

Adjuvant instant pre-operative renal artery embolization facilitates the radical nephrectomy and thrombectomy in locally advanced renal cancer with venous thrombus: A retrospective study of 54 cases

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Abstract

Background: The role of renal artery embolization (RAE) in the therapeutic armamentarium is always controversial. The present study aimed to assess the safety and the surgical outcomes of the instant renal artery embolization (I-RAE) prior to nephrectomy and thrombectomy in locally advanced renal cell carcinoma patients with venous thrombus.

Methods: We performed a retrospective analysis of 54 patients treated with nephrectomy and thrombectomy between Jan 2012 and Jan 2019. Twenty-four patients were treated by I-RAE before surgery. Thirty patients were performed surgery alone (Non-RAE). The patient demographics, operation time, blood loss, transfusion requirements, complications and other surgical parameters were analyzed between the two groups.

Results: The mean tumor size in I-RAE group was significantly larger than that in the Non-RAE group (11.1cm versus 7.9cm; $p = .001$). The mean estimated blood loss was significantly lower in I-RAE group compared to Non-RAE group (596ml versus 827ml; $p = .015$), and the patients in the Non-RAE group were more likely to receive blood transfusion (RBC units, 4U versus 6U, $p = .025$; plasma volume, 200ml versus 400ml, $p = .01$). No differences were found in operative duration, ICU stay, perioperative complications and length of postoperative hospitalization.

Conclusions: The adjuvant instant pre-operative renal artery embolization (I-RAE) is a safe technique. It facilitates the nephrectomy and thrombectomy by reduction of blood loss, transfusion requirements and complication of delayed operation, providing the urologists with a reliable option for locally advanced RCC with tumor thrombus.

Background

The renal cell carcinoma (RCC) is the 6th most frequent cancer in men and 8th in women, accounting for 5% and 3% of all malignancies respectively, with the incidence generally higher in developed countries. Up to 400,000 new cases were diagnosed, and ~ 175,000 deaths were recorded for 2018, worldwide^[1]. Although most cases are diagnosed with small renal masses, a significant number of patients develop into the locally advanced stage and harbor metastasis. Up to 10% of cases are accompanied by intravascular invasion into the renal vein and inferior vena cava (IVC), forming tumor thrombus associated with poor prognosis^[2]. In the past two decades, the surgical management of renal tumor shifted significantly from the open approach to minimal-invasive surgeries. However, the locally advanced renal tumors with venous thrombus are always surgical dilemmas to urologists.

The renal artery embolization (RAE) prior to surgery has been clinically practiced over 40 years. In the 1970s, the renal artery embolization was performed to control the symptomatic hematuria and palliate the metastatic RCC^[3]. Later, the indication had extended to the management of angiomyolipoma, vascular malformation, traumatic renal hemorrhage, renal cell carcinoma and complications after renal

surgeries^[4]. Although many studies on the RAE have been conducted, its role in the therapeutic armamentarium is always controversial^[5-7]. Therefore, we evaluate the surgical outcomes of the instant renal artery embolization (I-RAE) in locally advanced renal cell carcinoma with venous thrombus in our center.

Methods

Patients and study design

In this series, we retrospectively reviewed the locally advanced renal cancer patient with venous thrombus receiving radical nephrectomy and thrombectomy at our institution between January 2012 and January 2019. The instant percutaneous renal artery embolization(I-RAE) was performed within 1 ~ 3 hours prior to the operation. The right common femoral artery was prepared and draped in standard sterile fashion. After accessing the appropriate renal artery with diagnostic catheter, an angiography was obtained to visualize the renal arteries system, the RCC and its supplying vessels (Fig. 1A, B). The vessels supplying the tumor were then selected using a micro-catheter and micro-wire. Angiography was again performed to confirm catheter location prior to embolization. The gelatin sponge was used as the embolic agent. All embolization was performed under careful fluoroscopy to prevent reflux into non-target vessels. Technical success for embolization was defined as the stasis of all supplying arteries without further tumoral blush on postembolization angiography (Fig. 1C).

The surgery was performed within 3 hours after embolization, to prevent the post-infarction syndrome and revascularization of tumor. The strategy of surgery as follows: (1) division the renal hilar structures and ligation the renal artery, (2) complete separation of the kidney and tumor, (3) mobilization the inferior vena cava. The liver was mobilized to control the hepatic veins and IVC. The cardiopulmonary bypass was performed in the patients with suprahepatic and right atrial thrombus. (4) completion of nephrectomy and thrombectomy or vena cavotomy with extraction of thrombus. We utilized the cardiopulmonary bypass to facilitate the treatment of level \geq tumor thrombus (Fig. 1D). The patient demographics, operation time, blood loss, transfusion requirements, complications and other surgical parameters were analyzed between the two groups.

