WHICH PATIENTS WITH CLINICAL LOCALIZED RENAL MASS WOULD ACHIEVE THE TRIFECTA AFTER PARTIAL NEPHRECTOMY? THE IMPACT OF SURGICAL TECHNIQUE.

Running head: Impact of surgical technique on the trifecta's achievement after partial nephrectomy

Lorenzo Bianchi[1-2], Riccardo Schiavina[1-2], Marco Borghesi[1-2], Francesco Chessa[1-2], Carlo Casablanca[1], Andrea Angiolini[1], Amelio Ercolino[1], Cristian Vincenzo Pultrone[1-2], Federico Mineo Bianchi[1], Umberto Barbaresi[1], Pietro Piazza[1], Fabio Manferrari[1-2], Alessandro Bertaccini[1-2], Michelangelo Fiorentino[3], Matteo Ferro[4], Angelo Porreca[5], Emanuela Marcelli[2-6], Eugenio Brunocilla[1-2]

[1] *Department of Urology, S.Orsola-Malpighi University Hospital, University of Bologna, Italy*

[2] *Department of Specialistic, Diagnostic and Sperimental Medicine (DIMES), University of Bologna, Italy*

[3] *Laboratory of Oncologic Molecular Pathology, S.Orsola-Malpighi Teaching Hospital, University of Bologna, Italy*

[4] *Istituto europeo di Urologia, Milano, Italy*

[5]*Department of Urology, Abano Terme Hospital, Padua, Italy.*

[6] *Laboratory of Bioengineering, Department of Experimental Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy.*

*** Corresponding author:**

Lorenzo Bianchi, MD

Department of Urology, S.Orsola-Malpighi University Hospital, University of Bologna, Italy S. Orsola-Malpighi Hospital, Bologna, Italy

Tel: +39 051 6362747

Fax: +39 0516362535

Email: lorenzo.bianchi3@gmail.com

Word count: 3188; Abstract word count: 253; Tables: 3; Supplementary Tables: 2; Figures: 4; References: 40; Pages: 20

ABSTRACT

BACKGROUND: To develop a clinical nomogram aimed to predict the achievement of trifecta in patients treated with open, laparoscopic and robotic partial nephrectomy (PN) for localized renal masses (<cT2).

METHODS: We retrospectively evaluated 482 consecutive patients who underwent PN with open (OPN: 243), laparoscopic (LPN: 156) and robotic (RAPN: 83) approach for T1 renal mass at single tertiary center. Trifecta was defined as follows: warm ischemia time (WIT) <20 min and no positive surgical margins (PSM) and no postoperative complications. First, we compared clinical, pathologic and perioperative outcomes within the three surgical approaches. Second, multivariable logistic regression was performed to identify the independent predictors of the trifecta's achievement. Finally, regression-based coefficients were used to develop a nomogram predicting the likelihood to achieve the trifecta and 200 bootstrap resamples were used for internal validation.

RESULTS: The three cohorts were comparable in terms of demographics and clinical characteristics. Trifecta has been achieved in 49%, 50.6% and 69.9% of patients undergoing OPN, LPN and RAPN, respectively (p=0.003). At multivariable analyses, American Anesthesiologists Score (ASA) score 3-4 (Odd Ratio [OR]: 0.63; p=0.02), urinary collecting system (UCS) involvement (OR 0.56; p=0.02) and surgical approach (LPN and OPN vs. RAPN: OR: 0.39 and 0.38, respectively; p=0.001) were independent predictors of trifecta's achievement. A nomogram based on covariates included in the multivariable model demonstrated bootstrap-corrected predictive accuracy of 63%.

CONCLUSIONS: ASA score, UCS involvement and the surgical technique were independent predictors of trifecta outcome. Our nomogram could facilitate the preoperative counselling and to choose the best surgical approach for PN.

Keywords: renal cancer; partial nephrectomy; surgical approach; trifecta's achievement; nomogram

