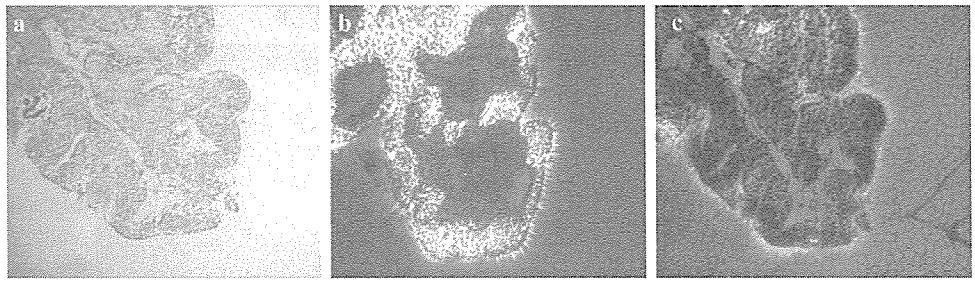

FIG. 2. *In situ* gelatinolytic activity in bladder cancer tissue. *a*, frozen section stained with hematoxylin and eosin. *b*, *in situ* gelatinolytic activity. *c*, suppression of *in situ* gelatinolytic activity by MMP inhibitor 1,10-phenanthroline. Most activity in cancer tissue was suppressed. Reduced from ×40.

TABLE 1. *FIZ patterns and clinicopathological factors in bladder cancer*

	Total No. Pts	No. FIZ Pattern				p Value
		A	B	C	D	
No. pts		0	11	5	9	
Tumor stage:						
pTa	5	–	4	1	–	0.0284
pT1	10	–	6	2	2	
pT2a	4	–	2	2	–	
pT2b	1	–	–	–	1	
pT3	3	–	–	–	3	
pT4	2	–	–	–	2	
Local recurrence:						
Neg	15	–	6	6	4	0.563
Pos	10	–	6	8	8	
Grade:						
G1	3	–	2	–	1	0.029
G2	13	–	8	3	2	
G3	9	–	1	2	6	
Vessel invasion:						
Neg	14	–	9	3	2	0.006
Pos	11	–	2	2	7	

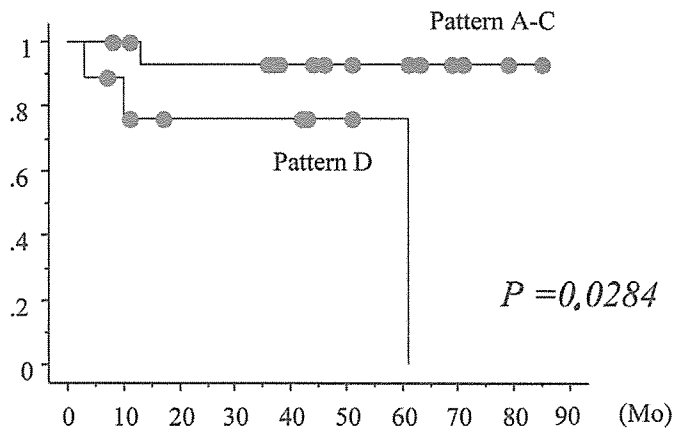

FIG. 3. Kaplan-Meier cause specific survival curves according to FIZ pattern. Diffuse groups (pattern D) showed worse cause specific survival than nondiffuse groups (patterns A to C).

DISCUSSION

Bladder cancer can be dichotomized according to distinct biological activity and prognosis as low grade noninvasive tumors and high grade invasive tumors. Briefly, bladder cancer consists of noninvasive tumors (less than T1) in 75% to 85% of patients and invasive (T2 or greater) or metastatic tumors in 15% to 25%. More than 70% of patients with noninvasive cancer have 1 or more recurrences after initial treatment. Primary therapy is based on clinical staging and morphological assessment. However, tumors may behave differently despite morphological similarity. It is of great importance to identify patients who are likely to have recurrent or progressive disease. In addition to conventional prognostic factors such as stage and grade, FIZ may be a new prognostic marker with which to identify patients at risk for future progression.

MMP-2 and MMP-9 have the ability to degrade type IV collagen and they are believed to have an important role in destruction of the basement membrane. MMP activity is regulated by 2 mechanisms. 1) The secreted latent proenzyme forms of MMPs must undergo proteolytic activasion. 2) Ubiquitous tissue inhibitor of metalloproteinase (TIMP) can interfere with MMP proteolytic activation and enzymatic activity.

Davies et al measured levels of MMP-2 and MMP-9 in 42 TCC tissues and 7 normal bladder tissues using quantitative GZG.[10] The levels of MMP-9 and active MMP-2 correlated with higher tumor grade and invasion, suggesting the prognostic value of MMPs for carcinoma of the bladder. Kanayama et al investigated the expression of MMP-2, TIMP-2 and MT1-MMP by RT-PCR in 41 TCC tissues.[11] They found that MMP-2 and TIMP-2 expression was significantly higher in muscle invasive than in superficial tumors and high MMP-2, TIMP-2 and MT1-MMP expression was significantly associated with decreased survival. In addition, Gerhards et al used GZG to measure MMP-2 and MMP-9 excretion in the urine of patients with bladder cancer to evaluate their diagnostic clinical validity.[12] They found that urinary excretion of MMP-2 and MMP-9 was associated with a high stage and grade of bladder cancer.

These studies resulted in the detection of MMP/TIMP proteins or mRNA in bladder carcinoma tissues. However, GZG and RT-PCR cannot directly detect *in situ* gelatinolytic activity. In contrast, FIZ enables us to detect *in situ* gelatinolytic activity. To our knowledge the current study is the first to examine *in situ* gelatinolytic activity in relation to clinicopathologic factors in bladder carcinoma.

Our results show that MMP-2 activity but not MMP-9 activity correlates with the gelatinolytic activity of bladder

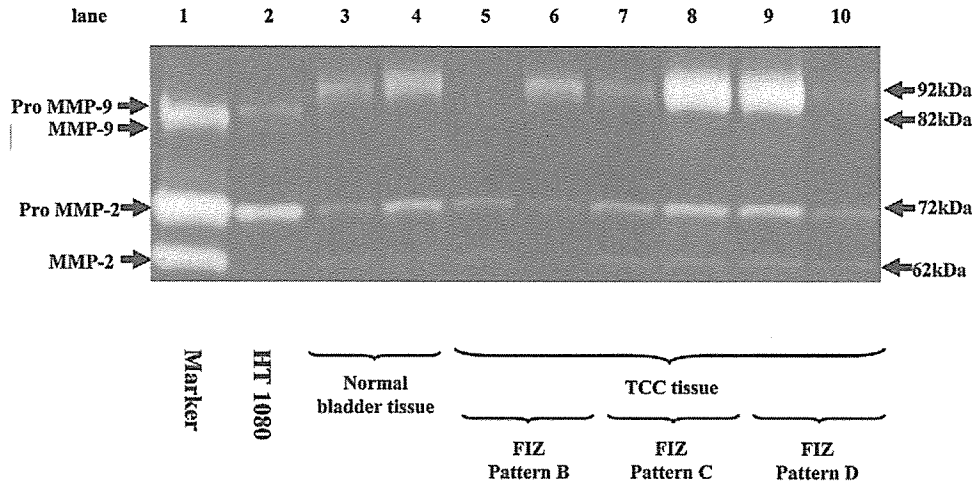

FIG. 4. MMP profiles of representative bladder cancer cases with different *in situ* gelatinolysis patterns on GMZ. ProMMP-2, MMP-2 and proMMP-9 were detected in all cases, while MMP-9 expression was not seen.

TABLE 2. *FIZ patterns, and expression of pro and activated MMPs forms by GZG*

	Mean FIZ Pattern ± SE			p Value
	B	C	D	
No. pts	11	5	9	
proMMP-9	0.90 ± 0.20	0.97 ± 0.09	1.12 ± 0.46	0.40
proMMP-2	0.24 ± 0.12	0.31 ± 0.15	0.74 ± 0.23	0.0004
MMP-2	0.15 ± 0.07	0.20 ± 0.08	0.45 ± 0.16	0.0008
MMP-2/proMMP-2	0.65 ± 0.14	0.67 ± 0.07	0.62 ± 0.19	0.73

MMPs amounts are expressed as a relative value, as quantified by a densitometer.

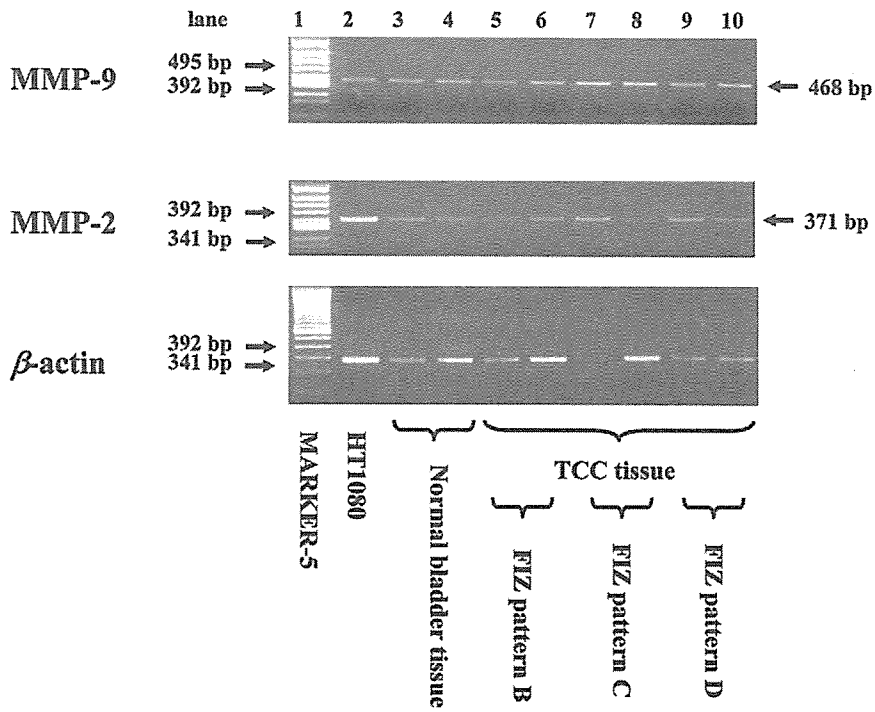

FIG. 5. MMP mRNA production by bladder cancer tissues. Virtually all tissues expressed MMP-2 and MMP-9 mRNA

carcinoma *in vivo*. Gelatinolytic activity correlates with tumor grade, stage, vessel invasion and cause specific survival. These results suggest that MMP-2 activity is an important factor in the *in vivo* biology of bladder carcinomas.

