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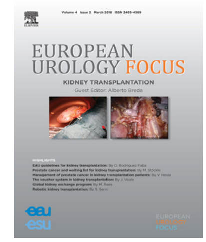

Kidney Cancer

Perioperative Outcomes of Open, Laparoscopic, and Robotic Partial Nephrectomy: A Prospective Multicenter Observational Study (The RECORd 2 Project)

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Abstract

Background: Partial nephrectomy (PN) has a non-negligible perioperative morbidity. Comparative evidence of the available surgical techniques is limited.
Objective: To compare the perioperative outcomes of open, laparoscopic, and robotic PN.
Methods: Data of 2331 patients treated with PN for cT1 renal tumors were extracted from the RECORd2 database, a prospective multicenter project. Multivariable regression models assessed the relationship between surgical technique and surgical margins,

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warm ischemia time, postoperative complications, and acute kidney injury (AKI). The probability of achieving a modified trifecta (negative margins, warm ischemia time <25 min, and no Clavien–Dindo ≥2 complications) was examined for each surgical approach.
Results: Minimally invasive techniques had lower rate of Clavien–Dindo ≥2 complications than that of open surgery (odds ratio [OR] for robotic surgery: 0.27; 95% confidence interval [95% CI]: 0.15–0.47, $p < 0.0001$; OR for laparoscopy: 0.52; 95% CI: 0.34–0.78; $p = 0.002$). The probability of receiving ischemia was highest for robotic PN ($p < 0.001$). Among on-clamp PN, laparoscopy had longer ischemia than open (estimate: 1.09; 95% CI: –0.00 to 2.18; $p = 0.050$) and robotic (estimate: 1.36; 95% CI: 0.31–2.40; $p = 0.011$) surgery. When compared with open PN, the risk of AKI was roughly halved for patients treated by robotic and laparoscopic surgery (both $p < 0.0001$). Positive margins rate did not differ between the groups (all $p \geq 0.1$). The likelihood to achieve a modified trifecta was not affected by surgical technique in the overall population (all $p \geq 0.075$). In Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score < 10 lesions, robotic surgery had higher probability of achieving a modified trifecta than open PN (OR: 1.66; 95% CI: 1.09–2.53; $p = 0.018$) and laparoscopy (OR: 1.34; 95% CI: 0.94–1.90; $p = 0.11$).
Conclusions: In PADUA < 10 renal tumors, robotic PN allows for higher rates of trifecta than open and laparoscopic surgeries. The impact of surgical technique on perioperative outcomes of PN might be limited in more complex lesions.
Patient summary: We evaluated the association between surgical technique and perioperative outcomes of partial nephrectomy. In less complex (Preoperative Aspects and Dimensions Used for an Anatomical [PADUA] score < 10) lesions, robotic PN allows for higher rates of trifecta when compared with other surgical techniques.

1. Introduction

Partial nephrectomy (PN) represents the gold standard for active treatment of cT1 renal masses [1–3]. Minimally invasive approaches such as laparoscopy or robotic surgery might offer similar oncological efficacy [4] and better perioperative outcomes [4–6] when compared with the open technique. However, given the lack of high-quality evidence, the current EAU guidelines do not recommend a surgical approach over the other [1].

The comparison of perioperative outcomes between open and minimally invasive techniques has been subject to considerable attention in the recent years. Accordingly, a clear need of a standardized proxy for surgical quality has raised. Previous studies investigated surgical margins status [7], complications rate [6], and intraoperative ischemia time [8] to compare different surgical techniques. Recently, these three parameters have been combined in the trifecta [9], used to describe favorable outcomes after PN, and considered a proxy for surgical quality.

Previous investigations have compared the trifecta rates between open and minimally invasive surgery [10–13]. However, reported differences between the surgical approaches may be related to different definition of the outcome or inclusion criteria. Moreover, a comparison of all the three surgical approaches available for nephron-sparing surgery is rarely described. To date, only few papers have analyzed the perioperative outcomes of open, laparoscopic, and robotic PN [4,14–16]. Nonetheless, such studies are affected by relevant limitations, which include the inability to account for relevant confounders (ie, nephrometry score) [14,16], selective inclusion criteria (ie, only T1a [15] or T1b [14] lesions), or small sample size [4]. Thus, current literature does not allow for definitive conclusions about the impact of surgical technique on perioperative outcomes. For this reason, we sought to analyze data from our prospective, multi-institutional database to address this relevant clinical question.