INTRODUCTION

The advance in imaging technologies lead to a significant stage migration in renal cell carcinoma (RCC) and consequent increasing diagnosis of organ confided renal tumour[1,2]. Thus, nephron sparing surgery (NSS) had gained increasing enthusiasm[3]. In fact, nowadays partial nephrectomy (PN) is considered the surgical treatment of choice for clinical T1 tumours[4], due to comparable oncological outcomes[5] combined with better preservation of renal function and lower rate of long-term cardiovascular events compared to radical nephrectomy (RN)[6]. However, NSS is technically more challenging since the need to dissect the renal hilum for vascular control and to suture the renal defect may increase the risk of complications. As consequence, the diffusion of minim invasive surgical techniques, including both standard laparoscopic and robotic approaches[7], allowed to improve surgical outcomes of PN even in complex cases, allowing to expand the indication for NSS[8]. However, surgical outcomes are related to many factors, including surgical factors (i.e surgical approach) and host factors (i.e. patient's characteristics and tumour's characteristics)[9]. Concerning tumour's characteristics, many authors proposed to classify renal masses by considering clinical size and anatomic features of the tumour to predict the risk of postoperative complications (including the most popular renal classifications scores as PADUA[10] and R.E.N.A.L. scores[11]). However, it's still debated whenever renal scoring systems could suggest the ideal surgical approach in each case. A part complication-free recovery, ideal surgical outcomes of NSS should comprehend negative surgical margins and maximal functional preservation: the simultaneous achievement of all three goals has been defined as trifecta outcomes[12]. Through years, many definitions of trifecta have been proposed for PN by combining different outcomes: surgery-related vs. overall postoperative complication-free state, warm ischemia time (WIT) <25 min[13] vs. <20 min[14], post-operative estimated glomerular filtration (eGRF) rate decrease <15%[15] vs. <10%[16]. We used the definition of trifecta proposed by Arora et al.[14] (negative surgical margins, no postoperative complications and WIT<20min), since it reflects both not modifiable parameters (tumour-related and patient-related) and modifiable parameter (surgery-related) offering a comprehensive picture of surgical outcomes for PN.

The aim of this study was to evaluate the impact of surgical technique on surgical outcomes of PN and to develop a model aimed to predict the achievement of trifecta in patients treated with open, laparoscopic and robotic PN.

MATERIAL AND METHODS

Study population

Patients with clinical localized renal mass (cT1 a and cT1b) treated with PN between 2006 and 2017 at single tertiary center were identified (n=644). Before surgery all patients were investigated with abdominal and chest contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) to define the clinical stage and anatomical characteristics of the tumor. No patients included in our study had preoperative evidence of distant metastases. In order to evaluate the impact of clinical and radiological characteristics on surgical outcomes, our analyses included exclusively individuals with available images from preoperative imaging (abdominal CT or MRI) to retrospectively review each radiologic parameter included in PADUA and RENAL scores, complete clinical, surgical and pathologic data. This resulted in a final population of 482 patients (75%).

Surgical approaches to PN include open PN (OPN, n=243), laparoscopic PN (LPN, n=156) and robot-assisted PN (RAPN, n=83), performed by surgeons with extensive experience in each surgical technique. OPN was performed though a retroperitoneal flank incision between the XI and XII ribs, as previously described[17]. In some cases, the tip of the XII rib was removed. In 18 (7.4%) cases of OPN, a transperitoneal approach was used with midline or subcostal incision due to concomitant abdominal surgery. LPN and RAPN were performed with transperitoneal approach as previously described[18,19,20]. LPN was performed using three 12 mm trocars and one 5 mm trocar. RARP was performed using DaVinci Xi platform with four arm and the Airseal system. In case of posterior tumor, 32 (20.5%) and 14 (16.9%) patients were referred to retroperitoneal LPN and RAPN[17], respectively. In case of clamping approach to the renal hilum we adopted warm ischemia: a selective or super-selective clamping approach was performed whenever feasible.

Covariates

All patients had complete reports concerning age at surgery, body mass index (BMI), American Society of Anaesthesiologists (ASA) score, clinical size of the renal mass and clinical stage of disease according to TNM, preoperative creatinine levels and eGFR, anatomical tumour parameters according to PADUA and R.E.N.A.L. classifications, WIT, need of UCS suture, pathological results, transfusion rate, intraoperative and postoperative complications.

Complication reports

Intraoperative and postoperative complications were reported. At 3 months follow-up postoperative complications (defined as any postoperative event altering the normal postoperative course and/or delaying discharge), were classified according to the Dindo modification of the Clavien system[21]. Then, postoperative complications were classified as minor (grade I–II) or major (grade ≥III). Moreover, postoperative complications were categorized in medical and surgical complications. Medical complications include: cardiac, deep vein thrombosis and/or pulmonary embolism, neurologic, pulmonary, infection, sepsis and acute renal injury (AKI, defined as a greater than 50% increase in postoperative serum creatinine compared to baseline)[22]. Surgical complications include renal haemorrhage (bleeding from the kidney requiring blood transfusion or surgical or radiological intervention), urine leak (requiring urine drainage or surgical or radiological intervention) and surgical site infection.

Pathological evaluation

All surgical specimens were processed by a dedicated uropathology's team at our institution.

Tumours were restaged according to the 2010 American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification[23]. Tumour's histology was reported according to the World Health Organization classification[24]. Tumour's grade was assessed according to the Fuhrman system. Positive surgical margins were defined as cancer cells at the level of the inked parenchymal excision surface.

