(10.5%) experienced hormone-refractory biochemical progression. Seven patients experienced clinical recurrence and received salvage radiation therapy to clinically recurrent foci. Three (2.9%) patients died of prostate cancer and eight (7.6%) died of other causes. The 5- and 10-year cancer-specific survival rates were 98.1 and 96.3%, respectively. The 5- and 10-year hormone-refractory biochemical progression-free survival rates were 94.3 and 88.3%, with 5- and 10-year clinical recurrence-free survival rates of 96.0 and 93.0%, respectively. The 10-year estimated overall survival rate was 85.7%.

Table 2 shows the hormone-refractory biochemical progression-free survival rates calculated from Kaplan-Meier graphs, according to each clinicopathologic parameter. Univariate analyses using Cox proportional hazard models indicated that higher clinical stage (p = 0.013), higher Gleason score at biopsy (p = 0.001), seminal vesicle invasion (p = 0.003) and microlymphatic invasion (p = 0.006) were predictive factors for hormone-refractory biochemical progression (Table 2). Multivariate analyses identified Gleason score at biopsy and (p = 0.027) seminal vesicle invasion (p = 0.030) as independent prognostic factors for hormone-refractory biochemical progression (Table 2).

Table 1 Patient characteristics (n = 105)

Parameter		*n*	(%)
Age, years (median 67.0)	<65	37	35.2
	≥65	68	64.8
PSA, ng/ml [median 14.3 (2.4 – 160.7)]	<10	35	33.3
	10 ~ 20<	36	34.3
	20 ~ 50<	23	21.9
	≥50	11	10.5
Clinical stage	T1	20	19.0
	T2	25	23.8
	T3	59	56.2
	T4	1	1.0
Gleason score at biopsy	5 ~ 6	34	32.4
	7	33	31.4
	≥8	38	36.2
Seminal vesicle invasion	–	63	60.0
	+	42	40.0
Surgical margin	–	12	11.4
	+	93	88.6
Microlymphatic invasion	–	72	68.6
	+	33	31.4
Microvascular invasion	–	54	51.4
	+	51	48.6
Perineural invasion	–	11	10.5
	+	94	89.5
Gleason score at prostatectomy	5 ~ 6	16	15.2
	7	54	51.4
	≥8	35	33.3

Discussion

Despite widespread use of PSA measurement, pT3N0M0 prostate cancer still occurs in 25–58% of clinical T1 and T2 prostate cancer patients [1-4]. In the current study, about half of the patients (43%) were also understaged preoperatively as having organ-confined disease. Although pT3N0M0 prostate cancer is not rare, there have been few reports of treatment outcomes in these patients. The optimal postsurgical management for patients with such unfavorable pathological features remains questionable. We therefore analyzed clinical data from patients with pT3N0M0 prostate cancer to obtain detailed information and long-term outcome data.

The patients in this study achieved 5- and 10-year cancer-specific survival rates of 98.1 and 96.3%, respectively, and 5- and 10-year hormone-refractory biochemical progression-free survival rates of 94.3 and 88.3%, respectively. In a previous study, Inagaki et al. reported 1- and 3-year biochemical progression-free survival rates of 53.7 and 34.1% in 106 patients with pT3N0M0 prostate cancer treated with radical prostatectomy alone, after a mean follow-up of 1.5 years [10]. Delongchamps et al. and Briganti et al. reported 5-year biochemical progression-free survival rates of 48 and 45.0% in 147 and 500 patients with pT3N0M0 prostate cancer, respectively, treated with radical prostatectomy alone, after median follow-up periods of 5 and 3.9 years [11,12]. Thompson et al. reported 10-year metastasis-free survival rates and overall survival rates of 61 and 66% in 211 patients with pT3N0M0 prostate cancer treated with radical prostatectomy, even after salvage radiotherapy [5]. Single-modality therapy involving surgery alone might be of limited use in patients with stage pT3N0M0 prostate cancer, and a multimodal approach may be more beneficial. Three studies found that adjuvant radiotherapy after radical prostatectomy reduced the risk of subsequent biochemical recurrence in randomized clinical trials [5-7]. Thompson et al. reported a survival benefit of adjuvant radiotherapy, with a 10-year estimated survival rate of 74% in 214 patients with pT2-3 N0 prostate cancer treated with adjuvant radiotherapy, compared with 66% in 211 cases treated with surgery alone, after median follow-up period of 12.5 years [5,6]. This cohort included patients with pT3N0 and pT2N0 with positive surgical margins, and patients were allowed to receive salvage hormonal therapy during the follow-up period. Regarding the combination of radical prostatectomy and adjuvant hormonal therapy, Dorff et al. reported favorable outcomes in an interim report of a prospective randomized trial of 481

