M-VAC (METHOTREXATE, VINBLASTINE, DOXORUBICIN AND CISPLATIN) FOR POOR PROGNOSIS PATIENTS WITH UROTHELIAL TUMORS AND EFFECT OF DOSE INTENSITY

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The effects of the M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen, which has been reported to improve the outcome of patients with urothelial cancers, were studied on 41 patients treated at our hospital. The patients were divided into adjuvant (24 patients), neoadjuvant (5 patients), and salvage (12 patients) groups. We investigated the dose intensity, the cause-specific survival, response rate and toxicities in the three groups.

Although 36 patients received ≥95% of the initial doses projected, the mean dose intensity (±standard deviation) in the adjuvant, neoadjuvant, and the salvage groups was 77 (±11), 73 (±4), and 74 (±12)%, respectively. The five-year cause-specific survival in the adjuvant group was 69% (95% confidence limit: 50–88%). Only 2 of the 5 patients (40%) in the neoadjuvant group survived 23 months after the initiation of the treatment, and all patients in the salvage group died of cancer or treatment-related toxicity within 33 months. The median survival was 38 months in the adjuvant group, 21 months in the neoadjuvant group, and 7 months in the salvage group. A dose intensity ≥ 75% did not improve survival in any group. The overall response rate was 33% in 15 patients with evaluable lesions. A complete response was noted in 1 patient and a partial response was noted in 4 patients. Two patients died of treatment-related complications. Nausea and vomiting were observed in all patients. Leukopenia, thrombocytopenia and anemia ≥WHO grade 3 were observed in 25 (61%), 4 (10%), and 7 (17%) patients, respectively. Thrombocytopenia, anemia, and pyrexia ≥ grade 3 were seen relatively more often in the patients receiving a dose intensity <75%. Stomatitis ≥ grade 3 appeared to be more frequent in the patients receiving a dose intensity ≥75%.

Adjuvant M-VAC might be beneficial, while its efficacy was limited in the neoadjuvant and salvage settings. Although dose intensity is considered to be important, it did not appear to be related to survival, the response rate, or the toxicity of M-VAC.

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Key words: Urothelial tumor, M-VAC, Dose intensity

INTRODUCTION

The prognosis of patients with disseminated or locally advanced urothelial cancers is reported to be poor[1] Since Sternberg et al. first reported favorable results with M-VAC on urothelial cancers[2], this has become the most common regimen for treatment of patients with invasive urothelial tumors[3,4] We also have utilized M-VAC to improve the survival of poor-risk patients with urothelial tumors[5,6] as adjuvant, neoadjuvant or salvage chemotherapy. Several trials have been conducted to determine the efficacy of adjuvant or neoadjuvant chemotherapy on survival and/or bladder preservation[7-9].

Adherence to the protocol is important for improving the results of chemotherapy. Since urothelial cancers mainly occur in the elderly, the scheduled dose often can not be given because of severe toxicity. The concept of dose intensity is thought to be a good indicator for observance of the protocol[10,11]. Kotake et al. stated that of a dose intensity of more than 70% should improve the response to M-VAC[12] In this study, we investigated the results of M-VAC in relation to the dose intensity on urothelial cancers in patients treated at Nagoya University Hospital.

PATIENTS AND METHODS

From August 1985 to April 1993, we treated 69 patients who had been diagnosed as having invasive urothelial cancers without prior chemotherapy in Nagoya University Hospital. Of these, 46 poor prognosis patients were treated with chemotherapy. The term "poor-prognosis" used when; 1) a tumor component of grade 3 with stage ≥T1, 2) invasion of the deep muscle layer regardless of the grade category, 3) vascular/lymphatic invasion or 4) metastatic disease to the lymph nodes and/or distant organs[5,6] The subjects were 41 patients who received M-VAC, while 5 other patients were

excluded since they received a modified regimen of chemotherapy including carboplatin instead of cisplatin because of renal insufficiency. The salient characteristics of the patients in this study are summarized in Table 1. There were 30 men and 11 women with an average age of 60.9±8.6 years (range: 39 to 77). All patients were evaluated prior to the start of chemotherapy by computed tomographic scans (CT), cystoscopy, urine cytology, intravenous urography, chest radiography, bone scintigraphy, and/or pathologic examination. Thirty-one of the patients had a performance status (PS) of 0, 5 had a PS of 1, 4 had a PS of 2, and 1 had a PS of 3.

