Could salvage surgery after chemotherapy have clinical impact on cancer survival of patients with metastatic urothelial carcinoma?

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Abstract

Background：The clinical impact of salvage surgery after chemotherapy on cancer survival of patients with metastatic urothelial carcinoma is controversial. To verify the clinical role of salvage surgery by analyzing the long-term outcome in patients with urothelial carcinoma treated by chemotherapy.

Methods：Between 2003 and 2010, thirty-one of 47 patients (66%) with metastatic urothelial carcinoma showed objective responses (CR in 4, PR in 27) after multiple courses of Cisplatin/Gemcitabine /Paclitaxel-based chemotherapy, and a cohort of patients with partial response (PR) were retrospectively enrolled, at a single institution. Twelve (10 male and 2 female, median age 64.0 yrs) of 27 patients with PR underwent salvage surgeries after the chemotherapy: metastatectomy of residual lesions (10 retroperitoneal lymph nodes, 2 lung), and 6 radical surgeries for primary lesions as well. Progression-free survival and over-all patient survival rates were analyzed retrospectively and compared with those of patients without salvage surgery.

Results： All 12 patients achieved surgical CR. Pathological findings of metastatic lesions showed viable cancer cells in 3 patients. In univariate analysis, sole salvage surgery affected over-all survival in 27 patients with PR to the chemotherapy (p=0.0037). Progression-free survival and over-all survival rates in patients with salvage surgery were better than those in 15 PR patients without the surgery (39.8% vs 0%, and 71.6% vs 12.1% at 3 years, p = 0.01032 and 0.01048; log-rank test).

Conclusions：Salvage surgery for patients with residual tumor who achieve partial response to chemotherapy could have possible impact on cancer survival.

Mini-abstract

Salvage surgery for patients with residual tumor who achieved partial response to the chemotherapy could have possible impact on cancer survival.

Keywords： Chemothrapy, Metastatectomy, Metastatic urothelial carcinoma, Salvage surgery, Urothelial carcinoma,

Introduction

Modern cisplatin-based combination systemic chemotherapies for metastatic urothelial cancer have shown over-all response rates of approximately 50–70% with median survival of about 13 months [1-5]. Of these chemotherapies, methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) had been the standard regimens for initially unresectable or metastatic urothelial cancer. Recently, the combination of gemcitabine/cisplatin (GC) has become a new standard treatment in metastatic urothelial cancer in Europe and North America, based on randomized trials showing similar survival but having a more favorable toxicity profile for GC when compared to MVAC[5].

Although chemotherapy can achieve relatively high response rates in patients with metastatic urothelial cancer, fewer patients, even responders, can survive long-term by chemotherapy alone [6]. As part of a multidisciplinary approach, salvage surgery for residual metastatic masses after chemotherapy may improve prognoses of patients with metastatic urothelial cancer. Cowles et al, writing on the concept of surgical treatment for metastatic urothelial cancer, reported a median 5-year survival rate for six patients following thoracotomy for solitary pulmonary metastatic lesion [7]. Due to the promising responses to chemotherapy, the therapeutic concept of surgery for metastatic urothelial cancer has been addressed again, a decade after the initial reports [8-14]. These reports support the therapeutic approach by surgical resection of metastatic lesion in patients with metastatic urothelial cancer. In addition, most tumor relapses after an initial response to systemic chemotherapy occur at prior sites of disease, which provide a possible rationale for salvage surgery of these residual masses [15]. Cisplatin/Gemcitabine-based chemotherapy allows salvage surgery immediate following treatment due to its mild toxicity. However, the clinical impact of salvage surgery on survival benefit in responders to chemotherapy is still controversial. In this study, we verify the clinical role of salvage surgery by analyzing long-term outcome in patients with metastatic urothelial cancer treated by Cisplatin/Gemcitabine-based chemotherapy, focusing especially on a cohort of patients with partial response (PR), at a single institution.

Patients and Methods

Between 2003 and 2010, 47 patients with metastatic urothelial cancer (34 male and 13 female, median age 64.2 yrs) were treated by systemic Cisplatin/Gemcitabine/Paclitaxel based chemotherapy [16]: Gemcitabine 1000mg/m2 plus Paclitaxel 80mg/m2 on days 1 and 8 and Cisplatin 70mg/m2 on day 1 as GCP therapy (1-8 courses; median 3 courses) at our hospital with the approval of our Institutional Cancer Board. Seven patients were treated without Paclitaxel, and two were treated without Gemcitabine, due to the drug allergy. All patients had distant metastases (visceral metastases or distant lymph node (LN) metastasis) and 19 had simultaneous advanced primary lesions. Fourteen patients received MVAC as prior chemotherapy before the GCP therapy. Thirty-one of the 47 patients (66%) showed objective responses in RECIST criteria (complete response (CR) in 4, PR in 27) after multiple courses of the chemotherapies.