2. Materials and methods

The Italian REgistry of COnservative and Radical surgery for cortical renal tumor Disease (RECORd 2 Project) is a prospective, observational project promoted by the Italian Society of Urology whose collection criteria were previously described [17]. Institutional Review Board approval was obtained for data sharing through the different centers.

For the scope of this study, we analyzed data of 2331 patients diagnosed with a cT1 N0 M0 renal mass at computed tomography or magnetic resonance imaging and treated with open, laparoscopic, or robotic PN from 2013 to 2016. Patients with multiple tumors ($n = 137$) and with missing data (age, $n = 15$; body mass index [BMI], $n = 11$; Preoperative Aspects and Dimensions Used for an Anatomical [PADUA] score [18], $n = 28$; preoperative estimated glomerular filtration rate [eGFR], $n = 35$; peritoneum access, $n = 9$) were excluded, resulting into 2096 patients eligible for analyses. All patients treated with on-clamp PN received warm ischemia.

Our primary aim was to evaluate the impact of surgical technique on grade-specific complication rates, surgical margins, warm ischemia time, and acute kidney injury (AKI). Moreover, we assessed the relationship between surgical approach and a modified trifecta outcome, that is, a combination of negative surgical margins, warm ischemia time < 25 min, and absence of postoperative (up to 3 mo) Clavien–Dindo [19] ≥2 complications. Although the trifecta originally included any-grade complications [9], we chose to include only clinically significant events. Because there is wide clinical variability for postoperative day 1 eGFR, we described differences between the groups for this parameter, but it was not included in subsequent analyses as an endpoint of interest. AKI was defined according to the risk/injury/failure/loss/end-stage (RIFLE) criteria [20] (>25% reduction in preoperative baseline eGFR or >1.5-fold increase in preoperative creatinine, both at discharge from hospital).

Our statistical analysis involved four steps. First, differences in baseline characteristics between patients treated with open, laparoscopic, and robotic surgery were assessed using the Kruskal–Wallis and chi-square tests. For descriptive purposes, we reported the ischemia time for on-clamp procedures that had such variable available ($n = 1231$). The subsequent analyses also included clampless procedures.

Second, we investigated the impact of surgical technique on perioperative outcomes using multivariable linear or logistic regression models for continuous or categorical outcomes, respectively. The identified covariates consisted of age, gender, Charlson Comorbidity Index [21] (categorized as 0–1 vs 2–4 vs ≥5), BMI, single kidney status, preoperative eGFR, total PADUA score (6 vs 7–9 vs ≥10), peritoneal access (retro- vs trans-peritoneal), type of resection (enucleation vs enucleoresection), and median annual caseload per center (per surgical approach; continuous). When ischemia time was the outcome of interest, we assessed the probability of receiving on-clamp PN and, to allow for easier comparison with other studies, we repeated the analyses after excluding clampless procedures.

Third, we evaluated the association between surgical approach and the modified trifecta outcome. Overall rates were calculated for each group and all the analyses were repeated for this new endpoint. We also examined whether our results might be affected by a different definition (ie, trifecta [9] and Margin, Ischemia, and Complications score [22]). In the presence of significant difference between the groups for a different definition, we repeated the analyses using such endpoint.

Finally, we hypothesized that the relationship between surgical technique and the achievement of the modified trifecta might be influenced by tumor complexity. Accordingly, we used an interaction test between surgical approach and PADUA score for the prediction of the modified trifecta.

3. Results

3.1. *Patients characteristics and surgical features*

Descriptive characteristics of the study cohort are reported in Table 1. We found significant differences between treatment modalities concerning age and clinical tumor stage, with patients in the laparoscopic group being younger and with smaller tumors. Moreover, as the PADUA score increased, we observed a slightly higher number of patients treated with open surgery. Intraoperative and postoperative outcomes are described in Supplementary Table 1. The rate of clampless procedures was 49%, 43%, and 23% for open, laparoscopic, and robotic PN, respectively. Conversion to open approach was registered in seven (1%) and one (<1%) of laparoscopic and robotic procedures, respectively. The distribution of annual caseload per center is described in Supplementary Table 2.

