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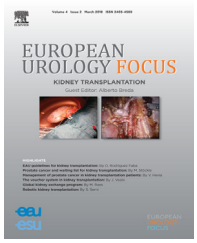

Head to Head Impact of Margin, Ischemia, Complications, Score Versus a Novel Trifecta Score on Oncologic and Functional Outcomes After Robotic-assisted Partial Nephrectomy: Results of a Multicenter Series

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Abstract

Background: There is a paucity of data describing the ability of margin, ischemia, complications, score (MIC) and trifecta in predicting long-term outcomes of robotic-assisted partial nephrectomy (RAPN).
Objective: To compare a novel trifecta (negative margins, no significant complications, and perioperative estimated glomerular filtration rate [eGFR] decrease $\leq$30%) versus standard MIC as predictors of oncologic and functional results in a large series of RAPNs.
Design, setting, and participants: : Between 2009 and 2019, a multicenter dataset was queried for patients with nonmetastatic renal masses who underwent RAPN at eight participating institutions.
Intervention: RAPN.
Outcome measurements and statistical analysis: MIC and trifecta achievement were determined for the overall cohort and a subgroup undergoing off-clamp RAPN (ocRAPN), respectively. The overall survival (OS), recurrence-free survival (RFS), and new onset of end-stage renal disease (ESRD; defined as eGFR <30 ml/min) probabilities were assessed by the Kaplan-Meier method. Cox regression analyses were used to identify predictors of OS, RFS, and ESRD. For all analyses, two-sided $p < 0.05$ was considered significant.
Results and limitations: Out of 1807 patients, MIC and trifecta were achieved in 71.1% (n = 1285) and 82.6% (n = 1492), respectively, and once restricted to the ocRAPN cohort, in 95.6% (n = 625) and 81.6% (n = 534), respectively. On Kaplan-Meier analysis, both MIC and trifecta achievement predicted higher OS and lower ESRD probabilities (all $p < 0.014$), while only trifecta achievement was a predictor of RFS probabilities ($p = 0.009$). On multivariable Cox regression, MIC did not predict any of the endpoints

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independently, while trifecta achievement was an independent predictor of higher OS (hazard ratio [HR] 0.4, 95% confidence interval [CI] 0.18–0.86; p = 0.019) and lower ESRD development probabilities (HR 0.32, 95% CI 0.15–0.72; p = 0.005).
Conclusions: Trifecta, initially described as comprehensive measures of perioperative outcomes, needs to stand the test of time. Compared with MIC, the recent trifecta was an independent predictor of clinically significant endpoints, namely, survival and ESRD development probabilities.
Patient summary: Our novel trifecta represents a reliable method for estimating survival and development of end-stage renal disease after robotic-assisted partial nephrectomy.

1. Introduction

Since its first description, the concept of "trifecta" for standardizing the results of robotic-assisted partial nephrectomy (RAPN) in a single scoring system has become a convenient tool to assess perioperative outcomes and optimize reproducibility between series [1,2]. In recent years, alternative definitions and refinements of the original trifecta have been proposed; however, the extensive variability used across authors to evaluate acute kidney injury (AKI) may have had a significant impact on reported outcomes [3,4]. With a lack of agreement on standard definition of main surgical factors, it is very hard to measure trifecta achievement objectively, with the consequent risk of unreliable description of results [5].

To date, margin, ischemia, complications, score (MIC) and the original trifecta proposed by Khalifeh et al [2] are the most widely used standardized reporting system for evaluating outcomes of RAPN [6,7]. However, reproducibility of these tools for off-clamp procedures remains questionable; moreover, their predictive role in both oncologic and functional outcomes has not directly been compared or explored in large series [8]. In this context, we have described recently a novel comprehensive trifecta for RAPN replacing the warm ischemia time (WIT) with perioperative estimated glomerular filtration rate (ΔeGFR) variations, in order to include clampless procedures also [9,10].

Herein, we performed a head-to-head comparison of our novel trifecta definition with the standard MIC in a multicenter series of RAPN. The aim of this study was to assess and compare the ability of these scoring systems in predicting oncologic outcomes and the risk of progression to ESRD after surgery.

2. Patients and methods

This observational, retrospective, multicenter study received internal review board approval at each contributing center. Out of 1949 cases, patients with tumors in solitary kidneys (n = 45), those with multiple renal masses (n = 12), and cases with missing data (n = 85) were excluded from the analysis; 1807 patients who underwent RAPN for cT1-cT2 renal masses between September 2006 and April 2020 at eight participating institutions were included in the analysis. Inclusion criteria included diagnosis with a single, organ-confined, contrast-enhancing, cT1-cT2 nonmetastatic renal tumor. Indication to surgery was elective in all cases. All patients were preoperatively evaluated with a computed tomography scan or magnetic resonance imaging.

