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Outcomes of Laparoscopic and Robotic Partial Nephrectomy for Large (>4 Cm) Kidney Tumors: Systematic Review and Meta-Analysis

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ABSTRACT

Purpose. The aim of this study was to assess the outcomes of minimally invasive (laparoscopic and robotic) partial nephrectomy (MIPN) for large renal masses.

Materials and Methods. A systematic literature review was performed up to September 2016 using multiple search engines to identify studies comparing MIPN for tumors larger than 4 cm (>cT1a) with MIPN for tumors smaller than 4 cm (cT1a). The preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria were used for article selection. Baseline demographics and surgical, functional, and oncological parameters were extracted from the included studies whenever available. An overall analysis including all studies was performed, then sensitivity analyses were performed for studies on laparoscopic partial nephrectomy (PN) only, and, finally, for studies on robotic PN only.

Results. Overall, 13 case-control studies comparing the outcomes of PN in tumors <4 cm ($n = 4441$) with those of PN for tumors >4 cm ($n = 1024$) were included. Warm ischemia time was shorter for the <4 cm group [weighted mean difference (WMD) 3.75 min; 95% confidence interval (CI) −6.4 to −0.7; $p = 0.01$] and the odds of perioperative complications was lower [odds ratio (OR) 0.62; 95% CI 0.5–0.8; $p < 0.001$]. There were no significant differences in terms of postoperative estimated glomerular filtration rate (WMD 4.2 ml/min; 95% CI 0.45–8.97; $p = 0.08$), as well as onset of postoperative chronic kidney disease (risk ratio 0.71; 95% CI 0.48–1.04; $p = 0.08$). In addition, no difference was found in the likelihood of positive surgical margins (OR 0.74; 95% CI 0.43–1.28; $p = 0.29$).

Conclusions. MIPN represents a viable treatment option for renal masses larger than 4 cm (higher than cT1a) as it offers good functional outcomes, without increased risk of positive surgical margins. An increased rate of complications should be taken into account when approaching these tumors.

Over the past few years, elective nephron-sparing surgery has been increasingly adopted for renal masses beyond the 'traditional' standard cut-off size of 4 cm (clinical stage T1a). The American Urological Association (AUA) guidelines suggest partial nephrectomy (PN) as alternative standard of care to radical nephrectomy for cT1b masses,[1] while the European Association of Urology (EAU) guidelines recommend PN, whenever technically feasible, for kidney tumors larger than 4 cm[2]. Open PN for

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these larger masses has represented the gold standard.[3–6] Adoption of laparoscopic PN was mostly in the setting of cT1a, and while high-volume centers reported on the feasibility of this approach for larger tumors,[1,7–10] concerns regarding prolonged ischemia times and higher risk of complications have hindered its adoption.[11] Recently, robotic-assisted laparoscopic kidney surgery has gained momentum, and indications of robot-assisted PN (RAPN) have been expanded to include larger kidney tumor.[12–14] Nonetheless, controversy continues as to the safety and efficacy of the application of minimally invasive (laparoscopic and robotic) PN for larger masses in comparison with smaller tumors.

We sought to perform a cumulative analysis of comparative studies examining perioperative outcomes of minimally invasive (laparoscopic and robotic) PN (MIPN) for large (>4 cm; >cT1a) versus small (cT1a) renal masses.

MATERIALS AND METHODS

Search Strategy, Inclusion Criteria, and Study Eligibility

A systematic literature review was performed up to September 2016 using multiple search engines (PubMed, Ovid, and Scopus) to identify pertinent studies. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) criteria were used for article selection (www.prisma-statement.org) (Fig. 1). The following types of studies were included: original studies comparing outcomes of laparoscopic or robotic PN for small (<4 cm) and larger (>4 cm) renal tumors. All titles were screened for manuscripts written in English, and were restricted to adult patients. Titles of articles were first reviewed to ascertain whether they might potentially fit the inclusion criteria. After assessing the abstract, a more thorough subsequent assessment was performed by looking at the full text. Studies not having primary data (i.e. reviews, commentaries, letters) were also excluded. References of included studies were manually reviewed to identify additional studies of interest.

Assessment of Study Quality

Level of evidence was rated for each study included in the meta-analysis,[15] and the quality of the study was determined using the Newcastle-Ottawa scale (NOS) for non-randomized controlled trials.[16] A total score of 5 or less was considered low quality, 6–7 was considered intermediate quality, and 8–9 was considered high quality.

