Outcome of metastasectomy for urothelial carcinoma: A multi-institutional retrospective study in Japan.

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ABSTRACT

Purpose: To determine prognostic factors associated with prolonged survival after metastasectomy for urothelial carcinoma (UC).

Materials and Methods: Forty-two patients who underwent resection of metastases of UC with curative intent at 4 different Japanese university hospitals were included. Most of the patients (41/42) underwent systemic chemotherapy before and/or after metastasectomy. Overall survival was analyzed using the Kaplan-Meier method, and the relationship between the clinical characteristics and survival was analyzed using the log-rank test.

Results: Details of metastasectomy were as follows: lymph node dissection (n=20), pulmonary resection (n=12), pelvic exenteration (n=3), resection of local recurrence (n=2), resection of subcutaneous metastasis (n=2), liver resection (n=1), and others (n=2). The median overall survival time was 29 months (interquartile range [IQR]: 19-80 months) from the initiation of treatment for metastases and 26 months (IQR: 11-90) from metastasectomy. The overall 5-year survival rate from metastasectomy was 31%. On univariate analysis, patients undergoing metastasectomy for solitary lung or solitary lymph node metastasis showed a significantly longer survival than the others undergoing metastasectomy (median survival time: 81 months in patients with solitary lung or solitary lymph node metastasis vs. 19 months in the others, log-rank test $p = 0.0296$).

Conclusions: Long-term cancer control could be achieved in a subgroup of patients undergoing metastasectomy, especially in those with solitary lung or solitary lymph node metastasis.

Key Words: urothelial carcinoma, metastatic urothelial carcinoma, metastases, metastasectomy

INTRODUCTION

Systemic chemotherapy is the mainstay of treatment for metastatic urothelial carcinoma (UC). Although initial response rates are 50-70% [1, 2], these responses are usually transient. Long-term survival is achieved in only a small proportion of patients. In order to improve the outcome, several investigators have advocated the resection of metastases (so-called "metastasectomy") for surgical consolidation. [3-10] For example, our group previously reported a median survival of 42 months in 12 patients undergoing complete resection of all detectable metastases, which was significantly longer than that of patients who did not undergo metastasectomy (10 months). [6] However, its role and characteristics associated with long-term survival after metastasectomy remain undetermined.

The aim of this retrospective multi-institutional study was to examine the long-term outcomes and characteristics associated with prolonged survival after metastasectomy of UC.

MATERIALS AND METHODS

Each institutional review board approved the retrospective review and analysis of metastatic UC patients undergoing metastasectomy during the study period. Between 1989 and 2012, 42 patients with metastatic UC underwent resection of metastasis at 4 different Japanese university hospitals. These surgeries were performed with a curative intent. Patients undergoing metastasectomy for symptom palliation were not included. Demographic, surgical, pathological, and follow-up data were retrospectively collected from medical charts. During the study period, all therapeutic decisions including the extent of lymph node dissection (LND) at the time of radical cystectomy or nephroureterectomy, indication of neoadjuvant or adjuvant chemotherapy, or the choice of the respective chemotherapy regimens at the development of metastasis, were left to the discretion of each attending doctor on the basis of individual disease characteristics and patients' requests. Regarding the indication of metastasectomy, we considered metastasectomy when patients had metastasis in a single organ with a small number of metastases, a good performance status, and showed a favorable response to chemotherapy, although we did not have strict prospective criteria. In a situation contrasting to the above-mentioned one (e.g., more than five lung metastases, several organ metastases), we considered second-line chemotherapy. Generally, the disease status was re-evaluated with a chest X-ray or chest CT scan and CT scan of the abdomen and pelvis every 3–6 months. In patients

receiving systemic chemotherapy, tumor responses were assessed every two or three cycles by CT scan, although confirmation was not always carried out. Bone scans were conducted if symptoms were present.

Overall survival was analyzed from the initiation of treatment for metastatic UC or the time of metastasectomy until death or the last follow-up according to the Kaplan-Meier method, using the log-rank test to assess the significance of differences. The variables considered in survival analysis were sex (male vs. female), age (<68 vs. ≥68), primary site (bladder only vs. others), disease-free interval between primary surgery and the development of metastases (<12 vs. ≥12 months, <24 vs. ≥24 months), systemic chemotherapy before metastasectomy (yes vs. no), and metastatic sites (lymph node (LN) only vs. lung only vs. others, LN/ lung only vs. others, solitary LN / solitary lung metastasis vs. others). All calculations were performed using JMP® version 6.03. P-values < 0.05 were considered significant.

