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Original Paper

Genitourinary Group Phase II Study of Chemotherapy in Stage T3–4 N0–X M0 Transitional Cell Cancer of the Bladder: Prognostic Factor Analysis

T.A.W. Splinter,[1] M. Pavone-Macaluso,[2] D. Jacqmin,[3] J.T. Roberts,[4] P. Carpentier,[5] M. de Pauw[6] and T. Sahmoud[6]

[1]Department of Medical Oncology, University Hospital Dijkzigt, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands; [2]Department of Urology, University of Palermo, Italy; [3]Hospices Civils, Strasbourg, France; [4]General Hospital, Newcastle, U.K.; [5]O.L. Vrouw Hospital, Aalst, Belgium; and [6]EORTC Data Centre, Brussels, Belgium

The aim of this study was to examine prognostic factors for survival of patients with invasive bladder cancer who had received neoadjuvant chemotherapy followed by further treatment. From 1986 to 1990, 149 eligible patients with T3–4 N0–X M0 bladder cancer were entered into a phase II trial of neoadjuvant chemotherapy, consisting of cisplatin and methotrexate. Patients received two or four courses of chemotherapy, depending on the absence or presence, respectively, of a major clinical response after two courses. 136 patients were evaluable for clinical response after two courses of chemotherapy, and 75 patients were evaluable for pathological response after two or four courses. A multivariate analysis, based on pretreatment variables and the post-treatment variables, clinical response and pathological response, showed that performance status, tumour size and clinical response after two courses of chemotherapy were the only independent prognostic factors for all eligible patients. A second multivariate analysis in the selected subgroup of patients, who underwent a cystectomy, showed that the G-cagetory and pathological response were the only independent prognostic factors. In conclusion, in this group of patients, the response to chemotherapy was a strong and independent prognostic factor in addition to other independent variables. However, it was not accurate or strong enough to allow an impact on the choice of locoregional therapy. Copyright © 1996 Elsevier Science Ltd

Key words: muscle-invasive bladder cancer, neoadjuvant chemotherapy, prognostic factors
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INTRODUCTION

After 10 years of investigations on the use of adjuvant or neoadjuvant chemotherapy and surgery or radiotherapy, the essential question on its effect on survival still remains unanswered [1]. Two large ongoing trials on neoadjuvant chemotherapy [2, 3] will hopefully produce conclusive data in the future. If neoadjuvant chemotherapy has a beneficial effect on survival, such an effect will probably be a modest 10–15%. Careful selection of patients, therefore, seems to be mandatory. In a retrospective study of 147 patients, from eight different centres, who underwent a partial, total or radical cystectomy following chemotherapy, it was shown that patients with a major pathological response had a 5-year survival of 70 versus 20% for pathological non-responders [4]. Such data seem to indicate that if neoadjuvant chemotherapy will improve survival by killing micrometastases, the patients who will benefit will belong to the group with a major pathological response. In 1986, the European Organisation for Research and Treatment of Cancer–Genitourinary Group (EORTC-GU) started a large prospective phase II trial of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer. The analysis of the evaluation of clinical response was published in 1992. It was shown that clinical complete and partial remissions were a heterogeneous group, but non-responders could be delineated with a 100% accuracy by clinical response evaluation and transurethral resection biopsy only. Furthermore, it was found in a number of patients

Correspondence to T.A.W. Splinter.
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that, by increasing the number of chemotherapy courses from two to four, histologically proven T2 tumours were further downstaged to P0 [5]. Only two studies have been published on prognostic factors for survival of patients with invasive bladder cancer, who have been treated with either neoadjuvant chemoradiotherapy, followed by more radiotherapy ($n = 40$) [6] or neoadjuvant chemotherapy alone ($n = 111$), followed by surgery in the majority of patients [7]. The purpose of this paper is to report the analysis of prognostic factors for response and survival after a median follow-up of 42 months and a maximal follow-up of 79 months of 149 eligible patients with invasive bladder cancer, entered into a phase II trial of neoadjuvant chemotherapy, and of 75 patients, who underwent a cystectomy after chemotherapy.