Data Analysis

Baseline demographics and clinical disease characteristics [age, tumor size, baseline estimated glomerular

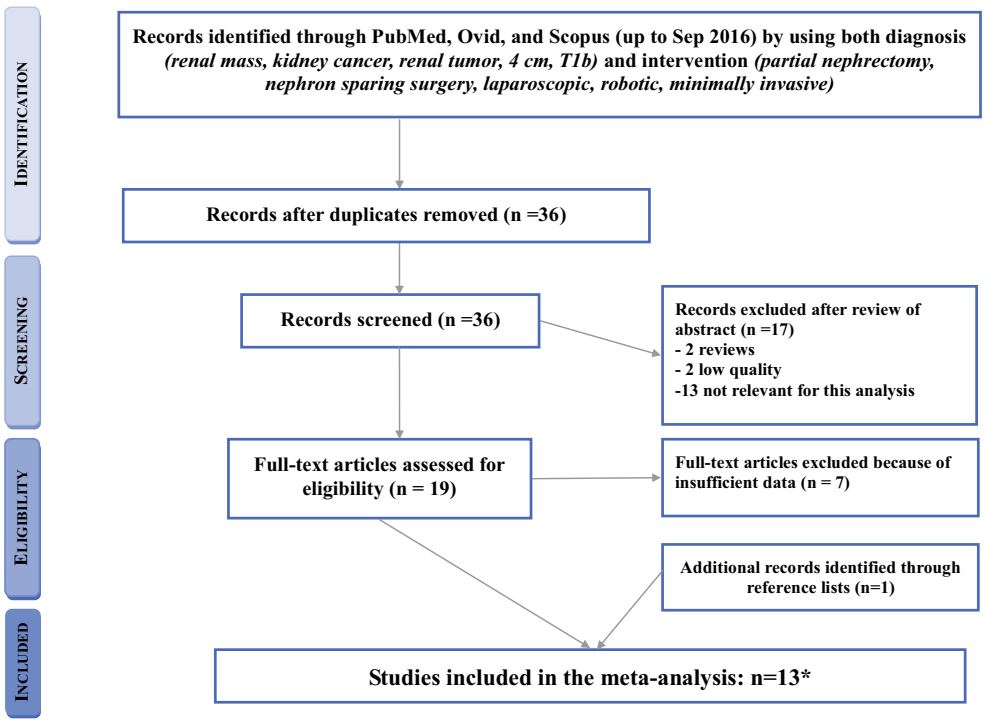

FIG. 1 PRISMA flow diagram. *PRISMA* Preferred reporting items for systematic reviews and meta-analyses

filtration rate (eGFR), baseline chronic kidney disease (CKD), rate of solitary kidneys, RENAL nephrometry score[17] or tumor location and tumor histology], surgical [operative time, warm ischemia time, estimated blood loss (EBL), rate of perioperative complications, length of hospital stay], functional (postoperative renal function, postoperative onset of CKD, decline in eGFR), and oncological (positive margin rate) outcome parameters were extracted whenever available. An overall analysis including all studies was initially performed, then sensitivity analyses were conducted including only studies on laparoscopic PN,[7–10,18,19] and, finally, only studies on robotic PN.[12–14,20–22] One study where both techniques were reported together was not used for this sensitivity analysis.[23]

For continuous outcomes, the weighted mean difference (WMD) was used as a summary measure, whereas for binary variables, odds ratio (OR) or risk ratio (RR) were calculated with reporting of 95% confidence intervals (CIs). RR was preferred in cases of a high number of events to avoid overestimation. As only means and standard deviations are permitted for the computational portion of meta-analyses, for those studies reporting medians and ranges, a validated mathematical model was used to convert medians (ranges) to means (standard deviations). Pooled estimates were calculated using the fixed-effect model, if no significant heterogeneity was identified. Alternatively, the random-effect model was used when significant heterogeneity was detected. All statistical analyses were performed using Review Manager 5 (Cochrane Collaboration, Oxford, UK).

RESULTS

Overall, 13 case-control studies comparing the outcomes of PN in tumors <4 cm (n = 4441) with those of PN for tumors >4 cm (n = 1024) were included (Table 1). In six studies, standard laparoscopy was used,[7–10,18,19] while robot-assisted laparoscopy[12–14,20–22] was used in another six studies [including one on robotic laparoendoscopic single-site (LESS) surgery,[21] and, in one study, laparoscopic and robotic procedures were analyzed together.[23]

Overall Outcome Analysis (Laparoscopic + Robotic Partial Nephrectomy PN])

There was no difference between groups in terms of age ($p = 0.79$), baseline eGFR (WMD 0.59 ml/min; 95% CI −7.7 to 8.9; $p = 0.89$), and proportion of solitary kidneys ($p = 0.92$). Furthermore, there was no significant difference in terms of the proportion of tumors with malignant histology (63.9% for the <4 cm group vs. 68.4% for the >4 cm group; $p = 0.72$).

Both operative time (WMD 15.8 min; 95% CI −24.1 to −7.4; $p < 0.001$) and warm ischemia time (WMD 3.75 min; 95% CI −6.4 to −0.7; $p = 0.01$) were shorter in the < 4 cm group, while EBL (WMD −56.9 ml; 95% CI −74.5 to −39.4; $p < 0.001$) and risk of perioperative

TABLE 1 Minimally invasive (laparoscopic and robotic) partial nephrectomy for tumors larger than 4 cm: overview of the 13 studies included in the meta-analysis