RESULTS

Table 1 shows the patients' characteristics. The median patient age at the start of treatment for metastatic disease was 67.5 years (range: 36-80). The primary tumor site was the bladder in 21 patients, upper urinary tract in 18 patients, and both in 3 patients. In this cohort, 39 patients had metastatic disease involving a single organ, while 3 had disease involving double organs at the presentation of metastases. The number of metastases was one in 23 patients, 2 or more in 14 patients, and uncountable due to aggregated metastatic LNs in 5 patients. Thirty-six patients developed metastasis after resection of the primary site, while 6 already demonstrated metastases at the diagnosis of primary cancer. In the present study, of the 8 patients with disease in the regional LNs, five patients developed regional LN recurrence after nephroureterectomy (pathological node status at nephroureterectomy, pN0: n=1, pN+: n=1, pNx: n=3) and 1 after radical cystectomy (pathological node status at radical cystectomy, pN0: n=1). Of the remaining two patients, one had aggregated LN metastasis at the initial presentation and underwent LND at the time of nephroureterectomy after systemic chemotherapy with a complete response of lung metastasis, and the other patient underwent LND after salvage systemic chemotherapy, although LND had been discontinued at the time of nephroureterectomy after induction chemotherapy. The median disease-free interval between surgical resection of the primary cancer and the

development of metastasis was 16 months (range: 0-103). All but one patient received systemic chemotherapy, and the dominant treatment course was "metastasectomy after systemic chemotherapy" (n=34). Table 2 shows a summary of chemotherapy regimens used in the present cohort. In the present cohort, MVAC/ MEC/ GC regimens were used as induction chemotherapy in most of the patients. Paclitaxel or docetaxel-including regimens were performed in 21 patients as salvage therapy after induction chemotherapy, or for disease recurrence after cisplatin-based neoadjuvant or adjuvant chemotherapy. Finally, during the treatment course, 23 patients received at least two different chemotherapy regimens.

Table 3 presents a summary of metatstasectomy. No patient underwent biopsy before metastasectomy. The interval between the last systemic chemotherapy and metastasectomy (n=34) was a median of one month (interquartile range [IQR]: 1-2.25), which suggested that a large proportion of patients had undergone metastasectomy immediately after systemic chemotherapy. LND (retroperitoneal LNs below aortic bifurcation: n=6, retroperitoneal LNs above aortic bifurcation: n=9, distant lymph nodes: n=5) and pulmonary resection (n=12) were frequent procedures in this cohort. Two patients underwent the simultaneous resection of primary cancer and metastasis after systemic chemotheapy (cervical LNs and initially unresectable abdominal LNs). The pathology demonstrated viable cancer in 30 patients. Only necrosis was detected in 12 of the 34 patients undergoing systemic chemotherapy before metastasectomy.

There was no operative mortality. Seven patients underwent repeat metastasectomy.

Figure 1a and 1b represent the Kaplan-Meier estimate of overall survival for all patients. The median overall survival time was 29 months (IQR: 19-80) from the initiation of treatment for metastases and 26 months (IQR: 11-90) from the metastasectomy. The overall 5-year survival rate from the metastasectomy was 31%. Table 4 shows the results of univariate analysis for the prognostic significance after metastasectomy. Patients undergoing metastasectomy for solitary lung or solitary lymph node metastasis showed a significantly longer survival than the others undergoing metastasectomy (median survival time: 81 months in patients with solitary lung metastasis or solitary lymph node metastasis vs. 19 months in the others, Figure 1c, log-rank test $p = 0.0296$).