Outcome

The primary outcome of the study was to assess the independent predictors to achieve the trifecta in patients treated with PN with different surgical approach. Trifecta was defined as the simultaneous achievement of WIT <20 min, absence of PSM and absence of any kind of postoperative complication.

Statistical analyses

Our statistical analyses consisted of several steps. First, we compared clinical, pathologic, intraoperative and perioperative outcomes within the three surgical approaches (namely, OPN, LPN and RAPN). Chi-squared test and ANOVA test were used to compare categorical variables and continuous variables, respectively. Second, the main causes of unsuccessful Trifecta's achievements were reported in overall population and after stratifying according to surgical techniques. Third, a multivariable logistic regression model was performed to determine the independent predictors of the trifecta's achievement, including the following significant co-variates at univariable analysis: ASA score (3-4 vs. 1-2), surgical technique (RARP vs. LPN vs. OPN), clinical tumor's size (continuous variable) and UCS dislocated/involved (yes vs. no). Finally, regression-based coefficients of the multivariable model, were used to develop a nomogram predicting the likelihood to achieve the trifecta. The predictive accuracy of the nomogram was quantified using the Harrell concordance index (discrimination) and the extent of over- or underestimation of the observed achievement of trifecta was explored graphically in logistic calibration plots. The nomogram was subjected to 200 bootstrap resamples for reduction of overfit bias and for internal validation. All statistical tests were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) with a 2-sided significance level set at $P<0.05$.

RESULTS

Baseline characteristics

Table 1 depicts the baseline characteristics of patients included in the study. Median age was 64 (IQR 53-71) years. Overall, 7.7%, 56.6%, 33.6% and 2.1% of patients were classified as ASA score 1,2,3 and 4, respectively. Median size of renal mass was 3 cm (IQR 2-3.7): 407 (84.4%) and 75 (15.6) lesions were cT1a and cT1b, respectively. Patients treated with RAPN and OPN had significantly higher RENAL score, as compared with those referred to LPN ($p<0.001$), while no differences were found between three groups concerning Padua score.

Complications

The overall intraoperative complication rate was 8.9%. LPN had lower intraoperative complication (3.2%) referred to OPN (12.3%) and RAPN (9.6%, $p=0.007$; Table 2). Supplementary Table 1 shows the types of intraoperative complications stratified according to surgical approach: pleural injury was significantly higher with open approach (7.8%) compared with minim-invasive approach (0% in LPN and 4.1% in RAPN; $p<0.001$). Postoperative complications were reported in 144 (29.9%) cases, including 8.9% and 21% of medical and surgical complications. Postoperative complications rate was significantly higher in patients treated with OPN (36.8%) compared to LPN (23.1%) and RAPN (22.9%; $p=0.005$; Table2). However, we found no difference between the three surgical approach with regards of low-grade and high-grade complications. Supplementary Table 2 shows the types of postoperative complications stratified according to surgical approach: AKI, renal bleeding and urinary fistulas were reported in 4.1%, 8.1% and 1.9%, respectively; surgical site infection and sepsis were significantly higher with open approach (14.4% and 4.9%) compared with laparoscopic technique (4.5% and 1.9%) and robotic surgery (1.2% and 0%; all $p\leq0.04$)

Achievement of Trifecta

Median WIT was significantly lower with open and robotic approach (14 min in both groups) compared with laparoscopic technique (19 min; Table 2, $p<0.001$). Moreover, WIT <20 min was achieved in 211 (86.8%), 122 (78.2%) and 73 (88%) patients undergoing OPN, LPN and RAPN, respectively ($p<0.001$). PSM rate was 11.5 %, 16.7% and 3.6% with open, laparoscopic and robotic approach, respectively ($p=0.01$). Overall, trifecta was achieved in 49%, 50.6% and 69.9% of patients undergoing OPN, LPN and RAPN, respectively ($p=0.003$; Table 2). Fig 1a-b depict the causes of unsuccessful achievement of the trifecta in overall population (Fig 1a) and considering each surgical approach (Fig 1b): 11.8%, 15.8% and 29.9% of patients did not reach the trifecta due to PSM, WIT≥20 min and complications, respectively. Table 3 shows the multivariable model to predict the achievement of trifecta: ASA score 3-4 (OR: 0.63), UCS involvement (OR 0.56) and surgical approach (LPN and OPN vs. RAPN, OR: 0.39 and 0.38, respectively) were independent predictors of trifecta (all $p\leq0.02$; AUC: 0.65). The coefficients of covariates included in the multivariable model were used to develop a novel nomogram to predict the likelihood to achieve the trifecta (Fig 2). After 200 bootstrap-validation, the Harrell's C index was 0.63. The calibration plot of predicted probabilities against observed trifecta's achievement, indicated good concordance (Fig 3).

