The extent of lymphadenectomy does affect cancer specific survival in pathologically confirmed T4 renal cell carcinoma

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**Background:** Controversies exist regarding the effect of lymphadenectomy (LND) in renal cell carcinoma (RCC). We hypothesized that patients with locally advanced cancer invading beyond Gerota’s fascia (pT4 N any Many RCC) might benefit from an extended LND not only for staging but also for survival purposes.

**Materials and Methods:** Clinical and pathologic data were prospectively gathered in 1,847 patients treated at a single Academic Center, between 1987 and 2011. Only patients with pT4 RCC (TNM 2009, n=44, 2.4%) were included. Univariable (UVA) and multivariable (MVA) Cox regression analyses targeted the association between the number of lymph nodes removed and cancer specific mortality (CSM). Analyses were adjusted for age, Fuhrman grade, symptoms at presentation, metastases at diagnosis, ECOG performance status, tumor size, number of positive nodes, and presence of necrosis or sarcomatoid features.

**Results:** Mean number of nodes removed was 11.8 (median 8, range 1-37). Mean number of positive nodes was 4.8 (median 2, range 0-36). Cancer-specific survival rates at 1, 2 and 3 years of follow-up were 39.3%, 25.0% and 8.6%, respectively. When stratified for nodal status, cancer-specific survival rates at 1, 2 and 3 years of follow-up were 65.0, 36.1, and 9.0% vs. 13.3, 13.0, and 6.7%, for pN0 vs. pN+ cases, respectively (p=0.004). At MVA, after adjusting for all the possible confounders, the number of positive nodes resulted independently associated with CSM (HR 1.25, p=0.001). Interestingly, at MVA, the number of nodes removed achieved the independent predictor status, as well (HR 0.84, p=0.007) showing a protective effect on survival. The risk of dying increased of 16% every positive node found (p<0.001), and decreased of 8% every node removed (p=0.02) (Table II).

**Conclusions:** A more extended retroperitoneal lymphadenectomy at the time of nephrectomy statistically significantly decreased CSM in pT4 cases.

**Key Words:** Renal cell carcinoma, Lymphadenectomy, Lymph node dissection, Cancer-specific survival, Locally advanced disease

**Parole Chiave:** Carcino ma a cellule renali, Linfoadenectomia, Sopravivenza cancro specifica, Malattia localmente avanzata

Accepted: April 15, 2012
INTRODUCTION

Although the European Organization for Research and Treatment of Cancer (EORTC) prospective trial failed to demonstrate a significant survival benefit of lymphadenectomy (LND) in low-risk RCC patients (1), many retrospective reports suggested that LND might be beneficial in the presence of unfavorable conditions (2-7). Tumor invasion beyond Gerota’s fascia into adjacent organs (pT4 according to TNM 2009), with or without concomitant metastatic disease, is a relatively uncommon entity (8). Indeed, only two previous reports focused their attention exclusively on pT4 patients, though without testing the effect of performing an extended retroperitoneal LND (9, 10). However, individuals with pathologically confirmed T4 tumors represent the subgroup of patients with the highest probability of harboring lymph node invasion (LNI) (11) and, therefore, they represent the ideal population for testing the survival benefit of LND in exclusively high-risk cases.

In the current study, we hypothesized that patients with locally advanced cancer invading beyond Gerota’s fascia (pT4 Nany Many RCC) might benefit from an extended LND not only for staging but also for survival purposes.

METHODS

Study population

For each patient, comprehensive clinical and pathologic data were prospectively collected and entered into a computerized database. Patient records were retrieved and yielded 1,847 RCC patients treated with nephrectomy between 1987 and 2011 at a single tertiary care institution. The current study was undertaken with the approval and institutional oversight of the Institutional Ethics Committee Review Board. For the aim of the current manuscript, only patients with pathologically confirmed T4 RCC (pT4 TNM 2009) were included (n=44, 2.4%).

