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Neoadjuvant Chemotherapy with Cisplatin and Methotrexate in Patients with Muscle-Invasive Bladder Tumours

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This prospective, randomized study based on two associated trials was designed to evaluate the effect of neoadjuvant chemotherapy with cisplatin and methotrexate with folinic acid rescue or no chemotherapy prior to local treatment in patients with T2-T4b, NX-3, MO transitional cell carcinoma of the bladder. In the first trial, local treatment consisted of cystectomy (DAVECA 8901) and in the other trial the treatment was radiotherapy (DAVECA 8902); 153 eligible patients were randomized. The majority of the patients (89%) completed the protocol. The overall time to progression for all 153 patients was 12.9 months. Median time to progression was 14.2 months with chemotherapy and 11.4 months without chemotherapy. The actuarial 5-year overall survival rate for all 153 patients was 29%, and 29% for both treatment groups. Multivariate analyses showed that T-stage, tumour size and serum creatinine were independent prognostic factors for survival. The cystectomy trial included 33 patients. Median survival was 78.9 months, 82.5 months with chemotherapy and 45.8 months without chemotherapy ($p = 0.76$). The radiotherapy trial included 120 patients. The median survival was 17.6 months. Median survival was 19.2 months in the group receiving chemotherapy and 16.3 in the group not receiving chemotherapy. The 5-year survival rate was 19% in the group receiving chemotherapy and 24% in the groups not receiving chemotherapy ($p = 0.98$). Late toxicity grade 3 or 4 of the bladder was recorded in 25% of the patients (actuarial rate). Neoadjuvant chemotherapy with cisplatin and methotrexate did not significantly improve disease-free or overall survival in 153 randomized patients with invasive bladder cancer.

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During the past 15 years, the addition of systemic treatment for locally advanced urothelial cancer has been investigated in order to eliminate unrecognized disseminated disease and improve outcome. In metastatic disease, survival improvement has been documented using the most effective regimens with cisplatin and methotrexate with or without vinblastine/doxorubicin (CM, CMV, MVAC) compared with less effective combinations or single drugs (1–3). A recent phase III trial has documented gemcitabine and cisplatin (GC) to been as effective but less toxic than MVAC (4).

Several phase II studies have reported a reductive effect in primary tumour of muscle-invasive bladder cancer (5), but current available studies have failed to show a significant advantage of neoadjuvant or adjuvant chemotherapy in overall survival (6–10).

This prospective, randomized study based on two associated trials was designed to evaluate the effect of neoadjuvant chemotherapy with cisplatin and methotrexate or no chemotherapy prior to local treatment on local control, time to progression and overall survival. In the first trial, local treatment consisted of cystectomy (DAVECA 8901) and in the other trial it was radiotherapy (DAVECA 8902).

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MATERIAL AND METHODS

Between March 1989 and November 1993, 154 patients with invasive bladder cancer stage (T2-T4b, NX-3, M0) plus two patients with T1 tumours were enrolled in a study comprising two associated trials (DAVECA 8901 and 8902). The first trial was designed for patients suited for cystectomy (DAVECA 8901) and the other trial was designed for patients suited for radiotherapy (DAVECA 8902). In both trials, the patients were randomized to receive or not to receive neoadjuvant chemotherapy. Thus, the main objective for the entire study (DAVECA 8901 + 8902) was to evaluate the effect of neoadjuvant chemotherapy followed by radical local treatment. The goal of inclusion was 150 patients in the radiotherapy trial and 150 in the cystectomy trial, but the trials were closed before this goal could be reached, because of a continuously decreased inclusion rate during the past few years. Inclusion into the study required histologically proven transitional cell carcinoma of the bladder. Patients were ineligible if there was evidence of distant metastases, including lymph node metastases proximal to the bifurcation of the common iliac vessels. Furthermore, inclusion required normal blood count values and normal or only slightly decreased renal function (clearance > 60 ml/min). No prior radiotherapy or systemic chemotherapy was allowed. The Local Ethic Committees and the National Board of Health approved the protocol and written informed consent was obtained from all patients before study entry.

