Outcomes and prognosticators of stage 4 renal cell carcinoma with pathological T4 primary lesion using a large, Canadian, multi-institutional database

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Cite as: *Can Urol Assoc J* 2020;14(2):24-30. http://dx.doi.org/10.5489/cuaj.5941

Published online July 23, 2019

Abstract

Introduction: The primary objective of this study was to evaluate outcomes and prognosticators in patients who underwent radical nephrectomy (RN) or cytoreductive nephrectomy (CN), depending on the clinical stage of disease preoperatively, with a pathological T4 (pT4) renal cell carcinoma (RCC) outcome. There is little data on the outcome of this specific subset of patients.

Methods: From 2009–2016, we identified patients in the Canadian Kidney Cancer information system (CKCis) who underwent RN or CN and were found to have pT4 RCC. Clinical, operative, and pathological variables were analyzed with univariable and multivariable Cox proportional hazard models to identify factors associated with overall survival (OS). Survival curves were created using Kaplan-Meier methods and compared using the log-rank test.

Results: A total of 82 patients were included in the study cohort. Median patient age was 62 years (interquartile range [IQR] 55, 70). Fifty (61%) patients had clear-cell histology and 14 (17%) had sarcomatoid characteristics. Median followup was 12 months (IQR 3, 24). At last followup, eight (10%) patients are alive with no evidence of disease, 27 (33%) are alive with disease, four (5%) were lost to followup, 36 (44%) died of disease, and seven (8%) died of other causes. Tumor histological subtype (clear-cell vs. non-clear-cell) (p=0.0032), larger tumor size (cm) (p=0.012), and Fuhrman grade (G4 vs. G2–G3) (p=0.045) were significantly associated with mortality in a multivariable Cox regression model.

Conclusions: For patients with pT4 RCC after RN or CN, survival is poor. Sarcomatoid features, non-clear-cell histology, and presence of systemic symptoms were associated with worse OS.

Introduction

In 2017, there were an estimated 63 990 new cases of kidney cancer diagnosed in the U.S., with 14 400 estimated deaths.[1] While renal cell carcinoma (RCC) stage migration has resulted in more than 50% of patients being diagnosed with AJCC stage I disease, largely attributed to the increased use of cross-sectional imaging, nearly 20% of patients are still diagnosed with pathological stage 4 disease, and pathological stage 4 disease has remained relatively constant over time.[2] Despite advances in systemic therapies, survival rates for patients with locally advanced disease are poor, with the 10-year cancer-specific survival (CSS) and median CSS for pathological T4 (pT4) disease at 11.6% and 0.9 years, respectively.[3]

While there is a lack of evidence supporting the use of neoadjuvant therapy in locally advanced kidney cancer, results of recent clinical trials evaluating the feasibility of anti-angiogenic agents (vascular endothelial growth factor receptor tyrosine kinase inhibitors [VEGFr TKI]) have demonstrated a radiological response to systemic therapy in 26–32% of patients.[4-7] Adjuvant therapy with sunitinib following nephrectomy in non-metastatic RCC was granted FDA approval in November 2017. Approval was based on the recently updated S-TRAC trial, which demonstrated improved disease-free survival (DFS) in the sunitinib group.[8] An updated subgroups analysis continued to demonstrate improved DFS across all subgroups, as well as those with advanced locoregional disease (T3 Nx, Fuhrman grade ≥2, Eastern Cooperative Oncology Group [ECOG] performance status ≥1, T4 and/or nodal involvement). Median overall survival (OS) at the time of publication was not reached for the treatment or placebo arms.[8] Results from the ASSURE and PROTECT trials, which looked at sunitinib, sorafenib and pazopanib in the adjuvant setting, failed to demonstrate