DISCUSSION

The concept of trifecta, regardless different definitions, is worldwide recognised as the primary ideal outcome of PN, since it considers simultaneously the oncologic cure (negative surgical margins) and the functional outcomes (minimal loss of renal function and absence of complications). Through years, many definitions of trifecta have been proposed for PN by combining different outcomes: surgery-related vs. overall postoperative complication-free state, warm ischemia time (WIT) <25 min[13] vs. <20 min[14], post-operative estimated glomerular filtration (eGRF) rate decrease <15%[15] vs. <10%[16]. Despite surgical margin status has not the same oncologic value of other long term oncologic outcomes (namely recurrence-free and metastases-free survival[25]), it can be considered as surrogate of complete tumour excision[26]. Moreover, since surgical small renal masses have low oncological potential, renal functional outcomes of PN assume equal importance in contributing to overall survival[12]. The postoperative renal function is related to several aspects: preoperative renal function, comorbidity, age, gender, size and anatomical complexity of the renal mass, entity of resection of peritumoral healthy renal parenchyma, suture of renal defect, ischemia time and type of ischemia[27]**.** However, renal functional preservation after PN has not been defined in a standard manner: some authors proposed to evaluate the differences between the last postoperative value of eGFR and the preoperative eGFR with <15%[15] or <10%[16] as best cut off for minimal renal function loss, other to compare the degree of ipsilateral renal function preservation assessed by renal scan after surgery[28]. Interestingly, Hung A.J. and colleagues evaluated the predicted postoperative eGFR calculated by multiplying preoperative eGFR by the percent of total kidney tissue preserved after PN[12]. Despite the postoperative eGFR directly reflects the post-surgical renal function, it could be altered by several aspects regardless surgery. Exclusively the type of resection (that may cause excessive resection of healthy parenchyma) and ischemia remain the primary surgically modifiable and controlled factors[29]. Indeed, WIT reflects the surgical damage during PN to the postoperative renal function and it should not exceed 25 minutes[30] or 20 minutes[31]. Moreover, to maximize the functional outcomes of PN, different clamping approaches have been proposed, including early unclamping, selective clamping super-selective clamping[32], zero-ischemia and off-clamping[33]. Finally, considering the ideal surgical outcomes of PN, the absence of surgical complications[12-16] or severe complications (Clavien >2)[15] or global postoperative complications has been considered[14]. Despite the absence of surgical complications is the goal of NSS, many patient-related comorbidities could cause postoperative complications (not necessary surgery-related) that may alter the normal postoperative convalescence and prolong discharge[34]. As consequence, overall postoperative complications should be considered as un-reached outcome of patients treated with PN[35]. In this field, available nephrometric score are optimal to predict both surgical complexity and complications of PN. However, regardless anatomical features, other characteristics, including patient's comorbidity and surgical technique, can increase the risk of post-operative complications or renal function damage. As consequence, the available nephrometric scores[36] are suboptimal to predict the trifecta outcome that considers both complications, surgical margin status and ischemia time. Moreover, the surgical approach for NSS is not considered as covariate of nephrometric scores and surgeons usually choose the surgical technique basing on personal experience. Thus, we aimed to evaluate the impact of the surgical technique (open, laparoscopic and robotic approach) on surgical outcomes of PN.

Several aspects are noteworthy. First, despite preoperative characteristics of renal masses were comparable between the three surgical approaches, the median WIT was significantly lower with robotic and open approach (14 minutes) as compared with laparoscopic technique (19 minutes; $p<0.001$): it could be explained with higher intraoperative complexities of pure laparoscopic technique, that may prolong ischemia during resection. Second, the overall postoperative complications were significantly higher in patients treated with open approach compared with those referred to minim-invasive techniques (36.8% vs. 23.1% for laparoscopic and 22.9% for robotic), with no differences with respect of major complications (grade<2). However, considering the surgical complications, RAPN showed lower rate of complications (12%) compared to LPN (17.3%) and OPN (26.3%; $p=0.009$). Moreover, LPN had higher rate of urinary fistulas (3.8%) compared with OPN (1.2%) and RAPN (0%), despite no statistically significant difference (Supplementary Table 2). Third, RAPN had lower PSM

