

## Original Article

# Nephron-sparing surgery with preoperative selective arterial embolization in management of giant renal angiomyolipomas

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**Abstract:** This study aimed to evaluate the effect of nephron-sparing surgery (NSS) along with preoperative selective arterial embolization (SAE) on the treatment of giant renal angiomyolipomas (AML). Between July 2010 and October 2014, 3 men and 8 women with 11 sporadic giant renal AMLs were treated by NSS along with preoperative SAE in our center. The tumor size ranged from 10.4 to 24.2 cm. The medical data were collected. Of the 11 giant AMLs, 8 were completely devascularized by SAE, and the other 3 were mostly devascularized. The rate of post-embolization syndrome was 27.2% (3/11). NSS was successfully performed after SAE in all patients. The operating time was 70-155 min (mean, 115 min). Blood loss was 50-150 ml (mean, 70 ml). The warm ischemia time was 8-25 min (mean, 15 min). The incidence of perioperative complications was 18.2% (2/11), and no severe complications occurred after NSS. The hospitalization time after NSS was 5-10 d (mean, 6.6 d). There was no statistical difference in kidney function pre- and post-surgery. No evidence of recurrence was found during the follow-up period. NSS with preoperative SAE can be considered a viable and effective treatment option for giant renal AMLs, for it avoids excess blood loss and shortens warm ischemia time during NSS.

**Keywords:** Giant renal angiomyolipoma, nephron-sparing surgery, selective arterial embolization, complication

## Introduction

Renal angiomyolipoma (AML) is a benign neoplasm composed of varying admixtures of blood vessels, smooth muscle cells, and adipose tissue [1]. The majority of renal AMLs are of sporadic origin, while approximately 20% are associated with the tuberous sclerosis syndrome [2]. It occurs in less than 0.2% of the general population, [3] and occurs 4-fold more frequently in women [4].

The diagnosis of AML is based on the presence of macroscopic intra-tumoral fat, detected with 100% sensitivity on computed tomography (CT) scans. The presence of fat within the lesion (indicated on CT by a negative attenuation of -10 Hounsfield units or lower), is pathognomonic of AMLs [5, 6].

The majority of renal AMLs are found incidentally during the workup of unrelated symptoms, and the increased use of cross sectional imaging has led to a rise in the diagnosis of these lesions [7]. The most dramatic morbidity asso-

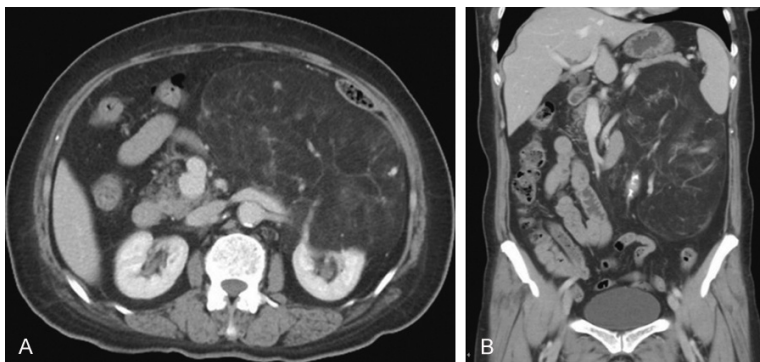
ciated with AMLs is Wunderlich syndrome, which is retroperitoneal hemorrhage resulting from the spontaneous rupture of an AML [8]. Patients with this sudden, painful, and often life-threatening event are most often first seen in the emergency department, and the life-threatening retroperitoneal hemorrhage can occur in 20% of patients presenting with hemorrhages [7]. Considering the benign nature of AMLs, the goals of treatment for AMLs should be preservation of renal function while ameliorating any symptoms and decreasing the risk of hemorrhage. Renal sparing approaches, including selective arterial embolization (SAE) and nephron-sparing surgery (NSS), should be selected [3].

