

Cardiovascular Mortality as a Negative Control Outcome for the Apparent Survival Benefit of Cytoreductive Nephrectomy in De Novo Metastatic Renal Cell Carcinoma

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Abstract

Purpose

Registry studies report a large survival benefit of cytoreductive nephrectomy in synchronous metastatic renal cell carcinoma, whereas randomised trials do not. We quantified how much of the registry-based association reflects bias, using cardiovascular death as a negative control outcome.

Methods

In this retrospective population-based cohort study, patients with de novo metastatic renal cell carcinoma diagnosed in 2010–2022 were identified in the SEER 17 registries. All-cause and cardiovascular death were analysed with the same overlap-weighted Cox models, with missing grade multiply imputed. The negative control hazard ratio (HR) was used to calibrate the all-cause HR across a bias-transportability parameter λ of 0.50–2.00, with 500 bootstrap resamples including full re-imputation.

Results

Of 16,736 patients, 5,988 (35.8%) underwent nephrectomy; 13,621 died, 394 from cardiovascular causes. The weighted HR was 0.424 (95% CI 0.403–0.447) for all-cause death and 0.528 (0.391–0.701) for cardiovascular death. At $\lambda = 1$, the calibrated all-cause HR was 0.804 (0.610–1.082), and bias accounted for 74.6% of the association; the calibrated estimate remained significant only when λ was 0.75 or less. Results were similar in a 3-month landmark analysis (calibrated HR 0.779, 0.546–1.127) and with alternative handling of missing grade. A direct effect of surgery could explain the cardiovascular association only if nephrectomy reduced cardiovascular death by 47%.

Conclusion

Much of the survival benefit attributed to cytoreductive nephrectomy in registry data appears to reflect patient selection rather than a treatment effect. These findings concern the interpretation of observational evidence, not individual treatment decisions.

Introduction

Many patients with renal cell carcinoma have distant metastases at diagnosis [1, 2]. In the cytokine era, two randomised trials showed longer survival with nephrectomy followed by interferon alfa than with interferon alfa alone [3, 4], and cytoreductive nephrectomy became standard practice [5]. In the targeted-therapy era, however, sunitinib alone was noninferior to nephrectomy followed by sunitinib in CARMENA [6], and deferring nephrectomy did not worsen outcomes in SURTIME [7]. Registry analyses nevertheless

continue to report survival benefits far larger than any observed in trials [8]; a recent Surveillance, Epidemiology, and End Results (SEER) analysis reported a 71% reduction in all-cause mortality [9].

Registry studies usually rely on more extensive adjustment or matching, which cannot account for factors that registries do not capture but that largely determine who is offered surgery, such as performance status, comorbidity and the laboratory components of prognostic scores [8, 10]. An instrumental variable analysis found no association between nephrectomy and survival [11], and a SEER study matched patients on predicted other-cause mortality [12], but neither quantified how much of a conventionally estimated hazard ratio is attributable to bias.

Negative control outcomes offer a way to measure this bias [13, 14]. An outcome that shares the confounding structure of the outcome of interest but cannot plausibly be affected by the exposure should show no association; any association that is observed reflects bias and can be used to calibrate the primary estimate. Cardiovascular death fits this role reasonably well, because frailty, comorbidity and socioeconomic circumstances influence both the decision to operate and cardiovascular risk. Nephrectomy could, however, affect cardiovascular death directly, by reducing renal function [15] or by removing tumour thrombus, so this assumption needs to be tested.

We used cardiovascular death as a negative control outcome to estimate how much of the apparent survival benefit of cytoreductive nephrectomy in de novo metastatic renal cell carcinoma is non-causal, and examined how sensitive this estimate is to a direct effect of nephrectomy on cardiovascular death.