a difference in DFS.[9,10] The different results of these trials may be explained by differences in their patient population. In S-TRAC, only T3 and T4 RCC were included, and there was also a higher proportion of T4 relative to the ASSURE and PROTECT trials. Furthermore, clear-cell histology was mandatory in S-TRAC, but not in ASSURE or PROTECT. Five randomized adjuvant trials currently accruing patients evaluating immune checkpoint inhibitors (ICPIs) — PROSPER (nivolumab in treating patients with localized kidney cancer undergoing nephrectomy); IMmotion010 (azetzolizumab as adjuvant therapy in patients with RCC following nephrectomy);[11] INmotion151 (atezolizumab plus bevacizumab as first-line agents compared to sunitinib (Motzer et al, 2018);[12] CheckMate-9ER (nivolumab plus cabozantinib in patients who are treatment-naive with advanced or metastatic RCC (ClinicalTrials.gov, 2017);[13] and KEYNOTE-426 (pembrolizumab in treating patients with treatment-naive advanced/metastatic RCC (Atkins et al, 2016)[14] — will provide insight into the role of ICPIs as adjuvant therapy in patients with kidney cancer. CheckMate-214 (nivolumab plus ipilimumab) noted improved survival outcomes as compared to sunitinib in treatment-naive metastatic RCC (Motzer et al, 2018).[15]

In SURTIME, an EORTC randomized, control trial, patients were randomized to sunitinib followed by cytoreductive nephrectomy (CN) and subsequent sunitinib vs. upfront CN followed by sunitinib. On intention-to-treat analysis, deferred CN was non-inferior to upfront CN (hazard ratio [HR] 0.57) favoring deferred nephrectomy (p=0.032). The data suggested that deferring CN was likely not detrimental in the targeted therapy era.[16] CARMENA, a French, randomized trial, compared metastatic RCC patients to CN and sunitinib vs. sunitinib alone. The results in the sunitinib-alone group were non-inferior to those in the nephrectomy-sunitinib group with regard to OS (HR 0.89).[17]

Since pT4 RCC is relatively rare and difficult to study in large trials, we sought to evaluate the outcomes of patients with pT4 RCC using a large, multi-institutional database. Our primary objective was to evaluate OS for our cohort of patients who underwent radical nephrectomy (RN) or CN for RCC and were found to have pT4 disease. Our secondary objective was to establish predictors of worse OS.

Methods

The Canadian Kidney Cancer information system (CKCis) is a collaborative, multi-institutional database from 13 centers in six provinces and has been described previously.[18-20] This dataset was initiated in 2011 and includes data entered retrospectively and prospectively for a sample of patients with renal tumors treated as of 1998. Demographic, clinical, pathological, and oncological variables are collected, and the dataset is updated regularly. Institutional review board approval was obtained from each contributing site.

We identified patients in CKCis who underwent RN or CN, depending on the clinical stage of disease preoperatively, and were found to have pT4 RCC. Patients with node-positivity or metastasis were not excluded. pT4 disease was defined according to the 2010 TNM cancer staging system as involvement beyond Gerota's fascia or tumor that extends into the ipsilateral adrenal gland.[21] Patient information was prospectively collected from 2009–2016.

Demographic, clinical, operative, and pathological data were obtained. Demographic variables included age, sex, ECOG performance status, body mass index (BMI), and smoking history. Clinical and operative factors included time to nephrectomy, followup time, clinical TNM staging, recipients of first-line adjuvant VEGFr TKI, preoperative laboratory results (including hemoglobin, estimated glomerular filtration rate [eGFR], alkaline phosphatase [ALP], lactate dehydrogenase [LDH], corrected calcium, platelets), presence of systemic symptoms, presence of local symptoms (including gross hematuria or flank pain), intraoperative blood loss, surgical approach, and operative duration. Pathological characteristics, including histological subtype, Fuhrman grade, pathological TNM staging, tumor size, adrenal involvement, presence of sarcomatoid characteristics, positive margin status, and tumor necrosis, were analyzed.

As the number of deaths in our cohort was high, outcomes such as CSS were not assessed. The Kaplan-Meier method was used for OS and the log-rank test was used to test for differences. Univariable and multivariable Cox regression analysis identified predictors for mortality. Variables significant in the univariate analysis were included in the multivariable model, with the exception of those variables with a large proportion of missing data. The only univariable significant predictor that was omitted from the multivariable model due to missing data was blood loss (32% missing). Statistical significance was defined as $p<0.05$.

