Cytoreductive nephrectomy in the modern era: Predictors of use, morbidity, and survival

Brian J. Minnillo, MD[1]; William Tabayoyong, MD, PhD[1]; John J. Francis, MD[1]; Matthew J. Maurice, MD[1]; Hui Zhu, MD, ScD[2]; Simon Kim, MD, MPH[1]; Robert Abouassaly, MD, MSc[1]

[1]Urological Institute, University Hospitals Case Medical Centre, Case Western Reserve University; [2]Urology Section/Surgery Service, Louis Stokes Cleveland Veterans Affairs Medical Centre; Cleveland, OH; United States

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Abstract

Introduction: To determine tumour, patient, and provider factors associated with cytoreductive nephrectomy (CN) use and to identify those factors that predicted short-term and long-term surgical outcomes.

Methods: We performed a retrospective review (1998–2011) of the National Cancer Database, a U.S. population-based oncology outcomes database. The review included 36 549 patients with metastatic renal cell carcinoma (mRCC). We assessed predictors of CN use, length of stay (LOS), 30-day readmission, and 30-day mortality using multivariable logistic regression. The Cox proportional hazards model assessed predictors of overall survival (OS).

Results: Overall, 10 809 (29.6%) patients received CN, increasing from 15.2% to 36.1% over time. Private insurance (odds ratio [OR] 1.26; 95% confidence interval [CI] 1.16–1.37) and academic facilities (OR 1.83; 95% CI 1.68–1.99) were associated with receiving CN ($p<0.0001$). Charlson score ≥2 and older age group were less likely to undergo surgery ($p<0.0001$). Median LOS was five days (interquartile range [IQR] 3–7), while 30-day readmission and 30-day mortality were 5.3% and 3.3%, respectively. Undergoing CN (hazard ratio [HR] 0.48; 95% CI 0.44–0.52; $p<0.0001$) and treatment at academic centres (HR 0.88; 95% CI 0.81–0.95; $p=0.001$) were independently associated with improved OS. Limitation includes retrospective design with possible selection bias.

Conclusions: Increased CN use continues in the modern era, with relatively low surgical morbidity. Further study is required to determine if the finding of lower all-cause mortality in patients treated at academic centres is due to improved care or unmeasured confounders.

Introduction

Since randomized studies in 2001 demonstrated a survival advantage in patients with metastatic renal cell carcinoma (mRCC) treated with immunotherapy, cytoreductive nephrectomy (CN) has played an integral role in these patients' management.[1,2] In 2006, Food and Drug Administration (FDA) approval of angiogenesis inhibitors offered a new systemic option for mRCC,[3-5] yet the role of CN in patients treated with these agents is uncertain.[6] In the immunological era, younger patients with good performance status were considered better candidates for CN, yet which patients are offered surgery does not appear uniform.

Despite a reported 40–50% increase in survival after CN, some studies demonstrate significant perioperative morbidity, including high mortality and prolonged length of stay (LOS), particularly in elderly patients.[7-10] Additionally, there are limited data on short-term morbidity. While reports suggest a varied safety profile for CN in the elderly, survival benefit needs to be balanced against surgical risk.[7-10] Understanding independent factors that predict readmission or mortality in CN may help optimize therapy for this patient population. Our primary aim is to assess recent trends in CN use in those patients treated surgically and, secondarily, to identify factors predictive of short-term morbidity and overall survival (OS).

Methods

Data source

Data were obtained using the National Cancer Data Base (NCDB), a joint project of the Commission on Cancer and the American Cancer Society. The NCDB has been described elsewhere.[11-13]

Patient characteristics

We identified all patients from 1998–2011 with primary kidney cancer (456 127) using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) kidney code (C649). We only included the 386 357 patients with

histologically confirmed RCC, excluding patients with concomitant malignancies (n=94 230). The final study population included only patients with metastatic disease beyond regional lymphatics (n=36 549). The cTxNxM1-3 classification is based on T, N, and M elements as defined by the American Joint Committee on Cancer (AJCC). CN was defined using the surgery-to-primary-site codes. (n=10 809).

Objective and endpoints

Our primary aim was to assess changes in CN use and to determine factors associated with the decision to treat surgically in the immunological and targeted therapy era. Our secondary aim was to assess short-term surgical outcomes, such as 30-day readmission rate, 30-day mortality, and LOS in those who underwent CN (n=10 809). Finally, we examined OS data in patients with a minimum of five years of follow up (n=20 793).