Demographic, perioperative, pathologic, oncologic, and functional outcome data were gathered in a single customized dataset. Evaluated preoperative clinical and demographic characteristics included age, gender, race, body mass index, American Society of Anesthesiologists (ASA) score, baseline estimated glomerular filtration rate (eGFR; ml/min/1.73 m^2), baseline chronic kidney disease (CKD) stage, clinical tumor size, and RENAL nephrometry score. Perioperative variables included postoperative eGFR, ΔeGFR, WIT, clamping technique (yes/no), % perioperative complications, and surgical margin status (positive surgical margin [PSM]). Oncologic outcomes included final histology, staging (according to the tumor, node, metastasis [TNM] classification system), local tumor recurrence (recurrence-free survival [RFS]), and overall survival (OS). Long-term functional outcomes consist of new-onset CKD stage 4, 5, defined as end-stage renal disease (ESRD), at the last recorded follow-up.

Baseline eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula to determine baseline renal function [11]. The first postoperative eGFR was considered eGFR at discharge. The ΔeGFR was estimated for evaluating the impact of the surgical procedure on renal function. Baseline and postoperative CKD stages were assessed according to KDIGO International Guidelines [12]. Complications within 30 d after surgery were recorded and graded according to the Clavien-Dindo classification [13]. Major complications were categorized as Clavien grade III or higher according to European Association of Urology guidelines [14]. Tumor size was selected by the largest dimension with the RENAL nephrometry scoring system to classify the complexity of tumor [15]. PSMs were defined by the presence of tumor cells at the level of parenchyma excision surface [16]. All patients with PSMs were followed up with thoracoabdominal computed tomography scan every 6 mo during the 1 st year after treatment and every 12 mo thereafter.

Data were used to outline two binary variables for the achievement of MIC (defined as the contemporary absence of negative margins, ischemia time <20 min, absence of major complications [Clavien-Dindo ≥3]) and trifecta (defined as the contemporary absence of PSMs, major complications, and ≤30% postoperative eGFR reduction) [6,9].

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MIC and trifecta achievement rates were analyzed in the whole cohort and in a subgroup cohort of patients receiving off-clamp RAPN (ocRAPN). Descriptive analyses were used. Frequencies and proportions were reported for categorical variables, while means and standard deviations were reported for continuously coded variables. OS, RFS, and ESRD probabilities were computed by Kaplan-Meier curves, and compared for MIC and trifecta achievement with the log-rank test, respectively.

Univariable and multivariable Cox regression analyses were performed to identify predictors of OS, RFS, and ESRD. For all analyses, two-sided $p < 0.05$ was considered significant. Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS) software v.26.0 (IBM Corp, Armonk, NY, USA).

3. Results

Descriptive statistics of the study population are shown in Table 1 and Supplementary Table 1. The mean patient age was 61 yr (range 22–90 yr). The mean clinical tumor size was 4.7 cm (range 1–20 cm), while the mean RENAL score was 6.79 (range 4–12). Overall, 874 patients (48.4%) had a RENAL score of 4–6, 740 (41%) had a RENAL score of 7–9, and 193 (10.7%) had a RENAL score of >9. The Mean preoperative eGFR was 88.2 ml/min (range 6–156). At baseline, 1597 patients (88.4%) had CKD stage 1–2, 183 (10.1%) had CKD stage 3a-3b, and 27 (1.5%) had ESRD.

Perioperative and pathologic outcomes are summarized in Table 2 and Supplementary Table 2. The Mean WIT was 11.9 min (range 0–59 min). A total of 368 patients (20.4%) had a WIT of >20 min, while 654 (36.2%) underwent a clampless procedure. PSMs were observed in 60 patients (3.3%). The overall complication rate was 12.6%. More in detail, the distribution by Clavien grade was 203 grade I–II complications (11.2%) and 20 grade III–V complications (1.1%). At final pathology, a benign tumor was described in 251 cases (13.8%). At a mean follow-up of 30.7 mo (range 0–107 mo), 80 patients (4.4%) developed a local recurrence (Table 3).

Overall, MIC was achieved in 71.1%, with 1355 patients (75%) achieving a WIT of <20 min. The trifecta rate was 82.6%, with 1592 patients (88.1%) achieving a ΔeGFR of ≤30%. In the off-clamp subgroup, the MIC was 95.6% (n = 625), with seven patients (1%) reporting no major

Table 1 – Patients' demographic and preoperative characteristics according to MIC and trifecta achievement.

