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Balancing Cardiovascular and Cancer Death among Patients with Small Renal Mass: Modification by Cardiovascular Risk

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Abstract

- To assess modification of comparative cancer survival by cardiovascular (CV) risk and treatment strategy among older patients with small renal masses.
- Patients with localized T1a renal cell carcinoma were identified in the Surveillance, Epidemiology and End Results-Medicare database (1995–2007).
- Patients were stratified by CV risk, using major atherosclerotic CV comorbidities identified by the Framingham Heart Study, to compare overall (OS), cancer-specific (CSS), and cardiovascular-specific survival (CVSS) for those who deferred therapy (DT) to those undergoing either partial (PN) or radical nephrectomy (RN).
- Cox proportional hazards and Fine and Gray competing risks regression adjusted for demographics, comorbidities, and tumor size.
- A total of 754 (10.5%) patients deferred therapy, 1849 (25.8%) patients underwent PN, and 4574 (63.7%) patients underwent RN.
- Patients at high CV risk who deferred therapy experienced the greatest CV-to-cancer mortality rate ratio (2.89), and CV risk was generally associated with worse OS and CVSS.
- Patients in the high CV risk strata had no difference in CSS between treatment strategies (DT vs. PN: HR 0.59 (95%CI 0.25–1.41); DT vs. RN: HR 0.81 (95%CI 0.46–1.43)) while there was a 2–4 fold CSS benefit for surgery in the low CV risk strata.
- Cancer survival was comparable across treatment strategies for older patients with small renal masses at high risk CV disease.

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- Greater attention to CV comorbidity as it relates to competing risks of death and life expectancy may be deserved in selecting patients appropriate for active surveillance because patients at low CV risk might benefit from surgery.

Keywords

small renal mass; renal cell carcinoma; active surveillance; comorbidity; SEER; Medicare

Introduction

Along with a steady rise in incidence, the management of small renal masses (SRMs) has evolved dramatically over the past several decades [1]. The shift from radical nephrectomy (RN) to increased utilization of nephron-sparing treatments (partial nephrectomy (PN) and energy ablation) has, recently, been combined with an interest to identify patients that may be candidates for active surveillance (AS) [2–4]. The balance between death from cancer and death due to competing risks has made patient comorbidities increasingly important in the selection of candidates for AS [5]. Cardiovascular (CV) comorbidity and survival is especially relevant for patients with renal cell carcinoma [6–8].

While early data on AS for SRMs have demonstrated encouraging outcomes in carefully selected cohorts, recent population-based reports comparing patients who have deferred therapy (DT) to those undergoing surgery have raised concerns for inferior cancer survival [9–11]. One potential explanation is inadequate patient selection at the population-level, and although DT is distinct from institutional AS cohorts, it provides a unique opportunity to study patient selection and outcomes. Major atherosclerotic CV diseases have been identified as important predictors of postoperative complications in the validated Revised Cardiac Risk Index and also as predictors of long-term survival by the Framingham Heart Study [12,13]. However, prior studies have focused only on CV outcomes without risk-stratification [6–8]. No study has specifically assessed the impact of CV risk on comparative survival for patients who either undergo surgery or defer therapy for SRMs.

The goal of the current study is to assess modification of survival, especially cancer survival, by CV risk for patients who have undergone DT compared to those who underwent either PN or RN in a nationally representative population-based cancer registry with comorbidity data derived from Medicare.

Patients and Methods

Cohort

Institutional Review Board approval was obtained to query the Surveillance, Epidemiology and End Results (SEER) cancer registry and Medicare claims data from 1995 to 2007 for patients >65 years old diagnosed with clinically localized, T1a (≤4cm) renal cortical tumors with staging based on the 2009 American Joint Committee on Cancer TNM system. Kidney cancer diagnosis codes ICD-0-2, C64.9 and 9th revision ICD-0-9, 189.0 were used to identify patients. Exclusions included lacking Medicare A and/or B coverage, enrollment in managed care plans during treatment, regional disease (T3-4 N0M0, TxN1-2M0), distant

metastases (TxNxM1), unknown stage, upper tract transitional cell carcinoma or ureteric, non-cortical renal tumors, multiple procedures, and/or bilateral tumors.