Table 2 Hormone refractory biochemical progression-free survival according to each clinicopathological parameter

Univariate and multivariate analyses for hormone refractory biochemical-progression free survival rates									
Parameter		Hormone refractory biochemical progression-fee survival rates		Univariate analysis			Multiivariate analyses		
		5 years	10 years	HR†	95% CI††	*p*	HR†	95% CI††	*p*
Age, years (median 67.0)	<65	94.6	89.9						
	≥65	94.1	87.6			0.687			
PSA, mg/ml [median 15.1 (3.5–160.7)]	<10	97.1	97.1	1					
	10-20<	88.9	80.8	6.18	1.1, 116.8	0.043			
	20-50<	100.0	100.0	0.0	0,.	0.315			
	≥50	90.9	60.6	12.9	1.9, 254.0	0.008			
Clinical stage	T1,2	100.0, 100.0	100.0, 88.9	1			1		
	T3~4	90.0	84.8	7.47	1.4, 137.1	0.013*	3.65	0.7, 68.6	0.161
Gleason score at biopsy	5~7	98.5	98.3	1			1		
	≥8	86.8	70.3	8.38	2.2, 55.0	0.001*	4.73	1.2, 31.7	0.027*
Seminal vesicle invasion	−	98.4	98.4	1			1		
	+	88.1	73.1	7.42	1.9, 48.7	0.003*	4.53	1.1, 30.1	0.030*
Surgical margin	−	100.0	100.0						
	+	93.6	86.7			0.183			
Microlymphatic invasion	−	97.2	95.0	1			1		
	+	87.9	74.4	5.33	1.5, 24.7	0.006*	2.18	0.9, 12.8	0.140
Microvascular invasion	−	96.3	90.5						
	+	92.2	85.6			0.468			
Perineural invasion	−	100.0	100.0						
	+	93.6	86.7			0.242			
Gleason score at prostatectomy	5–7	95.7	89.6						
	≥8	91.4	71.4			0.114			

†Hazard ratio by Cox proportional-hazard models
††Confidence interval

patients with pT2-3 N0-1 prostate cancer, including 61% of T3 and 16% of N1 patients [14]. Although longer observation periods are awaited, they reported 5-year biochemical progression-free and overall survival rates of 92.5 and 95.5%, respectively, in patients treated with adjuvant hormonal therapy consisting of goserelin and bicalutamide, after a median observation period of 4.4 years. Some studies reported encouraging results in more challenging patients with more severe pathological stages. Spahn et al. reported on 173 patients with pT3N0-1 tumors, including 43.3% of N1, who had undergone prostatectomy [15]. They reported an 8-year cancer-specific survival rate of 86.3% and an overall survival rate of 77.3% after a median observation period of 5.7 years in patients treated with adjuvant hormonal therapy comprising an LHRH analog with or without flutamide. Siddiqui et al. reported an advantage of adjuvant hormonal therapy with an LHRH analog, bilateral orchiectomy, or anti-androgens in a retrospective study of 191 pT3bN0M0 prostate cancer patients [9]. They found that, although the overall survival rate was similar to that in the matched control cohort, the biochemical progression-free and cancer specific survival rates were improved, with 10-year biochemical progression-free and cancer-specific survival rates of 60 and 94%, respectively, after a median follow-up of 10 years [9]. In accordance with this previous report, subgroup analyses of pT3bN0 patients in the current study demonstrated excellent outcomes, with 5- and 10-year cancer-specific survival rates of 95.1 and 90.8%, respectively. These results indicate that the combination of radical prostatectomy and adjuvant androgen deprivation therapy may produce excellent outcomes in patients with pT3N0M0 prostate cancer.

