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Safety and Efficacy of Angio-embolization for Complex Renal Cell Carcinoma and Angiomyolipoma: Experience and Results in 20 Patients

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Abstract: *Objective:* To evaluate the efficacy and safety of renal artery embolization in treatment of complex angiomyolipoma and renal cell carcinoma. *Patients and Methods:* Twenty patients were included in this study, 11 patients with primary renal cell carcinoma and 9 patients with AML. These patients were examined by US, CT or and MRI before RAE to evaluate size of the tumor, assess extension of renal cell carcinoma, exclude distant metastasis and assess the complications of angiomyolipoma. Renal artery embolization yield, complications and the impact of patient`s management were analyzed. *Results*: This study included 20 patients (12 males and 8 females). The age range was 17-75 (47.8±15.5) years. The type of renal masses were renal cell carcinoma in 11 patients and angiomyolipoma in 9 patients (5 bilateral and 4 unilateral). According to the modified Clavien system, 4 patients developed Grade I complication (3 patients developed flank pain (15%) treated with oral analgesics and 1 patient (5%) developed self-limiting perinephric hematoma which resolved spontaneously under antibiotic coverage. *Conclusion:* RAE is a safe, effective and well tolerated treatment of AML either if large sized which is liable to rupture or symptomatic to stop bleeding. Also, it allows preoperative de-vascularization of RCC to facilitate its surgical resection and as palliative treatment if RCC is un-resectable or metastatic.

Keywords: Renal Artery Embolization, Renal Cell Carcinoma, Angiomyolipoma

1. Introduction

Renal artery embolization (RAE) is an effective minimally invasive procedure for treatment of a variety of renal conditions. Since its first introduction in 1970s, technical advances and growing experience have extended its indications, not only for treating symptomatic hematuria or palliation for metastatic renal cancer, but also for preoperative de-vascularization of renal cell carcinoma (RCC), treatment of angiomyolipomas (AML), and vascular malformations. [1].

RAE refers to the occlusion of the renal artery, or some of its branches, by injection of an embolic agent through an endovascular catheter to decrease or completely terminate the arterial blood flow. Logically, this will facilitate the surgical resection or treat and prevent life-threatening hemorrhage as in the case of AML. [2] It is a safe and effective technique, well tolerated with few complications particularly if the time interval from embolization to surgery is less than 48 hours. [3] However, RAE in the pre-operative or palliative management of advanced malignant renal tumors remains debated. [4].

Herein, we report our results of RAE in treatment of AML and RCC in a series of 20 patients.

2. Patients and Methods

Between December 2015 and December 2017, 20 patients with renal tumors were included in this prospective study for RAE. This study was approved by our institutional review board. Inclusion criteria were patients presented with renal AML or RCC who were fit and signed an informed consent. Exclusion criteria were patients who were unfit for surgery or having an acute illness e.g. septicemia.

All patients were subjected to full history, including history of allergy to contrast media, and examination. Full laboratory investigations were performed in all patients. Abdominal ultrasound (US) was done for characterization of the renal masses and any other abdominal abnormalities (hepatic focal lesions, intraperitoneal fluid collection). MSCT and/or MRI were done for all patients for better and accurate assessment the renal masses (site, size, nature, relation to surrounding structures, renal vascularity), assessment of the other kidney and other abdominal organs.

2.1. Patient Preparation

The procedure was carefully explained to the patient. A written consent was obtained from all patients before the procedure. Fasting 8 hours preoperatively was ensured. Venous access through a wide bore cannula was done. Prophylactic antibiotic (ceftriaxone 2 gm IV) was adminstered. Local anesthesia (5 CC Lidocaine hydrochloride 2% [xylocaine] solution) was infiltrated under skin around the puncture site and superficial to the femoral artery.