Reference	Study period	Study design	Study setting	Study origin	N of cases (<4/≥4 cm)	Surgical technique	Study quality[a]	Level of evidence[b]
Simmons[7]	1999–05	Prospective non-randomized	Single center	US	367/58	Lap	8	IIb
Rais-Bahrami[8]	2000–05	Retrospective	Single center	US	274/34		7	III
Lifshitz[18]	ns	Prospective non-randomized	Single center	US	149/35		8	IIb
Porpiglia[19]	2005–09	Prospective non-randomized	Single center	Italy	67/33		8	IIb
Nouralizadeh[9]	2003–08	Retrospective	Single center	Iran	32/28		7	III
Eng[10]	2002–07	Retrospective	Single center	US	76/26		7	III
Papalia[23]	2010–11	Prospective non-randomized	Single center	Italy	78/43	Lap/Robotic	8	IIb
Petros[20]	2006–10	Retrospective	Multicenter	US	362/83	Robotic	8	III
Ficarra[13]	2008–10	Retrospective	Multicenter	Belgium, Italy, US	298/49		7	III
Tiu[21][c]	2009–11	Retrospective	Multicenter	Korea, US	47/20		7	III
Patel[22]	2007–09	Retrospective	Single center	US	56/15		7	III
Kim[14]	2006–15	Retrospective matched pair analysis	Single center	Korea	60/60		8	IIb
Janda[12]	2008–14	Retrospective	Single center	US	168/64		8	III

ns not specified

[a] According to Newcastle Ottawa scale;

[b] According to Oxford Centre for Evidence-based Medicine

[c] robotic LESS

complications (OR 0.62;3 95% CI 0.5–0.8; $p < 0.001$) were lower in this same group (Fig. 2). Hospital stay was also shorter in the <4 cm group (WMD −0.39 days; 95% CI −0.53 to −0.26; $p < 0.001$). There was no significant difference in terms of postoperative eGFR (WMD 4.2 ml/min; 95% CI 0.45–8.97; $p = 0.08$), as well as onset of postoperative CKD (RR 0.71; 95% CI 0.48–1.04; $p = 0.08$). Positive surgical margin rates were 2.1 and 3.5% for the <4 cm and >4 cm groups, respectively, with no difference in the likelihood of positive surgical margins (OR 0.74; 95% CI 0.43–1.28; $p = 0.29$).

Sensitivity Analysis (Laparoscopic PN Only)

There was no difference between groups in terms of age (WMD 0.49; 95% CI −3.2 to 4.2; $p = 0.8$), baseline eGFR (WMD −1.7 ml/min; 95% CI −14.5 to −11.1; $p = 0.80$), and proportion of solitary kidneys ($p = 0.45$). Furthermore, there was no difference in terms of frequency of malignant histology between the groups (73.6% for the <4 cm group vs. 67.2% for the >4 cm group; $p = 0.5$). Tumors were more frequently located at the lower pole in the >4 cm group (31.3% for the <4 cm group vs. 45.5% for the >4 cm group; $p = 0.002$).

Operative time was shorter for the <4 cm group, but without reaching a significant statistical difference (WMD −10.9 min; 95% CI −23.8 to −1.8; $p = 0.09$). In addition, no difference was observed for warm ischemia time (WMD 1.92 min; 95% CI −6.9 to 3.1; $p = 0.46$). EBL was lower for the <4 cm tumor group (WMD −72.2 ml; 95% CI −87.9 to −57.5; $p < 0.001$), as was the risk of perioperative complications (OR 0.70; 95% CI 0.5–0.98; $p = 0.04$) [Fig. 3]. Hospital stay was similar (WMD −0.2 days; 95% CI −0.5 to 0.13; $p = 0.24$). There was no significant difference in terms of postoperative eGFR (WMD 3.2 ml/min; 95% CI −1.7 to 8.3; $p = 0.20$), as well as onset of postoperative CKD (RR 0.7; 95% CI 0.4–1.1; $p = 0.16$). Positive surgical margin rates were 1.2 and 3.2% for the <4 and >4 cm groups, respectively, and no difference was noted in the likelihood of positive surgical margins (OR 0.53; 95% CI 0.21–1.33; $p = 0.18$).

Sensitivity Analysis (Robotic PN Only)

There was no difference between groups in terms of age (WMD −0.03, 95% CI −2.8 to 2.8; $p = 0.98$), baseline eGFR (WMD −3.1 ml/min; 95% CI −6.5 to −12.8; $p = 0.52$), and frequency of malignant histology (55% for the <4 cm group vs. 67% for the >4 cm group; $p = 0.84$). The < 4 cm group presented a lower nephrometry score (WMD −1.4; 95% CI −1.6 to −1.2; $p < 0.001$).

Operative time (WMD −23.8 min; 95% CI −32.6 to −14.9; $p < 0.001$) and warm ischemia time (WMD −5.05 min; 95% CI −6.5 to 3.6; $p < 0.001$) were significantly shorter for the < 4 cm group, as it. EBL (WMD −52.7 ml; 95% CI −78.3 to −27.1; $p < 0.001$) and risk of complications (OR 0.61; 95% CI 0.43–0.87; $p = 0.007$) were lower for the <4 cm group (Fig. 4). The <4 cm group also had shorter hospital stay (WMD −0.45 days; 95% CI −0.6 to 0.3; $p < 0.001$). Positive surgical margin rates were 2.9 and 3.7% for the <4 and >4 cm groups, respectively, and no difference was found in the likelihood of positive surgical margins (OR 0.92; 95% CI 0.45–1.88; $p = 0.82$).

