Oncology

Functional and Oncological Outcomes of Renal Surgery for Hilar Tumors: Informing the Decisions in Risk-Adapted Management

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OBJECTIVE To describe the safety and efficacy of partial nephrectomy (PN) in comparison to radical nephrectomy (RN) for surgically managed renal hilar tumors.

MATERIALS AND METHODS We retrospectively reviewed institutional records of patients with a small (<5 cm) solitary renal (hilar or non-hilar) mass who underwent PN or RN between 2008 and 2018. Hilar tumors were defined as those at medial position, abutting the renal vessels. Recurrence-free, cancer-specific, and overall survival were estimated using the Kaplan-Meier method.

RESULTS Of 1,951 eligible patients, 399 had hilar tumors (292 scheduled for PN, 107 RN) and 1,552 had non-hilar tumors (scheduled for PN). We found no significant differences in survival measures between hilar and non-hilar tumors in patients selected for PN. Patients scheduled for PN for hilar tumors had higher rates of ≥grade II postoperative surgical complications compared to patients scheduled to receive PN for non-hilar tumors (13% vs 8.6%; log-rank $P = .018$) and non-statistically significantly elevated rates of ≥grade II complications compared to patients scheduled for RN for hilar tumors (13% vs 6.5%; difference 6%, 95% CI 0.4%, 13%; log-rank $P = .07$).

CONCLUSION PN for hilar and non-hilar renal masses (<5cm) experience comparable oncologic outcomes though increased risk of complications for hilar masses. PN for hilar tumors was associated with better renal function and overall survival with non-statistically elevated risk of grade II or higher complications than RN. A renal tumor located at the hilum should not be a contra-indication for performing PN. UROLOGY 00: 1–7, 2021. © 2021 Elsevier Inc.

The main curative treatment option for localized RCC is surgical resection with either partial nephrectomy (PN) or radical nephrectomy (RN).[1] The benefits of PN over RN include the preservation of normal renal parenchyma, improved renal function and cardiovascular health, making PN a preferable treatment option when feasible. The location of renal tumors adjacent to the renal hilum has been viewed as a limiting factor for safely performing a PN. Some authors suggest that PN should be contraindicated in patients with renal hilar tumors, citing an increased the risk of perioperative complications and compromised oncologic control with limited, if any, functional benefits compared to RN.[2,3]

The American Urological Association Guideline on localized renal cancer recommends a risk-adapted approach to surgical decision-making, prioritizing PN for small renal tumors but allowing that RN may be an option in patients without renal dysfunction if increased oncologic potential is suggested based on tumor size, location, and complexity, and if the surgeon deems that PN is not feasible or advisable.[1] In this balance between organ sparing and oncological safety, many patients with hilar tumors end up receiving a radical approach due to fear of greater surgical difficulty or worse survival outcomes.

The aspects of technical feasibility are undefined, highly variable and largely based on surgeon judgement which is difficult to quantify. Physician experience, tumor characteristics, patient co-morbidities and health decision making factors all play a role. Foundational information in developing these risk-adapted decisions is the need for

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data on oncologic and safety risks associated with surgical treatment of tumors based on tumor location. We therefore sought to determine the safety and efficacy of PN for treating renal hilar tumors by evaluating functional and oncologic outcomes of patients who were scheduled to receive a PN at our institution. We compared outcomes to patients with small renal hilar tumors with non-hilar location. We additionally performed a secondary analysis comparing the outcomes of patients with hilar tumors scheduled initially to receive PN or RN.

METHODS

Study Population

We conducted a retrospective study and identified 1,951 consecutive eligible patients with a solitary small renal mass (less than 5 cm) who underwent either RN or PN by 4 experienced surgeons (JAC, AAH, PR, KAT) for renal cell carcinoma (RCC) between 2008 and 2018 at Memorial Sloan Kettering Cancer Center. Of these, 399 patients (20%) had a hilar tumor, 292 of whom (73%) were scheduled to undergo PN and 107 (27%) scheduled to receive RN. The remaining 1,552 (80%) patients had non-hilar tumors and were all scheduled for PN. Hilar tumors were defined as renal masses that abut the main renal artery and/or vein or its segmental branches, identified on preoperative cross-sectional imaging and subsequently confirmed intraoperatively. Nephrometry score was characterized in all tumors to describe complexity, although not considered when deciding on surgical approach. Patients who underwent multiple nephrectomies were grouped according to their first procedure, with subsequent procedures excluded from analysis. All statistical analyses were conducted using STATA 15.0 (StataCorp, College Station, TX).