Using FIZ, Ikeda et al examined gelatinolytic activity in implanted tumor tissues, finding that activated MMP-2 but not pro-MMP-2 shows gelatinolytic activity in FIZ.[15] They also noted that gelatinolytic activity in their experimental system was derived primarily from MMPs. They suggested that FIZ can detect net MMP activity in tumor tissues. Our previous study also demonstrated that activated MMP-2 shows gelatinolytic activity in FIZ and gelatinolytic activity examined by FIZ correlates with tumor size, grade and vessel invasion of renal cell carcinomas.[14,17]

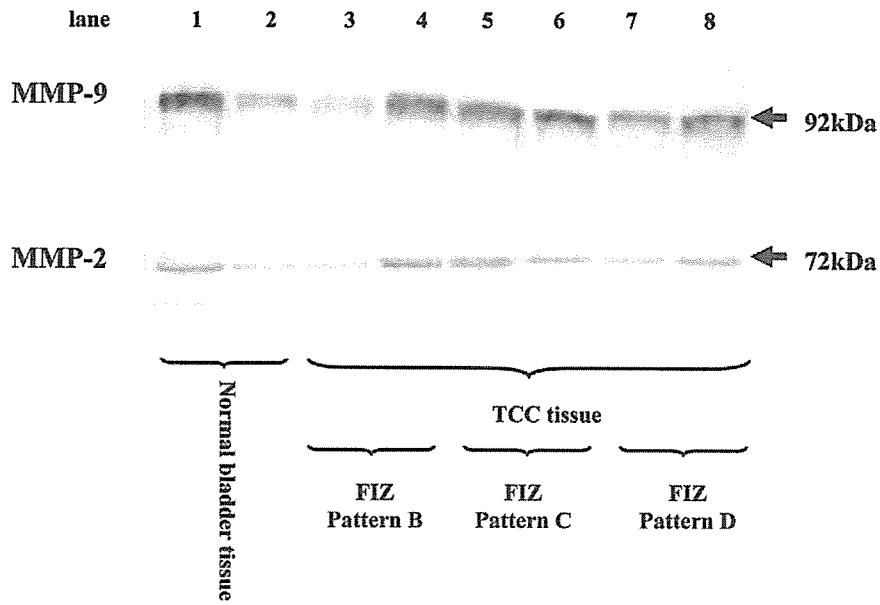

FIG. 6. Production of 72 kDa MMP-2 and 92 kDa MMP-9 by bladder cancer tissues. Virtually all tissues expressed antigens

CONCLUSIONS

Our results indicate fundamental biochemical differences between low and high grade bladder tumors. Different FIZ patterns may explain differences in invasive and metastatic behavior among tumors. FIZ may be a useful prognostic indicator in patients with bladder carcinoma and it may be helpful for designing treatment protocols. For example, the clinical point is the timing of radical cystectomy for G3 pT1 bladder carcinomas because delayed cystectomy is directly related to a serious threat to patient survival. FIZ may assist in choosing treatment for G3 pT1 bladder carcinomas.

REFERENCES

1. Shima, I., Sasaguri, Y., Kusukawa, J., Yamana, H., Fujita, H., Kakegawa, T. et al: Production of matrix metalloproteinases-2 and metalloproteinases-3 related to malignant behavior of esophageal carcinoma. A clinicopathologic study. Cancer, **70:** 2747, 1992
2. Sier, C. F., Kubben, F. J., Ganesh, S., Heerding, M. M., Griffioen, G., Hanemaaijer, R. et al: Tissue levels of matrix metalloproteinases MMP-2 and MMP-9 are related to the overall survival of patients with gastric carcinoma. Br J Cancer, **74:** 413, 1996
3. Liabakk, N. B., Talbot, I., Smith, R. A., Wilkinson, K. and Balkwill, F.: Matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) type IV collagenases in colorectal cancer. Cancer, **56:** 190, 1996
4. Talvensaari-Mattila, A., Paakko, P., Hoyhtya, M., Blanco-Sequeiros, G. and Turpeenniemi-Hujanen, T.: Matrix metalloproteinase-2 immunoreactive protein: a marker of aggressiveness in breast carcinoma. Cancer, **83:** 1153, 1998
5. Bramhall, S. R., Stamp, G. W., Dunn, J., Lemoine, N. R. and Neoptolemos, J. P.: Expression of collagenase (MMP2), stromelysin (MMP3), and tissue inhibitor of the metalloproteinases (TIMP1) in pancreatic and ampullary disease. Br J Cancer, **73:** 972, 1996
6. Stearns, M. and Stearns, M. E.: Evidence for increase activated metalloproteinase 2 (MMP-2a) expression associated with human prostate cancer progression. Oncol Res, **8:** 69, 1996
7. Montironi, R., Lucarini, G., Castaldini, C., Galluzzi, C. M., Biagini, G. and Fabris, G.: Immunohistochemical evaluation of type IV collagenase (72-kd metalloproteinase) in prostatic intraepithelial neoplasia. Anticancer Res, **16:** 2057, 1996
8. Kallakury, B. V., Karikehalli, S., Haholu, A., Sheehan, C. E., Azumi, N. and Ross, J. S.: Increased expression of matrix metalloproteinases 2 and 9 and tissue inhibitors of metalloproteinases 1 and 2 correlate with poor prognostic variables in renal cell carcinoma. Clinic Cancer Res, **7:** 3113, 2001
9. Kugler, A., Hemmerlein, B., Thelen, P., Kallerhoff, M., Radzun, H.-J. and Ringert, R.-H.: Expression of metalloproteinase 2 and 9 and their inhibitors in renal cell carcinoma. J Urol, **160:** 1914, 1998
10. Davies, B., Waxman, J., Wasan, H., Abel, P., Williams, G., Krausz, T. et al: Levels of matrix metalloproteinases in bladder cancer correlate with tumor grade and invasion. Cancer Res, **53:** 5365, 1993
11. Kanayama, H., Yokota, K., Kurokawa, Y., Murakami, Y., Nishitani, M. and Kagawa, S.: Prognostic values of matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-2 expression in bladder cancer. Cancer, **82:** 1359, 1998
12. Gerhards, S., Jung, K., Koenig, F., Daniltchenko, D., Hauptmann, S., Schnorr, D. et al: Excretion of matrix metalloproteinases 2 and 9 in urine is associated with a high stage and grade of bladder carcinoma. Urology, **57:** 675, 2001
13. Furuya, M., Ishikura, H., Nemori, R., Shibata, M., Fujimoti, S. and Yoshiki, T.: Clarification of the active gelatinolytic sites in human ovarian neoplasms using in situ zymography. Hum Pathol, **32:** 163, 2001
14. Zheng, K., Nagai, Y., Kishimoto, T., Yamazawa, K., Tate, S., Nemori, R. et al: A quantitative evaluation of active gelatinolytic sites in uterine endometrioid adenocarcinoma using film in situ zymography: association of stronger gelatinolysis with myometrial invasion. Jpn J Cancer Res, **93:** 516, 2002
15. Ikeda, M., Maekawa, R., Tanaka, H., Matsumoto, M., Takeda, Y., Tamura, Y. et al: Inhibition of gelatinolytic activity in tumor tissues by synthetic matrix metalloproteinase inhibitor: application of film in situ zymography. Clinic Cancer Res, **6:** 3290, 2000
16. Lengyel, E., Schmalfeldt, B., Konik, E., Spathe, K., Harting, K., Fenn, A. et al: Expression of latent matrix metalloproteinase 9 (MMP-9) predicts survival in advanced ovarian cancer. Gynecol Oncol, **82:** 291, 2001
17. Kamiya, N., Kishimoto, T., Suzuki, H., Sekita, N., Nagai, Y., Oosumi, N. et al: Increased in situ gelatinolytic activity in renal cell tumor tissues correlates with tumor size, grade and vessel invasion. Int J Cancer, **106:** 480, 2003
18. Ozdemir, E., Kakehi, Y., Okuno, H. and Yoshida, O.: Role of matrix metalloproteinase-9 in the basement membrane destruction of superficial urothelial carcinomas. J Urol, **161:** 1359, 1999
19. Hara, I., Miyake, H., Hara, S., Arakawa, S. and Kamidono, S.: Significance of matrix metalloproteinases and tissue inhibitors of metalloproteinase expression in the recurrence of superficial transitional cell carcinoma of the bladder. J Urol, **165:** 1769, 2001
20. Papathoma, A. S., Petraki, C., Grigorakis, A., Papakonstantinou, H., Karavana, V., Stefanakis, S. et al: Prognostic significance of matrix metalloproteinases 2 and 9 in bladder cancer. Anticancer Res, **20:** 2009, 2000

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ORIGINAL ARTICLE

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Gemcitabine plus carboplatin; and gemcitabine, docetaxel, and carboplatin combined chemotherapy regimens in patients with metastatic urothelial carcinoma previously treated with a platinum-based regimen: preliminary report

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Abstract
Background. The aim of this study was to evaluate the efficacy and safety of two combined chemotherapy regimens in the treatment of previously treated metastatic urothelial carcinoma: gemcitabine plus carboplatin (GC), and gemcitabine, docetaxel, and carboplatin (GDC).
Methods. Sixteen patients with metastatic urothelial cancer, previously treated with a platinum-based regimen, were studied. GC (gemcitabine 750 mg/m^2, on days 1, 8, and 15; carboplatin 200 mg/m^2, on day 2) was administered every 28 days to 15 patients. GDC (gemcitabine 750 mg/m^2, on days 1 and 8; docetaxel 50 mg/m^2, on day 1; carboplatin 200 mg/m^2 on day 1) was administered every 21 days to 9 patients. Eight of the 9 GDC-treated patients had earlier been treated with GC and had become refractory.
Results. With the GC therapy, 7 of the 15 treated patients (47%; 95% confidence interval, 21%–73%) showed an objective response, with 3 achieving a clinical complete response (CR) and 4 a partial response (PR). With the GDC therapy, 6 of the 9 treated patients (67%; 95% confidence interval, 29%–92%) showed an objective response, with 1 achieving CR and 5, PR. Five of the 8 (63%) GC-refractory patients responded to GDC therapy. The median duration of response was 4 months (range, 2–10+ months) on GC therapy, and 3 months (range, 3–5 months) on GDC therapy. Toxicities associated with GC were less than those with GDC.
Conclusion. GC was effective for refractory metastatic urothelial cancer, and GDC was effective for GC-refractory cancer.

