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Performing an early systematic Doppler-ultrasound fails to prevent hemorrhagic complications after complex partial nephrectomy

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Abstract

Background: The aim of this work was to assess the clinical relevance of a systematic postoperative Doppler-ultrasound (DU) after complex partial nephrectomy (PN).

Materials and methods: All patients who underwent open, laparoscopic or robotic PN from 2014 to 2017 at our institution were included. Postoperative hemorrhagic complications (HCs) were defined as the occurrence of blood transfusion, hemorrhagic shock, arterial embolization, or re-hospitalization for hematoma. DU was systematically performed between post-op day 4 and 7 for every complex tumor (RENAL score $\geqslant 7$). DU was considered positive in the presence of pseudoaneurysm (PA) or arteriovenous fistula (AVF).

Results: Among 194 patients, 117 underwent DU (60.3%). We reported 22 HCs (11.3%) requiring 8 selective embolization procedures (4.1%). HCs occurred during the hospital stay in 17 patients (77.3%), thus directly diagnosed on a computed tomography scan. Among the five patients (22.7%) with HC occurring after hospital discharge, between day 7 to 15, four had a previously negative systematic DU. Overall, systematic DU was positive in only five patients (4.3%) with only one patient of 194 (0.5%) undergoing preventive embolization of a PA-AVF. The negative predictive values (NPVs) and positive predictive values of DU were respectively 96.5% and 5%, with 20% sensitivity and 96.5% specificity.

Conclusions: Our results may suggest offering systematic DU in patients under antiplatelet therapies, with high tumor size (>T1b), or early postoperative hemoglobin variations. A high NPV of DU might be counterbalanced by its low sensibility. Since all secondary HCs occurred between postoperative day 7 to 15, our results may suggest differing DU in selected cases.

Keywords: Doppler-ultrasound, kidney cancer, oncology, partial nephrectomy

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Introduction

Partial nephrectomy (PN) is a standard of care for patients with renal cell carcinoma of low stage (T1/T2), whenever feasible.[1] Along with the development of imaging leading to an increased fortuitous diagnosis of renal masses, the expansion of robotic surgery amplified the range of kidney tumors manageable by nephron-sparing surgery leading to a wide diffusion of PN even for complex lesions.[2] The postoperative complications of PN are rare but potentially severe and life threatening.[1,3,4] They include mostly urinary fistulae and renal parenchymal bleeding due to the highly vascularized renal parenchyma.[5] The hemorrhagic complications (HCs) due to renal artery pseudoaneurysm (PA) and arteriovenous/excretory system fistulas (AVFs) are reported with a low incidence of

3–10%.[4–8] However, onset of HCs is associated with tumor complexity that may be assessed using the RENAL score.[5,9] HCs may occur in the early postoperative course during the hospital stay or after the patient's discharge[10] and are mainly treated using blood transfusions, but may occasionally require embolization, re-intervention, or rarely nephrectomy.[11]

Thus, the potential severity of HCs may suggest that an early detection of PA and AVFs using Doppler-ultrasound (DU)[6] could contribute to reduce morbidity after complex PN. We therefore postulated that performing systematic DU before a patient's discharge after complex renal tumorectomy (RENAL $>$ 7) could lead to improved surgical outcomes.

The objective of this study was to evaluate the current relevance of this strategy after PN by earlier diagnosis of PA or AVFs (PA-AVFs). The primary objective was to evaluate the predictive values, sensitivity and specificity of DU to detect HCs and the secondary objective was to assess their risk factors.

Methods

Patient population

All consecutive patients undergoing lumbotomy or robotic PN at our institution from November 2014 to April 2017 were prospectively included in our database. A consent was obtained for each patient operated on by kidney surgery in our department.

PN was completed after a hilar or parenchymal clamping, with classical resection of the tumor and renorrhaphy.

Collected data included patient and renal tumors characteristics, perioperative data and postoperative follow up. The tumor size was classified according to the TNM and to the RENAL score (0–4 cm, 4 cm and $\geqslant$7 cm). In addition, surgical approach, occurrence of hematuria or postoperative hemorrhage, type of postoperative radiological examination, the ultrasound diagnosis of a PA-AVF and the delay before the onset of hemorrhagic complication were assessed.

