Value of Nephrectomy Following Renal Artery Embolization vs. Nephrectomy Alone for Big Renal Cell Carcinoma: A Retrospective Analysis

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Abstract

Renal cell carcinoma (RCC) is the most common malignant renal tumor and the third most frequent malignant tumor encountered in urology [1]. Surgical resection is the first-line treatment for RCC. Big RCC and end-stage kidney neoplasms are known to grow into the renal pelvis and subsequently into the renal vein and inferior vena cava [2]. The treatment of choice for RCC is radical nephrectomy, which involves adrenalectomy with the removal of the fat kidney capsule and the proximal urethra [3]. Therefore, there are difficulties associated with surgery for big RCC.

In the 1970s, Almgard [4] proposed transarterial renal embolization as a means of inducing kidney necrosis with the goal of improving the treatment of RCC. Since then, this treatment has been accepted for advanced and unreseetable renal cell tumors with persistent bleeding or manifestations of paraneoplastic syndrome. RAEE can be useful for reducing blood loss and facilitating cleavage of the tumor, and the predominant benefit of preoperative renal embolization is a reduction in operative blood loss associated with nephrectomy [5], and this procedure also decreases vena cava tumor size and creates an easier dissection plane as a result of tissue edema [6].

Currently, imaging examinations such as abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) are helpful in the initial detection of big renal neoplasms [7]. We have collected 237 cases of big RCC treated since 2000. Of these cases, 124 patients refused RAEE therapy due to the financial burden concerns of embolization.

However, there are only a limited number of reports available which detail the clinical data associated with RAEE followed by nephrectomy. Therefore, the aim of this study was to evaluate the clinical outcomes of nephrectomy following RAEE compared with nephrectomy alone for the treatment of big RCC.

Materials and Methods

This study retrospectively enrolled 237 patients from March 2000 to March 2012. There were 114 females, and 123 males. One hundred and thirteen patients with big RCC underwent preoperative embolization followed by nephrectomy, and 124 patients who underwent nephrectomy alone served as the control group. Nephrectomy was performed 24-48 h after RAEE under general anesthesia by nephrectomy. The primary technical success rate was 100% in both group, post-operation complication rate in RAEE group was 7.4% compared with 21.5% in the control group (P=0.016). The perioperative blood transfusion volume, transfusion rate, blood loss volume, operating time, hospitalization duration, and hospitalization expenses in the RAEE group and control group were 523±153 mL vs 1075±390 mL (P=0.012), 24.5% vs 40.8% (P=0.016), 242±984 mL vs 1431±86519 mL (P=0.009), 2.4±0.5 h vs 3.6±0.8 h (P=0.036), 9±2 days vs 14±3 days (P=0.031), and 4102.2±829.1 USD vs 8193.6±9699.0 USD (P=0.014), respectively. The five-year follow-up showed that there was no difference in overall survival rate between the two groups (P=0.769), disease free survival (P=0.562) and cancer specific survival (P=0.751). RAEE prior to nephrectomy resulted in less severe perioperative complications and cost compared with resection alone in patients with big RCC.

Introduction

The patients' demographic data and intraoperative parameters were compared between the two groups (Table 1). The Institutional Review Board approved the study protocol, all patients provided written informed consent, and all procedures were conducted according to the guidelines approved by the Ethics Committee.

All patients with identified kidney masses and clinical suspicion underwent color Doppler ultrasonography (General Electric Inc., Fairfield, CT, USA) examinations, CT (General Electric Inc.) scans, or MRI (General Electric Inc.) of the abdomen to confirm or refute the clinical diagnosis.
simultaneously affected by the tumor. All patients received intravenous hilum or the aorta were removed. The adrenal gland was resected if excised in all patients. All involved lymph nodes adjacent to the renal manipulation or propagation of tumor thrombi into the systemic The renal vein was first ligated before nephrectomy to minimize the via a midline abdominal incision with retroperitoneal dissection.

Inc., Bloomington, IN, USA) was placed in the distal portion of the were used to embolize the feeding vessels, and the coil (3 mm, Cook Boston Scientific Corp., Boston, MA, USA) particles (300-500 μm) of the RCC artery was performed, and the endpoint of embolization obtained to identify the renal arteries. Selective catheterization was routinely performed, and abdominal aorta angiograms were obtained to identify the renal arteries. Radiologists with at least seven years of experience in vascular findings were reviewed based on the consensus of two interventional radiologists.

The technical success of RAE was defined as complete occlusion of the proximal renal artery, which was no longer observed to be opacified on immediate post-embolization angiography. The angiographic findings were reviewed based on the consensus of two interventional radiologists with at least seven years of experience in vascular interventions and embolization procedures. The complications were classified according to the Clavien Dindo Scale.