The cancers originated from the bladder (n=28), the renal pelvis and/or ureter (n=11), or the renal pelvis/ureter/bladder (n=2). Pure transitional cell carcinomas (TCC) were diagnosed in 32 patients (78%), TCC including other components was found in 8 patients (19.5%), and undifferentiated carcinoma in 1 patient (2.5%). Twenty-eight patients (68.2%) had a grade 3 tumor, 31 (75.6%) had tumors≥stage T3, and 21 (51.2%) had lymph node metastases. Surgical interventions included radical cystectomy (n=25), radical nephroureterectomy (n=9), radical nephroureterocystectomy (n=2), and laparotomy (n=2). Three patients were inoperable after chemotherapy.

We administered M-VAC to those with urothelial cancers as adjuvant (24), neoadjuvant (5), or salvage (12) chemotherapy. Adjuvant chemotherapy was given after the complete resection of the primary lesion when the pathologic examination suggested that the patient had a poor prognosis. Neoadjuvant chemotherapy was given for patients who had been diagnosed as having incompletely resectable tumors, but no distant metastases. Salvage chemotherapy was used for patients with unresectable bulky tumors and/or distant metastases.

Methotrexate (30 mg/m^2) was given on day 1, followed by adequate hydration to obtain a minimum 2000 mL of urine output. On day 2, vinblastine (3 mg/m^2), doxorubicin (30 mg/m^2), and cisplatin (70 mg/m^2) were administered. On days 15 and 22, methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) were administered. Two cycles of M-VAC were given for adjuvant or neoadjuvant chemotherapy, while three to four cycles were generally given for salvage chemotherapy. The dose intensity of the chemotherapy was calculated using Hryniuk's formula[10]. First, the actual total dose of each drug administered during all the courses of chemotherapy was calculated. Second, the dose of each drug was divided by the number of weeks required to complete the chemotherapy and by the body surface area. The number of days required for the last course of M-VAC was calculated, as 6 added to the date when the drugs projected to be administration day 22 were actually administered. Third, the dose of each drug in M-VAC, when given according to the protocol, was calculated (methotrexate; 22.5 mg/m^2/week, vinblastine; 2.25 mg/m^2/week, doxorubicin; 7.5 mg/ m^2/ week, cisplatin; 17.5 mg/m^2/week). Fourth, for each drug we calculated the percentage of the projected dose actually given per week. Finally, the average percentage of the dose intensity delivered was calculated. Since the average dose intensity was 75.7±10.8 (46–99.2)%, "≥75%" was chosen as an indicator for good dose intensity.

We determined the response of each evaluable lesion to the chemotherapy. Fifteen of 17 patients who received the neoadjuvant or the salvage M-VAC had evaluable lesions (8 primary tumors, 8 metastasized lymph nodes, 4 lung metastases, 2 bone metastases, and 1 liver metastasis). The response was classified as complete response (CR), when all the measurable lesions disappeared after chemotherapy for at least 4 weeks, confirmed by either imaging or pathology, partial response (PR), when the tumor size was decreased ≥50% without any new lesions for at least 4 weeks, no change (NC), when the tumor size was decreased <50% or an increase of ≤25%, and progressive disease (PD) when the tumor was enlarged ≥25% or new lesions were found.

Fisher's exact test and t-test were used to compare backgrounds of patients, responses, and toxicities.

Table 1. Characteristics of patients with urothelial cancer treated with M-VAC

		Adjuvant (24)	Neoadjuvant (5)	Salvage (12)
Gender	Male/Female	19/5	2/3	9/3
Age	Mean±S.D. (Range)	59.3±8.3 (43–74)	64.4±6.0 (54–69)	62.7±10.0 (39–77)
PS*	0,1/2,3	23/1	5/0	8/4
Primary lesion	Bladder	17	3	8
	Upper urinary tract	7	2 (1)**	4 (1)**
Histology	TCC only/TCC+Others	21/3	5/0	6/6(1)***
Grade	G2/G3	8/16	2/3	3/9
Stage	T1/T2/T3/T4	3/6/13/2	0/0/2/3	1/0/4/7
Lymph node metastasis	N0/N+	17/7	2/3	1/11

*: Performance status, ( )**: with bladder lesion, ( )***: undifferentiated carcinoma

We determined the cause-specific survival in each chemotherapy group. Survival was calculated by the Kaplan-Meier method and compared by the Log-rank test. The survival intervals were defined as the time from the date when the chemotherapy started to the last date of observation. Patients with no evident disease or those who died of other causes were defined as censored cases. Furthermore, we investigated the effect of the dose intensity on the survival and on the toxicities based on the World Health Organization (WHO) classification.

