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Perinephric Toxic Fat: Impact on Surgical Complexity, Perioperative Outcome, and Surgical Approach in Partial Nephrectomy

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Keywords

Adhesive perinephric fat · Mayo adhesive probability score · Partial nephrectomy · Renal cancer · Surgical approach

Abstract

Introduction: To assess influencing factors on perinephric toxic fat (high Mayo Adhesive Probability [MAP] score) and the impact of high MAP scores on surgical complexity, perioperative outcome, and surgical approach in patients with localized renal tumors undergoing open (OPN) and robot-assisted partial nephrectomy (RAPN). ***Methods:*** 698 patients were included in this study. Based on preoperative imaging, adherent perinephric fat (APF) was assessed to define MAP scores. Regression analyses assessed influencing parameters for high MAP scores (≥3), predictors of surgical outcome, and influencing factors on surgical approach. ***Results:*** OPN was performed in 331 (47%) patients, and 367 (53%) patients underwent RAPN. Male gender ($p < 0.001$), age ≥65 ($p < 0.001$), and BMI ≥27.4 kg/m^2 ($p < 0.001$) showed to be significantly influencing factors for the presence of APF. High MAP scores showed to be an influencing factor for a prolonged surgery duration (OR = 1.68, 95% CI 1.22–2.31, $p = 0.002$) and a significant predictor to rather undergo OPN than RAPN (OR = 1.5, 95% CI 1.05–2.15, $p = 0.027$). ***Conclusion:*** Older, male patients with high BMI scores have a higher risk for APF. The presence of APF increases surgery time and may have an impact on decision making regarding the preferred surgical approach.

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Introduction

Partial nephrectomy (PN) is currently the standard of care for patients with localized renal cell carcinoma (RCC) <7 cm in size (T1 stage) and for larger suspected RCC, whenever feasible, regardless of the surgical approach (open vs. laparoscopic vs. robot-assisted technique) [1, 2]. Since 2009, when Kutikov et al. [3] first proposed the R.E.N.A.L. nephrometry score, preoperative planning of PN includes an assessment of the tumor complexity using renal morphometry scoring systems, such as the R.E.N.A.L. score or the PADUA prediction score, to quantify anatomical characteristics of the pathologic tissue and to evaluate the potential difficulty of the surgery and the likelihood of postoperative complications [4]. In 2014, Davidiuk et al. [5] developed the

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Mayo Adhesive Probability (MAP) score to expand the existing radiographic scores and add another dimension to the prediction of tumor complexity, with a focus on a more patient-specific factor, namely the adherent perinephric fat (APF) or so-called perinephric toxic fat. APF is characterized as a tumor surrounding sticky fat tissue, which may increase the difficulty of tumor dissection during PN [6]. Its pathogenesis is unknown, and there is no standardized definition for APF, but a series of studies suggest inflammation, cardiovascular risk factors, idiopathic fibrosis, or an autoimmune response to be risk factors for the development of APF [7, 8]. The MAP score is an image-based scoring system describing and predicting the presence of APF. It was shown to be an independent predictor for conversion from laparoscopic to open PN (OPN) or to radical nephrectomy [9]. A significantly prolonged dissection phase could be observed with increasing MAP scores in patients undergoing robot-assisted PN (RAPN), underlining the assumption of a limited mobilization of the kidney and difficult tumor isolation [10]. In addition, higher MAP scores showed to be associated with a higher total operative time in patients undergoing laparoscopic nephrectomy and PN [11, 12]. Khene et al. [9] found an association of higher MAP scores with operation time and blood loss. It was stated that the MAP score had no effect on postoperative complications, although higher MAP scores were adversely associated with TRIFECTA achievement. Contrary to the above mentioned findings, Franquet et al. [13] observed an association of higher MAP scores (cutoff MAP ≥3) and a higher risk of peri- and postoperative complications in patients undergoing laparoscopic nephrectomy. Similar findings concerning the association of higher MAP scores with major surgical complication could be observed in other studies [14]. The influence of the MAP score was mostly examined in laparoscopic PN and nephrectomy, and Davidiuk et al. [5] developed the score in a cohort of patients undergoing RAPN. To our knowledge, there is limited information about influencing factors for a high MAP score and, vice versa, about the influence of a high MAP score on perioperative outcome parameters in patients undergoing PN. The effect on postoperative complications is inconsistent. In this study, we assessed the mentioned factors in a large study population undergoing OPN and RAPN and evaluated whether a high MAP score, as patient-centered characteristic, could also be a possible influencing factor on the surgical approach and, thus, a factor worth considering before deciding on OPN or RAPN in patients with renal cancer.