2.2. Angiographic Technique

The procedure was done using Toshiba (CAT805 B) machine. Arterial puncture was obtained through femoral artery. Using the Seldinger's technique [2], the patient is placed in the supine position. A hollow-core needle is introduced into the artery; a guidewire is inserted through the needle and advanced into the artery. The needle is exchanged for a vascular sheath (5 or 6 French [Fr]). Subsequent catheter movement and exchange is performed over a guide wire under fluoroscopic guidance. Abdominal aortography was first performed to determine the entire vascular anatomy, exclude main renal artery lesions and the number of feeding renal arteries. The renal artery was selectively catheterized via cobra catheter (Cordis, USA) (4 or 5 Fr). Non-ionic contrast media (Omnipaque 350mg/ml) was used in all patients. Manual injection was used in selective angiography (Dose of 8-10 ml of contrast media in each injection). Diagnostic images were carefully assessed for the presence of vascular pathology and to localize the lesion and the branch of the renal artery supplying the area of the lesion. The catheter was further advanced subselectively into the segmental branch of the renal artery feeding the lesion (Dose of 4-5 ml of contrast media in each injection). Additional oblique and magnification views were used to help in delineation of the exact location of the vascular injury. Post insertion of the embolizing material, selective angiography was made while the catheter in main renal artery for assessment of arterial occlusion by manual injection of contrast media (8 -10 ml of contrast media in each injection) about 2 minutes after the insertion. After the procedure, the catheter and sheath were removed and compression of the puncture site was performed. This was followed by tight sterile bandage over the puncture site.

In case of embolization of RCC, the efficacy of pre-operative embolization was correlated with the operative data (easy resection of the tumor and less bloody operative field). In case of AML, follow up contrast enhanced CT (CECT) was done after 2-3 months from embolization to evaluate size of the mass, intra-tumoral aneurysm and to confirm no recurrence of the bleeding.

Statistical analysis was done using SPSS (Statistical Package for the Social Science, version 20). For continuous variables, the mean and SD ratio (descriptive statistics) were calculated. For categorical variables, frequencies with a P values < 0.05 indicated statistical significance.

3. Results

This study included 20 patients (12 males and 8 females). The age range is 17-75 (47.8 ± 15.5) years. The type of renal masses were RCC in 11 patients and AML in 9 patients (5 bilateral and 4 unilateral). The median BMI was 29 kg/m^2 (range 20-39). Median Karnofsky Performance status scale was 90. For the RCC group, the median clinical tumor size was 11 cm (ranged from 7 - 16 cm), whereas for the AML, it was 8.3 cm (ranged from 8 -16 cm). The indications for angio-embolization, type of embolizing agents and the types of embolization were shown in table 1.

Table 1. *Patients' characteristics, indication for angio-embolization, type of embolizing agents and the types of embolization.*

	No. (%)
Age (years)	17-75
(Mean ± SD)	(47.8 ± 15.5)
Sex, n (%)	20
Male	12 (60)
female	8 (40)
Type of renal mass (N,%)	
RCC	11 (55)
T.S	5 (25)
Solitary AML	4 (20)
Indications of angio-embolization	
TS	5 (25)
Stop bleeding (hematuria)	3 (15)
Complicated AML with subcapsular hematoma	2 (10)
AML	4 (20)
Complicated with intra lesional aneurism	1 (5)
Complicated with perinephric hematoma	1 (5)
Extended to IVC	1 (5)
Intra lesional dilated tortuous vessels	1 (5)
RCC	11 (55)
Pre-operative total embolization	9 (45)
Palliative treatment	1 (5)
Combined with RFA	1 (5)
Type of embolizing Agent	
Alcohol + microcoils	7 (35)
Microcoils	6 (3)

	No. (%)
Balloon catheter + Alcohol	5 (25)
Emphosphere particle	1 (5)
Gel foam + alcohol	1 (5)
Type of embolization	
Total	8 (40)
Selective	12 (6)
Complications	
Perinephric hematoma	1 (5)
Flank pain	3 (15)

No major complications occurred after embolization; there were no cases of coil migration, adjacent organ injury or RAE-related death. According to the modified Clavien system, 4 patients developed Grade I complication (3 patients developed flank pain (15%) treated with oral analgesics and 1 patient (5%) developed self-limiting perinephric hematoma which resolved spontaneously under antibiotic coverage.

The 11 patients with RCC underwent nephrectomy at the same day of angio-embolization. Post infarction syndrome occurred in 14 (70%) patients; all of them required pharmacological treatment. All patients with RCC underwent open surgery, lymphadenectomy was carried out in 8/11 (72.7%) of RCC patients. The median blood loss was 250 ml (50-500 ml) for RCC. Median surgical time was 130 min (ranged from 90 to 210 min) for the RCC group. In the patient with RCC who underwent RAE before RFA, the type of electrode used for ablation was single tip electrode. Median length of hospital stay was 6 days for both groups. The 5 years cancer free survival for RCC was 81.8%.