The current study achieved a 10-year cancer-specific survival rate of 96.3% and a 10-year estimated overall survival rate of 85.7% after a median follow-up period of 8.2 years. These survival rates were higher than those in previous reports, which may require an explanation. Immediate commencement of adjuvant androgen deprivation therapy after radical prostatectomy, and its comparatively long duration (at least 5 years), may have contributed to the beneficial effect. Supportive treatment strategies, such as prompt adjustment or alteration of hormonal therapy

in the event of a slight increase in PSA levels, may also have improved the treatment efficacy. It is also possible that Japanese men are more sensitive than other ethnic groups to hormonal therapy after radical prostatectomy. Akaza et al. reported 5- and 10-year cancer-specific survival rates of 90 and 69%, respectively, in 68 Japanese patients with clinical T3N0M0 tumors who were treated with hormonal therapy alone [16]. However, Ueno et al. reported 5- and 8-year progression-free survival rates of 59.8 and 48.1%, respectively, in 245 Japanese patients with clinical T3N0M0 cancers treated with combined androgen blockade (63.5%) or castration [17].

The Asia Consensus Statement 2013 in the NCCN Clinical Practice Guidelines in Prostate Cancer states that androgen deprivation is a candidate treatment option for post-radical prostatectomy recurrence in Asian patients negative for distant metastasis. The results of the current study suggest that a treatment strategy consisting of radical prostatectomy and immediate adjuvant androgen deprivation therapy may offer favorable cancer control in Japanese patients with pT3N0M0 prostate cancer. This strategy was also feasible and well tolerated. Immediate adjuvant androgen deprivation therapy thus represents an attractive option for patients with pT3N0M0 prostate cancer.

Few studies have reported on prognostic factors in patients with pT3 prostate cancer. The current study found that higher clinical stage, higher Gleason score at biopsy, and seminal vesicle and microlymphatic invasion were unfavorable factors, and multivariate analyses identified seminal vesicle invasion and Gleason score at biopsy as independent prognostic factors for hormone-refractory biochemical progression. Interestingly, no patients with clinical T1 tumors (n = 20), negative surgical margin (n = 12), or negative perineural invasion (n = 11) experienced hormone-refractory biochemical progression. In partial agreement with our results, previous studies identified Gleason score, PSA, seminal vesicle invasion and lymphovascular invasion as prognostic predictors in patients with pT3N0 stage prostate cancer undergoing radical prostatectomy [10-13].

The limitations of this study included its retrospective nature and the relatively small sample size. Further investigations, including prospective studies, are needed to compare the additive effects of multimodal therapies in patients with pT3N0, to allow the better selection of patient populations most likely to benefit from treatment. The current study indicated a significant hazard ratio for seminal vesicle invasion or with higher Gleason score at biopsy, suggesting that patients with pT3b or with higher Gleason score may be the leading candidates for such studies.

These findings were based on pathologic results. The majority of the patients included in the study were considered to have lower grade and stage at diagnosis, and T3N0 was only diagnosed after radical prostatectomy. These results suggest that radical prostatectomy is a reasonable option for the initial treatment of prostate cancer, and allow for the better selection of patients who will require additional therapies.

Conclusions

Radical prostatectomy with immediate adjuvant androgen deprivation therapy may be a valid treatment option for patients with pT3N0 prostate cancer.

Competing interests

The authors declared that they have no competing interests.

Authors' contributions

YTS made substantial contributions to conception and design, analysis and interpretation of data and was involved in drafting the manuscript. HF made substantial contributions to conception and design, analysis and interpretation of data and was involved in revising it critically for important intellectual content. MS, TF, TN and HN made substantial contributions to acquisition of data. HK made substantial contributions to conception and design and helped to draft the manuscript. TM and MF evaluated the pathological specimens in a manner blinded to the clinical information. YH conceived and supervised the study, helped to draft the manuscript and was involved in revising it critically for important intellectual content. All authors read and approved the final manuscript.