However, to date, the management of giant AMLs that are >10 cm [9, 10] is complex. For giant AMLs, the symptoms cannot be relieved entirely by SAE, and tumor growth and hemorrhage tend to recur after SAE [11]. Although NSS provides complete resection of the lesion, this surgical approach runs the risk of significant hemorrhage and extension of warm isch-

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**Table 1.** Patient's demographic and tumor characteristics

| Variable                                  | Data             |
|---|------------------|
| Gender                                    |                  |
| Male, number                              | 3                |
| Female, number                            | 8                |
| Median age at presentation, years (range) | 47 (28~72)       |
| Symptoms at presentation                  |                  |
| Retroperitoneal bleeding, number          | 3                |
| Gross hematuria, number                   | 5                |
| Pain, number                              | 7                |
| Palpable mass, number                     | 3                |
| Side of AMLs                              |                  |
| Right, number                             | 7                |
| Left, number                              | 4                |
| Mean maximal tumor size, cm (range)       | 13.3 (10.4~24.2) |



**Figure 1.** Contrast enhanced CT scan of the abdomen, axial section (A) and coronal section (B), showed a hypodense lesion anterior to the left kidney, with a maximum diameter of 24.2 cm.



**Figure 2.** Emergency contrast enhanced CT scan, axial section, showed a right retroperitoneal hematoma (red arrow) and exophytic, fat-containing lesion (white arrow) of the right kidney, with a maximum diameter of 19.3 cm.

emia time (WIT) [7], and is associated with higher rates of complications [12].

Preoperative embolization of large tumors is recommended to avoid excess blood loss during NSS, but there are only anecdotal reports in the literature [13-15]. Here we presented our experience of applying NSS with preoperative SAE for the management of giant renal AMLs.

## Materials and methods

### Patients

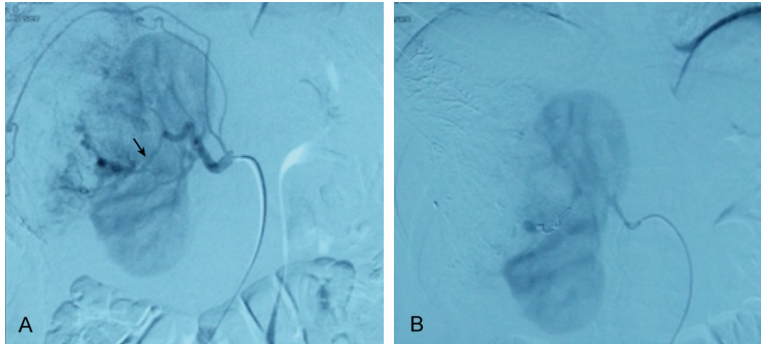
Eleven patients with 11 giant renal AMLs giant tumors underwent NSS with preoperative SAE at our institution from July 2010 to October 2015 and completed follow-up in our institution. Patients' demographics were described in **Table 1**. The giant AMLs were confirmed by contrast-enhanced CT for all patients before treatment. Tumor size was calculated as previously described in the literature, and was defined as the greatest cross-sectional dimension recorded on enhanced CT at presentation [11, 16, 17]. The mean size of the AMLs was 13.3 cm (range: 10.4 to 24.2

cm). **Figures 1** and **2** demonstrated the abdominal CT images of two giant AMLs. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Peking Union Medical College Hospital (PUMCH). Written informed consent was obtained from all participants.

### SAE procedures

SAE procedures were classified as elective and acute procedures. Eight were elective procedures, and 3 were acute procedures for patients presenting with retroperitoneal hemorrhage. Patients underwent gastrointestinal tract preparation, except for the 3 patients who had acute embolization. SAE was performed through the common femoral artery with 5-French angiographic catheters. Renal arteriography was used to evaluate the arterial feeders

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**Figure 3.** A giant AML was embolized with a mixture of lipiodol and coils. A. Pre-embolization angiography through microcatheter revealed a big branch of the right middle segmental renal artery which was considered as tumor-feeding (arrow); B. Post-embolization angiography showed the abnormal vascularity was eliminated and the coils remained in the branch supplying the lesion.

**Table 2.** Data of selective arterial embolization

| Variable                       | Number |
|--------------------------------|--------|
| Elective SAE                   | 8      |
| Acute SAE                      | 3      |
| Complete embolization          | 8      |
| Incomplete embolization        | 3      |
| Embolization materials         |        |
| Gelfoam                        | 4      |
| Iodized oil                    | 5      |
| Iodized oil mixed with gelfoam | 1      |
| Iodized oil missed with coils  | 1      |
| The angiographic appearance    |        |
| A single feeding vessel        | 6      |
| 2 feeding vessels              | 3      |
| 3 feeding vessels              | 2      |
| Post-embolization syndrome     |        |
| Fever                          | 2      |
| Flank pain                     | 1      |
| Nausea                         | 0      |
| Distension                     | 0      |

