Impact of lymphadenectomy in management of renal cell carcinoma

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Abstract  Purpose: To evaluate the impact of regional lymphadenectomy as part of a management plan on morbidity, morbidity and survival in renal cell carcinoma (RCC).

Patients and methods: A retrospective study reviewing 158 cases diagnosed as RCC at the National Cancer Institute, Cairo university, Egypt, during the time period from 2000 to 2007. Histopathological data and significant operative and postoperative events were retrieved to compare three lymphadenectomy groups; Group A, where more than 5 nodes were dissected, Group B where 5 or less nodes were dissected and Group C where no nodal dissection was done.

Results: More positive lymph nodes were seen in group A (37.8%) compared to group B (9.6%) (p = 0.002). Lymph node positivity was significantly associated with higher grade (p = 0.005), but not with larger tumor size (p = 0.221). There was no significant difference in overall survival between the three lymphadenectomy groups (p = 0.163). Overall survival was not significantly affected by lymph node status (p = 0.585).

Conclusion: Regional lymphadenectomy in RCC has no impact on the mortality or morbidity.

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Introduction

Renal Cell Carcinoma (RCC) accounts for approximately 3% of adult malignancies. It is generally accepted that RCC usually metastasizes to distant organs through blood circulation rather than lymphatogenous dissemination. Clinical and autopsy studies have revealed that most lymph node [LN] metastases accompany distant metastases [1]. Positive LNs were frequently accompanied with advanced stage and poor prognosis, which suggested the diagnostic and prognostic significance of lymphadenectomy (LND) [2]. The role of lymph node dissection (LND) in renal cell carcinoma (RCC) remains controversial [3].

Although LND in patients with low-risk disease had no benefit in a randomized clinical trial; LND in patients with high-risk disease improved stage assessment and might prolong survival [4–6]. The indications for and extent of LND in patients with advanced RCC could be based on clinical and/or pathologic fac-
Several investigators attempted to select patients for LND during radical nephrectomy based on predictors of regional lymph node involvement [8,9].

Patients and methods

This was a retrospective study reviewing cases diagnosed as renal cell carcinoma (RCC) who presented to the National Cancer Institute (NCI), Cairo University, Egypt, during the time period 2000 to 2007. All patients were treated with radical nephrectomy. All patients had a pre-operative routine laboratory work-up, pelvi-abdominal ultrasound and/or abdominal CT. Patients presented with metastatic disease were excluded from this study.

Full histopathological data were obtained for each patient including tumor site and size, pathological type and grade, peri-nephric fat infiltration, venous involvement and status of lymph nodes.

Patients were classified into 3 main groups based on the number of lymph nodes dissected according to their pathology report; group A (n = 37) included patients with >5 lymph nodes in the pathology report, group B (n = 52) including patients with ≤5 lymph nodes and group C (n = 69) including those with no lymph nodes in the pathology report. Patients were followed up till 2010 by clinical examination, ultrasound and computerized tomography (CT scan).

Statistical methods

Data were analyzed using SPSS win statistical package version 15 (SPSS Inc., Chicago, IL). Chi-square test was used to examine the relation between qualitative variables. Survival analysis was done using Kaplan–Meier method and a comparison between two survival curves was done using log-rank test. A p value <0.05 was considered significant.

Results

Patients’ mean age at presentation was 53.7 years ± 14.2; 46.8% were in the age group of 41–60 years. There was a slight female predominance (male to female ratio, 0.93). The main presenting symptom was loin pain (n = 116) followed by hematuria (n = 27) and abdominal mass (n = 13).

Renal capsular and perinephric fat infiltration were manifested in 51% of cases and 11% showed hilar vascular invasion. Clear cell carcinoma was the main pathological type (47%) followed by granular cell carcinoma (20%) and mixed cell tumors (18%). Nearly 73% of cases had grade 2 tumors while 13% had grade 1 and 14% had grade 3. Tumor size was >7 cm in 74.7% of cases.