Key words Gemcitabine · Docetaxel · Metastatic urothelial cancer

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Introduction

Gemcitabine, a cell-cycle-specific pyrimidine nucleoside analog, is converted within the cell to triphosphate metabolites. The incorporation of gemcitabine triphosphate into actively replicating DNA and masked-chain termination results in the inhibition of DNA synthesis.[1,2]

Gemcitabine exhibits significant activity in metastatic transitional cell cancer (TCC), with minimal toxicity, but it has little effect on increasing patient survival. Trials of gemcitabine in combination with other active agents have thus been suggested.[3] Paclitaxel was originally a natural product derived from the bark of the North American yew tree, *Taxus brevifola*. Clinical studies using paclitaxel commenced in the mid-1980s. French researchers produced an extract of the European yew, *Taxus baccata*, and modified it with a chemically synthesized side chain. Docetaxel emerged as a result of these efforts and entered clinical trials in 1990.[4] Docetaxel is capable of inducing bcl2 phosphorylation and apoptotic cell death at 100-fold lower concentrations than paclitaxel.[5]

At present, the combination of cisplatin, methotrexate, doxorubicin, and vinblastine (M-VAC)[6] is most widely used for advanced TCC and has shown overall response rates of 40%–72% in phase II studies and 35%–45% in phase III studies, with a median survival of approximately 12 months. These modest results and unsuccessful attempts to increase

Table 1. Characteristics of patients receiving GC and/or GDC chemotherapy

Patient no.	Age (years)	Sex	Disease site	Previous chemotherapy	Response to GC	Response duration (months)	Response to GDC	Response duration (months)	Survival after GC and/or GDC chemotherapy (months)
1	52	M	LN, lung	MEC, M-VAC	PD				3
2	72	M	LN	M-VAC, ITP	CR	5			8
3	68	M	Bone	MEC, ITP	NC				24+
4	56	M	Bone	MEC, M-VAC	PD				8+
5	68	M	LN	MEC, ITP	CR	5			8+
6	71	M	LN	MEC, ITP	CR	10+			11+
7	61	M	LN, Lung, liver	ITP	PD				3
8	46	M	Lung	MEC	PD		PR	3	12+
9	68	M	Lung	MEC	PR	3	CR	3	6
10	73	M	Liver	M-VAC	PR	8	PR	5	15
11	66	M	Lung	MEC	PR	2	PR	3	4+
12	68	M	LN	MEC, ITP	PD		PD		10+
13	51	M	LN, lung, liver	MEC, ITP	PD		PD		12
14	69	M	LN, lung, liver	M-VAC	PD		PD		5+
15	55	M	Liver	M-VAC	PR	3	PR	3	10+
16	73	M	LN, liver	MEC			PR	5	6+

M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; MEC, methotrexate, epirubicin, cisplatin; ITP, ifosfamide, paclitaxel, cisplatin; GC, gemcitabine, carboplatin; GDC, gemcitabine, docetaxel, carboplatin; LN, lymph node; PD, progressive disease; CR, complete response; PR, partial response; NC, no change

the efficacy with dose-intensive M-VAC schedules have prompted the identification of new agents active against TCC, such as the taxanes and gemcitabine. The overall response rates for two-drug regimens consisting of cisplatin-paclitaxel, carboplatin-paclitaxel, and cisplatin-gemcitabine range from 63% to 72%, 14% to 65% and 42% to 66%, respectively. The overall response rates for platinum-paclitaxel-gemcitabine three-drug regimens range from 58% to 80%.[7]

We administered two-drug and three-drug combinations of these new drugs as a pilot study in patients with metastatic urothelial carcinoma whose tumors were refractory to or had shown no response to platinum-based regimens.

Patients and methods

From August 1998 to May 2003, we treated 16 patients with metastatic urothelial cancer who had previously received one or more platinum-based regimens. The previous chemotherapies had been MEC[8] (methotrexate, epirubicin, cisplatin) in 11 patients, M-VAC[6] in 6, and ITP[9] (ifosfamide, paclitaxel, cisplatin) in 7 patients. Informed consent was obtained from all patients, and this clinical study was done with the Institutional Review Board's approval.

The patients were all men, with a mean age of 64 years (range, 46 to 73 years). Thirteen patients had bladder cancer and 3 had pelvic or ureteral cancer. The pathological diagnoses of the primary tumors were all grade II to III TCC. Two patients had already undergone radical cystectomy and 2 patients, nephroureterectomy. Metastases were limited to the lymph nodes in 4 patients; to the lymph node and lung in 1 patient; to the lymph nodes, lung, and bone in 1 patient; and to the lymph nodes, lung, and liver in 3 patients. Metastases were restricted to only the lung in 3 patients, to only the bone in 2, and to only the liver in 2 (Table 1).

Treatment

The treatment schedule for the combination of gemcitabine and carboplatin (GC) was gemcitabine 750 mg/m^2 over 30 to 60 min on days 1, 8, and 15; and carboplatin 200 mg/m^2 on day 2. Cycles were repeated every 28 days.[10] The treatment schedule for the comination of gemcitabine, docetaxel, and carboplatin (GDC) was gemcitabine 750 mg/m^2 on days 1 and 8, docetaxel 50 mg/m^2 on day 1, and carboplatin 200 mg/m^2 on day 1. Cycles were repeated every 21 days.[11,12] These treatments were carried out for a maximum of eight cycles of GC and six cycles of GDC in responding patients or patients with stable disease, but they were discontinued in the presence of disease progression. A detailed medical interview, clinical examination, and laboratory studies were obtained before each drug administration. Dose adjustment was based on assessment of the hematological and nonhematological toxicities. In particular, only 75% of the gemcitabine dose was administered when granulocytes measured 1.0–1.4 $\times$ 10^9/l and/or platelets were 75–99.9 $\times$ 10^9/l. If granulocytes were 0.5–0.9 $\times$ 10^9/l and/or platelets were 50–74.9 $\times$ 10^9/l, 50% of the full dose was administered. If the cell counts fell below the lower level of either range, further treatment was delayed until recovery.

GC was administered to 15 patients and GDC to 9 patients. Eight of the 9 GDC-treated patients had previously been treated with GC and had become refractory (Table 1). The median time from discontinuation of GC to the start of GDC in these 8 patients was 1 month. The median number and range of cycles of GC therapy were 3 and 2 to 8. The median number and range of cycles of GDC therapy were 3 and 1 to 6.

Evaluation of response and toxicity

All patients who completed at least one therapy cycle (three injections of gemcitabine and tumor reassessment after a 1-week interval) were analyzed for chemotherapeutic efficacy. All enrolled patients were analyzed for toxicity and survival and were reviewed every month to assess efficacy and toxicity. After discontinuation of treatment, patients were evaluated every month to assess the survival and disease-free status. The evaluation of the tumor response was based on the standard WHO criteria for measurable disease.[13]

For the evaluations of the tumor response and survival, the following definitions were used: time to response, the time from first injection to first objective response; time to progression, the time from first injection to the date of evidence of progression; time to treatment failure, the time from first injection to date of withdrawal from the study for any reason (progression, toxicity, refusal); duration of partial response (PR), the time from first evidence of PR to the time of disease progression; duration of complete response (CR), the time from first evidence of CR to the time of disease progression; and survival, the time from first injection to death.

Kaplan-Meier analysis was used for analysis of the survival and time to progression, and the 95% confidence interval (CI) was also calculated.

Results

Response

Fifteen patients received at least two courses of GC and 9 patients received at least one course of GDC, so only these patients were evaluated for response and toxicity. With the GC therapy, 7 of the 15 patients (47%; 95% CI, 21%–73%) showed an objective response, with 3 achieving a CR and 4, a PR. The time to response in all responders was within 2 months. With the GDC therapy, 6 of the 9 treated patients (67%; 95% CI, 29%–92%) showed an objective response, with 1 achieving CR and 5, PR. Five of the 6 responders were refractory to GC therapy, and in all 6 patients the time to response was 1 month. The median duration of response was 4 months (range, 2–10+ months) with GC and 3 months (range, 3–5 months) with GDC (Table 1). The median times to progression with the GC and GDC therapies were 4.5 months and 4 months, respectively. The median survival for all patients was 8 months.

All three CRs in patients on GC therapy occurred in the lymph nodes, while the one CR in the patient on GDC therapy occurred in the lung. The four PRs in patients on GC therapy occurred in the liver and lungs, while the PRs in patients on GDC therapy occurred in lungs in two patients and the liver in three patients.

Three of the six patients with liver metastasis achieved a PR. Patient 10 (patient number in Table 1) had multiple liver metastases, jaundice, and total bilirubin of 10 mg/dl when he was referred to our hospital. GC therapy was performed by hepatic arterial infusion by inserting an arterial infusion catheter into the femoral artery through a port set in the femoral subcutaneous area. PR was obtained within two cycles. After eight cycles; however, new liver metastasis appeared, and so we switched to GDC therapy. The new liver metastasis decreased, and PR was obtained again and continued for 5 months. His bilirubin level dropped to the normal range, and tumor markers[14] (carcinaembryonic antigen [CEA], carbohydrate [CA] 19-9, and CA125) also decreased to almost normal ranges. However, with these chemotherapies (eight cycles of GC and five cycles of GDC) computed tomography (CT) showed atrophy of liver without elevation of aspartate aminotransferase (AST)/alanine aminotransferase (ALT), or alkaline phosphatase (ALP), but endoscopy showed esophageal varices. We diagnosed the occurrence of liver cirrhosis caused by fibrotic change of massive metastatic liver tumor necrosis after chemotherapy. Accordingly, we terminated the chemotherapy, and the patient died 2 months later, with multiple liver metastases and ascites. In patient 15, the liver lesion responded to GC and GDC therapies and PRs were obtained and continued for 3 and 3 months, respectively. In patient 16, a 1.5-cm liver metastasis had appeared during the previous MEC therapy for pelvic lymph node metastases. The liver lesion responded to GDC therapy, and PR was obtained and continued for 5 months.

In patient 9, lung metastasis occurred during GC therapy but responded to GDC therapy; CR was obtained, but the duration was only 3 months. GDC therapy resulted in a PR of 3 months' duration in patients 8 and 11 with lung metastasis which had become refractory to GC therapy.

Toxicity

The treatments were generally well tolerated (Tables 2, 3). Grade 3 pancytopenia was observed in two patients treated with GC and in seven patients treated with GDC. The incidence of infection related to neutropenia was 11% (1/9) in patients on GDC therapy, with no WHO grade 3–4 infections. There were no cases of WHO grade 3–4 biochemical toxicity of AST/ALT, ALP, or bilirubin, and no transient elevation of AST, ALT, or ALP. No patients had WHO grade 3–4 elevation of the serum creatinine level or blood

Table 2. Toxicity of GC according to WHO toxicity scale(n = 15)

Toxicity	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	0	0	7	7
Anemia	0	0	7	7
Thrombocytopenia	0	0	13	0
Neuropathy	0	0	0	0
Myalgia	0	0	0	0
Alopecia	0	0	0	0
Diarrhea	13	0	0	0

GC, gemcitabine, carboplatin; WHO, World Health Organization

Table 3. Toxicity of GDC according to WHO toxicity scale (n = 9)

Toxicity	Grade			
	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	0	0	22	55
Anemia	0	0	55	22
Thrombocytopenia	0	0	33	33
Neuropathy	0	0	0	0
Myalgia	0	0	0	0
Alopecia	0	50	50	0
Diarrhea	22	11	0	0

GDC, gemcitabine, docetaxel, carboplatin; WHO, World Health Organization

urea nitrogen (BUN). With regard to symptomatic toxicity, nausea and vomiting were generally modest. Alopecia occurred in all GDC-treated patients.

Discussion

Transitional cell carcinoma (TCC) of the urothelium is a chemosensitive tumor, as demonstrated by its overall response rate of 35%–70% with the M-VAC drug combination.[6] The toxicity of this regimen, however, is significant, and the median survival of all treated patients does not greatly exceed 12 months.[15,16] These results have prompted a search for new active agents which could be incorporated into more effective and less toxic regimens.