Three patients were ineligible, two of them having squamous cell carcinoma only, and one patient had distant metastases diagnosed before entering the study, leaving 153 patients for analysis (33 in the cystectomy trial and 120 in the radiotherapy trial). The urologist decided on local treatment on the basis of tumour and nodal stage. Patients with stage T2-T4a, N0 tumours were treated with cystectomy if they were considered medically suitable for surgery and patients with T4b or N + tumours were given radiotherapy. Furthermore, two patients with T1 tumours were included in the cystectomy trial. The initial evaluation comprised specific symptoms, performance status, chest radiograph, intravenous excretory urogram, ultrasound/MR/CT scan of the abdomen, renal function test (Cr-EDTA clearance), and baseline blood tests including blood counts, s-creatinine, alkaline phosphatase, lactate dehydrogenase and aspartate aminotransferase. Staging procedure using the 1987 TNM classification (IUCC) included transurethral examination with resection, biopsies and bimanual palpation under general anaesthesia (11). Size, histology and whether or not the tumour had been completely resected were registered. A separate pelvic lymph node exairesis was performed on the obturator lymph nodes prior to actual planned treatment to determine the N-stage of patients with tumours < T4B. The operation was performed unilaterally corresponding to the localization of the tumour. In midline tumours, the operation was performed bilaterally. Percutaneous nephrostomy was performed in most cases of hydronephrosis. Response to treatment was evaluated by transurethral inspection and biopsies.

Patients were randomized to receive (group 1: 79 patients) or not receive (group 2: 74 patients) three cycles of cisplatin 100 mg/m^2 and methotrexate 250 mg/m^2 with leucovorin rescue at 3-week intervals. Leucovorin was started 24 h after MTX at a dose of 15 mg orally every 6 h for a total of 8 treatments. Blood counts and s-creatinine were measured weekly. Doses of chemotherapy were reduced in the case of leucopenia on the day of treatment (white blood cell count less than 3.0) or grade 3 or 4 emesis. Cisplatin alone was reduced if a significant reduction of renal function occurred. Cystectomy was performed 3–4 weeks after chemotherapy and radiotherapy was initiated 3 weeks after chemotherapy.

Cystectomy was performed as a radical cystectomy including pelvic lymphadenectomy. The type of urinary diversion was chosen in accordance with the urologist's advice and patient preference.

Radiotherapy: the entire bladder with tumour and inclusion of the pelvic lymph nodes were treated with a 3- or 4-field box technique. In some cases, contoured fields were used. The patients received a total dose of 60 Gy in daily doses of 2 Gy. The radiation treatment was delivered by a linear accelerator with beam energy of 6–16 MV. Patients receiving radiotherapy were staged according to TNM 3 months after completion. The response was considered complete if no tumour was visible on cystoscopy and the tumour-site biopsy was negative.

Toxicity was recorded according to the WHO criteria of acute toxicity (12), and the late radiation morbidity was recorded according to the RTOG/EORTC late radiation morbidity-scoring scheme.

Statistics

Randomization was performed as a central randomization with stratification for each of five uro-oncological centres and was performed independently in the two trials. It was predefined to analyse the efficacy of neoadjuvant chemotherapy for the entire study and for each of the two associated trials. Survival was measured from the day of randomization to death or censoring (13). Survival analyses were all based on intention to treat in order to avoid the bias of changing treatment (14). Time to disease progression was measured from the day of randomization to the day when either local or distant (or both) relapse or progression was diagnosed. Patients were censored at the date of last follow-up without recurrence or at the date of death from unrelated courses. Variables that were significant at the 0.10 level in univariate analyses were entered in a multivariate regression model—the Cox proportional

Table 1

Patient characteristics[1]

		Cystectomy trial	Radiotherapy trial
Total number of patients		33	120
Age, median years		66	63
Male/female		26/7 (79%/22%)	98/22 (82%/18%)
Performance status (3)	0	17 (55%)	44 (37%)
	1	13 (42%)	69 (58%)
	2	1 (3%)	6 (5%)
Tumour size (15)	<1	1 (3%)	1 (1%)
	1–2.9	8 (27%)	12 (11%)
	3–4.9	15 (50%)	51 (47%)
	>5	6 (20%)	44 (41%)
Macroscopic gross resection (10)	Yes	25 (86%)	18 (16%)
	No	4 (13%)	96 (84%)
Tumour histology (1)	TCC only	29 (88%)	92 (77%)
	Mix	4 (12%)	27 (23%)
Tumour grade (3)	2	0	3 (3%)
	3	28 (88%)	88 (74%)
	4	3 (9%)	28 (24%)
Tumour stage (2)	1	2 (6%)	0
	2	7 (21%)	16 (13%)
	3A	13 (39%)	33 (28%)
	3B	6 (18%)	33 (28%)
	4A	4 (12%)	19 (16%)
	4B	0	18 (15%)
N-Stage	0	33 (100%)	3 (3%)
	1		48 (40%)
	2		23 (19%)
	3		1 (1%)
	Unknown		45 (38%)
Haemoglobin, median		8.7	8.4
Creatinine, median		95	98
Alkaline phosphatase, median		185	182

