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Influence of symptomatic pseudoaneurysms on postoperative renal function after partial nephrectomy: results of a matched pair analysis

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Abstract

Purpose A symptomatic pseudoaneurysm (SPA) is a rare but severe complication after partial nephrectomy (PN). Selective trans-arterial embolization (TAE) is the treatment of choice with high success rates. However, the influence of this intervention on postsurgical renal function has not been studied.

Methods Between 2005 and 2016 we performed 1047 PNs at our institution. Postsurgical SPA occurred in 40 patients (3.8%). Patients with and without SPA were matched in a 1:2 ratio concerning tumor complexity (RENAL) and pre-operative renal function (CKD stage). Any CKD upstage and a relevant CKD progression (CKD ≥ III) were defined as endpoints. Furthermore, the influence of the amount of contrast agent applied during TAE was assessed.

Results All patients with SPA were treated successfully with TAE. No significant difference could be detected concerning clinical, functional and surgical aspects. Median follow-up time accounted for 12.5 (6.75–27.5) months. Kaplan–Meier analyses detected an increased rate of any CKD upstage ($p = 0.066$) and relevant CKD progression ($p = 0.01$) in patients with SPA. Multivariate analysis identified post-operative SPA to be an independent predictor for a relevant CKD progression (HR 4.15, $p = 0.01$). The amount of contrast agents used did not have an impact on the development of a relevant CKD progression ($p = 0.72$).

Conclusion Patients treated with TAE after PN show an additional risk for an impairment of renal function over time. Hence, those patients should explicitly be informed about possible consequences and closely monitored by nephrologists.

Keywords Renal mass · Partial nephrectomy · Spontaneous pseudoaneurysm · Embolization · Kidney function

Introduction

Nephron sparing surgery (NSS) has been established as standard treatment of renal masses smaller than 4 cm and is increasingly used for larger organ-confined renal tumors [1, 2]. PN offers improved preservation of renal function without compromising oncological outcome [3–5]. Patients after PN have a reduced risk for chronic kidney disease and potentially fewer cardiovascular events underlining the importance of renal function preservation compared to radical nephrectomy [1, 6, 7]. However, PN is associated with a greater risk for the development of vascular lesions, such as symptomatic pseudoaneurysms (SPA), arteriovenous fistulas, or arterial bleedings [8, 9]. Thereby, the most common entity of vascular lesion is the SPA, which can be accompanied by an arteriovenous fistula or vessel injury. The incidence of the SPA varies and it occurs in up to 5%, depending on surgical approach and tumor complexity [10, 11]. Of

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note, the actual incidence of pseudoaneurysms after PN is most probably higher due to asymptomatic SPAs. Although SPA is rare, it harbors the risk of clinically significant blood loss and hemorrhagic shock making it a severe and potentially life-threatening complication. Selective trans-arterial embolization (TAE) of the renal vessels feeding the lesion is an effective and minimal invasive treatment option [12–14]. However, the effect of TAE on mid- and long-term renal function remains unclear. Potentially, the TAE associated quantitative renal parenchymal volume loss could lead to a worsening of renal function over time [15]. Furthermore, contrast agents used during embolization could add to the possible impairment of renal function as contrast-induced kidney injury is regarded as an important adverse effect of contrast agents [16–19]. Currently, available studies assessing renal function after TAE for SPA are strongly limited by sample size, follow-up and the proper distinction of surgical and interventional CKD [12, 15, 20]. Therefore, the objective of this study was to comprehensively assess the impact of TAE for SPA on kidney function in patients who underwent PN in a nephrometry matched-pair analyses.

