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Minerva Urology and Nephrology 2023 August;75(4):425-33
DOI: 10.23736/S2724-6051.23.05123-6

ORIGINAL ARTICLE

Partial *versus* radical nephrectomy for complex renal mass: multicenter comparative analysis of functional outcomes (Rosula collaborative group)

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ABSTRACT

BACKGROUND: Utility of partial nephrectomy (PN) for complex renal mass (CRM) is controversial. We determined the impact of surgical modality on postoperative renal functional outcomes for CRM.

METHODS: We retrospectively analyzed a multicenter registry (ROSULA). CRM was defined as RENAL Score 10-12. The cohort was divided into PN and radical nephrectomy (RN) for analyses. Primary outcome was development of *de-novo* estimated glomerular filtration rate (eGFR)<45 mL/min/1.73 m^2. Secondary outcomes were *de-novo* eGFR<60 and ΔeGFR between diagnosis and last follow-up. Cox proportional hazards was used to elucidate predictors for *de-novo* eGFR<60 and <45. Linear regression was utilized to analyze ΔeGFR. Kaplan-Meier Analysis (KMA) was performed to analyze 5-year freedom from *de-novo* eGFR<60 and <45.

RESULTS: We analyzed 969 patients (RN=429/PN=540; median follow-up 24.0 months). RN patients had lower BMI (P<0.001) and larger tumor size (P<0.001). Overall postoperative complication rate was higher for PN (P<0.001), but there was no difference in major complications (Clavien III-IV; P=0.702). MVA demonstrated age (HR=1.05, P<0.001), tumor-size (HR=1.05, P=0.046), RN (HR=2.57, P<0.001), and BMI (HR=1.04, P=0.001) to be associated with risk for *de-novo* eGFR<60 mL/min/1.73 m^2. Age (HR=1.03, P<0.001), BMI (HR=1.06, P<0.001), baseline eGFR (HR=0.99, P=0.002), tumor size (HR=1.07, P=0.007) and RN (HR=2.39, P<0.001) were risk factors for *de-novo* eGFR<45 mL/min/1.73 m^2. RN (B=-10.89, P<0.001) was associated with greater ΔeGFR. KMA revealed worse 5-year freedom from *de-novo* eGFR<60 (71% *vs*. 33%, P<0.001) and *de-novo* eGFR<45 (79% *vs*. 65%, P<0.001) for RN.

CONCLUSIONS: PN provides functional benefit in selected patients with CRM without significant increase in major complications compared to RN, and should be considered when technically feasible.

(*Cite this article as*: Cerrato C, Meagher MF, Autorino R, Simone G, Yang B, Uzzo RG, *et al.* Partial *versus* radical nephrectomy for complex renal mass: multicenter comparative analysis of functional outcomes (Rosula collaborative group). Minerva Urol Nephrol 2023;75:425-33. DOI: 10.23736/S2724-6051.23.05123-6)

KEY WORDS: Carcinoma, renal Cell; Renal insufficiency, chronic; Glomerular Filtration Rate; Nephrectomy.

Partial nephrectomy (PN) has emerged as the reference standard for most clinical T1 and T2 Renal Cortical Masses and Renal Cell Carcinoma (RCC)[1-4] with oncological equipoise to radical nephrectomy (RN)[5-9] and may be considered an option in selected T3a tumors with indication for nephron preservation.[10-12]

Controversy continues with respect to efficacy and benefit of PN in management of complex renal masses (CRM)[5] with concerns regarding oncological outcomes, burden of complications and possible lack of functional benefit. A robust comparison of renal functional outcomes between minimally invasive PN *vs.* RN for CRM is lacking.[13, 14]

We sought to compare renal functional outcomes of radical and partial nephrectomy for CRM.