Definition of HCs

Postoperative HCs were defined as the occurrence of any of the following: postoperative blood transfusion, hemorrhagic shock, arterial embolization or re-hospitalization for retroperitoneal hematoma within 30 days postoperatively.

Design of the study

Indication for DU was systematic for RENAL tumors $\geqslant$7 and to the discretion of the operator for lower RENAL score tumors. The DU was performed by a radiologist senior on a Toshiba Aplio 500 ultrasound scan, in a mode B analysis of the kidney operated on (assessing for perirenal hematoma or complication on urinary tract), completed by a pulsatile and colorimetric Doppler (assessing for vascular complication). Resistance index assessment were systematic to look for vascular injury due to renal artery clamping.

DU was considered positive in the presence of PA-AVF. Hence, the negative predictive value (NPV) of this examination was defined by the absence of HCs after a negative DU.

PA was suspected when perirenal hematoma was found on ultrasound or when an anechogenic circular image with vascularization inside was found in Doppler mode. AVF was suspected when no abnormality was found in mode B Doppler associated with an 'aliasing' artefact in colorimetric Doppler, containing a turbulent arterial flow in pulsatile Doppler.

When a PA-AVF was diagnosed on DU, it was confirmed on a contrast enhanced computed tomography (CT) scan. Angio-embolization was decided if an active bleeding was found or in presence of a supra-centimetric PA-AVF. When no active bleeding was found on a CT scan, patients were closely followed up with iterative DU until spontaneous regression of the PA-AVF.

Statistics

Continuous variables are described using means and standard deviations (SDs) or median and interquartile ranges (IQRs). Nominal data were expressed as counts and percentages. We compared means and proportions between groups using a Student's t test (or Mann–Whitney test if appropriate) and Fisher's exact test.

Logistic regression was applied to quantify the odd ratios (ORs) and the 95% confidence intervals (CIs) for the risk of postoperative hemorrhagic complication. The final multivariable

regression model was obtained by entering the risk factors from the univariate model that achieved $p \leqslant 0.20$ as the thresholds in a single multivariable regression model. Factors with a p value $\leqslant 0.05$ were considered as independently associated with the risk of postoperative hemorrhagic.

All analyses were performed using R using GPU® software and Stata® version 15.1 (StataCorp, College Station, TX, USA)

Results

Among 194 included patients, 122 (62.9%) underwent open partial nephrectomy (OPN) and 72 (37.1%) had robot-assisted PN (RAPN). No patient underwent laparoscopic-assisted PN (LAPN).

Patient characteristics are presented in Table 1. Patients were divided into two groups according to surgical outcome: with or without HCs.

Systematic DU

Eventually, 117 patients (60.3%) underwent a systematic DU between postoperative day 4 (D4) and day 7 (D7) as shown in Figure 1. Overall, systematic DU was positive in five patients (2.6%; two PA and three AVF); among them, only one patient (0.5%) presented a HC requiring a blood transfusion and angioembolization with diagnosis of perirenal hematoma at postoperative D7. In the DU-negative group, four patients experienced HCs occurring after hospital discharge (between D7 and day 15).

The negative and positive predictive values of DU were respectively 96.4% and 20% with 20% sensitivity and 96.4% specificity. Among the 77 patients without systematic DU, 17 patients had a CT scan for early HCs occurring before postoperative day 4, that is, before hospital discharge, and the remaining 61 others experienced no HCs.

HCs

The details of HCs occurring after PN and their treatments are presented in Table 2.

Overall, we reported 22 HCs (11.3%) occurring on average 4.8 days (0–15) postoperatively and requiring 8 selective embolization procedures (4.1%), 18 blood transfusions (9.23%), 1 re-intervention (0.5%) and 5 re-hospitalizations (2.5%).

HCs occurred during the hospital stay in 17 patients (77.3%) before D4, thus directly diagnosed on a CT scan (4 perirenal hematomas, 1 AVF, 3 PA and 6 active bleedings without PA-AVF). Among them, 14 required blood transfusions, 6 embolizations and 1 re-intervention. No HCs occurred after patient discharge among patients without systematic DU.