CPT and ICD-9-CM codes were used to classify patients as undergoing PN (CPT 50240, 50280, 50290, 50543 or ICD-9-CM 55.51, 55.52, 55.54) or RN (CPT 50220, 50225, 50230, 50545, 50546 or ICD-9-CM 55.51, 55.52, 55.54). Notably, Medicare claims and SEER data have a high agreement (97%) for classifying PN versus RN [14]. There is also a high concordance in identifying patients who do not undergo cancer-directed surgery [15]. Therefore, patients lacking a procedural code within six months of diagnosis, the time frame for which SEER collects cancer therapy procedure codes, were classified as DT. Previous studies have termed this group non-surgical management, but the term DT is used here to recognize a small percentage (<4%) undergo intervention after six months, which constitutes a very minor portion of the overall cohort [10,11,16]. SEER data were used to ascertain patient demographic data including age, sex, race, marital status, urban-rural residence, tumor size, and year of intervention. Histologic subtype was excluded from analysis due to a significant proportion of missing data from SEER.

Cardiovascular Risk

Comorbidity data were collected from claims records, and Charlson comorbidity index (CCI) was calculated using the Medicare Provider Analysis and Review file [17]. The definition for comorbidities classified as high CV risk was based on the Framingham Heart Study, which identified cardiac failure, stroke, coronary disease, and peripheral artery disease as major atherosclerotic CV diseases [13]. Therefore, high CV risk was adapted from CCI comorbidities and defined as presence of congestive heart failure (CHF), cerebrovascular disease (CVD), history of myocardial infarction (MI), or peripheral vascular disease (PVD) while low risk was defined as the absence of any of these [13,17–20]. Diabetes and hypertension serve as highly prevalent predisposing risk factors to these comorbidities but were not classified as major cardiovascular diseases or competing risks of death in isolation [13,21].

Outcomes

Person-time contributed by each patient during follow-up was calculated from the date of diagnosis for DT and date of surgery for PN and RN until date of death or end of follow-up. The outcomes were overall survival (OS) through May 31, 2010 based on Medicare follow-up as well as kidney cancer-specific survival (CSS) and cardiovascular-specific survival (CVSS) through December 31, 2007 per SEER follow-up and data on cause-specific death. Medicare follow-up for death extended beyond SEER follow-up, which was accounted for in survival models. Cardiovascular causes of death to determine CVSS were defined based on SEER recodes 50060–50110 (Supplemental Table).

Statistical Methods

Kaplan-Meier survival functions were calculated stratified by CV risk and treatment strategy for OS, CSS, and CVSS. Unadjusted and adjusted Cox proportional hazards regression was performed to compare the high and low CV risk cohorts. Models were adjusted for demographics, comorbidity, tumor size, and year. A number of causes of death are in

competition for patients with SRMs, so competing risks regression was employed according to the method described by Fine and Gray [22]. The CV-to-cancer mortality rate ratio was calculated by treatment strategy to visualize the effect of competing CV causes of death on the relative likelihood of death from kidney cancer. Finally, modification of survival by CV risk for DT patients as compared to surgery was assessed using Cox proportional hazards models with competing risks regression. Statistical analyses were performed using STATA v.12.0 (STATA Corp, College Station, TX, 2011).

Results

A total of 7177 patients met the inclusion criteria with statistically significant differences for baseline characteristics by treatment strategy (Table 1). Patients who deferred therapy had higher CCI scores and were more often African-American ($p < 0.01$). Median follow-up for OS was 56 months (interquartile range 38–85 months). A total of 334 (4.7%) and 522 (7.3%) patients died of kidney cancer and cardiovascular-related causes, respectively. There were 1236 (17.2%) patients classified as high CV risk based on presence of CHF, CVD, MI, or PVD. For surgical patients, 66% were treated within 1 month of diagnosis, and <1% were in the sixth month.

The final adjusted Cox proportional hazards model showed a significantly worse OS [hazard ratio (HR) (95% confidence interval) 1.61 (1.46–1.78)] and CVSS [HR 2.04 (1.68–2.48)] for patients at high versus low CV risk (Table 2). Notably, CSS was comparable between groups [HR 1.14 (0.86–1.51)] showing the difference in OS was driven by CVSS. CV risk had the greatest influence on competing causes of death for DT patients (Figure 1). For example, the CV-to-cancer mortality rate ratio increased from 1.22 for patients at low CV risk to 2.89 for patients at high CV risk. Therefore, DT patients at high CV risk died of a cardiovascular cause at nearly three times the rate of kidney cancer mortality.