Table 2 shows the results of our multivariable regression models.

Table 1 – Descriptive characteristics of 2096 patients who underwent partial nephrectomy, stratified by surgical approach.

	Open (*N* = 682; 33%)	Laparoscopic (*N* = 625; 30%)	Robotic (*N* = 789; 38%)	*p* Value
Age, yr	66 (56–73)	63 (55–71)	64 (55–72)	0.007
Body mass index, kg/m^2	26 (23–29)	26 (24–28)	26 (24–28)	0.6
Sex				
Male	438 (64%)	421 (67%)	491 (62%)	0.13
Female	244 (36%)	204 (33%)	298 (38%)	
Charlson comorbidity index				
0–1	57 (9%)	75 (12%)	91 (12%)	0.10
2–4	377 (55%)	354 (57%)	440 (56%)	
5+	248 (36%)	196 (31%)	258 (33%)	
Year of surgery				
2013	210 (31%)	132 (21%)	145 (18%)	<0.0001
2014	176 (26%)	197 (32%)	183 (23%)	
2015	177 (26%)	152 (24%)	194 (25%)	
2016	119 (17%)	144 (23%)	267 (34%)	
Clinical T stage				
T1a	500 (73%)	505 (81%)	592 (75%)	0.004
T1b	182 (27%)	120 (19%)	197 (25%)	
PADUA score				
6	120 (18%)	128 (20%)	172 (22%)	<0.0001
7–9	418 (61%)	433 (69%)	512 (65%)	
10+	144 (21%)	64 (10%)	105 (13%)	
Peritoneum access				
Retro-	577 (85%)	243 (39%)	76 (10%)	<0.0001
Trans-	105 (15%)	382 (61%)	713 (90%)	
Side of lesion				
Right	374 (55%)	315 (50%)	395 (50%)	0.14
Left	308 (45%)	310 (50%)	394 (50%)	
Solitary kidney	17 (2%)	6 (1%)	7 (<1%)	0.018
Preoperative eGFR	85 (68–99)	87 (72–100)	86 (71–101)	0.042
Ischemia time, mins (*N* = 1231)	16 (13–20)	16 (13–20)	15 (11–20)	0.053
Operative time, min	122 (100–155)	120 (87–150)	150 (120–190)	<0.0001
Estimated blood loss, ml (*N* = 2081)	200 (100–300)	150 (80–265)	100 (50–200)	<0.0001

eGFR = estimated glomerular filtration rate; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical (score).
Data are presented by frequencies and proportions and medians and interquartile ranges for categorical and continuous variables, respectively. The number in parenthesis indicates the number of patients with available data.

Table 2 – Multivariable logistic and linear regressions to assess the relationship between surgical approach and each endpoint of interest.

Outcomes	Laparoscopic vs Open OR – estimate (95% CI)	p Value	Robotic vs Open OR – estimate (95% CI)	p Value	Robotic vs Laparoscopic OR – estimate (95% CI)	p Value
Clavien–Dindo ≥ 2 complications	0.52 (0.34–0.78)	0.002	0.27 (0.15–0.47)	<0.0001	0.54 (0.33–0.91)	0.020
Warm ischemia time	1.57 (0.45–2.69)	0.006	4.92 (3.56–6.28)	<0.0001	3.31 (2.16–4.45)	<0.0001
Acute kidney injury	0.50 (0.37–0.68)	<0.0001	0.49 (0.34–0.69)	<0.0001	0.99 (0.72–1.35)	0.9
Positive margins	1.26 (0.79–2.01)	0.3	0.89 (0.51–1.55)	0.7	0.68 (0.43–1.08)	0.10
Modified trifecta achievement	1.28 (0.94–1.74)	0.12	1.39 (0.97–1.99)	0.075	1.15 (0.84–1.57)	0.4

CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odd ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical (score).
Models adjusted for age, gender, Charlson comorbidity index, body mass index, single kidney status, preoperative eGFR, total PADUA score, peritoneal access, type of resection, and median annual caseload per center.

