Is postoperative Doppler ultrasound useful to early detect asymptomatic pseudoaneurysm and prevent haemorrhagic complications after partial nephrectomy?

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Abstract:

Objective: To assess clinical utility of systematic Doppler ultrasonography (DUSS) following robotic partial nephrectomy (PN) in order to detect renal artery pseudoaneurysm (PA) and offer pre-emptive arterial embolization to reduce the postoperative bleeding risk.

Materials and Method: A retrospective study was conducted including all consecutive patients treated with robotic PN for renal tumour from 2015 to 2017. Every patient underwent a renal DUSS in the early post-operative period. The presence of PA, arteriovenous malformation or collection on the DUSS as well as the incidence of hemorrhagic complication and need for transfusion/embolization were assessed.

Results: Eighty-three patients were included with a median age of 58 [19-80] years. The median follow-up was 5 [1-30] months. Mean tumour size was 31 (+/-13.1) mm, median RENAL score was 6 [4-11], and the mean warm ischemia time was 22 (+/-7) min. Hemostatic agent was used in 12 patients (14.5%). No patients encountered hemorrhagic complication postoperatively, and no patient required transfusion. The median time [IQ] to DUSS post-operatively was 7 days [6-8]. DUSS revealed one asymptomatic PA (1.2%) which was treated with pre-emptive embolization. This was the only patient who encountered a Clavien grade III complication, while 15 patients (18%) had a complication grade I/II.

Conclusion: No hemorrhagic complications occurred in our population, although one asymptomatic PA was found. It was early diagnosed with DUSS allowing pre-emptive management with embolization. These results suggest a potential clinical utility of early postoperative DUSS in order to screen for PA to reduce the risk of post-PN hemorrhagic complication.

Introduction:

The use of partial nephrectomy for the treatment of renal cell carcinoma has dramatically increased over the past decade, especially for small renal tumors but also more recently for complex lesions [1,2]. Haemorrhagic complications are a major concern after partial nephrectomy (PN), and have been reported in 5 to 10% [3–5]. The postoperative bleeding risk is mostly related to the presence of pseudoaneurysm (PA), typically occurring within the first 14 days after PN [6]. Such a complication is not uncommon and is potentially life-threatening due to a risk of acute bleeding in the case of rupture. Symptomatic PA requiring urgent treatment have been reported in 1 to 5 % following PN in the largest series [6–8]. Due to this relatively low rate, PA following PN have not been well documented and no standardized management exists for both its diagnosis and treatment strategy. Commonly, no systematic postoperative screening is recommended following PN to exclude PA. However, the usefulness of such a systematic assessment of PA after PN remains unclear in the aim of offering a pre-emptive embolization of asymptomatic PA in order to decrease the risk of post-operative bleeding.

In this context, three contemporary series from the same team assessed the incidence of PA in patients treated with PN using a systematic enhanced computed tomography scan (CT) in the early postoperative period [9–11]. Surprisingly, this systematic assessment demonstrated high rates of post-operative asymptomatic PA ranging from 15% to 21.7% of the patients. Symptomatic PA following PN have been reported significantly less frequently as well as the very low rate of PA found later at the first postoperative CT in the setting of routine renal cancer follow-up. As such, these results raise the possibility of potential over-diagnosis of asymptomatic PA with spontaneous favourable outcomes. Though, there is a potential risk of overtreatment driven by the use of enhanced-CT for systematic postoperative assessment [12]. Considering these results, the exposure to ionizing radiations and to intravenous contrast agent related to CT-scan as well as its cost, systematic postoperative use of CT-scan doesn't appear as an appropriate option for the screening of PA after PN. However early detection of significant asymptomatic PA could be helpful to prevent bleeding complication after PN, and some alternatives including Doppler ultrasonography (DUSS) could be more relevant in this indication. To our knowledge the usefulness of a systematic DUSS of the operated kidney at the early post-operative period hasn't been assessed with the aim to early diagnose PA.