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Original Article

Prognostic Factors for Metastatic Urothelial Carcinoma Undergoing Cisplatin-based Salvage Chemotherapy

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Objective: To assess the clinicopathologic factors influencing survival in patients with metastatic urothelial carcinoma undergoing salvage chemotherapy.
Methods: A retrospective review was conducted on cases of metastatic urothelial carcinoma who underwent cisplatin-based salvage chemotherapy at our institution between April 2003 and July 2011. The association of various clinicopathologic factors with survival was assessed. Survival curves were constructed by the Kaplan–Meier method. A log-rank test for univariate analysis and a Cox proportional hazards model for multivariate analysis were used.
Results: Eighty-three cases were identified in the study. Among them, 64 patients were dead during the follow-up. The median survival was 14.6 months. Multivariate analysis evaluating variables at the start of chemotherapy demonstrated that liver metastasis, performance status score $\geq$2 and leukocyte counts $\geq$8000/μl were significant predictive factors for poor outcome. Based on these three pre-induction variables, a risk model predicting the overall survival from the initiation of chemotherapy was constructed, which classified patients into three groups with significantly different overall survival ($P < 0.0001$). Additionally, factors after induction of chemotherapy were studied, and poor response for chemotherapy and absence of focal treatment for metastatic lesions were also significantly associated with poorer survival.
Conclusions: Liver metastasis, poor performance status and higher leukocyte counts were independent poor prognostic indicators for metastatic urothelial carcinoma. Our risk classification enables an accurate prediction of survival that can be useful in deciding which patients are likely to benefit from salvage chemotherapy.

Key words: bladder cancer – chemotherapy – metastasectomy – prognostic factor – urothelial carcinoma

INTRODUCTION

In 2008, more than 380 000 patients worldwide were estimated to be diagnosed with urothelial carcinoma (UC) resulting in more than 150 000 deaths (1). In Japan, UC is the sixth most commonly diagnosed cancer and accounts for ~7000 deaths annually (2). Metastatic UC is known to be intractable and rarely has the median survival of untreated cases exceeding 3–6 months (3). Even after the introduction of cisplatin-based chemotherapy, the median survival still remains at ~15 months (4,5). Although a few cases achieve a long-term survival, studies are lacking to evaluate the predictive and prognostic factors in metastatic UC. The present retrospective study was conducted to assess the clinicopathologic factors influencing survival in cases with metastatic UC undergoing salvage chemotherapy.

PATIENTS AND METHODS

Cases of metastatic UC who underwent cisplatin-based salvage chemotherapy at our institution between April 2003 and July 2011 were reviewed. The chemotherapy included

Table 1. Patient characteristics

	n	Range
Total no. of patients	83	
Sex		
Male	69	
Female	14	
Age (years)	Median 67	36–82
Initial ECOG PS score		
0	72	
1	8	
2	2	
3	1	
Primary site		
Bladder	36	
Upper urinary tract	40	
Both	7	
Resection of primary site		
Yes	59	
No	24	
Preceding adjuvant chemotherapy		
Yes	23	
No	60	
First-line regimen		
MVAC	30	
GC	48	
DIP (docetacel, ifosfamide, cisplatin)	5	
Metastatic site		
Lung	33	
Bone	18	
Liver	10	
Lymph node	61	
Lymph node alone	27	
Baseline laboratory data		
Leukocyte counts, cells/μl	Median 6900	3100–25 200
Hemoglobin, g/dl	Median 11.8	7.2–16.8
Lactate dehydrogenase, IU/l	Median 222	108–647
Alkaline phosphatase, IU/l	Median 280	85–2286
C-reactive protein, mg/dl	Median 0.39	0.03–16.33
eGFR, ml/min	Median 53	29–170
Focal treatment for metastatic lesions		
Yes	33	
No	50	
Follow-up, months	Median 14.6	11.6–21.5

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; GC, gemcitabine/cisplatin; DIP, docetaxel/ifosfamide/cisplatin; eGFR, estimated glomerular filtration rate.

three regimens: MVAC (methotrexate/vinblastine/doxorubicin/cisplatin), GC (gemcitabine/cisplatin) and DIP (docetaxel/ifosfamide/cisplatin) (6). All patients underwent evaluations that included routine blood test, chest X-ray and CT scan every 1–6 months. The charts were reviewed thoroughly and the status of each patient was assessed by office visit and/or phone call to the patient. Follow-up information was obtained as of September 2012.