Variable	Overall (n = 1807)	MIC (n = 1285; 71.1)	Trifecta (n = 1492; 82.6)
Age (yr), mean ± SD	61.1 ± 11.8	61.2 ± 11.7	60.6 ± 11.9
Male gender, n (%)	1211 (67)	855 (66.5)	995 (66.7)
BMI (kg/m^2), mean ± SD	28 ± 5.9	27.6 ± 5.5	27.7 ± 5.6
ASA score, n (%)			
1–2	1217 (67.3)	918 (71.4)	1019 (68.3)
3–4	590 (32.7)	367 (28.6)	473 (31.7)
Center, n (%)			
Careggi	492 (27.2)	243 (18.9)	421 (28.2)
IRE	449 (24.8)	428 (33.3)	347 (23.3)
OLV	421 (23.3)	315 (24.5)	363 (24.3)
Cleveland Clinic	133 (7.4)	56 (4.4)	104 (7)
San Luigi Gonzaga	133 (7.4)	103 (8)	105 (7)
HSR	96 (5.3)	83 (6.5)	81 (5.4)
Brescia	62 (3.4)	37 (2.9)	51 (3.4)
VCU	21 (1.2)	20 (1.6)	20 (1.3)
Clinical tumor size (cm), mean ± SD	4.7 ± 3.2	4.7 ± 3.4	4.5 ± 3.2
RENAL score, n (%)			
4	260 (14.4)	216 (16.8)	227 (15.2)
5	325 (18)	260 (20.2)	271 (18.2)
6	289 (16)	225 (17.5)	246 (16.5)
7	271 (15)	186 (14.5)	232 (15.5)
8	252 (13.9)	158 (12.3)	193 (12.9)
9	217 (12)	124 (9.6)	179 (12)
10	126 (7)	69 (5.4)	93 (6.2)
11	57 (3.2)	38 (3)	42 (2.8)
12	10 (0.6)	9 (0.7)	9 (0.6)
Off-clamp approach, n (%)	654 (36.2)	625 (48.6)	534 (35.8)
Preoperative GFR (ml/min/1.73 m^2), mean ± SD	88.2 ± 25.9	89.9 ± 25.4	88.9 ± 25.5
Baseline CKD, n (%)			
1	833 (46.1)	599 (46.6)	700 (46.9)
2	764 (42.3)	563 (43.8)	629 (42.2)
3a	128 (7.1)	77 (6)	102 (6.8)
3b	55 (3)	27 (2.1)	37 (2.5)
4	23 (1.3)	16 (1.2)	20 (1.3)
5	4 (0.2)	3 (0.2)	4 (0.3)

ASA = American Society of Anesthesiologists; BMI = body mass index; CKD = chronic kidney disease; GFR = glomerular filtration rate; MIC = margin, ischemia, complications, score; SD = standard deviation.
Data are reported as mean (SD).

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Table 2 – Perioperative and pathologic data according to MIC and trifecta achievement.

Variable	Overall (n = 1807)	MIC (n = 1285; 71.1)	Trifecta (n = 1492; 82.6)
PSM, n (%)	60 (3.3)	0	0
Overall complications (any), n (%)	229 (12.6)	124 (9.6)	168 (11.2)
Perioperative Clavien grade, n (%)			
1	Ileus (56), wound dehiscence (15), fever (9), colitis (4), vomit (6)	Ileus (25), wound dehiscence (9), fever (5) vomit (3),	Ileus (45), wound dehiscence (10), fever (9), vomit (3), colitis (4)
2	Anemia (115), pneumonia (4)	Anemia (80), pneumonia (2)	Anemia (93), pneumonia (4)
3	Urinary leakage (10), severe active bleeding (7), cardiac arrhythmia (1)	–	–
4	Acute myocardial infarction (1), atrial fibrillation (1)	–	–
5	–	–	–
EBL (ml), mean ± SD	172.2 ± 213.4	130 ± 128.09	158.3 ± 183.7
WIT (min)[a], mean ± SD	11.99 ± 11.1[a]	7.05 ± 7.3[a]	11.6 ± 10.6[a]
OT (min), mean ± SD	160.5 ± 60.9	148.6 ± 53.2	157.4 ± 54.8
LOS (d), mean ± SD	4.6 ± 2.1	4.3 ± 1.7	4.4 ± 2.02
Postoperative eGFR (ml/min/1.73 m^2), mean ± SD	80.14 ± 27.31	82 ± 26.8	84.4 ± 25.7
ΔeGFR, mean ± SD	–8.84 ± 21.25	–7.9 ± 20.7	–4.19 ± 17.80
Benign histology, n (%)	251 (13.8)	205 (16)	218 (14.6)
pT stage, n (%)			
pT1a	990 (54.8)	736(57.3)	844 (56.6)
pT1b	382 (21.1)	238 (18.5)	303 (20.3)
pT2a	35 (1.9)	25 (1.9)	26 (1.7)
pT2b	11 (0.6)	10 (0.8)	8 (0.5)
pT3a	138 (7.6)	71 (5.5)	93 (6.2)

EBL = estimated blood loss; eGFR = estimated glomerular filtration rate; LOS = length of hospital stay; MIC = margin, ischemia, complications, score; OT = operative time; PSM = positive surgical margin; RAPN = robotic-assisted partial nephrectomy; SD = standard deviation; WIT = warm ischemia time.
Data are reported as mean (SD).
[a] Data refer to the on-clamp RAPN subgroup.