Clinical and pathologic evaluation

Dedicated genitourinary pathologists examined all surgical specimens. TNM stages were assigned according to the 2009 American Joint Committee on Cancer/Union Internationale Contre le Cancer classification (AJCC/UICC) (8). Cases before the introduction of the most updated classification were reclassified. Concordantly, pT4 RCC patients were defined as harboring tumor invading beyond Gerota’s fascia (including contiguous extension into the ipsilateral adrenal gland). Tumor size definition was based on pathological specimens and was defined as the greatest tumor diameter in centimeters.

Patients were staged preoperatively with computed tomography (CT) of abdomen and pelvis, chest CT or chest x-ray, serum electrolytes, and liver function tests. According to the European Association of Urology (8) and NCCN guidelines (12), a bone and brain scan assessment was performed in patients at high risk of bone and/or brain metastases, or in case of local/distant metastases in abdominal and thoracic imaging.

A regional LND (hilar region plus, on the right side, pre-caval nodes or, on the left side, para-aortic nodes, from the adrenal vein to the level of aortic bifurcation) was systematically performed. In 21 of 44 patients (47.7%), an extended LND was performed according to the preference of the operating surgeon. In those cases, extended LND included, on the left, para-aortic and preaortic nodes from the crus of the diaphragm to the aortic bifurcation and, on the right, retro- and precaval nodes from the adrenal vein to the level of aortic bifurcation. Interaortocaval nodes were always removed when an extended LND was sought.
Follow-up

Clinical and radiologic follow-up consisted of a postoperative baseline visit. Subsequently, the minimum follow-up consisted of at least two annual visits. The cause of death was obtained from medical charts and death certificates. Cancer specific mortality included deaths that were directly attributable to RCC.

Statistical analyses

Descriptive statistics were used to characterize the clinical characteristics of the study cohort at baseline. Kaplan-Meier method was used to depict cancer-specific mortality (CSM). Finally, univariable and multivariable Cox regression analyses assessed the effect of the number of nodes removed on CSM. Adjustment was performed for age, symptoms at presentation, metastases at diagnosis, ECOG performance status, tumor size, Fuhrman grade, number of positive nodes, and presence of necrosis or sarcomatoid features. A stepwise variable removal was then applied to the full multivariable model, according to the Akaike information criterion, with the intent of developing the most accurate and parsimonious model (13,14).

Statistical tests were performed using SPSS v.20 (IBM Corp., Somers, NY, USA).

RESULTS

Table I shows the descriptive characteristics of the entire cohort of pT4 RCC cases treated with nephrectomy plus LND (n=44). Mean tumor size was 9.9 cm (median 10, range 2.5-17). Overall, 24 (54.5%) patients showed distant metastases at diagnosis, as well.

Mean number of nodes removed was 11.8 (median 8, range 1-37). Mean number of positive nodes was 4.8 (median 2, range 0-36). Out of 28 cases with suspected lymphadenectomy at diagnosis (cN1), 25 (89.3%) had pathologically confirmed LNI.

The mean and median survival rates were 14.8 months (95% C.I. 10.1-19.5) and 7.8 months (95% C.I. 0.7-14.9), respectively. Cancer-specific survival rates at 1, 2 and 3 years of follow-up were 39.3%, 25.0% and 8.6%, respectively. When stratified for nodal status, cancer-specific survival rates at 1, 2 and 3 years of follow-up were 65.0, 36.1 and 9.0% vs. 13.3, 13.0 and 6.7%, for pN0 vs. pN+ cases, respectively (p=0.004, Figure 2). When stratified for metastases at diagnosis, cancer-specific survival rates at 1, 2 and 3 years of follow-up were 45.5 vs. 36.1%, 27.3 vs. 24.1% and 18.2 vs. 6.0%, for M0 vs. M1 cases,

