Neo/Adjuvant Therapy in Upper Tract Urothelial Carcinoma

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1. Introduction

Urothelial carcinomas of the renal pelvis and ureter are relatively uncommon, accounting for an estimated 5–6% of urothelial malignancies [1].

The majority of patients present with disease that has not penetrated through the muscularis (Tis–T2). These patients are generally treated with radical nephroureterectomy or with renal-sparing procedures in select patients. However, limited surgery may have its drawbacks. While the incidence of metastatic disease was similar, conservative surgery resulted in a 23% ureteric stump recurrence rate in one study [2]. Multivariate analysis of risk factors

Abstract

Objective: Urothelial carcinoma of the renal pelvis and ureter is a relatively uncommon malignancy. The majority of patients present at a stage in which disease has not penetrated through the muscularis (Tis–T2). These patients are generally treated with radical nephroureterectomy or with renal-sparing procedures in select patients, and overall the prognosis is favorable in this group. However, in patients in whom disease has spread beyond the muscularis and involved adjacent tissues, organs, or lymph nodes, the prognosis is significantly worse, making it important to consider adjuvant or neoadjuvant therapy.

Methods: Literature search using PubMed was conducted to identify the related articles that formed the basis of this review.

Results: The role of adjuvant external beam radiotherapy in improving local control and survival is unclear both because of the limited number of patients and because of the contradictory results of different studies. Neoadjuvant chemotherapy and concurrent cisplatin administration during radiotherapy appears as an important factor in terms of survival at 5 yr. Similarly, available data in the literature indicate that neo/adjuvant systemic chemotherapy after nephroureterectomy may provide therapeutic benefit in patients with invasive transitional cell carcinoma of the upper urinary tract.

Conclusions: Adjuvant radiation therapy after radical upper urinary tract surgery has no impact upon clinical outcome, whereas systemic adjuvant or neoadjuvant chemotherapy does provide significantly better oncologic results.

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was performed in another study [3], and only tumor stage \((p = 0.017)\) and treatment modality (radical versus parenchymal sparing; \(p = 0.020\)) were identified as predictors of recurrence. It was concluded that radical nephroureterectomy achieved excellent local control even in the setting of locally advanced (pT3 or T4) disease.

However, in patients in whom disease has spread beyond the muscularis and involved adjacent tissues, organs, or lymph nodes, the prognosis is significantly worse, with 5-yr survival rates of 0–34% in patients with stage \(\geq T3\) disease [4–6], making it important to consider neo/adjuvant therapy in this group. This consideration certainly is not an easy task because it is practically almost impossible to perform a controlled prospective randomized trial because of the rarity of such tumors. Therefore, the role of neo/adjuvant therapy in this group of patients is not well-defined.

2. Locoregional disease recurrence and adjuvant radiation therapy

The relative risk of local recurrence and/or systemic relapse has been poorly quantified, and 5-yr survival is reported in the range of 20–40% by surgery alone in the presence of extramural extension [7]. In high-grade locally advanced disease, the incidence of locoregional failure has been reported in a wide range, most probably because of the differences in the assessment protocols. Nevertheless, inadequate local control of the disease led to the utilization of radiation as an adjunct to radical surgery in an attempt to control the tumor both locally and distantly. Although the role of locoregional disease relapse in subsequent development of metastatic spread is not completely verified, partly because it may be overlooked once metastatic disease is identified [8], it can be hypothesized that local disease may act as the source of subsequent metastatic disease. Therefore, locoregional control of the disease may be important in terms of prevention of metastases and prolongation of survival.

In a series of 26 patients with stage \(\geq T3\) urothelial carcinoma of the renal pelvis or ureter, Cozad et al [9] treated 17 patients with surgery only, and 9 received adjuvant radiation therapy (median dose: 50 Gy) in an effort to enhance the local control of the disease. Local failure occurred in 52.9% without and 11.1% with adjuvant radiation therapy \((p = 0.07)\). Actuarial 5-yr local control was 88% with and 34% without adjuvant radiation therapy. Cox step-wise regression confirmed adjuvant radiation therapy \((p = 0.006)\) and grade \((p = 0.006)\) as significant factors for local failure. There was no difference in local failure either with or without adjuvant radiation in low-grade tumors. However, high-grade lesions had a local failure rate of 15% with and 71% without adjuvant radiation therapy. Metastatic disease occurred in 44.4% and 47% with and without radiation therapy, respectively. No significant factors influencing distant failure were identified. Five-year actuarial survival was 44% with and 24% without adjuvant radiation therapy. The survival differences were not statistically significant on univariate or multivariate analysis. The authors concluded that high-stage urothelial carcinoma of the upper urinary tract had a substantial local failure risk after surgery alone. Adjuvant radiation therapy markedly reduced this risk but had no impact on distant disease, which occurred in approximately 50% of the cases.