Stratified survival analyses revealed several notable findings (Table 3). Kaplan-Meier survival curves for OS, CSS, and CVSS are presented in Figure 2. Both OS and CVSS were worse among DT patients as compared to those undergoing surgery (either PN or RN) regardless of the gross CV risk stratification ($p < 0.01$), which reflects the greater comorbidity burden and selection bias expected for the DT cohort. However, CV risk modified CSS so that surgery was favored over DT for patients at low cardiovascular risk [PN vs. DT, HR 0.33 (0.20–0.53); RN vs. DT, HR 0.55 (0.39–0.79)] while there was no statistically significant difference for patients at high cardiovascular risk [PN vs. DT, HR 0.59 (0.25–1.41); RN vs. DT, HR 0.81 (0.46–1.43)].

Discussion

In this retrospective review of 7,177 patients diagnosed with localized kidney cancer, cancer survival was similar regardless of CV risk. As expected, those at high risk were more likely to die of CV causes leading to worse CVSS and OS. The most notable finding of the present study may be that CV risk modified comparative survival resulting in similar cancer outcomes for patients at high CV risk regardless of treatment strategy. There was a noted CSS benefit for surgery at low CV risk. While the results may seem intuitive, prior studies

have largely focused on the effect of generalized comorbidity on OS or other-cause mortality to risk-stratify SRM patients without quantifying comparative CSS between treatment strategies [5,23,24].

Selection criteria, whether objective or subjective, drives most outcomes in patients undergoing treatment for cancer. This is especially evident in kidney cancer, where the most morbid interventions (complication rates of PN exceed those of RN) are reserved for the healthiest patients and patients with substantial comorbidity are selected for radical surgery or deferred therapy. As expected, patients undergoing PN had the lowest rate of patients at high CV risk and subsequently the lowest rate of CV death. A number of retrospective studies report favorable renal and cardiovascular outcomes for PN compared to RN in the treatment of SRMs compared to RN [6,7]. Interestingly, our study corroborates a previous report by Huang et al that even after controlling for comorbid conditions, cardiovascular events were found to occur more often after RN [8]. The most purported explanation holds PN may decrease the incidence of chronic kidney disease, which is a risk factor for CV outcomes. However, inherent patient selection biases are often reflected in population-based survival analyses, which measurements of comorbidity and other variables cannot account for fully [25,26]. The DT cohort represents an extreme case where patients did not undergo intervention for unknown reasons, but the most likely are age, comorbidity, tumor characteristics, and patient preference. The selection is also apparent from the decreased OS and CVSS. The high CV-to-cancer mortality rate ratio (2.89) for DT patients at high CV risk is reassuring and demonstrates that these patients, among all older individuals, may be most appropriately selected for AS.

AS is an option to reduce morbidity from surgery for suboptimal surgical candidates as well as patients not desiring surgery [4]. The goal is to reduce potential overtreatment without conceding oncologic outcomes [27]. AS implies the appropriate monitoring of patients with SRMs based on defined inclusion criteria and triggers for intervention and is distinct from the population-based practice represented in the DT cohort. However, the impact of comorbidities on survival can be translated into trade-offs of CV-to-cancer mortality and help inform evolving AS protocols. Appropriate selection is important because it has been suggested nephrectomy to treat renal cell carcinoma of any stage may be associated with better quality of life at one year after surgery as measured by the Karnofsky Performance Scale [24]. Recent reports in the SEER-Medicare population have also suggested patients >65 years of age may not be adequately selected to defer surgery, requiring greater emphasis on comorbidity and tumor risk-stratification [10,11]. Patients at high CV risk are very reasonable candidates for AS, but energy ablation is another option for patients deciding against observation.