<table>
<thead>
<tr>
<th>TABLE I - DEMOGRAPHIC, CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF THE COHORT (N=44)</th>
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<tr>
<td><strong>Clinical characteristics</strong></td>
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<td>Performance Status</td>
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<td>1</td>
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<td>Symptoms at diagnosis</td>
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<td>Clinical tumor size (cm)</td>
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<td>Clinical nodal status</td>
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<td>cN0</td>
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<td>Metastases at diagnosis</td>
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<td>Surgical characteristics</td>
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<td>Number of nodes removed</td>
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<td>Pathological characteristics</td>
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<td>Pathological tumor size (cm)</td>
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<tr>
<td>Fuhrman grade</td>
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<td>1-2</td>
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<tr>
<td>3-4</td>
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<tr>
<td>Pathological nodal status</td>
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<td>pN0</td>
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<td>pN1</td>
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<td>Number of positive nodes removed</td>
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<tr>
<td>Necrosis</td>
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<td>Sarcomatoid features</td>
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<td>Follow-up</td>
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<td>Mean (median) follow-up</td>
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<td>Mean (median) cancer specific survival</td>
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respectively (p=0.3, Fig. 3).

At UVA, only Fuhrman grade and the number of positive nodes were associated with CSM. Specifically, Fuhrman grade 3-4 tumors were associated with a 2.7-fold higher risk of CSM relative to low-grade cases (p=0.05). Moreover, the number of positive nodes demonstrated to be associated with CSM (HR 1.08, p=0.004).

At MVA, after adjusting for all the possible confounders, the number of positive nodes was detected to be independently associated with CSM (HR 1.25, p=0.001). Interestingly, at MVA, the number of nodes removed achieved the independent predictor status, as well (HR 0.84, p=0.007) showed a protective effect on survival. After MVA backward selection, the number of positive nodes and the total number of lymph nodes removed were the only two predictors included in the final reduced model (Tab. II). Finally, at MVA the risk of dying from the disease increased of 16% every positive node found (p<0.001), and decreased of 8% every node removed (p=0.02) (Tab. II).

DISCUSSION

The most widely used clinical guidelines in RCC setting (Tab. III) consider LND merely as a staging procedure. This is also a consequence of the recently published final results of the EORTC prospective trial, which provided evidence-based data that LND is not beneficial in clinically T1–T2 N0 RCC cases, namely patients at very low risk of developing LNI. In contrast, many retrospective reports suggested that LND might increase cancer control in T3–4 cases or in the presence of unfavorable conditions (locally-advanced diseases, presence of coagulative tumor necrosis or sarcomatoid features, high Fuhrman grade, larger tumors, suspected lymphadenopathy at preoperative imaging, palpable nodes at surgery) (2-6). For instance, Schafhauser et al. reported that patients treated with nephrectomy and systematic extended LND (group A), although having more unfavorable characteristics at diagnosis, showed improved survival rates compared to patients treated with nephrectomy plus resection of gross nodes only (group B) or nephrectomy only (group C) (15). Besides, Giuliani et al. showed that the 5-year CSM rate in LNI patients treated to extended LND at the time of nephrectomy was 48% compared with 93% of patients with distant metastases(16). Moreover, Pantuck et al suggested that LND improved survival in LNI cases by increasing response to immunotherapy (17).

Pathologically-confirmed T4 patients represent the ideal population to test the survival benefit of LND for two key reasons.1) Firstly, as it has been already demonstrated in other urological settings, patients who may benefit most from LND are those with a higher risk of harboring nodal metastases (18). Therefore, since LNI prevalence shows a stage-specific distribution in RCC cases, with substantially higher LNI rates in higher stages (11), pT4 cases represent the cohort of patients at the highest risk of harboring
vessels by cancer cells, collateral lymphatic drainage and invasion of tissue with different lymphatic drainage (e.g. perinephric fat (3)).

Notwithstanding those premises, only two previous reports focused their attention exclusively on pT4 patients, though without testing the effect of LND on CSM (9,10). Specifically, Margulis et al. demonstrated in 12 patients with pathologically-confirmed pT4 disease that nodal involvement was