Statistical analysis

Continuous variables were compared using the Student *t*-test for normally distributed data and Mann-Whitney *u*-test for non-normally distributed data. Categorical variables were compared using the Pearson *Chi-square* test. Statistical analysis was performed using SPSS version 24 (SPSS, Chicago, IL, USA), a *p* value < 0.05 was considered statistically significant.

Results

Patient characteristics are summarized in Table 1. Overall, fifty-four patients were performed nephrectomy and thrombectomy. The majority of patients were male (72.2%, 39/54). The mean age was

59.2, and the mean BMI was 23.3 kg/m². The renal tumors were right-sided (n = 28, 51.9%) or left-sided (n = 26, 48.1%). Twenty-four patients were treated by instant RAE prior to surgery (I-RAE group, 24/54, 44.4%). Thirty patients were performed surgery without embolization (Non-RAE group, 30/54, 55.6%). The mean maximum diameter of the tumor in I-RAE group was significantly larger than that in the Non-RAE group (11.1 cm versus 7.9 cm, $p = .001$). Tumor thrombus was found at level-0 in 14 (6 versus 8), level-I in 16 (9 versus 7), level-II in 15 (6 versus 9), level-III in 6 (2 versus 4) and level-IV in 3 (1 versus 2), without statistical significance ($p = .83$). The clinical T-staging, NYHA and ASA score systems were summarized in Table 1, without significances. There was no patient diagnosed with metastasis at the time of surgery.

Table 1
Patient characteristics

Characteristic	RAE(n = 24)	Non-RAE(n = 30)	<i>p</i> Value
Age (years)	59.0±11.8	59.3±8.9	0.9
Sex (n)			0.15
Male	15 (62.5%)	24 (80%)	
Female	9 (37.5%)	6 (20%)	
BMI Kg/M ²	23.1±2.8	23.4±3.3	0.74
Affected kidney (n)			0.76
Right	13 (54.2%)	15 (50%)	
Left	11 (44.8%)	15 (50%)	
Tumor size (cm)	11.1±3.5	7.9±2.7	0.001*
Clinical T stage (n)			0.91
T3a	9 (37.5%)	10 (33.3%)	
T3b	13 (54.2%)	18 (60%)	
T3c	2 (8.3%)	2 (6.7%)	
Thrombus level (Mayo)			0.83
0	6 (25%)	8 (26.7%)	
I	9 (37.5)	7 (23.3%)	
II	6 (25%)	9 (30%)	
III	2 (8.3%)	4(13.3%)	
IV	1 (4.2%)	2 (6.7%)	
NYHA classification			0.56
I	16 (66.7%)	16 (53.3%)	
II	7 (29.1%)	13 (43.3%)	
III	1 (4.2%)	1 (3.4%)	
ASA score			0.81
I	1 (4.2%)	1 (3.4%)	
II	8 (33.3%)	14 (46.6%)	
III	14 (58.3%)	14 (46.6%)	

□	1 (4.2%)	1 (3.4%)
I-RAE: instant renal artery embolization; BMI, body mass index. * $p < 0.05$.		

The operative outcomes were outlined in Table 2. In the I-RAE group, all patients underwent embolization within 3 hours before surgery, and the mean interval was 128 minutes (57–172 minutes). The success of embolization was achieved in all cases. Three patients with mild flank pain were identified as post-infarction syndrome (3/24, 12.5%), which was self-limited. There were no cases of embolic agent migration, adjacent organ injury and other severe complications in I-RAE group. Eighteen patients had laparoscopic surgery (8 in I-RAE group, 10 in Non-RAE group), and the remaining patients received open approach (16 in I-RAE group, 20 in Non-RAE group). The mean operative time for the patients who had embolization was 219 minutes, while it was 233 minutes for the non-embolization group without significant difference ($p = .45$). There was significant difference between the two groups with regard to estimated blood loss (596 ml versus 827 ml; $p = .015$). Furthermore, the patients in the Non-RAE group were more likely to receive transfusion (62.5%, 15/24 versus 90%, 27/30; $p = .016$). The transfused RBC units (median 4U, range 2-6U, versus median 6U, range 2-8U; $p = .025$) and plasma volume (median 200 ml, range 200–600 ml versus median 400 ml, range 200–800 ml; $p = .01$) were significantly greater in Non-RAE group patients. No statistically significant differences were identified between the two groups according to the ICU stay (34 h versus 37 h; $p = .58$), surgical drainage (median 4, range 2–16 versus median 3.5 range 2–15; $p = .92$) and postoperative hospitalization (median 7, range 4–22 versus median 7, range 4–15; $p = .67$). The postoperative complications were outlined in Table 2, without statistic differences between the two groups. Three cases were diagnosed with lower limb deep vein thrombosis. Three patients had acute kidney injury after nephrectomy. Four patients suffered the wound infection. The ileus was observed in two patients. All of them recovered after conservative treatment. No perioperative death occurred.

