Retroperitoneal Lymph Node Dissection (RPLD) in Conjunction with Nephroureterectomy in the Treatment of Infiltrative Transitional Cell Carcinoma (TCC) of the Upper Urinary Tract: Impact on Survival

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Abstract

Objectives: To evaluate the prognostic impact of retroperitoneal lymph node dissection (RPLD) performed during nephroureterectomy on time to recurrence and survival in patients with infiltrative transitional cell carcinoma (TCC) of the upper urinary tract.

Methods: The charts of 82 patients with T2–T4 TCC of the upper tract were retrospectively reviewed. The median patient age was 67.7 yr. Seventy-nine patients underwent nephroureterectomy and three had partial nephrectomy. Forty patients (48.8%) had RPLD with removal of more than five nodes after nephroureterectomy (group 1), whereas 42 (51.2%) had nephroureterectomy only (group 2). Median follow-up was 64.7 mo. The prognostic role of RPLD, T (2 vs. 3–4), G (2 vs. 3), N (0 vs. 1–2 vs. x), age (<65 vs. >65 yr) and sex on time to recurrence and survival were evaluated.

Results: Median time to recurrence and overall survival were 51.2 and 52.5 mo, respectively, in group 1 and 18.5 and 21.2 mo in group 2. Univariate analysis demonstrated that RPLD and T and N status were significantly related both to time to recurrence ($p = 0.009, 0.008, and 0.009$, respectively) and survival ($p = 0.000006, 0.003$, and $0.003$). When analyzed using the Cox proportional hazard model, RPLD and T category were the only two factors demonstrating independent significance on overall survival ($p = 0.004$ and $0.008$).

Conclusions: The results indicate a possible curative role of RPLD in the treatment of patients with infiltrative TCC of the upper urinary tract. Further randomized trials are needed to confirm these results.

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1. **Introduction**

Transitional cell carcinoma (TCC) of the upper urinary tract is relatively uncommon accounting for 2–10% of all urothelial tumors [1]. About 30% of patients have tumors invading the musculature of the renal pelvis or the ureter and an additional 30% have an involvement of peripelvic or periureteral soft tissue, renal parenchyma, or regional lymph nodes at the time of initial diagnosis [2]. The standard treatment for infiltrative TCC of the upper urinary tract consists of nephroureterectomy with removal of a bladder cuff. The definitive role of lymphadenectomy and its extension has not been established. Some authors suggest its possible therapeutic benefit in selected patients with lymph node metastases, whereas others suggest it only for staging [1,3]. The aim of this retrospective study was to evaluate the prognostic impact of retroperitoneal lymph node dissection (RPLD) in conjunction with nephroureterectomy in patients with advanced TCC of the upper urinary tract on time to recurrence and survival.

2. **Patients and methods**

The charts of 83 consecutive patients with advanced TCC of the upper urinary tract treated from January 1980 to December 2002 at the Department of Urology of the Estense Institute in Modena and the B. Ramazzini Hospital in Carpi (Modena) were reviewed. Because of insufficient data, one patient was excluded from this analysis. This report includes 82 patients who were treated, fully evaluated, and regularly followed-up. The median age was 67.7 yr (range: 35–82 yr); 59 patients were men and 23 women.

2.1. **Diagnosis**

Urinary cytology, intravenous pyelography (IVP), and abdominal ultrasound (US), or computed tomography (CT) was used for diagnosis and staging. Ureteroscopy was performed in only three patients, whereas urethrocystoscopy was always done before surgery to detect any associated bladder tumors. After 1999, URO-CT was routinely adopted instead of IVP. In 48 patients (58.5%) tumors were on the right side and on the left in 34 patients (41.5%). In 47 patients (57.3%) tumors were localized in the renal pelvis or calices, in 28 cases in the ureter (34.1%), and in 7 patients (8.5%) in both. Fifteen of 82 patients (18.3%) had a concomitant tumor of the bladder detected during the initial cystoscopy. They were all non-muscle-invasive tumors. Five of 82 patients (6.1%) presented with distant metastases in the lung (3), adrenal (1), and colon (1) at the time of initial diagnosis.

2.2. **Treatment**

Seventy-nine patients underwent nephroureterectomy with the excision of a bladder cuff including the ureteral meatus, whereas three patients with tumors located in the renal pelvis and calices in a solitary kidney had a partial nephrectomy. In 40 patients (48.8%) unilateral RPLD was performed in conjunction with nephroureterectomy (group 1); in 42 patients (51.2%) nephroureterectomy alone was done (group 2). RPLD was performed in patients with an infiltrative disease or with enlarged nodes on a preoperative evaluation (CT), in case of enlarged nodes discovered perioperatively, and at the surgeon’s discretion. Before 1999 limited RPLD was performed in one institution and the number of nodes removed varied from 5 to 10 (mean, 7.1); after the results of our first report [4], which showed a clear positive prognostic impact of lymphadenectomy, an extended RPLD was routinely adopted. The number of lymph nodes removed varied from 5 to 24 (mean, 11.5).