Materials and Methods

Data Collection

Data from the combined database from two German centers (Klinikum Wuerzburg Mitte Missioklinik and University Medical Center Mannheim) were retrospectively evaluated in the time frame 2014–2020. PN was offered whenever technically feasible and oncologically reasonable. The decision of the surgical technique with either the open (n = 331) or robot-assisted approach (n = 367) was based on the individual surgeon's choice without knowledge of the MAP score. The choice was made based on the surgeon's preference and on individual patient and tumor-specific characteristics. Demographic and perioperative parameters were available for all patients. Postoperative complications were classified according to the Clavien-Dindo classification (CDC) system of complications with subdivision into minor (1–2) and major (3–4) complications [15]. To assess functional and oncological outcomes, TRIFECTA criteria (negative surgical margins, warm ischemia time [WIT] <25 min, no complications) were applied [16].

Assessment of Tumor Complexity and Perinephric Fat

Radiological assessment was based on preoperative cross-sectional imaging (computed tomography or magnetic resonance imaging). In one center, the assessment of the MAP score was performed by two residents who were trained by a specialized (uro)-radiologist. Regular quality controls were performed. In the other center, MAP score was evaluated by one senior physician (urologist) and one resident. Further, anatomic analyses included the R.E.N.A.L. nephrometry score with stratification into low (R.E.N.A.L. 4–6), intermediate (R.E.N.A.L. 7–9), and high complexity groups (R.E.N.A.L. 10–12) [4]. To predict APF, the MAP score was assessed retrospectively as described by Davidiuk et al. [5]: fat thickness was measured posteriorly as a perpendicular line from the kidney capsule to the abdominal wall on the level of the renal vein (0 points: <10 mm, 1 point: 10–19 mm, 2 points: ≥20 mm). Stranding was defined as increased perinephric fat density with graduation as 0 (no stranding), type 1 (thin stranding, 2 points), or type 2 (thick stranding, 3 points). The resulting sum score of stranding and thickness ranged from 0 to 5.

Surgical Technique

RAPN was performed at Klinikum Wuerzburg Mitte Missioklinik by two experienced surgeons who have each already performed at least 150 RAPNs. The surgery was performed via a transperitoneal or retroperitoneal approach, as described previously [17]. OPN was performed by 11 experienced surgeons in our highly standardized technique at the University Medical Center Mannheim. Five of the surgeons were very experienced and have already performed >200 open partial nephrectomies. Six of them were less experienced and have performed <100 open partial nephrectomies. Complex surgeries were performed only by very experienced surgeons and less experienced surgeons were mostly supervised by them.

In OPN, a 10–15 cm lumbar incision gave access to the retroperitoneal space [18]. In both techniques, warm ischemia with early unclamping was used in the majority of the cases followed by closure of the collecting system and renorrhaphy. Intraoperative ultrasound was used when beneficial to improve the localization of the tumor, especially in endophytic renal masses.