[1] Numbers in parentheses in the left row represent number of patients with missing values.

hazard regression model (15)—taking into account the simultaneous effect of several variables. Selection of variables that had an important effect on survival was based on a forward and backward stepwise procedure using the maximum partial likelihood ratio method. Proportional hazard plots were made to assure the assumption of proportional hazards.

The significance of differences between proportions was determined using the Fisher exact test (two-tailed) or Pearson's $?^2$ test. A p-value of less than 0.05 was considered significant. Statistical analyses were performed using BMDP software 4F, 1L, 2L and New System (BMDP Statistical Software, Cork, Ireland).

RESULTS

For the study, 153 eligible patients were randomized. Details of patient and tumour characteristics are presented in Table 1. As expected from the eligibility criteria, the cystectomy patients had smaller tumours at lower stages, which were usually macroscopically resected before inclusion, than patients in the radiotherapy trial. There was no marked imbalance in the distribution of patient characteristics between the study randomization groups (data not shown).

The majority of patients (89%) completed the protocol as specified or with minor deviations. The overall time to progression for all 153 patients was 12.9 months. Median time to progression was 14.2 months in the group receiving chemotherapy and 11.4 months in the control group. The overall median survival time was 22.4 months—22.1 months with chemotherapy and 22.7 without chemotherapy. The actuarial 5-year overall survival rate for all 153 patients was 29%. The 5-years' survival was 29% in both groups (Fig. 1). Survival rates according to different characteristics were estimated. In Table 2 it is shown that survival was related to T-stage, N-stage, tumour size and the level of serum-creatinine. In a multivariate analysis it was shown that T-stage, tumour size and s-creatinine, but not randomization group, were independent prognostic factors for survival (N-stage was not included, because of the number of missing values).

Haematuria was the most common symptom, followed by cystitis symptoms and pain (Table 3). A larger proportion of patients had hydronephrosis and impaired renal

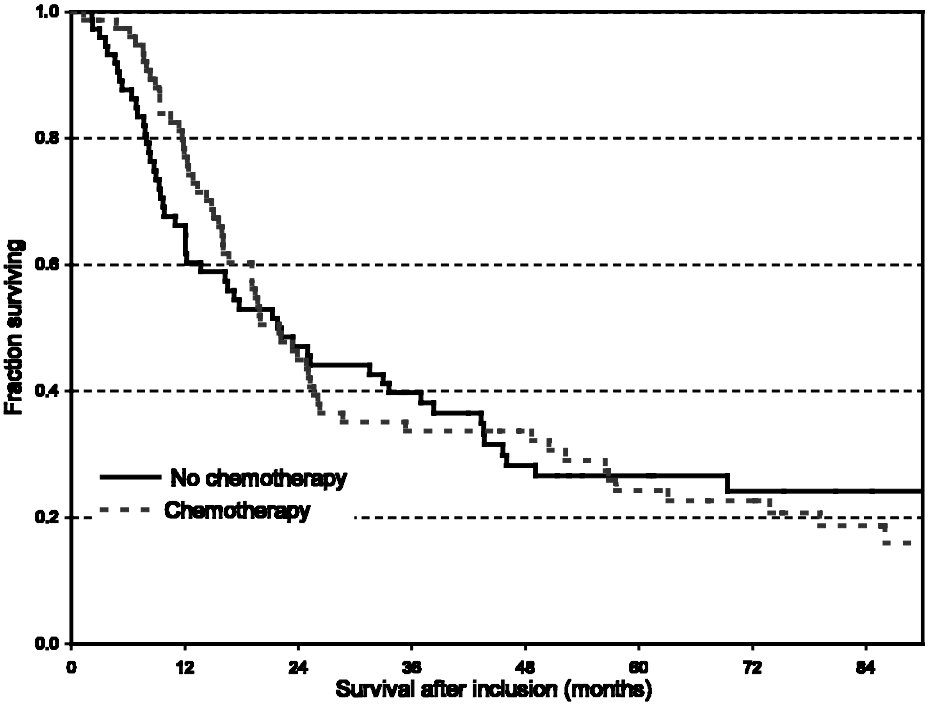

Fig. 1. Survival according to randomization group in all patients included (n = 153).