Patients and methods

Study design, data collection, and patient matching

We retrospectively assessed consecutive patients undergoing partial nephrectomy (PN) at our institution between 2005 and 2016. Patients with SPA and subsequent TAE were identified and matched (1:2) with patients without this complication. Required follow-up for enrollment of the patients was at least 6 months. The matching criteria were RENAL score (absolute number, not risk group), pre-operative CKD stage, sex, age, and BMI. Medical charts, laboratory investigations, and radiological reports of all patients were carefully reviewed. The CKD stage was determined using the estimated glomerular filtration rate (eGRF) which was estimated using the MDRD study equation with the parameters age, serum creatinine level, and sex [21]. The CKD stage was defined using the KDIGO classification [22]. Any CKD upstage and a relevant CKD progression (CKD ≥ III) were defined as endpoints of this study. Furthermore, the influence of the amount of contrast agent applied during TAE was assessed. This parameter was available in 26 of 34 patients only. Only clinically symptomatic patients were included in this study. A general screening for vascular lesions by means of imaging did not take place.

Surgical technique

Open partial nephrectomy was the operative approach used in most of the patients. Robot-assisted PN was performed using the da Vinci Xi® surgical system and laparoscopic PN was performed via a transperitoneal approach. Open PN was performed via approach to the retroperitoneal cavity with a 10–15 cm flank incision above the 11th or 12th rib, depending on the localization of the tumor. After complete exposure of the kidney, tumor resection was performed either with clamping of the renal vessels (on-clamp excision) or in zero ischemia technique without clamping the renal vessels. Bleeding vessels were treated using polyfilament sutures and opened collecting system was treated using monofilament sutures. Renorrhaphy sutures were needed to adapt the edges of the renal wound surface by using one or two layers of monofilament sutures and in some cases hemostatic agents were applied (TachoSil®). Clips were not used for renorrhaphy. Perirenal fat was used to cover the kidney after the renorrhaphy. Finally, the tissue layers were adapted and the wound was closed [20].

Diagnosis and TAE

Possible SPAs were diagnosed clinically, when patients presented with severe flank pain, gross hematuria, or decrease of the hemoglobin level after recently performed PN. To confirm the suspicion of a SPA and to assure the diagnosis, patients underwent a multiple phase contrast-enhanced CT examination consisting of an arterial and venous phase of the abdomen, including a native CT scan. Arterial bleedings, SPAs and arteriovenous fistulas were identified performing a CT angiography. In the next step, selective renal angiography of the feeding vessels was performed and microcoils were placed close to the SPA to embolize it superselectively. In case of residual perfusion of the SPA additional microcoils were placed until no perfusion could be detected [20].

Statistical analysis

All statistical analyses were performed using statistical software JMP® from SAS (version 13 for Windows, SAS Institute Inc.). For descriptive data with normal distribution, mean ± standard deviation (SD) or the arithmetic mean was given. Comparisons between the groups were performed using the two group mean comparison *t* test. A p value < 0.05 indicated statistical significance. To analyze potential influencing and risk factors for an aggravation of renal function uni- and multivariate logistic regressions were performed. Log-rank analysis was performed to compare the probability not to develop a relevant CKD progression or any CKD upstage between groups. Kaplan–Meier curves visualize the probability over time.

Results

Overall, we assessed 1047 patients who underwent a partial nephrectomy. In 40 (3.8%) patients a SPA was diagnosed and subsequently treated with TAE. Due to incomplete follow-up we excluded 6 patients. The remaining 34 cases were matched to 68 patients without post-operative SPA in a 2:1 manner.

Table 1 shows the patient characteristics of the two groups. Patient age, BMI, ASA score, gender as well as diabetes and hypertension as accompanying diseases were assessed. No significant difference between both groups was found concerning any of the patient characteristics. Tumor characteristics and surgical outcome are presented in Table 2. Surgical approach (open PN, conventional laparoscopic PN, robot-assisted laparoscopic PN), tumor size, tumor classification, RENAL score and parameters such as on-clamp excision, median operation time (OT), warm ischemia time (IT), and estimated blood loss (EBL) were assessed amongst other characteristics. No significant difference could be detected between both groups. However, blood transfusion rates were significantly higher in patients with post-operative SPA compared to those without (44.1% vs. 1.5%, $p = 0.0001$) and patients with a consecutive SPA had a significantly longer hospital stay compared to the patients without SPA (11 days vs. 8 days, $p = 0.0001$). TAE was technically and clinically successfully performed with re-embolization in only two patients due to further bleeding after embolization. There were no complications after TAE. None of the patients needed radical nephrectomy after TAE.