DISCUSSION

Herein, we report the first cumulative analysis of studies comparing the outcomes of MIPN for masses on the basis of tumor size (<4 cm vs. >4 cm), providing level 2a evidence on this topic. Overall, 13 studies including over 5000 cases were analyzed and significant conclusions can be drawn on the current and evolving role of MIPN in the setting of larger renal masses, where the established gold standard has been open PN.[13]

With respect to surgical outcomes, warm ischemia time was shorter for the <4 cm group (a 4-min difference), which is an expected finding as the resection and renorrhaphy times for a larger tumor would be expected to be longer. However, this difference also has limited clinical significance as the concept that 'every minute counts' has been questioned.[24,25] Recent evidence shows that using a dichotomous cut-off (25 or 30 min) for the 'optimal' ischemia time is unreliable, and quality and quantity of preserved renal parenchyma are more important predictors of ultimate renal function after PN.[24,26]

The risk of perioperative complications was lower for MIPN overall in the <4 cm group (OR 0.62; $p < 0.001$), and this was also the case when looking at subanalyses focusing on laparoscopic series and robotic series only. This finding has been consistently reported in the past for open series.[27] For laparoscopy, Porpiglia et al. noted a significant correlation between the central growth pattern of the mass and the risk of complications. Their complication rate was 4.5% for masses <4 cm versus 15% for those >4 cm.[19] Even higher rates were later reported by Lifshitz et al. for laparoscopic PN (12% for cT1a and 25.7% for cT1b).[18] In the field of robotic PN, Patel et al. also reported a higher complication rate for larger tumors (26.6 vs. 8.9%);[22] however, this finding was not confirmed by the multicenter study by Petros et al., the largest comparative series reported to date (445 patients, 83 with a tumor >4 cm), where no increased risk of adverse outcomes was recorded.[20] On the other hand, in another large multicenter series including 49 patients, Ficarra et al.