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Table 1. Patient and tumor characteristics for the total cohort and the subgroups MAP <3 and MAP ≥3

	All patients	MAP <3	MAP ≥3	*p* value
Patient, *n*	698	354	344	<0.001
Age, median (IQR), years	65 (57–73)	62 (53–69)	67 (60–74)	
Gender, *n* (%)				
Male	467 (66.9)	178 (50.3)	289 (84)	<0.001
Female	231 (33.1)	176 (49.7)	55 (16)	<0.001
BMI, median (IQR)	27.4 (24.5–30.4)	26.1 (23.4–29.4)	28.3 (25.8–31.8)	<0.001
ASA, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.122
Single kidney, *n* (%)	29 (4.3)	16 (4.5)	13 (3.8)	0.706
R.E.N.A.L. score, *n* (%)				
Low complexity	226 (32.4)	110 (31.1)	116 (33.7)	0.467
Moderate complexity	365 (52.3)	181 (51.1)	184 (53.5)	0.545
High complexity	107 (15.3)	63 (17.8)	44 (12.8)	0.074
MAP score, *n* (%)				
0	165 (23.6)	165 (46.6)	–	0.1
1	93 (13.3)	93 (26.3)	–	
2	96 (13.8)	96 (27.1)	–	
3	116 (16.6)	–	116 (33.7)	
4	178 (25.5)	–	178 (51.7)	
5	50 (7.2)	–	50 (14.5)	
Tumor size, median (IQR), cm	3.0 (2.2–4.3)	3.0 (2–4.2)	3.2 (2.3–4.3)	
Pathologic T stage, *n* (%)				
T1a	366 (68.3)	186 (72.4)	180 (64.5)	0.052
T1b	128 (23.9)	51 (19.8)	77 (27.6)	0.042
T2a	9 (1.7)	6 (2.3)	3 (1.1)	0.323
T2b	1 (0.2)	0 (0)	1 (0.4)	1.0
T3a	32 (6)	14 (5.4)	18 (6.5)	0.716
≥T3b	0 (0)	0 (0)	0 (0)	1.0
Positive surgical margin, *n* (%)	26 (3.7)	14 (4)	12 (3.5)	0.843
Tumor side, *n* (%)				
Left	356 (51)	179 (50.6)	177 (51.5)	0.821
Right	342 (49)	175 (49.4)	167 (48.5)	0.821
Malignant, *n* (%)	544 (77.9)	260 (73.4)	284 (82.6)	0.005
Histology if malignant tumor, *n* (%)				
Clear cell	340 (62.5)	159 (61.2)	181 (63.7)	0.537
Papillary type	135 (24.8)	66 (25.4)	69 (24.3)	0.843
Chromophobe	47 (8.6)	23 (8.8)	24 (8.5)	0.88
Others	22 (4)	12 (4.6)	10 (3.5)	0.524
Surgical approach, *n* (%)				
OPN	331 (47.4)	149 (42.1)	182 (52.9)	0.005
RAPN	367 (52.6)	205 (57.9)	162 (47.1)	<0.001
Surgery duration, median (IQR), min	130 (107–160)	122 (100–151)	138 (115–168)	<0.001
Ischemia, *n* (%)	605 (86.7)	309 (87.3)	296 (86)	0.657
Ischemia duration, median (IQR), min	12 (7–17)	11 (6–16)	12 (7–18)	0.063
Ischemia duration ≥25 min, *n* (%)	59 (8.5)	29 (8.2)	30 (8.7)	0.892
Blood loss, median (IQR), mL	100 (50–300)	100 (50–200)	150 (53–383)	<0.001
Transfusion, *n* (%)	40 (5.7)	23 (6.5)	17 (4.9)	0.418
Clavien-Dindo grade ≥3, *n* (%)	54 (7.7)	22 (6.2)	32 (9.3)	0.156
TRIFECTA achievement, *n* (%)	463 (66.3)	245 (69.2)	218 (63.4)	0.11
Length of stay, median (IQR), days	8 (6–9)	8 (7–10)	8 (6–9)	0.119

ASA, American Society of Anesthesiologists; IQR, interquartile range; MAP, Mayo Adhesive Probability; *n*, number; OPN, open partial nephrectomy; RAPN, robot-assisted partial nephrectomy.

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Table 2. Influencing factors for MAP ≥3

	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
MAP ≥3						
Gender (male)	5.2	3.64–7.42	<0.001	5.83	3.98–8.54	<0.001
Age ≥65 (median)	2.01	1.49–2.72	<0.001	2.57	1.83–3.61	<0.001
BMI ≥27.4 (median)	2.31	1.71–3.13	<0.001	2.18	1.56–3.04	<0.001
Tumor size (≥4 cm)	1.18	0.85–1.63	0.322	1.31	0.91–1.88	0.15
Malignant histology	1.71	1.18–2.47	0.004	1.16	0.76–1.76	0.492

BMI, body mass index; CI, confidence interval; MAP, Mayo Adhesive Probability.

