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Clinical and pathological evaluations of methotrexate, vinblastine, Adriamycin and cisplatin chemotherapy for advanced urothelial cancers*

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Summary. We have treated advanced transitional-cell carcinoma of the urothelial tract with methotrexate, vinblastine, Adriamycin, and cisplatin (M-VAC) chemotherapy since July of 1985. We analyzed the effect of that chemotherapy in 26 patients with advanced urothelial cancer who were treated in our hospital and followed up. They were divided into two groups. Group 1 consisted of 15 patients with distant metastases. In all, 11 of them received M-VAC as adjuvant chemotherapy for metastatic lesions after surgical removal of the primary lesion, and the remaining 4 patients were not operable since they had very advanced-stage tumors; they received only M-VAC chemotherapy. Group 2 contained 11 patients who received M-VAC neo-adjuvant chemotherapy. In group 1, the overall response rate was 57.1% and the mean duration of response was 12.6 months. In the 11 patients who had received M-VAC as adjuvant therapy after surgical removal of the primary tumor, the mean duration of response was 14.1 months. After M-VAC chemotherapy, six patients underwent surgical resection of metastatic lesions and restaging was done pathologically in these cases. The clinical response coincided with the pathological response in all six cases. In group 2, 5 of 11 patients experienced histological downstaging of the resected bladder. M-VAC chemotherapy combined with surgical resection of residual tumors has proved to be an effective option against advanced urothelial cancer.

Introduction

Combination chemotherapy is the main modality of recent chemotherapy because it provides the possibility of increasing the therapeutic effect while reducing the side effects of the drugs. In 1985, the use of systemic chemotherapy consisting of four drugs, i.e., methotrexate (MTX), vinblastine (VLB), Adriamycin (ADM), and cisplatin (CDDP); (M-VAC regimen), was reported for advanced urothelial cancers [10]. M-VAC therapy has drawn much attention because of its high effectiveness, especially the complete responses (CRs) obtained. However, the maintenance of CRs is very difficult using this therapy alone [11, 14]. In the present study, we gave M-VAC therapy to patients with advanced urothelial cancers and carried out residual tumor resection in the responders. We report the clinical and pathological responses of our treated patients.

Materials and methods

Patients. During the 5-year period from July 1985 through November 1990, 26 patients were admitted to our hospital for advanced transitional-cell carcinoma of the urinary tract (Tables 1, 2). This population included 23 men and 3 women whose mean age was 61 years (range, 42–79 years). The patients were divided into two groups. Group 1 consisted of 15 patients with distant metastases, and group 2 contained 11 patients who received neo-adjuvant chemotherapy.

In group 1, the site of the primary lesion was the bladder in 11 patients, the pelvis in 3 subjects, and the ureter in 1 case. Histologically, all of the tumors were transitional-cell carcinomas (TCC) except case 12, which was a mixed type of TCC and squamous-cell carcinoma (SCC). The degree of differentiation was grade 3 in all cases examined, but no biopsy was performed in cases 13 and 14. The site of metastatic lesions was the lymph nodes and lungs in 7 patients each, bone in 5 subjects, the liver in 3 patients, and muscle and subcutaneous tissue in 1 patient each. The median Karnofsky performance status (PS) was 64.3%. In all, 8 patients underwent radical cystectomy, 2 subjects underwent total nephroureterectomy, and 1 patient underwent partial cystectomy as the surgical resection procedure prior to M-VAC therapy. The remaining 4 patients had presented with metastases at the first medical examination, and their primary lesions were not resectable.

Histologically, all tumors in group 2 were grade 3 TCC. In 5 of the 11 patients, evaluable tumors were resected by transurethral operation; 4 of them received 1 course of M-VAC chemotherapy and 1, case 16, whose tumors were located in the diverticulum of the bladder, received 2 courses of chemotherapy. The remaining 6 patients underwent only transurethral tumor biopsies before receiving M-VAC chemotherapy. Of these, 3 were evaluated as showing no response after 1 course of chemo-

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Table 1. Clinical and pathological findings in group 1 patients treated with M-VAC

