Chapter 3:

Neoadjuvant Methotrexate, Vinblastine, Doxorubicin and Cisplatin for Histologically Proven Lymph Node Positive Bladder Cancer

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Journal of Urology 2005; 174(1): 80-85

Abstract

Purpose: To gain insight into the effect of neoadjuvant chemotherapy (CT) and subsequent surgery in bladder cancer patients with tumour-positive lymph nodes.

Materials and Methods: 52 patients with histologically proven positive lymph nodes (by lymph node-dissection or aspiration-cytology) were treated with CT and post-chemo surgery in case of partial or complete response. We evaluated response in both the primary tumour and lymph nodes, long-term clinical outcome, and clinicopathological features potentially predictive for survival.

Results: Complete response (CR), partial response (PR) and stable/progressive disease (SD) was attained in 29%, 57% and 14%, and resulted in a 5-year survival of 42%, 19% and 0% respectively. Objective response (HR=4.1), especially CR (HR=8.0), was independently associated with survival. The prognostic values of lymph node status and bladder-tumour status after MVAC were evaluated separately: a tumour-negative bladder combined with tumour-negative nodes was associated with improved survival (HR=4.4), as was a tumour-negative lymph node region in the presence of residual bladder disease (HR=2.8). All patients with post-chemo tumour-positive nodes died within two years.

In the resected specimens residual disease was found in 4/15 clinically complete responders, while no tumour could be detected in 3/29 patients clinically assessed as partial responders.

Conclusions: Response to chemotherapy is associated with improved survival, and our data suggest that lymph node status after MVAC is more important than local tumour status in this aspect. Post-chemo surgery in this series was, in the absence of reliable non-invasive methods, the most adequate method of response evaluation, and led in limited partial responders to long-term progression free survival.

Introduction

Lymph node metastases are common in patients with bladder cancer and the risk of node involvement is related to the depth of primary tumour invasion.[1] Their presence, the number, and the volume of involved nodes are related to survival.[2] Five-year survival rates up to 57% have been reported in patients with clinically unsuspected pN1 disease, compared to 0 – 27% for patients with N2-N3 disease. In the majority of these patients local treatment fails due to occult systemic disease.[1,3] Several options might improve survival, by using either neo-adjuvant or adjuvant systemic chemotherapy. The optimal regimen so far is platinum-based combination chemotherapy.[4]

Most neoadjuvant trials studied the effect of chemotherapy in patients with clinically negative nodes or unknown nodal status; of all patients included in the recently published MRC meta-analysis only 4% was clinically node-positive (N1 or N2), while node status was unknown in 48%.[5] Adjuvant chemotherapy trials suggest that patients who may benefit most from this multimodality approach are patients with urothelial cancer not confined to the bladder, or patients with lymph node-positive disease.[6,7] However, results are still debated, culminating in a transatlantic phase III study (EORTC-trial 30994).

From 1990, patients presenting at our institute with histopathological proof of lymph node-positive bladder cancer (either by aspiration cytology or lymph node dissection) but without evidence of distant metastasis were considered for neoadjuvant chemotherapy, consisting of methotrexate (MTX), vinblastine (VBL), doxorubicin (ADM), and cisplatin (CDDP) (MVAC). Patients scheduled for cystectomy underwent pelvic lymphadenectomy with frozen section. It was customary in the Netherlands to abort the cystectomy in patients with tumour-positive frozen section. In this approach the primary tumour, positive lymph nodes, or both, could serve as marker-lesion to enable evaluation of response to chemotherapy. To gain insight into the effect of systemic chemotherapy and the role of surgery in this selected group of patients we analyzed response rates in both the primary tumour and lymph nodes, long-term clinical outcome, and clinicopathological features potentially predictive for survival.