Risk factors of HCs

In the univariate analysis, the following variates presented a p value <0.2 and were then included in the multivariate analysis: tumor size >7 cm [OR 5.51; 95% CI (1.539–19.73), $p = 0.0167$], variation of preoperative hemoglobin between preoperative day (D–1) and postoperative day 1 (D1) [OR 1.917; 95% CI (1.374–2.675), $p < 0.0001$], RENAL score [OR 3.447; 95% CI (1.132–8.76), $p = 0.0556$], diagnostic of postoperative PA-AVF [OR 27.05; 95% CI (7.270–100.615), $p < 0.0001$] and use of antiplatelet aggregating agent [OR 2.429; 95% CI (0.862–6.845), $p < 0.0931$] were significantly associated with HCs. In multivariate analysis, only the use of an antiplatelet aggregating agent [OR 7.928; 95% CI (1.979; 31.749), $p = 0.003$] and variation of hemoglobin between D-1 and D1 [OR 2.214; 95% CI (1.518; 3.227), $p < 0.001$] were significantly associated with HCs.

Discussion

In our study, the incidence of HCs after PN was 11.3%, requiring medical intervention in 82% of cases. Since four out of the five patients with HCs occurring after discharge had a negative systematic DU, we conclude that performing a systematic DU after complex PN failed to improve surgical outcomes.

Our proposed strategy may have been irrelevant because of the early timing of DU (between postoperative D4 and D7), hence explaining its low predictive positive value (5%). All HCs during hospitalization occurred before postoperative D4 and all late HCs after postoperative D7 suggesting that performing a systematic DU before discharge is too late to prevent immediate bleeding and too early to detect secondary complications. In the literature, a mean delay of symptomatic HCs after PN was around day 12 which is similar to our results[4–6,12] (Table 4).

Table 1. Patient characteristics.

	No hemorrhagic complication ($n = 172$)	Hemorrhagic complications ($n = 22$)	*p*
Patient characteristics			
Age (years), mean (SD)	57.73 (13.55)	55.66 (18.59)	0.756
Sex male, No. (%)	117 (68.02)	12 (54.55)	0.234
BMI (kg/m^2), mean (SD)	26.94 (4.81)	25.83 (6.16)	0.105
eGFR (MDRD), (ml/min/1.73 m^2), mean (SD)	82.70 (19.73)	82.91 (20.21)	0.910
Antiplatelet aggregating agent, no. (%)	23 (13.37)	6 (27.27)	0.108
ASA score, no. (%)			
Score 1	62 (36.04)	6 (27.27)	
Score 2	100 (58.14)	16 (72.73)	
Score 3	8 (4.65)	0	0.497
Hemoglobin presurgery (g/dl), mean (SD)	14.20 (1.54)	13.87 (1.53)	0.461
Tumor's characteristics			
Tumor size (cm), median (IQR)	3.4 (2.5–4.8)	5 (3.7–6.8)	**<0.001**
RENAL score, median (IQR)	7 (6–9)	8 (8–9)	**0.018**
MAP score, median (IQR)	2 (0–3)	0 (0–2)	0.058
PADUA score, median (IQR)	9 (8–10)	10 (8–11)	0.262
Surgical variables			
Time of surgery (min), mean (SD)	148.39 (38.19)	149.25 (44.55)	0.939
Blood loss (ml), median (IQR)	150 (50–300)	175 (75–450)	0.349
Ischemia time (min), mean (SD)	18.06 (8.91)	15.2 (10.92)	0.315
Outcomes			
Hemoglobin at day 1 (g/dl), mean (SD)	12.86 (1.49)	11.05 (2.30)	**<0.001**
Delta Hb presurgery –day 1 (g/dl), mean (SD)	–1.33 (1.15)	–2.65 (1.93)	**0.009**
Hemoglobin the last day (g/dl), mean (SD)	12.19 (1.74)	10.62 (1.35)	**<0.001**
Delta Hb day 1 – last day (g/dl), mean (SD)	–0.67 (0.96)	–0.43 (1.85)	0.951
AVF, no. (%)	4 (2,33)	10 (45,45)	**<0.001**
Duration of hospitalization (day), mean (SD)	4.81 (1.55)	8.14 (4.40)	**<0.001**