function in the patients receiving radiotherapy (Table 3). None of the symptoms were related to survival (data not shown).

The cause of death was known to be bladder cancer in 101 patients (66%), treatment-related toxicity in 6 (4%) and other diseases (cardiovascular and lung cancer) in 13 patients (8%). The cause of death was unknown in 10 patients, leaving 23 patients alive (15%). Since the patients were selected for cystectomy or radiotherapy, we have analysed the data from each trial separately.

Cystectomy trial (DAVECA 8901)

The cystectomy trial included 33 patients, 17 of whom were randomized to chemotherapy. One patient refused chemotherapy and two needed dose reductions. Two patients did not undergo cystectomy, because of disease progression. One patient was given radiotherapy, in accordance with patient preference. The median survival was 78.9 months; 82.5 months with chemotherapy and 45.8 months without chemotherapy, $p = 0.76$ (Fig. 2B). The 5-year survival rates were 64% and 46%, respectively. The median time to progression was 40.5 months. At five years, the progression-free survival rate was 41% with chemotherapy and 36% without chemotherapy. Seven patients (21%) are still alive (median 91.8 months, range $75 \pm 115+$); 14 patients (42%) died of bladder cancer and 8 (24%) died of other diseases. Three patients from the control group received cisplatin-based chemotherapy at recurrence.

Toxicity. Toxicity was similar to that reported in a previous phase II trial in metastatic disease. None of the patients experienced grade 4 leucopenia. Emesis was pronounced, with the majority of the patients experiencing grade 3–4, and two patients declined further chemotherapy after the first course. No cardiopulmonary events were observed in relation to treatment. There were no delays in surgery due to chemotherapy toxicity, but two patients progressed during chemotherapy and did not have cystectomy.

Radiotherapy trial (DAVECA 8902)

The radiotherapy trial included 120 patients, 61 receiving neoadjuvant chemotherapy followed by radiotherapy and 59 had radiotherapy alone. Seven patients left the study before radiotherapy because of early death (2 pts), toxicity of chemotherapy (1 pt), diagnosis of dissemination (3 pts), or switch to cystectomy because of patient preference (1 pt). Two patients did not complete the course of radiotherapy due to diagnosis of distant metastases during treatment, leaving 111 patients (93%) who received 60 Gy in accordance with the protocol. Eight patients (7%) received only one course of chemotherapy: four of them because of

Table 2

Survival according to patient characteristics[1]

		Median survival (months)	5-year survival	p-value
All patients (n = 153)		22	29%	
Group 1 (Chemotherapy)		22	29%	
Group 2 (No chemotherapy)		22	29%	0.87
Performance status (3)	0	24	32%	
	1	17	23%	
	2	8	0	0.11
Tumour size, cm (13)	<1	74	100%	
	1–2.9	34	36%	
	3–4.9	25	28%	
	>5	12	20%	0.003
Tumour stage (3)	1	102	100%	
	2	24	35%	
	3A	38	31%	
	3B	17	22%	
	4A	15	14%	
	4B	10	14%	0.003
N-Stage	0	52	47%	
	1	16	12%	
	2	20	17%	
	3	8	0	0.0001
	X	20	29%	
S-creatinine (16)	Normal	23	29%	
	Elevated	12	5%	0.007
CrEDTA-clearance (36)	Normal	20	22%	
	Abnormal	12	11%	0.31

[1] Numbers in parentheses in the left row represent number of patients with missing values.

disease progression and four went off-study because of nausea and vomiting. Seventeen patients (14%) had dose reductions, mainly due to haematological and renal toxicity.