As shown in Fig. 1 the pre-operative eGFR showed similar values in both groups ($p = 0.788$). In both groups there was a significant decline in eGFR at a median follow-up of 12.5 months after partial nephrectomy ($p = 0.005$ and $p = 0.001$) compared to pre-operative values. However, at follow-up the eGFR was lower in the SPA group as compared to the control group (64 ml/min vs. 75 ml/min; $p = 0.034$).

Kaplan Meier analysis revealed an increased risk for any CKD upstage and for relevant CKD progression in patients, who were treated for a SPA after PN as shown in Fig. 2 ($p = 0.0663$ and $p = 0.0096$). The pre-operative rate of CKD ≥ 3 in the SPA group was 17.6% and the post-operative and post-embolization rate was 41.2% ($p = 0.061$). In the group of patients without SPA after PPN the rate of CKD ≥ 3 was 20.6% both, pre- and post-operative ($p = 1.0$).

Table 3 shows the results of the uni- and multivariate analysis of predictors of the development of a relevant CKD progression. The occurrence of a SPA after PN was found to be the only positive predictor for the development of a relevant CKD progression (univariate analysis: HR 3.92, CI 1.33–13, $p = 0.013$, multivariate analysis: HR 4.15, CI 1.39–13.87, $p = 0.011$), whereas other factors, such as RENAL score, pre-operative CKD stage and age did not have a relevant influence. The results of the uni- and multivariate logistic regression for any CKD upstage are given in Table 4. Here, higher RENAL scores (10–12) were found to be a positive predictor for the development of any CKD upstage (univariate analysis HR 2.90, CI 0.13–6.62, $p = 0.029$, multivariate analysis HR 3.07, CI 1.18–7.13, $p = 0.024$). SPA was not significant for any CKD upstage but there was a positive tendency.

Overall, the amount of contrast agent used during angioembolization was 147 ± 54 ml. There was no statistical difference in the amount of contrast agent used between the group of patients who developed a relevant CKD progression and those who did not ($p = 0.715$, Fig. 3). There was no difference in the decline of the eGFR between patients who received high and low amounts of contrast agent (cut-off median of 135 ml) (ΔeGFR 22 ± 24 ml/min vs. ΔeGFR 33 ± 24 ml/min; $p = 0.492$).

Complications after PN were measured by the Clavien-Dindo classification. In the SPA group the minimum grade was 3a due to the radiological intervention. One patient in

Table 1 Patient characteristics of 102 included patients

	All patients	Patients without aneurysm	Patients with aneurysm and TAE	*p* value
Number of patients (*n*)	102	68	34	
Age in years median (IQR)	64 (53–74)	62.8 (53.2–74.3)	65.9 (52.0–74.4)	0.410
BMI in kg/m^2 median (IQR)	26.8 (23.9–30.1)	27.0 (23.9–30.2)	26.4 (24.2–30.2)	0.972
Male, % (*n*)	79.4 (81)	79.4 (54)	79.4 (27)	1.0
ASA, median (IQR)	2 (2–2)	2 (2–2)	2 (2–3)	0.912
Diabetes, % (*n*)	12.7 (13)	11.8 (8)	14.7 (5)	0.756
Hypertension, % (*n*)	62.7 (64)	63.2 (43)	61.7 (21)	1.0
Time to occurrence of aneurysm in days, median (IQR)			9.5 (4.75–14.25)	