Methods

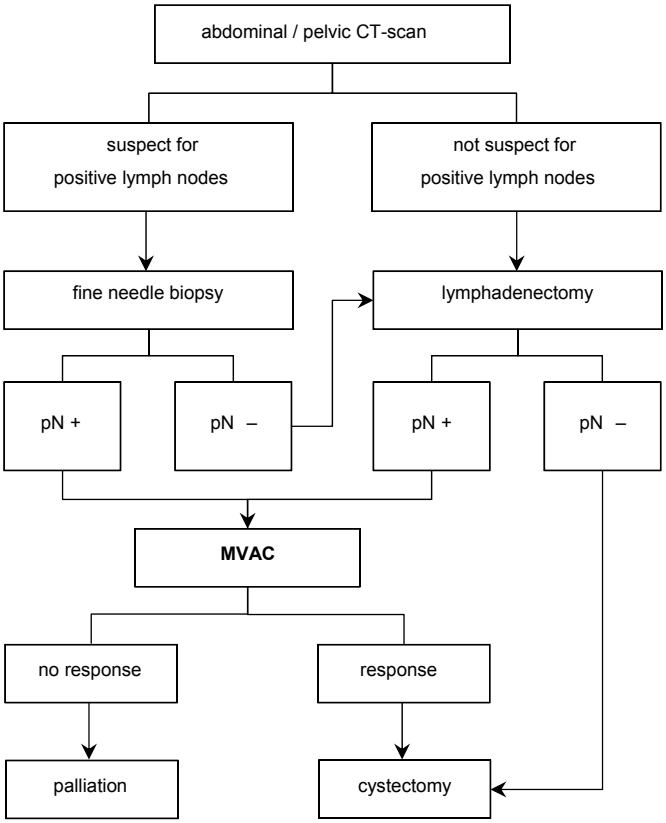
Between 1990 and 2003, 52 patients received neoadjuvant MVAC for lymph node-positive bladder cancer at the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital (NKI/AvL). All patients receiving at least one cycle of MVAC were included in the analysis, also patients who were scheduled for, but did not undergo definitive local surgery.

Diagnosis and treatment strategy

Patients considered had node-positive bladder cancer, no evidence of distant metastasis (i.e. any T, N1-3, M0), WHO-performance 0-1 or a Karnofsky performance ≥70, and a creatinine clearance of ≥60 ml/min. The majority of patients was diagnosed and treated according to the schedule depicted in figure 1. If clinical staging was suspicious for lymph node involvement, pathological proof was obtained by fine needle biopsy. If clinically not sus-

picious, the patient underwent pelvic lymphadenectomy at cystectomy. When positive nodes were found at surgery and confirmed by frozen section, cystectomy was aborted in favour of neoadjuvant chemotherapy. The primary tumour, residual positive lymph nodes, or both, served as marker-lesion. All patients with partial (PR) or complete response (CR) were candidates for cystectomy and residual lymph node dissection after MVAC, to complete and/or confirm response.

Figure 1: *Diagnostic work-up and treatment schedule*



Staging

Clinical tumour and lymph node classification were determined by pelvic-abdominal CT, chest X-ray, transurethral resection, and physical examination. Bone-scans were performed on indication (increased alkaline phosphatase or pain). All stages were converted to the 2002 TNM-system of the International Union Against Cancer. Tumour category T1 and T2 is defined as organ confined, tumour category T3 and T4 as non-organ confined.

Chemotherapy

Patients were treated with two different MVAC regimens during the study period; classic MVAC and high-dose-intensity MVAC (HD-MVAC).[8] These regimens are described in table 1. Dose-intensities were calculated to compare adjustments in time and dose.