Results

Clinical and pathological characteristics

Overall, 2442 patients within CKCis underwent RN since 2008. During the study period, 82 patients within the CKCis database were surgically treated for RCC and found to have pT4 disease. Adjacent organ extension included peritoneum tumor invasion (1), positive peritoneal nodule (1), omental tumor nodule (1), tumor extension into colon (1), and pancreatic invasion (2). Capsular tumor invasion (17), perinephric fat tumor invasion (53), renal vessel tumor invasion (26), and sinus fat tumor invasion (37) were also recorded. Median patient age was 62 years (interquartile range [IQR] 55,70), 58 (71%) were men, and 28 (34%) patients presented with systemic symptoms. Twenty-three (28%) patients had

clinical stage T4 preoperatively. Twenty (24%) had clinical N1 disease, and 33 (40%) had clinical M1 disease. Fifty (61%) patients had clear-cell histology and 14 (17%) had sarcomatoid characteristics. Final pathology demonstrated pN1 in 27 (33%) patients and pM1 in 32 (39%). Of the 32 patients with pM1 disease, six underwent metastasectomy. The sites for metastatectomy included bone (1), lung (2), lymph node (1), pancreas (1), and other location (1). Furthermore, 13 of the 32 patients with pM1 disease received stereotactic body radiation therapy (SBRT). Sixty-nine (84%) patients had Fuhrman grade 3 or 4, 44 (54%) had direct adrenal extension, 28 (34%) had regional lymph node involvement, and 29 (35%) had a positive margin (Table 1).

Survival

After a median postoperative followup of 12 months (IQR 3, 24), eight (10%) patients were alive with no evidence of disease, 27 (33%) are alive with disease, four (5%) were lost to followup, 36 (44%) died of disease, and seven (8%) died of other causes. As expected, patients with non-clear-cell histology (p=0.03), presence of systemic symptoms (p=0.045), and presence of sarcomatoid characteristics (p=0.027) had a significantly worse OS (Fig. 1). Univariable Cox proportional hazard regression analyses revealed that year of nephrectomy, ECOG performance status (1 vs. 0), tumor histological subtype (clear-cell vs. non-clear-cell), tumor size (cm), intraoperative blood loss (ml), Fuhrman grade (G4 vs. G2–G3), presence of systemic symptoms, and presence of sarcomatoid characteristics were significantly associated with mortality (Table 2).

In a multivariable Cox regression model including factors showing univariable association, we found that tumor histological subtype (clear-cell vs. non-clear-cell) (HR 0.36; 95% confidence interval [CI] 0.18–0.71), tumor size (cm) (HR 1.12; 95% CI 1.03–1.22), and Fuhrman grade (G4 vs. G2–G3) (HR 2.33; 95% CI 1.02–5.32) were significantly associated with OS (Fig. 2).

Table 1. Demographic, clinical, surgical, and pathological characteristics in patients with pathologic T4 renal cell carcinoma treated with radical or cytoreductive nephrectomy (n=82)

	n (%) or median (IQR)
All patients	82 (100)
Age, years	62 (55–70)
Sex	
Female	24 (29)
Male	58 (71)
BMI, kg/m^2	28 (23–31)
ECOG performance statusa	
0	24 (29)
1	22 (27)
2	4 (5)
3	1 (1)
Local symptoms recorded	32 (39)
Systemic symptoms recorded	28 (34)
Clinical (preoperative) T stage*	
<T4	53 (64)
T4	23 (28)
Clinical (preoperative) N stage*	
N0	24 (29)
N1	20 (24)
Nx	32 (39)
Clinical (preoperative) M stage*	
M0	11 (13)
M1	33 (40)
Mx	32 (39)
Hemoglobin	
Normal	21 (26)
Abnormal	48 (59)
LDH	
Normal	13 (16)
Abnormal	9 (11)
Alkaline phosphatase	
Normal	32 (39)
Abnormal	11 (13)
Corrected calcium	
Normal	13 (16)
Abnormal	6 (7)
Platelets	259 (222–368)

*Numbers do not always add to 82 because of missing values. BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LDH: lactate dehydrogenase; Lap: laparoscopic.