Gemcitabine has been studied as a single agent for the treatment of metastatic bladder cancer,[3,17] and, based on its mechanism of action, it was thought to have potential for synergism with cisplatin. This synergism was later confirmed.[18]

Liver metastases generally do not respond well to M-VAC. On the other hand, liver metastases have a chance to respond to gemcitabine, as noted by Pollera et al.[17] They reported that three of seven patients with liver metastasis responded well to gemcitabine. Stadler et al.[3] also stated that three of nine patients with liver metastasis achieved a CR on gemcitabine monotherapy. One of our patients with multiple liver metastases survived for 15 months. When he was referred to our hospital, his total bilirubin was 10 mg/dl and jaundice was seen. Arterial infusion chemotherapy with GC was dramatically effective, and his bilirubin value dropped after two courses of GC. Almost the same effect was observed in patient 16. In another patient, a 1.5-cm liver metastasis had been found during MEC therapy for pelvic lymph node metastasis, but GDC therapy was effective, and a PR was obtained.

GC provides a survival advantage similar to that seen with M-VAC, while having a better safety profile and tolerability.[19] This better risk ratio should lead to a change in the standard of care for patients with metastatic TCC, with chemotherapy changed from M-VAC to GC.

Our results showed that some tumors which had become refractory to GC were still sensitive to GDC. Among our eight patients refractory to GC treatment, five (63%) responded to GDC. The responding organ was the lung in two patients and the liver in three patients. Therefore, we think GC is suitable as a first-line chemotherapy, and GDC is useable as a second-line chemotherapy. However, the durations of the response to GC and GDC therapies were short, so a new combination chemotherapy showing a longer response is desired. The metastatic urothelial tumors which became refractory to GC had a chance to respond to GC plus docetaxel (GDC chemotherapy). To our knowledge, this is the first published report showing that GDC is effective for GC-refractory metastatic urothelial tumors. It remains unclear whether, in order to prolong the chemotherapy effect, GC should be used as first-line chemotherapy, with GDC as second-line therapy; or whether GDC should be used as first-line chemotherapy. Accordingly, a double-blind randomized study of two arms, GC to GDC and GDC, is now in progress.

All of our patients had previously received cisplatin-based chemotherapy and radiotherapy. GC showed mild toxicity (patients experienced little WHO grade 3 toxicity), which was easily manageable. GC is usually well tolerated and is suitable for outpatient use. Neither unexpected nor cumulative toxic effects were found. Furthermore, the absence of significant renal and cardiac toxicities makes this promising combination especially attractive for urothelial cancer, allowing GC to be used in patients who may not be able to tolerate more toxic chemotherapeutic regimens.

We showed that metastatic urothelial tumors refractory to GC therapy still responded to GDC therapy. However, GDC therapy had the disadvantage of a short duration of response. Accordingly, another combination chemotherapy of gemcitabine with an epidermal growth factor receptor inhibitor is now being investigated.[20]

References

1. Hertel LW, Boder GB, Kroin JS, et al. (1990) Evaluation of the antitumor activity of gemcitabine (2′,2′-difluoro-2′-deoxycytidine). Cancer Res 50:4417–4422
2. Lorusso V, Pollera CF, Antimi M, et al. (1998) A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. Eur J Cancer 34:1208–1212
3. Stadler WM, Kuzel T, Roth B, et al. (1997) Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. J Clin Oncol 15:3394–3398
4. Vaishampayan U, Parchment RE, Jasti BR, et al. (1999) Taxanes: an overview of the pharmacokinetics and pharmacodynamics. Urology 54 (Suppl 6A):22–29
5. Haldar S, Basu A, Croce CM (1997) Bcl2 is the guardian of microtubule integrity. Cancer Res 57:229–233
6. Sternberg CN, Yagoda A, Scher HI, et al. (1989) Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer 64:2448–2458
7. Bellmunt J, Guillem V, Paz-Ares L, et al. (2000) Gemcitabine/paclitaxel-based three-drug regimens in advanced urothelial cancer. Eur J Cancer 36 (Suppl 2):17–25
8. Kuroda M, Kotake T, Akaza H, et al. (1998) Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective

randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. Jpn J Clin Oncol 28:497–501
9. Bajorin DF, McCaffrey JA, Dodd PM, et al. (2000) Ifosfamide, paclitaxel, and cisplatin for patients with advanced transitional cell carcinoma of the urothelial tract: final report of a phase II trial evaluating two dosing schedules. Cancer 88:1671–1678
10. Lorusso V, Manzione L, De Vita F, et al. (2000) Gemcitabine plus cisplatin for advanced transitional cell carcinoma of the urinary tract: a phase II multicenter trial. J Urol 164:53–56
11. Pectasides D, Glotsos J, Bountouroglou N, et al. (2002) Weekly chemotherapy with docetaxel, gemcitabine and cisplatin in advanced transitional cell urothelial cancer: a phase II trial. Ann Oncol 13:243–250
12. Hussain M, Vaishampayan U, Du W, et al. (2001) Combination paclitaxel, carboplatin, and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 19:2527–2533
13. World Health Organization (1979) WHO Handbook for reporting results of cancer treatment. WHO, Geneva
14. Cook AM, Huddart RA, Jay G, et al. (2000) The utility of tumour markers in assessing the response to chemotherapy in advanced bladder cancer. Br J Cancer 82:1952–1957
15. Tannock I, Gospodarowicz M, Connolly J, et al. (1989) M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) chemotherapy for transitional cell carcinoma: the Princess Margaret Hospital experience. J Urol 142:289–292
16. 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
17. Pollera CF, Ceribelli A, Crecco M, et al. (1994) Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase I study. Ann Oncol 5:182–184
18. Peters GJ, Bergman AM, Ruiz van Haperen VW, et al. (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22 (Suppl 11):72–79
19. 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
20. Stadler WM (2002) Gemcitabine doublets in advanced urothelial cancer. Semin Oncol 29 (Suppl 3):15–19

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Clinical Outcome of a Large-Scale Multi-Institutional Retrospective Study for Locally Advanced Bladder Cancer: A Survey Including 1131 Patients Treated during 1990–2000 in Japan

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Abstract

Objective: We conducted a multi-institutional analysis to establish the contemporary clinical outcome of invasive bladder cancer treated with radical cystectomy in Japan.

Methods: A total of 1131 consecutive patients who underwent radical cystectomy for invasive bladder cancer between January 1990 and December 2000 at 32 hospitals were retrospectively analyzed.

Results: Histopathological analysis demonstrated that 1042 patients (92.1%) harbored transitional cell carcinomas (TCCs), whereas 89 patients (7.9%) presented non-TCCs, including squamous cell carcinoma and adenocarcinoma. Pelvic lymphadenectomy was performed in 1013 patients in total, and pathologically confirmed lymph node metastases were found in 162 (16.0%). The overall survival at 5 years was 68.0% and most deaths (79.0%) occurred within 3 years. Multivariate analysis demonstrated that gender, clinical stage, pathological stage, lymph node involvement and lymph node dissection were the independent predictive factors for survival, whereas histological type, sex and grade had no siginificant impact on survival.

Conclusions: These clinical results demonstrate that radical cystectomy with lymph node dissection results in good survival for invasive bladder cancer, providing standard data with which other forms of therapy can be compared.

Keywords: Bladder cancer; Radical cystectomy

1. Introduction

Bladder cancer is the second most common genitourinary malignancy, which comprises a broad spectrum of tumors, including transitional cell carcinomas (TCCs), squamous cell carcinomas (SCCs), adenocarcinomas, small cell carcinomas, and miscellaneous subtypes [1,2]. TCCs are the most common histological subtypes and represent nearly 90% of all bladder cancers in Western countries, and 20% to 40% of bladder cancers present with or develop invasive disease. Invasive bladder cancers are very aggressive and have poor prognosis with fewer than 15% of TCC patients surviving 2 years if untreated [3]. During the last two decades, radical cystectomy with lymph node (LN) dissection has emerged as one of the standard forms of therapy for patients with invasive bladder cancer [4–7]. Early results of radical cystectomy suggests that only about 40% of patients treated for

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high-grade invasive disease were cured and that most patients subsequently died of metastatic disease within 3 years of diagnosis [8,9]. Improvements in medical, surgical, and anesthetic therapy, however, have clearly reduced the morbidity and mortality associated with contemporary surgery, providing excellent results with regard to survival and prevention of local recurrence [6,7]. In the present study, we conducted a multi-institutional retrospective analysis to establish the clinical outcome of invasive bladder cancer treated with contemporary radical cystectomy in Japan.

2. Materials and methods

2.1. Patients characteristics

We registered all patients who underwent radical cystectomy between January 1990 and December 2000 at 32 Japanese institutions including three university hospitals (Kyoto University Hospital, Nagoya University Hospital, and Nara Medical University Hospital), containing detailed and comprehensive clinical and pathologic information. The clinical and pathological data that were collected from the medical records included age, gender, histologic grading according to the World Health Organization system, clinical staging and pathological (P) staging according to the 1997 TNM classification [10], and the presence of perioperative systemic chemotherapy.

As shown in Table 1, of these 1131 patients, 903 were males (79.8%) and 228 were females. The median age was 65.9 years (range 31–89 years). Updated follow-up information was obtained from patient records at every single center; for all those not followed until death or until the closing date of the study (December 31, 2001). Perioperative death occurred in 7 (0.6%) of 1131 patients. Median follow-up duration was 3.8 years. A total of 112 (9.9%) of the cases were lost to follow-up.

The follow-up procedures varied slightly among the institutions considered; however, some general statements should be made because of the long study period. All patients were followed for a period of 3–6 months between the follow-up visits during the first 2–3 years; the visits were every 6 months or annually thereafter. The follow-up included at each visit a physical examination (general and local). This prompted, when needed and according to the clinical suspicion of persisting/relapsing disease, the use of the same specific diagnostic tests performed during the baseline workup (e.g., ultrasonography, chest-XP, CT, and bone scan).

2.2. Study endpoints and statistical analysis

The overall survival was defined as the time from the radical cystectomy to any cause of death; all deaths from any causes were counted as an event and patients still being alive were treated as censored at the date of last follow-up before December 31, 2001. The survival proportions were estimated with the Kaplan–Meier method. The log-rank test was performed to test associations between patient characteristics and survival according to pathological stage. To identify the prognostic factors independently associated with the overall survival and to estimate the hazard ratios, the Cox proportional hazards model was applied. Two-sided $p < 0.05$ was regarded as statistically significant. All statistical analyses were performed using SAS version 8 (SAS Institute, Cary, NC, USA).

3. Results

Among the 1131 consecutive TCC patients undergoing radical cystectomy, histopathological analysis demonstrated that 1042 patients (92.1%) harbored TCCs, whereas 89 patients (7.9%) presented non-TCCs; 38 SCCs, 23 adenocarcinoma, and 28 miscellaneous tumors. Mean patient age was 66.0 years (range 31–89) and 64.5 (range 37–85) in the TCC and non-TCC group, respectively. The male/female ratio and follow-up duration in both groups were similar, as shown in Table 1.