ASA, American Society of Anesthesiologists; AVF, arteriovenous fistula; BMI, body mass index; eGFR (MDRD), estimated glomerular filtration rate (modification of diet in renal disease); IQR, interquartile range; last day, out day; MAP, Mayo adhesive probability score; PADUA score, preoperative aspects and dimensions used for an anatomical; RENAL, radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in mm, anterior/posterior location relative to polar lines nephrometry scoring system; SD, standard deviation.

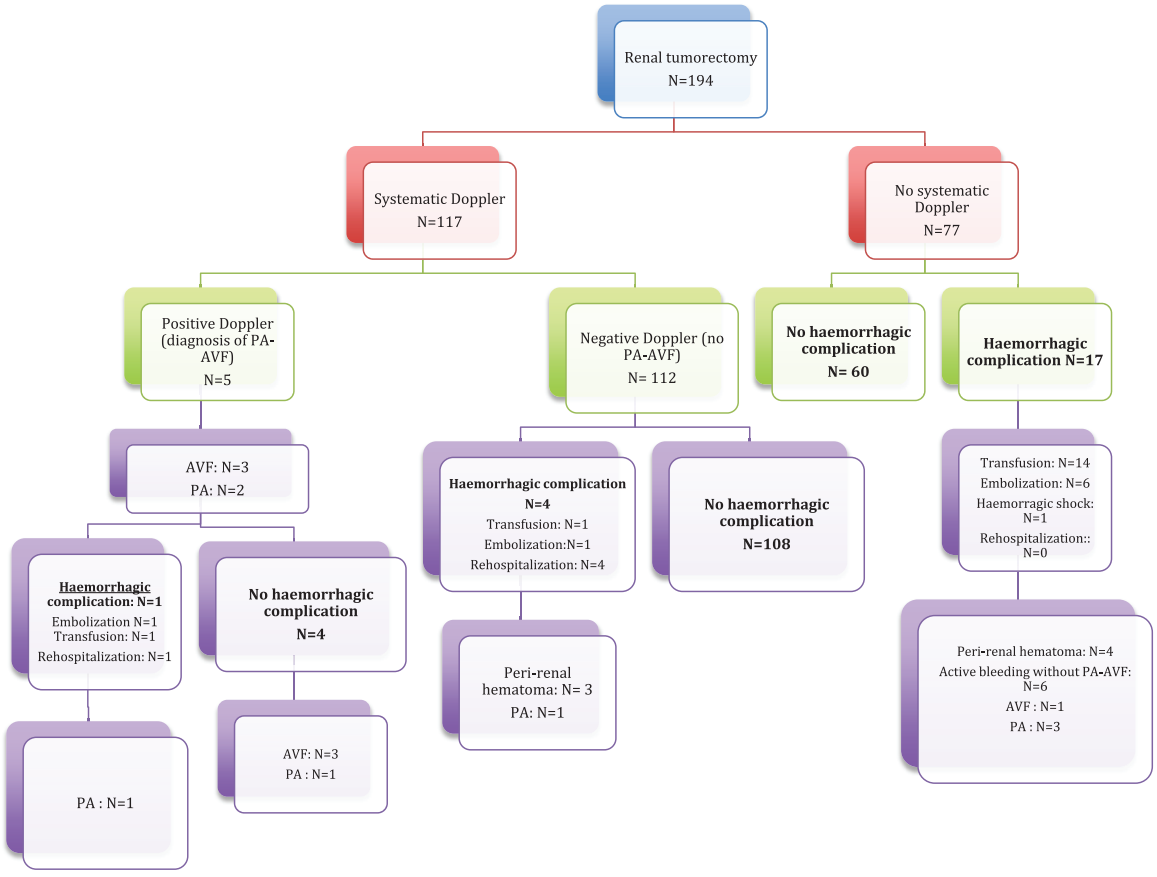

Figure 1. Flow chart.
AVF, arteriovenous fistula; PA, pseudoaneurysm.