The aim of this study was to assess the usefulness of systematic DUSS following RAPN in order to detect and treat postoperative PA to reduce the postoperative risk of haemorrhagic complications.

Patients and methods:

Patients:

An institutional review board-approved retrospective study was carried out of all consecutive patients treated with robot-assisted partial nephrectomy (RAPN) for kidney tumour performed by one experienced robotic surgeon (GC) at two centres between January 2015 and August 2017. The following data were collected: demographic characteristics, Charlson co-morbidity index, operative time, warm ischemia time, estimated blood loss (EBL) length of stay, pre-operative and post-operative haemoglobin (Hb) and renal function estimated using the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated glomerular filtration rate (GFR) [13]. The use of anticoagulant (AC) and antiplatelet (AP) treatment was collected as well as whether AC or AP treatment was stopped before surgery. AC or AP were discontinued pre-operatively at the discretion of the surgeon and the anaesthesiologist and resumed postoperatively at the surgeon's discretion. Complications were reported according to the European Association of Urology guidelines and classified using the Clavien-Dindo score [14,15]. Major complications were defined as Clavien score >=3. Radiological characteristics were collected and tumour complexity was assessed using the RENAL nephrometry score [16]. Post-operative haemorrhagic complications were defined as any symptomatic PA, arteriovenous fistula, heamatoma or haematuria requiring for blood transfusion. Histological results were also collected.

Surgical procedure:

Every procedure was performed by the same surgeon and was conducted following a standardized technique, using a 5 ports transperitoneal robot-assisted laparoscopic approach (4 robotic arms and 1 or 2 assistant ports), (DaVinci surgical system, Intuitive Surgical, Sunnyvale, California). The hilum was dissected to expose the renal pedicle. The kidney was mobilized in the Gerota's fascia in respect of the peri-tumour fat. A laparoscopic USS was systematically used to delineate the tumour margins before excision. A complete arterial clamping was performed using laparoscopic bulldog(s), +/- the vein was also clamped in some cases according to the surgeon's preference as per the tumour location. The procedure was conducted under warm ischemia. After the tumour excision, an elective suture of the main arteries and bleeding tissues seen to the tumour bed was performed using 4-0 Monocryl® (Ethicon, Cincinatti, Ohio, USA) elective stitches. A parenchymal suture was then applied to the tumour bed with a continuous double armed 2-0 Stratafix® (Ethicon, Cincinatti, Ohio, USA) suture tight between two hem-o-lock® (Teleflex, Wayne, Pennsylvania, USA) clips, and a capsular outer suture was performed using interrupted 2-0 Stratafix® tight between hem-o-locks® clips. A conventional unclamping was performed after the kidney repair was completed. Haemostatic agents (Tisseel®, 4ml, Baxter Healthcare corporation, Westlake Village, CA, USA) was used in some cases according to the surgeon's preferences. The Gerota's fascia was closed with a continuous suture of 3-0 stratafix®. An intraperitoneal drain was left at the end of the procedure.

Post-operative Doppler Ultrasound:

Every patient underwent a DUSS of the operated kidney at the early post-operative period in a median [IQ] postoperative time of 7 days [6-8]. The aim of this exam was to exclude any post-operative PA or arteriovenous malformation to the surgical site. Patients were scanned by two experienced sonographers using a Philips EPIQ 7G ultrasound machine (Amsterdam, Netherlands) or equivalent with a multifrequency curved linear array probe. Patients were positioned supine for the examination, with additional decubitus positioning, ipsilateral arm elevation and breath-holding manoeuvres performed as required. Optimised greyscale images of bilateral kidneys were obtained in transverse and longitudinal planes. Colour Doppler images were also obtained, with pulsed Doppler images obtained if an abnormality was suspected. Ultrasound examinations were reported by radiologists.

Management of pseudo-aneurysm:

In case of PA diagnosed on the postoperative DUSS, the patients were further assessed with a contrast enhanced CT-angiogram. Confirmed renal PA on CT-scan were then considered for pre-emptive arterial embolization.