Table 3 – Oncologic and functional outcomes according to MIC and trifecta achievement.

Variable	Overall (n = 1807)	MIC (n = 1285; 71.1%)	Trifecta (n = 1492; 82.6%)
Follow-up (mo), mean ± SD	30.7 ± 24.08	31.78 ± 23.5	31.97 ± 24.3
OS, % (n deaths)	97.7 (42)	98.3 (22)	98 (31)
RFS, % (n recurrences)	95.6 (80)	95.6 (57)	96 (61)
New-onset CKD 3a, n (%)	181 (10)	109 (8.4)	134 (8.9)
New-onset CKD 3b, n (%)	67 (3.7)	24 (1.9)	40 (2.7)
New-onset CKD 4, 5, n (%)	32 (1.7)	12 (0.93)	16 (1)

CKD = chronic kidney disease; MIC = margin, ischemia, complications, score; OS = overall survival; RFS = recurrence-free survival.

complications and 640 (97.9%) reporting negative surgical margins, while the trifecta rate was 81.6%, with 562 patients (85.9%) achieving a ΔeGFR of ≤30% (Supplementary Tables 1–3).

Overall, at a mean follow-up of 30.7 mo (range 0–107 mo), 181 patients (10%) developed a new-onset CKD stage 3a, 67 (3.7%) developed a stage 3b, and 32 (1.7%) developed a stage 4–5 (Table 3 and Supplementary Table 3).

On Kaplan-Meier analysis, patients achieving MIC and trifecta displayed significantly higher OS (p = 0.004 and p = 0.014, respectively; Fig. 1) and lower ESRD development probabilities (both $p < 0.001$; Fig. 2). RFS probability was predicted by trifecta achievement, and not by MIC (p = 0.009 vs p = 0.355; Fig. 3).

At multivariable Cox regression analysis, age (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01–1.08; p = 0.017), ASA score (HR 3.06, 95% CI 1.47–6.37; p = 0.003), baseline eGFR (HR 0.98, 95% CI 0.97–0.99; p = 0.009), and trifecta achievement (HR 0.4, 95% CI 0.18–0.86; p = 0.019) were all independent predictors of OS (Table 4). RENAL score (HR 2.10; 95% CI 1.08–4.10) and baseline eGFR (HR 0.98; 95% CI 0.97–0.99) were the only independent predictors of RFS (Table 5). With regard to functional outcomes, ASA score (HR 2.89, 95% CI 1.11–7.25; p = 0.023), baseline eGFR (HR 0.93, 95% CI 0.91–0.95; $p < 0.001$), and trifecta (HR 0.32, 95% CI 0.15–0.72; p = 0.005) were independent predictors of new-onset ESRD (Table 6).

4. Discussion

An ideal trifecta for RAPN should offer more inclusive and achievable criteria without compromising a comprehensive assessment of oncologic and functional results [17]. However, due to the complexity of surgical factors involved, both

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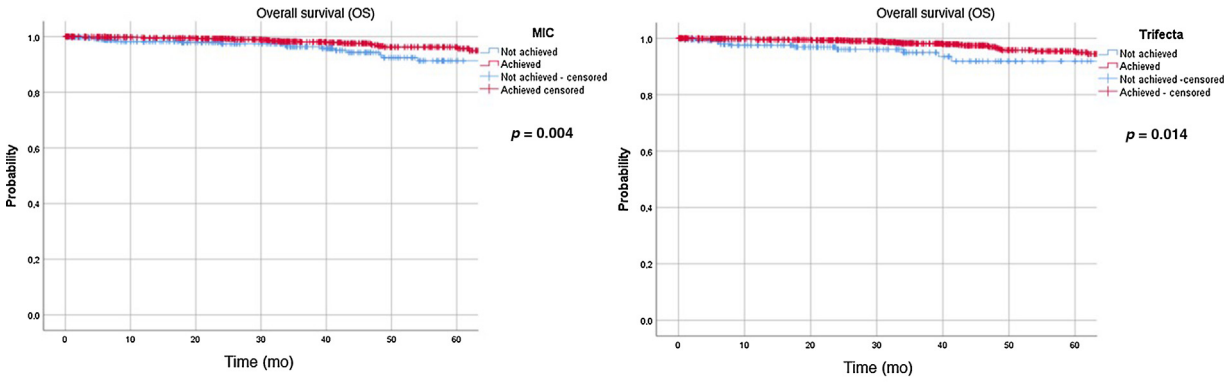