Clinicopathologic parameters were assessed at the start of chemotherapy and, additionally, factors after induction of chemotherapy were also analyzed. Estimated glomerular filtration rate was calculated using the revised formula for Japanese (7). Focal treatment for metastatic lesions was defined as either metastasectomy or radiotherapy intended to eliminate the metastatic site of more than 50 Gray. The maximum effect of chemotherapy was evaluated according to the RECIST guideline (8). The overall survival was calculated from the initiation of chemotherapy to death or last follow-up. Survival curves were drawn using the Kaplan–Meier method. Log-rank test and Cox proportional hazards model were used for univariate and multivariate analyses. All statistical analyses were carried out using JMP version 9.0.2 (SAS Institute, Cary, NC, USA). A P value of <0.05 was considered significant.

RESULTS

Eighty-three cases were identified in the current study. Table 1 lists the clinical and pathologic characteristics of the patients. There were 69 males and 14 females with a median age of 67 years (range: 36–82 years) at the start of chemotherapy. Primary tumor sites were bladder in 36 patients, upper urinary tract in 40 patients and both in 7 patients. First-line regimens were MVAC in 30 patients, GC in 48 patients and DIP in 5 patients. Among them 64 (77.1%) were dead during the follow-up. The median survival time was 14.6 months (95% confidence interval 11.6–21.5 months, Fig. 1).

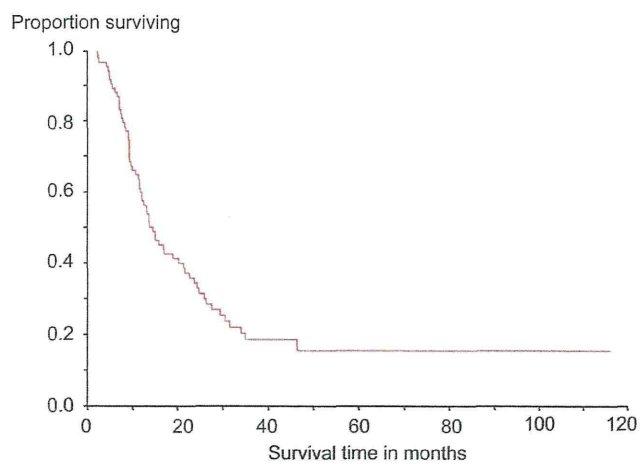


Figure 1. Kaplan–Meier analysis of overall survival after induction of salvage chemotherapy.

Table 2. Results of univariate analysis

	No. of patients	Median survival, months (95% CI)	*P* value
Sex			
Male	69	15.1 (11.8–21.7)	0.7598
Female	14	8.5 (5.6–29.5)	
Age, years			
<67[a]	38	21.7 (13.3–30.6)	0.0317*
≥67[a]	45	11.6 (8.5–15.1)	
Initial ECOG PS score			
≤1	80	15.1 (12.1–21.7)	0.0002*
≥2	3	7.7 (2.6–8)	
Primary site			
Bladder only	36	21.5 (12.6–26.4)	0.3281
Others	47	12.1 (9.3–17.1)	
Resection of primary site			
Yes	59	17.1 (13.2–24.4)	0.075
No	24	9.3 (7.2–15.1)	
Prior adjuvant chemotherapy			
Yes	23	13.7 (9.3–26.4)	0.7864
No	60	14.6 (11.4–21.7)	
Visceral metastasis			
Yes	49	13.2 (10.7–15.1)	0.0290*
No	34	24.8 (9.7–34.1)	
Lung metastasis			
Yes	33	13.2 (10–21.5)	0.4827
No	50	15.1 (11.4–24.8)	
Bone metastasis			
Yes	18	11.5 (6.7–13.8)	0.0180*
No	65	17 (12.1–24.8)	
Liver metastasis			
Yes	10	5.45 (2.3–7.2)	<0.0001*
No	73	17 (13.3–24.4)	
Lymph node metastasis			
Yes	61	15.9 (11.6–23.8)	0.5443
No	22	12.6 (7.5–21.5)	
Number of metastatic organs			
Single	44	21.5 (12.2–29.5)	0.0310*
Multiple	39	11.8 (9.3–15.9)	
Lymph node metastasis alone			
Yes	27	24.8 (12.1–.)	0.0162*
No	56	12.6 (9.7–15.1)	
Leukocyte counts, cells/μl			
<8000[b]	64	17.1 (13.2–26.4)	<0.0001*
≥8000[b]	19	9.3 (5.6–15.1)	
Hemoglobin, g/dl			
<13 Male (female 12)	63	13.7 (10–21.5)	0.2757
≥13 Male (female 12)	20	19.1 (11.6–34.1)	
Lactate dehydrogenase, IU/l			
<237[a]	57	15.9 (12.2–24.4)	0.0857
≥237[a]	26	11.95 (7.2–19.1)	
Alkaline phosphatase, IU/l			
<359[a]	77	15.1 (12.1–21.7)	0.1688
≥359[a]	6	8.15 (2.3–.)	
C-reactive protein, mg/dl			
<0.3[b]	35	21.5 (12.2–31.6)	0.0152*
≥0.3[b]	48	12.2 (9.1–15.1)	
eGFR, ml/min			
<60	48	14.15 (9.7–22.7)	0.6798
≥60	35	15.1 (10.7–26)	
Maximal effect of chemotherapy			
CR, PR	34	27.6 (15.9–.)	<0.0001*
SD, PD	49	11.6 (9.1–13.7)	
Cycles of chemotherapy			
<6	38	9.3 (7.2–12.2)	0.0025*
≥6	45	21.7 (15.9–26.4)	
Focal treatment for metastatic lesions			
Yes	33	22.7 (13.7–30.6)	0.0199*
No	50	12.15 (9.3–15.1)	