### TABLE II - UNIVARIABLE AND MULTIVARIABLE ANALYSES PREDICTING CANCER-SPECIFIC SURVIVAL IN N=44 PT4 PN\textsubscript{ANY} MANY RCC PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Univariable analyses</th>
<th></th>
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<th>Multivariable analyses</th>
<th></th>
<th></th>
<th>Reduced MVA model</th>
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<tbody>
<tr>
<td></td>
<td>HR (95% C.I.)</td>
<td>p</td>
<td>HR (95% C.I.)</td>
<td>p</td>
<td>HR (95% C.I.)</td>
<td>p</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.95-1.02)</td>
<td>0.4</td>
<td>0.99 (0.95-1.04)</td>
<td>0.7</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Symptoms at diagnosis</td>
<td>1.02 (0.44-2.41)</td>
<td>0.9</td>
<td>1.32 (0.50-3.45)</td>
<td>0.6</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>Metastases at diagnosis</td>
<td>1.43 (0.64-3.20)</td>
<td>0.3</td>
<td>2.99 (0.93-9.64)</td>
<td>0.07</td>
<td>-</td>
<td>-</td>
<td></td>
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<tr>
<td>ECOG Performance Status</td>
<td>1.09 (0.62-1.93)</td>
<td>0.7</td>
<td>0.54 (0.25-1.19)</td>
<td>0.1</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Pathological tumor size</td>
<td>1.01 (0.90-1.14)</td>
<td>0.8</td>
<td>1.13 (0.95-1.36)</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Fuhrman Grade 3-4</td>
<td>2.68 (0.99-7.21)</td>
<td>0.05</td>
<td>1.64 (0.48-5.58)</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Necrosis</td>
<td>1.51 (0.52-4.44)</td>
<td>0.4</td>
<td>3.06 (0.59-15.93)</td>
<td>0.2</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Sarcomatoid Features</td>
<td>1.02 (0.38-2.73)</td>
<td>0.9</td>
<td>1.22 (0.24-6.18)</td>
<td>0.8</td>
<td>-</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Number of positive nodes</td>
<td>1.08 (1.03-1.14)</td>
<td>0.004</td>
<td>1.25 (1.09-1.42)</td>
<td>0.001</td>
<td>1.16 (1.09-1.42)</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>Number of removed nodes</td>
<td>1.01 (0.96-1.05)</td>
<td>0.9</td>
<td>0.84 (0.73-0.95)</td>
<td>0.007</td>
<td>0.92 (0.73-0.99)</td>
<td>0.02</td>
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</tr>
</tbody>
</table>

### TABLE III - CURRENTLY AVAILABLE GUIDELINES REGARDING THE NEED FOR THE EXTENT OF LYMPHADENECTOMY IN RENAL CELL CARCINOMA

<table>
<thead>
<tr>
<th></th>
<th>Limited LND #</th>
<th>Regional/Extended LND^</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Association of Urology</td>
<td>For staging purposes, in patients with palpable or CT-detected enlarged lymph nodes, resection of the affected lymph nodes should be performed to obtain adequate staging information.</td>
<td>For staging purposes, if patients shows palpable or CT-detected enlarged lymph nodes, to obtain adequate staging information.</td>
</tr>
<tr>
<td>American Urological Association</td>
<td>Not covered</td>
<td>Not covered</td>
</tr>
<tr>
<td>National comprehensive Cancer Network</td>
<td>Not covered</td>
<td>Optional</td>
</tr>
</tbody>
</table>

CT=computerized tomography

^From the crus of the diaphragm inferiorly to the bifurcation of the aorta or vena cava. For right-sided tumors, dissections of the lateral caval, precaval, postcaval, and interaortocaval nodes. For left-sided tumors, dissections of the left para-aortic nodes, the left diaphragmatic nodes and the preaortic nodes.

LNI (56.8% in the current study), 2) Secondly, besides the anatomical unpredictability of lymphatic outflow, an additional confounder in RCC consists in the predilection for early hematogenic dissemination without lymph node dissemination. However, in pT4 cases it is more likely to find a spreading through the lymphatic outflow, conversely to pT1-pT3 cases, due to the local progression of the tumor, which induces neovascularization, blockage of lymphatic vessels by cancer cells, collateral lymphatic drainage and invasion of tissue with different lymphatic drainage (e.g. perinephric fat (3)).

