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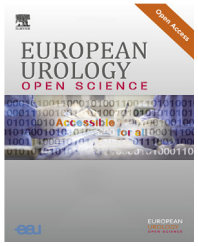

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Kidney Cancer

Selective Use of Neoadjuvant Targeted Therapy Is Associated with Greater Achievement of Partial Nephrectomy for High-complexity Renal Masses in a Solitary Kidney

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Abstract

Background: Partial nephrectomy (PN) is preferred for a renal mass in a solitary kidney (RMSK), although tumors with high complexity can be challenging.
Objective: To evaluate the evolution of RMSK management with a focus on achievement of PN.
Design, setting, and participants: Patients with nonmetastatic RMSK (n = 499) were retrospectively reviewed; 133 had high tumor complexity, including 80 in the pre-tyrosine kinase inhibitor (TKI) era (1999–2008) and 53 in the TKI era (2009–2022). After 2009, 23/53 patients received neoadjuvant TKI and 30/53 had immediate-surgery.
Outcome measurements and statistical analysis: Functional outcomes, adverse events and complications, dialysis-free survival, and recurrence-free survival (RFS) were the measures evaluated. Mann-Whitney and χ^2 tests were used to compare cohorts, and the log-rank test was applied for survival analyses.
Results and limitations: Overall, the median RENAL score was 10 and the median tumor diameter was 5.2 cm. Demographic characteristics, tumor diameter, and RENAL scores were similar between the pre-TKI-era and TKI-era groups. In the TKI era, 23/53 patients (43%) with clear-cell histology were selected for neoadjuvant TKI. These 23 patients had a greater median tumor diameter (7.1 vs 4.4 cm;

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p = 0.02) and RENAL score (11 vs 10; p = 0.07). After TKI treatment, the median tumor diameter decreased to 5.6 cm and the RENAL score to 9, and tumor volume was reduced by 59% (all $p < 0.05$). PN was accomplished in 21/23 (91%) the TKI-treated cases and in 27/30 (90%) of the immediate-surgery cases (2009–2022). PN was only accomplished in 52/80 (65%) of the patients from the pre-TKI era ($p < 0.01$). The 5-yr dialysis-free survival rate was 59% in the pre-TKI-era group and 91% in the TKI-era group. The 5-yr RFS rate was lower in the TKI-era group (59% vs 74%; p = 0.21), which was mostly related to more aggressive tumor biology, as reflected by a predominance of systemic rather than local recurrences.

Conclusions: Management of RMSK with high tumor complexity is challenging. Selective use of TKI therapy was associated with greater use of PN, although a randomized study is needed. RFS mostly reflected aggressive tumor biology rather than failure of local management.

Patient summary: For complex kidney tumors in patients with a single kidney, management is challenging. Use of drugs called tyrosine kinase inhibitors before surgery was associated with reductions in tumor size and greater ability to achieve partial kidney removal for cancer control. Most recurrences were metastatic, which reflects aggressive tumor biology rather than failure of surgery.

1. Introduction

Management of a renal mass in a solitary kidney (RMSK) can be complex, with the main goals being avoidance of dialysis and achieving durable cancer-free survival [1]. A recent analysis of 1024 patients with RMSK showed that partial nephrectomy (PN) was performed in 82%, thermal ablation in 10%, and active surveillance in 3%. Radical nephrectomy (RN) was only required in 5% of cases, mostly for severe pre-existing chronic kidney disease or inadequate parenchymal volume to save with PN. For PN, 5-yr dialysis-free survival and recurrence-free survival (RFS) rates were 97% and 83%, respectively [1].

The ultimate challenge for patients with RMSK is a tumor with high complexity, such as a RENAL score of 10–12. In this setting, preservation of adequate parenchymal volume can be challenging, as many such tumors have greater oncologic potential and surgical risks are often markedly higher [1,2]. These cases are uncommon, although most urologists will encounter a few in their career. However, the literature on management of RMSK with high tumor complexity is rather limited, with only a few studies on this topic, generally restricted to 20–30 patients or fewer [3–5]. Some groups have reported on the use of tyrosine kinase inhibitors (TKIs) in the neoadjuvant setting to downsize complex RMSK tumors and facilitate PN, but this approach is still considered experimental [1,6–8]. Prospective, randomized studies using neoadjuvant systemic treatments have been reported for locally advanced or metastatic renal cell carcinoma (RCC), but high-complexity RMSKs are an entirely different context [9–12].

Avoidance of RN in this setting is of paramount importance, because dialysis is associated with lower quality of life and compromised survival [13–15]. Thus, our analysis of outcomes for patients with RMSK with high tumor complexity focused on avoidance of RN as the primary outcome. We also evaluated the impact of neoadjuvant TKI in terms of the evolution of management of this patient population over the past few decades.

2. Patients and methods

2.1. Patient population

After approval from the institutional review board (IRB-20-836), a comprehensive retrospective review was performed of the Cleveland Clinic kidney cancer database (1999–2022), which identified 499 patients with RMSK with a RENAL score available. Of these, 366 patients had a RENAL score of <10, leaving 133 patients for analysis (Fig. 1). Patients were divided into two eras, before TKI (1999–2008) versus TKI (2009–2022), on the basis of the date of their surgery. The most challenging RMSK cases in the TKI era were considered for neoadjuvant TKI according to surgeon preference, although this was restricted to patients with biopsy-proven clear-cell histology.