The extent of lymphadenectomy was determined by the location of the primary tumors. For renal pelvis and upper ureteral tumors the para-aortic, paracaval, or interaortocaval nodes from the hilus to the inferior mesenteric artery were removed, for the mid-ureteric cancers lymphadenectomy was carried out from the renal hilus to the bifurcation of the common iliac artery, and for the lower ureteric tumors the pelvic nodes of the ipsilateral side were removed.

Nephroureterectomy was performed through a median transperitoneal incision in 74 patients and through a flank incision in 8. In these patients RPLD was not performed. Fifteen patients with bladder tumors underwent transurethral resection (TUR) in the same surgical session.

2.3. **Follow-up**

Patients were followed every 3 mo for the first year with urinary cytology and US. Cystoscopy was suggested after 3 mo and, if negative, every 6 mo for 5 yr and then yearly for a further 5 yr. IVP/CT or URO-CT were carried out every year for 5 yr and, if negative, every 2 yr for 10 yr. Ureteroscopy was used only in case of positive cytology with negative cystoscopy or bladder mapping. The results of cytology and cystoscopy were considered important for the further decision-making during follow-up. The median length of follow-up was 64.7 mo (range: 24–288 mo).

The Union Internationale Contre le Cancer (UICC) classification [5] was used for staging. Tumors were graded as G1 = well differentiated, G2 = moderately well differentiated, and G3 = poorly differentiated.

2.4. **Statistical analysis**

Univariate analysis was used to correlate RPLD and T and N status to recurrence and survival. The Cox proportional hazard model was used to evaluate the independent significance of RPLD, T, and N in terms of overall survival.

3. **Results**

The intraoperative mortality, within the first 30 d after surgery, was 0.

The pathologic stage was: pT2 in 38 patients (46.3%), pT3 in 36 patients (43.9%), and pT4 in 8
patients (9.7%). The tumor grade was: G2 in 44 patients (53.6%) and G3 in 38 patients (46.4%).

The patient characteristics are reported in Table 1, according to whether or not they underwent RPLD. Patients who had RPLD tended to have high stage (T3–T4) or high grade (G3) disease, pT3–T4 = 28 versus 16, G3 = 30 versus 8, compared to patients treated by nephroureterectomy alone.

Of the 40 patients in group 1, that is, those who underwent RPLD, 16 (40%) had positive nodes (N+), and 24 (60%) were N0. In group 2, all 42 patients were classified as Nx. Twenty-three of 42 Nx patients (54%) developed recurrences or progressed. In 4 patients a bladder recurrence was diagnosed during follow-up and they underwent TUR, whereas 19 had local or distant metastases. Five patients (12%) had recurrence in the retroperitoneal nodes (all were ureteral tumors) and 14 patients developed lung or bone (or both) metastases. Three Nx patients received chemotherapy after progression and one had radiotherapy.

The rates of disease-free survival (DFS) and disease-specific survival (DSS), calculated with log-rank univariate analysis, in patients who received RPLD (group 1) were 64.3% and 81.6%, respectively, whereas in patients who did not undergo RPLD (group 2), the rates were 46.3% and 44.8%. These differences were statistically significant (DFS, \( p = 0.03 \); DSS, \( p = 0.007 \)).

The median time to recurrence and overall survival were 51.2 and 52.5 mo, respectively, in group 1 and 18.5 and 21.2 mo, respectively, in group 2. At univariate analysis RPLD, stage, and N status (N0 vs Nx+) were significantly related both to time to recurrence (\( p = 0.009, 0.008, \) and 0.009, respectively) and survival (\( p = 0.000006, 0.003, \) and 0.003). When analyzed by the Cox proportional hazard model, RPLD and T category were the only two factors demonstrating independent significance on overall survival (\( p = 0.004 \) and 0.008, respectively; Fig. 1); none of the variables analyzed was able to independently predict recurrence.

4. Discussion

Patients with muscle-invasive TCC of the upper urinary tract or nodal involvement represent an extremely high-risk group for disease recurrence and cancer-related deaths following surgical management. The standard treatment of these tumors is nephroureterectomy with the removal of a bladder cuff including the ureteral meatus. The role of lymphadenectomy in conjunction with nephroureterectomy is still controversial.

The prognosis of patients with lymph node metastases is reported to be poor [1]. Johansson and Wahlqvist [6] reported that all the patients with renal pelvic cancer and lymph node metastases died within 1 yr of surgery, whereas Park et al [7] showed that ureteral TCC was associated with a higher local or distant failure rate than renal pelvis TCC. They suggested using a radical surgical approach for these tumors, including a meticulous RPLD.

