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Original Paper

Neoadjuvant Chemotherapy (MVAC) in Locally Invasive Bladder Cancer

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In order to evaluate the efficacy of neoadjuvant chemotherapy in invasive urothelial carcinoma of the bladder a retrospective analysis was performed. 54 patients without distant metastases (T2-T3b, N0-X, M0) received 3 cycles of neoadjuvant chemotherapy according to the MVAC protocol (methotrexate, vinblastine, doxorubicin and cisplatin) after transurethral resection (TUR) followed by cystectomy. 52 patients had previously undergone cystectomy immediately after TUR. Complete histopathological remission was observed in 9 patients (17.3%) after TUR and in 17 patients (31.5%) after TUR+MVAC. Neoadjuvant MVAC resulted, therefore, in a 14% higher rate of complete remissions. The overall response to TUR was significantly improved by MVAC therapy. Downstaging by neoadjuvant chemotherapy was more readily achieved in initially low-stage tumours (T2: 44.4% and 30.8%, T3a: 47.1% and 19%, T3b: 5.3% and 5.5% in patients receiving TUR+MVAC and TUR alone, respectively). Overall survival did not differ significantly between both groups. Patients who were successfully downstaged to pT0 had a significantly better prognosis, and patients resistant to chemotherapy had the poorest prognosis, showing the shortest survival. In conclusion, histopathological response at cystectomy was improved by neoadjuvant MVAC chemotherapy after TUR and can be expected to be prognostically relevant in those patients who can be downstaged to T0, although overall survival failed to be significantly increased in this relatively small patient sample. **Copyright © 1996 Elsevier Science Ltd.**

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INTRODUCTION

LOCALLY ADVANCED carcinoma of the urinary bladder includes tumours staged T2–T4, N0-N2, M0 according to the UICC classification [1]. If operable, the 'gold standard' of therapy is radical cystectomy with urinary diversion which produces a 5-year survival of approximately 50% [2]. Because of these disappointing results, neoadjuvant and adjuvant chemotherapies have been investigated for the treatment of locally advanced urothelial carcinoma [3–5].

Neoadjuvant therapy is thought to result in downstaging of the local tumour and in a reduction of micrometastases, and it may also prevent distant metastases. Response to neoadjuvant treatment can easily be evaluated after cystectomy (evaluation of chemosensitivity *in vivo*). However, the currently available results of relevant retrospective studies have been unsatisfactory. Most studies failed to show an advantage of chemotherapy in terms of survival [4, 5]. Only one randomised retrospective study showed a trend towards improved survival in the chemotherapy arm [6]. The preliminary results of two randomised studies with sufficient numbers of patients have been presented, but the results have not yet reached the level of statistical significance [7, 8].

Our study was performed to determine the extent of downstaging by neoadjuvant chemotherapy resulting in complete remission (CR), confirmed by histopathology, i.e. pT0, and to investigate whether the achievement of CR improves survival. In this retrospective study the MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) protocol was administered, which yields a 20–30% complete remission rate in

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Table 1. Demographic data

	Cystectomy	MVAC + cystectomy
Number of patients	52	54
Sex		
Male	40 (76.9%)	39 (72.2%)
Female	12 (23.1%)	15 (27.8%)
Age (years)		
Median	64	62
Range	49–74	51–75
Performance status (Karnofsky)		
Median	92	90
Range	60–100	60–100

palliative therapy of urinary bladder cancer, toxicity being the most limiting factor [9].

PATIENTS AND METHODS

A total of 106 patients with invasive carcinoma of the urinary bladder without distant metastases (T2–T3b, N0–X, M0) initially underwent differentiated transurethral resection in an attempt to remove the tumour radically. After histological verification of muscle-invasive tumour, the first 52 patients were treated by cystectomy with urinary diversion (TUR + cystectomy), the treatment option performed until 1989. The 54 patients treated after 1989 received three cycles of MVAC pre-operatively, and cystectomy was performed 4 weeks later (TUR + MVAC + cystectomy). The sex, age, performance status (Table 1), and tumour stage (Table 2) were comparable in both patient groups.

Computerised tomography of the abdomen and the pelvis was performed in all patients. The clinical examinations prior to cystectomy included laboratory parameters, urinary sediment, urinary cytology, excretory urography, and abdominal sonography. Bimanual palpation, a most important criterium in T3b, was also performed.