Methods

Data source and study population

This was a retrospective cohort study using population-based registry data from the SEER 17 registries (November 2025 submission, released April 2026), which cover approximately 26.5% of the US population. We included patients aged 18 years or older with a microscopically confirmed, first or only malignant tumour of the kidney (C64.9) with renal cell carcinoma histology, diagnosed between 2010 and 2022 with distant metastasis (M1) at diagnosis. Cases diagnosed in 2023 were excluded because surgery coding changed that year. We then excluded patients with missing survival time, surgery codes 10–15, 90, 99 or missing, unknown status of all four metastatic sites, or death with an uninterpretable cause-of-death code. Field definitions, code lists and further methodological details are given in Online Resource 1, which also contains Tables S1–S8 and Figs. S1–S6.

Exposure and outcomes

Cytoreductive nephrectomy was defined by surgery of primary site codes 30, 40, 50, 70 and 80 (partial, total or radical nephrectomy, nephrectomy with resection of other organs, or nephrectomy not otherwise specified); code 00 denoted no surgery. Codes 20–27 (local excision) were classified as no nephrectomy

in the primary analysis and as nephrectomy in a sensitivity analysis. The outcome of interest was all-cause death. The negative control outcome was death from heart disease or cerebrovascular disease; cerebrovascular death alone had initially been considered but yielded only 71 events in a preliminary analysis and is reported as a sensitivity analysis. Follow-up ran from the month of diagnosis to death or 31 December 2023.

Covariates and missing data

Covariates were age, sex, race and ethnicity, marital status, county income quartile, residence, year of diagnosis, histology, grade, T and N category (with TX and NX as separate levels), the number of involved sites among bone, brain, liver and lung (0–1, 2 or ≥ 3), and coding era (2010–2015, 2016–2017 and 2018–2022). Age and year of diagnosis were modelled with restricted cubic splines. Post-exposure treatments were not adjusted for. Missing grade, which occurred mainly in patients without surgery, was multiply imputed within exposure groups (10 datasets; chained equations with classification and regression trees).

Statistical analysis

Three Cox models were fitted for each outcome: unadjusted (M0), multivariable-adjusted (M1) and overlap-weighted (M2, primary analysis), with overlap weights derived from a logistic propensity score model including all covariates [16, 17]. Balance was assessed with standardised mean differences (SMDs) [17]. The difference in 60-month restricted mean survival time (RMST) was estimated from weighted Kaplan–Meier curves. Point estimates were averaged over imputations on the log scale, and 95% confidence intervals (CIs) were percentile intervals from 500 bootstrap resamples in which imputation, propensity score estimation and all model fits were repeated [18]; both outcomes were estimated in the same resamples.

Assuming that the negative control association arises entirely from bias [13, 14], the calibrated estimate was $\log \text{HR}_{\text{cal}} = \log \text{HR}_{\text{all}} - \lambda \times \log \text{HR}_{\text{NCO}}$, and the proportion of the all-cause association attributable to bias was $\lambda \times \log \text{HR}_{\text{NCO}} / \log \text{HR}_{\text{all}}$. The parameter λ describes how bias transfers between outcomes ($\lambda = 1$, equal bias, is the reference assumption) and was varied from 0.50 to 2.00.

Sensitivity analyses addressed a direct effect of nephrectomy on cardiovascular death, expressed as a true hazard ratio γ between 0.6 and 1.3 [15]; administrative truncation of follow-up at 12, 24, 36 and 60 months; immortal time bias, with a 3-month landmark analysis [19, 20]; pre-specified analytical variants, including the alternative exposure definition, non-neoplastic or cerebrovascular death as the negative control, exclusion of brain metastasis, restriction to diagnosis before or after CARMENA, inverse probability of treatment weighting (IPTW) and propensity score matching; exclusion of partial nephrectomy; alternative handling of missing grade (unknown grade as a category [21], or grade omitted); alternative specifications of age and age strata; and E-values [22]. Several analytical decisions

were made after a preliminary analysis (Online Resource 1). Analyses were performed in R 4.6.1, and reporting follows the STROBE statement [23].