Discussion

To our knowledge, our findings represent the largest evaluation of patients who underwent RN and were found to have pT4 RCC. We have demonstrated that more than three-quarters of patients (72%) were clinically understaged compared to their final pathology. Our findings indicate that pathological T4 disease following RN has poor OS. Patients with larger tumor size, higher Fuhrman grade (G4 vs. G2–G3), or non-clear-cell histology had worse survival on our multivariable analysis.

To date, only one study has evaluated outcomes and prognosticators of pathological T4 RCC. A single-institutional study of 61 patients diagnosed with pT4 RCC undergoing RN found that preoperative LDH and ALP, M stage, pN stage, and sarcomatoid de-differentiation were significantly associated with survival.[22] However, the aforementioned study was limited by a small cohort and it was also a single-institutional review. In contrast, our findings were collected from a national, multi-institutional database, possibly better reflecting real-world data.

Table 1 (cont'd). Demographic, clinical, surgical, and pathological characteristics in patients with pathologic T4 renal cell carcinoma treated with radical or cytoreductive nephrectomy (n=82)

	n (%) or median (IQR)
Creatinine	88 (73–103)
eGFR, ml/min/1.73m^2	79 (63–90)
>60	55 (79)
30–60	15 (21)
Preoperative systemic therapy recorded	8 (10)
Surgical approach	
Lap	13 (16%)
Open	64 (78%)
Unknown	5 (6%)
Tumor diameter at nephrectomy, cm	12 (9.0–13.5)
Laterality	
Bilateral	1 (1)
Left	43 (53)
Right	38 (46)
Pathological N stage	
N0	32 (39)
N1	27 (33)
Nx	23 (28)
Pathological M stage	
M0	5 (6)
M1	32 (39)
Mx	45 (55)
Histology	
Clear-cell	50 (61)
Non-clear-cell	32 (39)
Fuhrman gradea	
1	0 (0)
2	5 (6)
3	28 (34)
4	41 (50)
Sarcomatoid de-differentiation recorded	14 (17)
Necrosis recorded	13 (16)
Thrombectomy recorded	70 (85)
Direct adrenal extension recorded	44 (54)
Positive surgical margin recordeda	29 (35)
Regional lymph node involvement recorded	28 (44)

*Numbers do not always add to 82 because of missing values. BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; IQR: interquartile range; LDH: lactate dehydrogenase; Lap: laparoscopic.