Table 2 Tumor characteristics and surgical outcome

	All patients	Patients without aneurysm	Patients with aneurysm and TAE	*p* value
Number of patients (*n*)	102	68	34	
RENAL, % (*n*)				
Low complexity	26.5 (27)	26.5 (18)	26.5 (9)	1.0
Moderate complexity	58.8 (60)	58.8 (40)	58.8 (20)	1.0
High complexity	14.7 (15)	14.7 (10)	14.7 (5)	1.0
Operative approach, % (*n*)				
Open	90.2 (92)	89.7 (61)	91.2 (31)	1.0
Laparoscopic and robot-assisted	9.8 (10)	10.3 (7)	8.8 (3)	1.0
Tumor size in cm median (IQR)	3.5 (2.5–4.7)	3.4 (2.5–5.2)	3.8 (2.5–4.5)	0.785
Tumor side, % (*n*)				
Right	54.9 (56)	60.3 (41)	44.1 (15)	0.143
Left	45.1 (46)	39.7 (27)	55.9 (19)	0.143
Malignant, % (*n*)	83.3 (85)	79.4 (54)	91.2 (31)	0.166
Histology if malignant tumor, % (*n*)				
Papillary type	18.8 (16)	22.2 (12)	12.9 (4)	0.392
Clear cell	69.5 (59)	64.8 (35)	77.4 (24)	0.328
Chromophobe	8.2 (7)	9.3 (5)	6.5 (2)	1.0
Others	3.5 (3)	3.7 (2)	3.2 (1)	1.0
Transfusion, % (*n*)	15.7 (16)	1.5 (1)	44.1 (15)	0.0001
On-clamp excision, % (*n*)	82.4 (84)	82.4 (56)	82.4 (28)	1.0
Blood loss in (ml), mean ± SD	312 ± 273	307 ± 264	323 ± 301	0.788
Ischemia time (min), mean ± SD	21 ± 10	22 ± 12	21 ± 10	0.846
Operation time (min), mean ± SD	165 ± 60	159 ± 51	178 ± 74	0.148
Length of hospital stay (days), median (IQR)	8 (7–11)	8 (7–9)	11 (8–14.5)	0.0001

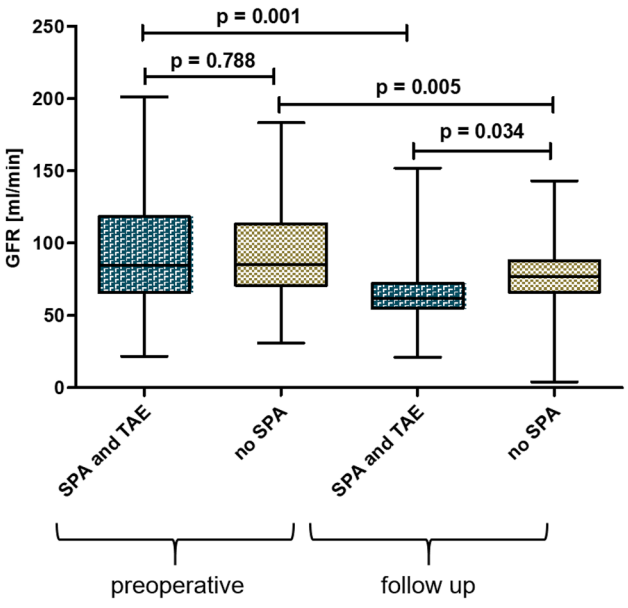

Fig. 1 Pre- and postsurgical eGFR values (91 ± 40 ml/min vs. 89 ± 32 ml/min and 64 ± 24 ml/min vs. 75 ± 25 ml/min) after a median follow-up time of 12.5 months

this group died. Thus, the maximum grade was 5. In the group without post-operative SPA the grades were 0–4a, as one patient needed dialysis after PN.

