Management of Ureteral Obstruction in Advanced Testicular Tumor with Lymph Node Metastasis

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Objective: Ureteral obstruction is one of the complications of testicular tumor with retroperitoneal lymph node metastasis that requires ureteral stenting for management. We elucidated the clinical courses of ureteral obstructions and changes in renal functions in patients with indwelling ureteral stenting.

Methods: The medical records of 56 patients who were treated for metastatic testicular tumors by chemotherapy at a single institute between 2002 and 2010 were retrospectively reviewed.

Results: Among 56 patients, 12 patients needed ureteral stenting before chemotherapy. The proportion of patients requiring ureteral stenting was significantly higher in seminoma than non-seminoma (47 and 12%, respectively, \( P < 0.05 \)). The ureteral stent was removed after chemotherapy or retroperitoneal lymph node dissection in all patients, except for one patient who died of cancer during chemotherapy. At retroperitoneal lymph node dissection, ureters were spared in three patients, a partial ureterectomy was needed in one patient, and no case underwent adjunctive nephrectomy. These 11 patients presented no local and distant recurrence at median follow-up of 44 months. Ureteral stenting increased the estimated glomerular filtration rate to more than 60 ml/min before chemotherapy in all patients, but it decreased to \(< 60 \text{ ml/min}\) in 6 of 11 patients after chemotherapy.

Conclusions: Ureteral obstruction due to testicular tumor was relieved after chemotherapy or retroperitoneal lymph node dissection. Ureteral stenting was effective to improve renal function before chemotherapy, although we should pay special attention to deterioration of renal function during or after chemotherapy.

Key words: ureteral stent – testicular tumor – retroperitoneal lymph node – hydronephrosis – chemotherapy

INTRODUCTION

Testicular tumor is one of the common malignancies in young men and is well known as a rapidly progressive disease. Between 1980 and 1990, effective chemotherapy regimens including cisplatin against advanced testicular tumors were established. These chemotherapies and surgical interventions like retroperitoneal lymph node dissection (RPLND) achieved a high cure rate even in patients with multiple metastases. On the other hand, intensive chemotherapy with or without surgical treatment leads to several late sequelae in long-term testicular cancer survivors, and persistently impaired renal function is one of them (1–3).

The RPLN is a common site of metastasis in advanced testicular tumors, and large metastases in RPLN occasionally
lead to ureteral obstruction and resultant hydronephrosis (4,5). Ureteral obstruction and the resultant hydronephrosis may cause renal impairment and urinary tract infection during chemotherapy. Importantly, renal impairment limits delivery of adequate doses of anticancer drugs including cisplatin, which might result in a lower cure rate. Therefore, effective interventions to prevent ureteral obstruction are recommended in the management of advanced testicular tumor (6).

Retrograde ureteral stenting is the most widely used initial treatment for malignant ureteral obstruction. Several investigators have described the efficacy and limitations of ureteral stenting for extrinsic ureteral obstruction due to pelvic malignancies such as gynecological cancer and colon cancer (7–9). These malignancies with ureteral obstruction due to metastasis are not curable, and generally ureteral obstruction progression follows disease progression. In contrast, ureteral obstruction should be relieved in patients with testicular tumor because most patients with advanced testicular tumor can be cured. However, the safety and efficacy of ureteral stenting during chemotherapy for advanced testicular tumor has not been well described. Also, it is not clear what proportion of patients can be stent-free after chemotherapy or will need adjunctive nephrectomy at RPLND due to resection of the ureter involved.

In this retrospective study, we reviewed our clinical experience with ureteral stenting in patients with advanced testicular tumor to elucidate how to manage ureteral obstruction and also examine the impact of ureteral stenting on renal function during and after chemotherapy.