Statistical Analysis

All statistical analyses were performed using statistical software JMP® from SAS (version 13 for Windows, SAS Institute Inc.). Mann-Whitney-U-test (median and interquartile range for continuous variables) and χ^2 analysis (numbers and percentage for categorical variables) were used for comparison of perioperative and postoperative data with statistical significance at p <0.05. Logistic regression was employed for univariate and multivariate analyses for predictive parameters for MAP score ≥3, surgical time ≥130 min, major complications (CDC ≥3), TRIFECTA achievement, and OPN as surgical approach.

Results

Overall, 698 patients undergoing partial nephrectomy were included in this study. A total of 354 patients showed a MAP score <3 and 344 patients were characterized as MAP ≥3. The patient and tumor characteristics of the total cohort and the two MAP subgroups are displayed in Table 1. In the total cohort, the median patient age was 65 (57–73) years; in the MAP <3 subgroup, 62 (53–69) years; and in the MAP ≥3 subgroup, 67 (60–74) years (p = 0.001). There were significantly more male patients in the MAP ≥3 subgroup (p < 0.001), and MAP ≥3 patients had a significantly higher average body mass index (BMI) compared to MAP <3 patients (28.3 vs. 26.1 kg/m^2, p < 0.001). Malignant tumors were detected in 78% (n = 544) of the patients with a higher proportion in patients with a MAP ≥3 (83 vs. 73%, p = 0.005). In the MAP <3 group, 58% of the PNs were performed in a robot-assisted approach, whereas only 47% of the patients in the MAP ≥3 underwent a robot-assisted PN (p < 0.001). Surgery time differed significantly in the two subgroups (MAP <3: 122 vs. MAP ≥3: 138 min, p < 0.001), while ischemia time was comparable (MAP <3: 11 vs. MAP ≥3: 12 min, p = 0.063). There was a significantly higher blood loss observed in patients with MAP ≥3 tumors (median blood loss MAP <3: 100 vs. MAP ≥3: 150 mL, p < 0.001).

To evaluate possible influencing factors for a MAP score ≥3, uni- and multivariate analyses were performed. The results are displayed in Table 2. In the multivariate analyses, male gender (p < 0.001), a median age ≥65 years (p < 0.001), and a median BMI ≥27.4 kg/m^2 (p < 0.001) showed to be significant predictors for a MAP ≥3, whereas a tumor size ≥4 cm and malignant histology did not show a relevant influence on a high MAP score.

Figure 1 visualizes the percentage of TRIFECTA achievement and development of major complications (CDC ≥3) in the MAP subgroups.

In uni- and multivariate analyses, patients with MAP score ≥3 showed a higher risk for a prolonged surgery duration (OR = 1.68, 95% CI: 1.22–2.31, p = 0.002). The same applies to patients undergoing OPN compared to RAPN (OR = 2.25, 95% CI: 1.64–3.10, p < 0.001). Furthermore, a BMI ≥27.4 kg/m^2 (OR = 1.73, 95% CI: 1.25–2.39, p < 0.001) and malignant histology (OR = 1.74, 95% CI: 1.18–2.58, p = 0.005) showed to be risk factors for a prolonged surgery time. The development of major complications (CDC ≥3) showed to be significantly influenced by the surgical approach (OPN vs. RAPN, OR = 4.48, 95% CI: 2.24–8.95, p < 0.001). Likewise, for TRIFECTA achievement only the surgical approach showed to be an independent predictor with a reduced probability to achieve the TRIFECTA criteria in the OPN group (OPN vs. RAPN, OR = 0.36, 95% CI: 0.25–0.52, p < 0.001). The results are displayed in Table 3.

