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(Article begins on next page)

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Achievement of trifecta in minimally invasive partial nephrectomy correlates with functional preservation of operated kidney: a multi-institutional assessment using MAG3 renal scan

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Abstract

Purpose

To validate and compare the values of "MIC" and "trifecta" as predictors of operated kidney functional preservation in a multi-institutional cohort of patients undergoing minimally invasive PN.

Methods

We retrospectively reviewed records of consecutive cases of minimally invasive PN performed for cT1 renal masses in 4 centers from 2009 to 2013. Inclusion criteria consisted of availability of a renal scan obtained within 2 weeks prior to surgery and follow-up renal scan 3–6 months after the surgery. The primary endpoint of the study was to compare the degree of ipsilateral renal function preservation assessed by MAG3 renal scan in relation to achievement of MIC and trifecta.

Results

Total of 351 patients met our inclusion criteria. The rates of trifecta achievement for cT1a and cT1b tumors were 78.9 and 60.6 %, respectively. The rate of MIC achievement for cT1a tumors and cT1b tumors was 60.3 and 31.7 %, respectively. On multivariable linear regression model, only the degree of tumor complexity assessed by R.E.N.A.L nephrometry score [coefficient B −1.8 (−2.7, −0.9); $p < 0.0001$] and the achievement of trifecta [coefficient B 6.1 (2.4,9.8); $p = 0.014$] or MIC (coefficient B 7.2 (3.8,0.6); $p < 0.0001$) were significant clinical factors predicting ipsilateral split function preservation.

Conclusions

Achievement of both MIC and "trifecta" is associated with higher proportion of split renal function preservation for cT1 tumors after minimally invasive PN. Thus, these outcome measures can be regarded not only as markers of surgical quality, but also as reliable surrogates for predicting functional outcome in the operated kidney.

Keywords

Trifecta of outcomesPartial nephrectomyRoboticMinimally invasiveFunctional outcomesMAG3

Introduction

Preservation of renal function is the discriminating factor differentiating partial nephrectomy (PN) from radical nephrectomy. The evolution of minimally invasive PN and in particular introduction of robotic technology have led to widespread uptake and utilization of PN [1]. In order to simplify and standardize the reporting and comparison of the outcomes of minimally invasive PN, various groups have proposed composite outcome measure tools, such as “MIC” (margin, ischemia and complications) and “trifecta” [2–5].

With regard to negative surgical margin and no manifestations of complications (albeit with some differences), there is consensus among the proposed measures, but with regard to best surrogates for renal function preservation, opinions vary [6].

Assessment of functional outcome after PN represents a complex issue with the involvement of several factors that might not be easily appraised in the perioperative phase [7, 8]. Purpose of the above-mentioned composite outcome measures is to streamline and simplify reporting PN outcomes. Although proven to be important, incorporation of factors such as amount of renal parenchyma resected, renal functional volume assessment or functional outcome assessment by renal scan into such composite outcome measures defies their primary purpose and limits their widespread adoption by other scholars.

From the proposed composite outcome tools [2–5], MIC (no major perioperative complications, negative surgical margins and warm ischemia time of <20 min) and our previously described trifecta of outcomes (no perioperative complications, negative surgical margins and warm ischemia time of ≤25 min) can be assessed retrospectively based on the available documented objective data, where the concept of trifecta proposed by Hung (no urological complications, negative surgical margins and renal function loss <10 %) also relies on the subjective assessment of the amount of renal parenchyma resected intraoperatively. The aim of the present study was to compare and validate two of the proposed composite assessment tools relying on objective perioperative data, namely MIC and trifecta, as predictors of operated kidney functional preservation in a multi-institutional cohort of patients undergoing minimally invasive PN.

Method

Patient population

Multi-intuitional data from two North American and two European centers were pooled for the purpose of this study. Institutional review board approval and data sharing agreement were obtained at each institute. Patients with a single clinical T1 (cT1) renal neoplasm undergoing (minimally invasive) laparoscopic or robotic PN with available operated kidney split function assessment before and after the surgery were selected for the study. Patients with a solitary kidney were excluded from the analysis.

Surgical technique

For laparoscopic and robotic PN, both transperitoneal and retroperitoneal approaches were utilized, and the details of each surgical approach have been previously reported [9–11]. Most procedures were performed with warm renal ischemia, but zero ischemia techniques were employed selectively [8, 12]. After tumor resection, renorrhaphy is performed as previously described [9].