Case	Age (years), sex (M/F)	PS (%)	Primary lesion	Histology	Prior therapy	Evaluable lesions	Number of courses	Dose (%)	Complication
1. Y. K.	54, M	20	Bladder	TCC, G3	Partial cystectomy	Bone (S) Subcutaneous mass (M)	1	100	Renal dysfunction
2. E. M.	60, M	80	Bladder	TCC, G3	Total cystectomy	Muscle (M)	4	80	–
3. I. H.	63, M	80	Bladder	TCC, G3	Total cystectomy	Lung (S)	3	80	–
4 K. K.	72, M	100	Bladder	TCC, G3	Total cystectomy	Lung (S)	4	80	–
5. E. I.	79, M	80	Bladder	TCC, G3	Total cystectomy	Lymph nodes (M)	3	80	–
6. K. N.	59, M	80	Renal pelvis	TCC, G3	Total nephro-ureterectomy	Lung (M)	5	80[a]	–
7. K. Y.	66, M	60	Bladder	TCC, G3	Total cystectomy	Lymph nodes (M)	2	100	Pulmonary emphysema
8. K. O.	55, M	80	Bladder	TCC, G3	Total cystectomy	Liver (S) Lymph nodes (S)	1	100	–
9. S. H.	56, M	40	Bladder	TCC, G3	Total cystectomy	Lung (M) Bone (S) Lymph nodes (M)	4	80	Coronary insufficiency
10. M. T.	66, M	60	Bladder	TCC, G3	Total cystectomy	Bone (S)	2	80	–
11. F. F.	64, F	80	Renal pelvis	TCC, G3	Total nephro-ureterectomy	Lung (M)	2	60	Hypo-thyroidism
12. H. O.	46, M	100	Bladder	TCC, G3 + SCC	–	Lymph nodes (M) Bladder (S)	6	80[b]	Acanthosis nigricans
13. T. E.	69, M	60	Renal pelvis	TCC	–	Lung (M) Lymph nodes (M) Renal pelvis (S)	2	100	–
14. S. T.	65, M	40	Ureter	TCC	–	Lung (M) Liver (M) Bone (M)	3	80	–
15. M. S.	44, M	80	Bladder	TCC, G3	–	Liver (S) Bone (M) Lymph nodes (M)	1	100	–

PS, Karnofsky performance status; TCC, transitional-cell carcinoma; SCC, squamous-cell carcinoma; S, Solitary lesion; M, multiple lesions

[a] 70% dose of MTX, VLB, and ADM and 40% dose of CDDP only in the 5th course

[b] M-VAC+ bleomycin (BLM); on days 1, 8, and 15, 10 mg BLM was given

Table 2. Clinical and pathological findings in group 2

Case	Age (years), sex (M/F)	PS (%)	Histology, grade	Number of courses	Dose (%)
16. S. N.	69, M	80	TCC, G3	2	100
17. T. H.	69, M	80	TCC, G3	2	100
18. M. H.	73, M	90	TCC, G3	1	100
19. R. M.	42, F	90	TCC, G3	1	70
20. R. M.	53, M	80	TCC, G3	2	70
21. F. I.	52, F	90	TCC, G3	1	100
22. Y. Y.	57, M	80	TCC, G3	2	70
23. T. S.	59, M	90	TCC, G3	1	70
24. O. F.	55, M	80	TCC, G3	2	70
25. J. K.	59, M	90	TCC, G3	1	100
26. K. K.	69, M	80	TCC, G3	1	100

PS, Karnofsky performance status; TCC, transitional-cell carcinoma

therapy; 2 of these nonresponders underwent radical cystectomy within 1 month and the other nonresponder received 1 additional course of chemotherapy before undergoing radical cystectomy. The other 3 patients responded well to the 1st course of M-VAC chemotherapy; they received 1 further course before undergoing radical cystectomy.

Method of medication. Medication was performed in accordance with the method of Sternberg et al. [11]; that is, 30 mg/m^2 methotrexate (MTX) was given on day 1, and 3 mg/m^2 vinblastine (VLB), 30 mg/m^2 Adriamycin (ADM), and 70 mg/m^2 cisplatin (CDDP) were given 24 h thereafter. The same doses of MTX and VLB were given on days 15 and 22.

The first patient (case 1) received 100% doses and died of sepsis after experiencing remarkable bone marrow suppression. On the basis of this experience, 80% of the original doses were given to cases 2–6, 9, 10, 12, and 14 and 70% of the planned doses were given to cases 19, 20, 22, 23, and 24. The criteria for administration on days 15 and 22 included a peripheral WBC of >3,000/mm^3 and a platelet count of $>10 \times 10^4$/mm^3. In 9 of 14 cases (excluding case 1), the chemotherapy scheduled to be given on day 15 and/or day 22 was postponed or discontinued.