The median time to progression was 10.4 months (range, 0.4 to 82.3+ months). Median time to progression was increased in the group receiving chemotherapy (12.1 months) versus the group not receiving chemotherapy (7.6 months), but the difference was not statistically significant (p = 0.82). Median survival was 17.6 months. Median survival in the group receiving chemotherapy was 19.2 months and 16.3 months in the group not receiving chemotherapy. The 5-year survival rate in the group receiving chemotherapy was 19%, and that in the control group was 24% (p = 0.98). In Fig. 2A it is shown that the difference in survival was present only in the first two years after inclusion. A total of 16 patients (13%) are still alive without evidence of disease, median observation time 77 months (42 ± 104+ months). The cause of death was bladder cancer in 87 patients (73%) and other diseases in 4 patients (3%). Two of the patients had a previous recurrence with carcinoma in situ and were treated with cystectomy or local installation of BCG, respectively. Bladder functioning was present in 15 patients.

N-staging was performed in 75 patients. A median of 5 (range, 1–19) lymph nodes were removed. Survival according to N-stage is shown in Fig. 3. There was no statistical difference in outcome among patients with N1 or N2 disease. The median survival time of patients with N1

Table 3

Symptoms and clinical findings at presentation[1]

		Cystectomy group	Radiotherapy group
Erectile potency (82)	No	3 (20%)	12 (27%)
	Yes	12 (80%)	32 (72%)
Haematuria (4)	No	6 (19%)	40 (34%)
	Yes	25 (81%)	78 (66%)
Incontinence (6)	No	29 (97%)	107 (91%)
	Yes	1 (3%)	10 (9%)
Cystitis symptoms (4)	No	16 (53%)	57 (48%)
	Yes	14 (46%)	62 (52%)
Pain (3)	No	24 (77%)	83 (70%)
	Yes	7 (23%)	36 (30%)
Symptoms from rectum (3)	No	30 (97%)	114 (96%)
	Yes	1 (3%)	5 (4%)
Abnormal pyelogram (44)	No	16 (69%)	25 (29%)
	Yes	7 (31%)	61 (71%)
Abnormal renogram (42)	No	13 (62%)	39 (43%)
	Yes	8 (38%)	51 (57%)
Abnormal s-creatinine (15)	No	24 (96%)	92 (83%)
	Yes	1 (4%)	21 (16%)

[1] Numbers in parentheses in the left row represent number of patients with missing values.