Results

Study population

Of 758,797 records, 16,736 patients were included (Fig. S1), of whom 5,988 (35.8%) underwent nephrectomy; the proportion declined from 41.5% in 2010–2015 to 28.3% in 2018–2022. Median follow-up was 69 months (interquartile range 38–109). Patients who underwent nephrectomy were younger (median 61 vs 65 years) and had a lower metastatic burden (three or more sites, 3.3% vs 11.7%) (Table 1). Fields that depend on a surgical specimen differed most: grade was unknown in 80.0% of patients without surgery and 16.5% of those with nephrectomy, and T category was TX in 23.8% and 2.1%.

Table 1
Baseline characteristics of patients with de novo metastatic renal cell carcinoma, by receipt of cytoreductive nephrectomy

Characteristic	Patients, n (%)			SMD	
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted	Overlap weighted
Demographics					
Age, median (IQR), years	64 (56–71)	65 (58–73)	61 (54–68)	–0.36	0.00
Age group, years					
< 50	1,805 (10.8)	957 (8.9)	848 (14.2)	0.17	–0.00
50–69	9,882 (59.0)	6,048 (56.3)	3,834 (64.0)	0.16	–0.02
≥ 70	5,049 (30.2)	3,743 (34.8)	1,306 (21.8)	–0.29	0.02
Sex					
Male	11,845 (70.8)	7,547 (70.2)	4,298 (71.8)	0.03	–0.00
Female	4,891 (29.2)	3,201 (29.8)	1,690 (28.2)	–0.03	0.00
Race and ethnicity					
NH White	10,668 (63.7)	6,726 (62.6)	3,942 (65.8)	0.07	–0.00
Hispanic	3,167 (18.9)	2,026 (18.9)	1,141 (19.1)	0.01	0.00
NH Black	1,554 (9.3)	1,145 (10.7)	409 (6.8)	–0.14	–0.00
NH Asian/PI	1,079 (6.4)	668 (6.2)	411 (6.9)	0.03	–0.00
NH AIAN	224 (1.3)	158 (1.5)	66 (1.1)	–0.03	0.00
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.					

Characteristic	Patients, n (%)			SMD	
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted	Overlap weighted
Demographics					
Unknown	44 (0.3)	25 (0.2)	19 (0.3)	0.02	0.01
Marital status					
Married	9,717 (58.1)	5,849 (54.4)	3,868 (64.6)	0.21	-0.00
Single	3,143 (18.8)	2,191 (20.4)	952 (15.9)	-0.12	0.00
Divorced/separated	1,821 (10.9)	1,234 (11.5)	587 (9.8)	-0.05	0.00
Widowed	1,422 (8.5)	1,053 (9.8)	369 (6.2)	-0.13	0.00
Unknown	548 (3.3)	362 (3.4)	186 (3.1)	-0.01	-0.00
Domestic partner	85 (0.5)	59 (0.5)	26 (0.4)	-0.02	0.00
County median household income					
Q1	4,741 (28.3)	3,057 (28.4)	1,684 (28.1)	-0.01	-0.00
Q2	4,627 (27.6)	2,858 (26.6)	1,769 (29.5)	0.07	-0.00
Q3	3,698 (22.1)	2,465 (22.9)	1,233 (20.6)	-0.06	0.00
Q4	3,670 (21.9)	2,368 (22.0)	1,302 (21.7)	-0.01	-0.00
Residence					
Metro ≥1M	9,343 (55.8)	5,984 (55.7)	3,359 (56.1)	0.01	-0.00
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.					

Characteristic	Patients, n (%)		SMD		
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted	Overlap weighted
Demographics					
Metro <1M	5,029 (30.0)	3,228 (30.0)	1,801 (30.1)	0.00	-0.00
Nonmetro	2,332 (13.9)	1,516 (14.1)	816 (13.6)	-0.01	0.00
Unknown	32 (0.2)	20 (0.2)	12 (0.2)	0.00	0.01
Diagnosis					
Year of diagnosis, median (IQR)	2017 (2013–2020)	2017 (2014–2020)	2016 (2013–2019)	-0.28	0.00
Coding era					
2018–2022	7,125 (42.6)	5,109 (47.5)	2,016 (33.7)	-0.29	0.00
2010–2015	6,956 (41.6)	4,066 (37.8)	2,890 (48.3)	0.21	-0.00
2016–2017	2,655 (15.9)	1,573 (14.6)	1,082 (18.1)	0.09	0.00
Metastatic burden at diagnosis					
Metastatic sites (of four)					
0–1	10,907 (65.2)	6,107 (56.8)	4,800 (80.2)	0.52	-0.00
2	4,370 (26.1)	3,380 (31.4)	990 (16.5)	-0.35	0.00
3+	1,459 (8.7)	1,261 (11.7)	198 (3.3)	-0.32	0.00
Bone	6,806 (40.7)	5,059 (47.1)	1,747 (29.2)	-0.37	-0.04
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.					