3.2. Surgical complications

Compared with the open group, the probability of Clavien–Dindo ≥ 2 complications was lower for robotic (odds ratio [OR]: 0.27; 95% confidence interval [CI]: 0.15–0.47) and laparoscopic procedures (OR: 0.52; 95% CI: 0.34–0.78; both $p \leq 0.002$). Robotic PN had a lower risk of Clavien–Dindo ≥ 2 complications than laparoscopic surgery (OR: 0.54; 95% CI: 0.33–0.91; $p = 0.020$). A full description of postoperative complications is available in Supplementary Table 1.

3.3. Warm ischemia time

In the overall cohort, the probability of receiving ischemia was higher for patients treated robotically than for those who underwent laparoscopy (OR: 3.33; 95% CI 2.44–4.54) or open surgery (OR: 4.78; 95% CI 3.31–6.90; both $p < 0.0001$). This helps explain our finding of longer ischemia for robotic PN than laparoscopy and open surgery (Table 2). In patients requiring on-clamp PN (Supplementary Table 4), laparoscopy had longer ischemia than open (estimate: 1.09; 95% CI: –0.00 to 2.18; $p = 0.050$) and robotic (estimate: 1.36; 95% CI: 0.31–2.40; $p = 0.011$) surgeries.

3.4. Acute kidney injury

Minimally invasive techniques had lower risk of AKI than open surgery (both $p < 0.0001$). The probability of AKI was not different between robotic and laparoscopic surgeries (OR: 0.99; 95% CI: 0.72–1.35; $p = 0.9$).

3.5. Surgical margins

The risk of positive margins was not different between minimally invasive approaches and open surgery nor between robotic and laparoscopic procedures.

3.6. Modified trifecta

Overall, 1545 (78%) patients fulfilled the criteria for a modified trifecta. Multivariable analysis did not show significant differences between the open and minimally invasive techniques or between robotic and laparoscopic procedures for the achievement of the modified trifecta (all $p \geq 0.075$).

We conducted sensitivity analyses to examine the robustness of our findings. Using Clavien–Dindo ≥ 3 complications as endpoint of interest, the risk of complications for minimally invasive approaches was still lower than that for the open technique (both $p \leq 0.009$), whereas the difference between robotic and laparoscopic surgeries was not statistically significant (OR: 0.65; 95% CI: 0.19–2.22; $p = 0.5$). When we explored trifecta rates according to different combinations of margins status, ischemia time, and complications, we found differences between surgical techniques for the achievement of trifecta using a different definition (that is, trifecta [9]; Supplementary Table 3). Accordingly, we repeated the analyses for the prediction of such outcome. Our results were unaltered for the comparison between robotic and laparoscopic techniques. When compared with open surgery, the probability of achieving the outcome was higher for both laparoscopic (OR: 1.42; 95% CI: 1.07–1.88; $p = 0.014$) and robotic (OR: 1.70; 95% CI: 1.22–2.38; $p = 0.002$) procedures.

Because the PADUA score differed between the groups, it is plausible that the rates of modified trifecta for each group might have been affected by tumor complexity. To address this point, we tested the hypothesis of a different relationship between surgical approach and the modified trifecta according to the baseline nephrometric score. The interaction test was significant ($p = 0.001$) and thus we repeated the analyses for tumors with a PADUA score <10 and ≥10, considered as a clinically reasonable threshold for complex lesions. As shown in Table 3, robotic PN had higher probability to achieve a modified trifecta than open PN for PADUA < 10 tumors (OR: 1.66; 95% CI: 1.09–2.53; $p = 0.018$). Although not statistically significant, the OR for robotic PN compared with laparoscopy suggests higher likelihood of achieving a modified trifecta in PADUA < 10 lesions (OR: 1.34; 95% CI: 0.94–1.90; $p = 0.11$). Given the difference between surgical techniques in PADUA < 10 lesions, we examined the determinants of the modified trifecta singularly. The results were similar to our main analyses with respect to ischemia time, complications rate, and AKI (Table 4). Conversely, robotic PN showed lower risk of positive margins when compared with laparoscopy in PADUA < 10 masses (OR: 0.59; 95% CI: 0.35–0.99; $p = 0.045$). When we restricted the analyses to PADUA ≥ 10 tumors, differences between the surgical techniques

Table 3 – Multivariable logistic model to predict the achievement of the modified trifecta according to baseline nephrometry score.

