Original Article

ADJUVANT CHEMOTHERAPY WITH CISPLATIN/CYCLOPHOSPHAMIDE/DOXORUBICIN FOR PATIENTS WITH UROTHELIAL CARCINOMA OF THE UPPER URINARY TRACT

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Abstract :
Background Urothelial carcinoma of the upper urinary tract is relatively uncommon and the benefit of adjuvant chemotherapy has not yet been established. We evaluated the efficacy of adjuvant chemotherapy after radical surgery for patients with primary urothelial carcinoma of the renal pelvis and ureter in a randomized controlled trial. ***Methods*** Forty patients who underwent radical surgery for localized and locally-invasive upper urinary tract carcinoma without metastasis were randomly assigned to two groups treated with and without adjuvant chemotherapy using cisplatin, cyclophosphamide and doxorubicin (CISCA) to compare the overall, cancer-specific, and recurrence-free survivals between them. UFT was administered orally at a dose of 200-400 mg/day to both groups for 2 years after surgery. ***Results*** The median follow-up was 80.5 months. The overall survival and cancer-specific survival rates showed no significant differences (p=0.61 and p=0.28, respectively) between the two groups. The 10-year recurrence-free survival rates also showed no difference between the 2 groups treated with and without adjuvant chemotherapy (68.8% and 54.4%, respectively, p=0.20). All recurrent cases showed recurrence of non-muscle invasive bladder cancer, and thereafter only one patient progressed with distant metastasis. The morbidity of recurrence, particularly within 2 years, and the total number of recurrences tended to be smaller in the adjuvant chemotherapy group than in the non-adjuvant chemotherapy group (p<0.063). ***Conclusion*** Adjuvant chemotherapy with CISCA after radical surgery showed no significant survival benefit for the patients with localized and locally-invasive urothelial carcinoma of the upper urinary tract while recurrence of bladder cancer decreased significantly in the adjuvant chemotherapy group compared to the non-adjuvant group.

Key words : upper urinary tract, urothelial carcinoma, adjuvant chemotherapy

INTRODUCTION

The standard treatment for localized urothelial carcinoma of the renal pelvis and ureter has been total nephroureterectomy with removal of a bladder cuff. Reportedly, the recurrence

rate is approximately 40–50% after radical surgery, and the 10-year disease-specific survival rate is less than 60% for T3 ≤ disease[1-4]. Several investigators reported that the tumor stage, grade, and lymph node metastasis in patients without distant metastases at the time of diagnosis were the most important prognostic factors[5-9].

Adjuvant chemotherapy and radiotherapy reportedly improve the prognosis of patients with locally advanced upper urinary tract carcinoma, including positive surgical margin and pathological N^+ disease[2-4]. Adjuvant chemotherapy decreased the postoperative metastatic recurrence rate[3,4] while adjuvant radiotherapy decreased the local recurrence rates in previous studies[2]. The combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been considered the standard chemotherapy for locally advanced or metastatic bladder cancer. However, the rarity of upper urinary tract urothelial carcinoma, which accounts for approximately 5% of all urothelial cancers[10], precludes the performance of prospective studies, and MVAC adjuvant chemotherapy is often associated with an incomplete or limited performance led by major loss of renal function after nephroureterectomy and high-grade toxicities. Therefore, there are no sufficient evidence-based data obtained from a prospective randomized trial on adjuvant chemotherapies for upper urinary tract carcinoma after radical surgery.

The combination of gemcitabine and cisplatin (GC) for advanced bladder urothelial carcinoma including upper urinary tract carcinoma is recommended as an alternative to MVAC owing to its favorable survival and low hematologic toxicity and nephrotoxicity[11,12]. The feasibility of adjuvant chemotherapy with paclitaxel and carboplatin for advanced urothelial carcinoma of the upper urinary tract was also reported[4]. On the other hand, CISCA regimen in combination with cisplatin, cyclophosphamide, and doxorubicin is a low-toxic and well-tolerable chemotherapy for patients with impaired renal function. However, MVAC or GC was nowadays preferred to CISCA for the treatment of advanced urothelial carcinomas because of a more favorable response, and the benefit of CISCA as an adjuvant chemotherapy for limited patients with urothelial carcinoma has not been clarified when compared to MVAC.