(3.6%) than OPN and LPN (11.5% and 16.7%, p=0.01, Table 2). This difference could be explained with many reasons: high definition view and precise surgical dissection with robotic approach can reduce PSM; the higher surgical difficulties related to laparoscopic technique and higher proportion of patients treated with clampless approach in LPN group, may justify that the margins of resection can be obscured by intraoperative bleeding resulting in higher PSM rates; patients with more complex tumours and with imperative indication to PN (solitary kidney, bilateral disease or severe CRF) at higher risk of PSMs, were preferably treated with open approach. Despite the overall PSMs rates (11.8%) were higher than those reported in literature[37,38] and local tumour bed recurrences were found to be higher in patients with PSM[39], the effect of margin status on long-term oncologic outcomes remains to be determined and would not translate necessary into worse survival outcomes[40]. Fourth, patients referred to RAPN had higher rates of trifecta achievements (69.9%) as compared with those treated with OPN (49%) and LPN (50.6%; p=0.003; Table 2). Postoperative complications consist of the main cause of trifecta failure achievement in OPN (36.6%) and RAPN (23%); in patients treated with LNP; the failure of trifecta achievement was equally caused by PSMs (16.7%), WIT≥20 minutes (21.8%) and complications (23%; Fig 1b). This underlines the importance to consider the surgical technique to predict surgical outcomes of PN. Of note, the surgical approach was found to be the strongest predictor of trifecta achievement in multivariable logistic regression analyses and it should be considered during patient counselling before PN: both laparoscopic and open approach had significant lower risk to reach the trifecta outcome compared to robotic technique (Table 3). In order to develop an alternative tool aimed to predict the achievement of trifecta as a comprehensive outcome of PN, we proposed a multivariable model which includes both patient-related comorbidities (ASA score), tumour-related anatomic characteristics (clinical tumor's size and UCS invasion) and the surgical approach as covariates. ASA score (OR: 0.63), UCS invasion (OR: 0.56), LPN and OPN vs. RAPN (OR: 0.39 and 0.38) were independent predictors of trifecta achievement (all p≤0.02; Table 3). Using the covariates of the multivariable model we ideated a nomogram to predict the achievement of trifecta in patients scheduled for PN (Fig 2). While nephrometric score include only anatomic characteristic of the tumour and were ideated to predict complications of NSS, our model includes non-modifiable factors related to the patient (namely, comorbidity as ASA score) and to the tumour (namely, clinical size and UCS invasion) and modifiable factor (i.e. surgical technique). After internal validation the nomogram revealed accuracy of 63% and the calibration curve indicated favourable trend for predicted value to reach the trifecta between 40% and 70% (Fig 3). This model might allow a more accurate risk stratification of patients scheduled for PN on individualized level before surgery. Moreover, it could be useful both during patient counselling. In fact, despite suboptimal accuracy, our model can be helpful to stratify the risk to achieve the trifecta according to different surgical approach thus helping surgeon to choose the best surgical technique for each patient.

Despite several strengths, our study is not devoid from limitations. First, this study is retrospective, and it could be biased from inherent and not modifiable confounding factors. Moreover, the different number of patients referred to the three surgical techniques may have influenced different outcomes in the three groups. Second, this study covers a long time period and robotic approach was used in the last time period, due to recent introduction in 2015 at our institution. Third, PN have been performed by several surgeons, with extensive surgical experience in each technique, thus providing a further potential bias in our analyses, since even challenging cases can achieve the trifecta in the hand of experienced surgeon. Moreover, each surgeon completed the learning curve in OPN and LPN groups, while the RAPN group include also the first cases of surgeon's learning curve. Fourth, due to retrospective nature of the study, we are not able to assess whenever the technique of tumour excision (resection vs. enucleo-resection vs. simple enucleation) and the type of clamping approach would impact the achievement of trifecta. Moreover, the parenchymal volume preservation as a surrogate of surgical quality was not available. Fifth, our model included only T1a and T1b cases, while the surgical benefit of PN aver radical nephrectomy in T2 tumours and tumour with higher complexity, need to be assessed in further evaluation. Finally, the single centre experience limits our results and external validation in multicentric cohorts would evaluate the real clinical utility of our model in routine preoperative decision making.

CONCLUSION

RAPN allowed to obtain higher rates of trifecta's achievement in patients scheduled for NSS, compared to LPN and RAPN. At multivariable analysis, ASA score, UCS involvement and the surgical technique (namely, robotic vs. open and laparoscopic approach) were independent predictors of trifecta's achievement and should be considered in preoperative planning of PN. Our clinical nomogram to predict a comprehensive surgical outcome, considers both patient's comorbidity, tumour characteristics and surgical technique: it could facilitate the preoperative counselling and the decision-making process to choose the best surgical approach for PN at individualized level.