Statistical analysis

We compared continuous variables using the student t-test and categorical variables using chi-square test. We used multivariable logistic regression to assess for independent predictors of CN use, readmission rates, and mortality in those who had surgery. Odds ratio (OR) estimates and 95% confidence intervals (CI) were obtained for all levels. Logistic model calibration and discrimination were assessed with Hosmer-Lemeshow. We used Kaplan-Meier method to examine unadjusted survival and Cox proportional hazard regression to examine the adjusted effect of CN on OS. Independent variables used for each outcome measure were: diagnosis year, age, sex, geographic location, Charlson/Deyo comorbidity score,[14] facility type, insurance status, and tumour characteristics. Statistical significance was defined as p values less than 0.05. All analyses were done using SAS v9.3 (SAS Institute Inc. Cary, NC, U.S).

Results

Baseline descriptive data

We identified 36 549 patients with mRCC from January 1998 to December 2011. Table 1 displays patient demographics and tumour characteristics. Median age at diagnosis was 64 years (interquartile range [IQR] 55–73 years), with 65.4% male and 34.0% greater than or equal to 70 years of age. Most patients were treated at comprehensive community cancer programs (50.9%), followed by academic centres (35.0%). Most patients had tumours larger than 7 cm and 8% of them were greater than 14 cm. Overall, 29.6% (10 809) underwent CN, with an increase in the proportion undergoing surgery from 15.2% in 1998 to a peak of 38% in 2008, and subsequently remained stable at approximately 36% (Fig. 1).

Predictors of surgery

After adjusting for covariates, patients with private insurance (OR 1.26; 95% CI 1.16–1.37; p<0.0001) and those treated at academic centres (OR 1.83; 95% CI 1.68–1.99; p<0.0001) were associated with receiving CN. Larger tumour size was associated with increased chance of surgery (p<0.0001). Charlson/Deyo score ≥2 and increasing age were associated with decreased odds of undergoing surgery (p<0.0001; Table 2).

Short-term surgical outcomes

In those who underwent CN, median LOS was five days (IQR 3–7). The 30-day readmission and 30-day mortality rates were 5.3% and 3.3%, respectively. Overall, 30-day readmission rate remained relatively stable, while 30-day mortality rate was downtrending, approaching statistical significance (p=0.06; Fig. 2).

After adjusting for confounders, Charlson/Deyo score ≥2 (OR 1.71; 95% CI 1.02–2.84; p=0.03), sarcomatoid histology (OR 2.68; 95% CI 1.80–3.99; p=0.0004), tumours >14 cm (OR 2.06; 95% CI 1.10–3.85; p=0.0002), and advanced age (70–79 and >80 years-old) were associated with increased 30-day mortality. Those treated at comprehensive community cancer programs (OR 0.49; 95% CI 0.31–0.77; p=0.01) or academic centres (OR 0.48; 95% CI 0.31–0.76; p=0.01) were the only covariates associated with decreased mortality within 30 days of surgery (Table 2). Sacromatoid histology and Western geographical location were associated with increased and decreased 30-day readmission, respectively.

Overall survival

Data from 199–2006 showed that 5176 (24.9%) of the 20 793 patients with mRCC underwent CN. Median OS was 5.8 months (IQR 2.2–15.7). Unadjusted median survival in those who had CN was 15.2 months (IQR 6.2–38.7), and 4.3 months (IQR 1.7–10.9) for those who did not have CN (Fig. 3).

After adjusting for confounders, Cox proportional hazard model revealed that CN was independently associated with improved OS (hazard ratio [HR] 0.48; 95% CI 0.44–0.52; p<0.0001). Patients treated at academic centres (HR 0.88; 95% CI 0.81–0.95; p=0.001) had improved survival compared to those treated at community programs. Conversely, older age (70–79, >80 years), higher Charlson/Deyo score, higher tumour T-stage, grade, size and sarcomatoid histology were associated with decreased OS (Table 3).