Table 1: *Details of the used chemotherapy regimens; classic MVAC and granulocyte colony-stimulating factor (G-CSF) + MVAC (HD-MVAC)*

	Drug	Dose	Day	
Classic MVAC	Methotrexate	30 mg/m^2	1, 15, 22	Every 28 days
	Vinblastine	3 mg/m^2	2, 15, 22	
	Doxorubicin	30 mg/m^2	2	
	Cisplatin	70 mg/m^2	2	
HD-MVAC	Methotrexate	30 mg/m^2	1	Every 14 days
	Vinblastine	3 mg/m^2	2	
	Doxorubicin	30 mg/m^2	2	
	Cisplatin	70 mg/m^2	2	
	G-CSF			

Response

Objective overall response was assigned based on the marker-lesion(s), i.e. primary tumour and lymph nodes. Clinical response assessment was done after every two cycles and pre-operatively by cystoscopy, abdominal/pelvic imaging and chest X-ray. CR was defined as complete disappearance of disease on physical examination, imaging and cystoscopy. PR was defined as a decrease of the summed products of diameters of all measured lesions, without simultaneous increase in size of any lesion or appearance of new lesions. In case of stable disease (SD) or progressive disease (PD), the tumour was considered chemo-insensitive and the combined modality treatment was terminated.

Post-chemotherapy surgery

Post-chemotherapy surgery was offered to all patients who achieved PR or CR, and were fit for surgery. Surgery consisted of cystectomy or anterior/total exenteration. One patient had a partial cystectomy with nephro-ureterectomy for a ureteral tumour. Lymph nodes between ureter crossing of the vessels, genitofemoral nerve, bladder wall, lateral pelvic wall, and obturator nerve were removed, provided that there was any tissue left to remove if lymphadenectomy had previously been performed. Para-aortal lymph nodes were removed if clinically suspicious positive nodes were present.

Statistical analysis

Survival was calculated using the Kaplan-Meier technique, and univariate tests of significance were performed using the log-rank test. Disease specific

survival was defined as time from initiation of chemotherapy until death from urothelial cancer or treatment, or last follow-up. Cox proportional hazard models were used to assess the associations between clinicopathological factors and disease specific survival. These factors included: tumour-category and node-status (cT and cN), age, tumour morphology, lymphadenectomy before MVAC (dissection vs. fine needle aspiration), and (bladder) tumour diameter before MVAC. Lymph node dissection was considered a staging procedure, not a therapeutic procedure. Therefore the pre-MVAC dissection could consist of "node picking", partial-, or bilateral complete lymphadenectomy. To adjust for this factor it was included in the multivariate models.

If diameter was unknown the median diameter was assigned. Analysis was stratified for known/unknown diameter. The variables response to MVAC, and tumour- and lymph node status after MVAC (positive vs. negative) were included as time-dependent variables, where the time from start of MVAC to the last cycle of chemotherapy was taken as the time until detection of response.

Results

Patient characteristics

Patient characteristics are depicted in table 2. Diagnosis of positive nodes was established by lymph node dissection in 31 patients, and by imaging and fine needle aspiration in 21 patients. Lymph node classification of the 31 patients with clinical unsuspicious nodes was pN1 in 10 and pN2 in 21 patients. Median follow-up was 68 months (range 11 – 105).

Table 2: *Patient characteristics; no. = 52.*

	No. (%)
Gender	
Male	39 (75)
Female	13 (25)
Age	
Mean (± SD)	61.3 (± 8.7)
UICC Tumour classification	
T1	2 (4)
T2	21 (40)
T3	16 (31)
T4	13 (25)
UICC lymphe node classification	
N1	11 (21)
N2	40 (77)
N3	1 (2)
Tumor Grade	
2	3 (6)
3	49 (94)
Tumor morphology	
Solid	7 (13)
Papillary	43 (83)
Unknown	2 (4)
Primary tumor size (cm)	
Mean (SD)	4,5 (2.0)
Median (range)	4.0 (1.0 – 10.0)
Positive lymph nodes diagnosed with	
Fine needle biopsy	21 (40)
Lymphadenectomy	31 (60)

Chemotherapy

Classic MVAC was administered to 31 patients, HD-MVAC to 21 patients. Detailed information on dosage was available in all patients except one. The median number of cycles administered was 4 in both schedules. Mean target- and obtained dose-intensities are depicted in table 3, revealing that there were no large differences in intended and achieved dose-intensities between both groups.