Preoperative planning

Tumor dimensions and R.E.N.A.L nephrometry score were assessed on preoperative cross-sectional imaging [computed tomography (CT) or magnetic resonance imaging (MRI)]. Renal scan was obtained 1–2 weeks prior to surgery. Split function for the operated kidney was assessed using MAG3 renal scan preoperatively and 3–6 months postoperatively. Our protocol and rationale for obtaining MAG3 renal scan have been previously published [7, 8].

Data analysis

For the purpose of this analysis, demographics data (patient age, BMI, sex, race, Charlson comorbidity index (CCI) [13], renal function, chronic kidney disease stage, tumor features (maximum tumor size, R.E.N.A.L nephrometry score) [14], modality of surgery (LPN or RPN), perioperative outcomes (operative time, ischemia type [warm vs. zero ischemia] and duration of warm ischemia time (WIT), estimated blood loss (EBL), intraoperative and postoperative complications), histopathology assessment (malignancy, positive surgical margin) and rate of trifecta and MIC achievements (as well as the rate of accomplishment for all the subcomponents including proportion of cases with WIT>25 min, WIT ≥20 min, positive surgical margin and any complications) were collected and assessed.

Split function of the kidney undergoing PN was documented before and after the procedure. Operated (ipsilateral) split function preservation was defined as the percentage of the postoperative-to-preoperative split function ratio. Details of all the variables were computed for the cT1a (≤4 cm) and cT1b (>4 and ≤7 cm) cohorts. The proportion of operated split function preservation was compared between the cases with and without trifecta achievement for each cT1 stage.

Trifecta of outcomes for minimally invasive PN was assessed based on our previously defined criteria of no perioperative complications, negative surgical margins and warm ischemia time of ≤25 min [5]. MIC achievement was defined as no major perioperative complications, negative surgical margins and warm ischemia time of <20 min. Postoperative complications were graded using Clavien classification [15]. Renal function was reported by assessment of GFR using MDRD formula [16]. Chronic kidney disease (CKD) staging was assessed based on NICE guidelines [17].

Characteristics of the cohort are presented using descriptive statistics. Continuous variables are presented as mean with standard deviation (age, BMI) or median with interquartile range (IQR) [CCI, GFR, tumor size, R.E.N.A.L score, split renal function, split renal function preservation, operative time, EBL, WIT) and categorical variables are expressed as frequency (percentages). For comparison of categorical variables, Chi-square test was utilized. For comparison of median split renal function preservation between trifecta and no trifecta subgroups, Mann–Whitney *U* test was employed. Multivariable linear regression model assessing modality of surgery, CCI, R.E.N.A.L score, trifecta/MIC achievement (not simultaneously) and preoperative GFR/ipsilateral split renal function (not simultaneously) was created to identify factors predicting ipsilateral split renal function preservation postoperatively. Significance was set at p value <0.05. Analyses were performed using SPSS version 21 software (IBM SPSS Statistics; IBM Corp, Armonk, NY, USA).

Results

During the study period 2009–2013, a total of 351 cases met our inclusion criteria and were included in the analysis (Fig. 1). Two hundred and forty-seven cases (70.4 %) were assessed as cT1a disease. The cohort's characteristics are outlined in Table 1. The median preoperative GFR for the cT1a cohort was 85.4 (69.7–100) mL/min/1.73 m^2 with 12.5 % of the cohort having CKD stage III or higher. For cT1b cohort, the median baseline GFR was 89 (66.5–100.4) mL/min/1.73 m^2 with 20.2 % of the population having CKD stage III or higher. The median tumor sizes were 2.8 and 5 cm with median R.E.N.A.L nephrometry scores of 6 and 8 for cT1a and cT1b cohorts, respectively. More than 60 % of the PN for each cohort was performed robotically, 60.7 and 63.5 % for cT1 and cT1b groups, respectively.