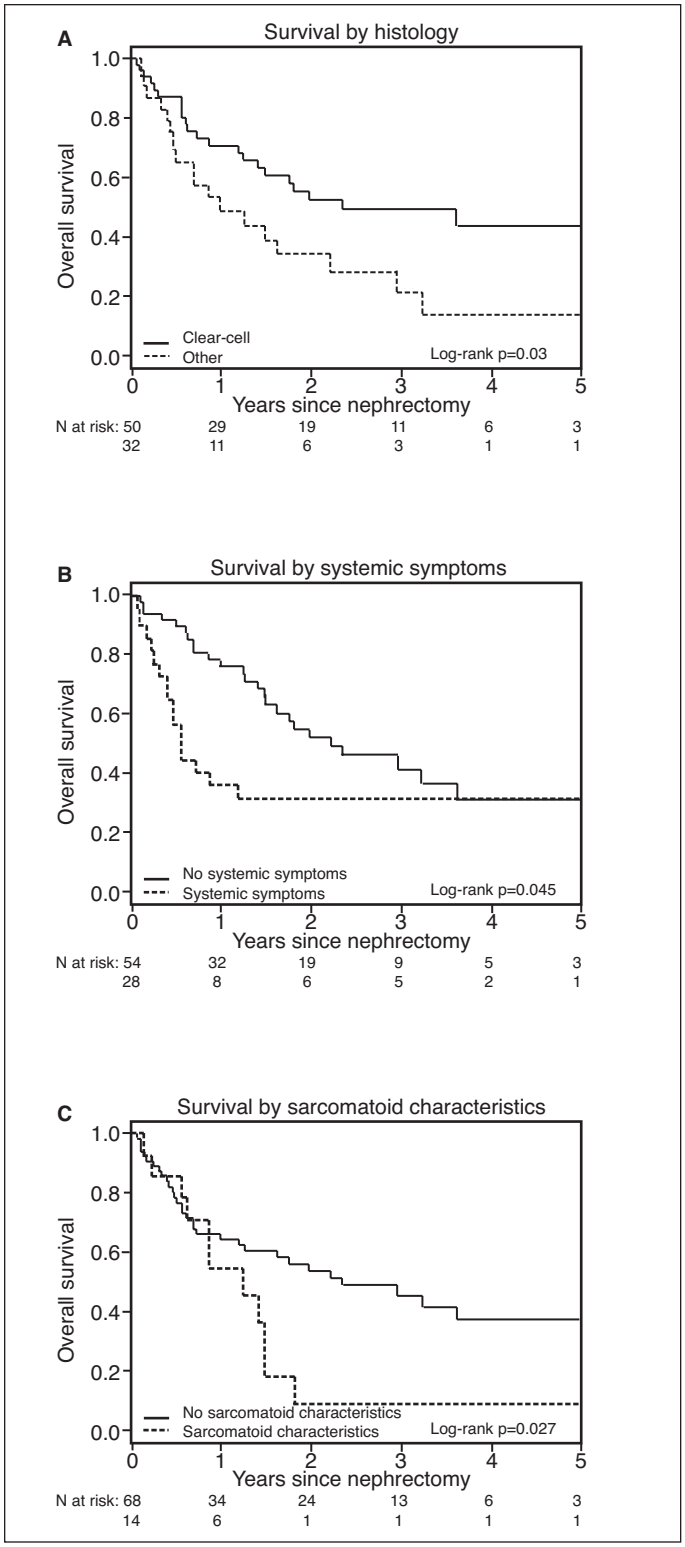

Fig. 1. (A) Overall survival stratified by histology subtype (log rank p<0.05). ***(B)*** Overall survival stratified by presence of systemic symptoms at time of diagnosis (log rank p<0.05). ***(C)*** Overall survival stratified by presence of sarcomatoid characteristics (log rank p<0.05).

Although targeted therapies have improved patients' outcomes among those with non-clear-cell RCC, survival is significantly inferior compared with clear-cell RCC patients.[23,24] Similar to our findings, symptomatic characteristics of renal tumors have been demonstrated to be an independent prognostic factor affecting survival.[25,26] In particular, tumors associated with anorexia, weakness, or symptoms of metastasis were associated with worse median OS compared to

Table 2. Univariable Cox regression analysis of clinical, operative, and pathological features for the prediction of overall mortality in patients with pT4 renal cell carcinoma treated with radical or cytoreductive nephrectomy (n=82)