Pelvic LN dissection was performed in 1013 patients in total, and pathologically confirmed lymph node metastases were found in 162 (16.0%). LN involvement increased with a more advanced P category. The rate of having nodal metastases was significantly higher in patients with P3 or greater (37.0%) than in those with P2b or less (7.5%) ($p < 0.001$), but it did not correlate with the histological subtypes of the tumor (Table 2).

During the follow-up period, 288 cases were identified as definitive treatment failure (alive with or died of disease). Treatment failures were due to local recurrences in 65 cases (5.7%), distant metastasis in 204 (18.0%) or both in 13 (1.1%). Treatment failures were documented in a significantly higher frequency of patients with positive nodes (57.1%), than those with negative nodes (19.1%) ($p < 0.001$). As well, recurrence was observed in significantly higher frequency in patients with P3 or more (47.4%) than those with P2b or less (16.3%)

Table 1
Patient characteristics

Characteristics	Total	TCC	Non-TCC	Non-TCC		
				SCC	Adeno	Others
Total patients (%)	1131	1042 (92.1)	89 (7.9)	38 (3.4)	23 (2.0)	28 (2.5)
Mean age (years) (range)	65.9 (31–89)	66.0 (31–89)	64.5 (37–85)	62.9 (37–85)	68.4 (52–80)	63.5 (50–84)
Gender (M/F)	903/228	841/201	62/27	25/13	15/8	22/6
Median follow up duration (years)	3.8	3.8	3.7	3.5	34	7.9

Table 2
Lymph node involvement relative to P-stage and histology

Histology	P2 or less			P3 or more		
	pN0	pN+	%	pN0	pN+	%
TCC	633	51	7.5%	168	94	35.9%
Non-TCC	34	3	8.1%	16	14	46.7%
SCC	16	2	11.1%	7	9	56.2%
Adeno	8	1	11.1%	6	3	33.3%
Others	10	0	0.0%	3	2	40.0%
Total	667	54	7.5%	184	108	37.0%

($p < 0.001$), but histological subtypes showed no impact on treatment failure.

The overall survival for all 1131 patients at 5 years was 68.0%, and 95% confidence interval (CI) ranged between 64.8% and 71.2%, and most deaths (79.0%) occurred within 3 years. Kaplan–Meier analyses estimated the 5-year overall survival in each subgroup stratified with several variables including age, gender, histological subtype, grade, clinical stage, pathological stage, LN involvement and LN dissection. As shown in Table 3, 5-year survivals were significantly declined in correlation with age, grade, stage, the presence of LN involvement and the presence of LN dissection.

Table 3
Five-year overall survival in different clinical and therapeutic subgroups of the entire series

Subgroups	No. patients	No. death	5-year survival (%)	*p*-value
Age (years)				
<70	691	186	71.4	
70–74	268	86	65.0	
75–79	110	39	59.7	
≥80	62	26	56.2	0.001
Gender				
Male	903	264	68.7	
Female	228	73	65.1	0.332
Histology				
TCC	1042	305	68.6	
Non-TCC	89	32	60.8	0.284
Grade				
G1	19	5	72.2	
G2	318	77	75.0	
G3	705	223	65.5	0.009
Clinical stage				
T1 or less	290	58	82.0	
T2	323	75	74.7	
T3	371	138	57.9	
T4	68	35	42.3	0.001
Pathological stage				
P2a or less	640	120	82.2	
P2b	149	54	60.2	
P3	237	109	47.8	
P4	94	50	28.0	0.001
LN involvement				
pN0	853	201	75.5	
pN+	163	90	35.1	0.001
LN dissection				
Without	121	54	54.1	
With	982	276	69.8	0.001

When comparing TCC and non-TCC, the 5-year survival for patients with TCC ($n = 1042$) and those with non-TCC ($n = 89$) was 68.6% and 60.8%, respectively (Table 3). On analyzing subgroups stratified with P-stages, the overall survivals were not significantly different between patients with TCC and those with non-TCC; the 5-year survival in stage P2b or less was 78.7% in TCC and 69.8% in non-TCC, respectively ($p = 0.20$), whereas that in stage pT3 or higher was 46.3% in TCC and 42.1% in non-TCC, respectively ($p = 0.51$) (Fig. 1a and b). When analyzing the patient group with TCC bladder cancers, the overall survival significantly declined as P and pN categories increased. The rates of 5-year survival for TCC patients without pathological lymph node involvement (pN0) were 84.5% for P2a or less, 64.9% for P2b, 58.5% for P3, and 43.4% for P4 patients, whereas those for TCC patients with pathological lymph node involvement (pN+) were 66.7% for P2a or less, 46.9% for P2b, 24.6% for P3, and 16.8% for P4 patients.

To identify the independent predictors of survival, multivariate analyses were performed, using various subsets of patients listed in Table 3. Factors significantly associated with better survival were age (70 years old or less), clinical stage (T3 or less), P-stage (P2a or less), negative LN involvement and cystectomy with LN-dissection, although gender and grade had no significant impact on survival (Table 4).

Table 4
Results of Cox regression analysis for overall survival

Factors	Category	Hazard ratio	95% CI	*p*-value
Age (years)	≤69	1.00		
	70–74	1.34	1.03–1.74	0.027
	75–79	1.44	1.01–2.06	0.044
	≥80	1.63	1.06–2.53	0.027
T	T3 or less	1.00		
	T4	1.61	1.09–2.38	0.017
pT	P2a or less	1.00		
	P2b	1.94	1.40–2.69	0.001
	P3	2.59	1.97–3.42	0.001
	P4	2.76	1.88–4.06	0.001
pN	pN0	1.00		
	pN1	1.50	1.03–2.18	0.037
	pN2–3	3.05	2.21–4.21	0.001
LN dessect	without	1.00		
	with	0.06	0.44–0.81	0.001

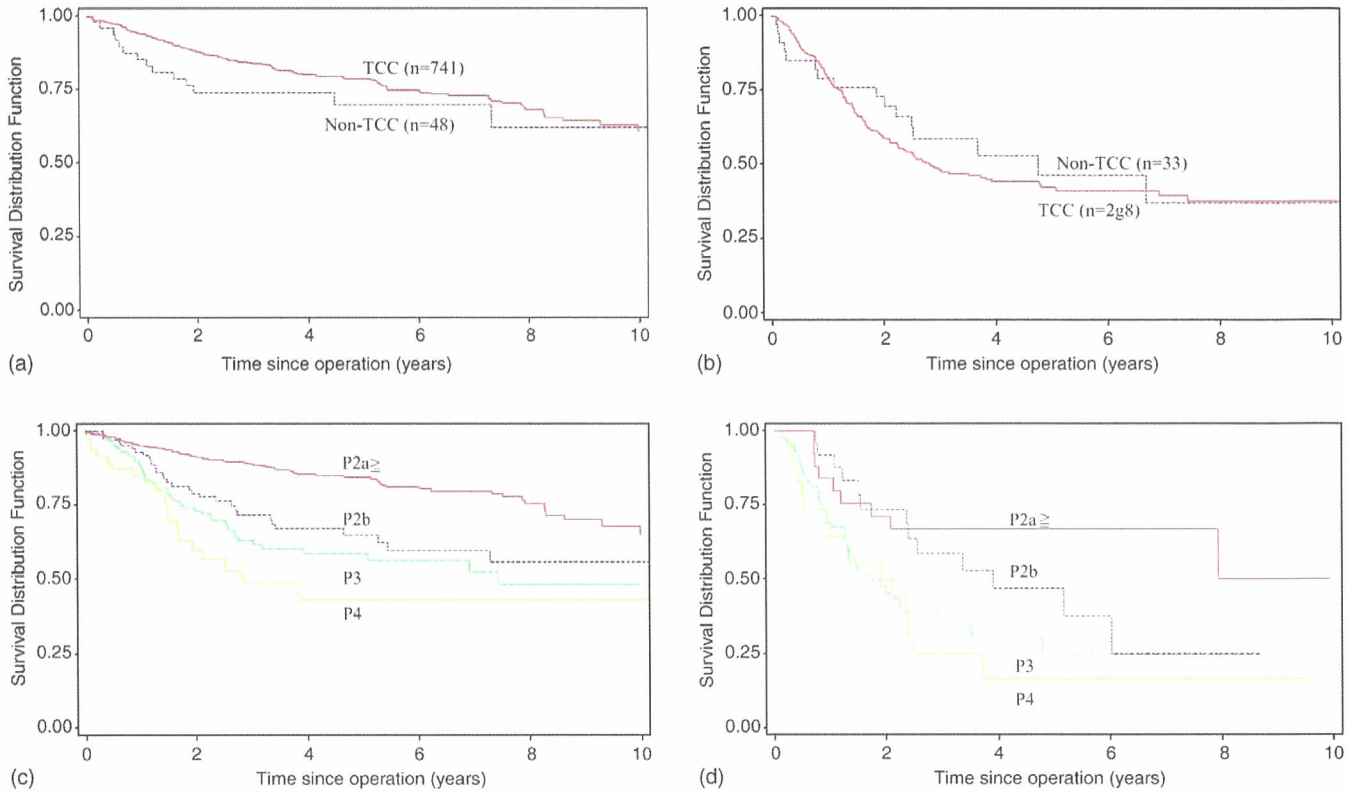

Fig. 1. Overall survival in TCC and non-TCC bladder cancers. Overall survivals were analysed by Kaplan–Meier estimates in pT2b or less (a) and pT3 or more (b). The five-year survival in pT2b or less was 78.7% and 69.8% in TCC and non-TCC ($p = 0.20$), whereas that in pT3 or greater was 46.3% and 42.1% in TCC and non-TCC ($p = 0.51$), respectively.

4. Discussion

Radical cystectomy has been established as a gold standard for locally advanced bladder cancer in the last two decades. Although only about 40% of patients survived at 5 years after the operation in the earlier studies [8,9] or from developing countries [11], recent advancements in medical and surgical therapy have clearly improved clinical results with overall survival rates of greater than 60% [6,7]. In our series of 1131 patients treated with radical cystectomy, the 5-year overall survival rate was 68.0%, which is comparable with those of other recent series [6,7].

In general, P-stage and LN status are well known as the most important predictors for survival [10]. The reported incidence of regional LN involvement varied between 14 and 27%, and this incidence correlated with the P-stage of the primary tumors [12–14]. In our entire series, the incidence of LN involvement was 16.0%. The rate of having nodal metastases was significantly higher in patients with P3 or greater (37.0%) than in those with P2b or less (7.5%) ($p < 0.001$). The reported 5-year survival following radical cystectomy and pelvic lymphadenectomy in patients with positive LNs ranged between 4 and 31% [6,7,15–17]. The present findings demonstrated that radical cystectomy with LN dissection could provide a 5-year survival of 35.1% for node positive cases compared with 75.5% for node negative cases, a percentage comparable with other series [6,7,15–17]. Thus, LN involvement is definitely an unfavorable prognostic sign, but long-term survival was seen in 20–30% of patients, emphasizing that LN dissection can be curative in a subset of patients [7,16,18]. The clinical significance of LN dissection on survival was supported by the results of our multivariate analysis, in which radical cystectomy with LN dissection provide significantly better survival than that without dissection, although the bias of patient selection should be taken into consideration.