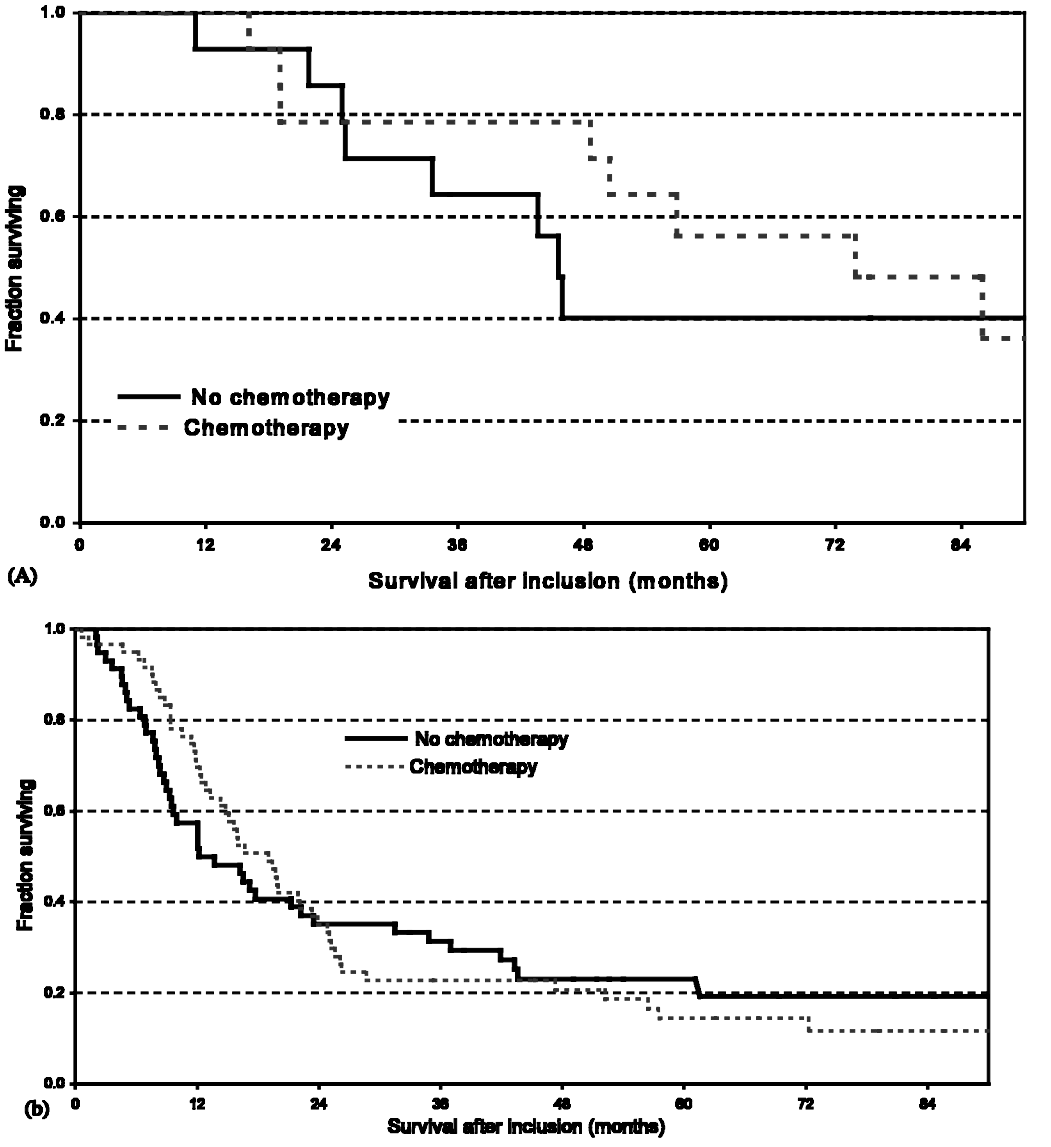

Fig. 2. Survival according to randomization group in the patients receiving (A) cystectomy (n = 33) and (B) radiotherapy (n = 120).

receiving radiotherapy only (n = 21) was 14.2 months with a 5-year survival rate of 13%. The median survival of N2 patients (n = 14) receiving radiotherapy only was 8.3 months with a 5-year survival rate of 7%.

Second-line treatment of distant metastases was performed in 10 patients, three patients in group 1 receiving mitomycin C or MVEC, and 7 patients in group 2 receiving cisplatin and methotrexate. The median survival time after second-line treatment was 5.7 months.

Response. Information about evaluation after 3–4 months was available in 91 patients (6 patients died before the time of evaluation, and no information was available on 23 patients). Complete response was diagnosed in 45 patients (48% of evaluated patients, 37% of all patients) but two patients had distant metastases. Persistent disease was diagnosed in 46 patients, 5 of whom had concurrent distant metastases. Of the patients with local disease only, salvage cystectomy was performed in 10 patients; one of these patients is free of recurrence; five developed distant metastases and 4 had locoregional recurrence. Six patients had local resection only, one of whom is alive and free from disease but the others died of bladder cancer.

Toxicity. Forty-four percent of the patients had no symptoms before radiotherapy, but this figure decreased to 20% during radiotherapy (Table 4). Grade 2 or more bladder symptoms were recorded in 50% of the patients during radiotherapy. Grade 3 or 4 late toxicity of the bladder in the radiotherapy trial was registered in 11 patients (5 patients from group 1). The actuarial 5-year toxicity rate was 25%. Grade 3 toxicity of the bowel was