Herein, we report the relatively long-term results of a prospective randomized controlled trial on adjuvant chemotherapy with CISCA following radical surgery for patients with non-metastatic (N0M0) localized and locally-invasive upper urinary tract carcinoma.

PATIENTS AND METHODS

Patient selection

In this prospective randomized controlled study, we enrolled patients who were diagnosed as having primary urothelial carcinoma of the renal pelvis or ureter without distant metastasis by diagnostic imaging and underwent total nephroureterectomy with removal of a bladder cuff and regional lymph node dissection at Nara Medical University Hospital and its affiliated hospitals between 1990 and 1999. The specimens were pathologically confirmed to be urothelial carcinoma without regional lymph node metastases. All tumors were graded and staged according to the TNM Classification of Malignant Tumors (6^{th} ed) and World Health Organization classifications.

The eligibility criteria for this study were pathological Ta-1/G2-3, $T2/G_{any}$, and T3/G1-2;

Eastern Cooperative Oncology Group performance status (PS) 0-3; age ranging from 20 to 79 years; and having organ function defined by a complete leucocyte count of at least 3000/μL; platelet count of at least 10000/μL; hemoglobin of at least 9.0g /dL; creatinine clearance of at least 60 ml/min; ALT, AST less than twice the upper normal limit; non-pregnant status for women; no prior or concurrent urothelial carcinoma in the urinary bladder; and no concurrent other malignancy. No patients received any chemotherapy or radiation therapy prior to surgery.

All patients gave their written informed consent before enrollment. The aims and methods of this study were approved by the institutional review committee at Nara Medical University Hospital in 1990.

Treatment schedule

The patients were randomly assigned to one of two treatment groups (Table 1). Cisplatin-based adjuvant chemotherapy (CISCA regimen) was initiated 4 to 6 weeks after surgery as follows: cyclophosphamide (CPM: 500 mg/m^2) and doxorubicin (DXR: 50 mg/m^2) were administered intravenously on treatment day 1, and cisplatin (CDDP: 100 mg/m^2) on treatment day 2. The cycles were repeated every 3 weeks until a maximum of 3 cycles were given. Adjuvant chemotherapy was discontinued if high-grade adverse events ensued. In the patients who had renal dysfunction during the chemotherapy, the dose of CDDP was dependent on the creatinine clearance (Ccr); e.g., 25% reduced dose at Ccr of 30-60 ml/min and 50% reduced dose at Ccr < 30 ml/min. UFT was administered orally at a dose of 200-400 mg/day to both groups at 2 to 4 weeks after surgery for 2 years. The patient's compliance for UFT was verified by interviews at the end of the treatment.

Table 1. Baseline patient characteristics

	Non-adjuvant chemotherapy group	Adjuvant chemotherapy group	*p* -value
No. patients	**n=20**	**n=20**	
Tumor location renal pelvis/ureter	**13/7**	**13/7**	**ns**
Age(yrs) median (range)	**62 (47-78)**	**60 (35-78)**	**ns**
Gender male/female	**18/2**	**17/3**	**ns**
Pathological tumor stage Ta/T1/T2/T3	**4/10/3/3**	**5/10/2/3**	**ns**
Grade G1/G2/G3	**0/16/4**	**1/14/5**	**ns**

Follow-up schedule and treatment of recurrence

The patients underwent cystoscopy with urine cytology every 3 months for the first 3 years, every 6 months for the following 2 years, and thereafter every year, with chest, abdominal and/or pelvic computed tomography (CT) every 6 months for the first 3 years, and then yearly. Intravenous urography was performed every year. Bone scintigraphy was performed in patients who had symptoms suggestive of bone metastasis. Intravesical recurrence or local recurrence of nodal metastases or distant metastases was treated appropriately according to the lesion; i.e., by transurethral resection (TUR), intravesical instillation therapy, systemic chemotherapy, radiation therapy or surgery of the recurrent or metastatic lesions.

Statistical analysis

The variables in the different groups were compared using the Mann-Whitney U-test. The independency of fitness of the categorical data was estimated by the chi-square test. The recurrence-free survival was calculated from the day of nephroureterectomy to the first recurrence. The overall and cancer-specific survivals were defined as the time from the day of nephroureterectomy to death resulting from any cause and urothelial carcinoma, respectively. All survival curves were estimated with the Kaplan-Meier method, and the survival functions were compared among different groups with the log-rank test. P value less than 0.05 was considered as statistically significant.