The findings of the present study also demonstrated that P-stage is an important survival determinant in patients undergoing cystectomy. The difference in survival between organ-confined tumors (P2b or less, according to the 1997 TNM system [10]) and extravesical tumors (P3 or more) is noteworthy [19]. In agreement with recent series [6,7,19], similar differences between organ-confined and non-organ-confined tumors were observed in our series: approximately 70% of patients with organ-confined disease were free of tumor at 5 years after the operation, whereas tumor

extension into perivesical fat or extravesical disease predicted a poor prognosis with less than 50% of 5 year overall survival.

Recently several studies reported the favorable clinical outcomes of large-scale patients with TCC bladder cancers [6,7]. To compare the present results in the same populations of patients, we evaluated the survival in TCC patients subgroups stratified with P- and pN-stages. The rates of 5 year survival were significantly lower for TCC patients with pN0 according with P-stage: 84.5% for less than P2a, 64.9% for P2b, 58.5% for P3, and 43.4% for P4 patients. Similar differences were noted when stratifying patients with pN+: 66.7% for less than P2a, 46.9% for P2b, 24.6% for P3, and 16.8% for P4 patients. The present results were comparable with the clinical outcomes of other recent large-scale series, in which 5-year overall survival was 62–78% for patients with organ-confined, lymph node-negative tumors (≤pT2, pN0) and 47–49% for non-organ-confined, lymph node-negative tumors (>pT2, pN0) [6,7]. This finding could provide validation of the new TNM nomenclature of 1997 with its distinction between P2b (deep muscle invasion) and P3a (microscopic invasion of perivesical fat).

Other than P-stage and LN status, there is no consensus on whether additional factors may significantly impact on the prognosis [6,7]. In the present series, multivariate analyses demonstrated that age and the presence of LN dissection are important survival predictors in cystectomy patients. Frazier et al. [20] based on the outcome analysis on a larger series of 531 patients, found age, grade, and the presence of positive margins to be additional independent predictors of disease specific survival. Gschwend et al. [21] demonstrated that the different independent variables impacted upon the outcome within the stratified patient category. The observed differences were most profound when comparing the prognostic variables of patients with organ-confined disease (P-stage, N-stage, age, and vascular invasion), N0 disease (P-stage, age, gender, tumor type, and vascular invasion) and N+ disease (only P-stage).

The patterns of treatment failure are important to realize the problems of radical cystectomy. Incidence of pelvic recurrences after radical cystectomy were reported recently to be an average of 10% (range 4% to 18%) [22]. Overall, the 5.7% local recurrence rate in the present series is at the lower end of this range. This is a result of earlier intervention, improved surgical technique, and better patient selection. Despite satisfactory local tumor control, distant metastases were observed in 208 patients among 228 patients presented as treatment failure. These findings suggest that reducing distant metastases is one of the most important problems for further improvements of survival. Although there has been a huge increase in the knowledge of molecular mechanisms for bladder cancer and the large number of markers investigated [23], this has not yet brought about a reliable discrimination between high- and low-risk patients on an individual basis. Markers are needed to allow for a better stratification, for example, for adjuvant chemotherapy protocols.

The present series also disclosed clinical features of non-TCC bladder tumors in Japan. Bladder cancer comprises a broad spectrum of tumors, including TCCs, SCCs, adenocaricnomas, and miscellaneous subtypes. In Western countries including USA and Europe, TCCs are the more prevalent tumors and other histological types, including SCCs and adenocaricnomas, encompass a small percentage (2–3%) [1,2]. On the other hand, SCCs account for approximately 80% in areas of Africa and the Middle East [11]. In the present series, TCCs are the most prevalent tumor, accounting for greater than 90%, and SCCs and adenocarcinomas both encompassed only 2–3%, suggesting that the distributions of histological subtypes in Japan resembled those in Western countries.

The clinical outcome of non-TCC bladder tumors remains controversial, because of their rarity. Some studies reported that adenocarcinomas and SCCs are generally invasive and are considered to be unfavorable prognostic factors compared with TCCs [23,24], whereas other studies demonstrated that adenocarcinoma and SCCs have a clinical behavior similar to that of TCCs [25–27]. Recently, Ghoneim et al. [11] reported the clinical outcome of 608 patients with SCCs in Egypt, who were treated with radical cystectomy, demonstrating that the distribution of stage, the frequency of lymph node involvement and the prognosis in SCCs was not significantly different from those in TCCs. In the present series, the male/female ratio, the distribution of stage, and the frequency of lymph node-involvement in non-TCCs, including SCCs and adenocarcinoma, were all not significantly different from TCCs. Furthermore, univariate analysis and multivariate statistical analysis demonstrated that tumor histology had no impact on their prognosis.

5. Conclusions

The outcome reported from this large group of patients demonstrates that radical cystectomy provides good survival results, with excellent local tumor control. A 5-year overall survival is expected in 68% of cases. The results from this large series of patients provide sound data and a standard with which other

forms of therapy for invasive bladder cancer can be compared.

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References

[1] Steineck G. Demographic and epidemiologic aspects of bladder cancer. In: Droller MJ, editor. Bladder cancer current diagnosis and treatment. Totowa (NJ): Humana Press; 2000. p. 1–25.
[2] Oosterlinck W, Lobel B, Jakse G, et al. Guidelines on bladder cancer. Eur Urol 2002;41:105–12.
[3] Prout G, Marshall VF. The prognosis with untreated bladder tumors. Cancer 1956;9:551–8.
[4] Monti JE, Straffon RA, Stewart BH. Radical cystectomy without radiation therapy for carcinoma of the bladder. J Urol 1984;131:477–82.
[5] Lerner SP, Skinner E, Skinner DG. Radical cystectomy in regionally advanced bladder cancer. Urol Clin North Am 1992;19:713–23.
[6] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: Long-term results in 1,054 patients. J Clin Oncol 2001;19:666–75.
[7] Madersbacher S, Hochreiter W, Burkhard F, et al. Radical cystectomy for bladder cancer today—a homogeneous series without neoadjuvant therapy. J Clin Oncol 2003;21:690–6.
[8] Giuliani L, Giberti C, Martorana G, et al. Results of radical cystectomy for primary bladder cancer: Retrospective study of more than 200 cases. Urology 1985;26:243–8.
[9] Pagano F, Bassi P, Galetti TP, et al. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor. J Urol 1991;145:45–50.
[10] Fleming ID, Cooper JS, Henson DE, et al., editors. AJCC Cancer Staging Manual, 5th ed. Philadelphia (PA): Lippincott-Raven; 1997. p. 241–3.
[11] Ghoneim MA, El-Mekresh MM, El-Baz MA, et al. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. J Urol 1997;158:393–9.
[12] Smith JA, Whitmore WF. Regional lymph node metastasis from bladder cancer. J Urol 1981;126:591–3.
[13] Skinner DG. Management of invasive bladder cancer: a meticulous pelvic node dissection can make a difference. J Urol 1982;128:34–6.
[14] Wishnow KI, Jhonson DE, Ro JY, et al. Incidence, extent and location of unsuspected pelvic lymph node metastasis in patients undergoing radical cystectomy for bladder cancer. J Urol 1987;137:408–10.
[15] Mills RD, Turner WH, Fleischmann A, et al. Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol 2001;166:19–23.
[16] Vieweg J, Gschwend JE, Herr HW, et al. Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. J Urol 1999;161:449–54.
[17] Leissner J, Hohenfellner R, Thuroff JW, et al. Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. Br J Urol 2000;85:817–23.
[18] Konety BR, Joslyn SA, O'donnell MA. Extent of pelvic lymphadenectomy and its impact on outcome in patients diagnosed with bladder cancer: analysis of data from the surveillance, epidemiology and end results program data base. J Urol 2003;169:946–50.
[19] Dalbagni G, Genega E, Hashibe M, et al. Cystectomy for bladder cancer: a contemporary series. J Urol 2001;165:1111–6.
[20] Frazier HA, Robertson JE, Dodge RK, et al. The value of pathologic factors in predicting cancer specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. Cancer 1993;71:3993–4001.
[21] Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. Eur Urol 2002;41:440–8.
[22] Schuster TG, Smith DC, Montie JE. Pelvic recurrences post cystectomy: Current treatment strategies. Semin Urol Oncol 2001;19:45–50.
[23] Raghavan D. Molecular targeting and pharmacogenomics in the management of advanced bladder cancer. Cancer 2003;97:2083–9.
[24] Sakamoto N, Tsuneyoshi M, Enjoji M. Urinary bladder carcinoma with a neoplastic squamous component: a mapping study of 31 cases. Histopathology 1992;21:135–41.
[25] Anderstrom C, Johansson SL, von Schultz L. Primary adenocarcinoma of the urinary bladder: A clinicopathologic and prognostic study. Cancer 1983;52:1273–80.
[26] Richie JP, Waisman J, Skinner DG, et al. Squamous carcinoma of the bladder: treatment by radical cystectomy. J Urol 1976;115:670–2.
[27] Kasahara K, Inoue K, Shuin T. Advanced adenocarcinoma of the urinary bladder successfully treated by the combination of cisplatinum, mitomycin-C, etoposide and tegafur-uracil chemotherapy. Int J Urol 2001;8:133–6.

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ORIGINAL ARTICLE

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The current status of perioperative chemotherapy for invasive bladder cancer: a multiinstitutional retrospective study in Japan

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Abstract
Background. We conducted a multiinstitutional analysis to clarify the clinical significance of perioperative chemotherapy, in invasive bladder cancers in Japan, and to identify the patient subpopulations who could benefit from perioperative chemotherapy.
Methods. A total of 913 consecutive patients aged less than 80 years who underwent radical cystectomy for invasive bladder cancer from 1990 to 2000 at 32 Japanese hospitals were retrospectively analyzed. Median follow-up was 3.8 years (range, 0.1 to 11.8 years).
Results. In total, 341 patients (37.3%) were treated with perioperative chemotherapy, including neoadjuvant chemotherapy (n = 174), adjuvant chemotherapy (n = 114), or a combination of both chemotherapies (n = 53). With cisplatin-based combination chemotherapy, the MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen was the one most frequently used for perioperative chemotherapy, but the average number of cycles was distinctly less than that in reported randomized trials. MEC (methotrexate, epirubicin, and cisplatin) chemotherapy had efficacy similar to that of the MVAC regimen. On analysis of patients stratified by stage, the overall survival of patients with adjuvant chemotherapy was significantly better than that of those without adjuvant chemotherapy, in patients with pT2b, pN0 or pT3, pN0 (P = 0.016 or 0.020, respectively), but adjuvant chemotherapy had no, or the opposite, effect on patients with pT2a, pN0, pT4, pN0, or pTany, pN+. On the other hand, neoadjuvant chemotherapy provided a statistically significant survival benefit only for patients with clinical T3N0 (P = 0.015). Of note, in the high-risk subgroup, the overall survival rate for patients with complete response (CR) after neoadjuvant chemotherapy was significantly better than that of patients with partial response (PR) or no change (NC)/progressive disease (PD) (P = 0.043).
Conclusion. In Japan, cisplatin-based combination chemotherapy has been the main modality adopted perioperatively for high-risk patients with radical cystectomy. This study's clinical results indicated that perioperative chemotherapy may improve survival in patients with T3N0 or pT2b/pT3, pN0 bladder cancer.