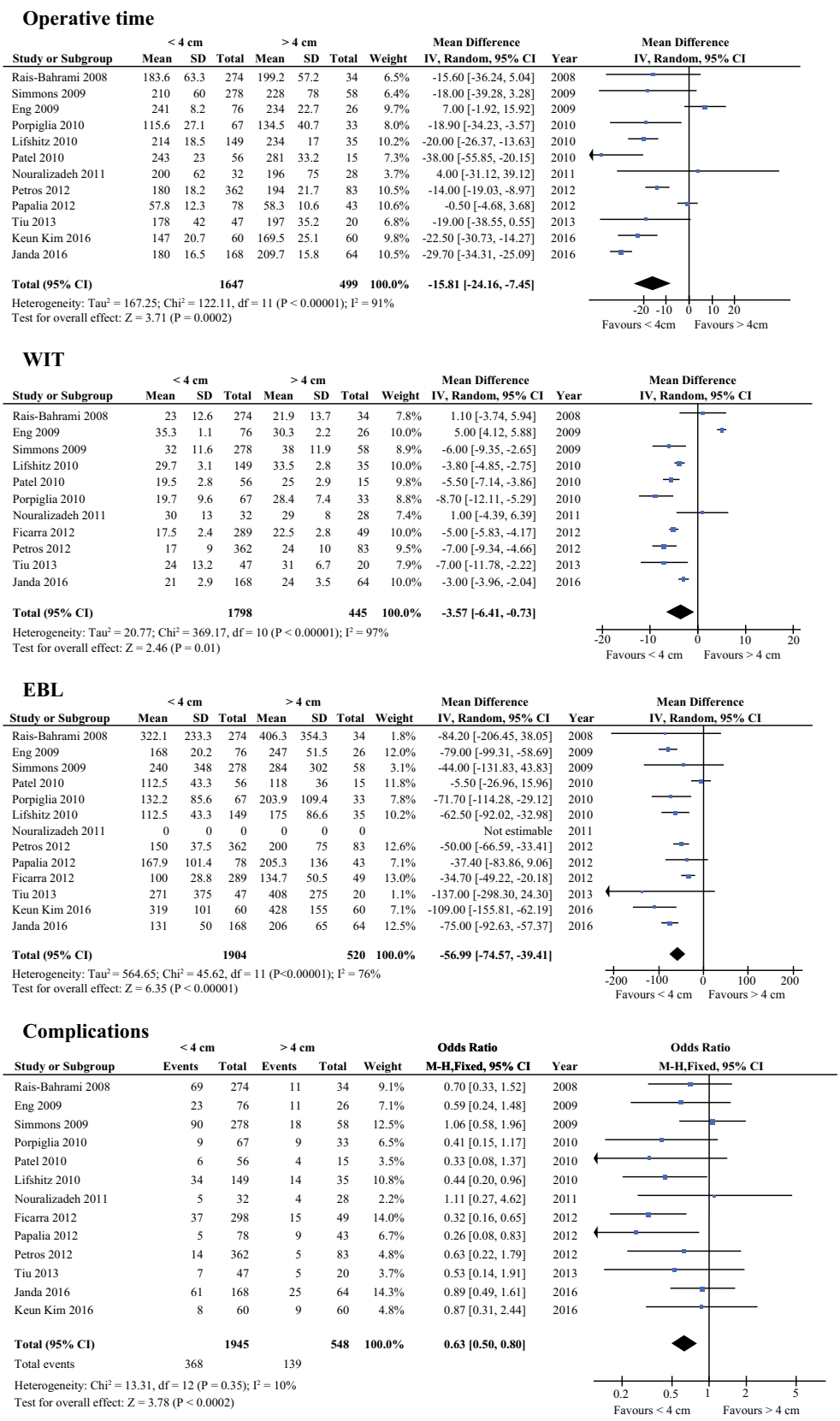

FIG. 2 Forest plots for relevant outcomes analysis (overall). *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of freedom, *WIT* warm ischemia time, *EBL* estimated blood loss, *M-H* Mantel-Haenszel

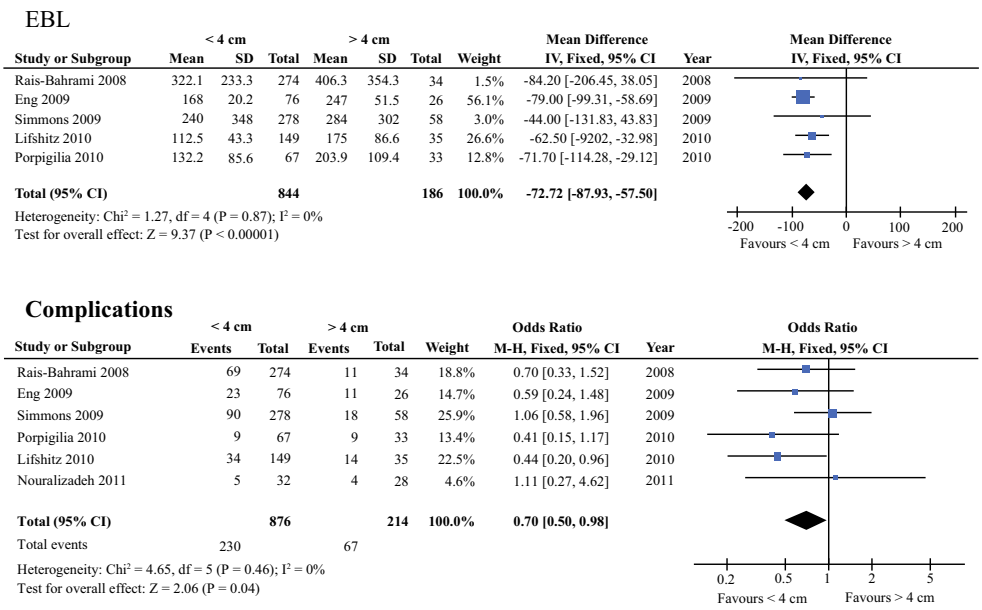

FIG. 3 Forest plots for relevant outcomes (sensitivity analysis for laparoscopic series only). *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of freedom, *EBL* estimated blood loss, *M-H* Mantel-Haenszel

reported a higher rate of postoperative complications for larger masses (26.5%) compared with smaller masses (9.4%).[13] Tiu et al. evaluated the comparative outcomes of robotic LESS PN and, despite longer ischemia time, did not detect differences in terms of adverse events when comparing tumors <4 cm (47 patients) with tumors >4 cm (20 patients).[21] This finding could be explained by the more selected patient population (lower tumor size and lower body mass index).

PN yields superior renal functional outcomes, as demonstrated by European Organisation for Research and Treatment of Cancer (EORTC) data recently published by Scosyrev et al.[28], and also by several robust analyses of national and large institutional databases.[29] Mir et al. recently reported a systematic review and meta-analysis looking at the outcomes of PN versus radical nephrectomy for larger renal masses. The authors found PN to be associated with better postoperative renal function, as shown by higher postoperative eGFR, lower likelihood of postoperative onset of CKD, and lower decline in eGFR.[30] In our analysis, there were no significant differences in terms of postoperative eGFR (WMD 4.2 mL/min; $p = 0.08$) and onset of CKD (RR 0.71; $p = 0.08$) for tumors <4 cm and >4 cm.