**PATIENTS AND METHODS**

**Patients**

A total of 56 advanced germ cell tumor patients were treated at Tsukuba University Hospital between June 2002 and August 2010. We retrospectively reviewed charts of these patients and identified 12 patients who underwent ureteral stenting for extrinsic ureteral obstruction due to retroperitoneal mass (Table 1). The median age at diagnosis was 39 years (range 26–58 years). They included 11 testicular tumor patients with RPLN metastasis and 1 retroperitoneal germ cell tumor patient. In 11 patients, retrograde ureteral stenting was performed before the start of chemotherapy. In the remaining non-seminoma patient, percutaneous nephrostomy (PCN) was initially required due to the inability to place a ureteral stent, but a ureteral stent was successfully placed after four courses of chemotherapy. A ureteral stent was placed in the left kidney in eight patients and the right kidney in five patients. One patient needed bilateral ureteral stenting.

**Treatment for Testicular Tumors**

Ten patients received a protocol consisting of bleomycin, etoposide and cisplatin (10) as the induction chemotherapy. Two patients who had risk factors for bleomycin pneumonitis were treated with four courses of etoposide and cisplatin. Dose reduction due to renal dysfunction was needed in 4 of 39 courses of induction chemotherapy. Postponements in the start of chemotherapy were observed in 6 of 27 subsequent treatment courses. The median duration of postponement was 3 days (1–6 days). In addition to the induction chemotherapy, six patients received a second-line or salvage chemotherapy for refractory or relapsed disease. The most frequently used second-line chemotherapy regimen was paclitaxel, ifosfamide and cisplatin (11). Three patients needed a third-line or further chemotherapy.

Principally, non-seminoma patients underwent surgical resection of residual operable masses when all tumor markers had normalized. However, surgery was omitted in seminoma patients with an adequately responding RPLN mass (≤3 cm in diameter or negative FDG-PET scan), and they were followed closely. One non-seminoma patient underwent salvage RPLND under a tumor marker-positive and chemo-refractory condition.

**Indication for and Management of Ureteral Stenting**

In principle, we adapted ureteral stenting when significant hydronephrosis due to ureteral obstruction was identified. During chemotherapy, the ureteral stent was exchanged at least once every 3 months. At each ureteral stent exchange, retrograde pyelography was performed to assess ureteral obstruction. When ureteral obstruction was relieved, the ureteral stent was removed. In patients who underwent RPLND, the ureteral stent was removed after recovery from surgery.

**Evaluation of Renal Function**

The glomerular filtration rate (GFR) was estimated based on the serum creatinine concentration using the formula

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
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<tr>
<td>Without stent placement (n = 44)</td>
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<tr>
<td>Age</td>
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<tr>
<td>Histology (S/NS)</td>
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<tr>
<td>IGCCCG category (G/I/P)</td>
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<tr>
<td>Size of RP mass (cm)</td>
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<td>Stent placement</td>
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<td>Left/right/bilateral</td>
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<td>Chemotherapy</td>
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<td>Induction</td>
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<td>Induction + salvage</td>
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S, seminoma; NS: non-seminoma; G, good risk; I, intermediate risk; P, poor risk; RP, retroperitoneal.

*Mean (range).

**N** = 31.

*P < 0.05.
reported by Matsuo et al. (12). This equation originated from the Modification of Diet in Renal Disease (MDRD) study group (13), designed for Japanese individuals and recommended by the Japanese Society of Nephrology: estimated GFR (eGFR, ml/min/1.73 m²) = 194 × serum Cr⁻¹.⁰⁹⁴ × age (years)⁻⁰.₂⁸⁷.

**Statistical Analysis**

Differences in patient age and RPLN mass size between groups were analyzed by Student’s t-test. χ² analysis was performed to compare histology, risk category and the proportions of seminoma and non-seminoma patients who underwent ureteral stenting. Pre-treatment eGFR was compared during and after treatment using one-factor repeated-measures ANOVA. A value of \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed using JMP software (version 9.02; SAS Institute Inc., Cary, NC, USA).