2.2. Data collection

Baseline characteristics, including demographics, tumor characteristics, and surgical approach, functional outcomes, and adverse events (AEs) and perioperative complications potentially related to TKI therapy were collected. The Modification of Diet in Renal Disease-2 equation was used to estimate the glomerular filtration rate (GFR) [16]. The RENAL score was used as a measure of tumor complexity [17]. All patients had preoperative and postoperative imaging studies <2 mo before surgery and 1–12 mo after surgery, respectively. New-baseline GFR was defined as the last GFR 1–12 mo after PN [18,19]. Preoperative TKI was given for two cycles (8 wk for axitinib or pazopanib or 12 wk for sunitinib) [6,10,11]. TKI was held at least 7 d before surgery, and all patients had surgery within 1–2 wk after completing TKI therapy [8]. AEs were graded according to Common Terminology Criteria for Adverse Events v4 and perioperative events were classified using the Clavien-Dindo scheme. Tumor grading was in accordance with the International Society of Urological Pathology [20]. Staging followed the 2016 American Joint Committee on Cancer/Union for International Cancer Control TNM scheme [21]. Our primary endpoint was achievement of PN rather than RN.

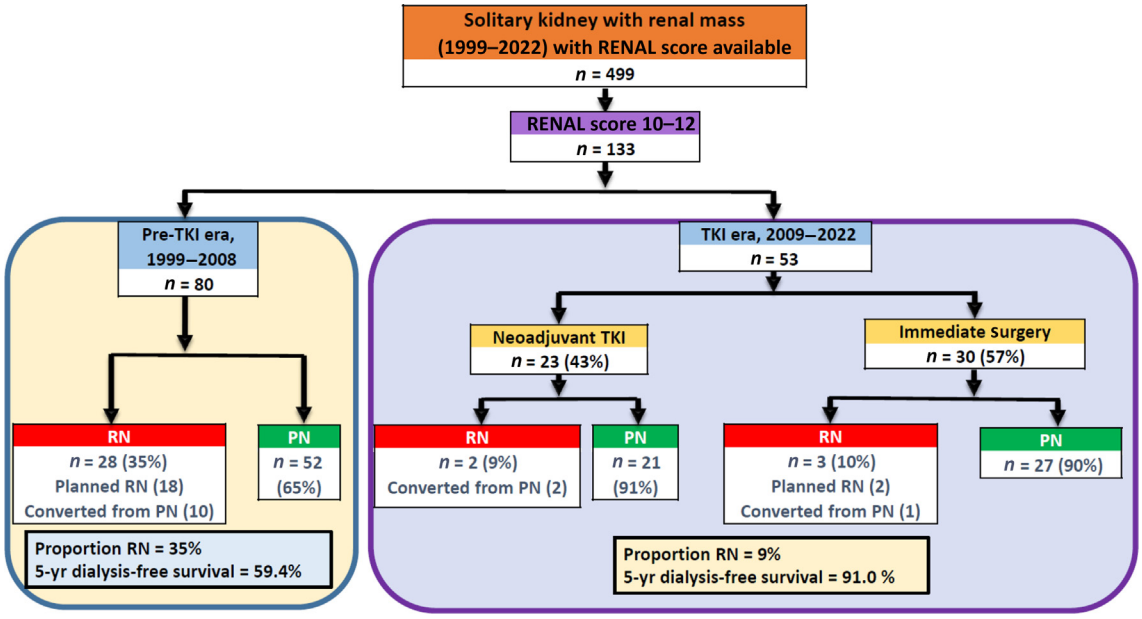

Fig. 1 – Patient cohorts for management of a renal mass with high tumor complexity in a solitary kidney (*n* = 133), including 80 patients in the pre-TKI era and 53 patients in the TKI era. In the TKI era, 23/53 patients received TKI therapy before surgery, and 30/53 had immediate surgery. PN was accomplished in 48/53 (91%) patients in the TKI era. In contrast, PN was only accomplished in 52/80 (65%) patients in the pre-TKI era. PN = partial nephrectomy; RN = radical nephrectomy; TKI = tyrosine kinase inhibitor.

2.3. *Statistical analysis*

Continuous variables are reported as the median and interquartile range and were compared using a Wilcoxon test. Categorical variables were compared using χ^2 or Fisher tests. Kaplan-Meier analysis was used to assess overall survival (OS), recurrence-free survival (RFS), and dialysis-free survival, with the log-rank test for comparisons. Time for overall survival or cancer recurrence was calculated from the procedure date to date of death or last documented imaging for local/systemic recurrence. For RFS, patients were censored at the time of last patient contact with negative imaging or death from other causes. Analyses were performed using R v4.2.0. Differences were considered statistically significant at $p < 0.05$.

3. Results

We evaluated 499 patients with RMSK from 1999–2022, of whom 133 presented with high tumor complexity (RENAL score ≥10; Fig. 1). Eighty patients underwent PN or RN in the pre-TKI era (1999–2008) and 53 in the TKI era (2009–2022). Overall, the median RENAL score was 10 and the median tumor diameter was 5.1 cm (Table 1). Demographics, tumor diameter, and RENAL scores were similar in the pre-TKI-era and TKI-era groups. For the pre-TKI versus TKI eras, Non–organ-confined pathology was found in 46% of patients in the pre-TKI-era group and 61% of the TKI-era group ($p = 0.16$) and tumor grade 4 or N1 disease in 9% and 16%, respectively ($p = 0.39$).