Table 2
Perioperative data

Variables	I-RAE	Non-RAE	<i>p</i> -Value
Surgery type			>0.99
Open	16 (66.7%)	20 (66.7%)	
Laparoscopy	8 (33.3%)	10 (33.3%)	
Operative time (min)	219±52	233±75	0.45
EBL (ml)	596±321	827±347	0.015*
Transfusion rate	15/24 (62.5%)	27/30 (90%)	0.016*
RBC (U)			0.025*
Median, Range	4 (2-6)	6 (2-8)	
Plasma (ml)			0.01*
Median, Range	200 (200-600)	400 (200-800)	
ICU stay (hours)	34±10	37±14	0.58
Postoperative hospitalization			0.67
Median, Range	7 (4-22)	7 (4-15)	
Day to surgical drain removed			0.92
Median, Range	4 (2-16)	3.5 (2-15)	
Interval (min)	128±34	-	
Post-infarction syndromes			
Flank pain	3 (12.5%)	-	
Postoperative complications			
DVT	2 (8.3%)	1 (3.3%)	0.43
Acute kidney injury	2 (8.3%)	1(3.3%)	0.43
Wound infection	3 (12.5%)	1(3.3%)	0.21
Ileas	1 (4.2%)	1(3.3%)	0.87
Pathology			0.82
ccRCC	22 (91.7%)	28 (93.3%)	
other	2 (8.3%)	2 (6.7%)	
Furhman Grade			0.57

□	15 (62.5%)	17 (56.7%)
□	7 (29.2%)	12 (40%)
□	2 (8.3%)	1 (3.3%)
I-RAE: instant renal artery embolization, EBL: estimated blood loss, Interval: Interval between RAE and surgery, DVT: Deep vein thrombosis, ccRCC: clear cell renal cell carcinoma. * $p < 0.05$.		

The pathology analysis of the tumors was summarized in Table 2. The histology type demonstrated a predominance of clear cell renal cell carcinoma in each group.

Discussion

The vascular invasion is common in advanced renal cancer, which is associated with elevated morbidity and mortality. The surgical challenging radical nephrectomy and thrombectomy are considered as the standard modality, as showing a prolonged survival^[8]. The renal artery embolization prior to surgery as adjuvant treatment in nephrectomy has been utilized for more than four decades. Craven et al.^[9] reported that the embolization minimized the oozing in nephrectomy, control troublesome hematuria and improved clinical status. Later, several studies showed that the renal embolization reduced bleeding and surgical procedure time in nephrectomy, increasing the ease of dissection through edema tissue^[10-12]. The embolization devascularized the tumor and allowed the renal vein to be ligated early, before control of the renal artery, without increasing the risk of tremendous hemorrhage from venous collaterals, which alleviated the nephrectomy in the cases with renal hilar structure invasion. This practice was also proposed to have immunological benefits, including augmentation of the natural killer cell and lymphoproliferative response, triggered by necrosis factor release, which caused the immune response^[13-15].

Conversely, there were some conflicting data regarding the utility of the adjuvant renal artery embolization prior to nephrectomy. A study^[6] evaluated the 227 renal cancer patients received embolization prior to nephrectomy matched with 607 patients treated with surgery alone. The investigators reported that there were no significant differences between the groups in complications, cancer-specific survival. However, the median follow-up was significantly lower in the surgical group than embolization group. This study showed that the blood transfusion requirements were significantly higher in embolization group. The explanation for that could be the incomplete occlusion of the renal artery, the obstruction of the inferior vena cava leading to hypertension of the bypass veins, which increased the hemorrhage of the venous collaterals around the renal capsule, when mobilizing the kidney and tumor. In Subramanian's study^[7], 231 patients underwent the radical nephrectomy and thrombectomy, of 135 received the pre-operative embolization. It was reported that the patients in embolization group had longer median operative time (390minutes versus 313minutes), received more blood transfusions than the control group (8units versus 4units). The authors pointed out that the embolization was significantly associated with higher mortality

(13% versus 3%). This series concluded that the embolization did not show meaningful advantages. However, the embolization group was composed of higher tumor stage, IVC thrombus level, ASA scores, and need for the utility of cardiopulmonary bypass. Besides, the patients received the embolization were almost associated with hilar invasion and lymphadenopathy. These could explain the longer operative time and more transfusion requirements in embolization group.