MIC not achieved

Follow-up mo	12	24	36	48	60
Probabilities ± SE	98.3 ±1	97.4 ±1	96.4 ± 1	94.3 ±2	91.3 ±2
N at risk (events)	359 (7)	222 (9)	179 (11)	125 (14)	83 (17)

Trifecta not achieved

Follow-up mo	12	24	36	48	60
Probabilities ± SE	97.5±1	96.9±1	94.9±2	91.9±3	91.9±3
N at risk (events)	216 (6)	151 (7)	84 (9)	59 (11)	26 (11)

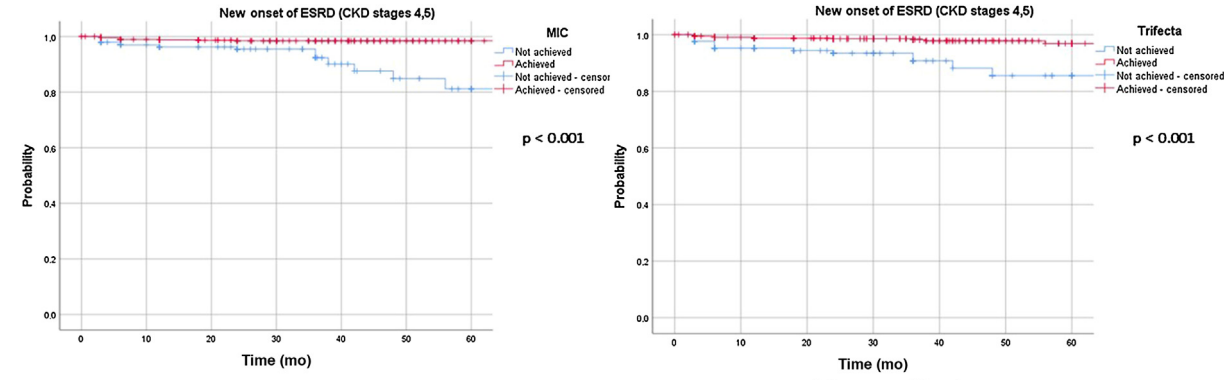
MIC not achieved

Follow-up mo	12	24	36	48	60
Probabilities ± SE	99.7±0.2	99.3±0.3	98.3±0.5	96.9±1	96.3±1
N at risk (events)	887 (3)	718 (6)	517 (12)	308 (17)	279 (19)

Trifecta not achieved

Follow-up mo	12	24	36	48	60
Probabilities ± SE	99.6±0.2	99.3±0.3	98.3±0.5	96.9±1	95.5±1
N at risk (events)	1036 (4)	823 (7)	597 (14)	367 (20)	285 (25)

Fig. 1 – Kaplan-Meier curves showing OS probabilities for patients achieving MIC and trifecta or not. MIC = margin, ischemia, complications, score; OS = overall survival; SE = standard error.



MIC not achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	97±1	96.3±1	95.5±1.3	87.6±4	81.2±6
N at risk (events)	311 (10)	261 (12)	129 (13)	36 (18)	23 (20)

Trifecta not achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	95.3±1.5	94.4±2	93.5±2	88.2±4	85.5±4.4
N at risk (events)	195 (10)	112 (11)	102 (12)	35 (15)	33 (16)

MIC achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	99±0.3	98.6±0.4	98.5±0.5	98.5±0.5	98.5±0.5
N at risk (events)	839 (9)	545 (11)	517 (12)	161 (12)	100 (12)

Trifecta achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	99.1±0.3	98.7±0.4	98.6±0.4	97.8±1	96.9±1.1
N at risk (events)	955 (9)	833 (12)	544 (13)	200 (15)	110 (16)

Fig. 2 – Kaplan-Meier curves showing ESRD (CKD 4, 5) probabilities for patients achieving MIC and trifecta or not. CKD = chronic kidney disease; ESRD = end-stage renal disease; MIC = margin, ischemia, complications, score.