The primary outcome was achievement of PN. Our data showed that 28 patients (35%) in the pre-TKI era were managed with RN versus only five (9%) in TKI era (Fig. 1 and Table 2). Overall, Clavien-Dindo grade III–V complications were observed in 38 patients (28%), with similar rates in the pre-TKI-era and TKI-era groups. A 90-d mortality event occurred for one patient in the TKI era; the overall mortality rate was 0.8% (Table 2). RN was planned for 18 patients in the pre-TKI era and two in the TKI era (Fig. 1). Surgical exploration to assess the feasibility of PN versus RN with a final decision to perform RN occurred in ten patients in the pre-TKI era and three in the TKI era. Reasons for performing RN in this setting were multifactorial (Supplementary Table 1).

Median follow-up for OS was 47 mo for the pre-TKI-era group and 40 mo for the TKI-era group, with 5-yr OS rates of 66% and 71%, respectively ($p = 0.36$). The 5-yr RFS rate was 74% for the pre-TKI-era group and 59% for the TKI-era group ($p = 0.21$; Fig. 2). The distribution of local versus systemic recurrences was similar between the pre-TKI-era and TKI-era groups, with systemic recurrences predominating in both eras (Table 2).

Overall, the median preoperative GFR was 57 ml/min/1.73 m^2, and median new-baseline and 5-yr GFR were 33 and 37 ml/min/1.73 m^2, respectively (Table 2). Median GFR preserved in the PN cohort was 66% in the pre-TKI-era group and 79% in the TKI-era group ($p < 0.01$). Dialysis was required in 32 patients in the pre-TKI-era group and only five in the TKI-era group, with 5-yr dialysis-free survival rates of 59% and 91%, respectively (Fig. 2; $p < 0.01$).

In the TKI era, 23 (43%) patients with biopsy-proven clear-cell histology were selected for neoadjuvant TKI. This cohort ($n = 23$) was challenging, with greater median tumor diameter (7.1 vs 4.4 cm; $p = 0.02$) and higher median RENAL score (11 vs 10; $p = 0.07$) in comparison to the cohort undergoing immediate surgery (Table 3). After TKI therapy, the median tumor diameter decreased to 5.6 cm and the RENAL score to 9 (both $p < 0.05$), and the median tumor volume was reduced by 59% ($p < 0.01$; Table 3 and Supplementary Fig. 1). PN was accomplished in 21/23 patients (91%) in

Table 1 – Patient and tumor characteristics

Variable	Pre-TKI era, 1999–2008 (*n* = 80)	TKI era, 2009–2022 (*n* = 53)	*p* value [a]
Patient-related			
Sex, *n* (%)			0.61
Male	54 (68)	38 (72)	
Female	26 (32)	15 (28)	
Median age, yr (IQR)	62.9 (54.3–68.8)	66.0 (58.6–69.7)	0.49
Median body mass index, kg/m^2 (IQR)	30.8 (26.0–34.6)	30.0 (26.7–33.2)	0.74
Median Charlson comorbidity index (IQR)	4 (3–5)	4 (3–5)	0.61
Tumor-related			
Median maximum tumor diameter, cm (IQR)	5.1 (3.9–8.0)	5.0 (3.6–7)	0.48
Median RENAL score (IQR)	10 (10–11)	10 (10–11)	0.29
RENAL score, *n* (%)			
RENAL 10	56 (70)	33 (62)	
RENAL 11	24 (30)	18 (34)	
RENAL 12	0	2 (4)	
Clinical stage, *n* (%)			
Confined to kidney or perinephric fat	76 (95)	49 (92)	0.95
Extension into renal vein or major branches	4 (5)	4 (8)	
Nodal enlargement	4 (5)	3 (6)	
Histology, *n* (%)			0.1
Clear cell	64 (80)	46 (87)	
Papillary	7 (9)	1 (2)	
Chromophobe	0	3 (6)	
Renal cell carcinoma unclassified	0	1 (2)	
Other malignant	5 (6)	2 (3)	
Oncocytoma	1 (1)	0	
Other benign	3 (4)	0	
pT stage, *n* (%)			0.57
pT1a	16 (20)	11 (20)	
pT1b	12 (15)	10 (19)	
pT2a	8 (10)	1 (2)	
pT2b	3 (4)	1 (2)	
pT3a	33 (41)	27 (51)	
pT3b	3 (4)	2 (4)	
pT4	0	1 (2)	
Tumor grade, *n* (%) [b]			0.07
Grade 1–2	37 (51)	15 (30)	
Grade 3	30 (41)	29 (58)	
Grade 4	6 (8)	6 (12)	
pN1 stage, *n* (%)	1 (1)	2 (4)	0.67
Positive margin, *n* (%)	9 (11)	12 (22)	0.11

IQR = interquartile range; TKI = tyrosine kinase inhibitor.
[a] *p* values were calculated using a χ^2 test for categorical variables and a Wilcoxon test for continuous variables. Fisher's exact test was used for comparison of categorical variables with low incidence.
[b] Data were available for 123 patients, 73 in the pre-TKI (1999–2008) era, and 50 in the TKI (2009–2022) era.