4. Case Presentation

Twenty years old male patient diagnosed with T.S. presented by recurrent attacks of hematuria. Pre and post contrast MSCT reveals bilateral enhanced renal masses with central fatty components (bilateral AML), the largest one was at the right side. Non-enhanced axial CT brain revealed: bilateral calcified tubers at both cerebral hemispheres. The patient underwent partial nephrectomy for right sided AML. On follow-up, contrast enhanced MSCT reveals local recurrent AML on the right side and the left sided AML developing aneurisms. Angio-embolization for left sided AML was done. Post embolization selective angiography showed no further filling of the aneurysms denoting complete occlusion. (Figure 1).

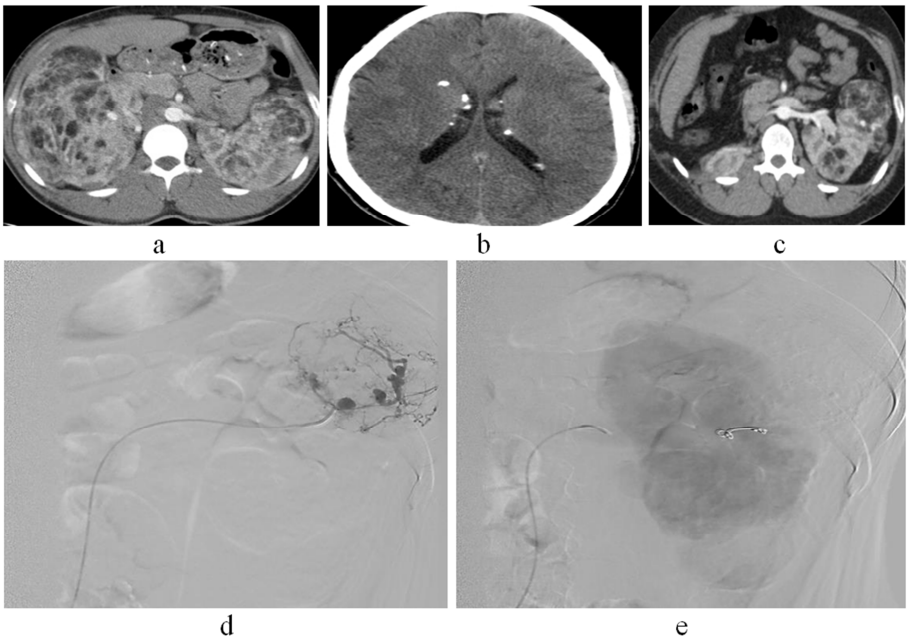

Figure 1. *a, Post contrast (coronal) CT image shows bilateral AML. b, Axial cuts of the brain shows bilateral cerebral calcified tubers. c, Post RT partial nephrectomy contrast CT image (coronal) shows local recurrent AML at right side and dilated aneurisms at middle zone of left sided AML planned for angio-embolization. d, Pre embolization shows left mid zone vascular lesion with multiple aneurysms. e, Post embolization selective angiography showed no further filling of the aneurysms denoting complete occlusion.*

Another male patient, 75 years, presented by an accidentally discovered right renal mass. MRI and postcontrast MSCT reveals right renal lower pole mass measures 5.3 x 3.7 cm with a metastatic left iliac soft tissue mass. The patient was unfit for surgery and planed for RAE as a palliative treatment. Right renal angiography shows 2 main divisions of the renal artery with two interlobar branches from the distal segmental artery are seen related to the mass. Selective catheterization of the feeding artery to the mass was done using micro catheter. Selective embolization was done using two micro coils. Post embolization angiogram showed no further opacification of the mass with preservation of the remaining right renal vasculature. Follow-up MSCT after 1 month, using a non-enhanced CT showed little enhancement of the mass with stranding and thickening of the perinephric fat and small perinephric hematoma. The 2nd follow-up after 3 month shows no significant enhancement of the mass with resolving of the perinephric

hematoma. Axial CT images of iliac bones shows nearly the same size of left iliac soft tissue mass. (Figure 2).