Table 1. Patient and tumour characteristics in patients with mRCC and patients treated with and without cytoreductive nephrectomy

Variable	All patients with mRCC, n (%)	Patients not treated with CN, n (%)	Patients treated with CN, n (%)	p
No. of patients (%)	36 549	25 740 (70.4)	10 809 (29.6)	
Age – median (IQR)	64 (55–73)	66 (57–75)	60 (52–67)	
Age categories in yrs				
<50	4501 (12.3)	2609 (10.1)	1892 (17.5)	
50–59	9042 (24.7)	5564 (21.6)	3478 (32.2)	<0.0001
60–69	10 574 (28.9)	7214 (28.0)	3360 (31.1)	
70–79	8189 (22.4)	6442 (25.0)	1747 (16.2)	
≥80	4243 (11.6)	3911 (15.2)	332 (3.1)	
Histology				
RCC NOS	24 530 (67.1)	19 718 (76.6)	4812 (44.5)	
Clear-cell adenocarcinoma	9089 (24.9)	4607 (17.9)	4482 (41.5)	
Sarcomatoid RCC	1641 (4.5)	771 (3.0)	870 (8.1)	<0.0001
Papillary adenocarcinoma	909 (2.5)	475 (1.9)	434 (4.0)	
Chromophobe RCC	190 (0.5)	86 (0.3)	104 (1.0)	
Collecting duct carcinoma	163 (0.5)	62 (0.3)	101 (1.0)	
Cyst associated RCC	27 (0.1)	21 (0.1)	6 (0.1)	
Gender				
Male	23 888 (65.4)	16 415 (63.8)	7473 (69.1)	<0.0001
Female	12 661 (34.6)	9325 (36.2)	3336 (30.9)	
Race				
White	31 484 (86.1)	21 884 (85.0)	9600 (88.8)	<0.0001
Black	3615 (9.9)	2834 (11.1)	781 (7.2)	
Other	1450 (4.0)	1022 (4.0)	428 (4.0)	
Hospital type				
Community cancer program	4015 (11.0)	3107 (12.1)	908 (8.4)	
Comprehensive community cancer program	18 605 (50.9)	13 704 (53.2)	4901 (45.3)	<0.0001
Academic/NCI comprehensive cancer centre	12 807 (35.0)	8039 (31.2)	4768 (44.1)	
Other cancer programs	1122 (3.1)	890 (3.5)	232 (2.2)	
Geographic location				
Midwest	9670 (26.5)	6727 (26.1)	2943 (27.2)	
Northeast	7265 (19.9)	5144 (20.0)	2121 (19.6)	<0.04
South	13 566 (37.1)	9648 (37.5)	3918 (36.3)	
West	6048 (16.5)	4221 (16.4)	1827 (16.9)	
Insurance status				
Private/managed care	17 131 (51.1)	10 605 (45.2)	6526 (65.0)	<0.0001
Medicare/Medicaid	16 394 (48.9)	12 874 (54.8)	3520 (35.0)	
Charlson/Deyo score				
0	17 943 (71.9)	11 639 (70.4)	6304 (74.9)	<0.0001
1	4986 (20.0)	3320 (20.1)	1666 (19.8)	
2	2026 (8.1)	1578 (9.5)	448 (5.3)	
Tumour size				
<4 cm	2887 (7.9)	2144 (8.3)	743 (6.9)	
4–7 cm	7489 (20.5)	5251 (20.4)	2238 (20.7)	
8–10 cm	8530 (23.3)	5285 (20.5)	3245 (30.0)	<0.0001
11–14 cm	6793 (18.6)	3974 (15.4)	2819 (26.1)	
>14 cm	2928 (8.01)	1655 (6.43)	1273 (11.8)	
Unknown	7922 (21.7)	7431 (28.9)	491 (4.5)	

CN: cytoreductive nephrectomy; IQR: interquartile range; mRCC: metastatic renal cell carcinoma; NOS: not otherwise specified; NCI: national cancer institute.