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
[a]Median.
[b]Facility criteria.
*Statistically significant.

Univariate analysis of the parameters at the start of chemotherapy showed that age ≥67 years, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score ≥2, visceral metastasis, bone metastasis, liver metastasis, multiple organ metastases, metastasis to other site than lymph node, leukocyte counts ≥8000/μl and serum C-reactive protein (CRP, ≥0.3 mg/dl) were associated with poor outcome (Table 2).

A Cox proportional hazards model demonstrated that liver metastasis [hazard ratio (HR) 12.65, $P < 0.0001$], ECOG PS (HR 7.099, $P = 0.0182$) and leukocyte counts (HR 2.890, $P = 0.0019$) were independent significant predictors (Table 3).

A risk model was also constructed using the three pre-induction risk factors found in this multivariate analysis: liver metastasis, ECOG PS score ≥2 and leukocyte counts ≥8000/μl. Each patient was then assigned to one of the three risk groups: those with zero risk factor (favorable risk, $n = 57$,

Table 3. Multivariate analyses of factors after the induction of salvage chemotherapy on Cox proportional hazard model

	HR (95% CI)	*P* value
Age, years		
<67[a]	Reference	
≥67[a]	1.393 (0.815–2.400)	0.2252
Initial ECOG PS score		
≤1	Reference	
≥2	7.099 (1.470–26.39)	0.0182*
Bone metastasis		
No	Reference	
Yes	1.573 (0.813–2.957)	0.1742
Liver metastasis		
No	Reference	
Yes	12.65 (4.718–33.48)	<0.0001*
Number of metastatic organs		
Single	Reference	
Multiple	0.865 (0.450–1.732)	0.6721
Lymph node metastasis alone		
Yes	Reference	
No	1.630 (0.751–3.496)	0.2127
Leukocyte counts, cells/μl		
<8000[b]	Reference	
≥8000[b]	2.890 (1.496–5.473)	0.0019*
C-reactive protein, mg/dl		
<0.3[b]	Reference	
≥0.3[b]	1.010 (0.550–1.859)	0.9738

HR, hazard ratio.
[a]Median.
[b]Facility criteria.
*Statistically significant.

68.7%), those with one (intermediate risk, $n = 21$, 25.3%) and those with two or three (poor risk, $n = 5$, 6.0%). The median overall survival was 22.7, 9.3 and 4.9 months in the favorable, intermediate and poor risk groups, respectively. There was a significant difference in the survival profiles of the three risk groups ($P < 0.0001$, Fig. 2).