Characteristic	Patients, n (%)		SMD		
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted	Overlap weighted
Demographics					
Brain	1,976 (11.8)	1,570 (14.6)	406 (6.8)	-0.26	-0.08
Liver	3,202 (19.1)	2,518 (23.4)	684 (11.4)	-0.32	-0.07
Lung	10,231 (61.1)	6,771 (63.0)	3,460 (57.8)	-0.11	-0.03
Tumour characteristics					
Histology					
Clear cell	8,719 (52.1)	4,440 (41.3)	4,279 (71.5)	0.64	0.00
Papillary	741 (4.4)	443 (4.1)	298 (5.0)	0.04	-0.00
Chromophobe	148 (0.9)	63 (0.6)	85 (1.4)	0.08	0.00
Sarcomatoid	568 (3.4)	320 (3.0)	248 (4.1)	0.06	-0.00
RCC NOS/other	6,560 (39.2)	5,482 (51.0)	1,078 (18.0)	-0.74	0.00
Grade					
G1	286 (1.7)	207 (1.9)	79 (1.3)	-0.34	0.00
G2	1,565 (9.4)	659 (6.1)	906 (15.1)	-0.22	-0.00
G3	2,909 (17.4)	952 (8.9)	1,957 (32.7)	-0.16	-0.00
G4	2,395 (14.3)	335 (3.1)	2,060 (34.4)	0.56	0.00
Unknown	9,581 (57.2)	8,595 (80.0)	986 (16.5)		
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.					

Characteristic	Patients, n (%)			SMD	
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted	Overlap weighted
Demographics					
T category					
T0	165 (1.0)	163 (1.5)	2 (0.0)	-0.17	-0.00
T1	2,796 (16.7)	2,140 (19.9)	656 (11.0)	-0.25	0.00
T2	3,124 (18.7)	2,364 (22.0)	760 (12.7)	-0.25	0.00
T3	5,909 (35.3)	2,187 (20.3)	3,722 (62.2)	0.94	0.00
T4	2,054 (12.3)	1,331 (12.4)	723 (12.1)	-0.01	0.00
TX	2,688 (16.1)	2,563 (23.8)	125 (2.1)	-0.68	0.00
N category					
N0	9,424 (56.3)	5,342 (49.7)	4,082 (68.2)	0.38	-0.00
N1	5,277 (31.5)	3,667 (34.1)	1,610 (26.9)	-0.16	0.00
NX	2,035 (12.2)	1,739 (16.2)	296 (4.9)	-0.37	0.00
Treatment and follow-up					
Recorded first-course systemic therapy	7,895 (47.2)	5,049 (47.0)	2,846 (47.5)		
Recorded radiotherapy	4,973 (29.7)	3,518 (32.7)	1,455 (24.3)		
Death from any cause	13,621 (81.4)	9,418 (87.6)	4,203 (70.2)		
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.					