Inclusion criteria for neoadjuvant treatment were leucocytes $>4.0 \times 10^9$/l, platelets $>100 \times 10^9$/l, total bilirubin <34 μmol/l, serum creatinine <140 μmol/l, and creatinine clearance >50 ml/min for 1.73 m^2. Patients with a solitary kidney, severe cardiac disease, a history of prior invasive carcinoma or other severe conditions were ineligible. Neoadjuvant chemotherapy according to the MVAC protocol was administered as described by Sternberg and coworkers [9].

MVAC was administered as follows: day 1: methotrexate 30 mg/m^2; day 2: doxorubicin 30 mg/m^2, vinblastine 3 mg/m^2, cisplatin 70 mg/m^2; days 15 and 22: methotrexate 30 mg/m^2, vinblastine 3 mg/m^2. The cycle interval was 4 weeks.

Urinary diversion was not handled uniformly, as orthotopic neobladders were increasingly used. In the group with TUR alone, ileal neobladders were used in 13, ileal conduits in 37, and continent pouches in 2 patients. In the TUR + MVAC group, urinary diversion was performed as ileal neobladder in 26, as ileal conduit in 25, and as continent pouch in 5 patients. The form of urinary diversion was different in the two groups, and, while it certainly influences the quality of life, it has no influence on the oncological outcome.

Table 2. Histological tumour characteristics

	Cystectomy	MVAC + cystectomy
Number of patients	52	54
Tumour stage (by TUR)		
T2	13 (25.0%)	18 (33.3%)
T3a	21 (40.4%)	17 (31.5%)
T3b	18 (34.6%)	19 (35.2%)
Positive lymph nodes		
N0	43 (82.7%)	45 (83.3%)
N1	5 (9.6%)	6 (11.1%)
N2	4 (7.7%)	3 (5.6%)
Grading		
G2	10 (19.2%)	7 (13.0%)
G3	42 (80.8%)	47 (87.0%)
Areas of squamous metaplasia	12 (23.1%)	17 (31.5%)
Concomitant carcinoma *in situ*	11 (21.2%)	9 (16.7%)

Statistical methods

BMPD statistical software (version 1990, IBM/CMS, Los Angeles, California 90025, U.S.A.) was used for data analysis. Frequencies were compared using Pearson's chi-square test, Yates's corrected chi-square test or Fisher's exact test. Comparison of Kaplan–Meier curves was performed using the Mantel Cox, Breslow and Peto-Prentic methods.

RESULTS

In the TUR-MVAC group, 9 (17.3%) cystectomy specimens revealed no residual tumour (pT0); 4 of these patients were initially staged T2, 4, T3a, and 1 T3b (Table 3). Histological understaging (UST) after TUR could be demonstrated in 12 (23.1%) patients.

In the TUR + MVAC group, 17 (31.5%) cystectomy specimens were classified as pT0. After TUR, eight of these tumours were staged T2, eight T3a, and one T3b (Table 3). Staging errors in terms of understaging after TUR were discovered in 9 (16.7%) cases.

The distributions of observed changes at cystectomy, i.e. improvements (19.2 and 51.9% in TUR alone and TUR + MVAC, respectively); equal outcomes (57.7 and 31.4% in TUR alone and TUR + MVAC, respectively), and understagings after TUR (23.1 and 16.7% in TUR alone and TUR + MVAC, respectively) differed significantly ($P<0.005$) between the two subgroups. The difference between the overall rates of complete remissions (17.3 and 31.5% achievement of pT0 in TUR alone and TUR + MVAC, respectively) failed to reach the limit of statistical significance, but after stratification by initial tumour stage, a trend ($P=0.07$) could be observed towards a beneficial effect of MVAC treatment in patients with initial tumour stages T2 or T3a (Table 3). No

Table 3. Comparison of pT0 (CR) in cystectomy specimens

	TUR alone		TUR + MVAC	
Tumour stage at TUR	*n*	pT0 at cystectomy	*n*	pT0 at cystectomy
T2	13	4 (30.8%)	18	8 (44.4%)
T3a	21	4 (19.0%)	17	8 (47.1%)
T2 + T3a	34	8 (23.5%)	35	16 (45.7%)
T3b	18	1 (5.5%)	19	1 (5.3%)
Total	52	9 (17.3%)	54	17 (31.5%)

difference between the groups was found regarding postoperative convalescence. The median duration of aftercare at the intensive care unit was 3 days in both subgroups (range 1–4 and 1–5 days for TUR alone and TUR + MVAC, respectively).

Overall survival did not differ significantly between the two treatment groups (Figure 1). After a median observation period of 57 months (range 1–106) in the TUR group and 20 months (range 1–47) in the chemotherapy group, the median survival was 78 months in the former group and has not yet been reached in the latter subgroup.