Although value of RPLD as a staging procedure has generally been accepted, its therapeutic role still remains controversial. Some authors have suggested that lymphadenectomy could be useful in selected patients with lymph node metastases, but others claim its importance in selecting patients for adjuvant therapies [3,8]. The results of our study,

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1</th>
<th>Group 2</th>
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<tr>
<td>Male/female</td>
<td>27/13</td>
<td>32/10</td>
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<tr>
<td>Median age</td>
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<td>67.1</td>
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<td>Tumor side</td>
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<td>21</td>
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<tr>
<td>Ureter</td>
<td>10</td>
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<tr>
<td>Renal pelvis + ureter</td>
<td>4</td>
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<td>G3</td>
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RPLD = retroperitoneal lymph node dissection.
metastatic sites are the right renal hilus and
tumors of the right renal pelvis, the primary
have been described recently by Kondo et al\[9\].I n
primary sites of nodal metastases in these tumors
curative.

advanced TCC of the upper urinary tract can be
accurate and extended RPLD in patients with
node or distant metastases, we believe that a very
static cascade and LVI is closely related to lymph
a fundamental step in the initiation of the meta-

upper urinary tract.

RPLD, and DSS in patients with advanced TCC of the upper urinary tract.[9]. The role of lymphovascular invasion (LVI) as a prognostic factor for survival in these tumors was also analyzed by Kikuchi et al in 173 patients[10]. LVI was found in 52 patients (30%) who underwent RPLD and was correlated with high grade (G3) and advanced stage (T3–T4). LVI was found in 100% of patients with nodal involvement on the surgical specimens compared with only 9% of patients without lymph node involvement. Distant metastases were found in 14% of patients without LVI compared to 72% of patients with LVI postoperatively. Patients were stratified into low risk (grade 1–2, LVI negative, pT2 or <), high risk (any G, LVI positive, pT3–T4), and intermediate risk (all others) groups with a significant difference in survival. They concluded that in addition to pT and grade, LVI is an independent prognostic factor for DSS in upper tract TCC.

Our data also confirm the correlation between pT, RPLD, and DSS in patients with advanced TCC of the upper urinary tract.

Because lymphatic diffusion of neoplastic cells is a fundamental step in the initiation of the metastatic cascade and LVI is closely related to lymph node or distant metastases, we believe that a very accurate and extended RPLD in patients with advanced TCC of the upper urinary tract can be curative.

The extent of RPLD is still a matter of debate. The primary sites of nodal metastases in these tumors have been described recently by Kondo et al[9]. In tumors of the right renal pelvis, the primary metastatic sites are the right renal hilus and paracaval and retrocaval nodes. Tumors of the upper two thirds of the right ureter primarily metastasize to the retrocaval and interaortocaval nodes. In tumors of the left renal pelvis, metastases occur primarily in the left renal hilus and in paraaortic nodes. Tumors of the upper two thirds of the left ureter metastasize to the paraaortic nodes. Tumors of the lower ureter primarily metastasize inferiorly to the aortic bifurcation. In our series 32 of 40 patients (80%) underwent an extended RPLD following the mentioned criteria.

The possible curative role of extended lymphadenectomy in patients with other urologic malignancies has also been debated. In infiltrative bladder cancer an extended lymphadenectomy has been shown to reduce local recurrence and to improve survival in patients treated with radical cystectomy and similar results have been produced in renal and prostate cancer[11–14]. The same results were confirmed in our study. In the group of patients having RPLD we observed a reduction in local recurrence and an improvement in overall and disease-specific survival compared to group 2 (no RPLD). The most important effect on survival was probably obtained in patients with negative nodes (N0). In fact when a step sections of lymph nodes or a quantitative detection of micrometastases by real-time reverse transcriptase polymerase chain reaction targeting prostate-specific antigen (PSA) and membrane PSA (PSMA) antigens was performed, the presence of neoplastic cells and therefore micrometastases was detected in 20–30% of patients[15]. This could explain our results; performing an accurate and extended RPLD in infiltrative TCC of the upper tract in N0 patients certainly eliminates this rate of micrometastases. Moreover, by removing a large number of nodes, we possibly prevent local recurrence and therefore future metastases.

A limitation of our study is its retrospective aspect and the fact that patients were not randomized to determine who underwent RPLD. However, to our knowledge, it represents one of the largest series of invasive TCC of the upper urinary tract with a comparison of nephroureterectomy in conjunction with RPLD and nephroureterectomy alone, even retrospectively.

The benefit of adjuvant therapies after surgery for infiltrative TCC of the upper urinary tract has not been established. Radiotherapy as adjunctive treatment for these patients has been shown to be of little value[16,17], whereas systemic chemotherapy appears to provide some benefit[2]. The appropriate selection of patients who will benefit from these treatments is fundamental for the results. Unfortunately, patient selection was not analyzed in these...
studies. In our experience only three patients with T3–T4 N+ (2) N0 (1) M+. TCC of upper urinary tract received adjuvant systemic chemotherapy (M-VAC). Survivals were 12, 31, and 52 mo, respectively.