RESULTS

Patient demography

A total of 40 patients who fulfilled the eligibility criteria were enrolled in this study (Table 1). The baseline patients' characteristics showed no differences between the two groups. Stage T1 and histological grade G2 were the most common pathological features in the two groups. Regional lymphadenectomy, including the ipsilateral renal hilar nodes and the nodes adjacent to the inferior vena cava and abdominal aorta, was routinely performed for all patients and proved to be negative for nodal disease.

Adjuvant chemotherapy

The mean number of chemotherapy cycles was 2.75 (range: 1 to 3 cycles). Two patients could not complete the three cycles because of impaired renal function after the first cycle. Six patients received 50% reduced CDDP dose due to renal dysfunction according to the dose-reduction criteria of CDDP. The most common side effects were nausea, neutropenia and alopechia, but no side effects over CTCAE (Common Terminology Criteria for Adverse Events, v3.0) grade 3 occurred in the adjuvant chemotherapy group. All patients, except for one complaining of epigastralgia continued UFT administration for the scheduled period.

Overall survival, cancer_specific survival and recurrence-free survival

The overall median follow-up was 80.5 months (range: 9 to 180 months). During follow-up, two patients in the adjuvant chemotherapy group died of other causes, and one patient in the non-adjuvant chemotherapy group died of cancer. The overall, cancer-specific,

and recurrence-free survival rates did not differ significantly between the groups with and without adjuvant chemotherapy (p=0.61, p=0.28, p=0.20, respectively). The 10-year overall survival rates in the adjuvant and non-adjuvant chemotherapy groups were 84.7% and 83.3%, respectively (Fig. 1). The 10-year cancer-specific survival rates in the adjuvant and non-adjuvant chemotherapy groups were 100% and 94.1%, respectively (Fig. 2). The 10-year recurrence-free survival rates in the adjuvant and non-adjuvant chemotherapy groups were 68.8% and 54.4%, respectively (Fig. 3).

Postoperatively, 5 patients (25%) in the adjuvant chemotherapy group and 9 patients (45%) in the non-adjuvant chemotherapy group subsequently developed bladder cancer. All of the 14 patients showed intravesical recurrence at their first recurrence. Regarding the aforementioned patients, 2 of 5 in the adjuvant chemotherapy group and 5 of 9 in the non-adjuvant chemotherapy group had intravesical recurrence more than once. The recurrent bladder cancers were all muscle non-invasive cancers, and in 9 (63%) of 14 patients with intravesical recurrence, the first recurrence was detected within 2 years after nephroureterectomy (Fig. 4). The incidence of intravesical recurrence within 2 years in the adjuvant chemotherapy group was smaller than that in the non-adjuvant chemotherapy group (p<0.063). The intravesical recurrences after nephroureterectomy did not correlate with the stage and location of the primary cancer in the upper urinary tract. One patient only had distant metastasis in the lung and recurrence in the contralateral renal pelvis resulting in cancer death.