Characteristic	Patients, n (%)		SMD	
	Overall (n = 16,736)	No nephrectomy (n = 10,748)	Nephrectomy (n = 5,988)	Unweighted Overlap weighted
Demographics				
Death from kidney cancer	11,531 (68.9)	7,979 (74.2)	3,552 (59.3)	
Death from any non-neoplastic cause	1,141 (6.8)	725 (6.7)	416 (6.9)	
Death from heart disease	323 (1.9)	224 (2.1)	99 (1.7)	
Death from cerebrovascular disease	71 (0.4)	37 (0.3)	34 (0.6)	
Values are n (%) unless otherwise indicated. SMD, standardised mean difference (nephrectomy minus no nephrectomy); weighted SMDs use overlap weights estimated in the first imputed dataset. Grade counts are shown before imputation; SMDs for grade are computed on imputed grade, because missing grade reflects the absence of a surgical specimen rather than a patient characteristic to be balanced. Nephrectomy denotes Surgery of Primary Site codes 30, 40, 50, 70 and 80. IQR, interquartile range; NH, non-Hispanic; PI, Pacific Islander; AIAN, American Indian or Alaska Native; RCC, renal cell carcinoma.				

The propensity score model had a c-statistic of 0.888, and 1.59% of patients lay outside the region of common support (Fig. S2). After overlap weighting, the absolute SMD of every covariate level in the model was 0.01 or less (Table 1, Fig. S3); two sparse covariate levels were merged (Table S1), and the effective sample sizes were 3,862 and 4,865.

All-cause death and the negative control outcome

During follow-up, 13,621 patients (81.4%) died, and 394 negative control events occurred (323 from heart disease and 71 from cerebrovascular disease), 133 in the nephrectomy group and 261 in the no-nephrectomy group. For all-cause death, the hazard ratio (HR) was 0.384 (95% CI 0.371–0.397) in M0, 0.406 (0.386–0.434) in M1 and 0.424 (0.403–0.447) in M2, and the 60-month RMST was 16.49 months (15.55–17.34) longer with nephrectomy (Table 2, Fig. S4). For cardiovascular death, the HR was 0.393 (0.313–0.482) in M0, almost identical to that for all-cause death, 0.519 (0.384–0.708) in M1 and 0.528 (0.391–0.701) in M2 (Table 2, Fig. 1a). Results were similar under the alternative exposure definition (all-cause 0.427, 0.407–0.450; negative control 0.541, 0.404–0.723). The all-cause association varied over time (proportional hazards test $P < 0.001$), whereas no departure was detected for cardiovascular death ($P = 0.54$).

Table 2
Association of cytoreductive nephrectomy with all-cause death and with the negative control outcome

Analysis	All-cause death HR (95% CI)	Cardiovascular death (negative control) HR (95% CI)
Events, nephrectomy / no nephrectomy	4,203 / 9,418	133 / 261
Primary exposure definition (codes 30–80)		
M0, unadjusted	0.384 (0.371–0.397)	0.393 (0.313–0.482)
M1, multivariable-adjusted	0.406 (0.386–0.434)	0.519 (0.384–0.708)
M2, overlap-weighted (primary)	0.424 (0.403–0.447)	0.528 (0.391–0.701)
RMST difference at 60 months, months	+ 16.49 (+ 15.55 to + 17.34)	+ 0.98 (+ 0.45 to + 1.47)
Alternative definition (adding local excision, codes 20–27)		
M0, unadjusted	0.385 (0.371–0.398)	0.399 (0.322–0.491)
M1, multivariable-adjusted	0.408 (0.387–0.435)	0.532 (0.401–0.738)
M2, overlap-weighted (primary)	0.427 (0.407–0.450)	0.541 (0.404–0.723)

Table 2
(continued). Calibration of the all-cause estimate against the negative control

λ	Calibrated HR for all-cause death (95% CI)		Proportion explained, %
	Primary definition	Alternative definition	Primary definition
0.50	0.584 (0.505–0.680)	0.581 (0.503–0.676)	37.3 (21.0 to 54.4)
0.75	0.686 (0.556–0.856)	0.678 (0.550–0.845)	55.9 (31.5 to 81.6)
1.00	0.804 (0.610–1.082)	0.790 (0.600–1.054)	74.6 (42.0 to 108.9)
1.50	1.107 (0.732–1.721)	1.075 (0.713–1.661)	111.9 (63.0 to 163.3)
2.00	1.524 (0.872–2.758)	1.462 (0.834–2.626)	149.2 (84.0 to 217.7)
HR, hazard ratio; RMST, restricted mean survival time. Point estimates are pooled over 10 imputations; 95% CIs are percentiles of 499 bootstrap resamples, each with complete re-imputation. The negative control outcome is cardiovascular death (diseases of the heart or cerebrovascular disease), analysed as cause-specific with other deaths censored. Calibrated log HR = log HR(all-cause) – $\lambda \times$ log HR(negative control); proportion explained = $\lambda \times$ log HR(negative control) / log HR(all-cause). $\lambda = 1$ (bold) is the reference assumption that bias transfers unchanged between outcomes.			