Functional Outcomes of Partial Nephrectomy for Hilar and Non-Hilar Tumors

We analyzed differences in 6-month postoperative estimated glomerular filtration rate (eGFR) (±3 months). eGFR was calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration formula. Mean 6-month postoperative eGFRs were presented and compared for both patients with hilar tumors and patients with non-hilar tumors, with 95% confidence intervals around the difference in means.

Outcomes and Complications

Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) in patients with hilar and non-hilar tumors managed with planned PN (n = 1,844) were evaluated using Kaplan-Meier curves to visualize differences in survival and the log-rank test was used to measure any differences between groups. We evaluated complication rates (according to the Clavien-Dindo classification)[4] 30 days following PN for renal hilar and non-hilar tumors. Two definitions of complications were used: (1) any grade II-V and (2) major complications, defined as grade III-V. For each of the 2 outcomes, a univariable logistic regression was used with planned surgery as the predictor and we extracted the effect size and tested for heterogeneity, where the null hypothesis was that the association between complication and tumor location does not differ based on the definition of complication. If there was no evidence to reject the null hypothesis of the heterogeneity test, the P value assessing differences between groups for complication was reported as defined by grade II or higher complications, which with more events would have greater statistical power; otherwise, if there was evidence that rejected the null hypothesis of the heterogeneity test, the results testing differences between groups for each definition of complication would be reported. As a secondary analysis, we compared the outcomes of patients with hilar tumors scheduled for either a PN (n = 292) or an RN (n = 107).

RESULTS

Outcomes of Partial Nephrectomy for Hilar and Non-Hilar Tumors

Patients with hilar tumors were more likely to have higher pathologic tumor stage, longer operative time, longer warm ischemia time, and higher estimated blood loss (all P <.0001; Table 1) than patients with non-hilar tumors. Surgical approach (open vs minimally invasive) and positive surgical margin rates were similar between the groups. The conversion rate from planned PN to RN was low overall though more common in hilar tumors (5.8% for hilar vs 0.6% for non-hilar, difference 5%; 95% CI 2.5%, 8%; P <.0001). The mean 6-month postoperative eGFR in patients with hilar tumors was lower compared to patients with non-hilar tumors (68 vs 74 mL/min/1.73m^2; difference -6; 95% CI -9, -3; P <.0001).

Among all patients scheduled to undergo a PN, 25 patients had a recurrence. Recurrence free survival was not significantly different in the hilar compared to non-hilar group (1-year recurrence rate 1.1% vs 0.5%, log-rank P = .7; Fig. 1). During follow up, 69 patients died from any cause, 6 of whom died from RCC. The median follow-up time for survivors is 3.4 years (IQR 1.4-6.0) after surgery. No significant difference was seen in cancer specific or overall survival in the hilar compared to the non-hilar group.

When we looked at the postoperative 30-day complication rates in patients scheduled for PN, 13% with hilar tumors had grade II or higher complications within 30 days of surgery compared to 8.6% of patients with non-hilar tumors (difference 4.4%; 95% CI 0.3%, 8%; P = .018). Results were similar using the second definition of complication (test of heterogeneity P = .8) for major complications (grade III or higher), where the rates were 7.2% in patients with hilar tumors compared to 5.0% in patients with non-hilar tumors (difference 2.2%; 95% CI -1%, 5%). A descriptive list of complications is showed in suppl. Figure 1.

Outcomes of Partial Nephrectomy or Radical Nephrectomy for Hilar Tumors

Table 2 illustrates the clinical and disease characteristics for patients with hilar tumors (399 patients), based on whether they were scheduled to undergo either PN (292, 73%) or RN (107, 27%). Patients scheduled to undergo PN were younger than those scheduled to undergo RN (median 60 vs 65, P = .003). The mean 6-month postoperative eGFR in patients scheduled for PN was 68 mL/min/1.73m^2; for patients scheduled for RN, the mean 6-month postoperative eGFR was 51 mL/min/1.73m^2 (difference 16; 95% CI 12, 21; P <.0001).