Variables	Univariable	
	HR (95% CI)	p
Age at nephrectomy	0.98 (0.95–1.01)	0.20
Year of nephrectomy	1.26 (1.02–1.56)	<0.05
Sex (M vs. F)	0.71 (0.37–1.35)	0.30
ECOG performance status		
1 vs. 0	2.61 (1.13–6.05)	<0.05
2–3 vs. 0	1.52 (0.68–3.37)	0.30
Systemic symptoms (yes vs. no)	1.86 (1.00–3.44)	<0.05
Started 1st line systemic therapy preoperatively	1.39 (0.55–3.55)	0.49
Presence of metastases at diagnosis	1.29 (0.70–2.36)	0.42
Smoking status (never vs. current)	0.65 (0.30–1.43)	0.29
Clinical (preoperative) T stage		
T2 vs. T1	2.48 (0.79–7.85)	0.12
T3 vs. T1	1.79 (0.58–5.54)	0.31
T4 vs. T1	1.85 (0.58–5.87)	0.29
Clinical (preoperative) N stage		
N1 vs. N0	1.75 (0.79–3.86)	0.17
NX vs. N0	0.92 (0.42–2.00)	0.83
Clinical (preoperative) M stage		
M1 vs. M0	1.88 (0.70–5.04)	0.21
MX vs. M0	1.23 (0.44–3.41)	0.70
Preoperative eGFR	1.01 (0.99–1.03)	0.40
Preoperative eGFR (60+ vs. 30–60)	0.89 (0.39–2.04)	0.79
Preoperative LDH	0.61 (0.31–3.43)	0.96
Preoperative ALP	1.72 (0.57–5.15)	0.33
Preoperative platelets	1.00 (0.99–1.0)	0.50
Preoperative corrected calcium	0.34 (0.067–1.68)	0.18
Preoperative creatinine	0.99 (0.98–1.01)	0.40
Preoperative hemoglobin	0.63 (0.30–1.32)	0.23
Preoperative BMI, kg/m^2	0.96 (0.88–1.05)	0.39
ASA status		
ASA 2 vs. 1	0.70 (0.18–2.73)	0.61
ASA 3 vs. 1	1.04 (0.29–3.78)	0.95
ASA 4 vs. 1	2.24 (0.54–9.21)	0.27
Surgical approach (open vs. lap)	1.25 (0.55–2.84)	0.59
Size of tumor (cm)	1.12 (1.04–1.21)	<0.01
Histology (clear-cell vs. non-clear-cell)	1.93 (1.05–3.54)	<0.05
Pathological nodal status		
N1 vs. N0	1.36 (0.66–2.80)	0.40
Nx vs. N0	0.88 (0.41–1.87)	0.74
Pathological M stage		
M1 vs. M0	1.66 (0.49–5.57)	0.41
MX vs. M0	0.95 (0.28–3.27)	0.94
Thrombectomy (yes vs. no)	1.57 (0.56–4.41)	0.39
Adrenal invasion (yes vs. no)	0.56 (0.30–1.03)	0.062
Sarcomatoid characteristics (yes vs. no)	2.12 (1.08–4.19)	<0.05
Tumor necrosis (yes vs. no)	1.41 (0.65–3.07)	0.39
Regional lymph node involvement (yes vs. no)	1.73 (0.90–3.33)	0.10
Fuhrman grade (G4 vs. G2–G3)	3.24 (1.62–6.48)	<0.01
Positive margin status (yes vs. no)	1.85 (0.97–3.53)	0.064

ALP: alkaline phosphatase; ASA: American Society of Anesthesiologists; BMI: body mass index; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; F: female; HR: hazard ratio; LDH: lactate dehydrogenase; Lap: laparoscopic; M: male.

asymptomatic patients, as well as those with a symptom presentation including hematuria, lumbar pain, or a palpable mass.[26] Our results for patients with sarcomatoid differentiation align with previous studies, which have illustrated worse outcomes, including more aggressive tumor biology, higher rates of tumor recurrence, and poor survival.[27,28]

Among patients with locoregional clear-cell RCC, neoadjuvant systemic therapy has demonstrated consistent primary tumor size reduction.[29] The potential advantages for neoadjuvant targeted therapy include making unresectable tumors resectable, surgical approach can be changed from radical to partial nephrectomy (PN), and renal tumors with inferior vena cava extension may be resected with lesser operations. In our study, only eight (10%) patients of the study cohort underwent preoperative systemic treatment. Lane et al reported on 72 patients who received sunitinib before planned PN and reported a mean reduction of 32% in tumor volume, and this reduction occurred in 65 (83%) tumors.[6] Rini et al evaluated 25 patients with localized, clear-cell RCC in a prospective phase 2 trial that received pazopanib for 8–16 weeks.[7] Therapy resulted in reduction in tumor burden and enabled PN. Karam et al reported on 24 patients with locally advanced, non-metastatic, clear-cell RCC who received axitinib.[4] Therapy was reportedly well-tolerated and median reduction in primary renal tumor diameter was 28.3%. Disease progression, however, was observed in 4–8% of patients. These data suggest that in a high-risk patient population with locoregional RCC, neoadjuvant therapy may reduce tumor burden and possibly the complexity of the surgery.