Table 3: *Mean intended- and obtained dose-intensities in patients treated with classic MVAC and HD-MVAC. Intended dose-intensity: intended dose (mg/m2) / intended duration of treatment (weeks). Obtained dose-intensity: actual dose administered (mg/m2) / overall duration of treatment (weeks).*

	Classic MVAC dose intensity in mg/m^2/wk			HD-MVAC dose intensity in mg/m^2/wk			Ratio of relative obtained DI's
Drug	Intended	obtained mean (SD)	relative obtained	Intended	obtained mean (SD)	relative obtained	
MTX	22.5	17.9 (3.9)	80 %	15	12.2 (2.5)	81 %	0.99
VBL	2.25	1.84 (0.33)	82 %	1.5	1.27 (0.20)	85 %	0.96
ADM	7.5	6.6 (1,3)	88 %	15	12.5 (2.3)	83 %	1.06
CDDP	17.5	15.4 (2,7)	88 %	35	28.9 (5.3)	83 %	1.06

Nine patients received less cycles than they were planned for because of drug related toxicity (WHO grade ≥3 toxicity: leucopenia (n=6), leucopenic fever (n=2), trombopenia (n=4), mucositis (n=2), creatinine rise (n=2). Some patients had more than one type of toxicity). Seven were treated with MVAC, two with HD-MVAC. Despite this, 4 of these 9 patients achieved a clinical CR or PR, and underwent cystectomy. In two patients (4%) severe side effects resulted in death.

Response and surgery

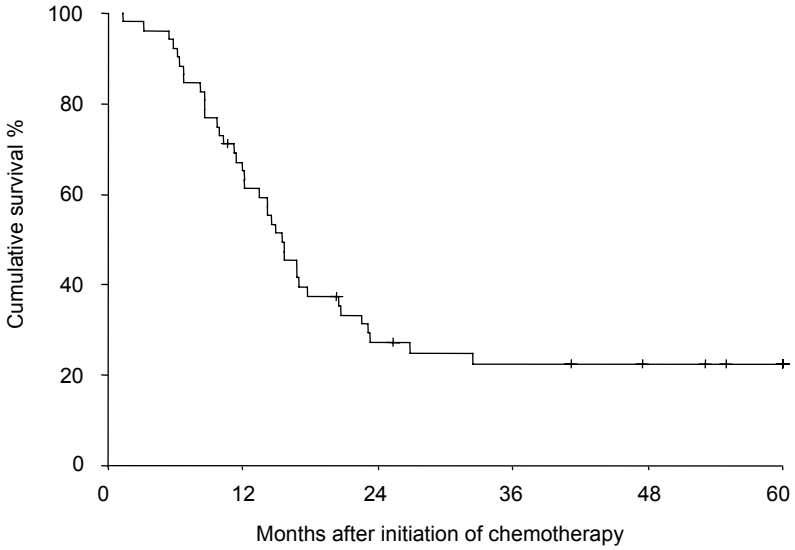
One patient died before response could be evaluated, so 51 patients were included in response assessment. In total 44 (86%) patients achieved an objective overall clinical PR/CR, i.e. measured in both lymph nodes and primary tumour (CR: 15 [29%], PR: 29 [57%]). SD or PD was seen in 7 patients (14%). Histopathology confirmed CR in 11/15 cases, while microscopic residual disease was found in 4/15 clinically complete responders. No tumour could be detected in the resected specimens of 3/29 patients clinically assessed as partial responders. In these cases the residual mass observed at imaging or cystoscopy consisted of necrosis only.

Twelve patients did not undergo post-chemo surgery for the following reasons: early death (2), no response (7), irresectable tumour despite PR (2), not fit due to MVAC-related toxicity (1). All died within 14 months (median 6.7 months). Cystectomy was combined with a lymphadenectomy in 19 out of 40 patients. In eight of those lymph nodes were still positive. In the remaining 21 patients there was no tissue to remove as a result of previous lymph node dissection and/or chemotherapy.

Survival

37 patients died, all bladder cancer or treatment related. The 5-year survival rate was 23% (95% CI: 11–35%), with a median survival of 15.4 months (fig 2).