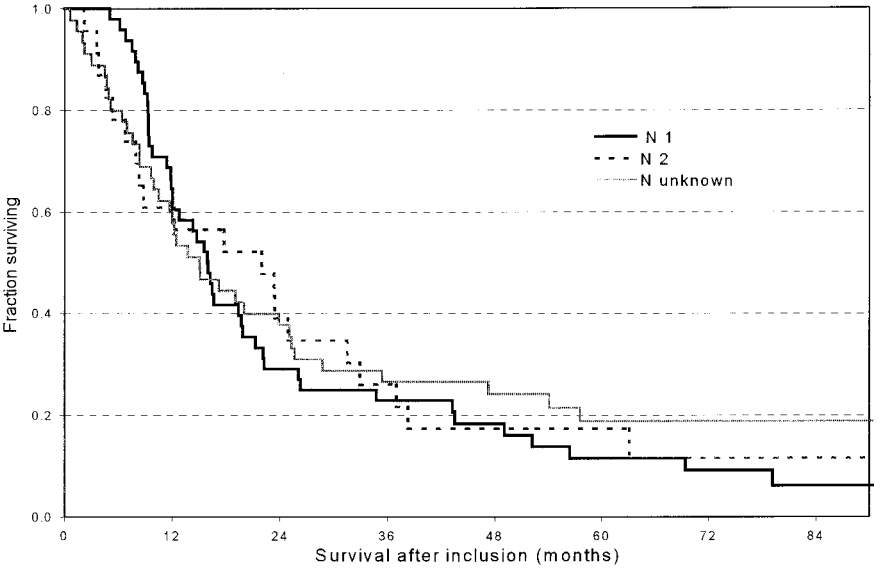

Fig. 3. Survival according to lymph node status in patients receiving radiotherapy.

recorded in 4 patients (one patient from group 1), and 2 patients died of late complications (one fistula and one bowel perforation). The corresponding actuarial 5-year rate of serious events was 19% and no serious events were recorded after 5 years.

DISCUSSION

Neoadjuvant chemotherapy can be used with different strategic aims. The indication in this study was to reduce the risk of dissemination by eradicating subclinical metastases to improve outcome. The use of neoadjuvant chemotherapy has several advantages. The efficacy of chemotherapy can be documented by tumour reduction and the volume of micro-metastases is likely to be minimal. Compliance is optimal because surgery or radiotherapy has not caused deterioration in the condition of the patient. The number of patients needed to prove the neoadjuvant treatment strategy has been reached in a single study, with combination chemotherapy showing no significant effect, and there are several explanations for this deficiency of additional large studies. Invasive bladder cancer is much less frequent than cancer diseases in which the effect of adjuvant systemic treatment has been proven, such as breast and colon cancer. The odds of proving the effect of chemotherapy is furthermore impaired because local therapy is debilitating and the patients are elderly, with smoking-related co-morbidity.

The compliance to chemotherapy in this study was comparable with that achieved in other studies with the same category of patients (16, 17). The compliance may have been more favourable if a more effective antiemetic therapy had been used, because several patients declined further chemotherapy due to emesis. However, lack of compliance cannot explain the lack of overall effect.

Results from a large number of phase II trials using primary chemotherapy in muscle-invasive bladder cancer have shown that approximately half of the tumours are down-staged and a quarter of the patients achieve complete response (5, 18). This study did not aim to evaluate response after chemotherapy and the combined complete response rate after chemotherapy and radiotherapy was 45 out of 120 (38%), which is comparable with results achieved with radiotherapy alone in patients with advanced-stage disease (19, 20). Cisplatin and methotrexate with leucovorin rescue may not be considered the most active combination in urothelial cancer, but it has never been proven to be less effective than CMV or MVAC. The number of courses, however, may not have been enough to eradicate distant metastases (21).

In the present study, the median survival times in the cystectomy trial and in the radiotherapy trial were 17.6 and 78.9 months, respectively, which reflects the selection of patients based on the tumour and nodal stage. The 5-year survival rates were 20% and 59%, respectively. The radiotherapy trial in this study included almost only patients with N + disease or locally advanced tumours (86%) in which cystectomy was not possible. The present results of radical radiotherapy alone are comparable with those achieved in other studies (22–24), and the survival time of patients selected for cystectomy is comparable with that reported from consecutive series (25, 26).

The impact on survival of neoadjuvant chemotherapy with cisplatin as a single drug has been reported in a

Table 4

Bladder and bowel toxicity before, during, and at the end of radiotherapy

	Before RT (%)	During RT (%)	End of RT (%)	Maximal toxicity during follow up
Urogenital toxicity	n = 107	n = 105	n = 103	n = 53
Grade 0	45	24	20	47
Grade 1	31	35	30	9
Grade 2	14	29	33	22
Grade 3	9	12	17	13
Grade 4	1	0	0	8
Gastrointestinal toxicity	n = 100	n = 99	n = 100	n = 58
Grade 0	97	28	28	76
Grade 1	3	21	18	12
Grade 2		49	51	3
Grade 3		0	3	7
Grade 4		1	0	2

meta-analysis of four different studies analysing data from 479 patients in four randomized trials (7). The patients had T2-T4 Nx tumours and received either radiotherapy or cystectomy as radical local treatment, similarly to this study. The results showed no significant effect of chemotherapy on overall survival, with a hazard rate of 1.02. This lack of significant effect of single-agent cisplatin was not unexpected since the response rate was only 10–30% in metastatic disease, and long-term survivors are seldom recorded.