Key words Bladder cancer · Radical cystectomy · Adjuvant chemotherapy · Neoadjuvant chemotherapy · Overall survival

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Introduction

Bladder cancer is one of the most common genitourinary malignancies, in which 20% to 40% of patients present with or develop invasive disease.[1] Invasive bladder cancer is very aggressive, and about half of the patients die of the disease within 5 years, even following radical cystectomy with lymph node dissection.[2,3] This high mortality rate has been considered to be due to micrometastasis that is present at the time of radical cystectomy. To improve the prognosis of invasive bladder cancer, perioperative systemic chemotherapy has been adopted empirically, in combination with radical cystectomy, because bladder cancer is sensitive to chemotherapy, as shown by an overall response rate of 12%–73%.[4,5] Several clinical trials have been performed since around 1985 to assess the efficacy of perioperative chemotherapy with definitive local therapy.[6–11] Most of the trials, however, failed to elicit conclusive results regarding the clinical significance of perioperative systemic

chemotherapy in the management of invasive bladder cancer. This may have been due to the suboptimal design of these clinical trials, including less effective chemotherapy regimens, sample sizes too small for important changes in survival to be detected or ruled out, inadequate selection of patients, and premature closure of the trials. We conducted a multiinstitutional retrospective study to clarify the current status of perioperative chemotherapy in invasive bladder cancers in Japan, and to identify the subgroups of patients who might benefit from perioperative chemotherapy.

Patients and methods

We have established a database at 32 Japanese institutions, including three university hospitals (Kyoto University Hospital, Nagoya University Hospital, and Nara Medical University Hospital), containing detailed and comprehensive clinical and pathologic information about all patients who have undergone cystectomy from January 1990 to December 2000.[12] The intent of the present analysis was to focus on a relatively homogeneous cohort of patients with invasive transitional cell carcinomas (TCCs) of the bladder who underwent a complete resection of all grossly evident tumors at the time of cystectomy. Although the records of 1131 consecutive patients were identified in the database, excluded from analysis were 89 patients with non-TCC bladder cancers, 115 patients who underwent simple cystectomy without bilateral iliac lymph node dissection, and 14 patients over 80 years old (because systemic chemotherapy is generally not indicated for these patients. These patients will be the subject of a separate report. These exclusions may create some biases; however, the analysis of patients with a completed cystectomy with curative intent remains a critical topic. The remaining 913 patients underwent radical cystectomy for primary TCC of the bladder with intent to cure, and were the focus of this analysis. For entry to this study, informed consent was not obtained from each patient, because the analysis was conducted retrospectively.

The clinical data that were collected from the medical records included age, sex, past history, histologic grading according to the World Health Organization system, clinical and pathological staging according to the TNM classification,[13] and the presence of and regimen of perioperative therapy. The follow-up procedures varied slightly among the institutions considered; however, some general statements should be made because of the long study period. Patients were followed every 3–6 months during the first 2–3 years; the visits were every 6 months or annually thereafter. The follow up at each visit included a physical examination (general and local). This prompted, when needed, and according to the clinical suspicion of persisting/relapsing disease, the use of the same specific diagnostic tests as those performed during the baseline workup (e.g., ultrasonography, chest X-ray, computed tomography [CT], and bone scan).

Table 1. Clinical characteristics of the 913 study patients

Characteristics	Number of cases
Total number of patients	913
Sex	
Male:Female	760:153
Clinical tumor stage	
T1 or less:T2:T3:T4:Tx	243:263:297:54:56
N0:N(+):Nx	855:25:33
Pathological tumor stage	
pT1 or less:pT2a:pT2b:pT3:pT4	369:171:120:185:68
pN0:pN+	773:140
Regimen of perioperative chemotherapy	
Neoadjuvant chemotherapy	227
MVAC:MEC:CISCA:PAM:other	99:35:35:3:55
Adjuvant chemotherapy	167
MVAC:MEC:CISCA:PAM:other	73:26:23:20:25

MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MEC, methotrexate, epirubicin, and cisplatin; CISCA, cisplatin, cyclophosphamide, and doxorubicin; PAM, cisplatin, adriamycin, and methotrexate

The overall survival was defined as the time from radical cystectomy to any cause of death; all deaths from any cause were counted as events, and surviving patients were treated as censored at the date of last follow-up before December 31, 2001. Median follow up was 3.8 years (range, 0.1 to 11.8 years). The survival rates were estimated with the Kaplan-Meier method. The log-rank test was performed to test associations between perioperative chemotherapy and survival according to stage. Two-sided P values of less than 0.05 were regarded as statistically significant. All statistical analyses were done by using SAS version 8 (SAS Institute, Cary, NC, USA).

Results

A total of 913 TCC patients (760 men [83.2%] and 153 women [16.8%]), with a mean age of 64.8 years (range, 31 to 80 years), were treated with radical cystectomy with bilateral lymph node dissection. As shown in Table 1, pathological findings demonstrated that 369 patients (40.4%) harbored bladder tumors of pT1 or less, 171 (18.7%) had pT2a tumors, 120 (13.1%) had pT2b tumors, 185 (20.3%) had pT3 tumors, and 68 (7.4%) had pT4 tumors. Eight hundred and fifty-five patients (93.6%) were without evidence of lymph node involvement. Regarding treatment strategy, 341 patients (37.3%) were treated with perioperative chemotherapy. Neoadjuvant chemotherapy was adopted for 174 patients, adjuvant chemotherapy for 114 patients, and a combination of both chemotherapies for 53 patients. The chemotherapeutic regimens used included MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), MEC (methotrexate, epirubicin, and cisplatin), CISCA (cisplatin, cyclophosphamide, and doxorubicin), and PAM (cisplatin, adriamycin, and methotrexate), as well as other miscellaneous regimens.[6,14–16] The MVAC regimen was the most frequently used for neoadjuvant or adjuvant

Table 2. The effects of adjuvant chemotherapy on overall survival in 406 analyzable patients without neoadjuvant chemotherapy

Pathological stage	Adjuvant chemotherapy	No. of patients	No. of deaths	Overall survival (%)		*P* value
				3-Year	5-Year	
pT2a,pN0	Without[a]	119	21	89.9	81.9	0.655
	With	7	1	83.3	83.3	
pT2b,pN0	Without	49	18	64.9	56.5	0.016
	With	24	3	90.8	90.8	
pT3,pN0	Without	65	28	51.5	51.5	0.020
	With	22	4	90.9	75.0	
pT4,pN0	Without	24	6	69.3	69.3	0.033
	With	7	6	17.9	0.0	
pTany,pN+	Without	53	32	40.6	29.8	0.210
	With	46	21	50.7	40.5	

[a] Without neoadjuvant chemotherapy

Table 3. The effects of neoadjuvant chemotherapy on overall survival in 466 analyzable patients without adjuvant chemotherapy

Clinical stage	Neoadjuvant chemotherapy	No. of patients	No. of deaths	Overall survival (%)		*P* value
				3-Year	5-Year	
T2N0	Without[a]	169	36	83.9	76.4	
	With	42	9	84.8	80.9	0.993
T3N0	Without	123	47	56.5	56.6	
	With	77	19	80.0	73.5	0.015
T4N0	Without	18	5	67.3	67.3	
	With	22	11	47.8	47.8	0.345
Tany,N+	Without	5	3	60.0	60.0	
	With	10	4	60.0	60.0	0.979

[a] Without adjuvant chemotherapy

chemotherapy. The indications for perioperative chemotherapy varied among institutions, but, generally, adjuvant chemotherapy was adopted mainly for patients with pT2b or greater tumors and those with pathological lymph node involvement (pN+; Table 2), whereas neoadjuvant chemotherapy was used mainly for patients with T3 or greater tumors, or those with N+ (Table 3).

During follow up, 249 patients (27.2%) died, and the overall survival rates for all 913 patients at 3 and 5 years were 77.3% and 71.6 %, respectively. The overall survival decreased proportionally with more advanced pathological stage. The rates for 5-year overall survival were 85.0% for organ-confined disease (pT0-2, pN0), 58.0% for locally invasive disease (pT3-4,pN0), and 37.3% for disease with lymph node involvement (pTany,pN+) (Fig. 1a). To identify the patients who benefited from perioperative chemotherapy, the effects of adjuvant chemotherapy on survival were assessed in subgroups stratified by pT and pN stage in those without neoadjuvant chemotherapy. The overall survival of patients with adjuvant chemotherapy was significantly better than those without adjuvant chemotherapy in patients with pT2b,pN0 or pT3,pN0 ($P = 0.016$ or 0.020, respectively), whereas adjuvant chemotherapy had no or opposite effects on patients with pT2a,pN0, pT4,pN0, or pTany,pN+ (Table 2). On the other hand, in the analysis of those without adjuvant chemotherapy, neoadjuvant chemotherapy provided a statistically significant survival benefit only for patients with clinical T3N0 ($P = 0.015$; Table 3).

The response was assessed in 176 patients who received neoadjuvant chemotherapy for whom information was available. The response rate (partial response/complete response; PR/CR) was 56.3%, and CRs were achieved in 27 patients (15.3%). Regarding the regimens, MVAC and MEC demonstrated similar response rates, and these were superior to those of CISCA and the miscellaneous other regimens (Table 4). Although the survival rates for patients with PR and those with no change/progressive disease (NC/PD) were not significantly different, the overall survival rate for patients with CR in the high-risk subgroup (patients with T3 or more or N+) was significantly better than that of those with PR or NC/PD ($P = 0.043$; Fig. 1b). Furthermore, although differences did not reach significance, the 5-year-survival rates of patients treated with MVAC/MEC as neoadjuvant chemotherapy tended to be better than those of patients with other neoadjuvant chemotherapy regimens or those without neoadjuvant chemotherapy in the T2/3N0 subgroup (77.3%, 74.0%, and 67.7%, respectively).