DISCUSSION

In 1982, Cowles and colleagues were the fist group to report the surgical outcomes in patients with pulmonary metastasis of UC. [7] They reported a median survival of 5 years for 6 patients following surgical resection for solitary pulmonary metastasis of UC without systemic chemotherapy. Since their report, several investigators have reported survival outcomes after metastasectomy in patients with metatstatic urothelial carcinoma. [3-6, 8-10] For example, Siefker-Radtke et al. reported outcomes for 31 patients undergoing postchemotherapy resection of metastatic lung (77%), brain (7%), skin (3%), and distal LNs (13%). The median OS from the time of surgery was 23 months, and a 33% 5-year OS rate was observed. [3] Lehman and colleagues reported outcomes in 44 patients from 15 different German centers, with distant metastases of UC, who underwent complete resection of all detectable metastases. The median OS from the time of resection was 27 months, and a 28% 5-year OS rate was observed. [8] In the present study, we observed a similar result of a median OS of 26 months after metastasectomy. Our observations further support the possibility of long-term cancer control after metastasectomy.

The appropriate selection of patients for metastasectomy is essential if this approach is to be considered for general use. As described in Methods, in the present cohort, metastasectomy was considered in patients with limited single organ metastasis or in those with residual disease after a major response to systemic chemotherapy.

Regarding the indication of metastasectomy, investigators described a similar opinion in their studies. Siefker-Radtke et al. indicated that their strategy was to consider metastasectomy in patients who responded to chemotherapy and showed recurrence at the initial or a single metastatic site, who had a tumor considered surgically resectable with clear margins, and showed a period of disease stability with no evidence of rapid progression (3-month observation interval between chemotherapy and metastasectomy), although these criteria were used as a general guideline and not an absolute requirement. [3] Lehmann stated that this therapeutic approach remains highly investigational and should only be offered to patients with relapse at a single site or at the initial site following chemotherapy, in whom complete resection of all detectable masses is feasible. [8] Svatek et al. from the MD Anderson Cancer Center reported that their approach was to consider the surgical consolidation of visceral metastases for patients with a tumor at a single distant site who respond well to chemotherapy and show no evidence of rapid progression elsewhere. [10] In the present univariate analysis, metastasectomy for solitary lung or solitary LN metastasis was significantly correlated with long-term cancer control (median survival time: 81 months in patients with solitary lung or solitary LN metastasis vs. 19 months in the other patients, log-rank test $p = 0.0296$). Kanzaki et al. also reported the same trend in the setting of surgical consolidation for lung metastases of UC, where the 5-year survival rate of patients with solitary metastasis was 85.7%, while that of patients with multiple metastases was

20.0%. [11] Taken together with these observations, clinicians should carefully select patients, considering the “stability”, “spread”, and “resectability” of metastatic disease. There was a negative report from Otto et al. in which the median survival time was 7 months after the surgical removal of metastases from bladder cancer refractory to systemic therapy. [12]

As described above, of the 8 patients with the disease in the regional lymph nodes, five patients developed regional LN recurrence after nephroureterectomy (pathological node status at nephroureterectomy, pN0: n=1, pN+: n=1, pNx: n=3) and 1 after radical cystectomy (pathological node status at radical cystectomy, pN0: n=1). The extended LND approach at the time of primary surgery may prevent such recurrence.[13, 14]

Our study was limited by the small sample size, heterogeneous cohort, retrospective nature, and diversity of treatment strategies. For example, our cohort included metastatic urothelial carcinomas derived from bladder and/or upper urinary tract together, which might have different biological behaviors regardless of the same histology. In addition, the timing of metastasectomy was not considered for study inclusion (8 patients received metastasectomy before and 34 patients underwent metastasectomy after systemic chemotherapy). The role of metastasectomy and selection criteria can only be definitively clarified with a well-controlled, prospective, randomized study. However, considering the global difficulty in the accrual of studies

on advanced UC, most information still comes from retrospective analyses. We consider that several important findings were generated by our study.

CONCLUSIONS

Long-term cancer control could be achieved in a subgroup of patients undergoing metastasectomy, especially in patients with solitary lung or solitary LN metastasis.