Table 2 – Surgical parameters and functional and survival outcomes

Variable	Pre-TKI era, 1999–2008 (*n* = 80)	TKI era, 2009–2022 (*n* = 53)	*p* value [a]
Surgical parameters			
Surgical approach, *n* (%)			<0.01
Open	75 (93)	46 (87)	
Laparoscopic	5 (6)	0	
Robotic	0	7 (13)	
Median EBL, ml (IQR)	400 (300–750)	300 (200–625)	0.13
Radical nephrectomy, *n* (%)	28 (35)	5 (9)	<0.01
Partial nephrectomy, *n* (%)	52 (65)	48 (91)	<0.01
Blood transfusion, *n* (%)	15 (19)	11 (21)	0.83
CD grade III–V complications (90-d), *n* (%)	22 (28)	16 (30)	0.70
90-d mortality, *n* (%)	0	1 (2)	0.22
Functional outcomes			
Median preoperative GFR, ml/min/1.73 m^2 (IQR)	53.8 (39.1–64.7)	57.8 (43.7–71.7)	0.20
Preoperative GFR stage, *n* (%)			
Stage 1 (>90 ml/min/1.73 m^2)	4	4	
Stage 2 (60–89 ml/min/1.73 m^2)	25	18	
Stage 3a (45–59 ml/min/1.73 m^2)	23	14	
Stage 3b (30–44 ml/min/1.73 m^2)	14	14	
Stage 4 (15–29 ml/min/1.73 m^2)	10	2	
Stage 5 (<15 ml/min/1.73 m^2)	4	1	
Median NB-GFR after PN, ml/min/1.73 m^2 (IQR) [b]	36.9 (25.3–50.7)	43.5 (34.0–53.9)	0.01
Median GFR preserved after PN, % (IQR) [b]	65.8 (48.4–77.6)	78.6 (60.9–93.1)	<0.01
Median long-term GFR after PN, ml/min/1.73 m^2 (IQR) [c]			
3 yr	40.2 (30.1–47.1)	39.0 (29.1–42.3)	0.59
5 yr	39.3 (30.0–50.5)	33.5 (29.6–45.0)	0.37
Dialysis required (*n*)	32	5	
5-yr dialysis-free survival (%) [d]	59.4	91.0	<0.01
Survival outcomes			
Median follow-up for overall survival, mo (IQR)	47.2 (2.47–121.0)	40.0 (10.9–62.8)	0.85
Local recurrence/distant metastasis (*n*/*n*)	5/12	5/11	
5-yr recurrence-free survival (%) [e]	73.5	59.0	0.21
5-yr overall survival (%)	66.1	71.3	0.36

CD = Clavien-Dindo; EBL = estimated blood loss; GFR = glomerular filtration rate, IQR = interquartile range; NB-GFR = new-baseline GFR; TKI = tyrosine kinase inhibitor.
[a] *p* values were calculated using a χ^2 test for categorical variables and a Wilcoxon test for continuous variables. Fisher's exact test was used for comparison of categorical variables with low incidence. Log-rank analysis was used for analyses of survival.
[b] Patients who underwent radical nephrectomy were excluded. Data were available for 52 patients in the pre-TKI era (1999–2008) and 48 in the TKI era (2009–2022).
[c] Patients who underwent radical nephrectomy were excluded. Functional data at 3 yr and 5 yr were available for 21 and 18 patients from the pre-TKI era (1999–2008), and 22 and 15 patients, respectively, from the TKI era (2009–2022).
[d] The follow-up time for dialysis-free survival was 48.9 mo for the pre-TKI era (1999–2008) and 38.0 mo for the TKI era (2009–2022).
[e] The follow-up time for recurrence-free survival was 30.7 mo for the pre-TKI era (1999–2008) and 24.9 mo for the TKI era (2009–2022).

the neoadjuvant TKI cohort (Fig. 3), and in 27/30 patients (90%) managed with immediate surgery during 2009–2022. By contrast, PN was only accomplished in 52/80 patients (65%) managed in the pre-TKI era. Systemic recurrences during 2009–2022 were observed in seven patients in the neoadjuvant TKI cohort and four in the immediate surgery cohort. Local recurrence occurred in two patients in the neoadjuvant TKI cohort and three in the overall immediate surgery cohort. The 5-yr OS rate was 64% in the neoadjuvant TKI cohort and 78% in the immediate surgery cohort, while the 5-yr RFS rates were 48% and 68%, respectively (Fig. 2).

In the TKI cohort (*n* = 23), fatigue (82%), hypertension (57%), and thrombocytopenia (56%) were the most common AEs (Supplementary Table 2). Grade 3 complicatiions potentially related to TKI therapy were observed in 14 patients (61%), including five urine leaks, three abscesses, and one postoperative bleed. All were managed successfully with observation, stenting or percutaneous drain placement, selective embolization, and/or antibiotics (Supplementary Table 3).