Lower abdominal pain and mild fever were considered to be indicative of post-embolization syndrome, which was not considered a complication. The major complications included those that resulted in prolonged hospitalization, permanent adverse sequelae, death, and unplanned increases in the level of care.

The clinical outcomes of all patients were obtained from medical records and telephone interviews, and clinical success was defined as successful devascularization which eased the resection and decreased blood loss or hematuria without repeated embolization. The recorded data, including perioperative blood transfusion, blood loss, operating time, hospitalization duration, hospitalization expenses, adverse reactions, and five-year survival rate, were compared between the two groups.

The hospitalization costs included the followings: medical imaging costs (including all diagnostic and therapeutic procedures, such as RAE, plain radiography, ultrasound examination, and CT and MRI imaging); the nephrectomy costs (including the operating room occupancy time, anesthesia, equipment, nursing, and recovery costs); nursing costs (including regular floor telemetry bed, and intensive care unit costs); other therapeutic costs (including pharmacy, transfusion, perioperative blood transfusion and laboratory service costs); and living costs (including the costs covered by the patient during the period of hospitalization). Total hospitalization expenses were converted into US dollars at a rate of 6.70 RMB:1.00 USD, which was based on the current market exchange rate.

Table 1: Comparison of patients' demographic data and intraoperative parameters between RAE and control group (7 ts).

<table>
<thead>
<tr>
<th>Group</th>
<th>RAE group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>113</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>50±11</td>
<td>61±12</td>
<td>0.060</td>
</tr>
<tr>
<td>Female</td>
<td>59</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td>Right</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>Tumor size(cm³)</td>
<td>489.1±149.2</td>
<td>456.7±189.6</td>
<td>0.095</td>
</tr>
<tr>
<td>Average maximum diameter (cm)</td>
<td>8.6±1.2</td>
<td>9.1±1.7</td>
<td>0.074</td>
</tr>
</tbody>
</table>

The quantitative data are presented as the means±SD. The differences between the groups were compared using one-way analysis of variance followed by LSD t tests. Differences were considered significant at P<0.05. The statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Results

The primary technical success rate of embolization was 100% in the RAE group (Figure 1), and the renal cell tumors were successfully resected in all patients. All the patients were matched in terms of the diagnosis on preoperative biopsy or postoperative pathological examination (Figure 2). There was no perioperative mortality in either group. Post-infarction syndrome developed in 28 patients (24.8%) in the RAE group. The complication rate in RAE group was 7.4% compared with 21.5% in the control group, there was statistical difference between two
During the five-year follow-up, 18 patients died with evidence of tumor progression which led to multiple organ failure or cancer-associated death in the RAE group and 11 patients in the control group, 13 due to myocardial infarction, six due to cerebral infarction, and two patients died due to an automobile accident. There was no difference in overall survival rate between the two groups ($P=0.769$), disease free survival ($P=0.562$) and cancer specific survival ($P=0.751$) (Table 2).

Perioperative autologous red blood cell transfusion volumes in the RAE and control group were 523±153 mL and 1075±390 mL, respectively, with statistically significant difference ($P=0.012$). The transfusion rate in RAE group was 24.5% and in the control group was 40.8%, there was statistically significant difference ($P=0.016$). Blood loss in the RAE and control group during nephrectomy was 242±984 mL and 1431±86519 mL, respectively, and the difference was statistically significant ($P=0.009$). The operating time in the RAE and

Figure 1: Right renal cell carcinoma in a patient who underwent RAE followed by nephrectomy. A 36-year-old woman with a 11×7 cm right renal cell carcinoma underwent preoperative right renal artery embolization followed by uneventful right nephrectomy with a total estimated blood loss of 200 mL. A, B: Ultrasound image showing a huge occupying lesion in the right kidney, presenting a mixed echo and moderate blood flow. C-D: Axial and coronal T2WI MRI images of the right renal mass with mixed signal. E: Selective right renal arteriogram demonstrating a large hypervascular renal cell carcinoma before embolization. F: Post-embolization selective right renal arteriogram demonstrating near-complete embolization of the right renal artery to stasis.

Figure 2: Pathology of renal clear cell carcinoma. The clear cell carcinoma was large and transparent, and the cytoplasm contained a large number of glycogen and lipid substances. A: × 200 times magnification; B: ×400 times magnification.
control groups was 2.4±0.5 h and 3.6±0.8 h, respectively, with statistically significant difference (P=0.036). The mean length of hospital stay in the RAE and control group was 9±2 days and 14±3 days (P=0.031), respectively. A comparison of the clinical variables between the two groups revealed an increased length of hospital stay in the control group compared with the RAE group (Table 3).