Materials and methods

Patient population

This was a retrospective multicenter analysis approved by the Institutional Review Board utilizing the ROSULA (RObotic SUrgery for LArge) renal mass consortium dataset for patients undergoing Robot Assisted Partial Nephrectomy (RAPN) or Minimally Invasive Radical Nephrectomy (MIS-RN) for CRM between January 2011 and January 2021. The database included 1572 patients who underwent renal surgery for suspected kidney cancer. Of them, 941 patients underwent RN for a cT2-cT3 renal mass, 455 underwent PN for cT2 (298/455) or cT3 (157/455) renal mass, and 176 either RN or PN for cT1 renal mass. CRM was defined as cortical neoplasm with RENAL Nephrometry Score [(R)adius, (E)xophytic/endophytic properties, (N)earness of tumor to collecting system or sinus, (A)nterior (a)/posterior (p), and (L)ocation relative to polar line] of 10-12.[15-17] Our protocols have previously been described.[7, 18] Informed signed consent was obtained by all patients. Preoperative evaluation included laboratory evaluations, cross-sectional imaging of the abdomen (CT or MRI), and chest imaging. All procedures were performed by urological oncological surgeons, who selected operation (RAPN *vs.* MIS-RN) and operative approach (laparoscopic or robot-assisted) according to preference. Follow-up was guided by pathological findings and guidelines.[4, 19] Patients with Renal Nephrometry Score <10, clinical node-positive disease (cN1+) or suspected metastasis were excluded from analysis.

Data collection

We analyzed the following clinical features, demographics: age, sex, Body Mass Index (BMI), diabetes (DM), hypertension (HTN); disease characteristics: clinical tumor size/stage, RENAL nephrometry score[15] assigned utilizing preoperative imaging and by individual treating surgeons, baseline estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, and mean eGFR. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[20]

We recorded the following operatory characteristics: surgical approach, tumor histology, complication rate[21] and length of hospital stay.

We analyzed as postoperative outcomes mean eGFR at 6-, 12- months and at last follow-up, eGFR variation at 6 months (ΔeGFR= 6-month eGFR – baseline eGFR) and at last follow-up (ΔeGFR= last available eGFR - 6-month eGFR), and *de-novo* eGFR downgrades <60 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2.

Data analysis

RAPN and MIS-RN groups underwent comparative descriptive and survival analyses. Primary

outcome was development of *de-novo* postoperative eGFR<45 mL/min/1.73 m^2. Secondary outcomes were development of *de-novo* eGFR <60 and ΔeGFR between diagnosis and last follow-up.

Statistical analysis

Descriptive statistics included *t*-test, and chi-square or Fisher's Exact Test for continuous or categorical variables, respectively. Cox proportional hazards multivariable analysis (MVA) was used to elucidate predictors for *de-novo* eGFR<60 mL/min/1.73 m^2 and <45 mL/min/1.73 m^2, while linear regression was utilized to analyze ΔeGFR. For multivariate models we considered as independent variables age, sex, mean tumor size, type of surgery, HTN, DM II, BMI, and baseline eGFR. Kaplan Meier Analysis (KMA) with Log-Rank Testing was performed to analyze 5-year freedom from *de-novo* eGFR<60 mL/min/1.73 m^2 and from *de-novo* <45 mL/min/1.73 m^2. Analyses were conducted utilizing SPSS v.27 (IBM, New York, USA), with a P<0.05 considered statistically significant.

Results

Baseline characteristics

Data from 969 patients who fulfill the criteria were consecutively collected at each institution (RN=429, PN=540; median follow-up 24 months, interquartile range [IQR] 7-48). Table I demonstrates demographics, clinical disease characteristics, and functional outcomes. No sig-