Acknowledgements: none

Conflicts of Interest:

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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TABLES

Table 1: Preoperative patients characteristics after stratifying according to surgical technique (OPN: open partial nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot-assisted partial nephrectomy)

Variable	**Overall**	**OPN**	**LPN**	**RAPN**	***p* value**
No. of patients, n (%)	482 (100)	243 (50.4)	156 (32.4)	83 (17.2)	-
Age (years)					
Median (IQR)	64 (53-71)	63 (53-71)	64 (55-71)	64 (53-71)	0.9
Sex, n (%)					
Male	317 (65.8)	161 (66.3)	100 (64.1)	56 (67.5)	0.9
Female	165 (34.2)	82 (33.7)	56 (35.9)	27 (32.5)	
BMI (kg/m²)					
Median (IQR)	26 (24-27)	26 (24-29)	27 (25-31)	26 (24-30)	0.6
ASA score, n (%)					
1	37 (7.7)	18 (7.4)	9 8 (5.8)	10 (12)	0.4
2	273 (56.6)	141 (58)	87 (55.8)	45 (54.2)	
3	162 (33.6)	77 (31.7)	57 (36.5)	28 (33.7)	
4	10 (2.1)	7 (2.9)	3 (1.9)	0 (0)	
Tumor side, n (%)					
Right	253 (52.5)	134 (55.1)	75 (48.1)	44 (53)	0.3
Left	218 (45.2)	101 (41.6)	79 (50.6)	38 (45.8)	
Bilateral	11 (2.3)	8 (3.3)	2 (1.3)	1 (1.2)	
Preoperative Hb (g/dL)					
Median (IQR)	14.4 (13.4-15.3)	14.1 (13.2-15.1)	14.5 (13.5-15.4)	14.5 (13.3-15.3)	0.07
Preoperative Creatinine (mg/dl)					
Median (IQR)	0.9 (0.8-1.10)	0.9 (0.8-1.12)	0.89 (0.8-1.10)	0.9 (0.8-1.10)	0.3
Preoperative eGFR (ml/min/1,73m²)					
Median (IQR)	84 (66-108)	81 (62-106)	87 (69-110)	88 (70-110)	0.08
Clinical stage, n (%)					
cT1a	407 (84.4)	204 (84)	138 (88.5)	65 (78.3)	0.1
cT1b	75 (15.6)	39 (16)	18 (11.5)	18 (21.7)	
Clinical tumor size (cm)					
Median (IQR)	3 (2-3.7)	3 (2.3-3.8)	2.5 (1.9-3.3)	2.6 (2-3.9)	0.06
PADUA score, n (%)					
6-7	243 (50.4)	114 (46.9)	92 (59)	37 (44.6)	0.1
8-9	182 (37.8)	96 (39.5)	51 (32.7)	35 (42.2)	
10-14	57 (11.8)	33 (13.6)	13 (8.3)	11 (13.3)	
R.E.N.A.L. score, n (%)					
4-6	257 (53.3)	106 (43.6)	107 (68.6)	44 (53)	<0.001
7-9	213 (44.2)	134 (55.1)	45 (28.8)	34 (41)	
10-12	12 (2.5)	3 (1.2)	4 (2.6)	5 (6)	
Surgery date, n (%)					
2000-2005	27 (5.6)	24 (9.9)	3 (1.9)	0 (0)	<0.001
2006-2010	99 (20.5)	79 (32.5)	20 (12.8)	0 (0)	
2011-2015	264 (54.8)	129 (53.1)	112 (71.8)	23 (27.7)	
2016-2017	92 (19.1)	11 (4.5)	21 (13.5)	60 (72.3)	

OPN: open partial nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot-assisted partial nephrectomy; BMI: body-mass index; Hb: hemoglobin; ASA: American Society of Anaesthesiologists; eGFR: estimated glomerular filtration rate; CKD: Chronic Kidney Disease

Table 2: Intra and postoperative patients characteristics after stratifying according to surgical technique (OPN: open partial nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot-assisted partial nephrectomy)