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Figure Legends

Figure 1

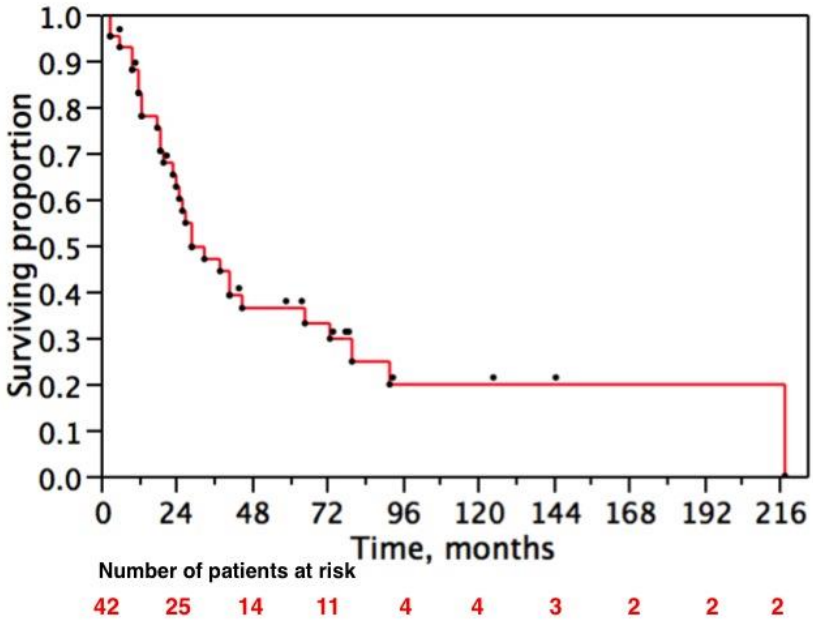
(a) Kaplan-Meier analysis of overall survival from the initiation of treatment for metastatic urothelial carcinoma.

(b) Kaplan-Meier analysis of overall survival from the time of metastasectomy.

(c) Kaplan-Meier analysis of overall survival from the time of metastasectomy for patients with solitary lung or solitary lymph node metastasis (—) compared with that of other patients (—).

Figure 1.

(a)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0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
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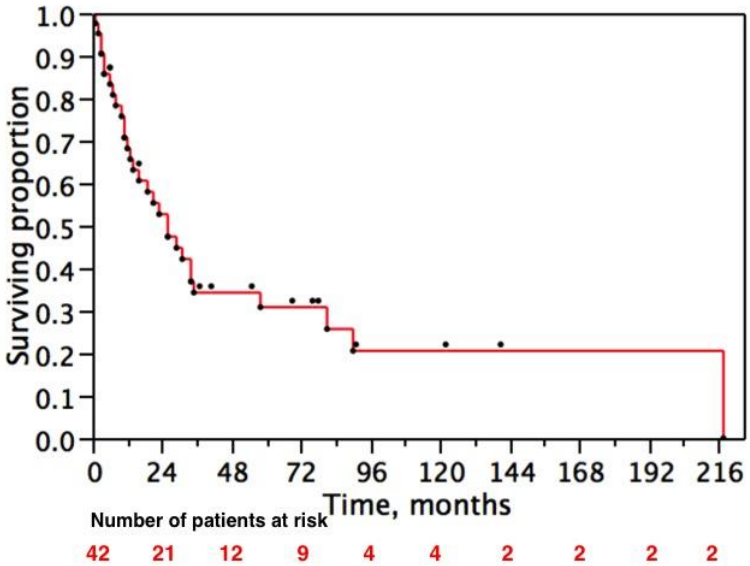
Time, months
Number of patients at risk
42 25 14 11 4 4 3 2 2 2

(b)


Surviving proportion
1.0
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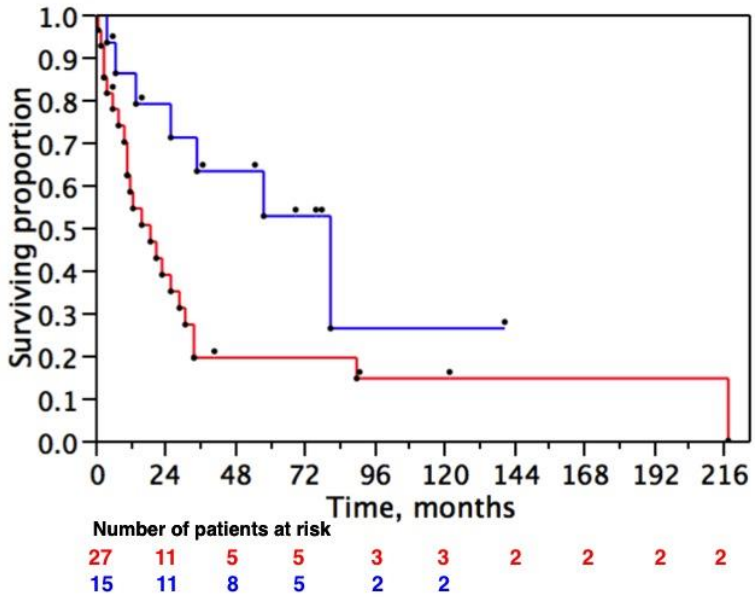
0 24 48 72 96 120 144 168 192 216
Time, months
Number of patients at risk
42 21 12 9 4 4 2 2 2 2