Of the 27 surviving patients, 23 in the TUR alone group, and 36 of 38 surviving patients in the TUR + MVAC group are currently tumour-free. So far, 20 patients of the TUR alone group and 12 patients of the TUR + MVAC group have died of their tumour. 5 patients treated with TUR alone and 4

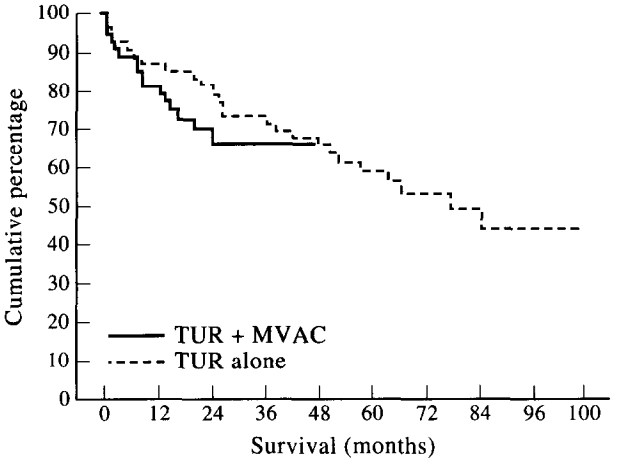

Figure 1. Kaplan–Meier overall survival curves for 54 patients treated with TUR + MVAC and 52 patients treated with TUR alone for locally invasive bladder cancer. The curves did not differ significantly (Mantel Cox: $P = 0.409$, Breslow: $P = 0.327$, Peto-Prentice: $P = 0.370$).

patients treated with TUR-MVAC died of causes not tumour related. Figure 2 shows that survival is significantly ($P<0.05$) shorter in patients who fail to achieve CR either by TUR alone or by TUR + MVAC.

Because of toxicity during the first chemotherapy cycle, only 36/54 (66.7%) patients received the full projected dose. The remaining 18 patients could not be treated on day 15 and 22 due to grade 3 leucopenia. Of these patients, 9 experienced thrombopenia grade 3 or 4 and had to be given platelet concentrates in addition to a dosage reduction by 30%. During the second cycle, 2 patients had septic problems and were treated with antibiotics. They did not receive any further chemotherapy on day 15 and 22. After the application of recombinant human granulocyte-monocyte colony stimulating factor (rh-GM-CSF), 90.7% of patients received the full dosage in the second cycle and 92.6% in the third cycle (Table 4).

5 patients suffered from hematological toxicities of WHO grade 3 or 4 (leucopenia and thrombocytopenia) which were fully reversible by rh-GM-CSF and platelet concentrates, and all patients recovered fully during the 4-week interval until

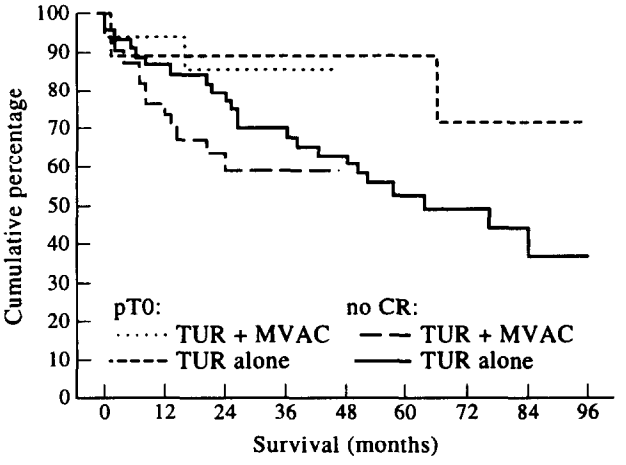

Figure 2. Kaplan–Meier survival curves stratified by tumour treatment response. Patients who had achieved CR (pT0) survived significantly ($P<0.05$) longer than less responsive or non-responsive patients. The differences between the two treatment groups (TUR + MVAC and TUR alone) did not reach the level of statistical significance (Mantel Cox: $P = 0.413$, Breslow: $P = 0.334$, Peto-Prentice: $P = 0.348$).