Table 3. Histological grading of therapeutic effects according to Oboshi-Shimosato's classification [9]

Grade 0	No change
Grade 1	Characteristic changes in tumor cells but not in tumor structures
Grade 2	Characteristic changes in tumor cells and tumor structures (viable cells remain) A: Viable tumor cells are frequently observed B: Viable tumor cells are few in number
Grade 3	Nonviable tumor cells only
Grade 4	No tumor cells A: Extensive areas of necrosis B: Granulation tissue C: Scar tissue

The clinical effect was judged by the standards for direct efficacy of solid-tumor chemotherapy [3]. Surgical specimens of residual tumors in partial responders (PRs) in group 1 and in all patients in group 2 were evaluated according to the criteria of Oboshi and Shimosato [9] (Table 3).

Results

Clinical effect

The responses of 14 patients in group 1 (excluding case 1) included 1 CR (7.1%), 7 PRs (50%), 3 cases of no change (NC; 21.4%), and 3 cases of progressive disease (PD; 21.4%). The objective response rate (PR+CR) was 57.1% (Table 4). The response rates for the metastatic lesions in group 1 are summarized in Table 5. For metastases to the muscle, lymph node, and lung, relatively high response rates were obtained (>50%); however, metastases to the liver and bone showed a poor response to M-VAC chemotherapy. In group 2, the responses of 11 patients (except the 5 whose evaluable tumors were resected by transurethral operation) included 3 PRs (cases 17, 22, and 24) and 3 NCs (cases 16, 19, and 20) after M-VAC neo-adjuvant chemotherapy.

Table 5. Response rate for 22 evaluable metastatic lesions in group 1

Metastatic site	Number of lesions				Response rate (CR+PR/total lesions)
	CR	PR	NC	PD	
Muscle	1	–	–	–	100%
Lymph node	–	5	2	–	71%
Lung	1	3	2	1	57%
Liver	1	–	1	1	33%
Bone	–	–	2	2	0

Histopathological effect

Surgical resection of the residual tumor was performed in six group 1 patients. Histopathologically, one case (case 10) was judged as grade 2A; four (cases 4–7), as grade 2B; and one (case 3), as grade 3 according to Oboshi-Shimosato's classification [9] (Table 4). In group 2, five patients achieved downstaging of their tumors after M-VAC neo-adjuvant chemotherapy. Histologically, one case (case 20) was judged as grade 1; five (cases 17, 19, 21, 24, and 25), as grade 2A; and five (cases 16, 18, 22, 23, and 26), as grade 2B according to Oboshi-Shimosato's classification [9] (Table 6).

Table 4. Summary of the results of M-VAC treatment in group 1

Case	Response			Response duration (months)	Surgical procedure for residual tumor	Survival (months)
	Clinical	Pathological[a]	Surgical			
1. Y. K.	–	–	–	–	–	1[b, d]
2. E. M.	CR	–	–	2	–	16[b]
3. I. H.	PR	3	CR	43	Partial resection of the lung	47
4. K. K.	PR	2B	CR	37	Partial resection of the lung	42
5. E. I.	PR	2B	CR	4	Lymphadenectomy	12[b]
6. K. N.	PR	2B	CR	9	Partial resection of the lung	22[b]
7. K. Y.	PR	2B	PR	3	Lymphadenectomy	5[c]
8. K. O.	PR	–	–	1	–	2[c]
9. S. H.	NC	–	–	–	–	6[b]
10. M. T.	NC	2A	NC	–	Laminectomy +	15[b]
11. F. F.	NC	–	–	–	partial tumorectomy	8[b]
12. H. O.	PR	–	–	2	–	11[b]
13. T. E.	PD	–	–	–	–	4[b]
14. S. T.	PD	–	–	–	–	5[b]
15. M. S.	PD	–	–	–	–	5

CR, Complete response; PR, partial response; NC, no change; PD, progressive disease

[a] Based on Oboshi-Shimosato's classification [9]

[b] Dead

[c] Evidence of disease

[d] Death due to chemotherapy with MVC-CAB: MTX, vincristine (VCR), CDDP, CPM, ADM, ACM, and BLM were given