Thus, one may suggest that performing systematic imaging around postoperative day 10 may improve its sensitivity to detect PA and AVF but no result from our study may corroborate this hypothesis.

The low sensitivity of DU in our study (20%) may also be explained by the choice of imaging technique. Thus, some authors assessed the contribution of early systematic CT scan after PN, with arterial and nephrographic phases in case of stable hemodynamics.[6] According to Cohenpour and colleagues,[6] a CT scan was more sensitive than DU to detect renal artery pseudoaneurysm since DU can be challenging with high inter-observer variability to distinguish a PA from a hematoma.

However, repeat CT scans expose patients to ionizing radiation and, most importantly, to the injection of contrast enhancement agents that may increase acute kidney injury in patients with recent renal surgery and arterial clamping. Smith-Bindman and colleagues[17] reported the radiation dose received after CT scans and assessed the associated risk for cancer in 1119 patients: the dose received by each patient for an abdominal CT scan was around 31 msv and the associated risk for cancer was estimated as high as 4 cancers per 1000 patients (range = 0.83–11.1). Regarding nephrotoxicity, Omae and colleagues[18] reported no difference in 1-year glomerular filtration rate (GFR) variations in patients with or without an early systematic CT scan after PN (−9.7 % in the CT scan group *versus* −9.1% in the no CT scan group). However, patients had two functioning kidneys with a baseline GFR of 64.5 ml/min/1.73 and mean clamping time of 23 min which represents a strong limitation to demonstrate the safety of early CT scan in that indication. Of note, DU is feasible at the patient's bedside, may be safely repeated, and improved by the utilization of contrast enhancement microbubbles, sparing the tubular cells.[19]

Table 2. Hemorrhagic complications and treatments.

	Number of patients (%)
Onset of hemorrhagic complications	$n = 22$ (11.28%)
During hospitalization	$n = 17$ (8.72%)
After discharge	$n = 5$ (1.03%)
Clinical presentation	
• Blood loss	n =13 (6.67%)
• Hemorrhagic shock	$n = 5$ (2.56%)
• Macroscopic hematuria	$n = 2$ (1.03%)
• Abdominal pain	$n = 2$ (1.03%)
Diagnostics	
• Perirenal hematoma with blood transfusion	$n = 5$ (2.56%)
• Perirenal hematoma without blood transfusion, with re-hospitalization	$n = 2$ (1.03%)
• Active bleeding on site of tumorectomy	$n = 6$ (3.1%)
• Renal artery pseudoaneurysm (RAP)	$n = 4$ (2.1%)
• Arteriovenous fistula	$n = 2$ (2.1%)
• Isolated blood loss	$n = 3$ (1.6%)
Treatments	
• Blood transfusion	$n = 18$ (9.23%)
• Angioembolization	$n = 8$ (4.1%)
• Salvage surgery	$n = 1$ (0.51%)

An early detection of renal vascular lesions like PA or AVF could theoretically lead to a prophylactic angioembolization before the onset of symptomatic HCs.

Morita and colleagues[7] evaluated the interest of early systematic CT scans (day 3–5) after PN (including OPN, RAPN and LAPN) with systematic angioembolization in the case of PA. Among 312 patients with a systematic CT scan, 8% (26/312) had prophylactic angioembolization of PA. They reported a rate of HCs of 0.6% which was significantly lower than in the group without a systematic CT scan (4.6%, $p = 0.038$). However, the reduction of risk for HCs has to be balanced with the specific risks of angioembolization (femoral artery injury and increased territory of renal ischemia). In our study, no prophylactic angioembolization has been performed for asymptomatic PA,

Our incidence of HCs and rate of angioembolization were similar to those reported in the literature (Table 4).[7–9,12] Of note, because data were collected prospectively, our study reports all hemorrhagic events including pauci-symptomatic hematoma with spontaneous resolution and blood transfusion whereas most authors mainly focus on HCs requiring surgical or radiologic intervention.[16,20]

Due to its prospective design and its significant sample size, our cohort enabled us to conduct univariate and multivariate analysis. Tumor size,

Table 3. Factors associated with hemorrhagic complications in the univariate analysis.