In terms of the chosen surgical approach, a MAP score ≥3 showed to be a significant factor to rather undergo OPN than RAPN (OR = 1.5, 95% CI: 1.05–2.15, p = 0.027). Furthermore, a high R.E.N.A.L. score (10–12) showed to be an independent predictor to rather undergo OPN with an OR of 2.48 (95% CI: 1.5–4.1, p < 0.001). Another factor

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Table 3. Influencing factors for surgical time, major complications and TRIFECTA achievement

	Univariate analysis			Multivariate analysis		
	odds ratio	95% CI	*p* value	odds ratio	95% CI	*p* value
A						
Surgical time ≥130 min (median)						
Surgical approach (OPN vs. RAPN)	2.41	1.78–3.28	<0.001	2.25	1.64–3.10	<0.001
BMI ≥27.4 (median)	1.89	1.40–2.56	<0.001	1.73	1.25–2.39	<0.001
MAP ≥3	2.01	1.49–2.72	<0.001	1.68	1.22–2.31	0.002
R.E.N.A.L. (10–12 vs. 4–9)	1.42	0.94–2.15	0.099	1.29	0.82–2.01	0.268
Malignant histology	2.18	1.51–3.16	<0.001	1.74	1.18–2.58	0.005
B						
Major complications (CDC ≥3)						
Surgical approach (OPN vs. RAPN)	4.83	2.45–9.54	<0.001	4.48	2.24–8.95	<0.001
BMI ≥27.4 (median)	0.99	0.57–1.72	0.965	0.93	0.52–1.68	0.818
MAP ≥3	1.55	0.88–2.72	0.129	1.38	0.76–2.51	0.290
R.E.N.A.L. (10–12 vs. 4–9)	1.65	0.84–3.25	0.147	1.26	0.63–2.64	0.517
Malignant histology	1.45	0.69–3.04	0.322	1.16	0.54–2.50	0.697
C						
TRIFECTA achievement						
Surgical approach (OPN vs. RAPN)	0.30	0.21–0.42	<0.001	0.36	0.25–0.52	<0.001
BMI ≥27.4 (median)	0.88	0.65–1.21	0.440	0.97	0.67–1.42	0.891
MAP ≥3	0.77	0.56–1.05	0.103	1.0	0.68–1.45	0.987
R.E.N.A.L. (10–12 vs. 4–9)	0.57	0.37–0.86	0.008	0.87	0.53–1.42	0.568
T-stage (≥T2 vs. <T2)	0.44	0.23–0.83	0.012	0.57	0.29–1.11	0.096

BMI, body mass index; CDC, Clavien-Dindo classification; CI, confidence interval; MAP, Mayo Adhesive Probability; OPN open partial nephrectomy; RAPN, robot-assisted partial nephrectomy.