RESULTS

Dose intensity of M-VAC

The mean number of cycles was 2.0±0.6 (1 to 4) in the adjuvant group, 2.0±0 in the neoadjuvant group, and 2.4±0.9 (1 to 4) in the salvage group. The dose intensity was 77±11 (54 to 99)% in the adjuvant group, 73±4 (67 to 76)% in the neoadjuvant group, and 74±12 (46 to 91)% in the salvage group. Four patients in the adjuvant group declined the second cycle. 36 patients received ≥95% of the initial doses projected. Fifteen patients in the adjuvant group, 3 in the neoadjuvant group, and 5 in the salvage group had a dose intensity ≥75%.

Cause-specific survival

The median cause-specific survival was 48 months in the adjuvant group, 21 months in the neoadjuvant group and 7 months in the salvage group (Fig. 1). Seven of 24 patients in the adjuvant group, 3 of 5 patients in the neoadjuvant group, and 10 of 12 patients died of urothelial cancer. Two patients in the salvage group died of toxicity related to chemotherapy. The 5-year cause-specific survival rate in the adjuvant group was 69% (95% confidence limit: 50–88%). If those with pT1 and pT2 diseases were excluded, the 5-year cause-specific survival rate

of 15 patients in the adjuvant group was 64% (95% confidence limit: 40–88%). In the neoadjuvant group, 2 of the 5 patients (40%) survived without recurrent disease 23 months after the initiation of the treatment. There were no significant differences in survival between those who received a dose intensity of ≥75%, and <75%, in each chemotherapy group (Fig. 2). The background, except gender in neoadjuvant and salvage group, was not different between the two dose intensity groups. Dose intensity was <75% in 8 of the 9 male patients and ≥ 75% in 3 of the 8 patients in the neoadjuvant and salvage group (p=0.04).

Response rate to M-VAC in the patients with evaluable lesions

The overall response rate was 33% (95% confidence limit: 9–57%) in the 15 patients with evaluable lesions (Table 2). A CR was confirmed pathologically in only 1 patients and lasted for 18 months, but she subsequently died of brain metastases. Four patients achieved PR and 3 of them died of cancer. The PR lasted for a mean of only 2.7 (3.1, 2.7 and 2.3) months. One patient underwent cystectomy about 1 month after chemotherapy, and he has not had any evidence of recurrent disease. The response rates were not significantly different between the patients who received a dose intensity ≥75% and <75%.

Three of the 8 primary lesions, 5 of the 8 lymph node metastases, 1 of the 4 lung metastases, and the one liver metastasis responded to M-VAC (Table 3). However, none of the bone lesions responded to chemotherapy. A CR was achieved in only 2 patients with lymph node involvement.

Toxicity

The toxicity is summarized in Table 4. Two patients undergoing salvage chemotherapy died from
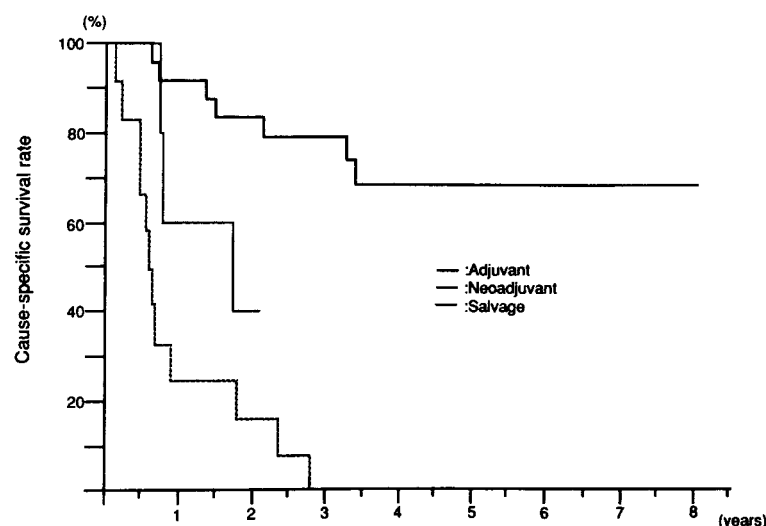