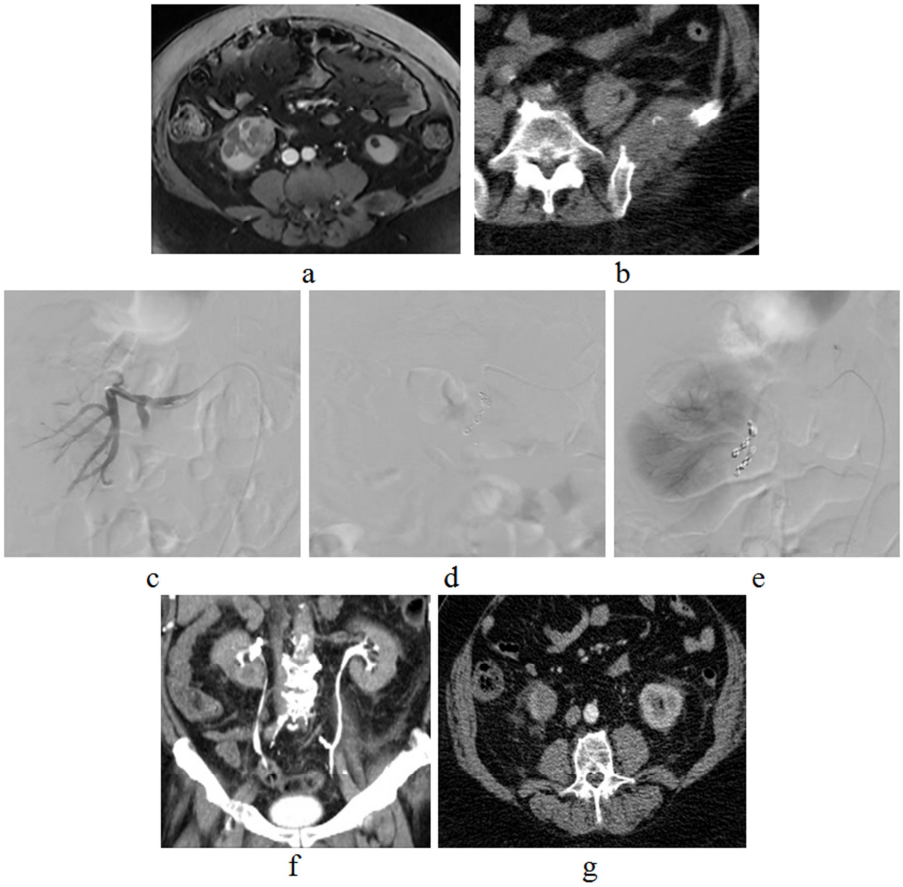

Figure 2. *a, Post contrast Axial MRI images shows ill-defined enhanced lower pole right renal mass with infiltration of the perinephric fat plans, b: Axial CT image of the pelvis shows destructive left iliac metastatic soft tissue mass lesion. c, Selective catheterization of the feeding artery to lower polar mass using micro catheter. d, Selective embolization was done using two micro coils. e, Post embolization angiogram show no further opacification of the tumor with preservation of the remaining right renal vasculature. f, 1st Follow up post contrast CT coronal excretory phase after 1 month duration shows little enhancement of the mass with stranding and thickening of the perinephric fat and small peri nephric hematoma. j) 2nd Follow up by post contrast axial CT image after 3 month duration shows no significant enhancement of the lower polar mass with resolution of the perinephric hematoma.*

5. Discussion

The most common adult renal epithelial caner is RCC. It accounts for > 90% of all renal malignancies and 2% -3% of all adult malignant tumors. [5] AML is the most common benign renal tumor that constitutes up to 2% of renal neoplasms. [6].

The indications for RAE in treatment of renal masses include: preoperative embolization before nephrectomy for primary RCC, palliation for advanced stage RCC, treatment of AML. [3].