**RESULTS**

**Factors Related to Ureteral Stenting**

Among 56 patients (14 seminoma and 42 non-seminoma) treated for metastasis of testicular tumors, ureteral stenting was performed on 12 patients before chemotherapy. As shown in Table 1, the proportion of patients with ureteral stenting was significantly higher in seminoma than in non-seminoma (47 and 12%, respectively, \( P < 0.05 \)). For risk classification, all seven seminoma patients were classified as having a good prognosis according to the International Germ Cell Consensus Classification Group (IGCCCG) criteria (14), whereas four of five non-seminoma patients (80%) were classified into the intermediate or poor prognosis group. The median RPLN size of 12 patients was significantly greater than that of 31 patients having RPLN metastases and treated without ureteral stenting (8.4 and 4.0 cm, respectively; \( P < 0.05 \)). There was no significant difference in age or IGCCCG category distribution.

**Clinical Course for Ureteral Obstruction**

There were no episodes of stent failure such as worsening hydronephrosis or inability to replace stent during the stent replacement procedure. One patient developed the definite upper urinary tract infection, which could be managed with broad-spectrum antibiotics. During chemotherapy, two complications directly related to ureteral stent were observed. One was intrarenal migration, which needed ureteroscopy for removal. Another was fistula formation between ureter and necrotized lymph node mass. In the case, partial ureterectomy was performed in combined with RPLND.

In all seven seminoma patients, the ureteral stent was removed after chemotherapy (Table 2). The ureteral stent was removed after induction chemotherapy in six patients and after salvage chemotherapy in the remaining seminoma patient. In contrast, the ureteral stent could not be removed after chemotherapy in non-seminoma patients. However, the ureteral stent was removed after RPLND in four of five non-seminoma patients. The remaining non-seminoma patient died of cancer without marker normalization and without removal of the ureteral stent.

During RPLND, the ureter was spared in three patients, and partial ureterectomy was needed in one patient, who had developed a fistula between the ureter and a necrotized lymph node mass during chemotherapy. There were no cases needing adjunctive nephrectomy at RPLND. As for the pathological findings at RPLND, no residual germ cell cancer or teratoma element was identified in three patients, and a few foci of adenocarcinoma in a residual teratoma were identified in a patient who underwent RPLND with α-fetoprotein (AFP)-positive status. In all four patients, no adjuvant chemotherapy was performed after RPLND. These 11 patients continued with no evidence of disease at a median follow-up of 44 months (range 6–97 months).

**Change of Renal Functions During and After Treatment**

Ureteral stenting tended to increase the median eGFR from 68.3 to 82.5 ml/min, although the difference was not statistically significant (Fig. 1). Importantly, three patients presented insufficient renal function for chemotherapy including cisplatin (<60 ml/min eGFR), and ureteral stenting improved eGFR to more than 60 ml/min in these three patients before chemotherapy. On the other hand, chemotherapy decreased eGFR significantly (\( P = 0.016 \)), and the eGFR was below 60 ml/min in 6 of 11 patients after treatment. However, no further deterioration in eGFR was observed at 1 year after the last treatment.

To identify the factors related to deterioration of renal functions, we compared patient profiles, treatment procedures and computed tomographic (CT) findings at the last follow-up of patients with eGFR above and below 60 ml/min after treatment (Table 3). The CT findings of the kidney at the last follow-up were normal in all patients whose eGFR was
above 60 ml/min. In contrast, persistent hydronephrosis or apparent kidney atrophy was observed in five of six patients whose eGFR was below 60 ml/min. There were no significant differences in age, histology, chemotherapy courses and history of RPLND between each group.

### DISCUSSION

Once inserted, a ureteral stent or PCN usually becomes permanent in patients with advanced cancers other than testicular tumor because they are not curable (7–9). On the other hand, most advanced testicular tumors can be cured by chemotherapy and surgery. Therefore, sparing the involved kidney and preservation of renal function are important clinical goals. However, to our knowledge, there has been no report focused on the outcome of ureteral stent management during chemotherapy for testicular tumor. In the present retrospective study, we showed that ureteral stenting effectively improved renal function, which allowed the completion of chemotherapy with adequate drug intensity. Second, we showed that involved ureters can be spared in most cases without worsening the oncological outcome.