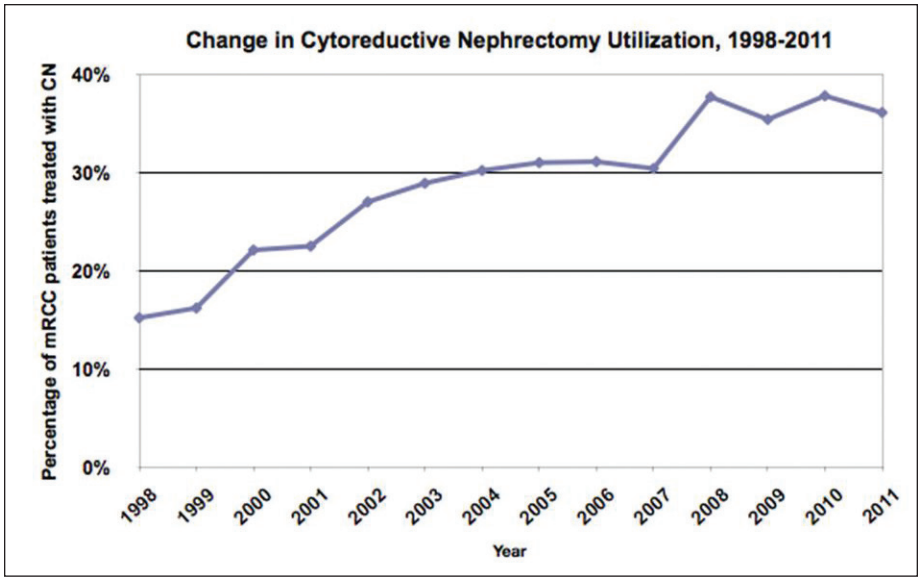

Fig. 1. Yearly use of cytoreductive nephrectomy (CN) from 1998–2011; mRCC: metastatic renal cell carcinoma.

Discussion

Patients initially diagnosed with metastatic disease have a poor prognosis, with an estimated one-year and five-year survival of 50% and 10–20%, respectively.[15-17] Current European and National Comprehensive Cancer Network (NCCN) guidelines recommend CN followed by systemic therapy for mRCC in those fit for surgery with a resectable primary and multiple metastases;[16,18] however, the potential survival benefit of CN should be balanced against perioperative risk, as several reports suggest a variable safety profile for CN, particularly in the elderly.[7-10] To better understand these issues, our study used a comprehensive nationwide cancer outcomes database to investigate predictors for CN use, short-term outcomes, and long-term survival

Rates of CN use increased from 15.2% to 36.1% during the study period. With the introduction of immunotherapy, CN use increased from 23% to 27% following the publication of two randomized, controlled trials in 2001 demonstrating a survival advantage in patients with mRCC treated with CN.1,2 With the introduction of targeted molecular therapies, CN use increased from 30% in 2005 to 38% in 2008. In contrast, previous reports using Surveillance, Epidemiology, and End Results (SEER) data showed a 30.5–44.5% CN ue rate in the immunotherapy era,[19,20] and a decline in use to 36% in the targeted molecular therapy era.[21,22] The SEER registry represents 26% of the U.S. population, while the NCDB database captures 70% of all newly diagnosed cancers. This could explain the discrepancy and suggests that our results are more reflective of CN use in the U.S.

We identified patient and hospital characteristics that were associated with CN use. Our data demonstrate that increasing tumour size and treatment at an academic facility were associated with CN. In contrast, older patients were less likely to be managed surgically, consistent with prior reports demonstrating that increasing age is inversely associated with CN.[19,23] Patients with private insurance were more likely to receive surgery. While this may be related to increased reimbursement rates, this could also be due to unmeasured confounders.

Short-term outcomes in the surgical group demonstrated that the 30-day readmission, 30-day mortality, and overall LOS were relatively low. Mortality decreased slightly over the study period, although not significantly. Our analysis demonstrated a 5.3% unplanned readmission rate. Sarcomatoid histology was the only predictor of 30-day readmission. Patients with sarcomatoid histology generally have more advanced disease and worse outcomes, which may explain the increased readmission rate. Notably, age, gender, comorbidity, hospital type, and tumour size were not predictors of readmission. Additionally, if a patient was readmitted within 30 days, the patient did not have an increased 30-day mortality. We are not aware of any previous reports documenting readmission rates after CN. This deserves emphasis, as hospital readmissions are a target improvement area in the U.S. Patient Protection and Affordable Care Act, with Centres for Medicare and Medicaid Services already decreasing reimbursement in select scenarios.[24]