TABLE I.—*Demographic and functional descriptive RAPN* vs. *MIS-RN (N.=969).*

Variable	RN (N.=429, %)	PN (N.=540, %)	P value
Age (median, IQR)	61.0 (53.0-70.5)	60.0 (50.0-68.0)	0.066
BMI (median, IQR)	27.2 (24.4-30.4)	28.9 (25.4-32.9)	<0.001
Diabetes (N., %)	88 (20.5%)	119 (22.0%)	0.582
HTN (N., %)	215 (50.1%)	288 (53.3%)	0.332
Sex (N., %)			0.064
Female	130 (30.3%)	195 (36.1%)	
Male	299 (69.7%)	345 (63.9%)	
RENAL (median, IQR)	11.0 (10.0-11.0)	10.0 (10.0-11.0)	<0.001
Median T size (median, IQR)	8.4 (7.6-10.5)	5.1 (3.8-7.5)	<0.001
Clinical stage (N., %)			<0.001
I	38 (8.9%)	345 (63.8%)	
II	257 (59.9%)	172 (31.9%)	
III	86 (20.0%)	20 (3.7%)	
IV	48 (11.2%)	3 (0.6%)	
Histology (N., %)			<0.001
Benign	15 (3.5%)	74 (13.7%)	
Malignancy	414 (96.5%)	466 (86.3%)	
Ischemia time (median, IQR)	25 (12-38)		
Surgical margins (N., %)			0.001
Positive	13 (3.1%)	43 (8.0%)	
Negative	416 (96.9%)	497 (92.0%)	
Total complication (N., %)	61 (14.2%)	129 (23.9%)	<0.001
Major complication (N., %)	11 (2.6%)	27 (5.0%)	0.702
Length of hospital stay (median, IQR)	4.0 (2.0-6.0)	4.0 (3.0-5.0)	0.026
Median follow-up (months) (Median, IQR)	20.0 (7.0-42.0)	27.7 (7.0-54.5)	0.002
Baseline eGFR<60 (N., %)	85 (19.8%)	126 (23.3%)	0.210
Baseline eGFR<45 (N., %)	19 (4.4%)	34 (6.3%)	0.135
Mean preoperative eGFR (mean±SD)	76.9 (± 21.4)	80.4 (± 24.8)	0.021
Mean eGFR 6 months (mean±SD)	51.5 (± 14.6)	69.3 (± 24.7)	<0.001
Mean eGFR 12 months (mean±SD)	51.1 (± 13.7)	74.2 (± 24.2)	<0.001
Mean eGFR last f/u (mean±SD)	56.5 (± 18.8)	67.4 (± 26.4)	<0.001
Delta eGFR 6 months (mean±SD)	-22.4 (± 18.9)	-11.4 (± 17.6)	<0.001
Delta eGFR last f/u (mean±SD)	-21.2 (± 18.3)	-12.8 (± 20.3)	<0.001
De-novo eGFR<60 (N., %)	167 (38.9%)	87 (16.1%)	<0.001
De-novo eGFR<45 (N., %)	81 (18.9%)	62 (11.5%)	<0.001

nificant differences were noted between groups with respect to age (P=0.066), sex (P=0.064), HTN (P=0.332) and DM (P=0.582). Patients undergoing PN had higher BMI (28.9 *vs*. 27.2 kg/m^2, P<0.001), smaller tumors (5.1 *vs*. 8.4, P<0.001) and higher proportion of benign histology (13.7% *vs*. 3.5%, P<0.001). PN patients had higher positive surgical margin (PSM) rate (8.0% *vs*. 3.1%, P=0.001). None of PSM patients from either cohort experienced cancer-specific mortality (CSM).

RN patients had a significantly higher clinical stage according to the AJCC classification[22] (P<0.001). While PN had a higher total complication rate (23.9% *vs*. 14.2%; P<0.001), no significant difference was noted with respect to rate of major (Clavien 3/4) complications (PN 5.0% *vs*. RN 2.6%; P=0.702). Major complications included acute kidney injury requiring dialytic therapy (7/38), active extravasation of the resection bed requiring embolization (3/38), stroke requiring ICU or endovascular therapy (2/38), pulmonary embolism requiring intubation or IVC placement (9/38), pneumothorax requiring chest tube placement (1/38), urinary leakage requiring ureteral stenting or surgical revision (13/38), septic events requiring transfer to ICU (3/38).

Functional outcomes

PN had lower ΔeGFR (mL/min/1.73 m^2) at the 6-month postoperative (-11.4 *vs*. -22.4, P<0.001) and at last follow-up (-12.8 *vs*. -21.2, P<0.001). At last follow-up, PN patients had lower rates of *de-novo* eGFR<60 mL/min/1.73 m^2 (16.1% *vs*. 38.9%, P<0.001) and *de-novo* eGFR<45 mL/min/1.73 m^2 (11.5% *vs*. 18.9%, P<0.001).

MVA for risk factors associated with functional decline are presented Table II, III, IV. Increasing age (HR=1.05, P<0.001), increasing BMI (HR=1.04, P=0.001), larger clinical tumor

TABLE II.—*Cox regression model for higher risk of* de-novo *eGFR decline <60 mL/min/1.73 m^2.*

Variable	HR	95% CI	P
Increasing age (continuous)	1.05	1.03-1.06	<0.001
Sex (male *vs*. female)	1.20	0.90-1.59	0.210
Increasing BMI (continuous)	1.04	1.02-1.07	0.001
Baseline eGFR	1.00	0.99-1.01	0.131
HTN (yes *vs*. no)	1.50	0.86-1.53	0.342
DM (yes *vs*. no)	1.22	0.90-1.65	0.209
Increasing tumor size (continuous)	1.05	1.00-1.11	0.046
Radical *vs*. partial nephrectomy	2.57	1.85-3.57	<0.001