Table 4. MVAC schedule in 54 patients

	Complete dosage of MVAC
Cycle	
I	36 (66.7%)
II*	49 (90.7%)
III*	50 (92.6%)

*Starting with the second cycle, patients with leucopenia after the first cycle ($n = 16$) received 250 μg/m² rh-GM-CSF (Aesca, Vienna, Austria).

surgery. Of the surviving patients, 34 received the full dose of chemotherapy. There were no delays of surgery due to chemotherapy toxicity and cystectomy was performed after neoadjuvant MVAC chemotherapy as scheduled. No tumour progression was observed in any patient during chemotherapy.

DISCUSSION

Retrospective analysis of our group of patients treated prior to 1989 confirmed that muscle-invasive tumours can be removed by TUR in only 10–15% of cases, and is comparable to results of the prospective experience of Herr [10]. The rate of 31.5% CR achieved by TUR and neoadjuvant MVAC treatment is also in accordance with previous reports [4, 5, 11]. Our analyses, however, are based on cystectomy specimens, while in most other reported cases only restaging by TUR was performed. The overall benefit of neoadjuvant chemotherapy, i.e. more than twice as many improvements with less stable disease and UST as compared with TUR alone, proved to be statistically significant in our study.

There is no controversy about the need to perform at least a partial cystectomy or other therapy after the achievement of CR by MVAC in patients with T2 and T3a. In our patient sample, only 1/19 patients with tumour stage T3b experienced CR, and lymph node metastases were present in both of the patients who died of tumour. None of the patients with initial tumour stage T2 or T3a and CR died of that tumour. We

therefore agree that MVAC will mostly fail to cure patients with a tumour stage >3a or with node-positive disease [12, 13]. In fact, cystectomy is a necessity after neoadjuvant chemotherapy, since failure to do so is associated with a high frequency of local and nodal relapses [13].

However, Herr and Scher have demonstrated that bladder-sparing therapy (partial cystectomy) and neoadjuvant MVAC may induce a 5-year survival rate of 87% in patients who have been downstaged to pT0 or pTis, while patients with remaining residual invasive cancer only show a 5-year survival rate of 30% [14]. Although there remained a risk for new tumour development, local recurrences were successfully treated by local therapy or salvage cystectomy. Patients undergoing partial cystectomy are highly selected and have to be identified by a detailed characterisation of their primary tumour using pretherapy parameters. Patients with a history of multifocal and recurrent disease, hydronephrosis, extension into the prostatic urethra or a diminished bladder capacity are not appropriate candidates. The results of Kaufman and coworkers from a conservative combination treatment (TUR, systemic multidrug chemotherapy, pelvic irradiation with concurrent administration of cisplatin) are equivalent to those reported for radical cystectomy, but that study did not include a control group [15].

In our study, we observed that a complete response of the primary tumour was associated with significantly prolonged survival. In contrast, achieving PR or SD has no influence on survival. Thus, the pT0 status was the most important point of our retrospective study. In a review of 1636 patients, Herr also demonstrated a benefit of the MVAC protocol in patients with tumour staged pT0 or pTis in comparison with residual stage pT2 disease [16]. In a retrospective analysis of 147 patients, patients with a major pathological response had a 5-year survival of 75% in contrast to 20% in the remaining non-responding patients [17].

The survival curves did not differ between the two groups, either in overall analysis or after stratification by treatment response. However, since survival is prolonged by treatment response and responsiveness has been shown to depend on the tumour stage, an initial tumour stage <T3b seems to be an important prognostic factor. In a carefully selected large sample of patients with tumour stages T2–T3a, the considerably higher response rate observed in our study should also be mirrored in improved survival times. In a neoadjuvant chemotherapy-study on invasive bladder cancer, the 5-year survival in a group of 111 patients treated with MVAC was also similar to that reported in a cystectomy series with surgery alone. Downstaging was associated with improved survival, but only for patients with extravesical disease [18].

In conclusion, our retrospective study has shown that neoadjuvant administration of MVAC in patients with muscle-invasive bladder tumours induces a 14% higher rate of CR than TUR alone, but does not result in improved overall survival. The three cycles of chemotherapy may have been adequate for local control, they are probably inadequate for patients with a high risk of metastases.

Considering the efficacy of the currently available chemotherapy regimens, such retrospective studies would require a large number of patients to show a survival benefit [19]. For selective bladder preservation relying on chemotherapy, prospective, randomised trials will have to be conducted to evaluate an effective alternative to radical cystectomy. However, response to neoadjuvant chemotherapy appears to be a favourable prognostic sign, while the lack of response results in poor survival. The pT0 status in the cystectomy specimen is an important prognostic factor and is more likely achieved in patients with initial low-stage tumours. This outcome is in agreement with the data of several other investigators [11, 12, 14, 15, 20].

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