In their multicenter series of 730 elective open PNs, Patard et al. did not find differences in positive surgical margins, local or distance recurrences, and overall or cancer-specific deaths between tumors larger and smaller than 4 cm.[27] This was also confirmed in the series of 618 elective open PNs reported by Pahernik et al., who showed no difference for cancer-specific survival and local recurrence-free survival at 5 and 10 years.[31] In our study, we could not look at more consolidated oncological endpoints, and the analysis was necessarily limited to the surrogate endpoint of positive surgical margin rate. Overall, we did not find a significant difference between the study groups (2.1 vs. 3.5% for tumors <4 and >4 cm, respectively; $p = 0.29$); this was also the case when separately looking at laparoscopic or robotic series. The role of surgical margins in the natural history of kidney cancer is still debated. In a systematic review of 69 studies, Marszalek et al. reported a rate of positive surgical margins after open PN of 0–7%, 0.7–4% after laparoscopic PN, and 3.9–5.7% after RAPN.[32] Although a relatively short mean follow-up (41 months) was observed, patients with positive surgical margins did not demonstrate local or distant tumor recurrence. Similar conclusions were reported by Bensalah et al. in another multicenter study.[33] More recent data suggested that the finding of a positive margin may have more impact than previously thought. Khalifeh et al. reported a large multi-institutional analysis of 943 RAPNs with a 2.2% positive margin rate, and found that a positive surgical margin was associated with an 18.4-fold higher hazard ratio (HR) for recurrence when adjusted for other variables.[34] In another multicenter analysis of 1240 patients, Shah et al. found that a positive surgical margin was significantly associated with a higher risk of recurrence (HR 7.48) in cases considered high-risk disease (higher pathologic stage and grade).[35] The likely explanation for the re-emergence of the clinical impact of a positive margin in more recent reports is attributable to tumors of higher oncological risk (size and complexity) undergoing PN. In light of these recent findings, it is reassuring to see from our analysis that the adoption of a minimally invasive approach for these larger masses (that are more likely to present worse pathological features) does not translate into

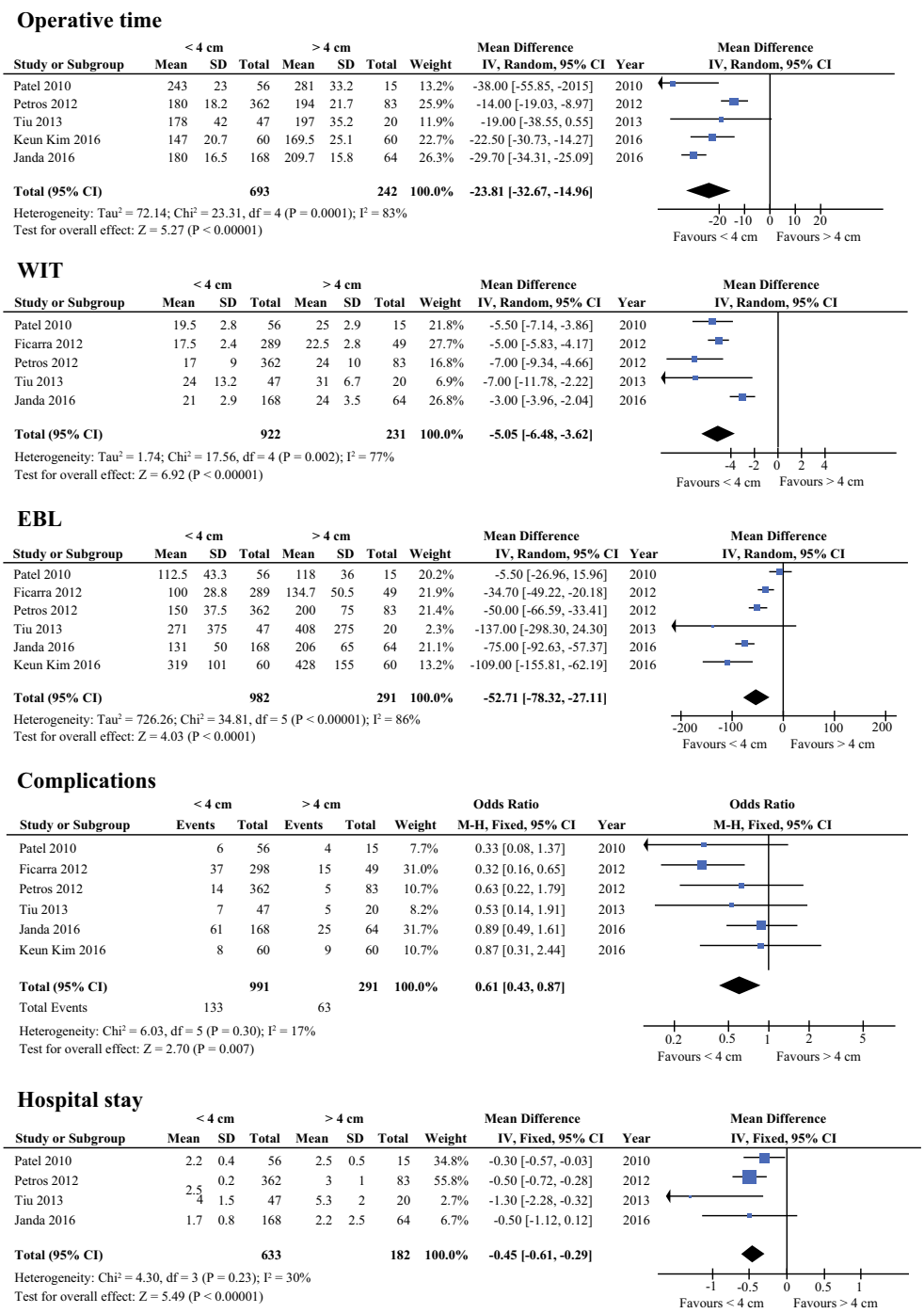

FIG. 4 Forest plots for relevant outcomes (sensitivity analysis for robotic partial nephrectomy series only). *SD* standard deviation, *IV* inverse variance, *CI* confidence interval, *df* degrees of freedom, *WIT* warm ischemia time, *EBL* estimated blood loss, *M-H* Mantel-Haenszel

a higher risk of local recurrence or systemic progression in this higher-risk cohort of patients (>4 cm tumor size).