Additionally, factors after induction of chemotherapy were also evaluated, and multivariate analysis revealed that a poor response for chemotherapy (stable disease or progressive disease, HR 2.778, $P = 0.0010$) and the absence of focal treatment for metastatic lesions (HR 1.795, $P = 0.0420$) were also significantly associated with poorer survival as well as the previously mentioned pre-induction factors (Table 4).

DISCUSSION

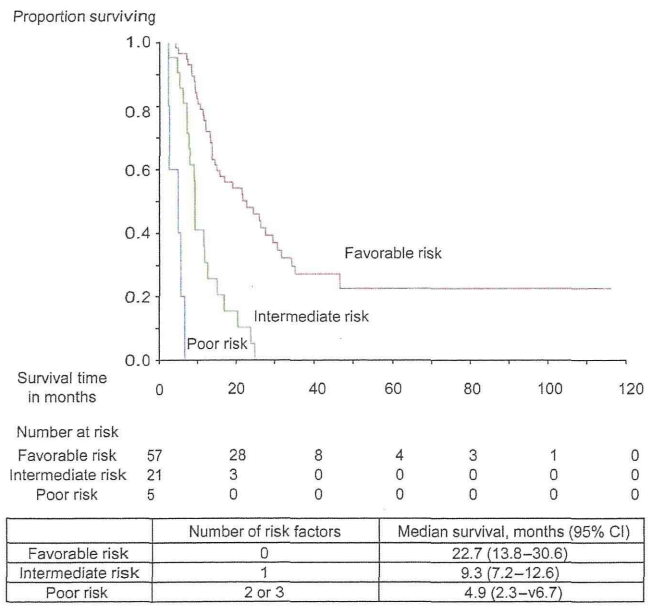
Several prognostic factors have been reported among patients who underwent cisplatin-based chemotherapy. Analyzing 203 unresectable or metastatic cases who underwent MVAC chemotherapy, Bajorin et al. (9) found that Karnofsky Performance Status (KPS) <80% and the presence of visceral metastasis were independent prognostic factors. The median survival time for patients who had zero, one or two risk factors were 33, 13.4 and 9.3 months, respectively, and this classification clearly separated the survival of these groups ($P = 0.0001$). Similarly, von der Maase et al. (5) reported that KPS <80%, presence of metastatic lesion, elevated alkaline phosphatase (ALP) level, number of disease sites (>3) and the presence of visceral metastases were significantly associated with poor overall survival among 405 advanced or metastatic cases with MVAC chemotherapy or GC chemotherapy. More recently, Abe et al. (10) showed that five or more chemotherapy cycles, absence of liver, bone and local recurrence, and resection of metastasis as independent significant predictors in a retrospective analysis of 48 patients with metastatic UC who underwent systemic chemotherapy.

Along with these reports, our study revealed that visceral metastasis was one of the poor prognostic factors and implied that liver metastasis was the most important predictor of poor survival among all metastatic sites, while lung metastasis was not. All 10 patients with liver metastasis died within 9.3 months from diagnosis. The median survival of eight patients who did not respond to chemotherapy was only 4.6 months (2.3–7.2 months), and even the other two patients who achieved a partial response survived only for 9.1 and 9.3 months, respectively.

Although performance status (PS) was also detected as statistically significant in our study, there were only three patients whose ECOG PS score was 2 or more, which substantially corresponds to KPS <80%. Moreover, as Abe et al. (10) had already mentioned, we also need to interpret this result carefully because PS could strongly correlate with several post-chemotherapeutic factors including the total number of chemotherapy and/or indication of metastasectomy (10). However, as a predictor, that is, excluding post-chemotherapeutic factors, PS remains an important independent factor.

Thus far, there have been few studies which investigated a variety of laboratory parameters. In addition to serum ALP reported by von der Maase et al. (5), the recent report by Nakagawa et al. (11) demonstrated that serum CRP and serum lactate dehydrogenase (LDH) levels were independent predictors of poorer survival, analyzing 114 patients who were treated with radical cystectomy for urothelial bladder carcinoma and subsequently developed metastases (11). Our study has shown that leukocyte counts ≥8000/μl was a significant risk factor on multivariate analysis, while the elevation of ALP, LDH or CRP was not. Although such inflammatory markers are likely to be associated with survival in various cancers, the importance of these markers in urinary tract cancer remains to be established. Therefore, further investigation is needed for confirmation.