Fig. 1. Cause-specific survival rate. The median cause-specific survival was 48 months in the adjuvant group, 21 months in the neoadjuvant group and 7 months in the salvage group.
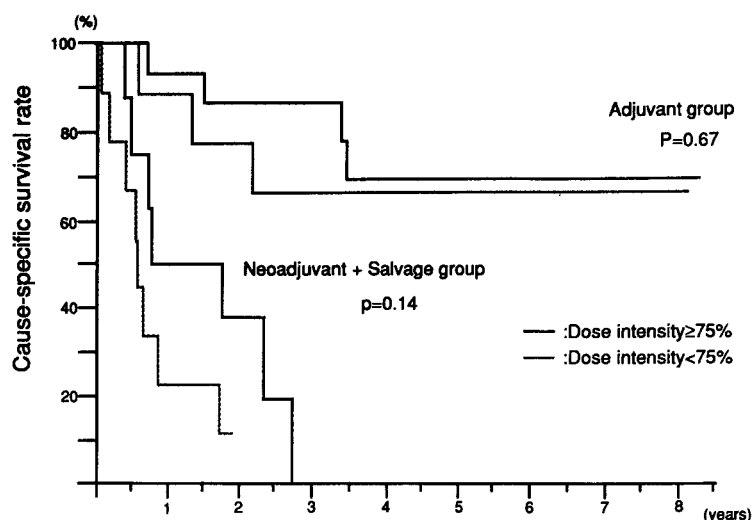
Fig. 2. Cause-specific survival curve according to the dose intensity. There were no significant differences in survival between those who received a dose intensity of ≥75%, and <75%, in all chemotherapy groups.

Table 2. Relationship between M-VAC dose intensity response

Dose intensity*	Response**				Objective responce (CR+PR)
	CR	PR	NC	PD	
≥75%	1	2	3	1	3/ 7 (43%)
<75%	0	2	4	2	2/ 8 (25%)
Total	1	4	7	3	5/15 (33%)

* : Dose intensity, percentage of initially calculated doses received.
** : CR: complete response, PR: partial response, NC: no change, PD: progressive disease

Table 3. Sites of lesions and response to M-VAC

Tumor site	Number	Response
Primary tumor	8	3 (38%)
Lymph nodes	8	5 (63%)
Lung	4	1 (25%)
Liver	1	1 (100%)
Bone	2	0 (0%)

M-VAC related complications. They eventually died of multiple organ failure during the first course of M-VAC.Their performance status was 0 and 1, and their ages were 64 and 72 years, respectively. One had suffered severe asthma attacks, and subsequently developed pneumonia. In the other patient pneumonia caused acute respiratory failure.

The frequency of all toxicities ≥WHO grade 3 listed in Table 4 was not significantly different between patients receiving a dose intensity <75% and ≥75%. However, thrombocytopenia, anemia, and pyrexia ≥ grade 3 appeared to occur relatively more frequently in the <75% dose intensity group. Greater than grade 3 liver and renal dysfunction was observed in the two patients who died of M-VAC toxicity. Grade 1 renal dysfunction in one patient

returned to normal after the discontinuation of chemotherapy. Nausea and vomiting were observed in all patients. Stomatitis ≥ grade 3 was seen more often in the ≥75% dose intensity group.

DISCUSSION

M-VAC has become the standard chemotherapy regimen for advanced urothelial cancers, since large-scale clinical trials revealed that M-VAC was superior to the combination of cyclophosphamide, doxorubicin and cisplatin[3] as well as single agent cisplatin[4] However, the duration of response has been reported to be short and long-term disease-free survival was achieved in fewer patients than anticipated despite good response rates[3,4,10,12]

Since 1985, we have administered M-VAC for poor-prognosis patients as either adjuvant, neoadjuvant, or salvage chemotherapy. We do not believe that all patients with invasive urothelial cancers need to receive M-VAC. Therefore, we have given adjuvant M-VAC to the patients with the following characteristics: a pathologic stage ≥3a, a grade 3 component, lymph node involvement, and/or lymphatic/vessel invasion[5,6] In this study, the 5-year survival rate in the adjuvant group was 69%. When those with pT1