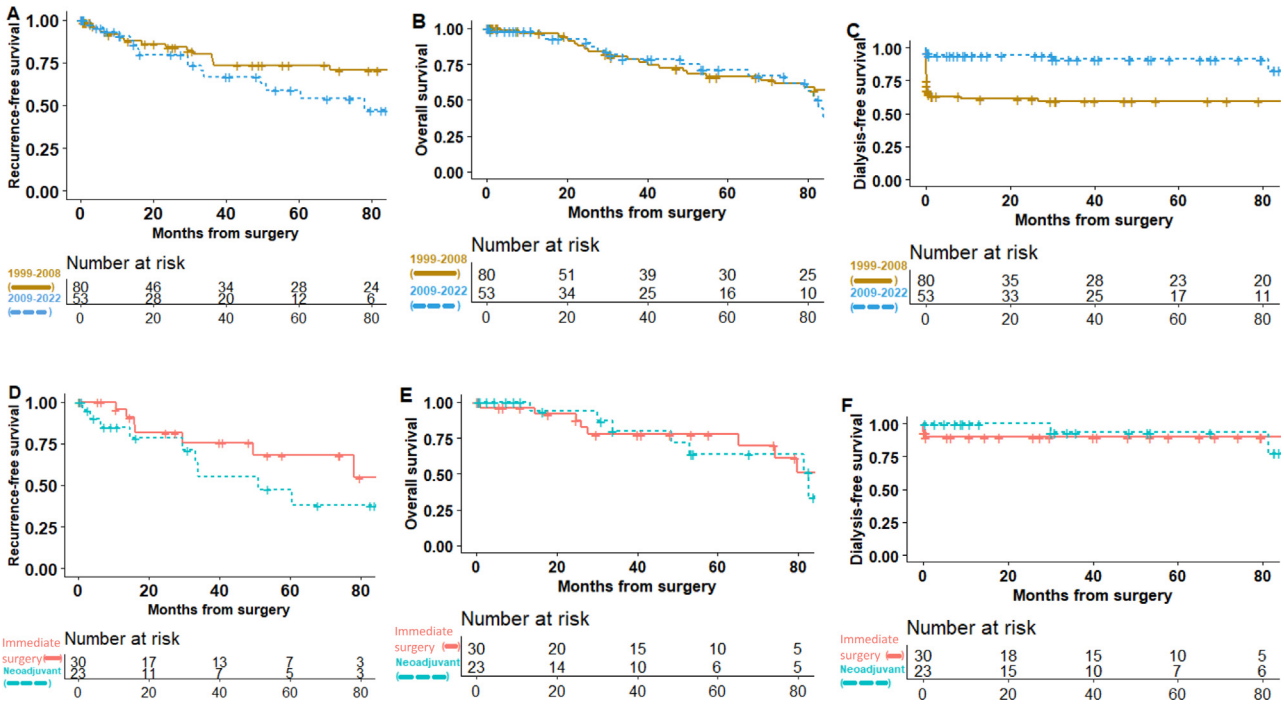

Fig. 2 – Kaplan-Meier survival estimates for patients with a high-complexity tumor in a solitary kidney. (A–C) Comparison of survival curves for the pre-TKI era (1999–2008) versus the TKI era (2009–2022). (A) Recurrence-free survival; log-rank $p = 0.21$. (B) Overall survival; log-rank $p = 0.36$; (C) Dialysis-free survival; log-rank $p < 0.001$. (D–F) Comparison of survival curves for management with immediate surgery versus neoadjuvant TKI followed by surgery in the TKI era (2009–2022). (D) Recurrence-free survival; log-rank $p = 0.21$. (E) Overall survival; log-rank $p = 0.53$. (F) Dialysis-free survival; log-rank $p = 0.73$. TKI = tyrosine kinase inhibitor.

4. Discussion

Patients with RMSK with high tumor complexity represent a major clinical and surgical challenge in obtaining strong oncologic and functional outcomes with acceptable perioperative morbidity [1]. However, the literature regarding surgery in this setting is sparse and the optimal approaches to achieve these goals are not well defined [1–4,22]. TKI therapy can lead to substantial downsizing that can facilitate PN in this specific patient population, but the use of such agents in the neoadjuvant setting remains controversial [12,23]. Prior experiences with TKIs for RMSK have been limited and it is not clear what risks and benefits are associated with this approach [1,23,24]. Avoidance of dialysis is a primary objective for RMSK cases given survival and quality-of-life implications [13–15], so our analysis focused on achievement of PN as the primary endpoint. We also evaluated the impact of TKI introduction on the evolution of our RMSK management and related outcomes.

Our study confirms how challenging RMSK with high tumor complexity can be, as RN was required in 28/80 patients (35%) in the pre-TKI era (1999–2008). When TKI therapy was explored for this population beginning in 2009, it was primarily reserved for patients with a large tumor size and high RENAL score, essentially the most challenging of cases. Of the 23 patients selected for neoadjuvant TKI after 2009, more than 90% were managed with PN. In the immediate surgery cohort (TKI era, 2009–2022), PN was also achieved in 90% of patients, which is not unexpected given that the more difficult cases had already been selected for TKI therapy. The net effect was that the incidence of RN decreased from 35% in the pre-TKI era to 9% in the TKI era, even though the demographics of the cohorts were similar and tumor characteristics were generally less favorable in the TKI era. This suggests that selective TKI use is associated with favorable outcomes in terms of the ability to achieve PN, and our data confirm that TKI therapy was generally safe and well tolerated in this setting. Other reasons explaining the increase in the rate of PN are improvements in surgical techniques and imaging quality, which may have made difficult operations more feasible. Stage migration could also be a factor, although our data suggest that tumor characteristics were actually less favorable in the TKI era. However, our data are retrospective and a randomized controlled trial will be needed to further study the potential utility of TKI therapy before surgery in this population.