Figure 2: *Disease specific survival after initiation of chemotherapy (all patients)*



Univariate analyses of factors potentially associated with disease specific survival are summarized in table 4. Clinical overall response (primary tumour and lymph nodes) showed to be related to survival with 5-year estimates of 42%, 19% and 0% for CR, PR and no response respectively (fig 3). Clinical overall response was independently associated with survival (Cox proportional hazard model: in terms of increased risk: HR: 4.1, 95% CI: 1.6–10.9). Especially achieving clinical CR was related to better survival (HR: 8.0, 95% CI: 2.4–27.0).

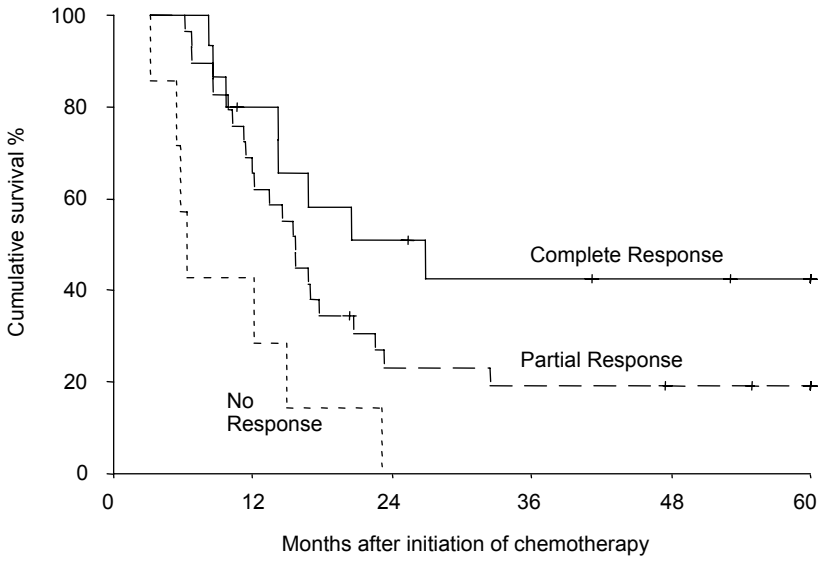
Table 4: *Univariate analysis of factors potentially associated with the risk of dying of bladder cancer*

Variable	P value	Hazard ratio (95% confidence interval)
Age > median	0.71	0.9 (0.5 – 1.7)
Lymph stage before chemotherapy >N1	0.15	1.8 (0.8 – 4.1)
Tumor morphology	0.38	1.5 (0.6 – 1.6)
cT organ confined versus non organ confined	0.74	1.1 (0.6 – 2.1)
Diameter more than 5 cm	0.61	1.2 (0.6 – 2.5)
Lymphadenectomy before MVAC	0.22	0.7 (0.4 – 1.3)

Subsequently, the prognostic values of node status and bladder-tumour status after MVAC (tumour-positive vs. tumour-negative) were evaluated separately in this model. Patients with clinical tumour negative bladder and tumour negative nodes were independently associated with improved survival (HR: 4.4, 95% CI: 1.6–12.2). Patients with clinical tumour-negative lymph nodes but

tumour-positive bladder after MVAC were independently related to better survival as well (HR: 2.8, 95% CI: 1.1–7.2).

Figure 3: *Disease specific survival after initiation of chemotherapy according to clinical response of lymph nodes and bladder tumour combined.*



All patients with residual tumour-positive nodes died within two years. Survival curves according to post-MVAC tumour status are depicted in figure 4a an 4b.