In this study, we focused on and analyzed the cohort of patients with PR to the chemotherapy. Twelve of 27 patients with PR underwent salvage surgeries after chemotherapy (10 male and 2 female, median age 64.0 yrs). These patients underwent salvage surgery for residual lesions (10 retroperitoneal LNs, 2 lung). All six patients with simultaneous primary lesions underwent radical surgeries for primary lesions as well. Resections of metastatic urothelial cancer to render patients free of disease were regarded as salvage surgery; resections only for the purpose of symptom palliation were not.

Salvage surgery was generally considered in situations where patients had residual visceral metastases in a solitary organ with a small number of lesions and/or residual distant LN metastases after good response (PR) to the chemotherapies and good performance status (PS), although we did not have strict prospective criteria. All therapeutic decisions were left to the discretion of our department on the basis of individual clinical features and patient request for aggressive treatment.

Patient progression-free survival and over-all survival rates were analyzed retrospectively. Survival was measured from the time of initiation of chemotherapy until death or the last follow-up. Clinical features were examined by univariate analysis for their association with survival. Variables considered were sex (male or female), age (≤65 yr or >65 yr), primary site (bladder alone or other), radical resection of primary lesion (yes or no), number of metastatic organs (single or multiple), LN metastasis (yes or no), lung metastasis (yes or no), presence of liver or bone metastasis (yes or no), and salvage surgery (yes or no). Survival curves were estimated by Kaplan-Meier method and survival distributions were compared

by the log-rank test; $p < 0.05$ was considered significant.

Results

Patients with PR to chemotherapy

The summary of characteristics of the 27 patients with PR to the chemotherapies is shown in Table 1. Eighteen patients had metastases at diagnosis of urothelial cancer, while metastases developed in 9 after the primary site had been treated surgically (radical surgery in 7; transurethral resection in 2). Patients received 3-9 courses of GCP therapy. Thirteen of PR patients died of cancer and the remaining 14 survive. The over-all and cause-specific survival rates were 84.6% at 1 year and 56.4% at 2 years, respectively. Fifty-percent survival duration was 26.0 months. Four patients with clinical CR survived without recurrence or progression.

Patients with salvage surgery

Twelve patients underwent salvage surgery after chemotherapy. Patient details are shown in Table 2. Median age was 64.0 years old (range: 41–73). The primary tumor site was the bladder in 4 patients and upper urinary tract in 8. Five had single metastatic lesions and seven had multiple lesions. Nine (75%) patients with salvage surgery underwent adjuvant chemotherapy (2-3 courses of GCP chemotherapy). As for pathological findings in the salvage surgical specimens of metastatic lesions, viable cancer cells were recognized in 3 patients (1 in lung, and 2 in LN) whereas necrotic tissues were confirmed in the other 9.

Univariate analysis

Although gender, primary site, resection of primary site, number of metastatic organs, and metastatic site did not affect progression-free survival, salvage surgery and age did. As for over-all/cause-specific survival, sole salvage surgery affected it strongly ($p = 0.0037$) (Table 3).

Figure 1a shows Kaplan-Meier progression-free survival curve with or without salvage surgery. Progression-free survival rates at 2 and 3 years in patients with salvage surgery were 63.6% and 39.8%, respectively and significantly longer than those in patients without salvage surgery (7.3% at 2years, $p = 0.01032$). Figure 1b shows Kaplan-Meier over-all/cause-specific survival curve with or without salvage surgery. The 3- and 5-year survival rates in patients with salvage surgery were both 71.6% and significantly longer than those in patients without salvage surgery (12.1%, $p = 0.01048$).