We also observed that patient age, comorbidities, and tumour size were associated with perioperative mortality. In our cohort, patients aged 70–79 years and >80 years had an increased risk of 30-day mortality and had a 15% and 36%, respectively, worse OS after accounting for other factors. These data are consistent with previous reports using M.D. Anderson and National Inpatient Sample cohorts demonstrating patients older than 75 years of age had an increased 30-day mortality compared to patients younger than 75 years.[9,10] Overall health status was also an important predictor, as a Charlson/Deyo score ≥2 was associated with increased 30-day mortality. Tumour size >14 cm and sarcomatoid histology were also associated with increased 30-day mortality. In addition, we found that treatment at comprehensive community cancer programs or academic centres were the only factors associated with decreased 30-day mortality. Although these differences may be related to unmeasured confounders, they may also be related to more intensive perioperative monitoring, selection/referral bias, and higher surgeon volume at these facilities.

Table 2. Multivariable logistic regression for factors associated with the use of cytoreductive nephrectomy, 30-day readmission, and 30-day mortality

Variable	Surgery OR (95% CI)	30-day readmission OR (95% CI)	30-day mortality OR (95% CI)
Age categories			
<50 (referent)			
50–59	0.80 (0.72–0.89)	0.94 (0.68–1.28)	1.26 (0.75–2.12)
60–69	0.65 (0.58–0.72)	0.80 (0.57–1.12)	1.22 (0.71–2.10)
70–79	0.46 (0.40–0.53)	0.92 (0.61–1.40)	2.08 (1.14–3.79)
≥80	0.16 (0.13– 0.19)	1.03 (0.56–1.88)	4.82 (2.39–9.71)
Histology			
Clear-cell adenocarcinoma (referent)			
Sarcomatoid RCC	0.96 (0.85–1.10)	1.99 (1.45–2.75)	2.68 (1.80–3.99)
Gender			
Male (referent)			
Female	0.97 (0.91–1.04)	1.15 (0.92–1.42)	1.05 (0.78–1.41)
Race			
White (referent)			
Black	0.55 (0.49–0.62)	1.10 (0.75–1.62)	1.63 (1.02–2.61)
Other	0.88 (0.75–1.04)	1.16 (0.68–1.97)	0.62 (0.25–1.54)
Hospital type			
Community cancer program (referent)			
Comprehensive community cancer program	1.10 (0.98–1.23)	1.31 (0.87–1.99)	0.49 (0.31–0.77)
Academic/NCI comprehensive cancer centre	1.83 (1.68–1.99)	0.94 (0.61–1.43)	0.48 (0.31–0.76)
Other cancer programs	0.87 (0.66–1.15)	0.61 (0.18–2.07)	0.45 (0.10–1.97)
Geographic location			
Northeast (referent)			
Midwest	1.20 (1.09–1.33)	0.85 (0.64–1.14)	1.03 (0.68–1.55)
South	1.24 (1.12–1.34)	0.82 (0.62–1.08)	0.91 (0.60–1.37)
West	1.09 (0.97–1.21)	0.37 (0.24–0.57)	1.19 (0.74–1.92)
Insurance status			
Medicare/Medicaid (referent)			
Private/managed care	1.26 (1.16–1.37)	0.82 (0.62–1.08)	0.69 (0.47–1.0)
Charlson/Deyo score			
0 (referent)			
1	0.99 (0.91–1.07)	1.01 (0.78–1.31)	1.40 (1.01–1.95)
2	0.62 (0.54–0.70)	1.29 (0.86–1.94)	1.71 (1.02–2.83)
Tumour size			
<4 cm (referent)			
4–7 cm	1.18 (1.04–1.34)	1.04 (0.66–1.63)	0.67 (0.35–1.29)
8–10 cm	1.67 (1.47–1.88)	1.02 (0.67–1.58)	0.92 (0.50–1.69)
11–14 cm	1.76 (1.54–2.00)	0.96 (0.62–1.48)	1.22 (0.67–2.23)
>14 cm	1.77 (1.53–2.07)	1.10 (0.69–1.76)	2.06 (1.10–3.85)
Unknown size	0.19 (0.16–0.23)	1.07 (0.47–2.45)	1.47 (0.49–4.31)

CI: confidence interval; NCI: national cancer institute; OR: odds ratio: RCC: renal cell carcinoma.