Fig. 1

Flowchart demonstrating the cohort selection

Table 1

Main demographics

Variables	Overall (*n* = 351)	cT1a (*n* = 247)	cT1b (*n* = 104)	*p* values
Patient-related				
Age, mean ± SD (years)	59.4 ± 12.1	58.9 ± 12.7	60.5 ± 10.6	0.27
Male, *N* (%)	233 (66.4)	166 (67.2)	67 (64.4)	0.61
BMI, mean ± SD (kg/m^2)	29 ± 6.1	29.1 ± 6.2	28.8 ± 6.1	0.72
CCI, median (IQR)	2 (0–3)	2 (0–3)	1 (0–3)	0.82
Pre-op eGFR, median (IQR) (mL/min/1.73 m2)	86.2 (69.4–100)	85.4 (69.7–100)	89 (66.5–100.4)	0.99
Proportion of patients with CKD stage 3–5 (%)	52 (14.8)	31 (12.5)	21 (20.2)	0.14
Tumor-related				
Tumor size, median (IQR) (cm)	3.2 (2.4–4.3)	2.8 (2.1–3.3)	5 (4.4–5.6)	<0.0001
R.E.N.A.L score, median (IQR) (cc)	7 (5–8)	6 (5–8)	8 (7–10)	<0.0001
Preoperative operated kidney	50 (47–52)	50 (47–52)	49.7 (45.1–53)	0.58
Split renal function, median (IQR) (%)				
Surgery-related				
RPN, *N* (%)	216 (61.5)	150 (60.7)	66 (63.5)	0.63
OR Time, median (IQR) (min)	147 (120–180)	137 (120–174)	162 (128–220)	<0.0001
EBL, median (IQR)(cc)	150 (100–250)	100 (75–200)	200 (100–300)	<0.0001
WIT, median (IQR) (min)	20 (16–25)	19 (15–24)	24 (20–27)	<0.0001
Zero WIT, *N* (%)	51 (14.5)	39 (15.8)	12 (11.5)	0.30
RCC, *N* (%)	285 (81.2)	198 (80.2)	87 (83.7)	0.44

BMI body mass index, *CCI* Charlson comorbidity index, *EBL* estimated blood loss, *eGFR* estimated glomerular function rate, *LPN* laparoscopic partial nephrectomy, *OR* operating room, *RPN* robotic partial nephrectomy, *WIT* warm ischemia time

Functional, trifecta and MIC outcomes are summarized in Table 2. The rate of trifecta of outcomes achievement for cT1a tumors (78.9 %) was higher than the rate observed for cT1b tumors (60.6 %) ($p < 0.0001$). This also was observed when assessing the rates of any complications (cT1a 2.4 vs.

cT1b 9.6 %; $p = 0.009$) and proportions of WIT >25 min (cT1a 15.8 vs. cT1b 35.6 %; $p < 0.0001$). We did not discern a statistically significant difference between the positive surgical margin rates between cT1a (1 %) and cT1b (4 %) groups ($p = 0.18$).

Table 2

Functional and composite outcomes

Variables	Overall	cT1a	cT1b	*p* value
Post-op GFR, median (IQR) (mL/min/1.73 m2)	83.8 (64.7–97.8)	86.7 (67.4–86.7)	72 (59.3–90)	0.002
Postoperative operated kidney split renal function, median (IQR) (%)	43 (37–48)	43 (38–48)	40 (33–47)	0.002
Ipsilateral split function preservation, median (IQR) (%)	86.3 (77.1–94.6)	87.8 (78.9–96)	82.6 (70.3–92.8)	<0.0001
Ipsilateral split function preservation	89.6 (78.7–96)	90 (80–96.1)	87.2 (77.4–94.5)	0.16
In cases with trifecta, median (IQR) (%)				
Ipsilateral split function preservation	81.1 (71.2–87.5)	84.4 (76.9–90.6)	76.6 (64.6–82.8)	0.001
In cases without trifecta, median (IQR) (%)				
Ipsilateral split function preservation	91.7 (81.8–96.3)	91.8 (81.8–98)	90.7 (80.5–94.8)	0.26
In cases with MIC, median (IQR) (%)				
Ipsilateral split function preservation	81.6 (70.6–90.5)	82.4 (74.2–91.4)	79.2 (66.7–87.3)	0.03
In cases without MIC, median (IQR) (%)				
Trifecta *N* (%)	258 (73.5)	195 (78.9)	63 (60.6)	<0.0001
WIT >25 min *N* (%)	76 (21.7)	39 (15.8)	37 (35.6)	<0.0001
Any complication *N* (%)	16 (4.6)	6 (2.4)	10 (9.6)	0.003
PSM *N* (%)	11 (3.1)	10 (4)	1 (1)	0.18
MIC *N* (%)	182 (51.9)	149 (60.3)	33 (31.7)	<0.0001
WIT ≥20 min *N* (%)	161 (45.9)	91 (36.8)	70 (67.3)	<0.0001
Major complication *N* (%)	4 (1.1)	2 (0.8)	2 (1.9)	0.58
Follow-up time, median (IQR) (months)	11 (6–17.5)	8.6 (5.7–16.3)	12 (6–18)	0.09

GFR estimated glomerular function rate, *PSM* positive surgical margin, *WIT* warm ischemia time

The rate of MIC achievement for cT1a tumors and cT1b tumors was 60.3 and 31.7 %, respectively. In total, 170 (50.4 %) of the cohort achieved the criteria for both classifications where 88 (25.1 %) did not meet any of the two measures.