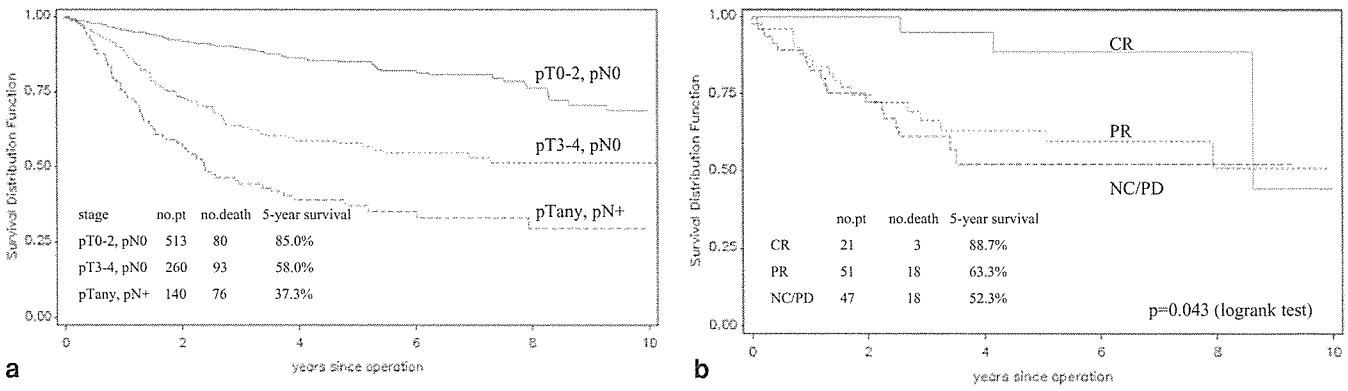

Fig. 1. **a** Estimated Kaplan-Meier overall survival curves for all patients (*pt*), stratified by alpathological stage. **b** Estimated Kaplan-Meier overall survival curves for patients with T3 or higher or N+, stratified by the response to neoadjuvant chemotherapy. *CR*, complete response; *PR*, partial response; *NC*, no change; *PD*, progressive disease

Table 4. Responses of 176 assessable patients to various regimens of neoadjuvant chemotherapy

Regimen of neoadjuvant chemotherapy	No. of patients	Average no. of cycles	Response to chemotherapy		
			CR	PR	NC/PD
MVAC	80	1.5	15 (18.8%)	33 (41.3%)	32 (40.0%)
MEC	34	2.1	7 (20.6%)	16 (47.1%)	11 (32.4%)
CISCA	30	1.2	1 (3.3%)	8 (26.7%)	21 (70.0%)
Other	32	2.3	4 (12.5%)	15 (46.9%)	13 (40.6%)
	176				

MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; MEC, methotrexate, epirubicin, and cisplatin; CISCA, cisplatin, cyclophosphamide, and doxorubicin; PAM, cisplatin, adriamycin, and methotrexate; CR, complete response; PR, partial response; NC, no change; PD, progressive disease

Discussion

In this multiinstitutional retrospective study, we demonstrated the current status of perioperative chemotherapy in the management of locally advanced TCC of the bladder in Japan and assessed the patients who could benefit from chemotherapy. In total, 341 patients (37.3%) were treated with perioperative chemotherapy, and the rates of neoadjuvant and adjuvant chemotherapy were similar. As for the regimen of perioperative chemotherapy, MVAC was the most frequently adopted in our series, and this is the global standard chemotherapy regimen for bladder cancer. Several modified regimens were developed on the basis of MVAC to reduce the toxicity of the chemotherapy or to enhance its effects. MEC (methotrexate, cisplatin, and epirubicin) was also used, and the response rates to MEC were almost the same as those of MVAC. Although the indications and regimens of chemotherapy varied among the institutions in this study, perioperative chemotherapy, in the form of cisplatin-based combination chemotherapy, was the main modality adopted for high-risk patients, and, therefore, we consider this series acceptable for analysis.

Adjuvant chemotherapy has been established for the treatment of other cancers, in which the response rates to chemotherapy are the same or lower than those in bladder cancer.[17,18] In invasive bladder cancers, two randomized trials revealed a benefit of adjuvant chemotherapy compared with radical cystectomy alone.[19,20] These two reports showed the apparent benefit of the chemotherapy in patients who had especially poor-risk cancers (pT3 or pN+), although each of these trials included fewer than 100 patients, and both were terminated prematurely, on the basis of an interim analysis favoring the chemotherapy group, without evaluating overall survival curves as an endpoint. In the present study, 5-year overall survival rates in patients with adjuvant chemotherapy were better than those in patients without adjuvant chemotherapy in the subgroup of patients with pT2b,pN0 or pT3,pN0 (P = 0.016 or 0.020, respectively), but adjuvant chemotherapy had no, or opposite, effects on patients with pT2a,pN0, pT4,pN0, or pN+. These results suggested that adjuvant chemotherapy may improve prognosis in locally advanced bladder cancer (pT2b or pT3 without lymph node metastasis), although retrospective studies do have a patient selection bias. On the other hand, 80% of patients with pT2a or lower stage bladder cancers survived for more than 5 years after radical cystectomy

alone; thus, an incremental survival benefit with chemotherapy may not have been detected in this subgroup. Conversely, massively advanced cancer, including extravesical invasion (pT4) or lymph node metastasis, may be beyond the therapeutic ability of adjuvant chemotherapy, because of the large residual tumor burden.

As for neoadjuvant chemotherapy, there were more studies than those of adjuvant chemotherapy in bladder cancer.[9–11,21,22] The neoadjuvant approach has several benefits: one is that it allows preoperative reduction of tumor size, which may make local therapy more effective. Second, patients may best tolerate chemotherapy before they have received potentially debilitating local treatment such as radical cystectomy. Furthermore, neoadjuvant chemotherapy can provide clinically important information about chemosensitivity. A recent metaanalysis[4] revealed a significant benefit of platinum-based neoadjuvant chemotherapy on overall survival in invasive bladder cancer, although several randomized trials have failed to demonstrate its effectiveness in invasive bladder cancer. Grossman and colleagues[23] reported the benefit of three cycles of neoadjuvant MVAC chemotherapy with radical cystectomy in a randomized trial enrolling 307 patients. Especially, the survival benefit of neoadjuvant MVAC appeared to be strongly related to downstaging of the tumor to pT0. In our study, the overall survival rate for patients with CR was demonstrated to be significantly better than that for those with PR or NC/PD, suggesting that neoadjuvant chemotherapy can provide a survival benefit only when tumors possess good chemosensitivity and the neoadjuvant chemotherapy achieves a CR.

When performing perioperative chemotherapy with radical cystectomy, important factors to consider, other than chemosensitivity, are: which regimens are suitable and how many cycles of chemotherapy are needed to improve survival. MVAC is the most cmmon regimen worldwide, and three cycles of MVAC have been adopted for randomized studies.[23] However, our data demonstrated that, in Japan, generally, MVAC or modified MVAC regimens (MEC or PAM) were used empirically for an average of two cycles, suggesting that three cycles of these regimens are not tolerable for Japanese. Recently, several novel cytotoxic compounds have been studied in the management of recurrent and metastatic bladder cancer. In particular, gemcitabine or paclitaxel are considered to be promising agerts for bladder cancer.[24,25] In the future, neoadjuvant chemotherapy, using these new compounds and molecular markers for predicting chemosensitivity, will need to be assessed by randomized prospective studies.

Conclusion

Our retrospective analysis indicated that perioperative chemotherapy may improve survival in patients with T3N0 or pT2b/pT3,pN0 bladder cancer who have a radical cystectomy. A significant survival benefit may be obtained in those who achieve pathological downstaging to a complete clinical response after neoadjuvant chemotherapy. To achieve maximum survival benefit from adjuvant chemotherapy and to avoid the administration of toxic chemotherapeutic agents to unresponsive patients, more reliable markers, and more attractive chemotherapeutic regimens should be carefully investigated by well-designed randomized trials.

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References

1. Raghavan D, Shipley WU, Garnick MB, et al. (1990) Biology and management of bladder cancer. N Engl J Med 322:1129–1138
2. Giuliani L, Giberti C, Martorana G, et al. (1985) Results of radical cystectomy for primary bladder cancer. Retrospective study of more than 200 cases. Urology 26:243–248
3. Pagano F, Bassi P, Galetti TP, et al. (1991) Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. J Urol 145:45–50
4. Advanced Bladder Cancer Meta-analysis Collaboration (2003) Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 361:1927–1934
5. Hussain SA, James ND (2003) The systemic treatment of advanced and metastatic bladder cancer. Lancet Oncol 4:489–497
6. Sternberg CN, Yagoda A, Scher HI, et al. (1985) Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium. J Urol 133:403–407
7. Studer UE, Bacchi M, Biedermann C, et al. (1994) Adjuvant cisplatin chemotherapy following cystectomy for bladder cancer: results of a prospective randomized trial. J Urol 152:81–84
8. Freiha F, Reese J, Torti FM (1996) A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 155:495–499
9. Martinez-Pineiro JA, Gonzalez Martin M, Arocena F, et al. (1995) Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: a prospective randomized phase III study. J Urol 153:964–973
10. Malmstrom PU, Rintala E, Hellsten S (2001) The Nordic experience of cooperative urinary bladder cancer trials. Semin Urol Oncol 19:69–70
11. International Collaboration of Trialists (1999) Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet 354:533–540
12. Nishiyama H, Habuchi T, Watanabe J, et al. (2004) Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990–2000 in Japan. Eur Urol 45:176–181
13. Fleming ID, Cooper JS, Henson DE, et al. (eds) (1997) AJCC cancer staging manual, 5th edn. Lippincott-Raven, Philadelphia, pp 241–243
14. Kuroda M, Kotake T, Akaza H, et al. (1998) Efficacy of dose-intensified MEC (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: a prospective randomized trial comparing MEC and M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese Urothelial Cancer Research Group. Jpn J Clin Oncol 28:497–501
15. Sternberg JJ, Bracken RB, Handel PB, et al. (1977) Combination chemotherapy (CISCA) for advanced urinary tract carcinoma. A preliminary report. JAMA 238:2282–2287

16. Oshima S, Ono Y, Fujita T, et al. (1987) Three-drug combination chemotherapy for advanced urothelial tract carcinoma. Cancer Chemother Pharmacol 20 Suppl:S20–S23
17. Chau I, Cunningham D. (2002) Adjuvant therapy in colon cancer: current status and future directions.Cancer Treat Rev 28:223–236
18. Maehara Y, Baba H, Sugimachi K. (2001) Adjuvant chemotherapy for gastric cancer: a comprehensive review. Gastric Cancer 4:175–184
19. Skinner DG, Daniels JR, Russell CA, et al. (1991) The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 145:459–464
20. Stockle M, Meyenburg W, Wellek S, et al. (1992) Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and three adjuvant cycles of chemotherapy. Results of a controlled prospective study. J Urol 148:302–306
21. Wallace DM, Raghavan D, Kelly KA, et al. (1991) Neo-adjuvant (pre-emptive) cisplatin therapy in invasive transitional cell carcinoma of the bladder. Br J Urol 67:608–615
22. Bassi P, Pappagallo GL, Sperandio P, et al. (1999) Neoadjuvant MVAC chemotherapy of invasive bladder cancer: results of a multicenter phase III trial (abstract). J Urol 161:264a
23. Grossman HB, Natale RB, Tangen CM, et al. (2003) Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859–866
24. 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 18:3068–3077
25. Roth BJ, Dreicer R, Einhorn LH, et al. (1994) Significant activity of paclitaxel in advanced transitional-cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. J Clin Oncol 12:2264–2270