The incidences of hydronephrosis in advanced seminoma and non-seminoma were reported to be \( \approx 25 \) and 35%, respectively (4,5). In our series, ureteral stenting was needed in 21% of advanced testicular tumor patients, especially in the patients with a larger RPLN mass (a median diameter of 8.4 cm). The proportion of ureteral stenting in seminoma was 45% in our series and higher than previous reports (4). This might be a result of selection bias since most seminoma patients were initially diagnosed at community hospitals and referred to our hospital for the treatment of advanced disease.

In the present study, all seminoma patients were cured by chemotherapy, and the stent could be removed in all cases after chemotherapy alone. In contrast, all non-seminoma patients underwent RPLND after chemotherapy, except one patient who died of the disease during chemotherapy. At RPLND, the involved ureter was spared in three patients, and partial ureterectomy was needed in the remaining one. The ureteral stent could be removed in all patients after RPLND. It is important to estimate the risk of residual viable cancer around the involved ureter and to decide whether involved ureters can be spared or resected adjunctively at RPLND. Nash et al. (15) reported that en bloc nephrectomy was performed at RPLND in 19% of post-chemotherapy non-seminoma patients. Stephenson et al. reported that adjunctive nephrectomy was necessary in 53% of non-seminoma patients with risk factors for residual viable cancer. The proposed risk factors for adjunctive nephrectomy include post-salvage chemotherapy, desperation RPLND, late relapse and reoperative RPLND (16). In the present study, pathological examination of RPLND specimens revealed only necrotic tissue in three of four patients. The other patient, who underwent desperation RPLND with elevated AFP, had a teratoma with malignant transformation, but the surgical margin was negative. There was no recurrence after RPLND in all patients. We consider kidney-sparing surgery possible in selected cases with attention to the surgical margin.

The primary purpose of ureteral stenting is safe delivery of chemotherapy and preservation of renal function during chemotherapy. In our data, ureteral stenting improved eGFR to more than 60 ml/min in all patients. As a result, induction chemotherapy was possible without dose reduction in 90% of treatment courses. The drug intensity of the induction chemotherapy was similar to that of our previous study (17). However, eGFR decreased significantly to below 60 ml/min
in 6 of 11 patients after chemotherapy even if ureteral obstruction was treated with ureteral stenting.

Previous studies have demonstrated a 20–30% reduction in the GFR in long-term follow-up after chemotherapy for testicular tumor (18). Age at treatment and the type of treatment were associated with renal impairment (2). We previously reported that patients who developed renal impairment during chemotherapy might be at risk of further elevation of serum creatinine during long-term follow-up (19). In the present series, the follow-up CT revealed progressive renal atrophy in three cases and persistent mild hydronephrosis in three cases in the patients whose eGFR fell below 60 ml/min. The patient age, histological type, number of courses of chemotherapy and undergoing of RPLND were not associated with eGFR after chemotherapy. The severity of hydronephrosis might be associated with the renal impairment, but we could not adequately grade hydronephrosis in the present retrospective study.

Testicular tumor is a highly curable cancer; therefore, assessment of the long-term morbidity is important due to the life expectancy of this group of young men (3). The morbidity includes secondary malignant neoplasms, neuropathy, gonadal dysfunction, nephrotoxicity and cardiovascular disease. The latter two morbidities may be associated with eGFR after chemotherapy. The impact of hydronephrosis on outcome of stage IIIB cervical cancer patients with disease limited to the pelvis, treated with radiation and concurrent chemotherapy: a Gynecologic Oncology Group study. J Urol 2010;184:270–5.

In conclusion, ureteral obstruction due to testicular tumor was relieved after chemotherapy or RPLND in most of cases. Ureteral stenting was effective to improve renal function before chemotherapy, although we should pay special attention to deterioration of renal function during or after chemotherapy.

Conflict of interest statement

None declared.

References