A recent European Multicenter retrospective series [10] showed a 5-yr locoregional recurrence rate of 62% in patients with nephroureterectomy without adjuvant therapy. However, the authors could not show any benefit of postoperative radiation therapy. Overall survival rates at 5 and 10 yr were 21% and 13% in patients with radiation, and 33% and 24% without radiation, respectively.

The authors discussed the higher pT stage, ureteral localisation, and higher grade of tumors in the adjuvant radiation group as possible reasons for the poor outcome.

Hall et al [11] reported their results on a series of 74 patients with stage T3 (66%) or T4 (34%) urothelial carcinoma of the upper urinary tract. Median follow-up was 21 mo (range: 1–236), and 30% of the patients with stage 3 and 52% with stage 4 disease received 40 Gy adjuvant radiotherapy to the tumor bed and regional lymph nodes. Isolated local recurrences were identified in five patients with stage 3 disease and one with stage 4 disease. All patients with local failure died of disease after a median of 37 mo. No actuarial 5-yr survival difference was observed in patients with (45%) and without (40%) adjuvant radiotherapy \((p = 0.642)\). These authors concluded that isolated local recurrences were uncommon following initial aggressive surgery and that the major clinical feature was distant metastasis. Also, no survival benefit was observed with adjuvant radiotherapy in this cohort; the need for more effective systemic therapy was reiterated.

Another small cohort of high-risk patients \((n = 23)\) with stage T3–4 disease were treated by surgery, and 11 of them received adjuvant radiotherapy [12]. None of the irradiated patients failed with local disease only, while there was one patient with local
and distant recurrence (9%). In contrast, the no-radiation group had five local failures (41.6%) and twice the number of failures overall. Median survival of the radiation and no-radiation groups were 35 and 26 mo, respectively; the differences were not significant because of the very small number of patients.

Maulard-Durdux et al [13] reported their experience with 26 patients treated for upper tract urothelial carcinoma. Stage 3 disease was present in 15 patients and 9 had lymph node metastasis. They were treated with postoperative radiation therapy at a mean dose of 45 Gy. Only 5 patients had relapse in tumor bed or regional lymph nodes. The overall 5-yr survival by surgery and adjuvant radiation therapy was 49% for the entire patient population and 19% for stage 3 disease. Disease-free survival at 5 yr was 64% for grade 2 and 0% for grade 3 disease. The authors concluded that local control was excellent following radical nephroureterectomy in contrast to some of the other series. Further, when they compared their results with surgical series alone, there was no additional benefit from adjuvant radiation therapy. The incidence of metastasis was 54% and apparently was unaffected by additional radiotherapy.

Similarly, Catton et al [14] also did not provide any evidence supporting the use of adjuvant radiation therapy. Adjuvant radiotherapy was performed in 86 patients, 64% of whom had undergone a complete nephroureterectomy. Stage 3-4 disease was present in 66 patients and 21% of them had local relapse. Most of the patients in this group failed by systemic disease. On the basis of their experience, the authors refuted the routine use of adjuvant radiation therapy.

More recently, in a series of 72 patients treated by radical surgery alone, local recurrences (tumor bed and/or regional lymph nodes) developed in only 6.9% of the patients, and 5-yr disease-specific survival and recurrence-free survival rates were 46.3% and 37.8% for invasive (T2–T4) tumors, respectively [15]. On multivariate analysis T stage, grade, and tumor location in the urothelium were the only significant variables for the 5-yr disease-specific and recurrence-free survival rates (Table 1).

Despite some of the controversies in local control of the disease after surgery by adjuvant radiation therapy, almost all of the clinical studies stressed the ineffective nature of this approach in prevention of systemic disease and subsequent death. Thus, the absence of any survival benefit by adjunctive radiotherapy certainly indicates the immediate need for an effective systemic therapy to prevent distant failure and related death in this patient population.

Table 1 – Five-year survival according to stage and grade in patients with upper urinary tract urothelial carcinoma in clinical series

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>T stage (%)</th>
<th>Grade (%)</th>
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<tr>
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<td>T2</td>
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<tr>
<td>Racioppi et al [2]</td>
<td>100</td>
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<td>Guinan et al [7]</td>
<td>611</td>
<td>87</td>
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<tr>
<td>Hall et al [11]</td>
<td>252</td>
<td>73</td>
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<td>Kwak et al [16]</td>
<td>32</td>
<td>–</td>
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<tr>
<td>Morioka et al [17]</td>
<td>93</td>
<td>89</td>
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<tr>
<td>Elliot et al [31]</td>
<td>44</td>
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* With adjuvant chemotherapy.
3. Neo/adjuvant systemic therapy

Results of adjuvant radiotherapy studies indicate improved local control albeit no additional benefit in prevention of metastatic disease, especially in high-grade, high-stage tumors. Therefore, prognosis is usually poor even with adjuvant radiation; more effective systemic therapies are required. Combined radiation and cisplatin-based chemotherapy proved to be effective in muscle-invasive bladder carcinoma, and a similar benefit may be possible for upper tract urothelial carcinoma as well.