Table 6. Tumor responses to neoadjuvant chemotherapy in group 2

Case	Stage		Oboshi-Shimosato's classification [9]	Survival (months)
	Clinical	Pathological		
16. S. N.[a]	T2 N0 M0	T1 N1M0	2-B	10
17. T. H.[a]	T3b N0 M0	T2 N0M0	2-A	10
18. M. H.	T1 N0 M0	T1b N0M0	2-B	8
19. R. M.	T3b N0 M1	T3b N0M1	2-A	7
20. R. M.	T4a N3 M1	T4 N3M1	1	6
21. F. I.	T3 N0 M0	T3b N1M0	2-A	5
22. Y. Y.[a]	T4a Nx M0	T1 N0M0	2-B	5
23. T. S.[a]	T2 N0 M0	Tis N0M0	2-B	5
24. O. F.[a]	T3a N1 M0	T2 N0M0	2-A	2
25. J. K.	T2 N0 M0	T3a N0M0	2-A	2
26. K. K.	T4a N0 M0	T4a N0M0	2-B	2

[a] Downstaged

Response duration and outcome

The overall mean duration of response in group 1 was 12.6 months (range, 1–43 months); if the primary lesion was resected successfully, the mean response duration was 14.1 months. The mean survival was 19.6 months (range, 2–47 months) for patients achieving PRs and CRs, 9.7 months (range, 6–15 months) for cases of NC, and 4.7 months (range, 4–5 months) for those showing PD (Table 4).

Patients 3 and 4 were long-term survivors. Their chief initial complaints were macroscopic hematuria, and they underwent total cystectomy and ileal conduit diversion following a diagnosis of bladder tumor (postoperative stage evaluation, pT3a and pT2, respectively). Follow-up of these two patients revealed a solitary metastasis in the right and the left lower lung field at 4 and 9 months post-surgery, respectively. Three or four courses of M-VAC were given to each patient; reductions in the size of the respective tumors amounting to 90% and 95% were confirmed by thoracotomography; thus, both patients showed a PR. Partial resection of the lung was performed to remove the residual tumor, and these cases were histologically assessed as being grade 3 and grade 2B, respectively, according to Oboshi-Shimosato's classification (Fig. 1). Both patients have been free of recurrence for 47 and 42 months, respectively.

Side effects

The most serious side effect encountered was bone marrow suppression. Patient 1, whose PS was 10%–20%, developed renal dysfunction (serum creatinine, 2.4 mg/dl) after the administration of full doses of M-VAC; he also suffered from sepsis followed by agranulocytosis, renal failure, and pulmonary mycosis. This patient died during the 2nd week after the initiation of M-VAC therapy. In the other patients, renal dysfunction was kept mild by means of sufficient diuresis, and only case 6 showed a meaningful increase in serum creatinine levels (2.1 mg/dl). Subjective side effects experienced highly frequently included nausea and vomiting, appetite loss, and alopecia (Table 7).

Discussion

Recent success in the treatment of advanced urothelial carcinoma has shown remarkable improvement [4, 7, 8, 11,