Among 399 patients with renal hilar tumors, 5 experienced recurrences. We found no significant differences in RFS (log-rank P = .3) or CSS (log-rank P = .4) among patients scheduled

Table 1. Clinical and perioperative characteristics among patients scheduled for partial nephrectomy, based on whether patients had hilar tumors

	Hilar (n = 292; 16%)	Non-Hilar (n = 1,552; 84%)	*P* Value*
Age at surgery (y)	60 (51-67)	60 (51-67)	.7
Male	183 (63%)	1047 (67%)	.12
Postoperative 6-mo eGFR			.10
<15	1 (0.3%)	0 (0%)	
≥15 and <30	0 (0%)	9 (0.6%)	
≥30 and <60	53 (18%)	245 (16%)	
≥60	236 (81%)	1279 (82%)	
Unknown	2 (0.7%)	19 (1.2%)	
American Society of Anesthesiologists score ≥3	182 (62%)	968 (62%)	1
Minimally invasive surgical approach	100 (34%)	569 (37%)	.5
Pathologic stage			<.0001
pT1	238 (82%)	1416 (91%)	
pT3	53 (18%)	135 (8.7%)	
pTx	1 (0.3%)	1 (<0.1%)	
Ischemia time (minutes) (n = 1,684)	31 (24-42)	24 (17-31)	<.0001
Operating room time (n = 1,835)	154 (128-191)	130 (110-162)	<.0001
Estimated blood boss (mL) (n = 1,820)	300 (150-500)	200 (100-300)	<.0001
Tumor size (cm)	3 (3-4)	3 (2-4)	<.0001
Length of stay (d) (n = 1,556)	2 (2-3)	2 (2-3)	<.0001
Positive surgical margin	19 (6.5%)	79 (5.1%)	.3
Presentation			.083
Incidental	229 (78%)	1277 (82%)	
Local	43 (15%)	181 (12%)	
Systemic	1 (0.3%)	1 (<0.1%)	
Unknown	19 (6.5%)	93 (6.0%)	
Histology on pathology			.002
Clear cell carcinoma	231 (79%)	1075 (69%)	
Papillary	28 (10%)	268 (17%)	
Chromophobe	7 (2.4%)	53 (3.4%)	
Clear cell papillary	12 (4.1%)	38 (2.4%)	
Unclassified	12 (4.1%)	97 (6.3%)	
Other RCC	2 (0.7%)	21 (1.4%)	
Postoperative 6-mo eGFR			.003
<15	2 (0.7%)	2 (0.1%)	
≥15 and <30	3 (1.0%)	8 (0.5%)	
≥30 and <60	86 (29%)	344 (22%)	
≥60	160 (55%)	991 (64%)	
Unknown	41 (14%)	207 (13%)	

All values are median (IQR) and frequency (%). (n = 1,844).
* Group comparison *P* values based on Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

to either undergo PN or RN for a hilar tumor (all 5 recurrences and 2 deaths from disease occurred in patients scheduled to undergo PN). Within this cohort, 29 patients died from any cause. The median follow-up times for survivors was 3.6 years (IQR 1.6-6.0) after surgery. Figure 2 depicts the probability of death from any cause where there was improved survival in patients who had a planned PN compared to patients with a planned RN (log-rank P = .0005). The 3-year probability of death from any cause was 12.9% in patients who were scheduled to undergo RN compared to 2.2% in patients scheduled to undergo PN (difference 10.8%, 95% CI 1.7%, 20%).

To examine 30-day complication rates, we conducted a heterogeneity test using our 2 definitions of complications (grade II-V and grade III-V), which yielded a nonsignificant *P* value (*P* = .9) suggesting that there is no significant difference in the association between planned procedure type (PN or RN) and rate of complications, based on the complication definition. Among patients with hilar tumors, 13% who had a planned PN had grade 2 or higher complications compared to 6.5% of patients with a planned RN (difference 6%, 95% CI 0.4%, 13%, *P* = .07). Using the alternative definition of complication, 7.2% of patients who had a planned PN compared to 3.7% of patients with a planned RN had a major complication (difference 3.5%, 95% CI -1.2%, 8%, *P* = .07).