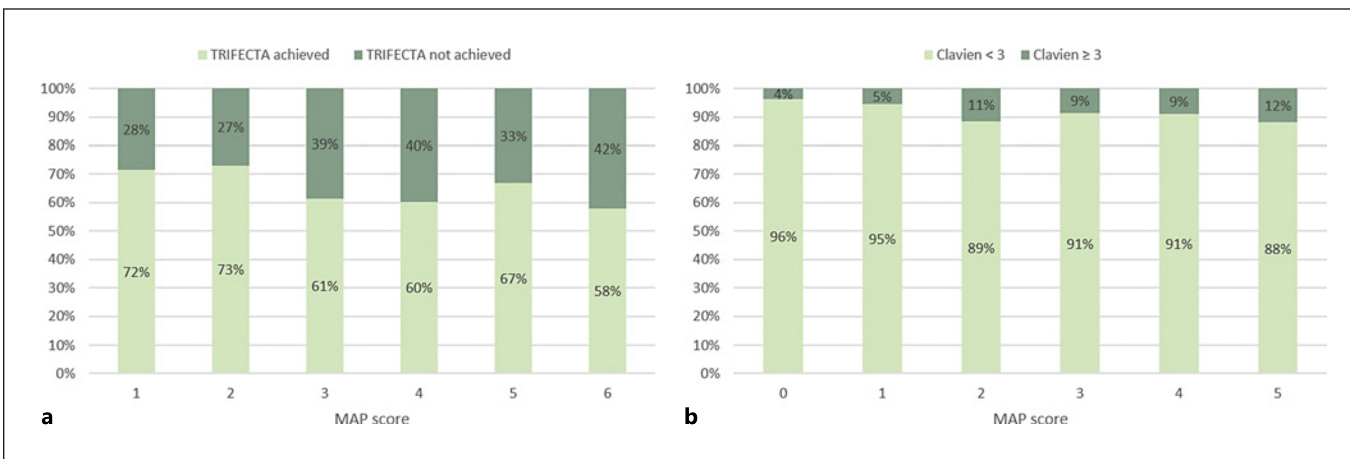

Fig. 1. TRIFECTA achievement (**a**) and major complications (CDC ≥3) (**b**) in the MAP subgroups.

influencing the surgical approach was a T stage ≥2 with an OR of 2.55 (95% CI 1.22–5.3, $p = 0.012$) while age >65 years, BMI ≥27.4 kg/m^2, and single kidney did not show to be predictors to rather decide for OPN as surgical approach than for RAPN in the multivariate analysis.

Discussion

The image-based MAP score for the prediction of the presence of APF showed to be a useful tool to broaden the spectrum of tumor-specific morphometry scoring sys-

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tems and to help predicting the complexity of PN. According to the literature, patients with high MAP scores or detection of APF are older than patients with lower MAP scores. Furthermore, they have higher BMI scores, and the proportion of males is higher in the cohorts with presence of APF and high MAP scores [19–21]. In our study, all those patient characteristics are independent predicting factors for a high MAP score.

Thus, our results underline the importance of considering those patient features during the preoperative surgery planning to estimate the probability of APF. In the presented analysis, an unfavorable MAP score could not be identified as an influencing factor on major postoperative complications. This is in line with other studies showing that a high MAP score can complicate the exposure of the tumor itself, but the removal is not affected due to APF and, therefore, major postoperative complications do not occur in a significant extent [9, 12, 21]. Similarly, Davidiuk et al. [5] and Bylund et al. [22] did not observe a significant correlation between high MAP scores and surgical complications rate [7]. Tomaszewski et al. [23] found the general health status of a patient, pictured by the comorbidities, to be the most important factor concerning the postoperative outcome and the development of severe postoperative complications in 1,092 patients undergoing PN or radial nephrectomy [24, 25]. Contrarily, Sempels et al. [14] recently observed adverse MAP scores to be strongly associated with major postoperative complications in a cohort of 181 patient undergoing RAPN or OPN. Furthermore, in laparoscopic donor nephrectomy, a high MAP score was associated with the risk of intra- and postoperative complications [13]. All in all, the results of diverse observations concerning the association of major postoperative complications and high MAP scores are inconsistent but the vast majority of authors states that the surgeon's experience and skills are a key factor to overcome intraoperative difficulties during APF dissection. Thus, a renal mass with a high MAP score in the hands of an experienced surgeon is unlikely to be an essential component for the development of major complications after PN.

In our study cohort, TRIFECTA achievement did not show to be associated with the MAP score. We did not observe a significant difference in warm ischemia time in both subgroups, and there was no difference in positive surgical margins or in overall complications. This is in line with Shumate et al.'s [26] recently published results of 205 patients undergoing RAPN. In that study, the presence of APF was not associated with warm ischemia time, positive surgical margins, or any postoperative complications [26]. Although Khene et al. [9] did not find high MAP scores to be an independent risk factor for the development of major postoperative complications, they found the MAP score as continuous variable to be adversely associated with TRFECTA achievement. However, stratified by groups (low vs. high MAP score) the association of MAP score and TRIFECTA achievement could not be confirmed.