to the tumor. After arteriography, the artery supplying the tumor was selectively catheterized. Vessel occlusion was carried out with gelfoam, iodized oil, microcoils, or a combination of these materials, which was expected to embolize the arteries supplying the tumors as completely as possible. A post-embolization angiogram was performed to confirm the devascularization of the AML. Electrocardiogram, blood pressure, and oxygen saturation were monitored for 24 hours after embolization. Expectant treatment, such as non-steroidal anti-

inflammatory drugs (NSAIDs) and analgesic medications, was administered. Movement was forbidden for 12 h after SAE to prevent the puncture point from bleeding.

### *Surgical procedures*

Open surgeries were achieved transabdominally for all patients. The kidney was carefully detached from the surrounding tissue and mobilized within Gerota's fascia. After exposure and temporary occlusion of the renal artery, partial nephrectomy or tumor enucleation was performed.

During resection, the tumor and renal parenchyma should be separated carefully as far as possible to reduce renal parenchymal damage. The collecting system and renal defect were closed. Hypothermia was not used routinely to protect the kidney against ischemic injury because of the huge volume of the tumors. The renal artery was reperfused and the renal blood supply recovered after suturing was completed satisfactorily. Data regarding operating time, WIT, estimated blood loss, the rate of complications, and hospitalization time after NSS were collected.

### *Follow-up*

All patients were followed up 3 months after the procedure and every 6 months thereafter. At the first follow-up, serum creatinine levels (Scr) and estimated glomerular filtration rate (eGFR) were tested, and a statistical analysis was performed on the changes of renal function before and after treatment.

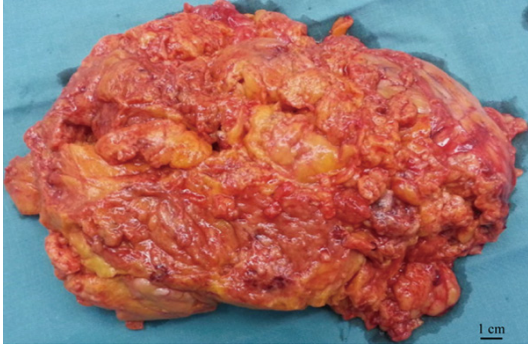
### *Statistical analysis*

Scr and eGFR expressed as mean  $\pm$  standard (SD) were analyzed using SPSS software. Student's t test was used.  $P < 0.05$  was considered statistically significant.

## **Results**

### *Results of arterial embolization*

The angiographic appearance of AML was characterized by a single feeding vessel (6 cases), 2



**Figure 4.** A giant AML was completely resected through nephron-sparing surgery.

feeding vessels (3 cases), and 3 feeding vessels (2 cases) to the giant tumor. Post-embolization angiogram confirmed that complete embolization of the tumor was performed in 8 patients, and in the other 3 patients, most arterial feeders were blocked. The embolization materials used were gelfoam in 4 patients, iodized oil in 5 patients, iodized oil mixed with gelfoam in 1 patient, and iodized oil mixed with coils in 1 patient. **Figure 3** demonstrates the angiography of a single arterial branch supplying the tumor before and after SAE. After SAE, 3 (27.2%) of the 11 patients had post-embolization syndrome, presenting with fever ( $n=2$ ) and flank pain ( $n=1$ ) (**Table 2**), which were successfully mitigated with analgesic and antipyretic medications.

### *Intraoperative and hospitalization results*

Eight patients underwent surgery within 24 hours after elective SAE, while 3 patients after acute SAE underwent surgery 3 months later. Successful NSS was achieved in all patients. **Figure 4** shows the specimen of a giant tumor resected by NSS. No patient required total nephrectomy. Histopathological examination confirmed the diagnosis of AML. The operating time was 70-155 min (mean, 115 min). The blood loss was 50-150 ml (mean, 70 ml), and no patient received a blood transfusion. In 3 patients, the renal artery was not occluded because the tumors were so large that the posterior renal pedicle was completely covered. In the other 8 patients, the WIT was 8-25 min (mean, 15 min). Two patients (18.2%) had complications, presenting with wound infection ( $n=1$ ) or ileus ( $n=1$ ). No postoperative hemorrhage, urine leakage, or acute renal failure was identified. All patients were discharged

home within 5 to 10 days after NSS, with a median duration of 6.6 days. The outcomes of NSS are presented in **Table 3**.