PATIENTS AND METHODS

Patients

Patients were eligible if they were 75 years old or younger, and had histologically proved transitional cell cancer of the bladder (stage T3–4 N0-X M0); performance status 0, 1 or 2 according to the World Health Organisation (WHO); a measurable marker lesion in the bladder to evaluate the response; serum creatinine less than 140 μmol/l and/or creatinine clearance of 60 ml/min or greater; no uncontrolled infection or cardiac disease; no previous treatment with cisplatin, methotrexate or radiotherapy; no second malignancy except for basal cell cancer of the skin or carcinoma *in situ* of the cervix, and adequate bone marrow reserve (white blood count 3.5×10^9/l or greater, platelets 120×10^9/l or greater). Informed consent was obtained from each patient. The trial design consisted of two courses of chemotherapy followed by evaluation of response. Patients with a clinical complete or partial remission then received another two courses of chemotherapy, while patients with clinical stable or progressive disease were withdrawn from the protocol. After chemotherapy, additional therapy was left to the judgement of the physician responsible. Chemotherapy consisted of 70 mg/m^2 cisplatin on day 1, and 40 mg/m^2 methotrexate on days 8 and 15 plus leucovorin rescue. The chemotherapy regime was based on a previous EORTC study [8]. Leucovorin rescue, 15 mg orally twice daily for 1 day starting 24 h after methotrexate administration, was advised because of unexpected toxicity observed in the latter study. Cycles were repeated every 3 weeks. Before each drug administration, blood cell counts and serum creatinine level were determined. When the serum creatinine level was greater than 140 μmol/l, no chemotherapy was given. If the serum creatinine level remained greater than 140 μmol/l for more than 2 weeks, the patient was withdrawn from the protocol. If serum creatinine increased by more than 50% of the starting value, but remained less than 140 μmol/l, methotrexate was given at 75% of the intended dose. If the white blood count was 2.0×10^9–3.5×10^9/l and/or platelets were 90×10^9–120×10^9/l, the cisplatin and methotrexate doses were lowered to 75%. At a white blood count of less than 2.0×10^9/l and/or platelets level less than 90×10^9/l, no chemotherapy was given. If after a delay of 2 weeks, the blood cell counts had not recovered the patient was withdrawn from the protocol.

Prechemotherapy staging consisted of physical examination, blood cell counts, chemistry, chest X-ray, cystoscopy and TUR biopsy, bimanual palpation, computerised tomography (CT) or ultrasound of the bladder and abdomen, and measurement of the residual tumour marker lesion. Bone scan was optional. At restaging after two and four courses of chemotherapy, physical examination, cystoscopy, biopsy and measurement of the tumour marker lesion were repeated.

Complete clinical response was defined as: complete disappearance of all clinical evidence of bladder cancer, including tumour-negative deep biopsies. Partial response was defined as: clinical partial remission of the marker lesion according to WHO criteria independent of histological evidence of bladder cancer or clinical complete remission plus histological evidence of bladder cancer. Stable disease: any other clinical response independent of histological evidence of bladder cancer. Progression: clinical progression of the marker lesion according to WHO criteria independent of histological evidence of bladder cancer. Patients were considered evaluable for pathological response if they had undergone radical, total or partial cystectomy. Complete pathological response was defined as: complete disappearance of all histological evidence of bladder cancer in cystectomy specimens (stage P0). Partial response: downstaging to non-invasive bladder cancer in cystectomy specimens (stages Pis, P1 or Pa). No remission: invasive bladder cancer still present in cystectomy specimens (stage P2 or greater).

Statistical methods

Duration of survival was estimated using the Kaplan–Meier technique [9]. Differences in duration of survival were analysed using a two-sided log-rank test [10]. The relative importance of the prognostic factors for the duration of survival was assessed using the Cox's proportional hazards regression model [11]. Response rates were compared using the logistic regression model [12], except for weight loss, since the response rate in one subgroup was 0%. Fisher's exact test was used to compare the response rates for that variable.