Our study is not devoid of limitations. Meta-analyses represent a robust statistical tool, but they certainly carry intrinsic biases.[36] Moreover, randomized controlled trials should ideally be included to obtain the highest level of evidence. In our analysis, most of the studies were either retrospective or prospective, non-randomized. Second, we could not take into account differences in terms of surgical technique that might exist among the centers. In this respect, it should be pointed out that available studies come from high-volume institutions with high surgical expertise, and therefore these same findings might not apply in different hospital settings. Our analysis was equally distributed between laparoscopic and robotic PN. It was beyond the scope of this analysis to 'directly' compare the two techniques as the lack of tumor complexity data for the laparoscopic series did not allow for controlling for this

impactful variable.[37] Unquestionably, the landscape of PN has witnessed a paradigm shift over the last decade with the increasing adoption of robot-assisted laparoscopy.[38] Finally, it was interesting to note that a similar rate of benign/malignant masses were found in the two groups (<4 and >4 cm). In a recent cumulative from Fox Chase Cancer Center (on 26 studies including over 27,000 cases), the frequency of benign tumors in surgically resected kidney masses ranged from 7 to 33%, and an inverse relationship between tumor size and benign pathologic features was reported.[39] Thus, we would have expected a higher rate of benign pathology in the smaller (<4 cm) tumor group. We can speculate that section bias might account for this similar rate of benign histology between the two groups. In addition, limited use of renal biopsy might have led to a more likely surgical resection of these kidney masses.

CONCLUSIONS

MIPN represents a viable treatment option for these renal masses (larger than 4 cm, higher than clinical stage T1a) as it offers good functional outcomes and no increased risk of positive surgical margin. An increased risk of complications should be taken into account when approaching these tumors, and this information should be considered for patient counseling. Overall, we recommend the use of MIPN for these tumors in centers where there is appropriate surgical expertise in minimally invasive techniques.

REFERENCES

1. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. *J Urol.* 2009;182(4):1271–9.
2. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol.* 2015;67(5):913–24.
3. Patard JJ, Shvarts O, Lam JS, Pantuck AJ, Kim HL, Ficarra V, et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol.* 2004;171(6 Pt 1):2181–5; quiz 435.
4. Leibovich BC, Blute M, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol.* 2004;171(3):1066–70.
5. Antonelli A, Ficarra V, Bertini R, Carini M, Carmignani G, Corti S, et al. Elective partial nephrectomy is equivalent to radical nephrectomy in patients with clinical T1 renal cell carcinoma: results of a retrospective, comparative, multi-institutional study. *BJU Int.* 2012;109(7):1013–8.
6. Kopp RP, Mehrazin R, Palazzi KL, Liss MA, Jabaji R, Mirheydar HS, et al. Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by R.E.N.A.L. nephrometry score. *BJU Int.* 2014;114(5):708–18.
7. Simmons MN, Chung BI, Gill IS. Perioperative efficacy of laparoscopic partial nephrectomy for tumors larger than 4 cm. *Eur Urol.* 2009;55(1):199–207.
8. Rais-Bahrami S, Romero FR, Lima GC, Kohanim S, Permpongkosol S, Trock BJ, et al. Elective laparoscopic partial nephrectomy in patients with tumors > 4 cm. *Urology.* 2008;72(3):580–3.
9. Nouralizadeh A, Simforoosh N, Tabibi A, Basiri A, Ziaee SA, Soleimani M, et al. Laparoscopic partial nephrectomy for tumours > 4 cm compared with smaller tumours: perioperative results. *Int Urol Nephrol.* 2011;43(2):371–6.
10. Eng MK, Bernstein AJ, Katz MH, Shikanov S, Zorn KC, Shalhav AL. Impact of renal lesion size on perioperative and pathologic outcomes in patients undergoing laparoscopic partial nephrectomy. *J Endourol.* 2009;23(3):439–43.
11. Gill IS, Kavoussi LR, Lane BR, Blute ML, Babineau D, Colombo JR Jr, et al. Comparison of 1,800 laparoscopic and open partial nephrectomies for single renal tumors. *J Urol.* 2007;178(1):41–6.
12. Janda G, Deal A, Yang H, Nielsen M, Smith A, Pruthi RS, et al. Single-institution experience with robotic partial nephrectomy for renal masses greater than 4 cm. *J Endourol.* 2016;30(4):384–9.
13. Ficarra V, Bhayani S, Porter J, Buffi N, Lee R, Cestari A, et al. Robot-assisted partial nephrectomy for renal tumors larger than 4 cm: results of a multicenter, international series. *World J Urol.* 2012;30(5):665–70.
14. Kim DK, Kim LH, Raheem AA, Shin TY, Alabdulaali I, Yoon YE, et al. Comparison of trifecta and pentafecta outcomes between T1a and T1b renal masses following robot-assisted partial nephrectomy (RAPN) with minimum one year follow up: can RAPN for T1b renal masses be feasible? *PloS One.* 2016;11(3):e0151738.
15. Centre for Evidence-Based Medicine. Explanation of the 2011 OCEBM Levels of Evidence. Available at: http://www.cebm.net/explanation-2011-ocebm-levels-evidence/
16. The Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
17. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol.* 2009;182(3):844–53.
18. Lifshitz DA, Shikanov SA, Deklaj T, Katz MH, Zorn KC, Shalhav AL. Laparoscopic partial nephrectomy for tumors larger than 4 cm: a comparative study. *J Endourol.* 2010;24(1):49–55.
19. Porpiglia F, Fiori C, Bertolo R, Scarpa RM. Does tumour size really affect the safety of laparoscopic partial nephrectomy? *BJU Int.* 2011;108(2):268–73.
20. Petros F, Sukumar S, Haber GP, Dulabon L, Bhayani S, Stifelman M, et al. Multi-institutional analysis of robot-assisted partial nephrectomy for renal tumors > 4 cm versus </= 4 cm in 445 consecutive patients. *J Endourol.* 2012;26(6):642–6.
21. Tiu A, Kim KH, Shin TY, Han WK, Han SW, Rha KH. Feasibility of robotic laparoendoscopic single-site partial nephrectomy for renal tumors > 4 cm. *Eur Urol.* 2013;63(5):941–6.
22. Patel MN, Krane LS, Bhandari A, Laungani RG, Shrivastava A, Siddiqui SA, et al. Robotic partial nephrectomy for renal tumors larger than 4 cm. *Eur Urol.* 2010;57(2):310–6.
23. Papalia R, Simone G, Ferriero M, Guaglianone S, Costantini M, Giannarelli D, et al. Laparoscopic and robotic partial nephrectomy without renal ischaemia for tumours larger than 4 cm: perioperative and functional outcomes. *World J Urol.* 2012;30(5):671–6.
24. Mir MC, Pavan N, Parekh DJ. Current paradigm for ischemia in kidney surgery. *J Urol.* 2016;195(6):1655–63.
25. Parekh DJ, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, et al. Tolerance of the human kidney to isolated controlled ischemia. *J Am Soc Nephrol.* 2013;24(3):506–17.
26. Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F, et al. Renal ischemia and function after partial nephrectomy: a