Table 2: Comparison of patient survival and complication rate in the RAE and control group (±s).

<table>
<thead>
<tr>
<th>Group</th>
<th>RAE group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>113</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Blood transfusion (mL)</td>
<td>523±153</td>
<td>1075±390</td>
<td>0.012</td>
</tr>
<tr>
<td>Transfusion rate (%)</td>
<td>24.5</td>
<td>40.8</td>
<td>0.016</td>
</tr>
<tr>
<td>Blood loss (mL)</td>
<td>242±984</td>
<td>1431±86519</td>
<td>0.009</td>
</tr>
<tr>
<td>Operating time (h)</td>
<td>2.4±0.5</td>
<td>3.6±0.8</td>
<td>0.036</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>9±2</td>
<td>14±3</td>
<td>0.031</td>
</tr>
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Note: Significant difference, P<0.05. These findings demonstrated that the mean total hospital costs were not significantly different between the two groups with the exception of imaging costs in the RAE group which was higher than the control group due to arterial angiography costs.

The mean total hospital costs in the RAE followed by nephrectomy group and the control group were 4102.2±829.1 USD and 8193.6±9699.0 USD, respectively (P=0.014). A comparison of hospital costs in terms of the categories of expenditure revealed significantly increased radiology costs in the RAE group compared with the control group. However, the control group had slightly higher blood cell transfusion costs and lower costs in the other expenditure categories than the RAE group. Finally, the mean total hospital cost was significantly lower in the RAE group than in the control group (Table 4).

Table 4: Comparison of patients’ mean total hospital costs between the RAE and control group (±s).

<table>
<thead>
<tr>
<th>Group</th>
<th>RAE group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>113</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Total hospital costs (USD)</td>
<td>4102.2±829.1</td>
<td>8193.6±9699.0</td>
<td>0.014</td>
</tr>
<tr>
<td>Imaging costs</td>
<td>1690.2±70.4</td>
<td>418.2±327.9</td>
<td>0.065</td>
</tr>
<tr>
<td>Nephrectomy costs</td>
<td>517.0±23.7</td>
<td>683.7±75.6</td>
<td>0.043</td>
</tr>
<tr>
<td>Nursing costs</td>
<td>380.9±56.4</td>
<td>478.6±73.4</td>
<td>0.034</td>
</tr>
<tr>
<td>Living costs</td>
<td>90.4±19.8</td>
<td>159.0±24.3</td>
<td>0.027</td>
</tr>
<tr>
<td>Other costs</td>
<td>1423.8±779.7</td>
<td>6474.1±484.2</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Discussion

RCC is the most common renal epithelial cancer in adults and accounts for more than 90% of all renal malignancies [8]. It is the most lethal of all urologic cancers and most commonly presents unilaterally [9]. There is evidence [10] demonstrating that nephrectomy for renal carcinoma combined with immunotherapy, targeted therapy, and other comprehensive treatment has a beneficial effect on these tumors. Big tumors and invasion to adjacent blood vessels or organs during surgical resection due to bleeding introduce difficulties in surgical resection [11].

Pre-surgical therapy is defined as preoperative medical therapy in patients with RCC, and has several potential advantages. Pre-surgical therapy may alleviate symptoms related to RCC before surgery and may reduce the primary tumor to facilitate subsequent resection. Since the 1970s when first developed, RAE has been used as a technique in which arterial blood flow can either be decreased or completely terminated to ensure the safety of patients with renal neoplasms in preparation for surgical resection or to therapeutically treat and prevent life-threatening hemorrhage [12]. RAE is a minimally invasive procedure that is increasingly used in the treatment of a wide range of conditions [13].

The purpose of preoperative biopsies was to confirm RCC and to exclude those not diagnosed with RCCs [14]. Published studies [15] have established a diagnostic rate of 62% - 96% with a mean of 83%. In the present study, the results of pathological detection by biopsy matched the post-operative pathological examination findings, and the diagnostic rate was higher than 95% [16], which is possibly because the larger volume tumors were favored by needle biopsy. Technical success of RAE can be achieved using a variety of embolization agents. After the selection or super selection of the artery or arteries feeding the tumor, depending on whether there was a large amount of shunting within the tumor, we used Embosphere particles (300-500 μm) to occlude the capillaries of the tumor and coil (3 mm) embolization of the main renal artery when necessary. However, a residual stump of the proximal renal artery should be spared to allow for surgical clamping and ligation during total nephrectomy without the problem of metallic coils hindering resection of the main renal artery or migrating back into the aorta and distal embolization. This procedure has been reported [17-18] to achieve stasis for 24 - 72 h, which is the regular time between embolization and subsequent nephrectomy. After embolization, a completion aortogram is then performed to evaluate accessary and parasitized arteries that may be supplying the tumor. Repeated embolization may be performed as necessary; however, in this study, there was no repeated embolization.