		Number of patient	Number of events	OR	95% CI	*p*
Patient's characteristics						
Patient's age (per 1-yr increment)		194	22	0.990	(0.9960–1.021)	0.5196
Sex	Female	65	10	1	–	
	Male	129	12	0.564	(0.230–1.385)	0.2116
BMI (per 1 kg/m^2 increment)		193	22	0.953	(0.865–1.047)	0.3281
eGFR (ml/min/1.73 m^2) (per 1 ml/min/1.73 m^2 increment)		187	22	1.001	(0.978–1.023)	0.9635
ASA score	0	29	8	1	–	
	⩾ 1	113	43	1.531	(0.569–4.115)	0.3987
Hemoglobin presurgery (g/dl), (per 1 g/dl increment)		180	20	0.875	(0.655–1.169)	0.3671
Antiplatelet aggregating agent	No	165	16	1	–	
	Yes	29	6	2.429	(0.862–6.845)	0.0931
Tumor characteristics						
Tumor size (cm)	[0–4]	115	7	1	–	
	[4–7]	59	10	3.149	(1.132–8.760)	
	⩾7	19	5	5.510	(1.539–19.73)	**0.0167**
RENAL score	0–7	57	3	1	–	
	⩾7	112	18	3.447	(0.971–12.240)	0.0556
PADUA score	0–9	115	7	1	–	
	⩾9	59	10	0.975	(0.390–2.433)	0.9562
Surgical variables						
Time of surgery (min)	0–150	120	11	1	–	
	⩾150	63	9	1.652	(0.646–4.225)	0.2952
Blood loss (ml)	0–150	101	10	1	–	
	⩾150	88	10	1.1667	(0.462–2.949)	0.7445
Ischemia time (min)	0–20	100	12	1	–	
	⩾20	89	8	0.724	(0.282–1.862)	0.5031
Outcomes						
Delta Hb presurgery –day 1(g/dl) (per 1 g loss)		180	20	1.917	(1.374–2.675)	**0.0001**
Delta Hb day 1 – last day (g/dl) (per 1 g loss)		180	20	0.816	(0.542–1.228)	0.3293
AVF	No	115	50	1	–	
	Yes	90	36	27.05	(7.270–100.615)	<**0.0001**

ASA, American Society of Anesthesiologists; AVF, arteriovenous fistula; BMI, body mass index; CI, confidence interval; eGFR estimated glomerular filtration rate; Hb, hemoglobin; last day, out day; OR, odds ratio; PADUA score, Preoperative Aspects and Dimensions Used for an Anatomical; RENAL radius, exophytic/endophytic properties, nearness of tumor to the collecting system or sinus in millimeters, anterior/posterior location relative to polar lines nephrometry scoring system.

Table 4. Comparison of incidence and treatments of HCs after partial nephrectomy.

Authors	Number of patients	Type of surgery	Postoperative hemorrhagic complications	Diagnosis PA/AVF	Postoperative angioembolizations	Mean delay between surgery and symptomatic HC (days)
Hyams and colleagues[13]	998	LAPN/RAPN	20 (2%)	PA: 16 (1.7%)	16 (1.7%)	14.5 (3–24)
Strobl and colleagues[14]	1425	NR	NR	PA: 26 (1.8%) AVF: 12 (0.8%) PA + AVF: 1(0.1%)	39 (2.7%)	15.3
Takagi and colleagues[15]	117	OPN: 73 (62.4%) LAPN: 44 (37.6%)	1 (0.85%)	PA: 17 (15%)	12 (10.3%)	9
Morita and colleagues[8]	589	OPN: 364 (61.8%) LAPN: 159 (27%) RAPN: 66 (11.2%)	15 (2.5%)	NR	NR	9 (4–98)
Montag and colleagues[9]	640	LAPN: 640 (100%)	13 (2%)	PA: 10 (1.6%) AVF: 2 (0.31%)	13 (2.03%)	16.8 (9;30)
Omae and colleagues[16]	101	LAPN: 60 (59.4%) RAPN: 41 (40.6%)	NR	22 (21.7%)	NR	NR
Singh and colleagues[4]	345	LAPN: 345 (100%)	6 (1.7%)	PA: 6 (1.7%)	6 (1.7%)	12 (8–15)
Shapiro and colleagues[10]	259	LAPN 259 (100%)	6 (2.3%)	PA: 6 (2.3%)	6 (2.3%)	12 (5–23)
Jeon and colleagues[11]	775	OPN: 452 (58.3%) RAPN: 323 (41.6%)	29 (4%)	PA: 18 (2.3%) AVF: 3 (0.4%)	29 (4%)	6 (1–32)
Ramani and colleagues[6]	200	LAPN: 200 (100%)	19 (9.5%)	NR	2 (1%)	16 (6–30)
Dominique and colleagues (this study)	194	OPN: 122 (62.9%) RAPN: 72 (37.1%)	22 (11.3%)	PA: 6 (3%) AVF: 4 (2%)	8 (4.1%)	4.8 (0;15)