Variable	Overall	OPN	LPN	RAPN	*p* value
WIT, n (%)					
0	169 (35.1)	68 (28)	83 (53.2)	18 (21.7)	<0.001
1-19	237 (49.2)	143 (58.8)	39 (25)	55 (66.3)	
≥20	76 (15.8)	32 (13.2)	34 (21.8)	10 (12)	
WIT, min*					
Median (IQR)	15 (10-19)	14 (9-17)	19 (14-25)	14 (10-17)	<0.001
Operative time (min)					
Median (IQR)	131 (102-180)	110 (93-136)	139 (105-185)	225 (190-265)	<0.001
Delta eGFR 24h after surgery (ml/min/1,73m²)	-11 (-23-0)	-12 (-24;-1)	-7 (-19;-7)	-13 (-23-0)	0.004
Intra-operative complications, n (%)					
No	439 (91.1)	213 (87.7)	151 (96.8)	75 (90.4)	0.007
Yes	43 (8.9)	30 (12.3)	5 (3.2)	8 (9.6)	
Global post-operative complications, n (%)					
No	338 (70.1)	154 (63.4)	120 (76.9)	64 (77.1)	0.005
Yes	144 (29.9)	89 (36.8)	36 (23.1)	19 (22.9)	
Post-operative complications grade, n (%)#					
Clavien 1-2	112 (77.8)	71 (79.8)	26 (72.2)	15 (78.9)	0.6
Clavien ≥3	32 (22.2)	18 (20.2)	10 (27.8)	32 (22.2)	
Medical post-operative complications, n (%)	43 (8.9)	25 (10.3)	9 (5.8)	9 (10.8)	0.2
Surgical post-operative complications, n (%)	101 (21)	64 (26.3)	27 (17.3)	10 (12)	0.009
Surgical complications grade, n (%)#					
Clavien 1-2	77 (76.2)	52 (81.3)	18 (66.7)	7 (70)	0.3
Clavien ≥3	24 (23.8)	12 (18.8)	9 (33.3)	3 (30)	
Positive surgical margins, n (%)					
No	425 (88.2)	215 (88.5)	130 (83.3)	80 (96.4)	0.01
Yes	57 (11.8)	28 (11.5)	26 (16.7)	3 (3.6)	
Length of stay (days)					
Median (IQR)	5 (4-6)	5 (4.8-6)	4 (3-5)	4 (3-5)	<0.001
Trifecta rate, n (%)					
No	226 (46.9)	124 (51)	77 (49.4)	25 (30.1)	0.003
Yes	256 (53.1)	119 (49)	79 (50.6)	58 (69.9)	
Pathological Tumor Size (cm)					
Median (IQR)	3 (2-3.8)	3 (2.3-4)	2.7 (2-3.5)	3.2 (2-4.1)	0.009

Histology, n (%)					
Oncocytoma	84 (17.4)	44 (18.1)	30 (19.2)	10 (12)	0.2
Angiomyolipoma	25 (5.2)	15 (6.2)	8 (5.1)	2 (2.4)	
Other benign renal tumours	18 (3.7)	9 (3.7)	8 (5.1)	1 (1.2)	
Clear-cell renal carcinoma	228 (47.3)	114 (46.9)	68 (43.6)	46 (55.4)	
Papillary renal carcinoma	83 (17.2)	34 (14)	31 (19.9)	18 (21.7)	
Chromophobe carcinoma	35 (7.3)	22 (9.1)	7 (4.5)	6 (7.2)	
Other maligne renal tumours	9 (1.9)	5 (2.1)	4 (2.6)	0 (0)	
Pathological tumor stage, n (%)					
pT1a	298 (80.7)	194 (79.8)	137 (87.8)	58 (69.9)	0.04
pT1b	64 (13.3)	36 (14.8)	12 (7.7)	16 (19.3)	
pT2a	6 (1.2)	3 (1.2)	1 (0.6)	2 (2.4)	
pT2b	0 (0)	0 (0)	0 (0)	0 (0)	
pT3a	23 (4.8)	10 (4.1)	6 (3.8)	7 (8.4)	

WIT: Warm Ischemia Time ; OPN: Open partial nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot-assisted partial nephrectomy
*only considering patients whom underwent surgery with warm ischemia; # only considering patients who developed post-operative complications.

Table 3: Univariable and multivariable logistic regression to predict the Trifecta achievement (negative surgical margins, absence of post-operative complications and warm ischemia time <20 minutes)

	Univariable Analysis		**Multivariable Analysis**	
Variables	**OR (95% C.I.)**	**P value**	**OR (95% C.I.)**	**P value**
Age (years)	1.01 (0.99-1.02)	0.3	-	-
ASA score				
1-2	1.0 (Ref)		2.0 (Ref)	
3-4	0.64 (0.44-0.93)	0.02	0.63 (0.43-0.93)	0.02
Preoperative creatinine level mg/dl (continuous variable)	0.92 (0.57-1.49)	0.7	-	-
BMI (continuous variable)	0.99 (0.96-1.04)	0.9	-	-
Gender			-	-
Male	1.0 (Ref)			
Female	1.13 (0.78-1.65)	0.5		
Padua Score			-	-
6-7	1.0 (Ref)	0.1		
8-9	0.93 (0.63-1.37)	0.7		
10-14	0.54 (0.30-0.97)	0.04		
R.E.N.A.L. Score			-	-
4-6	1.0 (Ref)	0.3		
7-9	0.75 (0.52-1.08)	0.1		
10-12	0.77 (0.24-2.46)	0.7		
Polar localization			-	-
Superior-inferior pole	1.0 (Ref)	0.9		
Parenchimal	0.98 (0.68-1.41)			
Tumor Location			-	-
Lateral	1.0 (Ref)	0.7		
Medial	0.93 (0.64-1.36)			
Renal sinus invasion			-	-
No	1.0 (Ref)	0.2		
Yes	0.72 (0.45-1.14)			
Tumor growth pattern	1.0 (Ref)		-	-
≥50% exophytic	0.73 (0.50-1.06)	0.9		
<50% exophytic	0.97 (0.44-2.16)	0.9		
Endophytic				
Clinical tumor size (cm)	0.83 (0.72-0.96)	0.01	0.86 (0.74-1.01)	0.07
Urinary collecting system			1.0 (Ref)	
Not involved	1.0 (Ref)	0.02	0.56 (0.33-0.93)	0.02
Dislocated/infiltrated	0.56 (0.35-0.90)			
Surgical technique				
RARP	1.0 (Ref)		1.0 (Ref)	
LPN	0.44 (0.25-0.78)	0.005	0.39 (0.23-0.68)	0.001
OPN	0.41 (0.24-0.70)	0.001	0.38 (0.22-0.69)	0.001