The median values of operated kidney (ipsilateral) split function preservation for cT1a and cT1b tumors were 87.8 % (78.9–96) and 82.6 % (70.3–92.8), respectively. The proportion of ipsilateral split function preservation for cT1a tumors with trifecta achievement was significantly higher than the cases without the trifecta achievement (90 vs. 84.4 %; $p = 0.014$). Similar phenomenon was observed in cT1b cohort with higher observed proportion of ipsilateral split function preservation for cases with trifecta achievement (87.2 vs. 76.6 %; $p < 0.0001$).

Similarly, the proportion of ipsilateral split function preservation for cT1a and cT1b tumors with MIC achievement was significantly higher than the cases without the MIC achievement (91.8 vs. 82.4 %; $p < 0.0001$) and (90.7 vs. 79.2 %; $p = 0.002$), respectively.

On multivariable analysis (Table 3), only the degree of tumor complexity assessed by R.E.N.A.L nephrometry score (coefficient B −1.8 (−2.7, −0.9); $p < 0.0001$)) and the achievement of trifecta (coefficient B 6.1 (2.4, 9.8); $p = 0.014$) or MIC (coefficient B 7.2 (3.8, 10.6); $p < 0.0001$) resulted to be significant clinical factors predicting ipsilateral split function preservation. Addition of center to multivariable analysis did not change the performance of the other variables, but center itself (both as linear and categorical variables) was also a predictor of ipsilateral split function preservation (data not shown).

Table 3

Multivariable analysis of factors predicting ipsilateral split function preservation

Variable	Coefficient B (95 % CI)	*p*
RPN versus LPN	−2.7 (−6.4, 0.9)	0.13
CCI	−0.5 (−1.5, 0.4)	0.27
Pre-op GFR* (mL/min/1.73 m^2)	0.05 (−0.02, 0.1)	0.16
Trifecta**	6.1 (2.4, 9.8)	0.001
MIC**	7.2 (3.8, 10.6)	<0.0001
RENAL score	−1.8 (−2.7, −0.9)	<0.0001
Pre-op split unction* (%)	−0.07 (−0.3, 0.2)	0.63

CCI Charlson comorbidity index, *eGFR* estimated glomerular function rate, *LPN* laparoscopic partial nephrectomy, *RPN* robotic partial nephrectomy

* And ** values were tested in the model independently

Discussion

All proposed classifications for assessing multiple outcomes after PN use surgical margin as one of the indictors of quality of surgery and as a surrogate for oncological outcomes [18]. Occurrence of perioperative complications is another component of the existing proposed composite outcomes although the definition of what should be included is variable among the existing classifications [6]. When it comes to preservation of renal function, there are considerable variations between the exiting proposed composite outcome tools. These variations stem from complex nature of factors influencing functional outcomes after PN. Based on the available evidence, we know that quantity of renal parenchyma resected, extended WIT and quality and amount of renal parenchyma preserved all influence the functional outcomes after PN [7, 19]. Stating this, currently we lack the perfect tool for predicting functional outcomes after PN. CT volume assessment [20], tumor contact surface area [21] and renal scan have all been shown to be useful in measuring renal functional outcomes, but require labor-intensive renal volume measurement, advance imaging technology or additional imaging. Furthermore, the information provided is often not available until after PN. In our study, achievement of trifecta/MIC was associated with significantly higher values of operated kidney split function than in cases where trifecta/MIC was not obtained. Achievement of trifecta was associated with 6.1 % increase in operated kidney split function preservation compared to 10 % increase observed with MIC achievement. The rate of trifecta achievement was lower in T1b tumors compared to T1a tumors; however, achievement of trifecta was associated with higher degree of ipsilateral renal function preservation for T1b tumors (87.2 vs. 76.6) as well as T1a cases (90 vs. 84.4) on univariable analysis. Similar results were observed with MIC criteria. These findings confirm that trifecta and MIC can be regarded as surrogates for quality of surgery and strong predictors of functional outcome after PN. However, the more strict WIT criteria (<20 min) necessary for MIC achievement had a large impact on the rate of MIC achievement compared to trifecta. For example, for cT1a tumors the use of MIC criteria instead of trifecta led to a decrease in the number of cases achieving the composite outcome from 195 (78.9 %) to 149 (60.3 %) with modest median split function preservation improvement from 90 to 91.8 %. The improvement for cT1b tumors was slightly more pronounced, 87.2–90.7 %, but the rate of composite outcome achievement decline was also more pronounced, 60.6–31.7 %. This comparison suggests that trifecta offers more inclusive and achievable criteria without comprising the functional assessment component.