MIC and trifecta share an intrinsic limitation, identifying WIT as the major determinant of renal function [18,19]. The lack of adjustment for the real amount of parenchyma preserved, tumor size, and baseline eGFR represent major drawbacks when assessing the role of WIT in predicting functional outcomes of RAPN [20]. Furthermore, the MIC score does not account for any renal damage that may potentially accrue during off-clamp procedures [21,22]. Initially, Hung et al [1] proposed a trifecta adopting predicted postoperative eGFR by the percent of kidney tissue preserved instead of WIT, but the subjective and complex assessment method of criteria precluded its adoption in clinical practice [2]. Recently, Brassetti et al [9,10] described a novel trifecta supporting ΔeGFR as a potential marker of AKI.

Any trifecta is initially conceived to provide a comprehensive measure of perioperative outcomes. The use of a WIT threshold, for instance, does not apply properly to a pure ocRAPN cohort: in fact, the overall increased number of patients achieving trifecta (n = 1492) compared with MIC (n = 1285) may be explained by the more flexible criteria used for AKI definition. Conversely, trifecta provided a stricter selection in patients, which may improperly be considered with MIC score achieving no ischemia by definition as in the off-clamp subgroup (81.8% vs 95.6%; Supplementary Table 1).

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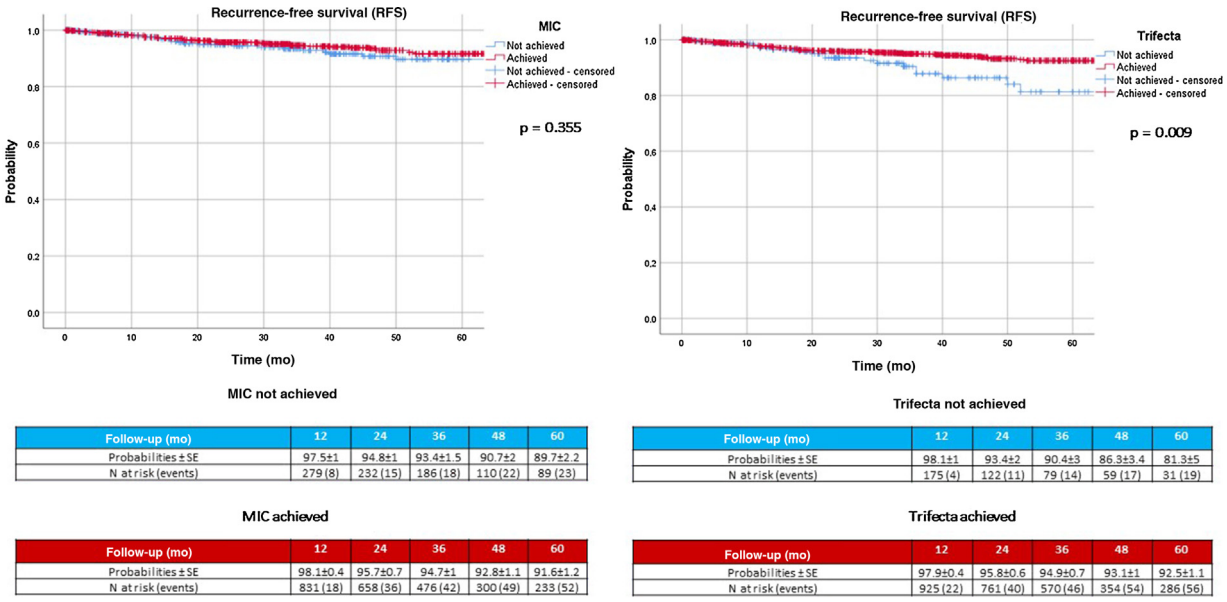

MIC not achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	97.5±1	94.8±1	93.4±1.5	90.7±2	89.7±2.2
N at risk (events)	279 (8)	232 (15)	186 (18)	110 (22)	89 (23)

Trifecta not achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	98.1±1	93.4±2	90.4±3	86.3±3.4	81.3±5
N at risk (events)	175 (4)	122 (11)	79 (14)	59 (17)	31 (19)

MIC achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	98.1±0.4	95.7±0.7	94.7±1	92.8±1.1	91.6±1.2
N at risk (events)	831 (18)	658 (36)	476 (42)	300 (49)	233 (52)

Trifecta achieved

Follow-up (mo)	12	24	36	48	60
Probabilities ± SE	97.9±0.4	95.8±0.6	94.9±0.7	93.1±1	92.5±1.1
N at risk (events)	925 (22)	761 (40)	570 (46)	354 (54)	286 (56)

Fig. 3 – Kaplan-Meier curves showing RFS probabilities for patients achieving MIC and trifecta or not. MIC = margin, ischemia, complications, score; RFS = recurrence-free survival.

Table 4 – Univariable and multivariable Cox regression analysis to identify predictors of OS.