Statistical analysis:

Means and standard deviations were reported for continuous variables. Rates were used for non-nominal variables. The presence of PA, arteriovenous fistula or collection on the DUSS as well as the incidence of haemorrhagic complication and need for transfusion/embolization were assessed.

Results:

Eighty-three patients met inclusion criteria for the study. Median age was 58 [19-80] years, 53 (64%) patients were male, the mean BMI was 29.1 (+/-5.9) kg/m2 and the median follow up was 6 [1-30] months. Twelve patients (12.5%) were on regular antiplatelet agents, nine had their treatment withhold peri-operatively and three patients were maintained on aspirin 100mg daily at the time of the procedure (3.5%). The mean tumour size was 31 (+/-12.9) mm, mean RENAL score was 6.1 (+/-3.2), and the mean warm ischemia time was 21.5 (+/-7.1) min. Haemostatic agent was used in 12 patients (14.5%). Histological analysis found 76 (91.5%) renal cell carcinoma and 7 (8.5%) benign lesions. Patients characteristics are detailed in **Table 1**.

No patients encountered haemorrhagic complication postoperatively, and no patient required transfusion during the follow-up. DUSS revealed one asymptomatic PA for one patient (1.2%) at day 6 postoperatively **(Figure 1)**. This PA was further assessed with CT angiogram reporting a size at 10 mm **(Figure 2)**. A pre-emptive embolization was performed the same day in order to reduce the risk of bleeding due to PA rupture **(Figure 3)**. This patient was on regular antiplatelet treatment which was withheld 5 days prior to the surgery and wasn't restarted at the time the PA was diagnosed. No haemostatic agent was used during his procedure. This was the only patient who encountered a grade III Clavien complication, while 20 patients (24%) had a complication grade I/II. In addition, ten asymptomatic peri-renal collections were reported (12%) which didn't require any intervention or follow up.

Discussion:

PN has become the standard for the treatment of renal masses, as it has been reported with equivalent oncological outcomes and better outcomes for renal function and overall survival than radical nephrectomy [17]. Based on these findings, multidisciplinary meeting discussion and their implementation lead to the rise of PN during the last 10 years [18]. However, PN is also known to have a higher morbidity rate than radical nephrectomy, and while hemorrhagic complications are rare, they remain among the most concerning as they can be life-threatening. Most of the postoperative PA are diagnosed when they become symptomatic in a context of an acute postoperative bleeding, requiring an urgent management based on resuscitation +/- arterial embolization, or rarely reoperation. As emergency management is not optimal, the clinical relevance of an earlier diagnosis based on a systematic screening for asymptomatic PA to offer preventative treatment appears favorable. To our knowledge, we report here the results of the first study assessing DUSS at the early post-operative period after PN aiming to prevent hemorrhagic complications.

Despite limited numbers, our results suggested the clinical utility of DUSS in detecting a post-operative PA of the operated kidney. Interestingly, DUSS was able to early diagnose that PA while it was asymptomatic, which allowed to successfully perform a pre-emptive arterial embolization apart of any urgent hemorrhagic context.

Due to the relative rarity of renal artery PA, there are no large studies to date which have compared the sensitivity and specificity of the different imaging modalities in diagnosis [19]. On ultrasound examination a renal PA manifests as a focal saccular or fusiform outpouching from a renal arterial branch, usually within the renal parenchyma. On grayscale images the PA is generally hypoechoic, although swirling low-level internal echoes may also be demonstrated. Color Doppler imaging classically reveals bi-directional swirling internal flow (the “yin-yang sign”) within the PA, with aliasing artefact (apparent flow reversal due to the under-sampling of a periodic process) and a to-and-fro waveform often seen at the neck of the aneurysm. Pulsed Doppler examination may also show a “to-and-fro” waveform at the neck [19,20]. On computed tomography, magnetic resonance or catheter angiography, the PA is seen as an outpouching in communication with the renal artery lumen which opacifies with contrast in the arterial phase (i.e. at the same time as the adjacent renal artery). Imaging differential diagnosis includes a renal cyst (which would not demonstrate internal Doppler flow on ultrasound or contrast opacification on angiographic studies) and a renal arteriovenous fistula (which is distinguished by the presence of a draining vein which simultaneously opacifies with contrast in the arterial phase on angiographic studies). In the context of a symptomatic suspicion of PA post PN, CT-scan is the mostly widely utilized. Ultrasound was reported as offering many advantages as a first-line modality due to the lack of ionizing radiation, lack of intravenous contrast exposure, ready availability of the study and no contra-indications. However, DUSS is also limited because the images it provides are of lower resolution, which may lead to more equivocal or, false-negative results [19]. However, given the relative rarity of PA, in a context of postoperative screening, CT-scan does not seem to be the best exam due to the exposure to ionizing radiation and intravenous contrast agent in patients who recently had a renal artery clamped during the PN increasing the risk of nephrotoxicity.