Discussion

Combination chemotherapy is the only treatment strategy providing the potential of long-term progression free survival in metastatic bladder cancer[9], and has shown to be more effective in patients with nodal metastases compared to visceral metastases.[10] The role of chemotherapy before (neoadjuvant) or after (adjuvant) local therapy in localized disease is less well defined. Although neoadjuvant platinum-based chemotherapy has been studied extensively, none of the individual studies had sufficient power to demonstrate a significant benefit on survival.[11-13] The MRC meta-analysis provided the first evidence in favour of neoadjuvant chemotherapy revealing a modest improvement of 5% in overall survival at 5 years with Cisplatin based combination chemotherapy.[5] Most patients studied in neoadjuvant trials have (clinically) tumour-negative nodes or an unknown lymph node status. The MRC meta-analysis comprises 2688 patients, of whom 4% was clinically lymph node-positive, while lymph node status was unknown in 48%.[5]

Most randomized adjuvant trials but one[6] are inconclusive about the effect of adjuvant chemotherapy on overall survival[14-17], though several suggest that it is successful in patients with lymph node-positive disease[6,7,17]. But inherent to adjuvant trials is the lack of in vivo evaluation of tumour response and its role in predicting survival.

Figure 4a: *Disease specific survival after initiation of chemotherapy according to post-MVAC lymph node status*

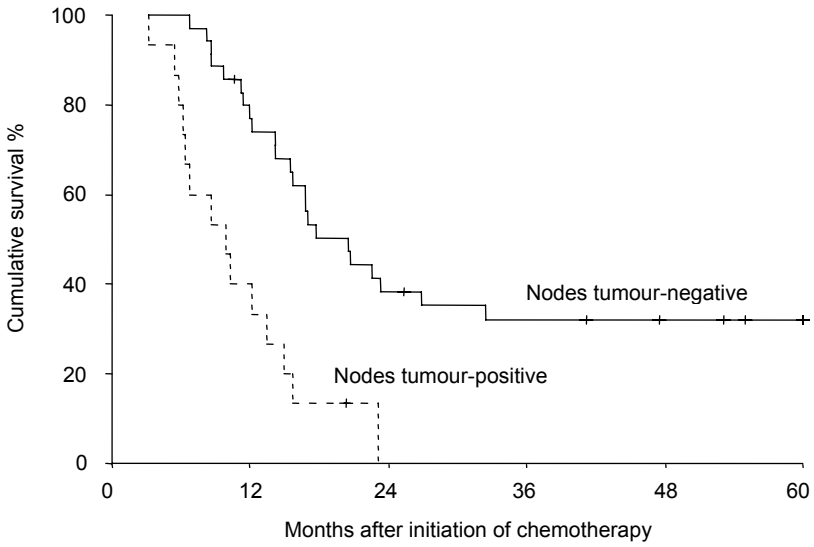
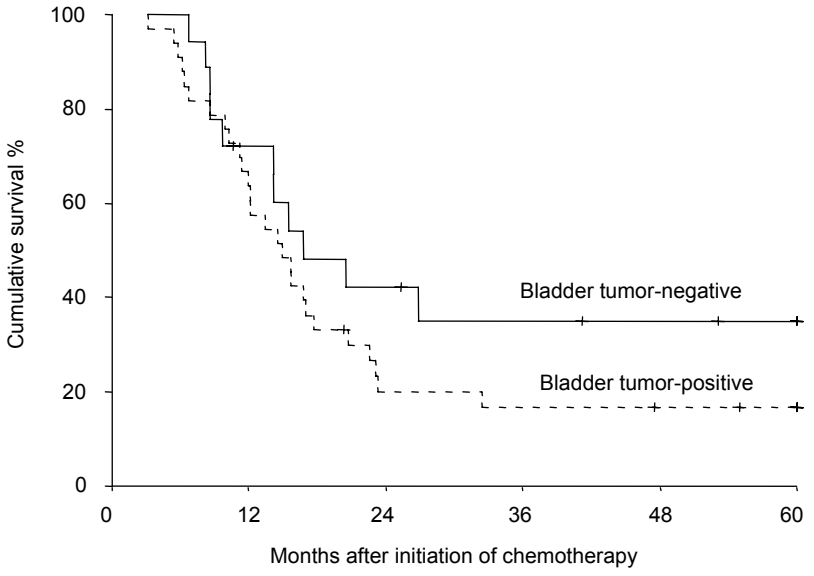


Figure 4b: *Disease specific survival after initiation of chemotherapy according to post-MVAC bladder status*



Impressed by the poor outcome it was common practice in the Netherlands not to perform a cystectomy and to abort surgery in favour of neoadjuvant chemotherapy if confronted with positive nodes. If cystectomy followed MVAC a complementary lymph node dissection was done if any tissue was left to remove. In this study we evaluated the use of MVAC before cystectomy in selected bladder cancer patients with positive lymph nodes only without distant metastases. This is different from many other studies.