### *Results of follow-up*

Clinical follow-up was available for all 11 patients, with a median duration of 24 months (range: 6 to 51 months). All patients remained symptom-free and had no relapse during follow-up. Changes of eGFR and Scr level before surgery and 3 months after surgery were collected to estimate the difference in renal function. Scr levels were all within normal limits and did not change after the treatment ( $57.46 \pm 22.98$   $\mu\text{mol/L}$  vs.  $60.76 \pm 19.45$   $\mu\text{mol/L}$ ;  $P=0.2092$ ). Although eGFR was lower than the reference value of 90 ml/min/1.73 m<sup>2</sup> before treatment, it did not change after the treatment ( $79.6 \pm 25.1$  ml/min/1.73 m<sup>2</sup> vs.  $76.4 \pm 24.3$  ml/min/1.73 m<sup>2</sup>;  $P=0.2365$ ) (**Table 4**).

### **Discussion**

Renal AMLs are vascularized by one or a few tortuous and aneurysmal end arteries derived from branches of the renal artery. Their arterial feeders are thought to possess poor elastic layers and a disorganized adventitial cuff of smooth muscle, making the vessels prone to rupture [18-20]. Although some AMLs are asymptomatic, common symptoms existed in 60% of AML patients, including flank pain, palpable mass, and gross hematuria. Tumors larger than 4 cm may confer a bleeding risk caused by spontaneous rupture of the tumor [3]. With the increase of the tumor size, the risk of bleeding increases and severe hemorrhagic shock can even occur in these patients [7]. For giant AMLs, the risk of life-threatening hemorrhage is the main clinical concern [21].

Considering the benign nature of AMLs and the possibility of renal insufficiency or poor quality of life after nephrectomy, nephron-sparing approaches are preferred.

NSS is an operative method for benign renal tumors and small renal cell carcinomas [22]. NSS has been advocated as a treatment alternative for AMLs with a tumor size of 4-7 cm [23]. The advantages of NSS include radical eradication of massive lesions, relief of symptoms, decreased risk of bleeding and recurrence [24-28]. However, larger renal masses cause greater difficulties during NSS [29]. For

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**Table 3.** Intra- and post-operative patient data (n=11)

| Variable                                     | Data         |
|--|--------------|
| Median (range) operating time, min           | 115 (70~155) |
| Median (range) blood loss, ml                | 70 (50~150)  |
| *Median (range) WIT, min                     | 15 (8~25)    |
| Unclamped, number                            | 3            |
| Blood transfusion, number                    | 0            |
| Median (range) hospital stay after NSS, days | 6.6 (5~10)   |
| Mean follow-up period (range), months        | 24 (6~51)    |
| Complications                                |              |
| Conversion to nephrectomy, number            | 0            |
| Postoperative bleeding, number               | 0            |
| Deep vein thrombosis, number                 | 0            |
| Wound infection, number                      | 1            |
| Urine leak, number                           | 0            |
| Acute renal failure, number                  | 0            |
| Ileus, number                                | 1            |

\*In the other 8 patients whose renal arterial is occluded, the WIT was 8-25 min (mean, 15 min).

**Table 4.** Comparison of serum creatinine, eGFR between pre- and post-operation

| Indicator | Before surgery                       | After surgery                        | P      |
|-----------|--------------------------------------|--------------------------------------|--------|
| Scr       | 57.46±22.98 umol/L                   | 60.76±19.45 umol/L                   | 0.2092 |
| eGFR      | 79.6±25.1 ml/min/1.73 m <sup>2</sup> | 76.4±24.3 ml/min/1.73 m <sup>2</sup> | 0.2365 |

giant AMLs, it is not easy to complete this procedure because of the uncontrolled massive blood loss during surgery. De Luca described 53 kidneys with AML treated surgically, all with lesions >4 cm, and 30% of them had total nephrectomy [27]. For giant AMLs, total nephrectomy is more common [30-34]. In addition, for giant tumors, perioperative complications, urinary fistula in particular, obviously increase [12, 24, 26, 28]. Mostly, WIT during surgery for giant renal tumors would also increase compared with tumors of small size. Renal ischemia is an important factor impacting the functional outcomes of NSS [22]. The critical value of WIT is considered to be <30 min, and renal function would be irreversibly damaged when WIT is over the critical value [35].