Variable	Univariable analysis				Multivariable analysis (MIC)				Multivariable analysis (trifecta)			
	HR	95% CI			HR	95% CI			HR	95% CI		
		Lower	Higher	*p* value		Lower	Higher	*p* value		Lower	Higher	*p* value
Age	**1.05**	**1.02**	**1.08**	**0.001**	**1.05**	**1.01**	**1.08**	**0.008**	**1.04**	**1.01**	**1.08**	**0.017**
Gender	1.23	0.63	2.41	0.533	–	–	–	–				
ASA score												
1–2	**4.6**	**2.42**	**8.75**	**<0.001**	**3.04**	**1.46**	**6.33**	**0.003**	**3.06**	**1.47**	**6.37**	**0.003**
3–4												
BMI	**1.04**	**1.01**	**1.09**	**0.049**	1.02	0.97	1.07	0.37	1.02	0.97	1.07	0.35
Tumor size	1	0.99	1.01	0.659	–	–	–	–	–	–	–	–
RENAL (4–9 vs 9–12)	1.28	0.60	2.68	0.515	–	–	–	–	–	–	–	–
pT stage	1.04	0.36	3.01	0.940	–	–	–	–	–	–	–	–
Benign/malignant	0.48	0.11	2	0.314	–	–	–	–	–	–	–	–
Preoperative eGFR	**0.97**	**0.96**	**0.99**	**<0.001**	**0.98**	**0.97**	**0.99**	**0.016**	**0.98**	**0.97**	**0.99**	**0.009**
MIC	**0.42**	**0.22**	**0.77**	**0.005**	0.71	0.37	1.36	0.304	–	–	–	–
Trifecta	**0.43**	**0.21**	**0.86**	**0.017**	–	–	–	–	**0.4**	**0.18**	**0.86**	**0.019**
Hurrell's C-index												
Full model						0.82				**0.8**		
Restricted						0.78				**0.84**		

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MIC = margin, ischemia, complications, score; OS = overall survival.

Moreover, perioperative outcomes do not necessarily predict maintenance of favorable long-term outcomes. Consequently, we aimed at assessing whether MIC and trifecta "stand the test of time" by analyzing the role of both MIC and trifecta in predicting main clinical outcomes, namely, OS, RFS, and ESRD probabilities. Our analysis showed interesting findings. At multivariable analysis, compared with MIC, trifecta was an independent predictor of both OS (p = 0.019) and ESRD (p = 0.005). Since postoperative eGFR after RAPN has recently been identified as a more significant predictor of long-term survival than WIT, it is reasonable to assume that incorporation of perioperative eGFR variations in our novel criteria turned into superiority of trifecta over MIC in predicting significant renal impairment and overall mortality by implication [5].

It is noteworthy that at univariable analysis, trifecta achievement significantly predicted RFS (p = 0.01), while MIC did not (p = 0.357). This finding may be explained by the slightly different distribution of patients who achieved trifecta compared with MIC in terms of tumor complexity (RENAL score >921.6% vs 18.7%) and pT stage (pT ≥2b 6.7% vs 6.3%), considering the negligible overall PSM rates observed (3.3%). We are aware that the achievement of negative surgical margins may certainly not replace long-

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Table 5 – Univariable and multivariable Cox regression analysis to identify predictors of RFS.

Variable	Univariable analysis				Multivariable analysis (TRIFECTA)			
	HR	95% CI			HR	95% CI		
		Lower	Higher	*p* value		Lower	Higher	*p* value
Age	1.01	0.99	1.03	0.244	–	–	–	–
Gender	1.53	0.91	2.57	0.10	–	–	–	–
ASA score								
1–2	1.50	0.93	2.45	0.09	–	–	–	–
3–4								
BMI	0.93	0.86	1.01	0.109	–	–	–	–
RENAL (4–9 vs 9–12)	**3.34**	**1.85**	**6.01**	**<0.001**	**2.10**	**1.08**	**4.10**	**0.029**
pT stage	**2.38**	**0.97**	**5.84**	**<0.001**	1.76	0.47	6.57	0.05
Benign/malignant	0.44	0.16	1.20	0.111	–	–	–	–
Preoperative eGFR	**0.98**	**0.97**	**0.99**	**<0.001**	**0.98**	**0.97**	**0.99**	**0.023**
MIC	0.79	0.48	1.29	0.357	–	–	–	–
Trifecta	**0.50**	**0.29**	**0.84**	**0.01**	0.66	0.32	1.36	0.268

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio; MIC = margin, ischemia, complications, score; RFS = recurrence-free survival.

Table 6 – Univariable and multivariable Cox regression analysis to identify predictors of newly onset of ESRD.