RESULTS

Between 1986 and 1990, 171 patients entered the study, of whom 22 patients were ineligible because of inadequate staging (16 patients), patient age (2 patients), absence of a measurable lesion (3 patients) or a second malignancy (1 patient). Among the 149 eligible patients entered from 23 different centres, 2 were not evaluable because they never received chemotherapy and 11 were evaluable only for toxicity because of insufficient treatment to evaluate the response. Thus, 136 patients (80%) were fully evaluable. For the analysis of possible pretreatment prognostic variables and post-chemotherapy clinical or pathological response, the patients were divided into two groups. The first group comprised all eligible patients ($n = 149$) who received chemotherapy, were evaluated for clinical response and then underwent different locoregional treatments. The pretreatment characteristics and clinical response data of this group are shown in Table 1. The second group comprised those eligible patients who received chemotherapy, were evaluated for clinical response then underwent a partial ($n = 9$), total ($n = 5$) or radical ($n = 63$) cystectomy. Two were not considered evaluable for pathological response because they had received pre-operative radiotherapy to the bladder after neoadjuvant chemotherapy. The pretreatment characteristics and clinical response after two courses of chemotherapy are shown in Table 1.

Of the 149 eligible patients, the median age was 64 years, with a range of 39–76 years; the male-to-female ratio was 7.3:1. Performance status (WHO) was 0 in 109 patients, 1 in 33 and 2 in 7. Previous therapy for bladder cancer included

Table 1. Pretreatment variables and post-treatment response data of all eligible patients and of all eligible patients who underwent surgery and were evaluable for pathological response

Characteristics	All eligible patients (n = 149)		Evaluable for pathological response (n = 75)†		Not evaluable for pathological response (n = 74)‡		P*
	n	(%)	n	(%)	n	(%)	
Age at entry (years)							
<64	70	(47)	36	(48)	34	(46)	0.802
≥64	79	(53)	39	(52)	40	(54)	
Sex							
Male	131	(88)	66	(88)	65	(88)	0.976
Female	18	(12)	9	(12)	9	(12)	
Weight loss during last 3 months							
≤5%	133	(89)	66	(88)	67	(91)	0.771
6–20%	13	(9)	7	(9)	6	(8)	
unknown	3	(2)	2	(3)	1	(1)	
Performance status							
0	109	(73)	62	(83)	47	(64)	0.008
1–2	40	(27)	13	(13)	27	(36)	
Previous treatment							
No	123	(83)	60	(80)	63	(85)	0.409
Yes	26	(17)	15	(20)	11	(15)	
Creatinine clearance (ml/min)							
>100	36	(24)	21	(28)	15	(20)	0.698
81–100	36	(24)	18	(24)	18	(24)	
≤80	56	(38)	28	(37)	28	(38)	
Unknown	21	(14)	8	(11)	13	(18)	
T-category							
T3A	78	(52)	47	(63)	31	(42)	0.011
T3B–T4	71	(48)	28	(37)	43	(58)	
G-category							
G1–G2	28	(19)	17	(23)	11	(15)	0.237
G3	112	(75)	54	(72)	58	(78)	
Unknown	9	(6)	4	(5)	5	(7)	
Largest diameter (cm)							
≤5 cm	91	(61)	44	(59)	47	(64)	0.676
>5 cm	48	(32)	25	(33)	23	(31)	
Unknown	10	(7)	6	(8)	4	(5)	
Response after two cycles							
CR	11	(7)	3	(4)	8	(11)	0.135
PR	66	(44)	38	(51)	28	(38)	
Other	72	(48)	34	(45)	38	(51)	
Pathological response							
pCR or pPR			23	(31)			
pNR			52	(69)			

* Chi-square test, based on all patients with known values. † 2 patients who underwent pathological evaluation for response were not considered evaluable because they had received pre-operative radiotherapy to the bladder after neoadjuvant chemotherapy. ‡ Patients who did not undergo pathological evaluation for response (n = 59) or had received insufficient or no chemotherapy (n = 13).

intravesical chemotherapy in 18 patients, systemic chemotherapy (mitomycin-C) in 1 and other treatments such as intravesical bacillus Calmette-Guerin in 7, while 124 had no prior therapy. Median creatinine clearance was 86 ml/min with a range of 48–178 ml/min. The initial T-category was T3 in 78 patients, T3b in 39, T4a in 24 and T4b in 8. Tumour grade was 1 in 2 patients, 2 in 26, 3 in 112 and unknown in 9. The median tumour size was 14 cm^2 (range 0–169) by bimanual palpation and 12 cm^2 (range 0–80) by CT-scan. Based on all eligible patients, the best clinical response after two courses of chemotherapy was: complete remission (CR) in 11 patients, partial remission (PR) in 66 (overall response in 77 patients or 52%, 95% confidence interval 44–66%), stable disease (SD) or progressive disease (PD) in 49 patients, called non-responding (NR) patients, unknown for 10 patients and 13 patients were not evaluable for response (2 never received chemotherapy and 11 had insufficient treatment).