The rationale for post-chemo surgery is the elimination of residual cancer and to complete surgically the response in partial responders. The 5-year survival after PR was 19%. We found residual disease in 27% of the patients clinically defined as complete responders. These sites are prone to be sites of recurrence.[18] By contrast, no tumour could be detected in the resected specimens of 14% of clinically partial responders. In the absence of reliable non-invasive methods, surgery is the most adequate evaluation of response. The concomitant extended lymph node dissection, which can have a curative role on its own is an attractive adjunct.[1,3]

Especially complete response or absence of tumour in the lymph nodes after MVAC is associated with improved survival. However, this should be interpreted with caution. It is incorrect to infer from a comparison between responders and non-responders that survival is prolonged as a direct result of treatment. In the presented study it is impossible to distinguish whether improved survival for major responders is the result of MVAC, subsequent surgery, or other factors. However, it demonstrates that response evaluation after MVAC identifies those patients with better prognosis. Furthermore, residual node status should be regarded as both the result of MVAC and lymphadenectomy in patients with pre-MVAC lymph node dissection.

Other reasons for cautious interpretation of results are the retrospective nature of this study, with inherent case selection bias, and the low number of patients. This might explain why differences in survival according to initial tumour or node status were not statistically significant, whereas in literature these factors are important prognosticators[1]. It is plausible that these factors will become evident in larger series. Other variables may have influenced results of this study, such as (in)complete chemotherapy, no subsequent cystectomy, and lower individual dose-intensities. The causal relationship between these variables and outcome however, is that the planned treatment is interrupted because these patients do worse. The reversed relationship (patients do worse because of changed treatment strategies) cannot be confirmed nor rejected with these data, but is less strong in our opinion. Nevertheless, we cannot exclude that these factors influence outcome.

Differences between mean achieved dose-intensities of both MVAC-schedules were minor. This lack of difference might also reflect small numbers. However, we did not intend to prove equivalence, but provided dose-intensities to show that differences are small. Consequently, they are not likely to cause important differences in outcome, which was confirmed in additional explorative analyses: choice of MVAC-schedule was of minor influence on outcome (HR: 0.98, data not shown), which is consistent with other studies.[8]

The median survival of the patients presented in this series is similar to survival figures of advanced disease in literature (median 12–13.5 months).[10,19] The proportion of patients achieving long-term survival however is higher. Survival in this series is in accordance with prior studies of patients with metastases confined to the lymph nodes.[7,19] On visual inspection of survival curves, the outcome of the

combined treatment in this group of patients seems to be decided within two years. We found recurrences in 2 patients (4%) 2 years after treatment, hence late recurrences are rare. This is important for counselling and planning of follow up, and consistent with other studies.[20]

TCC is a chemotherapy-sensitive disease, hence a definite role for chemotherapy analogous to other types of cancer is plausible in locally advanced disease. However, the magnitude of benefit appears modest, and the preferred sequence (adjuvant, neoadjuvant or deferred) is still unclear. Until these issues are clarified, high-risk patients should be treated preferably in the context of well-designed, multi-centre prospective trials.

Conclusions

Bladder cancer with involved lymph nodes is responsive to MVAC, albeit at the cost of considerable toxicity. Response to chemotherapy is associated with improved survival, and our data suggest that lymph node status after MVAC is more important than local tumour status after MVAC in this aspect. Post-chemo surgery in this series was, in the absence of reliable non-invasive methods, the most adequate method of response evaluation, and led in limited partial responders to long-term progression free survival.

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