Our OS analysis demonstrated an unadjusted survival advantage for CN, a difference of 10.9 months with a HR of 0.48, suggesting that survival was twice as likely for nephrectomy patients. However, limitations to this data include patient selection factors not available in the database, including volume and sites of metastatic tumour and percentage of tumour volume debulked following primary resection. Many of the factors associated with short-term outcomes were also predictive of long-term survival, including a direct relationship between survival and treatment at an academic centre and an inverse relationship between survival and older age, increased comorbidities, tumour size, and sarcomatoid histology. While it is clear that CN does provide an OS benefit compared to no surgery, rigor-

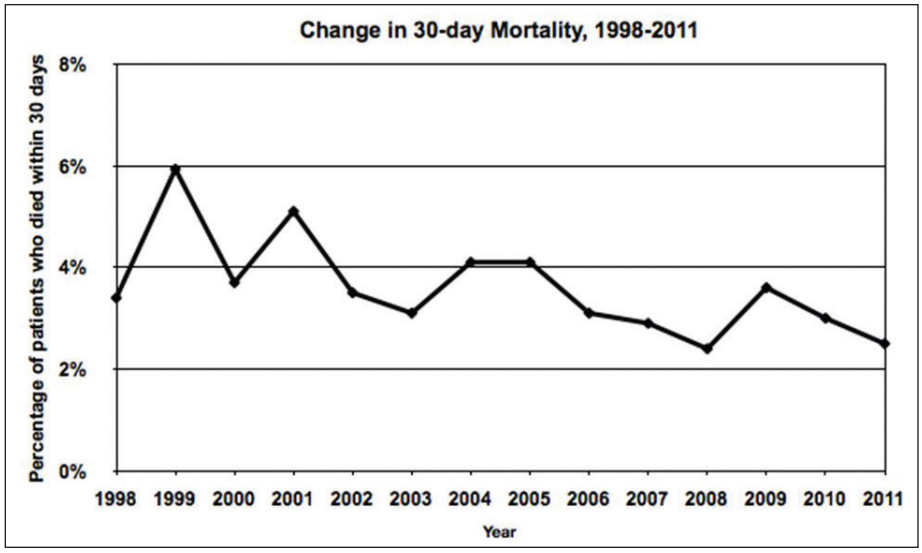

Fig. 2. Yearly 30-day mortality of patients undergoing cytoreductive nephrectomy (CN) from 1998–2011.

ous patient selection and counselling is important, as the perioperative mortality risks of surgery for certain patients may outweigh the survival benefit.

We acknowledge that our study has several limitations, one of which is its retrospective design. Patient performance status, individual surgeon volume, and case complexity data were not available. Although our study population is a large cohort with generalizability to the U.S. population, we cannot assess for referral patterns, which may influence outcomes.[13] Also, this dataset does not have detailed comorbidity information, cause of death, or reason for readmission. We are also unable to comment on the OS of patients undergoing CN in the targeted molecular therapy era, as these data are not available after 2006, when sorafenib and sunitinib were introduced.[3,4] Further analysis will be warranted once these data become available; however, it is expected that the survival advantage of CN will be maintained in the era of targeted therapy, as two recent studies, one using SEER data and the other using a multi-institutional database, have demonstrated that CN was associated with an increased OS for patients treated in the targeted therapy era.[22,25] Currently, two active randomized, phase 3 clinical trials are underway to

Table 3. Cox proportional hazard regression examining the effect of prognostic variables on survival

Variable	HR (95% CI)	p
Cytoreductive nephrectomy		
No surgery (referent)		
Yes	0.48 (0.44–0.52)	<0.0001
Age		
<50 (referent)		
50–59	1.03 (0.95–1.12)	0.49
60–69	1.08 (0.99–1.18)	0.07
70–79	1.15 (1.05–1.27)	0.003
≥80	1.36 (1.23–1.51)	<0.0001
Histology		
Clear-cell adenocarcinoma – 8310 (referent)		
Papillary adenocarcinoma – 8260	1.02 (0.88–1.19)	0.78
Sarcomatoid RCC – 8318	1.79 (1.61–1.99)	<0.0001
Gender		
Male (referent)		
Female	1.05 (1.00–1.10)	0.05
Race		
White (referent)		
Black	1.05 (0.97–1.14)	0.21
Hospital type		
Community program (referent)		
Comprehensive community cancer program	0.95 (0.88–1.03)	0.19
Academic/NCI comprehensive cancer centre	0.88 (0.81–0.95)	0.001
Other	0.86 (0.71–1.03)	0.10
Insurance status		
Medicare/Medicaid (referent)		
Private/managed care	0.92 (0.87–0.98)	0.005
Tumour T-stage		
pT1 (referent)		
pT2	1.02 (0.87–1.20)	0.78
pT3	1.18 (1.03–1.34)	0.01
pT4	1.50 (1.27–1.77)	<0.0001
Tumour grade		
Well-differentiated (referent)		
Moderately differentiated	1.11 (0.93–1.32)	0.26
Poorly differentiated	1.56 (1.32–1.84)	<0.0001
Charlson/Deyo score		
0 (referent)		
1	1.12 (1.06–1.19)	0.0001
≥2	1.20 (1.10–1.31)	<0.0001
Tumour size		
<4 cm (referent)		
4–7 cm	1.14 (1.04–1.25)	0.004
7–10 cm	1.27 (1.15–1.39)	<0.0001
10–14 cm	1.33 (1.21–1.46)	<0.0001
>14 cm	1.45 (1.30–1.63)	<0.0001