Czito et al [18] recently reported that adjuvant radiotherapy and chemotherapy improved treatment outcomes in pT3–T4 or node-positive upper urinary tract TCC. With the proper selection of patients with advanced disease, adjuvant chemotherapy may have a relevant role in treatment of this disease and should be re-evaluated.

5. Conclusions

The results of our study indicate that RPLD in conjunction with nephroureterectomy may have a possible curative role in the treatment of patients with infiltrative TCC of the upper urinary tract. A meticulous and extended node dissection should be performed according to the tumor site. Adjuvant chemotherapy in this advanced disease should be evaluated in controlled prospective studies. Also prospective, randomized trials comparing nephroureterectomy in conjunction with RPLD versus nephroureterectomy alone are needed to confirm our data.

Conflicts of interest

The authors have nothing to disclose.

References

[13] Schumaker M, Burkhart FC, Fleischmann A, Studer U. When performing extended pelvic lymphnode dissection, twice the number of positive nodes were removed than with limited lymphnode dissection in patients undergoing radical prostatectomy. J Urol 2006;175:516 (abstract no. 1601).
Although the importance of regional lymphadenectomy has been well established in the management of bladder cancer, considerable uncertainty exists regarding its role and utility in the treatment of upper urinary tract transitional cell carcinoma (UUT-TCC). Detractors of routine lymphadenectomy have argued that there is variability in the lymphatic drainage that precludes a standard template of dissection. In a recent study, Kondo et al [1] attempted to determine the primary site and incidence of lymph node metastases in UUT-TCC. In this study, 42 of 181 patients (23.2%) presenting with UUT-TCC were determined clinically or pathologically to have regional lymph node metastases. The incidence of lymphatic involvement varied according to stage and grade with 0%, 5%, 24%, and 84% of Tis/Ta/T1, T2, T3, and T4 and 0%, 11%, and 35% of G1, G2, and G3 tumors, respectively, involving regional lymph nodes. The location of lymph node metastases varied depending on the laterality and level of the primary tumor; however, a relevant finding was the risk of retrocaval and interaortocaval lymph node involvement in patients with renal pelvic and upper ureteral tumors especially in those with right-sided disease. This would suggest that if lymphadenectomy is to have therapeutic and not just diagnostic benefit it must be performed in an extended fashion resembling dissections performed for patients with testicular cancer.

In the current issue, Brausi et al [2] present their data suggesting improved survival in patients undergoing retroperitoneal lymph node dissection (RPLND) in conjunction with nephroureterectomy (NUT) for the treatment of UUT-TCC. These authors performed an extended lymphadenectomy in 32 of 40 patients who underwent RPLND for their stated indications of infiltrative disease or abnormal lymph nodes found on preoperative imaging or intraoperatively and compared outcomes to a group of 42 patients treated with NUT alone. There was a 40% incidence of positive lymph nodes in the group undergoing RPLND, which is in keeping with the high rates of nodal disease in other studies [1,3,4].

Patients undergoing RPLND had prolonged recurrence-free intervals and overall survival. These results do, however, need to be approached with caution. Although RPLND was significantly related to time to recurrence and survival in univariate analysis, in multivariate testing, it predicted only for overall and not recurrence-free survival. This is noteworthy in that if an intervention is truly adding therapeutic benefit, it would be expected to decrease recurrence rates and improve disease-specific survival, which would then translate into improved overall survival. The multivariate findings in the current study raise the question of selection bias. Indeed, of the 42 patients not having RPLND only 5 (12%) had recurrences in the retroperitoneal lymph nodes. The majority of recurrences in this group were lung or bone metastases and would not have been prevented with RPLND. An alternate consideration would be differences in the general health of the two patient groups. Nonetheless these results support previous findings suggesting therapeutic benefit to RPLND [4].

Currently the surgical management of patients with UUT-TCC is often performed in a minimally invasive fashion. Indeed, laparoscopic NUT has become an accepted standard. If the therapeutic benefit of RPLND especially with extended templates is substantiated this could have significant implications. Whereas laparoscopic NUT is relatively routine, laparoscopic RPLND is a technically advanced procedure. Furthermore its efficacy relative to open RPLND is questioned [5]. It is noteworthy that in the current study all patients were treated in an open fashion.

The authors are to be commended for attempting to address an area in oncology for which there is relative lack of data. Although their results are of interest, at this point the therapeutic role of concomitant RPLND at the time of NUT remains controversial and I agree with the authors’ conclusion that randomized trials are needed to fully define the role of RPLND in the management of UUT-TCC.

References


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