TABLE III.—*Cox regression model for higher risk of* de-novo *eGFR decline <45 mL/min/1.73 m^2.*

Variable	HR	95% CI	P
Increasing age (continuous)	1.03	1.02-1.05	<0.001
Sex (male *vs*. female)	0.99	0.75-1.31	0.956
Increasing BMI (continuous)	1.06	1.03-1.08	<0.001
Baseline eGFR	0.99	0.98-0.99	0.002
HTN (yes *vs*. no)	0.82	0.62-1.08	0.162
DM (yes *vs*. no)	1.16	0.85-1.57	0.350
Increasing tumor size (continuous)	1.07	1.02-1.13	0.007
Radical *vs*. partial nephrectomy	2.39	1.74-3.29	<0.001

TABLE IV.—*Linear regression for increasing delta eGFR.*

Variable	B	95% CI	P
Increasing age (continuous)	-0.019	-0.14 to -0.09	0.752
Sex (male *vs*. female)	-2.52	-5.33 to 0.29	0.079
Increasing BMI (continuous)	-0.21	-0.44 to -0.03	0.080
HTN (yes *vs*. no)	3.28	0.28 to 6.27	0.032
DM (yes *vs*. no)	-1.17	-4.59 to 2.24	0.500
Increasing tumor size (continuous)	0.73	0.21 to 1.24	0.006
Radical *vs*. partial nephrectomy	-10.89	-14.22 to -7.56	<0.001

size (HR=1.05, P=0.046) and RN (HR=2.57, P<0.001) were independent risk factors for *de-novo* eGFR<60 mL/min/1.73 m² (Table II). Increasing age (HR=1.03, P<0.001), higher BMI (HR=1.06, P<0.001), baseline eGFR (HR=0.99, P=0.002), larger tumor size (HR=1.07, P=0.007) and RN (HR=2.39, P<0.001) were independently associated to *de-novo* eGFR<45 mL/min/1.73 m² (Table III). RN (B=-10.89, P<0.001), larger clinical tumor size (B=0.73, P=0.006) and HTN (B=3.28, P=0.0032) were independently associated with a larger ΔeGFR between preoperative value and last follow-up at a median time of 24 months (Table IV).

KMA comparing RN and PN groups for freedom from development of eGFR<60 mL/min/1.73 m² and eGFR<45 mL/min/1.73 m², are demonstrated in Figure 1. Compared to PN, patients undergoing RN showed significantly worsened 5-year freedom from *de-novo* eGFR<60 mL/min/1.73 m² (71% *vs*. 33%, P<0.001; Figure 1A) and eGFR<45 mL/min/1.73 m² (79% *vs.* 65%, P<0.001; Figure 1B).

Discussion

We herein report the first comparison of functional outcomes of MIS-RN and RAPN in the setting of CRM. Our results suggest that PN provides a functional benefit, being associated with decreased ΔeGFR and risk from development of *de-novo* eGFR<60 and <45 mL/min/1.73 m² and without a significantly higher rates of major complications. As such, even in the setting of CRM, PN may be preferred when clinically indicated to preserve renal function and oncologically safe and appropriate.

Association of RN with development of postoperative CKD (eGFR decline below 60 and 45 mL/min/1.73 m²) is well described and accepted[23-27] and postoperative development of eGFR<45 is associated with increased risk of overall and non-cancer mortality,[25, 27, 28] even in preoperative CKD naïve populations.[29] Increasing RENAL score has been demonstrated to be a predictive factor for functional outcomes after partial nephrectomy.[30-32] Merhazin *et al.* demonstrated that each 1-point increase in RENAL score or 1-cm increase in tumor size caused respectively a 2.5% (P=0.002) and 1.8% (P=0.013) decrease in eGFR.[31] Increasing RENAL Score (OR 1.24, P=0.046) and decreasing preoperative eGFR (OR1.10, P<0.001) resulted independently associated to *de-novo* eGFR <60 mL/min/1.73 m.[31] Simmons *et al.* evaluated the reliability of RENAL on function after PN and noted that overall RENAL score was associated with long-term eGFR preservation, and that a per-unit change in tumor diameter and in RENAL Score caused respectively a 0.5% and 1.6% change in eGFR.[32] As such there has been concern that PN for complex masses may not provide significant