CI: confidence interval: HR: hazard ratio; NCI national cancer institute; RCC: renal cell carcinoma.

assess the optimal use and timing of CN in the targeted therapy era: the CARMENA trial (NCT00930033) and the SURTIME (NCT01099423) trial. The results of these two trials should provide meaningful answers to these outstanding questions.

Conclusion

Increased CN use continues with relatively low surgical morbidity. There were few significant predictors of receiving CN besides having private insurance and being treated at an academic centre. CN continues to show a significant survival advantage; however, rigorous patient selection is essential, as elderly patients, patients with significant comorbidities, or patients with tumours >14 cm have higher risk of perioperative mortality, which may outweigh the survival benefit. Further study is required to determine if the finding of lower all-cause mortality in patients treated at academic centres is due to improved care or unmeasured confounders.

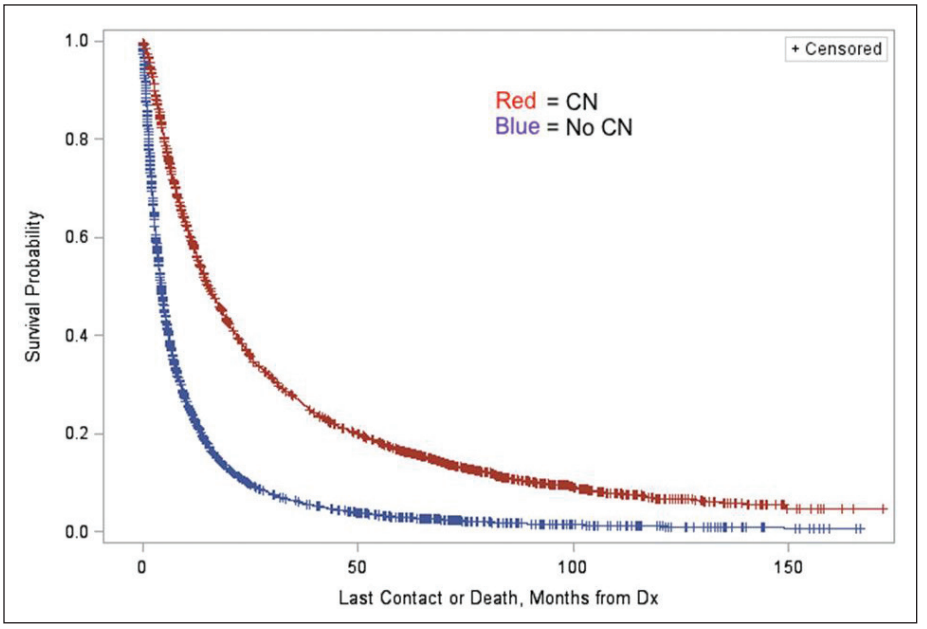

Fig. 3. Kaplan-Meier analysis of overall survival for patients undergoing cytoreductive nephrectomy (CN) from 1998–2006.

Competing interests: The authors report no competing personal or financial interests.

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This paper has been peer-reviewed.

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Correspondence: Dr. Robert Abouassaly, Department of Urology, Case Western Reserve University Urology Institute, University Hospitals Case Medical Centre, Cleveland, OH, United States; robert.abouassaly@uhhospitals.org