There are a number of limitations to consider when interpreting our results. The multi-institutional design, although advantageous to reduce biases found within single-center studies, is also subject to heterogeneity in data collection

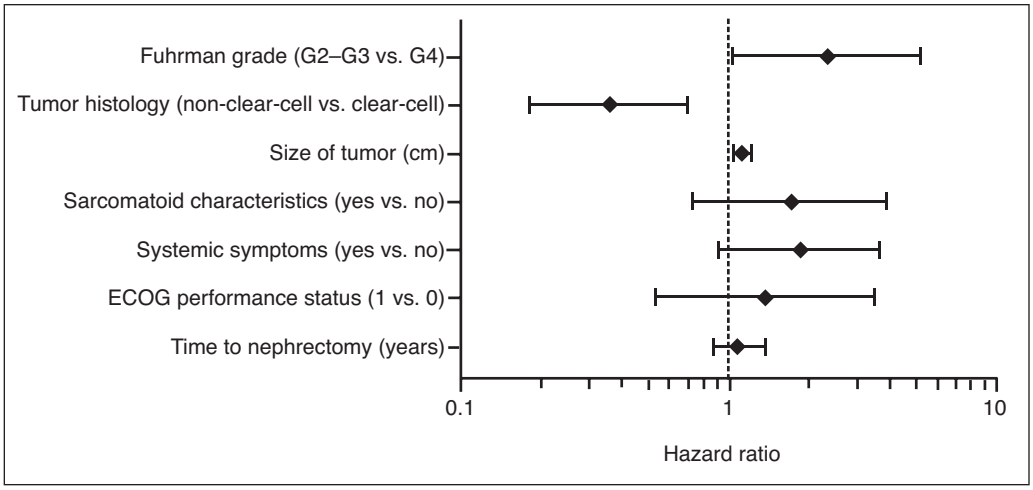

Fig. 2. Forest plot demonstrating multivariable cox regression analysis of clinical and pathological features for the postoperative prediction of overall survival in 82 patients with pT4 renal cell carcinoma treated with radical or cytoreductive nephrectomy. ECOG: Eastern Cooperative Oncology Group.

and followup. We also acknowledge that clinical stage is related to imaging characteristics, which was not centrally reviewed and may influence our findings. Further, we suspect that under-reporting of T4 disease may be due to limitations of cross-sectional imaging. Nazim et al noted that computed tomography scan had a poor sensitivity (68%) and positive predictive value (76%) for capsular invasion in RCC when compared to final surgical pathology.[30] Although all patients are offered CKCis, it doesn't capture all patients with the disease of interest, as not all urologists in Canada are involved with CKCis. Furthermore, both locally advanced and metastatic patients were included in the pT4 cohort, combining two different populations in the analysis.

Conclusions

For patients with pT4 RCC after RN, survival is poor. More than three-quarters of patients (72%) were initially clinically understaged compared to their final pathology. Sarcomatoid features, non-clear-cell histology, and presence of systemic symptoms, in particular, were associated with worse OS. Although pre-surgical VEGFr TKI therapy in a high-risk RCC population, such as ours, appears to induce tumor shrinkage, future studies to evaluate the benefit of neoadjuvant therapy in this population are still needed. For now, this approach should only be attempted in clinical trials until further studies investigating oncological and survival outcomes are conducted.

Competing interests: Dr. Lavallée has been an advisory board member for Ferring and Sanofi; and received a grant from Sanofi. Dr. Lattouf has been an advisory board member for and has received honoraria from Abbvie, AstraZeneca, Bayer, Novartis, Pfizer, and Takeda. Dr. Klotz has received honoraria from Abbvie, Amgen, Astellas, Aventis, Ferring, and Janssen. Dr. Moore has been an advisory board member for Amgen; a speaker for GSK, and has participated in clinical trials supported by Janssen and J&J. Dr. Kapoor has been an advisory board member for BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche; a speakers' bureau member for Eisai, Ipsen, Novartis, and Roche; and has received grants/honoraria from BMS, Eisai, Ipsen, Merck, Novartis, Pfizer, and Roche. Dr. Finelli has been an advisory board member for Abbvie, Astellas, Bayer, Janssen, Ipsen, Sanofi, and TerSera; and has participated in clinical trials supported by Astellas, Bayer, and Janssen. Dr. Rendon has been an advisory board and speakers' bureau member for, and has received honoraria from Abbvie, Amgen, Astellas, Astra Zeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Kawakami has received honoraria from Minogue Medical and is a stockholder/medical advisor for Vibe Bioscience. Dr. So has been an advisory board member for Abbvie, Amgen, Astellas, Bayer, Janssen, Ferring, and TerSera; and has participated in clinical trials supported by Astellas, Ferring, and Janssen. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed

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