DISCUSSION

This study confirms that PN for renal hilar tumors can be a more challenging and complex procedure requiring longer operative time, prolonged warm ischemia time, a higher rate of blood loss, and a higher rate of grade 2 or higher complications than non-hilar tumors. It is also not surprising that patients with hilar tumors have a higher rate of postoperative renal dysfunction compared to patients with non-hilar tumors. Accordingly, Takagi et al demonstrated that a central location and tumor size strongly correlate with increased renal parenchyma loss,

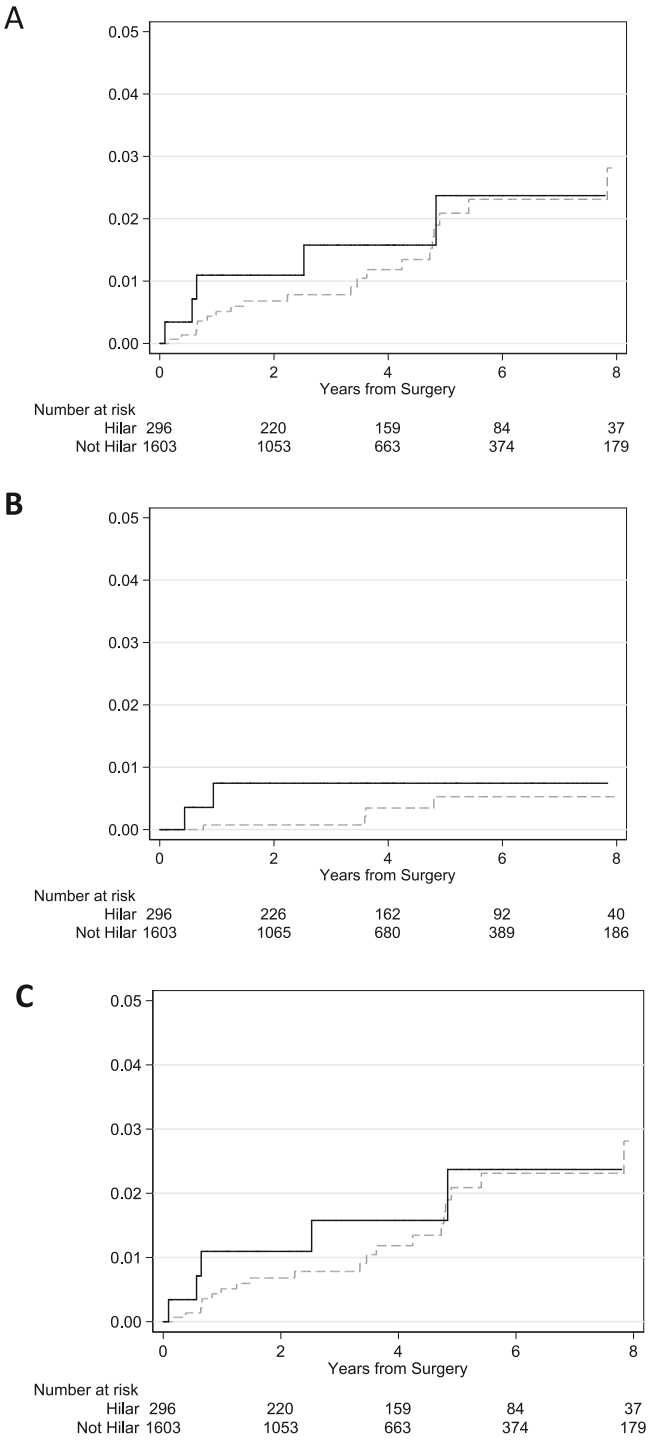

Figure 1. Probability of recurrence (A), death from disease (B) and death from any cause (C), stratified by hilar (solid black line) or non-hilar (dashed grey line) tumors undergoing planned PN.

suggesting that only 70%-80% of the vascularized parenchyma could be preserved in these tumors compared to more than 90% in smaller exophytic tumors.[5] Importantly, the major complication rate (i.e., grade III or more) was low across all groups in our study suggesting that PN can be performed safely, based on surgeon judgement, in the majority of selected patients with renal hilar tumors. It is recognized that the risk of complications, while low overall, are slightly higher for hilar tumors even in the hands of experienced surgeons but well within the range of safety from previously published series.[5]