The definition of CV risk deserves attention. High CV risk was defined as the presence of any major atherosclerotic CV disease which could act as a competing risk of death. The major diseases included were CHF, CVD, MI, and PVD as identified by the Framingham Heart Study [13]. Hypertension, hypercholesterolemia, diabetes, and cigarette smoking are considered risk factors for atherosclerotic disease as opposed to direct comorbidities acting as competing risks of death with renal cell carcinoma [13,19–21]. Conclusions from a gross stratification such as the presence or absence of any CV comorbidity should be taken with

caution when applied to individual patients. Kutikov et al recently showed an index such as CCI could be useful to stratify patient prognosis in terms of 5-year probabilities [5]. However, appropriate comorbidity weights for individual comorbidities may differ depending on the disease of interest [28]. A recent analysis of the same cohort demonstrated that the greatest predictors of non-cancer specific mortality in the SRM population were CHF and chronic kidney disease with higher hazard ratios than PVD, CVD, and MI (Abstract 1184, AUA 2013). CV comorbidity and survival may be most relevant for the SRM population as the present and prior analyses support [6–8].

The limitations of the present study deserve mention. Data was collected retrospectively from the SEER cancer registry and Medicare claims limiting the age of patients to 65 years as well as CSS and CVSS follow-up to 2007. Comorbidity data were obtained from inpatient hospital records using Medicare Provider Analysis and Review file. They do not allow insight into the severity or duration of illness which may provide a more precise prognosis. Outcomes of cardiovascular and renal events, outside of cause of death, were not available. As mentioned, the DT cohort is not a true AS cohort but rather reflects the current management in the United States so details about surveillance studies, duration, etc. are not available. Although there is some crossover from DT to intervention, the proportion is small and would also be expected in contemporary AS series where delayed intervention is one of the cost-effective options [9,29]. Residual and unmeasured confounding are also a concern when using population-based data. Nevertheless, the study assesses the impact of CV risk on comparative survival for patients undergoing surgery or DT.

In conclusion, CV comorbidities exert a significant impact on survival for patients with SRMs. Patients at high CV risk had similar CSS to patients at low CV risk, but CV risk modified comparative CSS between treatment strategies. Low CV risk patients had better cancer survival with surgery compared to DT while high CV risk patients had similar cancer survival regardless of treatment strategy. These data are important to highlight the role of CV comorbidity in selecting appropriate patients for AS as recent reports have suggested the population-based practice is lacking [10,11].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms

CCI	Charlson comorbidity index
CHF	congestive heart failure

CSS	cancer-specific survival
CVD	cerebrovascular disease
CVSS	cardiovascular-specific survival
DT	deferred therapy
HR	hazard ratio
MI	myocardial infarction
OS	overall survival
PN	partial nephrectomy
PVD	peripheral vascular disease
RN	radical nephrectomy
SEER	Surveillance, Epidemiology and End Results
SRM	small renal mass

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Figure 1.

Cardiovascular-to-cancer mortality rate ratios by cardiovascular risk and treatment strategy. Mortality rates are computed as number of cardiovascular or cancer deaths per 100,000 person-years in each strata. The cardiovascular mortality rate is divided by the cancer mortality rate to obtain mortality rate ratios. CV = cardiovascular, DT = deferred therapy, PN = partial nephrectomy, RN = radical nephrectomy.

Figure 2.

Kaplan-Meier survival curves for overall survival, cancer-specific survival, and cardiovascular-specific survival for low cardiovascular risk patients (A, B, and C, respectively) and high cardiovascular risk patients (D, E, and F, respectively). Overall and cardiovascular-specific survival are worse for patients at high compared to low cardiovascular risk while cancer-specific survival becomes more comparable across

treatment strategies. DT = deferred therapy, PN = partial nephrectomy, RN = radical nephrectomy, * = suppressed due to SEER-Medicare regulations.

Table 1

Demographic characteristics by treatment strategy, SEER-Medicare 1995–2007.