Calibration against the negative control

At $\lambda = 1$, the calibrated HR for all-cause death was 0.804 (0.610–1.082), and 74.6% (42.0%–108.9%) of the observed association was attributable to bias (Table 2, Fig. 1b). The calibrated HR was 0.584 (0.505–0.680) at $\lambda = 0.50$, 0.686 (0.556–0.856) at $\lambda = 0.75$, 1.107 (0.732–1.721) at $\lambda = 1.50$ and 1.524 (0.872–2.758) at $\lambda = 2.00$; a significant benefit thus remained only if λ was 0.75 or less.

Robustness analyses

With follow-up truncated at 12 to 60 months, the all-cause (0.363 to 0.424) and negative control (0.456 to 0.528) HRs moved towards 1 in parallel (rank correlation 1.000), and the proportion attributable to bias ranged from 74.2% to 77.5% (Table S2, Fig. 1c). The negative control association remained inverse in all analytical variants (HR 0.361–0.608; Table S3, Fig. 1d); with IPTW, the calibrated all-cause HR was 1.124 (0.798–1.631), and excluding 250 patients with partial nephrectomy gave 0.819 (0.620–1.103). If nephrectomy truly reduced cardiovascular death by 20% ($\gamma = 0.8$), the calibrated HR was 0.643 (0.488–0.866), with 48.5% still attributable to bias; the negative control association would be entirely caused by nephrectomy only at $\gamma = 0.53$ (Table S4, Fig. S5). The negative control HR was 0.487 at age 50–69 years and 0.712 at 70 years or older (Table S5, Fig. S6), and the E-values were 3.00 for all-cause and 2.48 for cardiovascular death (Table S6).

The 3-month landmark analysis excluded 3,185 patients (29.6%) without surgery and 379 (6.3%) with nephrectomy. In the remaining 13,172 patients, both HRs moved towards the null in parallel (all-cause 0.463, 0.439–0.489; negative control 0.594, 0.406–0.836), and the calibrated HR was 0.779 (0.546–1.127), with 67.6% attributable to bias (Table S7). With unknown grade as a separate category or with grade omitted, the calibrated HRs were 0.892 (0.640–1.243) and 0.871 (0.671–1.149), and 86.1% and 81.6% of the association were attributable to bias (Table S8).

Discussion

In this cohort of 16,736 patients, cytoreductive nephrectomy was associated with a 47% lower hazard of cardiovascular death in the same model that showed the expected reduction in all-cause death, and before adjustment the two HRs were almost identical. Assuming equal bias, about three-quarters of the apparent survival benefit was attributable to bias, and the calibrated HR (0.804) was no longer statistically significant.

This pattern is expected from the way cytoreductive nephrectomy is used. Surgery in patients with established metastases is a discretionary decision that depends on performance status, cardiopulmonary reserve, comorbidity and social support, all of which also affect cardiovascular survival [8, 10]. Multivariable adjustment removed about half of the crude departure of the cardiovascular HR from the null, but near-exact covariate balance did not change it further (0.519 to 0.528), which points to factors that SEER does not record. Some recorded fields, notably grade, TX and NX, were themselves largely determined by whether surgery took place.