In case of RCC, RAE will lead to preoperative de-vascularization which will logically ease the radical nephrectomy and decrease the blood loss; palliative therapy for un-resectable tumor or if surgery is contraindicated, and hemorrhagic complications treatment as spontaneous rupture of previously undiagnosed tumor.[7, 8] Additionally, some evidence suggests that preoperative RAE of RCC is associated with improved mortality rates when compared with surgical treatment alone.[9] On the other side, in case of AML, embolization is indicated if the presentation is hemorrhage and hemodynamic instability, as well as if AML > 4 cm. [4].

Pre-embolization imaging is very important, especially for assessing the tumor or aneurysmal lesions. Doppler ultrasonography, magnetic resonance angiography, and CT angiography are the modalities commonly used. The latter is used in patients with good renal function. Indeed, the three-dimensional imaging capability of modem CT scanners has made it a potent tool for renal imaging. [10] The 20 patients in our study were examined by US, CT and/or MRI before RAE to evaluate size of the tumor, assist extension of RCC, exclude distant metastasis and assess if there is complications of AML.

The Seldinger's technique is commonly used for angio-embolization of RCC and AML as performed in our study. [2] Subsequent surgery will be facilitated after angio-embolization in large locally advanced renal tumors by decreasing the perioperative blood loss, creation of a tissue plane of edema facilitating dissection, and reduction in tumor bulk including extent of vascular thrombus, when present. [3,

4] Therefore, the intra-operative transfusions and operative time were decreased. [11] None of RCC patients in our study required blood transfusion with a short operative time, as 9/11 patients underwent pre-operative total embolization (45%).

The time interval from embolization to surgery is recommended to be less than 48 hours to decrease the complications. [4] Sauk and Zuckerman (2011) reported that, the recommended delay between RAE and surgery is 24–72 hrs. The plane of dissection seems to be most pronounced at 72 hrs post RAE.[12] The 11 patients with RCC in our study underwent nephrectomy at the same day of angio-embolization with the same benefits.

Agents used for RAE can induce either a temporary or permanent occlusion. Some of these agents occlude large vessels (proximal embolization), whereas others induce an occlusion at the arteriolar or capillary level (distal embolization). [4] There are various embolic agents used for preoperative RAE of locally advanced tumors, but microparticles and coils seem particularly well-suited for this indication.[11] Proximal vascular plugs are also a common treatment choice. Attention must be paid to ensure a residual stump of the proximal artery to allow surgical clamping.[3] The embolizing agents used in our study were balloon catheter inflation with alcohol in 4 patients, alcohol with insertion of micro coils in 4 patients and Gelfoam with alcohol in 1 patient.

RAE in non-operable cases can alleviate severe local pain or recurrent hematuria. The paraneoplastic hypocalcaemia might also regress following RAE. [11-14] RAE as a palliative treatment was used in one patient in the current study who had RCC with destructive distant metastatic iliac mass. The embolizing agents used were 2 micro coils.

It was reported that, the combined use of radio frequency ablation (RFA) and RAE may reduce the rate of incomplete tumor ablation. Selective embolization of tumor feeding arteries prior to RFA improves its efficiency. In addition, when RAE used before RFA, this will improve the results of RFA especially for central located tumors, which having high rate of recurrence when its diameter > 3cm. [15, 16] One patient (5%) in our study with RCC underwent RAE as a combined treatment after two sessions of RFA to improve results of RFA. The embolizing agents were balloon catheter with alcohol.

RAE is well recognized therapy for the treatment of AML.[3] Symptomatic AMLs such as those with prior or active hemorrhage, flank pain, hematuria, or mass effect are the indications for RAE. AMLs > 4 cm have been shown to be associated with symptoms (80–90%) and spontaneous hemorrhage (50–60%). Therefore, prophylactic treatment of AMLs > 4 cm serves as another indication for RAE. [17-19].

The safety and efficacy of RAE for AML have been confirmed in multiple retrospective series since 2000 that provide a long-term follow-up. These studies show overall durable tumor treatment response, low surgical salvage rates, and recurrence rates ranging from 0-37%. The majority of recurrences are successfully managed with repeat RAE. [4].