Accordingly, DUSS which is widely used as a noninvasive imaging modality for the investigation of vascular disease, seems to be an interesting alternative as first-line exam [20]. In a recent literature review on DUSS for the diagnosis of PA regardless their locations, Mahmoud reported that sensitivity and specificity of DUSS for PA diagnosis have been reported at 94% and 97% respectively for peripheral arteries [20]. In addition, they also reported that despite a sensitivity assumed lower than in peripheral vessels, DUSS could be also useful as a first-line modality to diagnose intra-abdominal arteries PA [20]. However, DUSS has limitations as it is an operator dependent technique, and its sensitivity decreases in obese patients.

The incidence of PA following PN found in our study (1.2%) was consistent with the rates usually reported in the literature by the largest recent studies ranging from 1 to 5% [5–7,19]. In addition, these previous studies reported the rate of symptomatic PA, while we reported the incidence of asymptomatic PA. These findings suggest that the incidences of both symptomatic and asymptomatic PA could be close, and as subsequently, that the bleeding risk related to asymptomatic PA is high. These findings were also consistent with the review from Ngo, who reported similar rates of PA after PN and also reported that even if spontaneous resolution and closure of PA have been described, these case are the exception and surveillance should not be considered a prudent management in most patient with renal PA[19].

However, our results were conflicting with those from Takagi, Kondo and Omae, as in their series, using a systematic screening for PA following PN based on a CT-angiogram during the early postoperative period (**Table 2**). This group reported a rate of asymptomatic PA unexpectedly higher (15%-21.7%) [9–11]. Their results suggested that asymptomatic PA might be frequent after PN with a majority of them resolving spontaneously given the significantly lower rate of symptomatic PA as well as PA are rarely identified on delayed post-operative CT-scan performed in the setting of oncologic follow-up. Nevertheless, these three studies were conducted at the same center under the same team and their results haven't been confirmed since by other series. As we did not confirm their results either, the potential explanations to these conflicting results warrant discussion.

Firstly, as mentioned above, different imaging exams (CT-angiogram vs. DUSS) were used for the screening of the PA, which could have led to differences in the results due to the reasons described above. Secondly, from the surgical technique point of view, the three study populations from Takagi, Omae and Kondo were chronologically different, including respectively open and laparoscopic PN, laparoscopic and robotic PN, and finally robotic PN only. These differences within the time suggest they are reflective of changes in the practice during the different studies, especially the early phase of a robotic program including the results of the learning curve period [9–11]. If laparoscopic PN has been reported with higher rates of PA compared to the open access, it is not the case for robotic approach according to the largest series [5,21]. In comparison, our study included the results of one experienced robotic surgeon who had more than 7 years' experience with robotic surgery and performed more than 1000 robotic cases by the time of the first included patient was operated on. This may also have led to differences in the outcomes.