Variable	Univariable analysis				Multivariable analysis (MIC)				Multivariable analysis (trifecta)			
	HR	95% CI			HR	95% CI			HR	95% CI		
		Lower	Higher	*p* value		Lower	Higher	*p* value		Lower	Higher	*p* value
Age	**1.06**	**1.02**	**1.10**	**<0.001**	1.02	0.98	1.06	0.161	1.02	0.98	1.046	0.249
Gender	1.49	0.67	3.33	0.322	–	–	–	–	–	–	–	–
ASA score												
1–2	**8.7**	**3.92**	**19.6**	**<0.001**	**2.78**	**1.11**	**6.98**	**0.02**	**2.89**	**1.11**	**7.25**	**0.023**
3–4												
BMI	**1.06**	**1.01**	**1.11**	**0.016**	1	0.94	1.08	0.768	1	0.93	1.07	0.952
RENAL (4–9 vs 9–12)	**2.69**	**1.28**	**5.64**	**0.009**	0.20	0.05	1.63	0.160	0.22	0.04	1.19	0.079
Preoperative eGFR	**0.92**	**0.91**	**0.94**	**<0.001**	**0.92**	**0.90**	**0.94**	**<0.001**	**0.93**	**0.91**	**0.95**	**<0.001**
MIC	**0.19**	**0.09**	**0.39**	**<0.001**	0.45	0.17	1.15	0.09	–	–	–	–
Trifecta	**0.20**	**0.10**	**0.40**	**<0.001**	–	–	–	–	**0.32**	**0.15**	**0.72**	**0.005**
Hurrell's C-index												
Full model						0.95				**0.96**		
Restricted model						0.94				**0.95**		

ASA = American Society of Anesthesiologists; BMI = body mass index; CI = confidence interval; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; HR = hazard ratio; MIC = margin, ischemia, complications, score.

term oncologic outcomes of RAPN [23]. However, as local tumor recurrence is associated with multiple factors such as adverse pathologic features (renal hilum/sinus invasion) and tumor upstaging, it would have been interesting to adjust the model for these variables, but unfortunately, they were unavailable in our dataset [24]. Furthermore, the use of a broad definition of local recurrence (such as any new mass in the ipsilateral kidney following partial nephrectomy) could potentially have captured sporadic or metachronous recurrences and does not necessarily reflect a matter of surgical quality [25]. Finally, in our study, preoperative eGFR and RENAL score were also independent predictors of RFS ($p = 0.023$ and $p = 0.029$; respectively). These findings are in line with current evidence, suggesting that higher nephrometry scores are associated with shorter progression-free survival and higher recurrence rates as the oncologic risk of CKD in patients with kidney cancer is increased when the preoperative eGFR is significantly compromised [26,27].

Our study is not devoid of limitations. First of all, it is a retrospective analysis of data. In addition, multicenter databases provide a large cohort and thus a large amount of data, but undoubtedly imply different caseloads and different techniques, regardless of the tertiary care nature of all involved centers. Besides, we were unable to adjust regression models for all potential confounders: for instance, comorbidities were available for all cases only as ASA scores, tumor resection strategies were not available for all cases, and a rigorous measurement of preserved parenchymal volume preserved after surgery was not performed. Moreover, the role of medical comorbidities, namely, diabetes and hypertension, may play a role in long-term renal function that we were unable to account for. Eventually, our data require prospective external validation to confirm the

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strong predictive role of this novel trifecta in main long-term outcomes [28].

Despite these limitations, this trifecta showed interesting features such as a user-friendly profile, broader application for different surgical techniques of RAPN, and its independent predictive role in both OS and risk of developing a significant worsening of renal function in the long run. Compared with MIC, it could safely be adopted in clinical practice to help urologists in the assessment and comparison of RAPN outcomes rather than as a reliable, predictive tool of survival and ESRD.

5. Conclusions

Trifecta, initially described as a comprehensive measure of surgical outcomes, needs to stand the test of time. Our trifecta outperformed MIC in terms of the ability to predict oncologic outcomes and ESRD after RAPN, and proved to be an independent predictor of long-term OS and ESRD development probabilities. This new and easy clinical tool represents a comprehensive marker of surgical quality and a reliable method for estimating survival and development of ESRD during follow-up.

Author contributions: Umberto Anceschi 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: Anceschi, Simone, Gallucci, Brassetti.
Acquisition of data: Brassetti, Anceschi, Tuderti, Ferriero.
Analysis and interpretation of data: Anceschi, Capitanio, Dell'Oglio, Bertolo, Garisto, Antonelli, Veccia, Mari, Amparore, Larcher.
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Critical revision of the manuscript for important intellectual content: Gallucci, Mottrie, Porpiglia, Montorsi, Minervini, Carini, Kaouk, Autorino.
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Appendix A. Supplementary data

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