Over 94% of the patients in our study who planned to undergo a PN for a hilar tumor did successfully undergo a PN, suggesting that individual surgeon judgement in case selection for feasibility and safety was excellent. Recently, Petros et al published a single-center review showing that

Table 2. Clinical and perioperative characteristics among patients with hilar tumors, based on planned procedure type

	Planned RN (n = 107; 27%)	Planned PN (n = 292; 73%)	*P* Value*
Age at surgery (y)	65 (55-72)	60 (51-67)	.003
Male	73 (68%)	183 (63%)	.3
Preoperative eGFR			.017
<15	3 (2.8%)	1 (0.3%)	
≥15 and <30	2 (1.9%)	0 (0%)	
≥30 and <60	22 (21%)	53 (18%)	
≥60	80 (75%)	236 (81%)	
Unknown	0 (0%)	2 (0.7%)	
American Society of Anesthesiologists score ≥3	76 (71%)	182 (62%)	.12
Minimally invasive surgical approach	28 (26%)	100 (34%)	.15
Pathologic stage			<.0001
pT1	51 (48%)	238 (82%)	
pT3	56 (52%)	53 (18%)	
pTx	0 (0%)	1 (0.3%)	
Operating room time (n = 396)	127 (95-168)	154 (128-191)	<.0001
Estimated blood loss (mL) (n = 389)	200 (100-400)	300 (150-500)	.001
Tumor size (cm)	4 (4-5)	3 (3-4)	<.0001
Length of stay (d) (n = 363)	2 (2-3)	2 (2-3)	.003
Positive surgical margin	1 (0.9%)	19 (6.5%)	.020
Presentation			.2
Incidental	74 (69%)	229 (78%)	
Local	21 (20%)	43 (15%)	
Systemic	1 (0.9%)	1 (0.3%)	
Unknown	11 (10%)	19 (6.5%)	
Histology on pathology			.008
Clear cell carcinoma	83 (78%)	231 (79%)	
Papillary	4 (3.7%)	28 (10%)	
Chromophobe	6 (5.6%)	7 (2.4%)	
Clear Cell Papillary	1 (0.9%)	12 (4.1%)	
Unclassified	10 (9.3%)	12 (4.1%)	
Other RCC	3 (2.8%)	2 (0.7%)	
Postoperative 6-mo eGFR			<.0001
<15	2 (1.9%)	2 (0.7%)	
≥15 and <30	6 (5.6%)	3 (1.0%)	
≥30 and <60	53 (50%)	86 (29%)	
≥60	30 (28%)	160 (55%)	
Unknown	16 (15%)	41 (14%)	
Complexity based on R.E.N.A.L. score			<.0001
Low	0 (0%)	1 (0.3%)	
Moderate	26 (24%)	142 (49%)	
High	67 (63%)	124 (42%)	
Unknown	14 (13%)	25 (8.6%)	

All values are median (IQR) and frequency (%). (n = 399)
* Group comparison *P* values based on Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

hilar tumor location is an independent factor for conversion to RN, with 50% of converted patients having either a hilar tumor or evidence of renal sinus invasion.[6] AUA guidelines advise performing an RN in high-tumor complexity settings where PN would be challenging even in experienced hands. Such criteria are not well defined however and likely highly individualized. Attempts at classifying tumor/technical complexity by morphometrics have provided a means for reporting standards but prospective clinical utility in surgical decision making is not identified. At our center, such decisions are made independent of these criteria. As reported, nearly half of the patients with hilar tumors scheduled for PN in this series had a R.E.N.A.L. score ≥10 however these data were not used for choosing surgical approach or a surrogate for surgeon judgement.