Our experience shows a substantial impact of a relatively short course of neoadjuvant TKI therapy, which was associated with reductions in median tumor size from 7.1 to 5.6 cm and in median tumor volume from 131 to 51 cm^3 (both $p < 0.05$). The latter represented a 59% reduction in median tumor volume. The median RENAL score also decreased from 11 to 9 ($p < 0.01$). Essentially, neoadjuvant TKI therapy converted the most challenging of cases ($n = 23$) in the TKI era to potentially manageable cases, with similar tumor size and RENAL score to the 30 cases selected for immediate surgery in 2009–2022 (Table 3). Our data are consistent with recent literature on neoadjuvant TKI use, with reports of an absolute change in renal tumor diameter of 0.8–3.1 cm

Table 3 – Tumor characteristics and functional outcomes for patients treated in the TKI era (2009–2022)

Variable	Neoadjuvant TKI (n = 23)	Immediate surgery (n = 30)	p value [a]
Tumor parameters			
Median D_T, cm (IQR)	7.1 (5.1–7.8)	4.4 (3.5–6.7)	0.02
Median D_T after NAT, cm (IQR)	5.6 (4.2–6.25) [b]		
Median reduction in D_T after NAT, cm (IQR)	1.3 (0.9–2.2)		
Median tumor volume, cm^3 (IQR)			
Before TKI therapy	130.5 (52.5–192.7)		
After TKI therapy	50.5 (31.3–107.7) [b]		
Median reduction in tumor volume after NAT, % (IQR)	58.8 (40.7–67.8)		
Median RENAL score, (IQR)	11 (10–11)	10 (10–11)	0.07
Median RENAL score after NAT (IQR)	9 (9–10) [b]		
Histology at final pathology, n (%)			0.73
Clear cell	21 (92)	25 (83)	
Papillary	0	1 (3)	
Chromophobe	1 (4)	2 (7)	
Renal cell carcinoma unclassified	1 (4)	2 (7)	
pT stage, n (%)			0.43
pT1a	5 (22)	6 (21)	
pT1b	6 (26)	4 (13)	
pT2a	1 (4)	0	
pT2b	0	1 (3)	
pT3a	10 (44)	17 (57)	
pT3b	1 (4)	1 (3)	
pT4	0	1 (3)	
pN1 stage, n (%)	0	1 (3)	0.42
Tumor grade, n (%)			0.93
Grade 1–2	7 (32)	8 (29)	
Grade 3	12 (55)	17 (60)	
Grade 4	3 (13)	3 (11)	
Positive margin, n (%)	4 (17)	8 (27)	0.30
Surgical parameters			
Surgical approach, n (%)			0.27
Open	22 (95.7)	24 (80)	
Robotic	1 (4.3)	6 (20)	
Median estimated blood loss, ml (IQR)	300 (200–575)	375 (250–675)	0.47
Radical nephrectomy, n (%)	2 (8.7%)	3 (10%)	1.0
Partial nephrectomy, n (%)	21 (91%)	27 (90%)	1.0
Blood transfusion, n (%)	5 (22%)	6 (20%)	1.0
CD grade III–V complications (90-d), n (%)	8 (35%)	8 (27%)	0.55
90-d mortality, n (%)	0	1 (3%)	
Functional outcomes			
Median preoperative GFR, ml/min/1.73 m^2 (IQR)	55.0 (44.1–65.1)	58.5 (43.4–72.0)	0.71
Median NB-GFR after PN, ml/min/1.73 m^2 (IQR) [c]	43.9 (28.7–50.4)	41.6 (33.2–53.6)	0.83
Median GFR preserved after PN, % (IQR)	82.5 (60.5–92.1)	73.5 (52.6–92.1)	0.49
Median long-term GFR after PN, ml/min/1.73 m^2 (IQR) [d]			
3 yr	38.9 (28.7–40.0)	39.8 (30.2–45.6)	0.40
5 yr	32.0 (25.7–38.6)	37.6 (33.1–46.5)	0.20
Dialysis required (n)	2	3	
5-yr dialysis-free survival [e]	93.3%	89.6%	0.73
Survival outcomes			
Median follow-up for overall survival, mo (IQR)	31.0 (8.4–60.9)	44.7 (23.2–63.2)	0.28
Local recurrence/metastasis (n/n)	2/7	3/4	
5-yr recurrence-free survival (%) [f]	47.5	68.1	0.21
5-yr overall survival (%)	63.8	77.5	0.53

CD = Clavien-Dindo; D_T = tumor diameter; GFR = glomerular filtration rate; IQR = interquartile range; NAT = neoadjuvant TKI therapy; NB-GFR = new-baseline GFR; PN = partial nephrectomy; TKI = tyrosine kinase inhibitor.

[a] p values were calculated using a χ^2 test for categorical variables and a Wilcoxon test for continuous variables. Fisher's exact test was used for comparison of categorical variables with low incidence. Log-rank analyses were used for survival outcomes.