Discussion

NSS is the operative gold standard for organ-confined renal tumors and should be preferred to radical nephrectomy whenever possible. Besides the benefits of PN, such as a lower risk of post-operative chronic renal impairment, there is an increased risk of vascular complications, such as post-operative SPAs and arteriovenous fistulas. Although these complications are rare, they are potentially life-threatening and patients require immediate diagnosis and treatment. In such cases, TAE has been proven to be effective and safe [13, 23]. In our patient cohort we found a SPA rate of 3.8%, which is consistent with previous studies [9, 10, 12]. Generally, the risk of SPAs after NSS in patients who received laparoscopic NSS is higher than of those who received open surgery [10, 13]. However, the reason for a higher complication rate after laparoscopic surgery remains unclear [24]. One explanation proposed by Singh et Gill is the use of

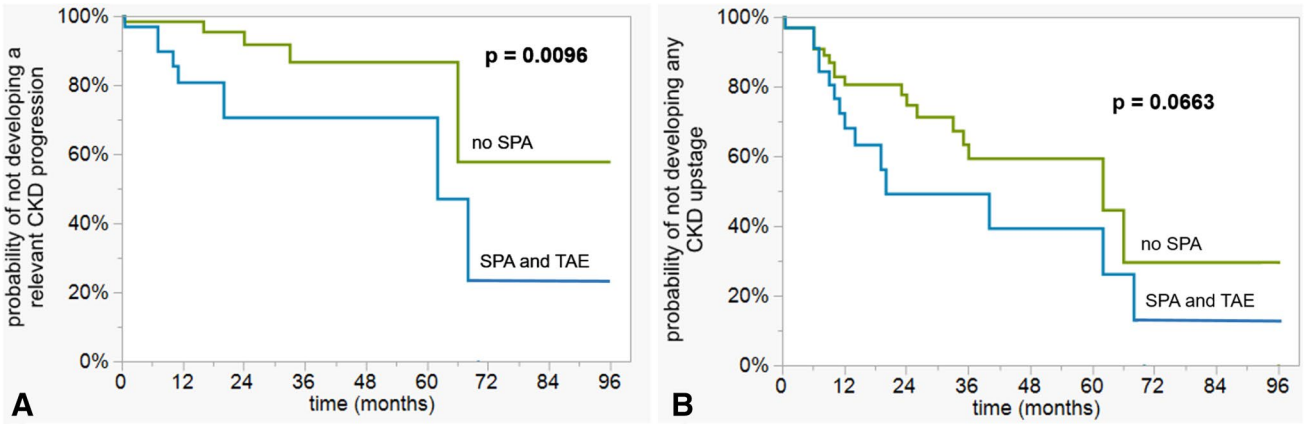

Fig. 2 Kaplan–Meier curves of the probability of not developing a relevant CKD progression (**a**) or any CKD upstage (**b**) over time

Table 3 Uni- and multivariate analyses for relevant CKD progression

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Probability to develop a relevant CKD progression						
Aneurysm	3.92	1.33–13.0	0.013	4.15	1.39–13.87	0.011
Pre-operative CKD stage (1–2 vs. 3–5)	0.88	0.22–5.83	0.872	0.56	0.12–4.02	0.513
Age (< 65 years vs. ≥ 65 years)	2.07	0.63–7.32	0.227	2.54	0.70–10.47	0.158
RENAL score (4–9 vs. 10–12)	0.95	0.17–17.74	0.962	0.98	0.17–18.71	0.988

Table 4 Uni- and multivariate analyses for any CKD upstage

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p* value	Hazard ratio	95% CI	*p* value
Probability to develop any CKD upstage						
Aneurysm	1.85	0.93–3.62	0.079	1.81	0.91–3.56	0.089
Pre-operative CKD stage (1–2 vs. 3–5)	1.91	0.67–7.99	0.249	1.81	0.60–7.86	0.319
Age (< 65 years vs. ≥ 65 years)	1.78	0.88–3.68	0.109	1.56	0.75–3.37	0.236
RENAL score (10–12 vs. 4–9)	2.90	0.13–6.62	0.029	3.07	1.18–7.13	0.024

larger needles during the laparoscopic approach with the result of a higher risk of vessel injury and post-operative bleeding into the parenchyma. Furthermore, in conventional laparoscopy the feasibility of accurate suturing of small bleeding vessels in the resection bed is inferior to open or robotic surgery [25].