The choice of the embolizing agent for AML is debated. Agents like ethanol, PVA, and Embospheres (Merit Medical) are commonly used. [3] The use of Onyx (Covidien, Plymouth, MN) in AML treatment has also been reported. [20] The utility of coils remains unclear. Some authors advocating their use and others suggest that it promotes collateral formation around the level of occlusion. Lenton et al reported a high intraprocedural aneurysm rupture rate (30%) as compared with others who did not report the occurrence of rupture. These authors concluded that this may be attributed to the use of PVA alone rather than PVA and coils. [21] Villalta et al found that smaller microspheres (<150 μm) were associated with both an increased recurrence rate requiring repeat embolization (odds ratio (OR) 5.88) and risk of pulmonary complications. These complications make the authors advocating the use of larger sized particles. [22] The embolizing agents used for AML in our study were; micro coils in 5 cases, alcohol with insertion of micro coils in 3 cases and emphosphere particles with insertion of micro coils in 1 case.

The large AMLs (≥ 10 cm) are considered more resistant to RAE. Chan et al, demonstrated that recurrences necessitating surgery only occurred when treating AMLs > 10 cm in size.[23] This is attributed to their large size, multiple feeding vessels, and greater difficultly in isolating them from normal renal parenchyma. While several series suggest efficacy of treatment of AMLs associated with TS. Active surveillance of this high-risk group is prudent. [24, 25] In fact, Kothary et al suggested that AMLs treated with RAE in this group may be associated with higher rate of regrowth. [26].

The optimal time from embolization to nephrectomy is significantly varied in the literature. It should be < 48 hours. [13] Post embolization syndrome (characterized by lumbar pain, nausea, and fever) occurs in a majority of patients 1-3 days post procedure. It can be minimized when nephrectomy performed within this time frame. Additionally, surgery is more difficult 72 hours after embolization, which is thought to be secondary to collateral vessel formation. [27] Some authors suggest a delay of 24- 48 hours after embolization, which allows edema to develop facilitating surgical dissection, while others have suggested that the delay should be as minimal as possible to prevent collateral vessel formation. [10, 11].

Post embolization syndrome could be reduced if the time between RAE and surgery is minimized. In a series by Lin et al, 8 patients underwent concomitant RAE and surgical resection as compared with 14 control patients who underwent staged preoperative embolization. [28] The concomitant group did not report the post-infarction syndrome if compared with 36% in the staged group. This increases the patient comfort, decreases the hospital stay, and as a result reducing health care costs. Another series by Carvajal et al studied 7 patients who underwent concomitant RAE and surgical resection.[29] This study was limited to tumors > 13 cm in size (Stage II, IIIA–B), but did demonstrate safety and increased patient comfort.

The complications after embolization of AML are rare. Also, renal insufficiency was not reported. [30] Post embolization syndrome is the most common complication, occurring in up to 64% of patients in one series. Most cases are self-limited and successfully treated with antipyretics and non-steroidal anti-inflammatory drugs. Major complications were abscess formation, coagulative necrosis, and self-limited non-targeted embolization to normal renal parenchyma, all successfully treated without long-term adverse squeal. [3].

Finally, some points are recommended to improve the outcomes: pre-embolization imaging is very important for assessing the tumor or aneurysmal lesions. The time interval from embolization to surgery should be 24–72 hrs as the plane of dissection seems to be most pronounced at 72 hrs post RAE and the post-embolization syndrome will be less frequent. After this, surgery will be more difficult due to the development of collaterals. Moreover, RAE will improve the results of RFA especially for central located tumors, which having high rate of recurrence when its diameter > 3cm. The large AMLs (≥ 10 cm) are considered more resistant to RAE. Future studies are required to determine cutoff radiological and hematological points to preoperatively distinguish the responders and non-responders.

The possible limitation of our study is the small number of patient and absence of randomization.

6. Conclusion

RAE is a safe, effective and well tolerated treatment of AML either if large sized which is liable to rupture or symptomatic to stop bleeding. Also, it allows preoperative de-vascularization of RCC to ease its surgical resection and aiding as palliative treatment if RCC is un-resectable or metastatic.

Conflict of Interest

No conflict of interest was declared by the author**.**

Financial Disclosure

The author declared that this study received no financial support.

Abbreviations

RAE	Renal artery embolization
RCC	Renal cell carcinoma
AML	Angiomyolipoma
US	Ultrasound
MRI	Magnetic resonance imaging
CT	Computed tomography
Fr	French
BMI	Body mass index
RFA	radiofrequency ablation

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