Pertaining to the oncologic outcomes, we saw no difference in the positive surgical margin rate, RFS, or CSS for PN based on hilar or non-hilar tumor location. It is, however, interesting that hilar tumors were associated with a higher proportion of clear cell RCC and pT3 disease compared to non-hilar tumors. Other studies support our finding,[7-9] but the reason for this is still unknown. Perhaps specific conditions in the hilar microenvironment, such as hypoxia and/or perfusion status[10] could be favorable for clear cell type development; more studies addressing this question are advisable. Although emerging evidence suggests there could be a pathologic difference between hilar and non-hilar tumors, Correa et al found no difference in the risk of malignancy, nuclear grade, or upstaging when comparing hilar to non-hilar cT1a renal masses.[11] However, they found more clear cell type when the

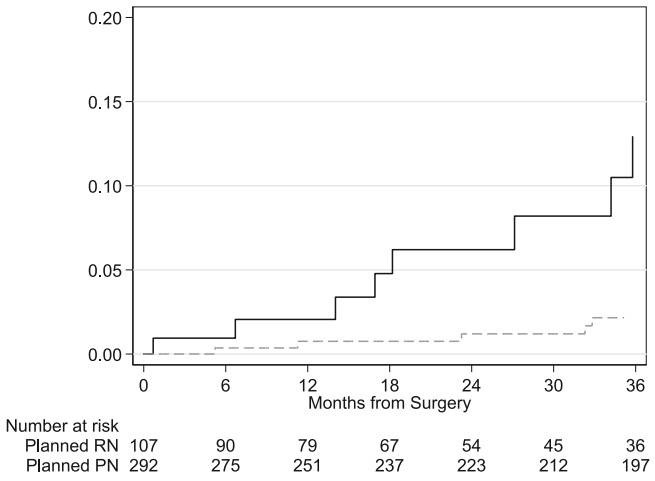

Figure 2. Kaplan-Meier estimated probability of death from any cause in patients with hilar tumors, stratified by planned RN (solid black line) or planned PN (dashed gray line) (adjusted Cox-model $P = .001$).

comparison was adjusted for tumors larger than 4 cm (T1b). Finally, they concluded that there is no biological reason to perform an RN based solely on the location of the renal tumor. In contrast, a recent report showed that hilar tumors may be histologically and molecularly distinct, with more aggressive features, suggesting that these patients may be better served with RN.[7] In our series, PN appears to be effective for oncologic control regardless of tumor location and, once again, hilar tumor location itself should not be a contraindication for performing a PN.

Although oncologic outcomes, including CSS, appear similar, OS was better in patients scheduled to receive PN for hilar tumors compared to RN. This could be because of several factors, including surgical selection based on patient age. The median age of patients scheduled to receive a PN was 60 years vs 65 years for RN patients scheduled to receive an RN; younger patients may have been assumed to better tolerate PN and thus live longer than their RN counterparts, a potential limitation in a retrospective analysis. Another reason could be that patients with hilar tumors scheduled to undergo PN had improved renal function 6 months after surgery compared to those planned to undergo RN. As demonstrated by Mashni et al, chronic kidney disease is associated with poorer survival, and the preservation of more nephrons with PN could potentially improve the rate of survival in patients managed with PN compared to RN, for hilar as well as non-hilar tumors.[12] Overall, our study does not support the concept that PN should not be performed for highly complex tumors because of the pT3 upstaging risk. Despite the increased risk of upstaging to pT3 in hilar tumors (upstaging risk in our study was 18% for hilar vs 8.7% for non-hilar), we found that PN did not undertreat these patients, with both groups (hilar and non-hilar tumors) presenting similar oncological outcomes (CSS, RFS, and OS).

The previously mentioned surgical selection bias is the critical limitation to this retrospective series. This bias is clear from the observed differences in baseline patient and tumor characteristics such as age and tumor size. Furthermore, the results of this study may not be extrapolated to all centers because the procedures we evaluated were performed by fellowship-trained urologic oncologists dedicated to the management of patients with kidney cancer. Because the adoption of PN is on the rise, if a urologist believes a hilar tumor may be amenable to PN but lacks the resources to successfully perform one, the patient may be best served by a referral to an expert center, particularly in the setting of preexisting renal dysfunction in which PN would be well advised.

CONCLUSIONS

Our study found that PN for small renal hilar tumors is safe and feasible, with low complication rates and similar oncologic outcomes as PN for non-hilar. Further, compared to RN in hilar tumors, PN presented better postoperative renal function preservation and overall survival. A renal hilar tumor should not hinder a urologist from performing a PN.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2021.07.014.