In patients with post-operative SPA the diagnosis was made 9.5 days (median, interquartile range 4.75–14.25 days) after NSS. This time frame corresponds to other reports [10, 12, 13, 23, 26, 27]. Only one patient showed a noticeable delayed development of SPA 42 days after PN. The variation in time until the SPA appears after PN emphasizes the need for close follow-up examination and even more important, the need for awareness of this complication especially within the first month after surgery. The most common clinical symptom of a SPA was gross hematuria (65%) with other presenting symptoms being flank pain or acute anemia due to blood loss [8, 28].

Selective TAE as therapeutic method of choice is a highly effective and safe procedure. By precise closure of only the feeding target vessel, microcoil embolization enables preservation of renal parenchyma and prevents renal impairment [29]. Parenchymal damage associated to TAE can be traced to different features of the procedure, such as the size of the microcoils, the experience of the interventional radiologist, good or poor accessibility of the vascular lesion by means of the catheter. Thus, the number of microcoils used may not implicitly be related to the size of the lesion and the extent of

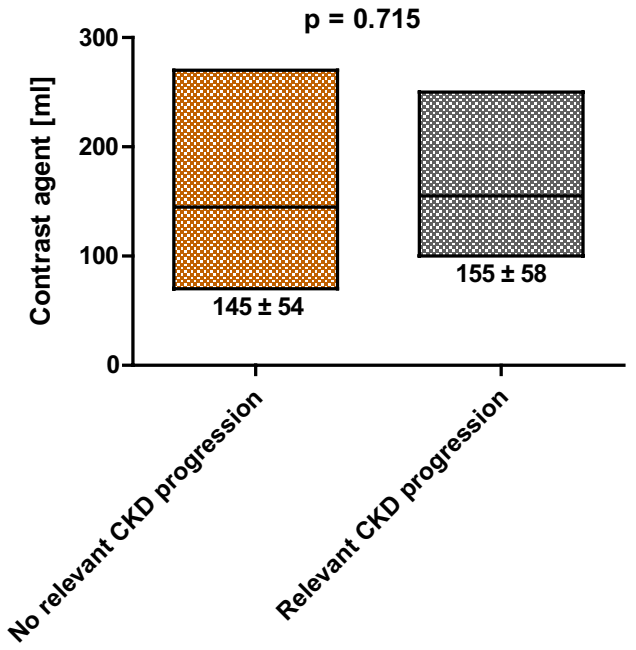

Fig. 3 Amount of applied contrast agent in ml (mean ± SD) in patients with relevant post-operative CKD progression and patients without relevant CKD progression

the loss of functional renal tissue. Although TAE has been shown to be effective in many small series its impact on mid- and long-term renal function remains unclear and is not well studied. Preservation of renal function is a major goal of NSS. Indeed, nowadays patients treated for a cT1 renal cell carcinoma are more likely to die of complications related to CKD as to the malignancy itself [30]. Therefore, knowledge on possible influencing factors of renal function is crucial to identify patients at risk for CKD. Remarkably, Strobl et al. found a mean loss of functional parenchyma volume of 25.2% after TAE for SPA [15]. Surprisingly, in this study the mean eGFR did not significantly decrease after embolization ($p = 0.501$), but after the preceding PN ($p < 0.01$) [15]. Of note, both eGFR measurements were collected only one day after the intervention (PN and embolization, respectively) and long-term data were not provided. Several other studies have similarly reported stable eGFR results after embolization in a comparable setting but mostly with a short follow-up time and small sample sizes as study limitations [31]. In addition, Gahan et al. did not find an eGFR reduction after embolization in 28 patients who developed a SPA after NSS in a non-comparative study, measured after a mean post-operative time of 362 days ($p = 0.501$) [12]. In our matched-pair study we investigated the mid-term outcome concerning renal function after PN and PN plus embolization of a SPA with a median follow-up time of 12.5 months (interquartile range 6.75–27.5 months). This allowed for differentiation between surgically induced renal damage and the impact of TAE on renal function. Due to the matched-pair approach, both groups showed similar pre-operative eGFR values. After a median follow-up time of 12.5 months the eGFR dropped in both groups significantly (75.24 ml/min vs. 64.07 ml/min, $p = 0.005$ and $p = 0.001$ respectively), reflecting the surgically induced renal function impairment. The comparison of the mid-term eGFR results of both groups showed significantly decreased eGFR values in the group of patients who underwent TAE compared to those who did not develop a post-operative SPA (mean eGFR 64.07 ml/min vs. 75.24 ml/min, $p = 0.034$) suggesting a potential impact of the TAE itself. Indeed patients were more likely to experience an upstage in CKD stage or develop CKD ≥ stage III, if a TAE was required. These results reflect the importance of detailed information about PN and possible associated complications and nephrological check-ups at regular intervals in case of a TAE.