Discussion

Recently several authors have reported on the benefits of surgical resection of metastatic sites during a multidisciplinary approach for metastatic urothelial cancer [8-14]. Dodd et al [8] reported that a 5-yr overall survival rate of 33% was achieved in 50 patients with a major response to initial chemotherapy. In an up-dated series from the institute, 58% of patients who underwent post-chemotherapy surgery survived from 9 months to 5 years, while one of 12 patients (8%) who refused surgery remained alive [10]. They concluded that chemotherapy plus surgical resection of residual cancer to attain a complete response is critical for long-term survival in select patients who would otherwise die of recurrent disease. The authors also described in their data that only one third of the patients were deemed to be candidates for post-chemotherapy surgery, and of these, about one third survived [15], meaning that post-chemotherapy surgery could save about 1 or 2 out of every 10 patients treated. Our results show that one quarter of patients with metastatic urothelial cancer were candidates for salvage surgery and are similar to or relatively less than the rates described above. In our study, an influence by bias of patients' selection for salvage surgery on the results should be considered. The patients underwent salvage surgery might be a cohort of relatively low risk of recurrence compared to the patients who could not undergo. No visceral metastasis except lung was treated by salvage surgery, and high rate (10/12) of patient with salvage surgery had retroperitoneal lymphnodes swelling alone. The difference of patients' backgrounds might affect on the outcome even statistical analysis in our small study could not reveal it. However, even considering the selection bias, survival benefits for patients with salvage surgery were so apparent in our series that we regard salvage surgery as a strong method in important addition to a multidisciplinary approach for metastatic urothelial cancer.

The pathological findings of our surgical specimens showed a higher incidence (9 of 12 patients) of non-viable cancer cells than in prior reports: 33% in the Memorial Sloan-Kettering Cancer Center [10] and 18% in the German Group [14]. Our patients were treated by Cisplatin/Gemcitabine/paclitaxel-based chemotherapy (GCP), which differs from prior reports where MVAC therapy mainly was used. In addition, four clinical CR patients survived without recurrence. The high rate of pathological CR might be a reason for the high rate of survival in our series. On the other hand, the pathological findings may lead a speculation that the patients underwent salvage surgery have a bias for relatively low risk of recurrence compared to the patients who could not undergo salvage surgery. Although these speculations may imply

that salvage surgery for residual mass could be over-treatment for patients with only scarring in the specimen, we believe, as investigators have pointed out [10, 17], that salvage surgery is still worthwhile; negative pathology could also mean that residual nests of microscopic tumors were simply not detected in a large fibrotic specimen. On the other hand, surgery for metastatic sites where clinical CR was achieved by GCP therapy is still controversial, although the primary site should be removed even if showing clinical CR.

The main issue is to identify patients most likely to benefit from salvage surgery [17]. Surgical resection has to be technically feasible and the number of metastatic foci limited. Salvage surgery should be curative. With palliative intent, Otto et al reported on 70 patients undergoing resection of metastatic lesions after proving refractory to M-VAC chemotherapy [19]. While symptomatic patients experienced at least some relief, asymptomatic patients showed no beneficial palliative effects. Surgery with palliative intent is not beneficial and patients who failed to respond to chemotherapy did not survive in prior reports. The response to systemic chemotherapy is therefore important for survival for patients treated with a multidisciplinary approach. Although our study is small and retrospective, salvage surgery should only be offered to patients with a major response to chemotherapy where complete resection of all detectable masses seems feasible. In addition, since post-chemotherapy radiographs and scans are still unable to distinguish patients who have no evidence of residual pathologic disease from those who do, it seems reasonable to consider salvage surgery in patients with a major response to chemotherapy. In our small number of patients with complete response to GCP therapy, long progression-free survival rates were obtained without additional surgery. Surgery for metastatic sites remains controversial.

As for objective sites in salvage surgery, as Herr et al described [18], limited nodal or a solitary visceral or lung lesion is most likely to benefit from surgical resection. Patients with multiple liver metastases or metastases involving more than one visceral site or abdominal organ or bone metastases, especially involving the pelvis or axial skeleton, might not be a candidate of salvage surgery even if showing a major response to chemotherapy since prognoses in such patients were poor in prior reports. However, positron emission tomography (PET) scans may help to identify residual viable cancer, providing an indication for salvage surgery to a sole residual site in such patients in future. Finally, patient motivation and stamina for aggressive treatment may be the most important factors for salvage surgery.

Conclusions

Salvage surgery for patients with residual tumor who achieve partial response to chemotherapy could have a possible impact on cancer survival.