The calibrated HR was compatible with randomised evidence: in CARMENA, the HR for death with sunitinib alone versus nephrectomy followed by sunitinib was 0.89 (95% CI 0.71–1.10) [6], and 0.97 (0.79–1.19) with longer follow-up [24]. It was also close to the HR of 0.92 obtained by instrumental variable analysis [11]. Because these approaches rely on different assumptions, their agreement is reassuring. Other-cause mortality matching [12] balances predicted non-cancer death, whereas our design uses observed cardiovascular death to measure the bias that remains after balancing.

Immortal time bias probably contributed, because SEER does not record the date of surgery [19, 20]. The landmark analysis moved both HRs towards the null while leaving the calibrated estimate almost unchanged, consistent with a design that captures immortal time bias and confounding together without separating them. The assumption that nephrectomy does not affect cardiovascular death is weaker for renal surgery than for most tumour resections. Reduced renal function after radical nephrectomy may increase cardiovascular events [15], which would make our estimates conservative, whereas removal of tumour thrombus could reduce deaths from pulmonary embolism coded under heart disease. A direct effect large enough to explain the observed association, a 47% reduction, is implausible, and even a 20% reduction left about half of the association attributable to bias.

This study has limitations. Calibration assumes that bias transfers between outcomes as specified by λ , which cannot be verified [14]; we therefore report a range of values. Death certificates misclassify cause of death, particularly for heart disease [25]. Grade was missing for most patients without surgery, although both alternative approaches attributed a larger share of the association to bias. SEER does not record systemic agents or whether surgery was performed with curative intent. Several analytical decisions were made after a preliminary analysis; we report them openly, and none changed the conclusions. Finally, our findings address whether operated patients survive longer, not which subgroups benefit, and do not specifically address the immunotherapy era [26], although the negative control HR among patients diagnosed from 2018 onwards (0.490) was similar to that in earlier years.

These findings bear on the interpretation of observational evidence rather than on individual treatment decisions, which should continue to rely on randomised trials and clinical judgement.

Conclusion

In registry data, the survival benefit associated with cytoreductive nephrectomy in de novo metastatic renal cell carcinoma includes a substantial non-causal component. Cardiovascular death, which surgery should not affect, was 47% lower after nephrectomy, and about three-quarters of the apparent all-cause benefit was attributable to bias. Registry studies of cytoreductive surgery should test whether their approach yields a null association for outcomes that surgery is not expected to affect.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

All data in the SEER database are anonymised and contain no information that could identify individual patients; access was obtained after signing the SEER Research Data Use Agreement. As a secondary analysis of publicly available anonymised data, this study was reviewed by the institutional ethics committee and exempted from ethical review. The study was conducted in accordance with the Declaration of Helsinki.

Consent to participate

Not applicable. The analysis used previously collected, anonymised registry records, and the requirement for informed consent was waived.

Consent to publish

Not applicable. No individual-level data or identifying information are presented.

Electronic supplementary material

Online Resource 1 Supplementary methods, Tables S1–S8 and Figs. S1–S6

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Author Contribution

X Huang: Protocol/project development, Data analysis, Manuscript writing/editing, Other: funding acquisition
J Kuang: Data collection or management, Data analysis, Manuscript writing/editing
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Data Availability

The data analysed in this study are available to researchers who complete the SEER Research Data Agreement at <https://seer.cancer.gov/data/access.html>. The database used was: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence – SEER Research Data, 17 Registries, Nov 2025 Sub (2000–2023) – Linked To County Attributes – Time Dependent (1990–2024) Income/Rurality, 1969–2024 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2026, based on the November 2025 submission.

Code availability

The R code used for all analyses is available from the corresponding author on reasonable request.