RAE prior to surgery has been recommended as it aids dissection due to edema of the tissue planes [19]. The benefits [12] of RAE in the preoperative setting include a decrease in perioperative blood loss and transfusion rate, the creation of a tissue plane of edema that facilitates dissection, and a reduction in tumor bulk that includes the extent of vascular thrombus upon presentation [20]. Wide variations in the reports of markers, such as a reduction in intraoperative blood loss, transfusion requirements, operating time, surgical complications, and survival outcomes, have limited the use of this procedure in local practice patterns [21].

In this study, the mean perioperative autologous red blood cell transfusion volume in the RAE group was lower than that in the control group; moreover, the mean intraoperative blood loss in the
RAE group was lower than that in the control group. One study [17] reported that almost half of all patients had vascular invasion with reported blood loss of only 1048 mL (median 725 mL) and average patient transfusion requirements over their entire hospital course was 3.9 units, and in the subset of patients who did not have vascular invasion, the mean blood loss was lower (mean 647 mL, median 425 mL). Our study findings are consistent with those in this report. In our study, the operating time in the control group was longer than that in the RAE group, and the mean length of hospital stay in the RAE group was shorter than that in the control group. A comparison of the clinical variables between the two groups demonstrated an increased length of hospital stay in the control group compared with the RAE group, and this difference was statistically significant. This result demonstrated that after RAE, the mean blood loss during surgery was small, the tumors were easily removed, and the length of hospital stay was shorter. This suggests that RAE reduces the likelihood of surgical bleeding, thereby reducing the relative length of hospital stay.

A major concern with the RAE approach is post-embolization syndrome, which is characterized by flank pain lasting 4 – 48 h, nausea, vomiting, ileus, fever, and leukocytosis associated with negative urine and blood cultures [22]. This syndrome is caused by acute infarction of a large parenchymal organ and has also been noted after non-renal embolization involving organs such as the liver and spleen [23]. The syndrome generally resolves with symptomatic treatment within 3-5 days [24]. In the present study, post-embolization syndrome was not observed in the patients who underwent simple surgical resection. There was no significant difference between the two groups of postoperative complications, showed that two kinds of operation were safe for big RCC, without which surgery was safer for big RCC.

There is no conclusive evidence that pre-operative RAE provides survival benefits in the management of surgically resected RCC [25]. However, a comparison of the five- and ten-year rates of lack of embolization between 118 patients who were embozized and a group of 116 patients not embozized prior to surgery has been reported [26]. The rates were found significantly different: 62% in the former group, and 35% was in the latter group. May [27] concluded that there was no survival benefit with RAE; thus, the survival outcomes are contradictory. This difference may be the result of different selection processes in the control groups. In our study, we selected cohorts who were matched in terms of age, sex, tumor size, grade, and stage. However, there was no difference in overall survival rate between the two groups, disease free survival and cancer specific survival. This result demonstrated that RAE with nephrectomy did not improve the survival rate compared with nephrectomy alone in patients with big RCC.

Studies have reported an improvement in hospital costs with RAE followed by nephrectomy compared with nephrectomy alone [28,29]. In our study, the differences of the mean total hospital costs in the RAE group followed by nephrectomy group and the control group was statistically significant. A comparison of hospital costs in the expenditure categories revealed significantly increased radiology costs in the RAE group compared with the control group. However, the control group had slightly higher blood cell transfusion costs and lower costs in the other expenditure categories compared with the RAE group. Finally, the mean total hospital cost was significantly lower in the RAE group than in the control group. Thus, the procedure in the RAE group was generally more economical than that in the control group, and the length of hospital stay was shorter. RAE followed by nephrectomy is recommended for patients with gross RCC following elimination of the fear of post-embolization syndrome among patients and their families.

In conclusion, this study demonstrated the role of an adjunctive endovascular procedure in facilitating surgical resection of big RCC. When performed jointly, preoperative RAE can minimize the blood loss associated with nephrectomy. Moreover, we believe that this approach minimizes post-infarction syndrome and reduces hospital costs compared with traditional nephrectomy and laparoscopic nephrectomy approaches. However, this approach did not improve the patients’ five-year survival rate.

The limitation of this study is that the number of cases was small in the two groups. Additional clinical studies are needed to further validate the benefit of the combined treatment in patients with big RCC.

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Competing Interests
The authors have no competing interests with the work presented in this manuscript.

References