The aforementioned results of our study are in line with multiple studies that have shown a significant correlation between high MAP scores and a prolonged operation time, whereas ischemia time is not affected by higher MAP scores [9]. Ishiyama et al. [10] divided the surgery duration in a dissection phase with freeing of kidney and the tumor surrounding sticky fat and a tumor resection phase and found that a high MAP score is strongly associated with the dissection phase. Even after eliminating effects associated with the steep learning curve of RAPN Shumate et al. [26] found APF to be significantly associated with an increased operation time suggesting that surgeon experience does not overcome the difficulties caused by APF in terms of tumor dissection. The usage of intraoperative ultrasound can be a helpful tool for identification and a precise exposure of the tumor when APF is encountered during surgery or when renal masses are located partly or completely endophytic [27–29]. In this study, intraoperative ultrasound was not used routinely but only if the surgeon saw a benefit in its usage. The correlation between the usage of intraoperative ultrasound and (high) MAP scores would be an interesting aspect to assess, but was not evaluated in this study.

Lately, there is evidence that robotic PN is feasible in large, complex, and hilar renal masses. However, to date, there is no general recommendation concerning the surgical approach in patients undergoing PN because of the lack of prospective randomized controlled trials. In this study, the MAP score, as a tool to predict the difficulty of dissection in patients undergoing PN, had a significant impact on the surgical approach. To our knowledge, this is the first study to evaluate whether patients rather undergo OPN or RAPN based on the MAP score. In our cohort, patients with a higher MAP score were more likely to undergo OPN. Multiple studies have shown that compared to OPN the advantages of RAPN are a decreased blood loss, less blood transfusions, lower perioperative complication rates, shorter length of hospital stay, and lower readmission rates. A systematic review from 2018 summarized these positive aspects but also reported a decreased operation time of OPN compared to RAPN [30]. In patient collectives absolutely requiring a short an-

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esthesia time, a lack of robot-experienced surgeons paired with unfavorable MAP scores may lead to OPN as reasonable surgical approach. Nonetheless, the advantages of RAPN always have to be considered as they may prevail even in the above mentioned scenario. Hence, additionally to tumor-centered morphometric scores and physical status scoring systems, the MAP score can be a supporting tool to decide whether OPN or RAPN is the best choice in terms of the overall outcome for a patient. Furthermore, the MAP score can help less experienced surgeons to select the surgical approach prospectively, as APF may complicate tumor isolation and thus, increase the risk of conversion to OPN [8, 9].

The present study has some limitations which have to be acknowledged. First, the retrospective study design might have introduced statistical bias and thereby limited the strength of the study. Second, there was no central radiological review concerning the MAP score, thus the evaluation of the radiological criteria could be biased by interobserver variability and weaken the reliability of the reported findings compared to studies installing a single expert (uro-) radiologist for MAP assessment. Moreover, our study includes two different surgical approaches, OPN and RAPN, which can be a confounder to our results. Furthermore, surgical experience itself might be a significant contributor to the outcomes. OPN and RAPN were performed by different surgeons with different levels of expertise in our cohort. This is important to consider in future trials to avoid learning curve effects.

A strength of this study is the large patient cohort with 698 patients and the homogenous division in the two subgroups MAP <3 and MAP ≥3. Moreover, the two considered surgical approaches were represented comparably.

Conclusion

In conclusion, our study results emphasize the need for high-quality preoperative imaging and the assessment of APF by using the MAP score in patients undergoing PN as further helpful aspect for adequate preoperative planning. Our case series highlighted that the MAP score might serve as a useful tool for choosing the most suitable surgical approach for each individual patient. Awareness of the clinical feature APF may help the surgeon setting expectations and evaluating surgical difficulty.

Acknowledgments

We thank the patients who participated in the study.

Statement of Ethics

The protocol for this research project has been approved by a suitably constituted ethics committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. University of Heidelberg's Ethics Committee II, Medical Faculty Mannheim, reference number 2014-526N-MA. All written informed consent was obtained from the subject(s) and/or their legal guardian(s).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Margarete Teresa Walach, Maximilian Christian Kriegmair, and Nina Natascha Harke: protocol/project development, manuscript writing/editing, and data analysis. Frank Schiefelbein, Andreas Schneller, Georg Schoen, Christoph A.J. von Klot, Olga Katzendorn, Julia Mühlbauer, and Philipp Nuhn: critical revision and scientific input.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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