Evidence emerging from the literature to support this notion to achieve a better outcome compared with radiation alone has been reported with a combination of radiotherapy and cisplatin chemotherapy. In a series of 31 patients with nonmetastatic upper tract urothelial carcinoma treated at Massachusetts General Hospital between 1970 and 1997, who initially underwent surgery with a curative intent, adjuvant radiation therapy with or without chemotherapy was incorporated in the management of these patients [8]. Tumors were located at the renal pelvis in 13, the ureter in 15, and both locations in 3 patients. The median total dose was 46.9 Gy (range: 34–63) to the tumor bed and regional lymph nodes; 9 patients also received cisplatinum-methotrexate-vinblastine chemotherapy followed by concurrent cisplatin during the radiation. A total of 7 patients (23%) had locoregional failure after a median follow-up of 2.6 yr, all of whom except 1 had distant metastases within 8 mo of local failure. Another 29% of the patients had failure with distant metastases without local failure. Overall 5-yr actuarial survival was 39% and disease-specific survival was 52%. Univariate analysis of data identified neoadjuvant chemotherapy and concurrent cisplatin administration during radiotherapy as the most important factors. Survival at 5 yr was 67% and 27% in patients with or without chemotherapy, respectively (p: 0.01). Similarly, 5-yr disease-specific survival was improved by chemotherapy (76% vs. 34%, p: 0.03), which achieved statistical significance in patients with stage 3/4 disease. Although there was a trend for the chemoradiotherapy group, no statistical significance was achieved in 5-yr locoregional failure rates (45% vs. 22%) or metastasis-free survival at 5 yr (38% vs. 67%) in patients treated with radiotherapy alone versus chemoradiotherapy, respectively. Interestingly, 20% of node-positive patients were long-term survivors (4 and 10 yr, respectively) after combined radiation and chemotherapy.

Kwak et al [16] treated their patients (n: 43; 36 male, 7 female) with or without cisplatin-based combination chemotherapy after nephroureterectomy. All patients underwent regional lymphadenectomy (hilar lymph nodes and nodes adjacent to the ipsilateral great vessels) during surgery. Postoperative adjuvant chemotherapy was administered to 74.4% (32 of 43) of the patients (methotrexate, vinblastine, adriamycin, and cisplatin [M-VAC] in 72%). The 5-yr disease-free survival rate in adjuvant chemotherapy and nonchemotherapy groups were 62.5% and 36.4%, respectively (p: 0.0439). Similarly, 5-yr overall survival rates in these groups were 78.1% and 36.4%, respectively (p: 0.0275). Multivariate analysis in this study revealed adjuvant chemotherapy, and nodal status was strongly associated with survival (relative risk [RR]: 9.19 and 8.28, respectively).

This beneficial effect seems to be valid with different regimens and even in very high-risk groups. An overall 5-yr survival rate of 52% and disease-free survival rate of 40.2% were achieved by a combination chemotherapy of paclitaxel and carboplatin in a rather poor-risk population (95% with >T3, 80% with grade 3 disease, 14% N+) by Bamias et al [32]. One of the important findings of this study was the ineffectiveness of systemic adjuvant chemotherapy in prevention of intravesical tumor recurrence (p: 0.467). However, no survival difference was observed in patients with or without bladder recurrence.

Thus, adjuvant chemotherapy combined with radical surgery improved the survival in patients with invasive and/or lymph node metastatic upper tract urothelial carcinoma. Postoperative radiotherapy did not seem to provide any additional benefit in the presence of systemic chemotherapy.

Finally, neoadjuvant chemotherapy appears to be at least equally effective in disease control of locally advanced upper urinary tract urothelial cancers [33]. A total of 15 patients with locally advanced urothelial cancers of the upper urinary tract were treated by cisplatin-based multiple-drug regimens (M-VAC, ME\textsuperscript{oposide}C or M-VE\textsuperscript{pirubicin}C) in a neoadjuvant setting. All patients underwent nephroureterectomy and response was evaluated pathologically. A pathologic complete response rate of 13%, pathologic partial response of 40%, and an overall response rate of 53% (95% confidence limits, 29–77%) were achieved in this patient population. The median duration of responses was 54 mo for patients with a pathologic complete response and 15.5 mo for patients with a pathologic partial response. There was a positive relationship between the pathologic response and prognosis. Long-term survival was quite likely if the tumor could be completely eradicated by neoadjuvant chemotherapy.
4. **Conclusions**

Development of metastatic disease is the common feature for treatment failure in patients with locally advanced upper tract urothelial carcinoma, despite the wide range of differences in local control rates in individual clinical series. Adjuvant radiation therapy may provide additional benefit in terms of prevention of locoregional disease without any effect on the development of systemic disease, which is the main reason of death in this patient population. Despite the infrequent nature of the disease and obvious disadvantage of small number of cases in each particular clinical series, evidence emerging from the literature indicates that systemic neo/adjuvant chemotherapy may prevent progression to metastatic disease and prolong survival.

**References**