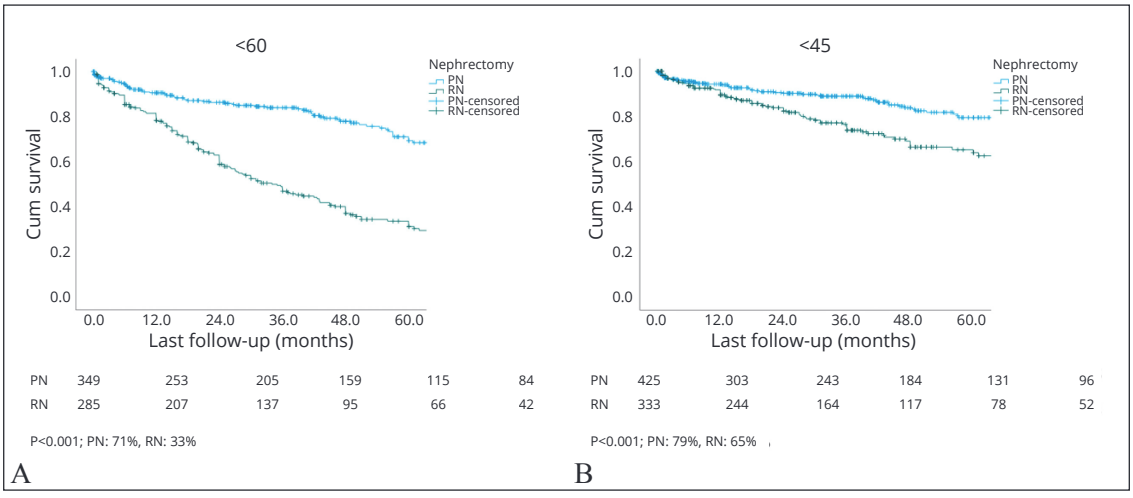

Figure 1.—Kaplan Meier curves describing freedom from *de-novo* eGFR<60 mL/min/m² (A) and *de-novo* eGFR<45 mL/min/m² (B).

functional benefit over RN to justify potential increased risk.[33]

Despite well-founded theoretical concerns, in our analysis we noted significantly improved functional preservation with PN compared to RN in CRM having higher freedom from *de-novo* eGFR<60 mL/min/1.73 m^2 (71% *vs.* 33%, P<0.001) and from *de-novo* eGFR<45 mL/min/1.73 m^2 (79% *vs.* 65%, P<0.001) when compared to RN, and being an independent factor associated with decreased ΔeGFR (P<0.001), decreased risk of *de-novo* eGFR <60 mL/min/1.73 m^2 (P<0.001), and *de-novo* eGFR<45 mL/min/1.73 m^2 (P<0.001). As such, our findings suggest that preservation of the remining parenchyma in CRM may nonetheless constitute a significant additional functional nephron mass compared to the complete loss of functional parenchyma in the affected kidney in RN and contribute to improved functional outcomes noted in PN.

PN has historically been associated with a worsened morbidity profile, which has called into question utilization of the procedure in settings of greater risk of complications.[1, 33] Indeed, previous studies showed that higher RENAL scores were associated with increased rates of urine leak or higher Clavien-Dindo complications.[34-36] However, these studies included significant numbers of open procedures and were at an earlier time point in the evolving experience of partial nephrectomy. More contemporary analyses from centers of excellence demonstrate a reduced risk of major complications in robotic as opposed to open partial nephrectomy approaches, and while they may be associated with selection bias, they nonetheless call for a more contemporary analytical comparison of risks and frequency of complications in partial nephrectomy.[14, 37] In a propensity score-matched (PSM) comparison of RAPN and MIS-RN for cT2aRM (T2aN0M0) Bradshaw *et al.* demonstrated that there were no differences in intraoperative complications (P=0.478), Clavien-Dindo Grade ≥III complications (P=0.063), and re-admission (P=0.238).[7] Our analysis in patients with CRM across different clinical disease stages yielded similar findings in that while PN may have had a higher total complication rate (14.2% *vs.* 23.9%, P<0.001), this does not reflect in major complication rate (2.6% *vs*. 5.0%, P=0.702). These data taken together suggest that progressive experience with nephron sparing surgery and application of minimally invasive technologies has resulted in a reduction of burden of complications, whereupon modern day RAPN approaches the major complication profile of radical nephrectomy when performed by experienced surgeons. Furthermore, even in the setting of a higher risk lesion such as CRM, partial nephrectomy may be performed without significant increase in burden of major morbidity.