In a Nordic randomized study of 325 patients, treatment with 2 cycles of cisplatin and doxorubicin compared to no chemotherapy followed by preoperative radiotherapy with 20 Gy and cystectomy has been evaluated. After 5 years, cancer-specific survival was 64% in the chemotherapy group and 54% in the control group ($p = 0.10$) (27, 28). The MRC/EORTC intercontinental trial has reported the results of 975 patient randomized between 3 cycles of cisplatin in combination with methotrexate and vinblastine (CMV) and no induction chemotherapy before definitive treatment (8). This treatment could be radiotherapy alone, cystectomy alone or a combination and was chosen by patient or institution preference. With a median observation time of 4 years, a 5.5% insignificant increase in 3-year survival was demonstrated (55.5% vs. 50.0%). The conclusion was that the trial failed to prove an increased survival rate due to neoadjuvant chemotherapy (8). A phase III study with three courses of neoadjuvant MVAC compared with an untreated control group before cystectomy has recently been reported, suggesting improved survival in the chemotherapy group. Detailed results from this study are awaited (10).

The present study has a long follow-up (minimum 42 months), and events have occurred in 83% of the patients. The results indicate that chemotherapy may increase disease-free survival in the first two years, but this effect is not sustained, and the overall result is negative. Salvage chemotherapy was used in 14 patients (9%), and although they were primarily patients from the untreated control group, we do not believe that this treatment explains the lack of overall difference between the two treatment groups. The most favourable outcome was achieved in patients with low-stage disease and normal renal function. Analyses of prognostic factors in other studies have revealed that primary stage and pathological response are related to survival (29, 30).

The results of survival according to nodal status showed that long-time survival could be achieved after radiotherapy in N-positive patients. We found no significant difference in the survival of N1 or N2 patients, but the small number of patients in each group could explain this finding.

Neoadjuvant chemotherapy has also been used as part of a treatment strategy aiming for bladder preservation. Patients included in these types of studies had bladder tumours confined to the bladder wall and had a better prognosis than the patients studied here. The results are therefore not comparable (18). In a randomized study by Shipley et al., neoadjuvant chemotherapy (2 cycles of CMV) was compared with no chemotherapy followed by radiotherapy and additional chemotherapy, or cystectomy in the case of failure. No significant difference in overall survival was found among 123 randomized patients (31).

Concomitant chemotherapy and radiotherapy may increase local response and eradicate distant metastases. Coppin et al. have evaluated the addition of concomitant cisplatin (100 mg/m^2 every second week) to a treatment schedule of 40 Gy in 20 fractions followed by either additional radiotherapy, or cystectomy in the event of no response. The 3-year survival rates were 47% and 33%, respectively (not statistically significant), and chemotherapy had no independent prognostic importance for survival in a multivariate analysis. Locoregional control was improved in the chemotherapy group, with a 19% survival rate after 5 years ($p = 0.036$) (32).

Two randomized trials that assessed the role of adjuvant chemotherapy after radial radiotherapy have been reported (33, 34). The compliance was poor because patients were debilitated by radiotherapy. No improvements in time to recurrence or survival were encountered.

Adjuvant chemotherapy after cystectomy has been reported in several small randomized and non-randomized studies (6, 9, 35–37). These studies suggest that chemotherapy may improve disease-free survival but the effect on overall survival is uncertain, primarily due to the small number of patients but also due to the short observation time.

CONCLUSION

Neoadjuvant chemotherapy with cisplatin and methotrexate did not significantly improve disease-free or overall survival in 153 randomized patients with invasive bladder cancer. A possible effect of neoadjuvant chemotherapy was only present in the first two years of follow-up in these high-risk patients. It is hoped that new, more effective and less toxic regimens in the future will be able to demonstrate a survival improvement when given together with local treatment in patients with muscle-invasive bladder cancer.

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