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Figures

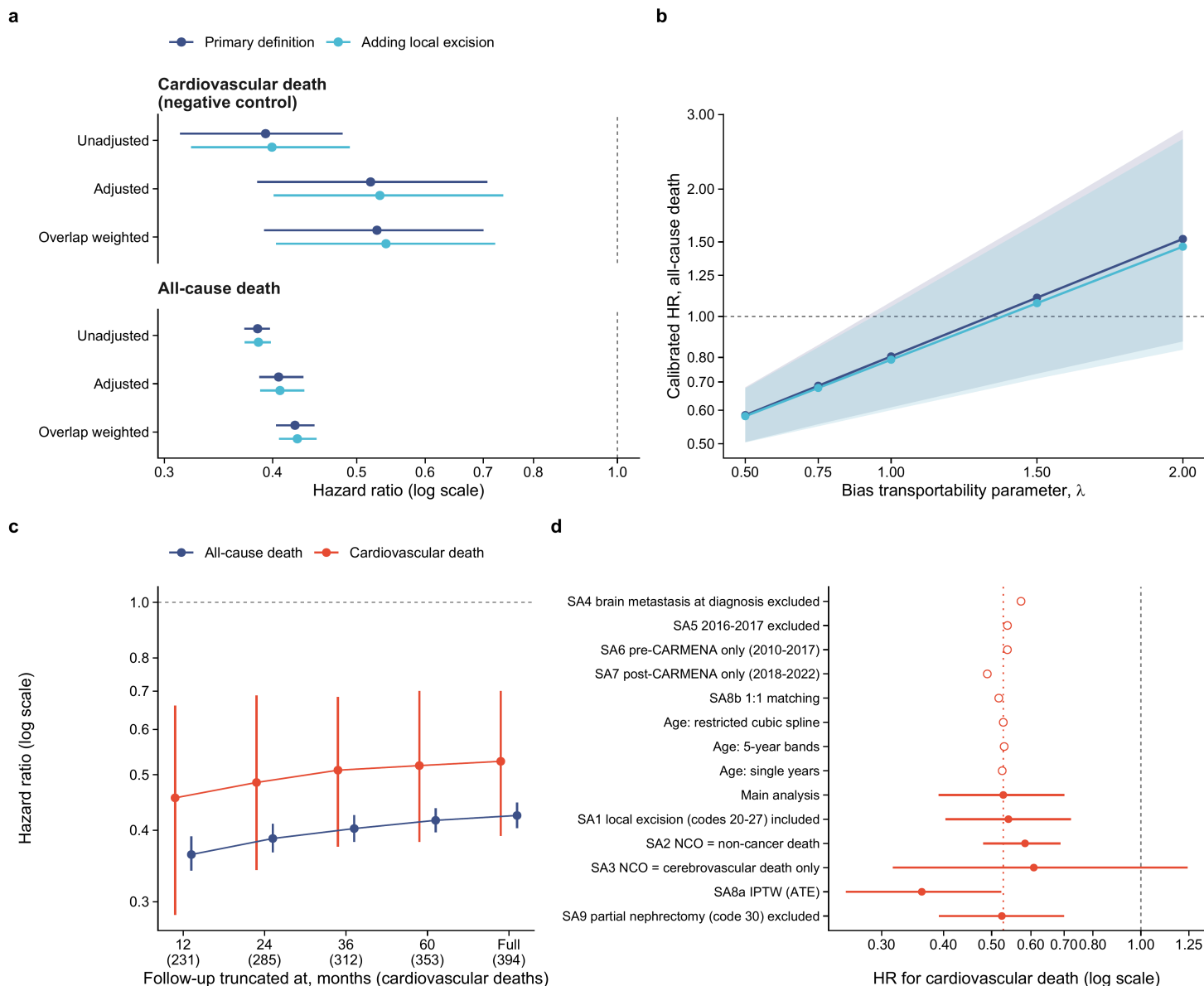


Figure 1

Negative control calibration and robustness. (a) Hazard ratios for all-cause and cardiovascular death from unadjusted, multivariable-adjusted and overlap-weighted models under the primary exposure definition and the definition that adds local excision. (b) Calibrated hazard ratio for all-cause death across the bias-transportability parameter λ ; shaded bands are 95% bootstrap confidence intervals. (c) Hazard ratios with follow-up truncated at 12, 24, 36 and 60 months and with full follow-up; numbers of cardiovascular deaths in parentheses. (d) Negative control hazard ratio across pre-specified analytical variants and functional forms for age; filled symbols with intervals denote variants for which the bootstrap was run

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