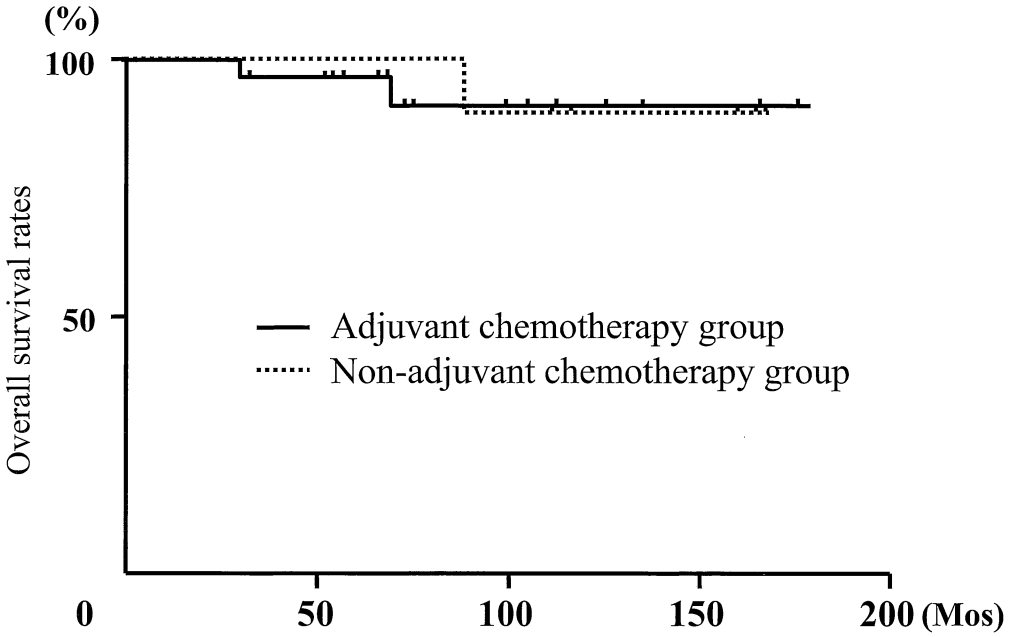

Fig. 1. The overall survival rates in the adjuvant chemotherapy group and the non-chemotherapy group. The 10-year overall-specific survival rates were 84.7% and 83.3%, respectively. There was no significant difference between the two groups (p=0.61).

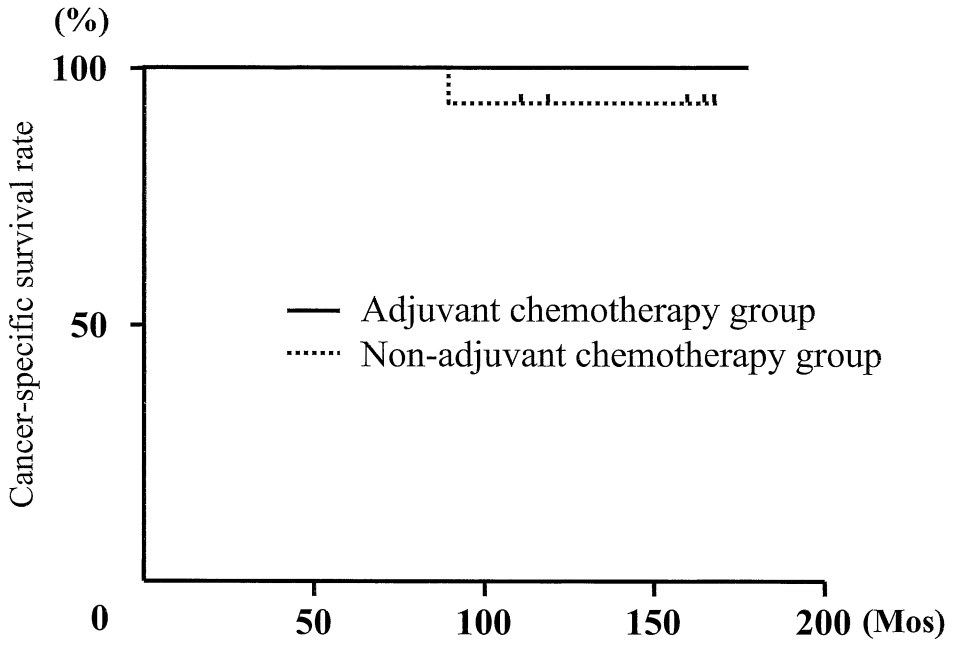

Fig. 2. The cancer-specific survival rates in the adjuvant chemotherapy group and the non-chemotherapy group. The 10-year cancer-specific survival rates were 100% and 94.1%, respectively. There was no significant difference between the two groups (p=0.28).