Although advanced T stage (≥T3) was a significant factor on the univariate analysis (log-rank test, $P = 0.0125$*), we



	Number of risk factors	Median survival, months (95% CI)
Favorable risk	0	22.7 (13.8–30.6)
Intermediate risk	1	9.3 (7.2–12.6)
Poor risk	2 or 3	4.9 (2.3–v6.7)

Figure 2. The overall survival of the patients with favorable, intermediate and poor risk. There was a significant difference in the survival profiles of the three risk groups, of the favorable vs. intermediate risk groups, and of the intermediate vs. poor risk groups (each log-rank test, $P < 0.0001$).

excluded T stage from this study, because for each T stage, there are some clinical and prognostic differences between upper urinary tract cancer and bladder cancer (12).

Response to chemotherapy and focal treatment for metastatic lesions were also significant factors, but not predictive parameters which can only be determined after initiation of treatment. For the past 10 years, clinical evidence has accumulated suggesting the efficacy of multimodal treatment including metastasectomy. Lehmann et al. (13) showed a overall 5-year survival rate of 28% among 44 patients undergoing complete metastasectomy for UC. On the other hand, based on the observation of 276 cases who received cisplatin-based chemotherapy, Herr et al. recommended that cases with a complete or partial response to chemotherapy and cases with limited nodal or a solitary visceral metastasis are most likely to benefit from metastasectomy. The study also concluded that surgery should be avoided in cases with multiple liver metastases, as well as metastases involving more than one visceral site or abdominal organ, or bone metastases, especially involving the pelvis or axial skeleton (14,15). More recently, Nakagawa et al. (11) showed that patients with solitary lung metastasis, long duration from radical surgery to recurrence, no neoadjuvant/adjuvant chemotherapy, no symptom and low CRP level were most likely to benefit from metastasectomy. Our study also showed that focal treatment for metastatic lesions was a statistically significant factor for better outcome. Multi-modal treatment including metastasectomy should be considered when possible.

Along with similar previous studies, the limitation of our study is a retrospective analysis of a limited number of cases in a single institution. Confirmatory studies with larger populations may be required. In addition, our model was fit to our sample but has not been validated externally.

In conclusion, liver metastasis, poor PS and higher leukocyte counts were independent poor prognostic indicators for metastatic UC. Our risk classification (zero, one and two or three risks) enables an accurate prediction of survival which

Table 4. Multivariate analyses including factors after inducing salvage chemotherapy on Cox proportional hazard model

	HR (95% CI)	*P* value
Age, years		
<67[a]	Reference	
≥67[a]	1.140 (0.654–2.001)	0.6439
Initial ECOG PS score		
≤1	Reference	
≥2	6.696 (1.237–29.82)	0.0294*
Bone metastasis		
No	Reference	
Yes	0.946 (0.470–1.853)	0.8732
Liver metastasis		
No	Reference	
Yes	11.62 (3.855–34.80)	<0.0001*
Number of metastatic organs		
Single	Reference	
Multiple	1.462 (0.721–3.094)	0.2973
Lymph node metastasis alone		
Yes	Reference	
No	1.237 (0.569–2.658)	0.5872
Leukocyte counts, cells/μl		
<8000[b]	Reference	
≥8000[b]	3.232 (1.577–6.496)	0.0016*
C-reactive protein, mg/dl		
<0.3[b]	Reference	
≥0.3[b]	0.660 (0.332–1.307)	0.2330
Maximal effect of chemotherapy		
CR, PR	Reference	
SD, PD	2.778 (1.504–5.299)	0.0010*
Cycles of chemotherapy		
≥6	Reference	
<6	1.946 (0.994–3.831)	0.0520
Focal treatment for metastatic lesions		
Yes	Reference	
No	1.795 (1.021–3.226)	0.0420*

[a]Median.
[b]Facility criteria.
*Statistically significant.

can be useful in deciding which patients are likely to benefit from salvage chemotherapy.

Conflict of interest statement

Prof. Yukio Homma is serving as a member of the advisory board for a scientific meeting that Nippon Kayaku holds.

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