Notwithstanding those premises, only two previous reports focused their attention exclusively on pT4 patients, though without testing the effect of LND on CSM (9,10). Specifically, Margulis et al. demonstrated in 12 patients with pathologically-confirmed pT4 disease that nodal involvement was
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The extent of lymphadenectomy does affect cancer specific survival in confirmed T4 renal cell carcinoma. A significant independent predictor of disease recurrence (hazard ratio 3.7, p=0.04) and CSM (HR 17.1, p=0.002). In that cohort, disease recurred in 10 of 12 (83.3%) of pT4 patients at a median of 13.3 months, respectively (9). In the second report, the Authors relied on competing risks regression analyses targeting 310 T4 N0-2 M0 RCC cases from the Surveillance, Epidemiology and End Results database (10). They demonstrated that, as long as there is no evidence of nodal metastases, nephrectomy improved survival in T4 RCC cases relative to patients who did not undergo surgery. In patients with nodal metastases, no difference was recorded between patients treated with nephrectomy or observation. Unfortunately, no data regarding LND effect on CSM was provided in those studies (10). Similarly, we confirmed that patients with RCC involving adjacent viscera show poor survival rates with a median survival of roughly 15 months. Moreover, as shown in metastatic settings, we confirmed that nodal status remains one of the most informative predictor of CSM, regardless of T stage, presence of metastases and all other possible confounders (19, 20).

For the first time, we demonstrated that a more extended retroperitoneal LND at the time of nephrectomy, statistically significantly improves survival in pT4 RCC patients. Our findings provide additional support to the concept that LND at the time of nephrectomy may affect survival in patients with nephrectomy or observation. In spite of some limitations due to sample size and potential selection biases, the current study represents the first attempt ever to demonstrate a survival benefit when patients with locally-advanced disease undergo LND at the time of nephrectomy, regardless of the clinical nodal status and the presence of metastases.

CONCLUSIONS

After adjusting for the number of positive nodes and for each possible confounder, in multivariable analyses the number of nodes removed proved to be an independent predictor of CSM, showing a protective effect on survival. A more extended retroperitoneal LND at the time of nephrectomy statistically significantly improves survival in pT4 RCC patients.

RIASSUNTO

Nel carcinoma renale (RCC) il ruolo della linfadenectomia (LND) è tuttora incerto. I risultati finali dello studio prospettico randomizzato EORTC non hanno evidenziato un impatto della LND sulla sopravvivenza dei pazienti con RCC. Tuttavia tali conclusioni sono applicabili soltanto nei pazienti a basso rischio di invasione linfonodale dato che la maggior parte dei pazienti inclusi in tale studio erano clinicamente in stadio T1-2 N0. Lo scopo del presente studio è di verificare se il numero di linfonodi rimossi in pazienti con tumore in stadio patologico T4 (TNM 2009), cioè ad alta probabilità di invasione linfonodale, modifica la mortalità cancro-specifica (CSM). Sono stati raccolti prospetticamente i dati di 44 pazienti con RCC in stadio pT4 trattati in un singolo istituto. Analisi di Cox univariate e multivariate sono state utilizzate per analizzare l’effetto del numero di linfonodi rimossi sulla CSM. Le analisi sono state aggiustate per età, performance status, sintomatologia, presenza di metastasi, Fuhrman grade, diametro del tumore, necrosi, aspetti sarcomatoidi e numero di linfonodi positivi. Il numero medio di linfonodi rimossi è risultato 11,8 (mediana 8, range 1-37). La sopravvivenza cancro-specifica a 1, 2 e 3 anni dopo chirurgia è risultata di 39,3, 25,0 e 8,6%, rispettivamente. All’analisi multivariata, dopo aver corretto per l’effetto delle altre variabili, il numero di linfonodi positivi è risultato un predittore indipendente di CSM (HR 1,25, p=0,001). In aggiunta, all’analisi multivariata, il numero di linfonodi rimossi è risultato una variabile indipendente predittiva e protettiva di CSM (HR 0,84, p=0,007). La probabilità di CSM è risultata aumentata del 16% per ogni linfonodo positivo trovato (p<0,001) e diminuita dell’8% per ogni linfonodo rimosso (p=0,02). In conclusione, l’estensione della linfadenectomia modifica la CSM nei pazienti con carcinoma renale in stadio T4.

Disclaimers

The authors have no proprietary interest with regard to this article.

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REFERENCES