In our study, we found that there was no significance in operative time between the two groups. One explanation could be that the tumor size in the I-RAE group was larger than that in the Non-RAE group, requiring more time for mobilizing and hemostasis. We also performed the renal artery embolization before laparoscopic surgery. The prophylactic embolization also had some merits in minimal-invasive surgery. Chopra and his colleagues^[16] performed the pre-operative embolization in 80% (20/24) patients in Robot-assisted Level II–III IVC Thrombectomy. They concluded that the renal artery embolization decompressed the venous collaterals, decreased blood loss and enhanced robotic efficacy. Wang et al^[17] reported that the pre-operative artery embolization could reduce intraoperative oozing, which was helpful for mobilizing the kidney, manipulating the vessels in Robot-assisted Inferior Vena Cava Thrombectomy. The embolization was necessary and critical for left renal cancer, as the thrombectomy was performed in the left decubitus position, it was very difficult to expose the left renal artery. The embolization allowed the left renal vein could be disconnected well before the left renal artery can be robotically secured, intraoperatively.

Several types of materials were available for renal artery embolization, such as metallic coils, gelatin sponge, polyvinyl alcohol, embospheres and N-butyl-2-cyanoacrylate (NBCA). We preferred the gelatin sponge, as it was cheapest. Its embolic effect could last for 2–3 weeks. Besides, it allowed surgical clamping and ligation during the nephrectomy with on hindrance. The most common complaints after embolization were post-infarction syndrome, characterized by nausea, vomiting, fever, flank pain, malaise, hematuria, transient hypertension and hyponatremia. The complications were self-limited and easily controlled with pre-medication and symptomatic treatment. The artery embolization techniques had developed significantly in the past 20 years. Imaging capabilities had improved dramatically. New embolic agents allowed for more effective and precise embolization. These decreased the complications caused by incomplete embolization or embolic material migration. The post-infarction syndrome always occurred in 1 to 3 day after the embolization. For the traditional embolization, the incidence of post-infarction syndrome ranged from 40–90%^[18]. Kalman et al^[11] reported that the nephrectomy should be performed within 48 hours. It became surgical difficult 3 days after the embolization, as the secondary collateral vessel formation. Minimizing the interval between the RAE and surgery could decrease the post-infarction syndrome. So, in this study, all the patients in I-RAE group underwent surgery within 3 hours after embolization, we didn't observe any major complications associated with RAE itself. The instant embolization had some advantages over the delayed surgery. First, the instant embolization alleviated the patients' emotional strain and anxiety of waiting for several days. Second, as the nephrectomy was performed within 3 hours, this minimized the post-infarction syndrome. Some studies reported that if the nephrectomy was performed more than 4 days after the embolization, the mortality may increase due to

septic complications^[19,20]. Last, the instant approach reduced the hospitalization and cost compared to the delayed surgery.

To date, as there are no randomized, large-scale, prospective trials, which compare the surgical outcomes of embolization and non-embolization, the European Association of Urology doesn't recommend the embolization as a routine procedure to manage RCC. However, in our study, the devascularizing of tumor reduced the intraoperative blood loss and transfusion, which facilitated the nephrectomy and thrombectomy in local advanced RCC with large size tumor and hilar invasion. The prophylactic embolization could make some non-resectable renal mass resectable, providing the urologists with a reliable option for locally advanced RCC. Besides, as the combination use of target drugs and immuno-check point inhibitor, the patients could benefit from the embolization-facilitated surgery.

Conclusions

In conclusion, we reported our experience with management of the instant renal artery embolization prior to nephrectomy in locally advanced renal cell carcinoma with venous thrombus. Our results have concluded that the embolization is a safe technique, and it facilitates the surgery by the reduction of intraoperative blood loss, transfusion requirements and complications of delayed operation. Clearly, well-designed, large-scale, prospective randomized clinical trials are necessary to shed the light on the pros and cons of the RAE in nephrectomy.

Abbreviations

RCC
renal cell carcinoma
RAE
renal artery embolization
RBC
red blood cell
IVC
inferior vena cava
BMI
body mass index.

