prospective clinical trials.[15]

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