OR: Odd Ratio; CI: Confidence Interval; ASA: American Society of Anaesthesiologists score; OPN: open partial nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot assisted partial nephrectomy

FIGURE LEGEND

Fig 1. a) Cause of trifecta's failure in the overall population of patients who did not achieve the trifecta outcome (n=226); b) cause of trifecta's failure in the overall population of patients who did not achieve the trifecta outcome after stratifying according to surgical technique (OPN, LPN e RAPN)

Fig 2. Clinical nomogram to predict the likelihood to achieve the trifecta outcome.

Fig 3. Calibration plot of the nomogram to predict the likelihood to achieve the trifecta. The 45° dotted line indicates perfect agreement between the predicted probability and the observed proportion of men who achieved the trifecta. Broken line indicates actual nomogram performance. The predicted probability of the multivariable model is depicted in the x-axis and the observed proportion of men who achieved the trifecta is depicted on the y-axis.

SUPPLEMENTARY MATERIALS

Supplementary Table 1: Intra-operative complications stratified by surgical technique (OPN: open; LPN: laparoscopic; RAPN: robot-assisted)

Variable	Overall	OPN	LPN	RAPN	*p* value
Bleeding, n (%)	15 (3.1)	7 (2.9)	4 (2.6)	4 (4.8)	0.6
Pleural injuries, n (%)	20 (4.1)	19 (7.8)	0 (0)	1 (4.1)	<0.001
Splenic injuries, n (%)	3 (0.6)	2 (0.8)	0 (0)	1 (1.2)	0.5
Ureteral injuries, n (%)	1 (0.2)	0 (0)	1 (0.6)	0 (0)	0.4
Bowel injuries, n (%)	1 (0.2)	0 (0)	0 (0)	1 (1.2)	0.09
Major vascular injuries, n (%)	3 (0.6)	2 (0.8)	0 (0)	1 (1.2)	0.5

OPN: Open partial Nephrectomy; LPN: laparoscopic partial nephrectomy; RAPN: robot-assistited partial nephrectomy.

Supplementary Table 2: Post-operative complications stratified by surgical technique (OPN: open; LPN: laparoscopic; RAPN: robot-assistited)

Variable	**Overall**	**OPN**	**LPN**	**RAPN**	***p* value**
Gastro-enteric					
Paralytic Ileus, n (%)	3 (0.6)	2 (0.8)	0 (0)	1 (1.2)	0.5
Cardio-valcular					
DVT-PE, n (%)	3 (0.6)	0 (0)	1 (0.6)	2 (2.4)	0.06
Cardiological, n (%)	10 (2.1)	5 (2.1)	3 (1.9)	2 (2.4)	0.9
Renal					
Acute renal failure, n (%)	20 (4.1)	12 (4.9)	6 (3.8)	2 (2.4)	0.6
Urinous fistula, n (%)	9 (1.9%)	3 (1.2)	6 (3.8)	0 (0)	0.07
Renal Bleeding, n (%)	39 (8.1)	19 (7.8)	14 (9)	6 (7.2)	0.8
Arteriovenous renal fistula, n (%)	2 (0.4)	1 (0.4)	1 (0.6)	0 (0)	0.8
Infection					
Wound infection, n (%)	43 (8.9)	35 (14.4)	7 (4.5)	1 (1.2)	<0.001
Sepsis, n (%)	15 (3.1)	12 (4.9)	3 (1.9)	0 (0)	0.04
Neurologic					
Neurological, n (%)	3 (0.6)	1 (0.4)	1 (0.6)	1 (1.2)	0.7
Pulmonary					
Respiratory failure, n (%)	7 (1.5)	4 (1.6)	2 (1.3)	1 (1.2)	0.9
Pneumonia, n (%)	3 (0.6)	2 (0.8)	0 (0)	1 (1.2)	0.5
Pleural effusion, n (%)	18 (3.7)	12 (4.9)	4 (2.6)	2 (2.4)	0.4
Pneumothorax, n (%)	6 (1.2)	3 (1.2)	0 (0)	3 (3.6)	0.06
DVT: Deep venous Thrombosis; PE: Pulmonary Embolism.					