Interestingly, the patient who had PA detected on DUSS was on regular aspirin 100mg daily. This treatment was stopped 5 days before the surgery and not resumed at the time the PA was diagnosed. Patients on regular AP or AC, have been described with a higher risk of hemorrhagic complications by Pradere disregarding the treatment was withheld or continued [22]. In our cohort, the rate of patients on AC or AP before the surgery (15.7%) was close to this related by Pradere (13.2%). The fact we found a PA on a patient on regular AP is in keeping with these previous finding and a potential higher risk of bleeding in that population. In this context, the benefit of using hemostatic agent to prevent bleeding risk is controversial [23–25]. Interestingly, the patient in our cohort who had a PA had no hemostatic agent applied during his procedure. However, the low incidence of PA in our results does not allow to further expound upon that question.

Although we report encouraging results regarding the utility of DUSS in this indication, the low incidence of PA found in our cohort is raising the question about the clinical relevance of the systematic use in every patient after PA. Indeed, 83 exams were required to diagnose one PA and avoid one potential bleeding as the PA found was asymptomatic and may have held spontaneously. Alternatively, a specific screening focused on patients “at risk” could be relevant, looking specifically at patients with higher risk of postoperative bleeding (on AC or CP), indeed, Pradere et al. reported a PA incidence of 10% for these patients, which is significantly higher than the global population. In addition, patients living in isolated rural areas with limited access to interventional radiology may also benefit from a systematic early postoperative screening for PA with DUSS before being allowed to go back home. This may help to reduce their risk of delayed bleeding at home as well as their length of stay close to an interventional radiology department before they go home.

Finally, we should emphasize some limitations of this study including its retrospective nature, the limited number of patients included and the single-surgeon experience, which may have led to some bias. Further, sensitivity and specificity analysis of the detection of PA following PN using routing DUSS was not available given the absence of comparative assessment with the ‘gold-standard’ of computerized tomography.

In conclusion, these results are encouraging as no hemorrhagic complications occurred in our population, although we found one case of asymptomatic PA early diagnosed with DUSS pre-emptively managed with embolization. These findings suggest the potential clinical utility of early post RAPN DUSS in order to screen for PA to reduce the risk of post-RAPN hemorrhagic complication. As DUSS is also a high safety non-invasive exam, it is appealing for use in postoperative screening, at least in patients at higher risk of postoperative bleeding. These results warrant confirmations by further investigations.

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<u>Legends to the figures:</u>

Figure 1:

a) Colour Doppler ultrasound image of the right kidney demonstrates a small rounded lesion in the right renal mid-pole parenchyma which appears to communicate with the renal vessels with internal colour flow and colour aliasing.