	Laparoscopic vs Open OR (95% CI)	p Value	Robotic vs Open OR (95% CI)	p Value	Robotic vs Laparoscopic OR (95% CI)	p Value
PADUA						
<10	1.29 (0.92–1.82)	0.14	1.66 (1.09–2.53)	0.018	1.34 (0.94–1.90)	0.11
≥10	1.68 (0.79–3.58)	0.2	0.84 (0.40–1.77)	0.7	0.50 (0.23–1.06)	0.071

CI = confidence interval; OR = odd ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical (score).

Table 4 – Multivariable logistic and linear regression model to predict Clavien–Dindo ≥2 complications, positive surgical margins, ischemia time, and acute kidney injury in PADUA < 10 lesions.

	Laparoscopic vs Open OR – estimate (95% CI)	p Value	Robotic vs Open OR – estimate (95% CI)	p Value	Robotic vs Laparoscopic OR – estimate (95% CI)	p Value
Clavien–Dindo ≥2 complications	0.50 (0.32–0.79)	0.003	0.25 (0.13–0.47)	<0.0001	0.54 (0.30–0.95)	0.031
Warm ischemia time	1.95 (0.76–3.14)	0.001	5.05 (3.57–6.53)	<0.0001	2.95 (1.72–4.18)	<0.0001
Acute kidney injury	0.49 (0.35–0.68)	<0.0001	0.48 (0.32–0.71)	0.0003	0.98 (0.69–1.38)	0.9
Positive margins	1.41 (0.84–2.39)	0.2	0.89 (0.47–1.70)	0.7	0.59 (0.35–0.99)	0.045

CI = confidence interval; eGFR = estimated glomerular filtration rate; OR = odd ratio; PADUA = Preoperative Aspects and Dimensions Used for an Anatomical (score).
Models adjusted for age, gender, Charlson comorbidity index, body mass index, single kidney status, preoperative eGFR, total PADUA score, peritoneal access, type of resection, and median annual caseload per center.

for the achievement of the modified trifecta were not statistically significant (all $p \geq 0.071$).

4. Discussion

Many studies have examined the perioperative outcomes of PN. It is reasonable that surgical technique might influence perioperative outcomes, but few papers allow for comparison between the three surgical approaches available for PN [4,14,15]. To date, the current report represents the largest comparative study on the perioperative outcomes of open, laparoscopic, and robotic PN.

We found that, when compared with open surgery, minimally invasive approaches did not affect the risk of positive margins, in keeping with prior literature [4,15]. We also noted that both laparoscopic and robotic techniques had longer ischemia time than open surgery, a finding mainly driven by the highest number of clampless procedures in the latter group. A number of prior investigators compared ischemia time during laparoscopic and robotic PN with that of open surgery, with controversial results. Ischemia time during minimally invasive PN was shorter [11,13] and longer [15,23,24] than that during open surgery, and this is consistent with systematic research that failed to demonstrate a difference between surgical techniques [5]. In this context, our results make a strong argument toward higher probability of receiving ischemia during robotic PN. There are several possible explanations for this finding, such as the absence of haptic feedback, risk of compromised visualization of the surgical field by excessive bleeding, and elevated skill needed by the entire surgical team. Taken together, it is possible that surgeons might be less confident to perform a clampless procedure during robotic PN.

Our findings give important insight into the relationship between surgical techniques, ischemia time, and AKI. In fact, we observed lower AKI rates in patients treated by minimally invasive techniques despite longer ischemia time, suggesting that acute damage and ischemia time might be partially independent. Indeed, the mechanisms determining AKI after PN is not fully understood [25]. Other factors such as the effect of pneumoperitoneum on renal blood flow, surgical manipulation, and suture/hemostatic techniques may affect early postoperative renal function and thus should be more carefully investigated in future research.