Positive lymph nodes were seen in 14/37 cases (37.8%) in group A and 5/52 cases (9.6%) in group B (p = 0.002). The relation between lymph node positivity and tumor size and grade is shown in Table 1. Grade 3 tumors had significantly higher frequency of positive nodes (54%) compared to grades 1 and 2 (16%).

Post-operative period was uneventful in the majority of cases (92.4%). Four cases (2.5%) died due to pulmonary embolism and 8 patients (5.1%) had complications in the form of postoperative hemorrhage, diaphragmatic injury and inferior vena cava (IVC) thrombosis. Overall survival was 65% as shown in Table 2. Loco-regional recurrences as well as metastasis were reported in 26 patients (16.5%).

There was no significant difference in overall survival between the three lymphadenectomy groups (Fig. 1). Fig. 2 shows that the overall survival was not significantly affected by lymph node status (p = 0.585).

Discussion

RCC is primarily a disease of the elderly patients, with typical presentation in the sixth and seventh decades of life, with a male-to-female predominance of 3:2 [10,11]. While Kwon

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>LN negative (n = 70)</th>
<th>LN positive (n = 19)</th>
<th>Total (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7 cm</td>
<td>18 (90.0%)</td>
<td>2 (10.0%)</td>
<td>20 (100.0%)</td>
<td>0.221*</td>
</tr>
<tr>
<td>&gt;7 cm</td>
<td>52 (75.4%)</td>
<td>17 (24.6%)</td>
<td>69 (100.0%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>LN negative (n = 70)</th>
<th>LN positive (n = 19)</th>
<th>Total (%)</th>
<th>p value</th>
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<tbody>
<tr>
<td>1 &amp; 2</td>
<td>64 (84.2%)</td>
<td>12 (15.8%)</td>
<td>76 (100.0%)</td>
<td>0.005**</td>
</tr>
<tr>
<td>3</td>
<td>6 (46.2%)</td>
<td>7 (53.8%)</td>
<td>13 (100.0%)</td>
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</table>

RCC: renal cell carcinoma; LN: lymph node.

*p < 0.05.
**p value not significant.

<table>
<thead>
<tr>
<th>n</th>
<th>Cumulative overall survival (%)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
<td>158</td>
<td>65.0</td>
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<tr>
<td>Study groups</td>
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<tr>
<td>Group A</td>
<td>37</td>
<td>73.3</td>
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<tr>
<td>Group B</td>
<td>52</td>
<td>68.0</td>
</tr>
<tr>
<td>Group C</td>
<td>69</td>
<td>59.0</td>
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<table>
<thead>
<tr>
<th>Lymph nodes</th>
<th>n</th>
<th>Cumulative overall survival (%)</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>+ ve</td>
<td>19</td>
<td>70.4</td>
<td>0.585**</td>
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<tr>
<td>– ve</td>
<td>70</td>
<td>69.8</td>
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</table>

*p < 0.05.
**p value not significant.
et al. found that the mean age was 52.6 years [12], in this study, the peak age of presentation in the majority of patients was in the age group of 40–60 years with slight female predominance (1.1:1.0). All the cases in this study were symptomatic on presentation mostly with loin pain. CT and ultrasound studies confirmed the diagnosis.

One unique feature of RCC is its predilection for involvement of the venous system, which is found in 10% of RCCs, more often than in any other tumor type [13]. In this study venous involvement was documented in 17 cases (11%). Perinephric fat infiltration by the tumors was found in 80 cases (51%).

In the present study, conventional RCC represented about 85% of the cases; this was in agreement with studies stating that conventional RCC accounts for approximately 70–80% and 87.7% of all cases [12–14].

In this study the number of documented cases of positive lymph nodes were 19 out of 89 cases in groups A and B (24.3%). This agreed with a study reporting a rate of lymph node affection in RCC of about 21% [16]. However, another study, and due to modern technique and early screening options, found only 37 out of 1503 patients with positive lymph nodes [12].