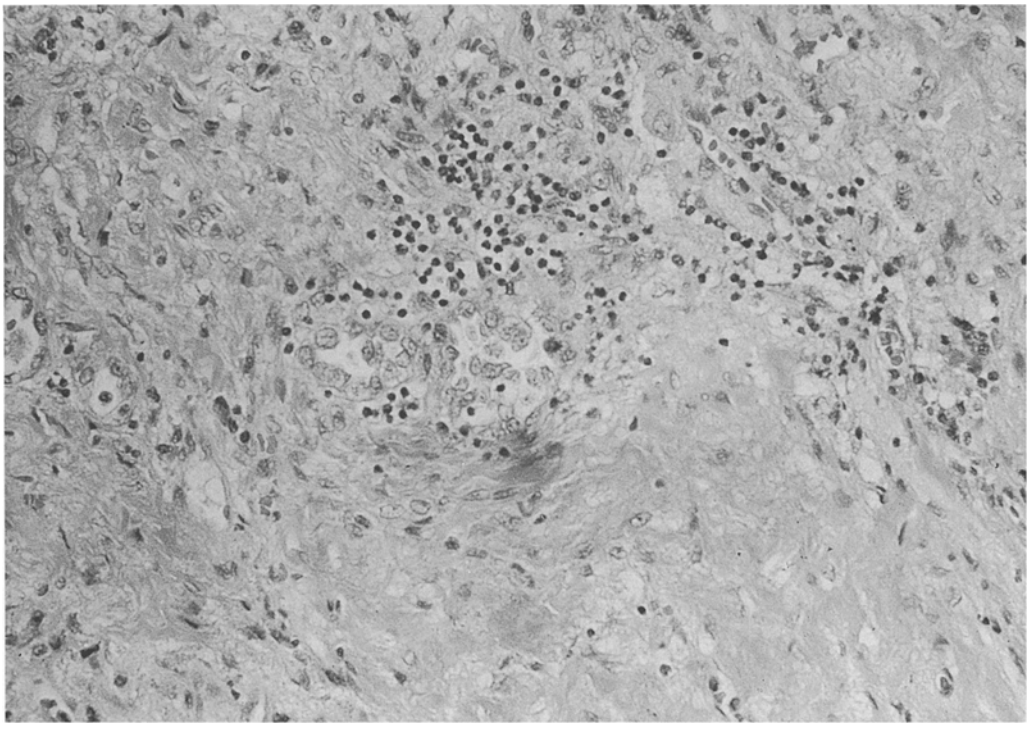

Fig. 1. Some remnants of cancer nests in the scar tissue (case 4; H&E, ×200)

Table 7. Side effects of M-VAC therapy

Side effect	Number of patients				
	Dose of M-VAC				Totals
	100%	80%	70%	60%	
Leukopenia (<3,000/mm³)	10 (91%)	9 (100%)	4 (80%)	1 (100%)	24 (92%)
Anemia (Hb, <10 g/dl)	6 (55%)	7 (78%)	2 (40%)	0 (0)	15 (58%)
Thrombocytopenia (<10 × 10⁴/mm³)	4 (36%)	3 (33%)	1 (20%)	0 (0)	8 (31%)
Nephrotoxicity (serum Cr, >2.0 mg/dl)	1 (9%)	1 (11%)	0 (0)	0 (0)	2 (8%)
Appetite loss	9 (82%)	9 (100%)	4 (80%)	1 (100%)	23 (88%)
Nausea and vomiting	7 (64%)	9 (100%)	4 (80%)	1 (100%)	21 (81%)
Alopecia	8 (73%)	9 (100%)	5 (100%)	1 (100%)	23 (88%)
Diarrhea	3 (27%)	2 (22%)	1 (20%)	0 (0)	6 (23%)
Peripheral neuropathy	0 (0)	2 (22%)	0 (0)	0 (0)	2 (8%)

Side effects more severe than grade 1 according to the criteria of the Japan Society for Cancer Therapy were handled as positive. Hb, Hemoglobin; Cr, creatinine

13]. Studies using cisplatin therapy for this particular form of malignancy have been carried out, and the efficacy rate of this drug has been increased by its combination with other agents.

In 1985, Sternberg et al. [10] gave M-VAC to 24 patients with advanced urothelial cancers and reported a response rate (PR + CR) of 71%, with 50% of patients achieving a CR. Moreover, in 1988, the same authors treated 83 patients and reported a 69% response rate, with 37% of patients achieving a CR [11]. However, these findings included a surgical CR (sCR) rate of 12%, i.e., cases of residual tumor resection.

In the present study, the response rate was 57%, with 7% of the patients in group 1 achieving a CR. However, the CR rate increased to 36% when surgery for metastatic lesions was performed after M-VAC chemotherapy; this result was slightly worse than that obtained by Sternberg et al. [11]. The mean duration of response was 12.6 months, which was relatively good, although slightly inferior to the 19 months reported by Sternberg et al. [11]. It is thought that these differences in response rate and mean response duration were due to the difference in the PS of the patients and to the M-VAC doses used. However, it is difficult to maintain a CR or a PR for long periods using M-VAC therapy alone [11, 14]. The use of a surgical procedure combined with chemotherapy may prove to be an effective method for achieving long-term CRs or PRs. We think that surgical resection should be performed even in inopera-