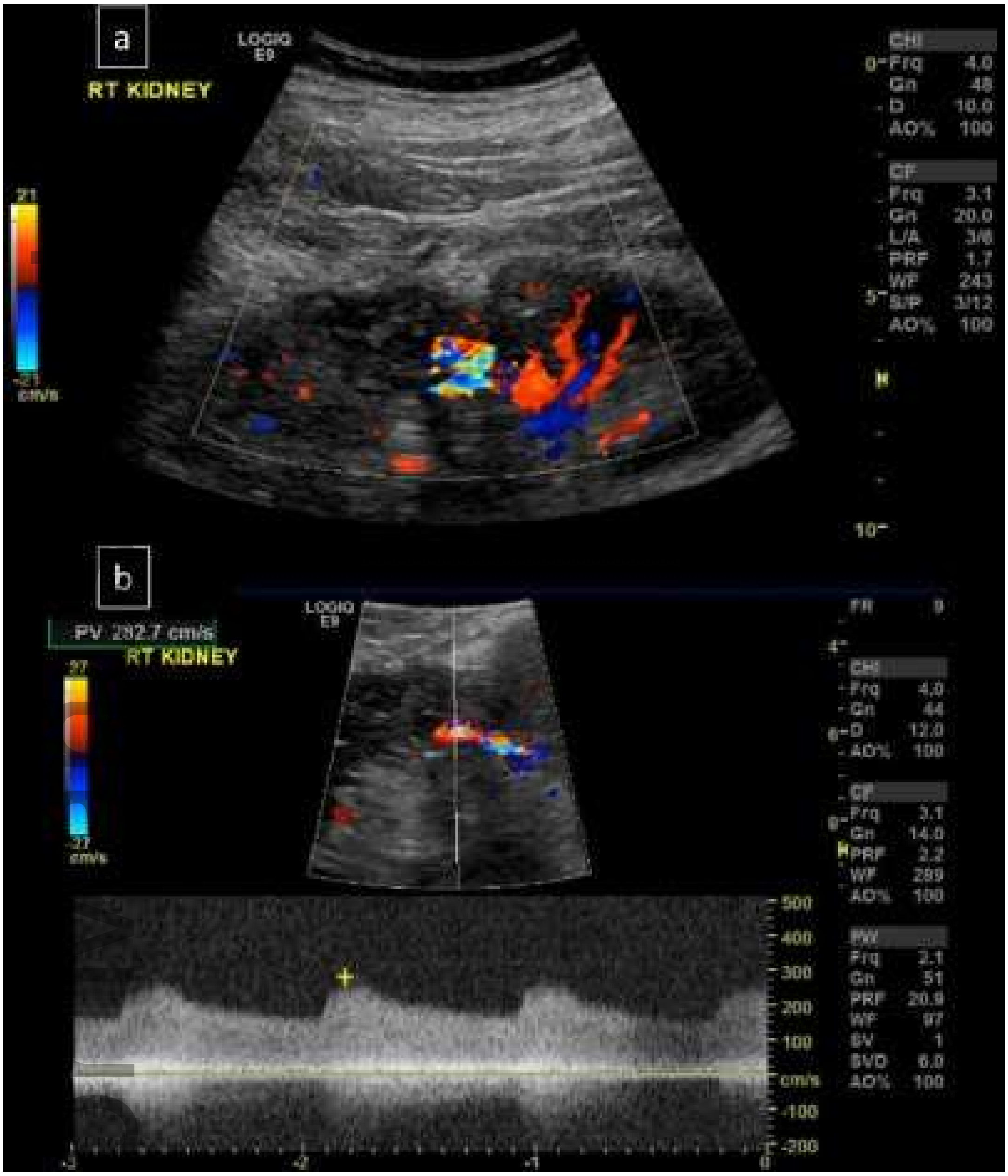
b) Pulsed Doppler ultrasound image of the right kidney demonstrates an arterial waveform within this lesion.

Figure 2:

Computed tomography angiogram of the abdomen demonstrates a rounded focus of arterial phase contrast opacification within this lesion, which communicated with a branch of the right renal artery.

Figure 3:

Digital subtraction catheter angiography images demonstrate catheterisation of the right renal artery with a saccular focus of contrast opacification arising from a right renal superior segmental artery in keeping with renal artery pseudoaneurysm. The second image shows selective catheterisation of the supplying artery, and the third image demonstrates no further opacification post coil embolization.