SAE is another nephron-sparing approach, which is clearly beneficial in treating acute hemorrhage from AMLs [18, 36]. Nevertheless, post-embolization syndrome reportedly occurs in 63.6-100% of cases, manifesting as flank pain, fever, and nausea [20, 37]. Meanwhile, 18.2-32% of the patients had tumor relapse after SAE due to neoangiogenesis, and the in-

creased rate of relapse is correlated with an increased volume of tumor [11, 38]. Furthermore, SAE has been shown to be of limited value in reducing tumor bulk because of an increase in the nonvascular component; hence, for giant AMLs related symptoms often cannot be relieved effectively after SAE [39]. Therefore, SAE may not be an effective method in the treatment of giant AMLs.

Alternatively, preoperative SAE has been proven to be a viable option to perform “zero-ischemia” partial nephrectomy for clinical T1 renal tumors [40, 41]. Although preoperative embolization of large AMLs is recommended to avoid excess blood loss during NSS, currently there are only a few reports of the

procedure [13-15, 42]. In the past few years, we have tried to apply preoperative SAE to reduce the blood supply of giant AMLs and make it possible to perform NSS. To our knowledge, this study represents the largest series reported to date. In our study, complete embolization of the tumor was achieved in 8 of 11 patients, and most arterial feeders were blocked in the other 3 patients, proving the effectiveness of SAE in devascularization. The rate of post-embolization syndrome is reported as high in some studies [19, 43, 44]. In contrast, Williams et al. reported a rate of post-embolization syndrome of 6% [45], and Ramon et al. described post-embolization syndrome in only 5 of 40 patients (12.5%) [18]. Our result was similar to that of Ramon et al. The lower rates in our study and other reports can be attributed to the use of prophylactic administration of NSAIDs and analgesic medications.

The optimal timing for NSS after SAE remains inconclusive. Luo et al. reported that surgery should be performed 1 month after SAE [42], while Shen et al. suggest that SAE should be performed 3 days before tumor resection [46].

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Considering the potential effect of post-embolization syndrome attributable to inflammatory mediators released after SAE therapy [20, 37], in our study the surgery was performed within 24 hours after elective SAE in 8 patients. For the 3 patients who had acute SAE, it might be understandable that the inflammatory reaction and adhesion after hemorrhage would remain for some time. For the 3 acute patients, surgeries were performed 3 months after SAE, when inflammatory reactions and adhesions had mostly disappeared, in order to reduce the difficulty of the surgery.

There was no conversion to total nephrectomy in this series, and no severe complications related to NSS occurred. The median operating time and blood loss are consistent with previous series of NSS for small AMLs [24, 26, 28], and compare favorably with some reports of NSS for giant AMLs [47-49]. We believe that preoperative SAE might actually decrease the chances of surgical complications and blood loss.

Springer *et al.* reported that the median WIT was 14.4 min in open partial nephrectomy for small renal tumors [50], similar to our result (15 min). Meanwhile, we were compelled to excise the AML with renal hilum unclamped in 3 patients because of the difficulty in exposing the renal artery. In addition to our study, it was reported in Yun Luo's study that a patient with bilateral giant AMLs was treated successfully with preoperative SAE and NSS without hilar clamping [42]. For some selected renal tumors, it was also confirmed that NSS without hilar control is possible [51].

There are no guidelines regarding follow-up after AML treatment. Our center does not have a standardized protocol, but most practitioners obtain a single CT scan for the first time 3 months after NSS and every 6 months thereafter. We compared the levels of Scr and eGFR before and 3 month after surgery, which represent total renal function and indirectly reflect renal function of the operated kidney before and after NSS. In our study, total renal function estimated based on Scr and eGFR did not change before and after treatment. This result was consistent with previous results about SAE for renal AML [10, 18, 45] and was anticipated if tumors were resected without damage of the renal parenchyma. Heidenreich *et al.* study

shows that NSS can result in a sustained recurrence-free survival for small renal AMLs [24]. In our study, with a median follow-up of 24 months, no evidence of recurrence was found.

The main limitation of our study was the small size of the study group due to the rarity of giant renal AML. In addition, this study was a retrospective, nonrandomized observation. However, the combination of SAE and NSS provided ideal results in our study. NSS was successfully performed after SAE in all patients, and no significant between pre-surgical and post-surgical values defining the kidney function were noted.

### Disclosure of conflict of interest

None.

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