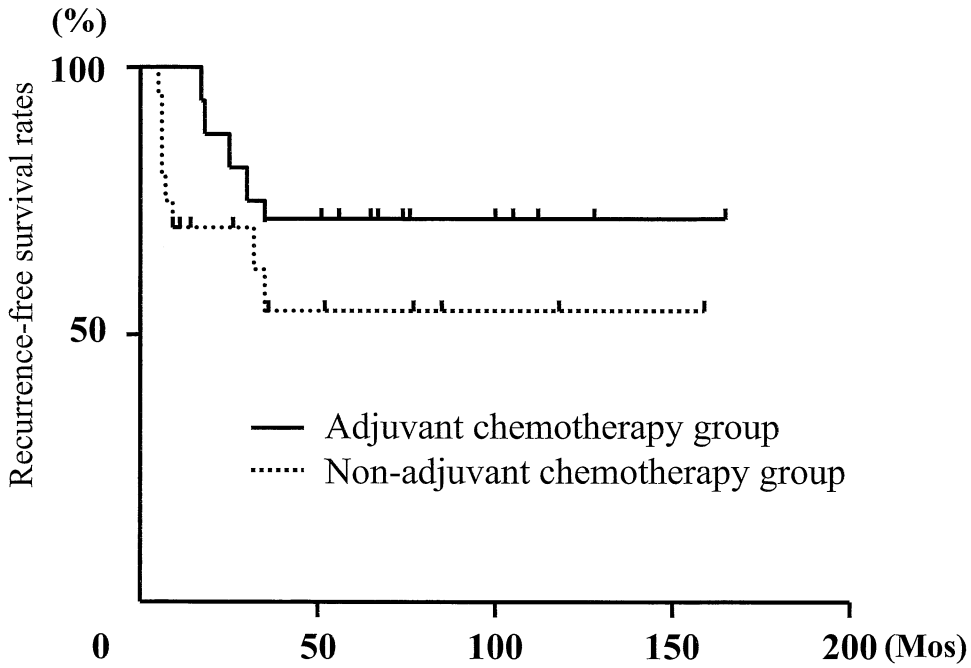

Fig. 3. The recurrence-free survival rates in the adjuvant chemotherapy group and the non-chemotherapy group. The 10-year recurrence-free survival rates were 68.8% and 54.4%, respectively. There was no significant difference between the two groups (p=0.20).

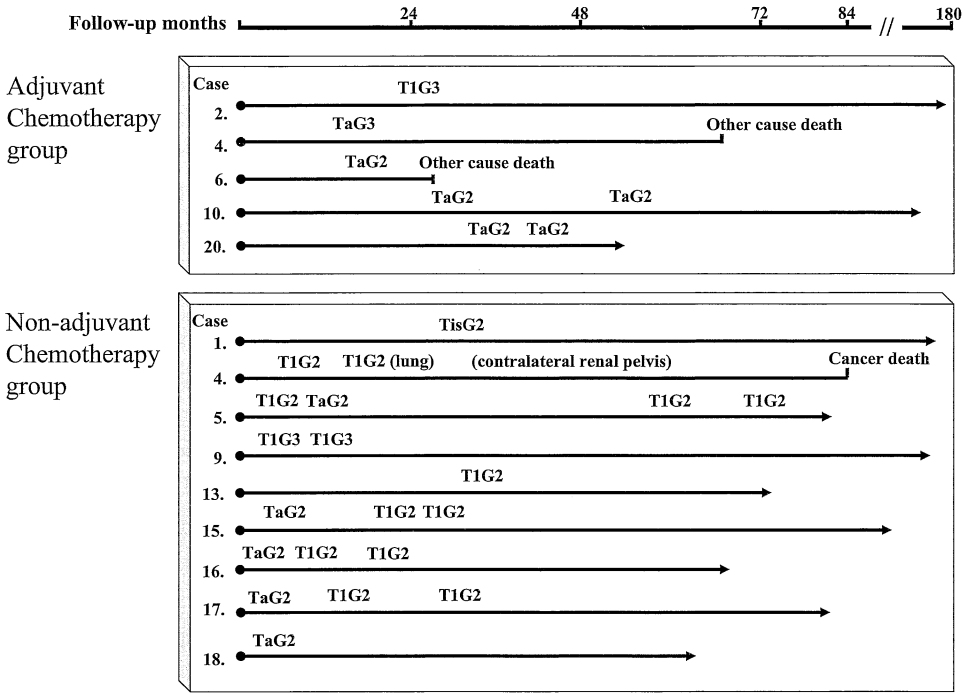

Fig. 4. All the recurrent cases detected during the follow-up. (–) corresponds to a developed bladder cancer, and (–) corresponds to a distant metastasis. In the chemotherapy group (A), 5 cases developed bladder cancer, and in the non-chemotherapy group (B), 9 cases developed bladder cancer, and one case had distant metastasis in the lung and contralateral renal pelvis, resulting in cancer death.

Treatment of recurrent tumors

All patients that developed intravesical recurrent tumor underwent TURBT. No patients underwent cystectomy for intravesical recurrence. Intravesical instillation of bacillus Calmette-Guérin (BCG) was selected according to the risk assessment in three patients of the non-adjuvant group with T1G3 tumor, carcinoma *in situ*, or repetitive intravesical recurrence. Four of 9 patients with recurrence in the non-adjuvant group and one of 5 with recurrence in the adjuvant group were treated with maintenance intravesical chemotherapy of epirubicin or pirarubucin. One patient only in the non-adjuvant chemotherapy group showed recurrence in the lung and contralateral renal pelvis, and he underwent a wedge resection of the lung metastasis and followed by palliative therapy for contralateral renal pelvic carcinoma until cancer death.