	Treatment Strategy ^d				p-value ^b
	DT (%)	PN (%)	RN (%)		
N	754	1849	4574		
Age					<0.01
65–69	115 (15.3)	589 (31.9)	1164 (25.5)		
70–74	159 (21.1)	569 (30.8)	1345 (29.4)		
75–79	164 (21.8)	463 (25.0)	1211 (26.5)		
80–84	153 (20.3)	191 (10.3)	638 (14.0)		
>85	163 (21.6)	37 (2.0)	216 (4.7)		
Race/Ethnicity					<0.01
White	605 (80.2)	1554 (84.1)	3933 (86.0)		
African American	103 (13.7)	162 (8.8)	352 (7.7)		
Other	46 (6.1)	133 (7.2)	289 (6.3)		
Sex					<0.01
Male	399 (52.9)	1070 (57.9)	2454 (53.7)		
Female	355 (47.1)	779 (42.1)	2120 (46.4)		
Residence					0.04
Large Metro	471 (62.5)	1146 (62.0)	2660 (58.2)		
Metro	173 (22.9)	470 (25.4)	1249 (27.3)		
Urban	38 (5.0)	100 (5.4)	276 (6.0)		
Less Urban	60 (8.0)	112 (6.1)	324 (7.1)		
Rural	12 (1.6)	21 (1.1)	65 (1.4)		
Marital Status					<0.01
Married	371 (51.2)	1214 (68.1)	2870 (64.8)		
Not Married	353 (48.8)	568 (31.9)	1556 (35.2)		
CCI^c					<0.01
0	260 (34.5)	983 (53.2)	2439 (53.3)		
1	241 (40.0)	514 (27.8)	1267 (27.7)		
2	132 (17.5)	212 (11.5)	497 (10.9)		

		Treatment Strategy ^a				p-value ^b
		DT (%)	PN (%)	RN (%)	RN (%)	
Tumor Size	3+	121 (16.1)	140 (7.6)	371 (8.1)		
	<2 cm	134 (17.8)	454 (24.6)	514 (11.3)		<0.01
	2–<3cm	258 (34.3)	776 (42.1)	1407 (30.8)		
	3– 4 cm	361 (47.9)	614 (33.3)	2643 (57.9)		
Year of Diagnosis						<0.01
	1995–1999	98 (13.0)	124 (6.7)	830 (18.2)		
	2000–2003	203 (26.9)	519 (28.1)	1581 (34.6)		
	2004–2007	453 (60.1)	1206 (65.2)	2163 (47.3)		

^aDT: Deferred therapy; PN: Partial nephrectomy; RN: Radical nephrectomy

^bChi-square (χ^2) test

^cCharlson comorbidity index

Table 2

The effect of cardiovascular risk on survival, SEER-Medicare 1995–2007.

Survival ^b	Group	Unadjusted			Adjusted ^a		
		HR	(95% CI)	p-value	HR	(95% CI)	p-value
OS	High vs. Low	2.04	(1.86–2.24)	<0.01	1.61	(1.46–1.78)	<0.01
CSS	Cardiovascular	1.64	(1.26–2.12)	<0.01	1.14	(0.86–1.51)	0.37
CVSS	Risk	2.96	(2.46–3.56)	<0.01	2.04	(1.68–2.48)	<0.01

^a Cox regression adjusted for age, sex, race, residence, marital status, tumor size, year of diagnosis, and all comorbidities; Fine and Gray competing risks regression used to obtain subhazard ratios for CSS and CVSS

^b OS: Overall survival; CSS: Kidney cancer-specific survival; CVSS: Cardiovascular-specific survival

Table 3
Stratified survival analysis by cardiovascular risk comparing treatment strategies, SEER-Medicare 1995–2007.

Survival ^a	Group ^b	Low Cardiovascular Risk			High Cardiovascular Risk		
		HR ^c	(95% CI)	p-value	HR ^c	(95% CI)	p-value
OS	PN vs DT	0.35	(0.29–0.41)	<0.01	0.48	(0.36–0.65)	<0.01
	RN vs DT	0.47	(0.41–0.54)	<0.01	0.65	(0.52–0.80)	<0.01
CSS	PN vs DT	0.33	(0.20–0.53)	<0.01	0.59	(0.25–1.41)	0.23
	RN vs DT	0.55	(0.39–0.79)	<0.01	0.81	(0.46–1.43)	0.47
CVSS	PN vs DT	0.34	(0.23–0.52)	<0.01	0.42	(0.24–0.75)	<0.01
	RN vs DT	0.53	(0.39–0.72)	<0.01	0.58	(0.39–0.85)	<0.01

^a OS: Overall survival; CSS: Kidney cancer-specific survival; CVSS: Cardiovascular-specific survival
^b DT: Deferred therapy; PN: Partial nephrectomy; RN: Radical nephrectomy
^c Cox regression adjusted for age, sex, race, residence, marital status, tumor size, year of diagnosis, and all comorbidities; Fine and Gray competing risks regression used to obtain subhazard ratios for CSS and CVSS