In our study, tumor complexity also influenced the degree of split renal function preservation, which is in line with our understanding of factors influencing renal function after PN. The tumor size and degree of complexity directly influence the amount of renal parenchyma resected and similarly the nature of renorrhaphy during the reconstruction phase of the procedure [20]. Although R.E.N.A.L score has been shown to be a predictor of trifecta achievement [4], given the weak correlation observed in our study and their clinical importance, we entered the two variables in our multivariable model simultaneously.

Conditions such as diabetes and hypertension could potentially impact the functional outcomes after PN, and we did not specifically control for such factors in our analysis, and this is a potential limitation; however, we did adjust for CCI as a surrogate for medical comorbidities. Inclusion of preoperative GFR also potentially acts as a surrogate for factors affecting functional outcomes after PN as it keeps their direct effects on preexisting renal function into consideration.

Other factors such as resected healthy renal tissue during PN, with known definitive impact on functional outcomes, were not included in the multivariable analysis. Tumor size (cT1 only tumors in this analysis) and R.E.N.A.L score control for this element to some extent. Furthermore, one of the key objectives of our study was to replace more complex assessment tools such as the amount of parenchyma resected with the more simplified perioperative outcome measures such as trifecta, and hence, the resected healthy renal tissue was omitted from our multivariable analysis.

The concept of trifecta after PN is generally applied to cT1 and more specifically to cT1a tumors, and hence, we provided the data for cT1a and cT1b tumors separately; however, on multivariable analysis assessing the utility of trifecta on functional outcomes, all cT1 tumors were included [6].

Further limitations beside the retrospective nature of data include lack of central pathology and radiology review that can be a source of data heterogeneity. Similarly, inclusion of laparoscopic and robotic cases and presence of trans- and retroperitoneal cases can be another source of data heterogeneity; however, we are not comparing the outcomes between these approaches and instead assessing the functional outcomes of cases with trifecta achievement regardless of how the procedure was performed, and this potentially enriches our cohort.

It could be contended that a selection bias may exist, based on availability of a renal scan obtained within 2 weeks prior to surgery and follow-up renal scan 3–6 months after the surgery and the current cohort might not represent our true consecutive experience and rather only include cases where renal scan was considered due to existence of potential confounders. In practice, obtaining renal scan has become a part of standard protocol for preoperative assessment and follow-up after PN in the contributing centers, but after applying the inclusion criteria, the cohort is unlikely to present the entire consecutive experience of each contributing center. But as we are comparing trifecta achievement to cases where trifecta was not achieved, selection bias is unlikely to influence the key findings of our study; however, the overall rate of trifecta achievement might be different.

Similar discussion applies to learning curve and surgical caseload, known to strongly correlate with PN outcomes. Lack of adjustment for these factors is a potential drawback of our analysis, but apart from potential impact on the overall rate of MIC or trifecta, this is unlikely to affect the conclusions of our study. Furthermore, inclusion of the center as a variable in the multivariable analysis did not influence the performance of other variables in the model; however, center itself was also a predictor of functional outcomes after PN likely as a factor controlling for operating skills, experience and overall patient care.

In this study, the rates of positive surgical margin and complications are lower than reported in the published literature [5]. As experienced high-volume minimally invasive surgeons performed the procedures in this cohort, current findings might not be applicable to other settings.

Conclusions

Achievement of both MIC and “trifecta” is associated with higher proportion of split renal function preservation for both cT1a and cT1b tumors after minimally invasive PN. Thus, these outcome measures can be regarded not only as markers of surgical quality, but also as reliable surrogates for predicting functional outcome in the operated kidney. “Trifecta,” defined as no perioperative complications, negative surgical margins and warm ischemia time of ≤25 min, offers more inclusive criteria compared to MIC without significantly compromising the functional assessment.

Author contributions

The authors listed below have made substantial contributions to the intellectual content of the paper as described below: Conception and design was done by Jihad Kaouk, Francesco Porpiglia, James Porter and Sisto Perdona. Acquisition of data was made by Homayoun Zargar, Giuseppe Quarto, Riccardo Bertolo and Riccardo Autorino. Homayoun Zargar and Riccardo Autorino analyzed and interpreted the data. Homayoun Zargar, Jihad Kaouk, Riccardo Autorino and James Porter drafted the manuscript. Jihad Kaouk and Francesco Porpiglia critically revised the manuscript for important intellectual content. Statistical analysis was done by Homayoun Zargar. Jihad Kaouk supervised the study.

Compliance with ethical standard

Conflict of interest

Jihad Kaouk was Consultant for Endocare. The remaining authors have nothing to declare in relation to this work

Ethical standard

Ethical standards have been observed during conduction and reporting of this work. Institutional review board has approved the protocol for this study.

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