DISCUSSION

Since carcinoma of the upper urinary tract is relatively rare, clinical assessment of adjuvant chemotherapy is immature and short of well-designed randomized controlled trials. Various risk factors reportedly correlated with the prognosis, and one of these factors is definitely lymph node metastasis in patients without distant metastasis at the time of

diagnosis[7-9]. Several studies have shown that adjuvant chemotherapy using paclitaxel and carboplatin or cisplatin-based regimens is considered feasible for locally advanced urothelial cancer of the upper urinary tract, and may reduce the risk of distant metastasis in high-risk cancer[3,4]. Kwak *et al.* reported that postoperative CDDP-based chemotherapy improved the 5-year recurrence-free survival rate and the overall survival rate significantly[3]. Bamias *et al.* noted the efficacy of adjuvant chemotherapy with paclitaxel and carboplatin in advanced carcinoma of the upper urinary tract[4]. These studies included pN^+ cases, and the efficacy of adjuvant chemotherapy in the patients who underwent radical surgery using randomized control trial has not been evaluated sufficiently.

In this study, we used a regimen of CISCA as adjuvant chemotherapy for the following reasons. One is that our study was designed as a prospective study in 1990 to elucidate the relatively long-term prognosis after adjuvant chemotherapy. Second, since the adjuvant chemotherapy was administered to the patients who underwent radical surgery for upper urinary tract cancer, we chose a regimen of mild chemotherapy. Indeed, only 2 patients could not complete the total cycles of CISCA, and no patients had severe adverse events with being supported by granulocyte colony stimulating factors and $5\text{-}HT_3$ antagonists. Third, the patient enrollment was limited to those who had pathologically no regional lymph node metastasis. The 10-year cancer-specific survival rates indicated good prognosis, being 100% and 94.1% in the non-chemotherapy group and the chemotherapy group, respectively. Only one patient in the non-adjuvant group progressed and died with postoperative distant metastasis after intravesical recurrence. These results are in consensus with those of Munoz and Ellison who reported that the disease-specific 5-year survival was over 90% for patients with localized carcinoma of the upper urinary tract[13].

On the other hand, the risk factors for intravesical recurrence have not been fully elucidated. Hisataki *et al.* reported that the extent and pathologic stage of cancer in the upper urinary tract were significant and independent factors for intravesical recurrence, and that systemic chemotherapy was ineffective for prophylaxis of recurrent bladder cancer, and the developed bladder cancer was not a prognostic factor in the patients with upper urinary tract urothelial carcinoma[14]. In our series of patients, the 10-year recurrence-free survival rates did not significantly differ between the adjuvant chemotherapy group (68.8%) and the non-chemotherapy group (54.4%). However, in the non-adjuvant chemotherapy group, most of the first recurrences were detected earlier (i.e., within one year after nephroureterectomy) when compared to the adjuvant chemotherapy group, and the total number of recurrences was significantly greater in the non-adjuvant chemotherapy group than in the adjuvant chemotherapy group. These results demonstrated that adjuvant chemotherapy was very likely to inhibit the intravesical recurrence, similarly to the results of adjuvant chemotherapy with MVAC reported by Soga *et al.*[15].

Finally, the limitations should be mentioned; our study was small scale as the number of patients was limited. Furthermore, most of the tumors were low stage, and we administered adjuvant chemotherapy using CISCA regimen without comparison with other regimens such as MVAC or GC. Our results demonstrated that CISCA was not significantly advantageous for the recurrence-free survival of the localized and locally-invasive upper urinary tract carcinoma after radical surgery. However, most of the recurrent tumors developed in the

urinary bladder and 74% of all recurrences developed in the non-adjuvant group. Then, the intravesical recurrence could be controlled by TUR and the properly-indicated intravesical chemotherapy. In conclusion, adjuvant chemotherapy with CISCA showed a prophylactic effect on intravesical recurrence of non-muscle invasive carcinoma, and these intravesical recurrences did not influence the cancer-specific survival in the favorable-risk or low-stage urothelial carcinoma of the upper urinary tract.

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