[b] For comparisons before and after NAT, the p value was <0.01 for tumor size, 0.02 for tumor volume, and <0.01 for RENAL score.

[c] Patients who underwent radical nephrectomy were excluded. Data were available for 21 patients in the TKI cohort and 27 in the immediate surgery cohort.

[d] Patients who underwent radical nephrectomy were excluded. Functional data were available at 3 yr and 5 yr for 13 and 7 patients in the TKI cohort, and for 9 and 8 patients, respectively, in the immediate surgery cohort.

[e] The follow-up time for dialysis-free survival was 34 mo for the TKI cohort and 41.1 mo for the immediate surgery cohort.

[f] The follow up time for recurrence-free survival was 14.6 mo for the TKI cohort and 27.6 mo for the immediate surgery cohort.

and a tumor volume reduction of approximately 21–46% [8,12,23,24]. In a retrospective review of the use of neoadjuvant TKI therapy, Lane and colleagues [8] reported that PN was achieved in 91%, 88%, and 43% of patients with clinical stage T1a, T1b, and T2–3, respectively. In our study, 91% of patients who received neoadjuvant TKI therapy were able to undergo PN, even though 11% presented with venous or nodal involvement, and the cohort was restricted to patients with a RENAL score of ≥10. In a study by Lebacle et al [7], neoadjuvant axitinib for clinical T2a disease was followed by PN in 16/18 patients (89%), again potentially supporting this approach. Ongoing trials are now also

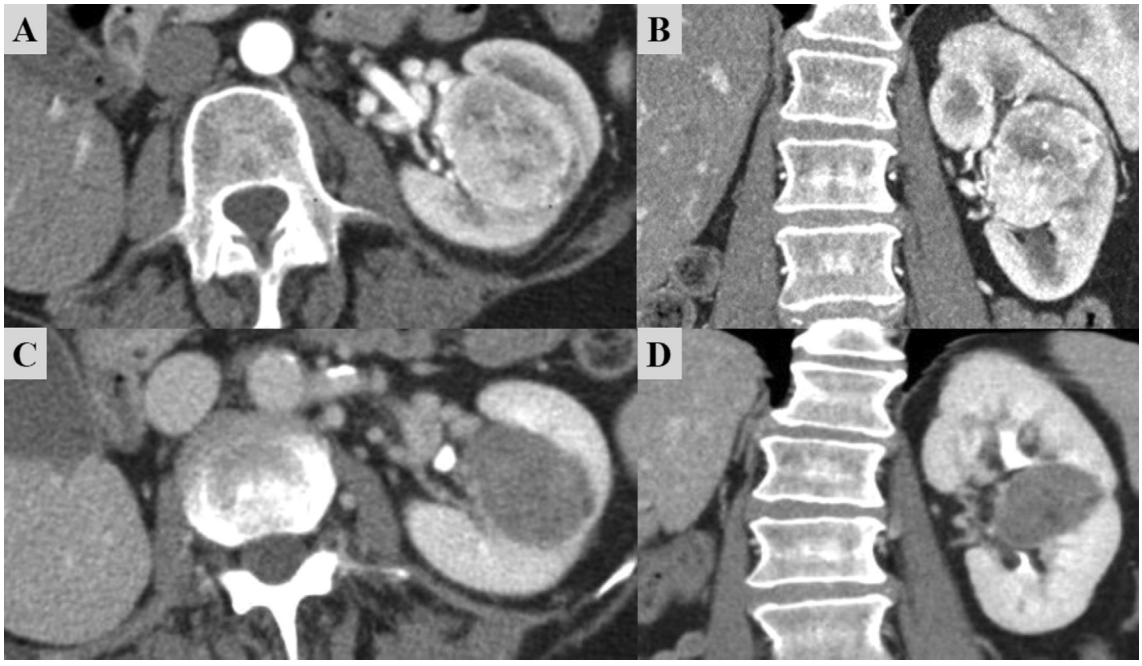

Fig. 3 – Imaging before and after TKI therapy for a patient with biopsy-proven clear-cell RCC in a solitary kidney. (A,B) Before TKI treatment, the tumor was 4.5 cm, entirely endophytic, and adjacent to the main vascular branches coming out of the hilum, with a RENAL. score of 11. The patient was then treated with 8 weeks of axitinib. (C,D) Post-TKI imaging shows a smaller tumor size and substantial tumor necrosis; the RENAL score had decreased to 10. The tumor also pulled away from the hilum to some degree. The patient underwent open clamped partial nephrectomy with hypothermia. Pathology demonstrated grade 2 clear-cell RCC with negative margins. Surgery preserved 77% of the glomerular filtration rate, and the patient is cancer-free with stable renal function after 2 yr of follow-up. RCC = renal cell carcinoma; TKI = tyrosine kinase inhibitor.

assessing the potential role of neoadjuvant immune checkpoint inhibitors (ICIs) [25–27], although short-term responses to ICIs appear to be less encouraging than those observed for TKIs, and some patients can experience pseudo-progression due to immune cell infiltration [28], which might negatively impact the feasibility of PN. Perhaps TKI/ICI combinations might be more promising in this setting [23,27]. Ongoing neoadjuvant trials for localized RCC are highlighted on ClinicalTrials.gov.