Table 4.   Toxicities of M-VAC observed in 41 evaluable patients

Toxicity	≥WHO Grade 1	≥WHO Grade 3		
	Total (41)	<75% (18)	75%≤ (23)	Total (41)
Hematologic				
Leukopenia	40 (98%)	11 (61%)	14 (61%)	25 (61%)
Thrombocytopenia	20 (49%)	3 (17%)	1 (4%)	4 (10%)
Anemia	37 (90%)	5 (28%)	2 (9%)	7 (17%)
Gastrointestinal				
Nausea & vomiting	41 (100%)	18 (100%)	22 (96%)	40 (98%)
Stomatitis	35 (85%)	2 (11%)	6 (26%)	8 (20%)
Pyrexia	21 (51%)	9 (50%)	8 (35%)	17 (41%)
Alopecia	40 (98%)	8 (44%)	11 (52%)	20 (49%)
Renal	3 (7%)	2 (11%)	0 (0%)	2 (5%)
Hepatic	13 (32%)	2 (11%)	0 (0%)	2 (5%)

and pT2 diseases were excluded, the 5-year survival rate was 64%. The 3-year survival rate of patients with ≥pT3 bladder cancer in our hospital was reported previously to be 26.8% before M-VAC[13]. In addition, the 5-year survival rate of patients with renal pelvis/ureter cancer invading beyond the musculature has been reported to be 29.5%[5]. Although it is difficult to strictly compare the results with those of our historical data, adjuvant M-VAC may improve the survival of poor-prognosis patients with urothelial cancer. Some randomized studies have been conducted to ascertain the efficacy of adjuvant chemotherapy. Stöckle et al. have reported that three courses of adjuvant M-VAC improved survival[7], while Skinner et al. have stated that four courses of adjuvant CAP delayed tumor progression.

We administered preoperative M-VAC to the patients whose local bulky tumors were felt to be incompletely resectable by surgery alone. Thus, our neoadjuvant therapy was similar to that of salvage therapy. Patients in the neoadjuvant group had a higher stage of tumor with lymph node metastases than did those in the adjuvant group (Table 1). The median cause-specific survival in the neoadjuvant and salvage groups was 21 months and 7 months, respectively. No patients in the salvage group survived for more than 32 months. Survival of the patients with advanced urothelial cancer was not satisfactory, as previously reported[4,14] Dimopoulos and associates noted that the majority of patients who had responded to cisplatin-based chemotherapy relapsed within a median of 12 months, and that the median survival after relapse was 9 months[15]

The overall response rate was 33% (5/15) in our study. A complete response was observed in only one patient (7%). The response rate to M-VAC has been reported to be 40 to 72% with a complete response rate of 13 to 19%[16,17]. Small, low stage tumors reportedly can be eradicated by the chemotherapy[9], and thus may be more sensitive to chemotherapy. Since our study included a large

number of patients with bulky, high stage tumors, this may account for our poorer results.

M-VAC is toxic including treatment-related deaths. In our study, two patients (5%) died of treatment-related toxicity. In both patients, pneumonia eventually resulted in multiple organ failure. Since urothelial cancers often arise in elderly people who have various medical problems or have organs with little reserve ability, we should try to strictly prevent infections. Leukopenia and thrombocytopenia of grade 3 or greater were observed in 61% and in 10% of the patients, respectively. Pyrexia, nausea and vomiting, and stomatitis of grade 3 or greater were observed in 41, 100, and 20% of the patients, respectively. The degree and incidence of toxicity in our study was somewhat higher than those reported by others[3,4] but similar to those reported by Kotake et al[12]

Hryniuk noted that the received dose intensity correlated with response[10], and can be used as an indicator of the completeness of the administered chemotherapy according to the protocol. In Japan, urologists administer chemotherapy, and reports on the dose intensity may permit comparisons with studies conducted by medical oncologists in other countries. Longo et al. have recommended the calculation using the duration of the actual treatment course[11] Based on their formula for example, a prolongation of 3.1 days in a cycle resulted in a 10% reduction in dose intensity. Omission of methotrexate and vinblastin on day 15 without a delay resulted in a 17% reduction in the dose intensity per cycle. The problem with this method of calculation is that the final date of the last cycle of chemotherapy was not clear. The number of days in the last cycle was calculated as 6 added to the date when the drugs were planned to be administered on day 22. The intensity might be higher in the patients who received fewer cycles of chemotherapy. Scher et al[7] reported the decrease of dose intensity in the third or fourth cycles because of the accumulated toxicity. Since it

has not been determined which drugs in M-VAC are of primary importance, we assumed that the four drugs contributed equally to the efficacy of this regimen.