(c)


Surviving proportion
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0.9
0.8
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0.2
0.1
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0
24
48
72
96
120
144
168
192
216
Time, months
Number of patients at risk
27 11 5 5 3 3 2 2 2 2
15 11 8 5 2 2

Table 1. Patients' characteristics.

	n=42
Age, years	median: 67.5 (range: 36-80)
Sex	
male	29
female	13
Primary tumor site	
bladder	21
upper urinary tract	18
both	3
Metastatic sites*	
regional LN recurrecnce	8
distant LNs	12
lung	14
bone	1
liver	2
adrenal gland	1
local recurrence	5
No. of metastasis	
1	23
2 or more	14
uncountable†	5
Disease-free interval between primary surgey and development of metastases, month	median: 16 (range: 0-103)
Treatment course	
metastasectomy after chemotherapy	34
chemotherapy after metastasectomy	7
metastasectomy only	1
Follow-up time, months	media: 28 (range: 3-218)
Follow-up time from metastasectomy, months	median: 22 (range: 1-218)

* There were 3 cases with overlapping metastatic sites.

† Difficult to count due to an aggregated mass of metastatic lymph nodes.

Table 2. Chemotherapy regimens used by the present cohort.

	No. of patients
MVAC (methotrexate, vinblastine, adriamycin, cisplatin)	19
MEC (methotrexate, epirubicin, cisplatin)	9
GC (gemcitabine, cisplatin)	11
Gemcitabine+carboplatin	5
Gemcitabine monotherapy	4
CISCA (cisplatin, cyclophosphamide, adriamycin)	2
Any paclitaxel or docetaxel-including regimen	21
Administration of at least 2 different regimens	23

Table 3. Summary of metastasectomy.

Procedure	
Lymph node dissection	
Retroperitoneal lymph nodes below aortic bifurcation	6
Retroperitoneal lymph nodes above aortic bifurcation	9
Distant lymph nodes	5
	20
Pulmonary resection	12
Exenteration	3
Resection of local recurrence	2
Resection of subcutaneous metastasis	2
Liver resection	1
Amputation of lower leg	1
Adrenalectomy	1
Pathology of metastasis	
Viable cells	30
Necrosis	12

Table 4. Results of univariate analysis of prognostic significance after metastasectomy.

Factor	No. of patients	Median survival time, months (95%CI)	*P*-value
Sex			
Male	29	26 (11-34)	
Female	13	31 (8-not reached)	0.2064
Age, years			
<68	21	21 (10-90)	
≥68	21	29 (13-81)	0.9988
Primary site			
Bladder only	21	21 (10-not reached)	
Others	21	34 (12-81)	0.9713
DFI between primary surgey and development of metastases			
<12	17	23 (11-58)	
≥12	25	26 (10-81)	0.9077
<24	30	26 (13-58)	
≥24	12	26 (3-not reached)	
Upfront chemotherapy before metastasectomy			
Yes	34	26 (13-35)	
No	8	29 (1-not reached)	0.9498
Metastatic sites			
Lymph node only	19	26 (13-not reached)	
Lung only	12	34 (13-81)	
Others	11	11 (3-29)	0.2858
Lymph node or lung	32	31 (16-81)	
Others	10	11 (1-29)	0.1933
Solitary lymph node or solitary lung metastasis	15	81 (14-not reached)	
Others	27	19 (10-29)	0.0296
		DFI=disease-free interval	