In the setting of complex renal masses and renal function preservation, nomograms and new technologies may play a role.[38-41] Mari *et al.* developed a new nomogram to predict the likelihood of ultimate a renal function loss >25% at four years after PN using a large multicenter series.[38] The use of nomogram like this may help in patients' stratification even in the decision algorithm for patients with CRM. In fact, patients at higher risk of renal function decline may be selected for PN over RN, improving their overall survival.

Amparore *et al.* evaluated the role of three-dimensional virtual models (3DVMs) in influencing postoperative renal function, and at multivariable analysis observed that the only protective factor against a significant loss of renal function (drop of >20% from baseline value) was the availability of a 3DVM (P=0.002), especially in the setting of high and intermediate-risk tumors (P=0.03 and P=0.01, respectively).[40] Similarly, Michiels *et al.* conducted a propensity scored matched analysis between 3D-Image guided RAPN group (3D-IGRAPN) and a control group.[41] The 3D-IGRAPN group resulted to be associated with higher RENAL Complexity Score (9 *vs*. 8, P<0.001), lower major complication rate (3.8% *vs*. 9.5%, P=0.04), lower eGFR variation (-5.6 *vs*. -10.4%, P=0.002), and higher trifecta achievement (55.7% *vs*. 45.1%, P=0.005).[41] These data suggest that pre- and perioperative use of 3D models may optimize renal function preservation, adding to the surgeon's armamentarium a novel tool to further enhance functional outcomes of nephron-sparing surgery.

Limitations of the study

Our study has some limitations. Firstly, it is a retrospective study and therefore it suffers from its inherent bias. Second, due to the nature of the study, the median follow-up was only 24 months long. Third, despite being a multi-institutional study, central laboratory or pathology review was not available. Fourth, it is possible that the two groups could have differences in other clinical variables that could influence eGFR, even if we considered those with the highest impact on kidney function variation in our analysis. Fifth, all patients were treated in high volume centers and surgeries were performed by experienced surgeons, so our results may not be applicable to smaller centers with lower skilled surgeons. Relatively to the surgical technique, we were not able to collect data on the renorrhaphy technique, and as such cannot comment on impact of renorrhaphy on functional outcomes. We did not take into account the ischemia time in models as this was comparison of radical and partial nephrectomy outcomes. Nonetheless, even for this cohort of complex renal mass, the median ischemia time was 25 minutes which is at the threshold for optimal functional preservation.[42-44] However, this is the first, large multicenter study, analyzing a cohort with CRM who underwent minimally invasive surgery and demonstrating that PN offers and advantage over RN in terms of clinical and functional outcomes, maintained over an adequate follow-up time.

Conclusions

In setting of CRM, PN offers improved functional preservation with respect reduced risk and rates of development of moderate to severe CKD and without increased risk of major complications when compared to RN. PN should be considered as an appropriate option in patients with desire or indication for nephron preservation.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding

Partial financial support was received from Stephen Weissmen Kidney Cancer Research Found.

Authors' contributions

Clara Cerrato and Margaret F. Meagher contributed equally. Ithaar H. Derweesh, Clara Cerrato, Margaret F. Meagher given substantial contributions to the research idea, to the design of the study, and manuscript draft writing and editing; Luke Wang, Dhruv Puri, Mimi Nguyen, Kevin Hakimi, Sohail Dhanji, Franklin Liu, Savio D. Pandolfo have given substantial contributed to data collection and management; Margaret F. Meagher, Clara Cerrato, Kevin Hakimi have given substantial contributions to data analysis; Riccardo Autorino, Giuseppe Simone, Bo Yang, Robert G. Uzzo, Francesco Porpiglia, Umberto Capitanio, James Porter, Alp T. Beksac, Andrea Minervini, Alessandro Antonelli, Maria A. Cerruto, Franklin Lau, Daniel Eun, Alexandre Mottrie, Carmen Mir, Alexander Kutikov, Francesco Montorsi, Aron Monish, Chandru Sundaram, Jihad Kaouk contributed to manuscript critical revision for important intellectual content; Ithaar H. Derweesh, Riccardo Autorino supervised the whole project. All authors read and approved the final version of the manuscript.

History

Manuscript accepted: June 16, 2023. - Manuscript revised: March 31, 2023. – Manuscript received: August 27, 2022.