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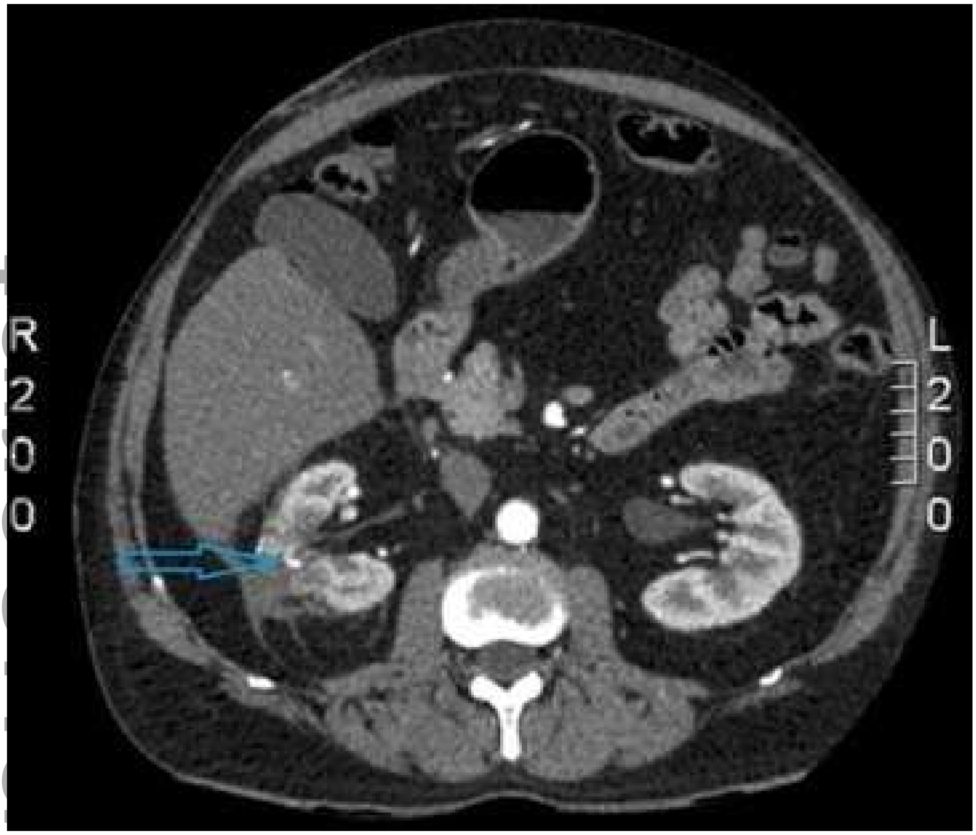

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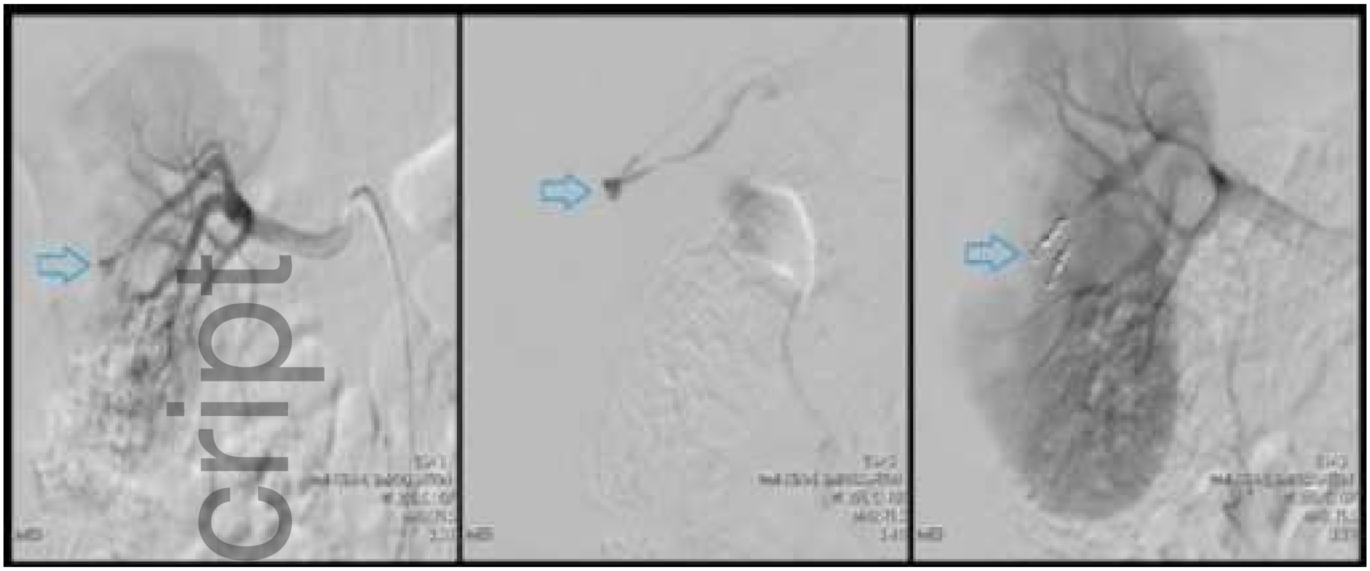

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