Declarations

Ethical statement

The study involving human participants was approved by the institutional review board of the Shandong Provincial Hospital (No. 2019 – 133). Written consent was obtained from all the participants. The

methods were carried out in accordance with the approved guidelines. All clinical research was performed on the basis of the principles expressed in the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests

Availability of data and materials

The patient data will not be shared. All of the patient data was collected from Shandong provincial Hospital surgical and pathological databases. All patients provided written consent for storage of their information in the hospital database only.

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Authors' contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Figures

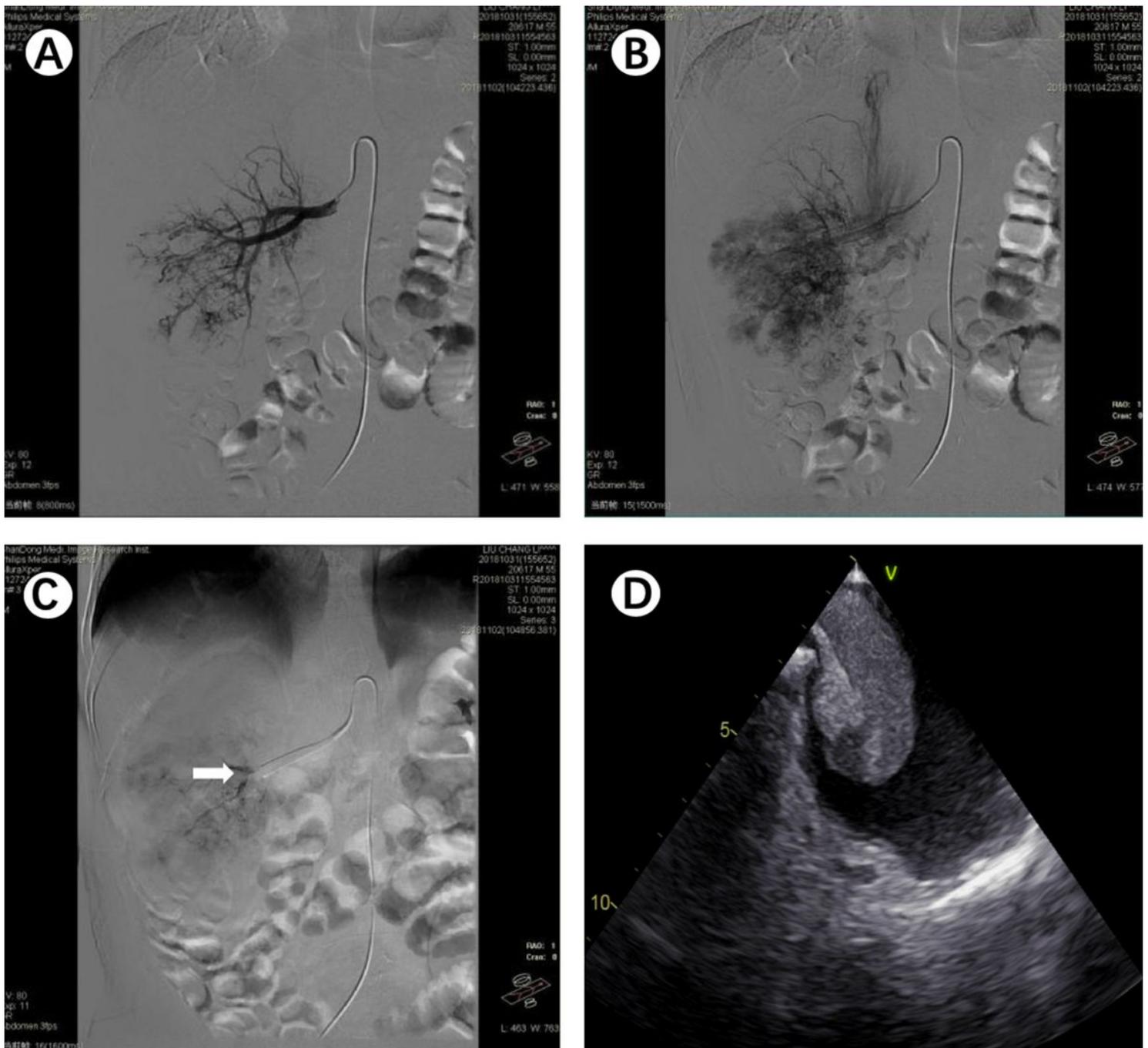


Figure 1

the renal arterial embolization of a 54-year old renal cancer patient. (A, B) Renal arterial angiography demonstrating a right hypervascular renal cell carcinoma. (C). Performing the embolization of tumor vessels with gelatin sponge (white arrowhead). (D) The intraoperative Trans-Esophageal Echocardiography showing the mobile thrombus mass extending across the tricuspid valve into the right ventricle.