Regarding the potential downside of neoadjuvant TKI therapy, a total of 19 grade 3 AEs were observed in 14 patients (61%) during the 8–12-wk course of therapy. However, all AEs were readily manageable via a dose reduction, temporary discontinuation, or adjustments for other medications, such as antihypertension regimens. Surgery was not delayed by AEs in this study. There were no grade 4 or 5 TKI-related AEs, probably because of the short therapy course. Postoperative urine leak was observed in five patients (24%) after neoadjuvant TKI therapy and PN, and three patients were diagnosed with perinephric abscess or urinoma, although all were managed conservatively with drain and/or stent placement along with selective use of antibiotics. One postoperative bleed was managed with selective embolization with good outcomes. TKIs can affect wound healing and may predispose patients to such complications, although patient selection for the most challenging of cases was probably a contributing factor [12,24]. We routinely hold the TKI for 7 d before surgery to optimize the healing process, but other groups do not follow this policy and have also reported encouraging results [7,11]. Fortunately, most such deleterious effects are readily managed with conservative measures and are associated with good long-term outcomes.

Another important consideration is oncologic control, because some have suggested that tumor regression related to TKI therapy might leave disease microsatellites adjacent to or within the capsule that could predispose to recurrence [29]. In our series, the RFS rate was 74% in the pre-TKI era and 59% in the TKI era (p = 0.21), but non–organ-confined pathology and grade 4 or N1 disease were more common in the TKI era and probably contributed to these findings. In the TKI era, the RFS rate was only 48% in the neoadjuvant TKI cohort versus 68% in the immediate surgery cohort (p = 0.21), but again tumor characteristics were discordant, with tumor size and complexity substantially greater in the TKI cohort, reflecting patient selection of larger and more challenging tumors for TKI therapy. Overall, our experience suggests that oncologic outcomes were primarily determined by tumor biology rather than the local management strategy. Differences in RFS were primarily driven by systemic recurrences, which predominated in all cohorts, rather than local recurrence. Overall, there were 23 systemic recurrences and only ten local recurrences, with a relatively even distribution between the two study periods. For the TKI era, local recurrences were similar and of relatively low incidence in the TKI and immediate surgery cohorts, but systemic recurrences were more frequent in the TKI cohort, most likely reflecting more aggressive tumor biology related to patient selection. Similar findings were observed in the neoadjuvant series described by Lebacle and colleagues [7], who also reported a predominance of systemic rather than local recurrence. For more rigorous

evaluation of potential oncologic concerns related to neoadjuvant TKI therapy before surgery in this setting, a randomized controlled trial will be required.

Regarding functional recovery, another vital outcome for patients with RMSK [1], our study showed that not only was PN accomplished more frequently in the TKI era but also that the percentage GFR preserved by PN increased. Focusing only on patients for whom PN was accomplished (Table 2), GFR preservation was only 66% in the pre-TKI era, versus 79% in the TKI era (< 0.01). The most challenging tumors in the TKI era were substantially reduced in size and complexity via neoadjuvant therapy before surgery, and this was probably the most important contributor to this finding. Neoadjuvant TKI therapy not only made PN more feasible but also facilitated greater preservation of the parenchymal volume and GFR. In a previous study by our center, we estimated the amount of parenchymal volume that could be theoretically saved with a standard PN, presuming removal of the tumor and a 1-cm rim of parenchyma related to tumor excision and some degree of devascularization that occurs during renal reconstruction. In that study of 25 patients with high tumor complexity, the estimated amount of ipsilateral parenchyma that could be saved was 107 cm^3 before TKI therapy versus 173 cm^3 after TKI therapy ($p < 0.01$), related to reductions in tumor size and complexity [6].

While our data suggest that neoadjuvant TKI therapy helped to facilitate PN in the most challenging of cases, we cannot prove a causal effect, and a randomized trial will be required to assess this in a more rigorous manner. We believe that such a trial should be randomized and placebo-controlled, and limited to patients with clear-cell histology, high tumor complexity, and imperative indications for PN. One consideration for the treatment arm would be a combination of a TKI to block the VEGF receptor, and belzutifan, which inhibits HIF-2α. Belzutifan recently demonstrated a strong response rate of 49% among patients with von Hippel-Lindau disease and is now approved by the US Food and Drug Administration [30]. This combination is being studied in advanced disease and should be complementary with respect to antiangiogenic effects, which should optimize tumor downsizing. The neoadjuvant regimen would be relatively short (8–12 wk) and is thus likely to be well tolerated. The main endpoints would be oncologic and functional outcomes, and the incidence and degree of AEs and perioperative complications should also be measured, particularly those potentially related to the healing process.

Our study has some limitations, including the retrospective single-institution design, only intermediate-term follow-up, and missing data. However, this is the largest study to evaluate the management of this challenging population and to provide hypothesis-generating data regarding the potential utility of TKI for facilitation of PN in comparison to the pre-TKI era. On the basis of previous studies, our use of TKI was primarily restricted to patients with biopsy-proven clear-cell histology. Hence, this approach cannot be universally applied, and we believe it should only be used when necessary until higher-level evidence has been obtained.

5. Conclusions

Selective use of TKI for RMSK with high tumor-complexity associated with increased achievement of PN. RFS mostly reflected aggressive tumor-biology rather than failure of local-management. A randomized trial will be required to provide higher-level evidence for this important issue.

Author contributions: Steven C. Campbell had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

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