References

1. Roth BJ, Bajorin DF (1995) Advanced bladder cancer: the need to identify new agents in the post-M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). world J Urol 153:894–900

2. Sternberg CN (1995) The treatment of advanced bladder cancer. Ann Oncol 6:113–126

3. Loehrer PJ Sr., Einhorn LH, Elson PJ, et al (1992) A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. J Clin Oncol 10:1066–1073

4. Logothetis CJ, Dexeus FH, Finn L et al (1990) A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 8:1050–1055

5. von der Maase H, Hansen SW, Roberts JT et al (2000) Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 17:3068–3077

6. Siefker-Radtke AO,.Millikan RE, Tu SM et al(2002) Phase III trial of fluorouracil, interferon alpha-2b, and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in metastatic or unresectable urothelial cancer . J Clin Oncol 20:1361

7. Cowles RS, Johnson DE, McMurtrey MJ (1982) Long-term results following thoracotomy for metastatic bladder cancer. Urology 20:390–392

8. Dodd PM, McCaffrey JA, Herr HW et al (1999) Outcome of postchemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin, and cisplatin in patients with unresectable or metastatic transitional cell carcinoma. J Clin Oncol 17:2546–2552

9. Miller RS, Freiha FS, Reese JH et al (1993) Cisplatin, methotrexate and vinblastine plus surgical restaging for patients with advanced transitional cell carcinoma of the urothelium. J Urol 150:65–69

10. Herr HW, Donat SM, Bajorin DF (2001) Post-chemotherapy surgery in patients with unresectable or regionally metastatic bladder cancer. J Urol 165:811–814

11. Abe T, Shinohara N, Harabayashi T et al (2007) Impact of multimodal treatment on survival in patients with metastatic urothelial cancer, Eur Urol 52:1106–1113

12. Sweeney P, Millikan R, Donat M et al (2003) Is there a therapeutic role for post-chemotherapy retroperitoneal lymph node dissection in metastatic transitional cell carcinoma of the bladder? J Urol 169:2113–2117

13. Siefker-Radtke AO, Walsh GL, Pisters LL et al (2004) Is there a role for surgery in the management of metastatic urothelial cancer? The M.D. Anderson experience. J Urol 171:145–148

14. Lehmann J, Suttmann H, Albers P et al (2009) Surgery for Metastatic Urothelial Carcinoma with Curative Intent: The German Experience (AUO AB 30/05). Eur Urol 55:1293-1299

15. Dimopoulos MA, Finn L, Logothetis CJ (1994) Pattern of failure and survival of patients with metastatic urothelial tumors relapsing after cis-platinum-based chemotherapy. J Urol 151:598–600

16. Bellmunt J, Albanell J, Paz-Ares L, Climent MA, González-Larriba JL, Carles J, de la Cruz JJ, Guillem V, Díaz-Rubio E, Cortés-Funes H, Baselga J (2002) Spanish Oncology Genitourinary Group. Pretreatment prognostic factors for survival in patients with advanced urothelial tumors treated in a phase I/II trial with paclitaxel, cisplatin, and gemcitabine. Cancer. 2002 Aug 15;95(4):751-757.

17. Herr HW (2009) Is Metastatectomy for urothelial carcinoma worthwhile? Eur Urol 55:1300-1301

18. Childs MA, Wood CG, Spiess PE et al (2010) Early results of chemotherapy with retroperitoneal lymph node dissection for isolated retoroperitoneal recurrence of upper urinary tract urothelial carcinoma after nephroureterectomy. Can.J Urol 17:5184-5189

19. Otto T, Krege S, Suhr J et al (2001) Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. Urology 57:55–59

Table 1

Sex	Male	20
	Female	7
Age	41-76yr(median 64.0)	
Primary site	Upper urinary tract	15
	Bladder	12
Metastatic sites	Lung	12
	Retroperitoneal lymph node	17
	Contrarateral kidney	1
	Liver	4
	Bone	1
Follow up	4.5-66.0 mo(median 17.4)	

Table 2

Sex	Male	9
	Female	3
Age	41-73yr(median 57.0)	
Primary site	Upper urinary tract	8
	Bladder	4
Metastatic sites	Lung	2
	Retroperitoneal lymph node	10
Salvage surgery	Pulmonary metastatectomy	2
	RPLND	10
Follow up	4.5-66.0mo(median 33.6)	