AVF, arteriovenous fistula; HC, hemorrhagic complication; LAPN, laparoscopic-assisted partial nephrectomy; NR, not recorded; OPN, open partial nephrectomy; PA, pseudoaneurysm; RAPN, robot-assisted partial nephrectomy.

use of antiplatelet agents, the RENAL score, postoperative diagnostic of AVF and variation of hemoglobin were significantly associated with HCs in univariate analysis but only use of antiplatelet agents and delta Hb between D–1 and D1 were significant in the multivariate regression. Interestingly, we observed a trend to an increased risk for HCs in the tumor RENAL score >7 in the univariate analysis (OR: 3.44, 0.971–12.240, $p = 0.0556$) without reaching significance in the multivariate analysis.

Kondo and colleagues[14] reported early unclamping as the only significant predictive factor of HCs in 96 patients after RAPN (HR,27, $p = 0.01$) whereas for Omae and colleagues,[18] only renal sinus exposure was predictive for HCs (OR 7.24, $p < 0.001$).[18] We believe that the identification of risk factors for HCs could lead to propose postoperative imaging only in selected patients at higher risk of HCs after PN;[13] in addition, we consider that some additional variables barely reported may also contribute to risk assessment

such as surgeon's experience, individual rate of complications, quality of tumor bed repair and renorrhaphy.

In our study, the drop in hemoglobin at day 1 was a significant independent risk factor for HCs. To the best of our knowledge, no previous study has assessed the variation in hemoglobin rate before surgery and at postoperative day 1, nor reported this variable as a predictive factor for HCs.

Thus, our results may suggest offering systematic DU in patients under antiplatelet therapies, with large tumor size (>T1b), or early postoperative hemoglobin variations because of its high NPV.

The need for early detection of HCs after PN has been emphasized with the development of robotic surgery and fast recovery protocols after surgery, allowing to reduce hospital length of stay to fewer than 3 days or even to outpatient surgery.[15] Since HCs represent a life-threatening condition requiring specific interventions not always available in primary care centers, the risk for HCs may become even more worrying when occurring as outpatient. In our study, HCs after discharge occurred in five patients. No death was reported in our population, but one patient required emergency care after hemorrhagic shock occurring at home and a hemoglobin rate of 4 g/dl before transfusion and angioembolization. In that case, proximity to hospital, detailed information to the patients allowing rapid diagnosis, and transportation have been determinant issues.

Our study presents some limitations. Like every monocentric study, actual results may not be necessarily transposed to general practice in terms of surgical or imaging expertise. Another bias is the indication for DU that remained on the surgeon's demand when the RENAL score <7. However, we believe it had minimal impact in our study since the sensitivity of DU was not higher in that group of patients. Moreover this strategy reflects real-life practice.

In conclusion, in the present study, performing a systematic DU between D4 and D7 after complex PN failed to prevent the onset of secondary HCs after patient discharge. Preventive treatment of PA-AVF was offered in only one case, without evidence of its necessity. The high NPVs of DU might be counterbalanced by its low sensitivity. Overall, our results may suggest discussing a systematic postoperative imagery (DU or CT scan) around day 10 in patients with tumors >T1b or with use of antiplatelet treatment or with early hemorrhage at day 1.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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