The dose intinsity in this study ranged from 46 to 99% with an average of 76±11%, despite the fact that 95% or more of the planned doses were administered as the initial dose in 36 of 41 patients. A reduction in the dose intensity usually is associated with significant toxicities. Loehrer et al.[20] have reported that only 24% of their patients received full-dose M-VAC without any dose modifications. In their study, a delay or dose modification was required in 20% of the patients, and omission of day 15 and/or day 22 methotrexate and vinblastine was required in 56%[3] Scher et al. have reported that the median relative dose intensity was 66.2% for patients completing 2 cycles[18]

Kotake et al. suggested that M-VAC with a relative dose intensity ≥70% be considered "standard"[12]. They found that standard dose M-VAC provided a 56.5% overall objective response, while M-VAC with <70% dose intensity yielded only a 40.0% response. However, they did not show a positive relationship between the dose intensity and the complete response rate or survival. We also did not find that the dose intensity affected the response rate or survival in the neoadjuvant or salvage chemotherapy groups. This may be attributed to the fact that our study included a relatively large number of patients with advanced, bulky tumors. Also in the adjuvant group, any effect of the dose intensity was not observed on survival.

Interestingly, thrombocytopenia, anemia, and pyrexia seemed rather more severe in the group with a dose intensity <75% in our study. This might be caused by the fact that the elderly people had various reserved organ functions and the patient subject to myelosuppressions would have treatment delay. Conversely, the incidence of high grade stomatitis appeared higher in the group with a dose intensity ≥75%. This may imply that patients with less myelosuppression received the chemotherapy in accordance with the standard protocol but suffered from nonhematologic mucosal toxicity.

In conclusion, adjuvant M-VAC may affect the survival of the patients with urothelial cancer. On the other hand, those with advanced urothelial cancer responded less well to M-VAC, and their survival was not improved. Although dose escalation was thought to be one way to overcome these poor results, Seidman et al. have failed to increase the dose intensity more than the original M-VAC even though they aggressively used granulocyte colony-stimulating factor[19] Loehrer et al. have shown high rates of treatment-related deaths in their trial of dose escalation[20] In agreement with Roth et al.[17], new combination regimens are needed to treat advanced urothelial cancers.

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和文抄録

進行性尿路上皮腫瘍に対する M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) 療法と治療強度に基づいた効果

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　M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) 療法は尿路上皮腫瘍患者の予後を改善すると報告されている．本研究では名古屋大学でのM-VAC 療法の治療成績を調査した．

　41人の患者を術後補助化学療法（24人），術前補助化学療法（5人），救済化学療法（12人），の3グループに分け，各群における治療強度，実測生存率，奏効率および副作用について調査した．

　36人の患者が予定量の95％以上の薬剤の投与を受けた．平均の治療強度は術後補助化学療法群77±11％，術前補助化学療法群73±4％，救済化学療法群74±12％であった．他因死を除いた5年生存率は補助化学療法では69％（95％信頼区間：50〜88％）であった．術前補助化学療法の5例中2例（40％）は治療開始より23カ月で癌なし生存，救済化学療法の全例は33カ月以内に癌死あるいは副作用で死亡した．生存期間の中央値は術後補助化学療法群で38カ月，術前補助化学療法群で21カ月，救済化学療法群で7カ月であった．

　75％以上の治療強度は各群において生存率を改善しなかった．評価可能病変を有する15症例の奏功率は33％であった．CR (complete response) は1例に，またPR (partial response) は4例に認められたのみであった．治療関連死は2例に生じた．嘔気，嘔吐はすべての症例に認められた．WHO 分類の grade 3 以上の白血球減少，血小板減少および貧血はそれぞれ25例（61％），4例（10％），7例（17％）に認められた grade 3 以上の血小板減少，貧血，発熱は治療強度75％以下の症例により多く認められた．一方，grade 3 以上の口内炎は治療強度75％以上の症例により多く認められた．

　以上より補助化学療法としての M-VAC 療法は有効であると考えられたが，術前補助化学療法，救済化学療法としては不十分であった．治療強度は重要であると考えられたが，生存率，奏功率，副作用との正の相関は認められなかった．

（泌尿紀要 **43**：89-96, 1997）