Table3

	Patient Number	Cause-specific survival (median) months		Time to progression. (median) months	
Sex					
male	20	4.5-62.4(37.9)	p=0.627423	3.8-56.1(24.8)	p=0.918485
female	7	7.4-66.0(38.2)		6.2-43.4(35.2)	
Age					
≤65	12	7.7-66.0(22.0)	p=0.266397	3.8-43.4(27.3)	p=0.045829
>64	15	4.5-62.3(14.5)		2.6-56.1(13.0)	
Primary site					
Upper urinary tract	15	4.5-66.0(37.4)	p=0.969227	3.0-43.7(23.5)	p=0.819823
Bladder	12	7.7-62.3(45.4)		2.6-56.1(14.6)	
Resection of primary site					
yes	20	4.5-66.0(47.2)	p=0.236936	3.0-56.1(25.6)	p=0.171848
no	7	7.7-40.0(24.4)		3.8-30.3(12.5)	
Resection of metastasis					
yes	12	4.5-66.0(47.2)	p=0.003691	3.0-56.1(23.0)	p=0.002953
no	15	7.7-40.0(24.4)		2.6-30.3(14.6)	
Number of metastatic organ					
1	20	4.5-66.0(37.9)	p=0.15698	2.6-56.1(25.6)	p=0.328646
2 or more	7	8.4-38.7(24.6)		5.2-32.9(19.6)	
Metastatic site					
Lymph node					
yes	19	7.7-66.0(36.4)	p=0.457592	3.8-43.7(12.5)	p=0.777152
no	8	4.5-62.3(15.2)		2.6-56.1(25.6)	
Lung					
yes	12	4.5-62.3(26.1)	p=0.129457	2.6-56.1(21.7)	p=0.278525
no	15	7.7-66.0(37.1)		3.8-43.7(18.2)	
Liver					
yes	5	8.8-19.9(12.3)	p=0.129379	6.2-17.6(9.7)	p=0.296174
no	22	4.5-66.0(37.9)		2.6-56.1(19.2)	

Table captions

Table1 Characteristics of the 27 patients with PR to the chemotherapy

Table2 Characteristics of the 12 patients with salvage surgery after the chemotherapy

Table3 Results of univariate analysis

Figure 1a

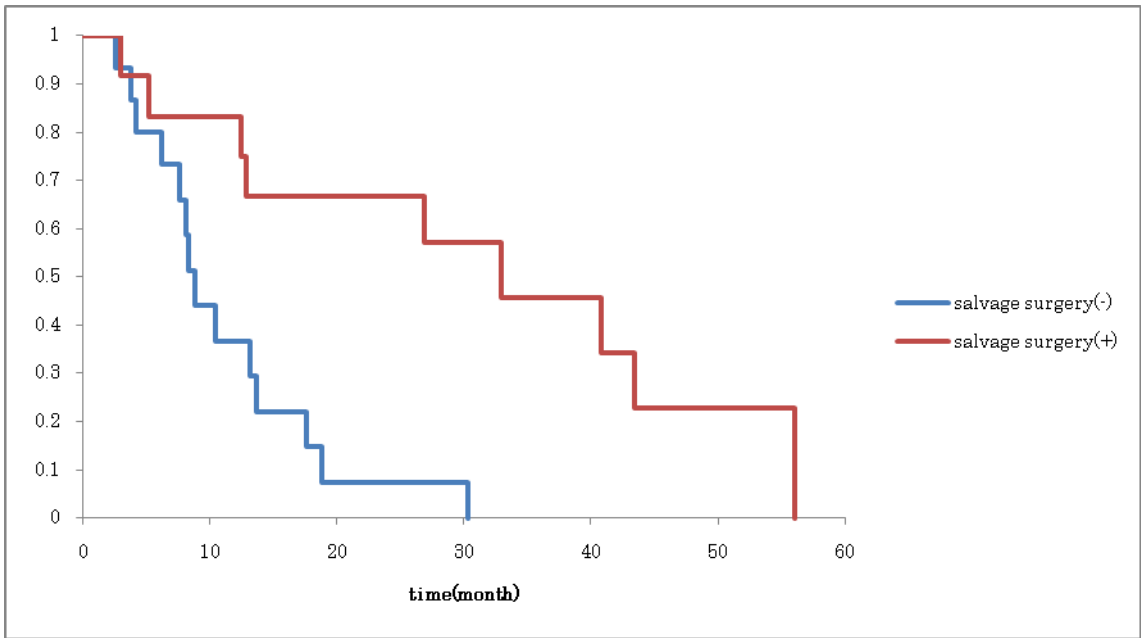

Figure 1b