collaborative review of the literature. *Eur Urol.* 2015; 68(1):61–74.
27. Patard JJ, Pantuck AJ, Crepel M, Lam JS, Bellec L, Albouy B, et al. Morbidity and clinical outcome of nephron-sparing surgery in relation to tumour size and indication. *Eur Urol.* 2007;52(1):148–54.
28. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *Eur Urol.* 2014;65(2):372–7.
29. Sun M, Bianchi M, Hansen J, Trinh QD, Abdollah F, Tian Z, et al. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol.* 2012;62(4):696–703.
30. Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. *Eur Urol.* 2017;71(4):606–617.
31. Pahernik S, Roos F, Rohrig B, Wiesner C, Thuroff JW. Elective nephron sparing surgery for renal cell carcinoma larger than 4 cm. *J Urol.* 2008;179(1):71–4; discussion 4.
32. Marszalek M, Carini M, Chlosta P, Jeschke K, Kirkali Z, Knuchel R, et al. Positive surgical margins after nephron-sparing surgery. *Eur Urol.* 2012;61(4):757–63.
33. Bensalah K, Pantuck AJ, Rioux-Leclercq N, Thuret R, Montorsi F, Karakiewicz PI, et al. Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. *Eur Urol.* 2010;57(3):466–71.
34. Khalifeh A, Kaouk JH, Bhayani S, Rogers C, Stifelman M, Tanagho YS, et al. Positive surgical margins in robot-assisted partial nephrectomy: a multi-institutional analysis of oncologic outcomes (leave no tumor behind). *J Urol.* 2013;190(5):1674–9.
35. Shah PH, Moreira DM, Okhunov Z, Patel VR, Chopra S, Razmaria AA, et al. Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. *J Urol.* 2016;196(2):327–34.
36. Zwahlen M, Renehan A, Egger M. Meta-analysis in medical research: potentials and limitations. *Urol Oncol.* 2008;26(3):320–9.
37. Schiavina R, Novara G, Borghesi M, Ficarra V, Ahlawat R, Moon DA, et al. PADUA and R.E.N.A.L. nephrometry scores correlate with perioperative outcomes of robot-assisted partial nephrectomy: analysis of the Vattikuti Global Quality Initiative in Robotic Urologic Surgery (GQI-RUS) database. *BJU Int.* 2017;119(3):456–463.
38. Patel HD, Mullins JK, Pierorazio PM, Jayram G, Cohen JE, Matlaga BR, et al. Trends in renal surgery: robotic technology is associated with increased use of partial nephrectomy. *J Urol.* 2013;189(4):1229–35.
39. Corcoran AT, Russo P, Lowrance WT, Asnis-Alibozek A, Libertino JA, Pryma DA, et al. A review of contemporary data on surgically resected renal masses: benign or malignant? *Urology.* 2013;81(4):707–13.