Most likely the negative impact of TAE on mid-term renal function is due to loss of perfused renal volume after TAE as previously described [15]. This adds up to the excisional volume loss during PN and a possible ischemia–reperfusion damage, putting the respective patients at high risk for CKD development [32]. Furthermore, TAE carries not only the risk of a reduced renal function via direct damage of renal parenchyma but also via the contrast load during angioembolization. There is evidence that contrast agent can lead to a contrast-induced nephropathy, especially when applied during trans-arterial intervention [33, 34]. Nevertheless, in our cohort, we could not identify a dose depended influence of the contrast agent on renal function outcome. The amount of contrast agent used during TAE did not significantly differ between patients who developed a relevant CKD progression and those who did not ($p = 0.715$). Likewise, the ΔeGFR (before and after angioembolization) of patients receiving high and low levels of contrast agent did not differ significantly ($p = 0.492$). Finally, another mode of action could include new onset arterial hypertension after TAE. Indeed, Collins et al. described an increase and aggravation of arterial hypertension after TAE for vascular lesions in some patients after therapeutic TAE [35, 36]. Since arterial hypertension leads to long-term renal damage this mode of action is less likely to be of relevance in our cohort with a median follow-up of 12.5 months.

Our analysis showed the development of a SPA to be an independent risk factor for the development of a relevant CKD progression. Furthermore, a higher complexity of the tumor, reflected by RENAL scores between 10 and 12, also showed to be an independent risk factor for the development of any CKD upstage, which is conform to another study showing the tumor complexity to be an independent risk factor for SPA [20].

There are several limitations in this study. First of all, the study design was retrospective. This might have caused

a selection bias as only patients who presented at our institution with SPA after PN were included and the incidence may be under-reported. Furthermore, we could not perform comparisons between different surgical approaches (open vs. laparoscopic vs. robot-assisted) as most of our patients underwent open partial nephrectomy. In addition, detailed data on the number and size of microcoils used, the duration of the intervention, the experience of the interventional radiologist, and the accessibility of the vascular lesion with the catheter were not available and included in the analyses. Moreover, we assume that the renal tissue loss due to TAE is the reason for the impairment of renal function over time but we could not confirm the amount of contrast medium to be associated with this.

Although superior to existing studies, our follow-up does only provide mid-term renal function outcomes.

Conclusion

SPAs are rare but severe and potentially life-threatening complications after PN. TAE is the method of choice to efficiently treat these vascular complications. Our data show that renal function can be affected to some extent by angioembolization and patients are at higher risk to develop CKD. Therefore, affected patients should be informed and examined regularly by a specialist.

Author contributions MTW: Protocol/project development, Manuscript writing/editing, Data analysis, NR: Data collection/ critical revision and scientific input, SP: critical revision and scientific input, DP: critical revision and scientific input, SJD: critical revision and scientific input, MR: critical revision and scientific input, MSM: critical revision and scientific input, NW: critical revision and scientific input, PH: critical revision and scientific input, MCK: Protocol/project development, Manuscript writing/editing, Data analysis.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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