Our results showed similar trifecta rates between minimally invasive and open PN, in line with prior studies [10,12,14]. We also found that the probability of positive trifecta was not statistically different between robotic and laparoscopic PN. Extensive literature reported higher probability to achieve the trifecta for the robotic than the laparoscopic technique [9,26,27]. However, a different definition of the outcome [9] or the lack of nephrometry score stratification [27] may limit the comparison with the present study. Moreover, other aspects deserve further considerations. When we repeated the analyses according to baseline tumor complexity, patients with PADUA < 10 lesions treated robotically were more likely to achieve a positive trifecta than those receiving open PN. In addition, while our results were unaffected when we restricted the analyses to PADUA ≥ 10 masses, the comparison between robotic and laparoscopic PN suggests better perioperative outcomes for robotic PN in PADUA < 10 tumors. Other investigators noted similar results for the comparison between robotic and open surgeries [13]. Still, this is the first study assessing the likelihood of a positive trifecta according to tumor complexity between the three surgical techniques available for PN.

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Our findings have several limitations that reflect the observational nature of our study. Although we adjusted for clinical characteristics, we cannot completely rule out residual confounding by differences in case mix. Such confounding could have resulted from surgeons at different level of experience for each surgical technique. However, we included the annual caseload per center as a surrogate for surgical experience, assuming more experienced surgeons performed surgery mostly at high-volume institutions. The inclusion of such covariate may limit another source of confounding, that is, the trend toward more complex cases treated at tertiary care centers. Because the distribution of surgical techniques changed during the study period (ie, increasing use of robotics from 2013 to 2016), we also explored whether the year of surgery might affect surgical outcomes, with no significant associations. This could be related either to the short period of study or to more surgeons performing fewer surgeries, resulting in higher number of cases not necessarily performed by more experienced surgeons. Finally, although our models included the type of resection, this information was not reported through a standardized instrument such as the surface-intermediate-base score [28], resulting in possible inaccuracy across centers. We also acknowledge that the probability of being treated by partial rather than radical nephrectomy might be not independent from surgical approach for patients with several comorbidities or with highly complex T1 renal masses. In other words, a first attempt for PN in challenging cases may be more likely performed by open surgery, resulting in higher rate of PADUA $\geq$ 10 tumors in such group. This assumption may be taken to suggest that open surgery had lower probability of conversion to radical nephrectomy (ie, exclusion from the present study). However, independent evidence showed that the risk of conversion from partial to radical nephrectomy is approximately 5%, regardless of the surgical approach [29]. Thus, the limited number of patients who may have contributed to such bias and the inclusion of the nephrometry score and Charlson comorbidity index in our multivariable models make us confident that our results were not affected.

A final limitation is that our study did not include a cost analysis. Given the lack of EAU recommendations in favor of a specific surgical approach for PN, an increasing number of comparative studies investigated whether minimally invasive surgery might represent a new standard of surgical care. However, because prior evidence showed different economic implications according to operating technique [30], a fair comparison between surgical approaches should include their costs. The multi-institutional nature of our study may have limited the availability of such data. However, further research should address this issue.

Our results are of clear interest for clinical practice, suggesting that the robotic technique is a valid option for PN, especially for PADUA < 10 lesions. By contrast, we did not find differences between surgical techniques in more complex masses. If replicated, our results may have important implications for surgical practice in PADUA $\geq$ 10 tumors as they suggest that the impact of surgical technique on perioperative outcomes might be limited in such lesions.

Our findings also have implications for empirical research. The evidence suggesting that minimally invasive techniques allow for better perioperative outcomes is increasing. It is still unclear, though, which is the compelling indication for either a surgeon or an institution to switch from open to minimally invasive surgery and, more importantly, whether this might translate into better long-term outcomes. Therefore, future research should examine differences between surgical techniques at long-term follow-up concerning functional outcomes, cost effectiveness, and surgical learning. In this regard, recent evidence showed that surgical experience may influence perioperative outcomes in minimally invasive PN [31]. As such, a different relationship between such outcomes and surgical technique may be postulated for more or less experienced surgeons. We intend to examine these possibilities in future studies.

5. Conclusions

In PADUA < 10 renal tumors, robotic PN allows for higher rates of trifecta than open and laparoscopic techniques. The impact of surgical technique on perioperative outcomes might be limited in more complex lesions.

Author contributions: Andrea Minervini 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.
Study concept and design: Minervini, Carini, Ficarra, Capitanio.
Acquisition of data: Mari, Barale, Bove, di Maida, Fiori, Li Marzi, Schips, Siracusano, Trombetta.
Analysis and interpretation of data: Larcher, Bravi.
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Appendix A. Supplementary data

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