The rate of positive lymph nodes was higher if more than 13 nodes were dissected (extended lymphadenectomy), with 21% positive nodes in patients with greater than or equal to 13 nodes dissected and 10% positive for patients with fewer than 13 nodes in the specimen [16]. In this study higher number of positive lymph nodes were found when more nodes were dissected; i.e., 14/37 cases (37.8%) in group A versus 5/52 cases (9.6%) in group B ($p = 0.002$).

In this study operative mortality was 2.5%, almost all died due to pulmonary embolism, while hemorrhage, diaphragmatic injury and IVC thrombosis were encountered in 5.1% of cases. Disease recurred in (13.4%), of which 17.3% with local recurrence and 82% with distant metastases. The most frequent site of local recurrence was the regional LNs, and the most frequent distant metastatic site was the lungs [12]. LN metastasis was a significant prognostic factor for 5-year survival but not in patients with stage N1 and N2. On univariate analysis, patients with pN0 tumors were significantly more likely to have distant metastasis and to die than were those with pNx tumors. After adjusting for tumor stage and nuclear grade, the differences in 5-year survival were statistically signifi-

Of the other 203 patients who underwent LND without suspicion of nodal enlargement (cN0), none had pathologically LN-positive disease [12].

Positive lymph nodes in the current study were found in 24.6% of cases with tumors >7 cm compared to 10% of smaller tumors, however, the difference was not statistically significant. It was previously documented that the rate of lymph node affection was stage dependent [16]. On the other hand, higher tumor grade was significantly associated with higher frequency of positive nodes ($p = 0.005$). This agreed with previous studies [12,16,17].

The study published in 2011 stated that patients with LN metastasis (pN 1) had larger tumors and greater pathologic T stage and grade than did the patients with stage pNx or pN0. Patients with negative LN metastasis (pN0) had larger tumors and greater pathologic T stage and grade than patients with stage p0x. Of the 763 patients who underwent LND, 560 (73.4%) had a clinically suspicious LN mass (LN enlargement 1 cm or contrast enhancement) on preoperative computed tomography, and LND revealed 37 (6.6%) with metastases. Of the other 203 patients who underwent LND without suspicion of nodal enlargement (cN0), none had pathologically LN-positive disease [12].
icant for patients with stage pNx and pN0 tumors \( p = 0.008 \). The survival rate did not vary according to the LN location, even when grouping patients according to hilar and other locations. It was observed that the differences in the survival rate were relative to the LN metastasis size. Accordingly, patients with LN metastases 3 cm or less had significantly better 5-year distant metastasis-free survival \( p = 0.003 \) [12]. Generally, overall operative mortality after radical nephrectomy was reported to be around 1% [16,17].

Metastasis and progression in RCC occurred in one third of the patients [16] and about (13.4%) [12] of the patients who presented with localized disease. In this study there were only 26 cases (16.46%) with documented progression of the disease in the form of metastasis and/or local recurrence of the tumor, with the percentage of distant metastases in relation to the pathological T stage showing increased percentage according to T stage as 13%, 16% and 17% for T1, T2 and T3, respectively.

The relation between LN status and progression of the RCC disease showed that 25% of cases with positive lymph node affection developed progression in comparison to 13% of cases with negative lymph nodes [17].

It was reported that there was a significant survival advantage in patients who were treated with extended lymphadenectomy with the radical nephrectomy. It was concluded that radical nephrectomy plus extended lymphadenectomy benefited at least 4% of all patients [17]. In this study only prognostic value of lymphadenectomy was demonstrated while therapeutic value was not significantly represented. The difference in overall survival rates was not statistically significant when comparing positive to negative lymph node status groups \( p = 0.163 \) as there was no significant difference in overall survival between the three lymphadenectomy groups. So the value of lymphadenectomy in RCC was only prognostic for stage determination but not of significant therapeutic value. Similarly, overall survival was not significantly affected by lymph node status \( p = 0.585 \).

We could conclude that, regional lymphadenectomy in RCC had no statistically significant impact on the mortality or morbidity.

References


Further reading