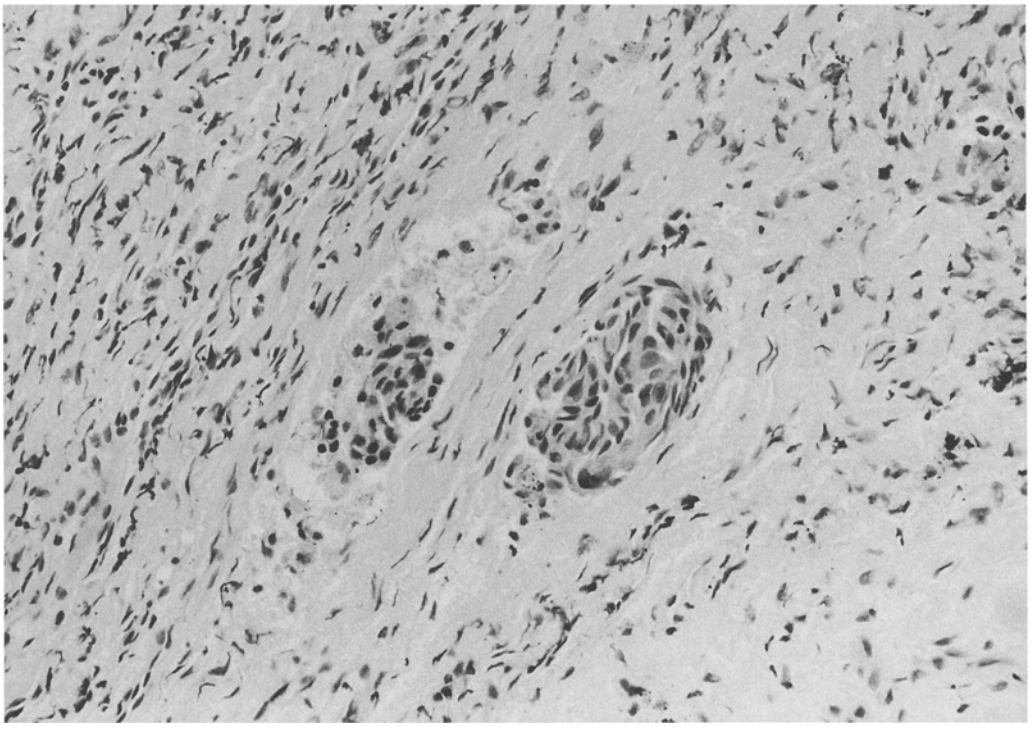

Fig. 2. Cancer nests in two lymph channels (case 6; H&E, ×200)

ble cases, with M-VAC treatment being given simultaneously.

We studied residual tumors that had been resected after M-VAC therapy and histopathologically restaged. Carcinoma cells were identified in all six PRs, and the clinical response coincided with the pathological response. This result differs from Sternberg's report that 5 of 18 PRs were also histological PRs (pPR), whereas viable tumor cells persisted in the other 13 cases. Thus, only surgical resection enables a precise histological diagnosis of CR or PR. After discontinuation of the chemotherapy, surgical resection should be performed in cases in which the tumor size has been reduced by >90% following 3 or 4 courses. In fact, we obtained prolonged survival in cases 3 and 4, whereas patient 6 died of an aortic rupture due to direct invasion of the mediastinal and para-aortic lymph-node metastases after 3 months, even following surgical resection for lung metastasis. The surgical specimen obtained from this patient showed almost complete necrosis but differed from those obtained from patients 3 and 4; that is, there was lymph-channel invasion by viable carcinoma cells (Fig. 2). This finding implies that additional adjuvant therapy is needed for cases in which the resected specimen shows lymph-channel invasion.

On the other hand, we treated 11 other patients using M-VAC as neo-adjuvant chemotherapy. It is well known that radical cystectomy and even radical cystectomy combined with radiation yield 5-year survival values of only 40%–50% and 35%–52%, respectively [2, 4–6]. Moreover, 40%–60% of patients with invasive bladder carcinoma present with lymph-channel involvement and vessel invasion at the time of surgery [1, 12]. Thus, neo-adjuvant chemotherapy with M-VAC is indeed warranted.

Scher et al. [7, 8] gave M-VAC to 65 patients as neo-adjuvant chemotherapy and obtained a combined CR + PR rate of 60% (21% CRs, 39% PRs). In all, 48 of those patients underwent restaging operations, and 11 were found to have downstaged in the histopathological examination. As the mean period of observation was only 24 months, the possibility of lymph-channel invasion could not be entirely ruled out. Thus, neo-adjuvant M-VAC chemotherapy has been found to be an effective therapeutic modality in patients experiencing downstaging of their primary lesions and in those with metastases to the lymph nodes [7, 8]. In the present study, 5 of 11 patients showed histopathological downstaging. Further long-term follow-up of our patients is under way.

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