16 patients had a pCR, 7 patients a pPR and 52 patients a pNR. Of the remaining 59 patients, 25 received no further treatment, 20 underwent radiotherapy only, 6 underwent extended transurethral resection (2 followed by radiotherapy), 7 underwent a laparotomy with lymph node sampling (3 followed by radiotherapy) and 1 patient underwent pelvic lymph node dissection and ureterectomy.

As shown in Table 1, performance status and T-category were significantly different between the cystectomy group

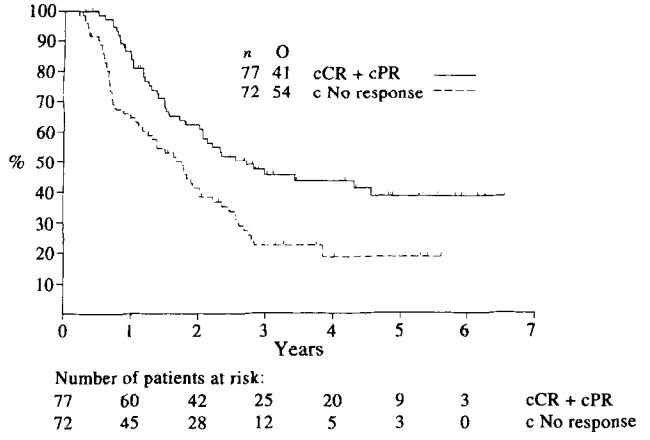

Figure 1. Survival of all eligible patients (n = 149). O = number of deaths.

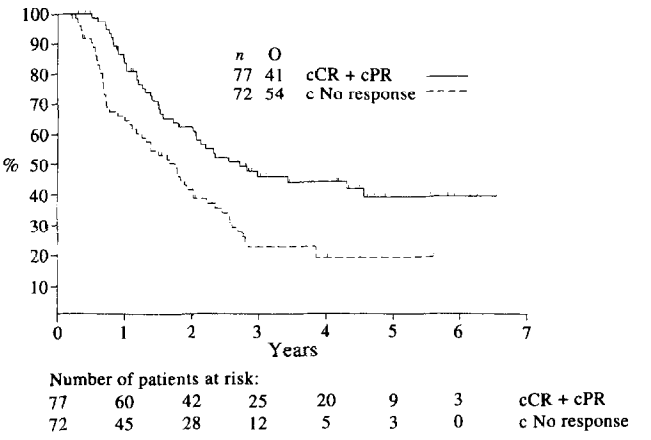

Figure 3. Survival of fully evaluable patients (n = 126) by presence or absence of a clinical response after two courses of chemotherapy; ——, cCR + cPR; ····, cNR. O = number of deaths.

and the remaining eligible patients, indicating a selection of excellent performance status and T3a tumours for surgery, independent of other prognostic factors and clinical response to chemotherapy.

Univariate analysis

Figure 1 shows the overall survival of 149 eligible patients. At the time of the analysis, 95 patients had died, the median survival was 24.2 months and the 5-year survival was 29% (95% confidence interval 21–37%). Based on all eligible patients, the analysis of all variables presented in Table 1 showed that patients with either a WHO performance status 0, a low G-category (G1–G2) or a tumour diameter ≤5 cm (Figure 2) had a significantly longer survival relative to patients with a performance status 1–2, G3 or a tumour diameter >5 cm, respectively. The median duration of survival for the 77 patients with a clinical response after two cycles of chemotherapy was 30.9 months and for the other 72 patients 17.9 months (Figure 3). None of the variables could significantly predict the clinical response after two cycles.

Among the 75 patients who were evaluable for pathological response, 7 patients had a pCR, 16 a pPR and 52 had no response. The prognostic factor analysis based on this group of patients showed that a low G-category and a tumour diameter ≤5 cm had border-line significance (P = 0.058 and P = 0.049, respectively) and that the WHO performance status was not statistically significant (P = 0.265). The only significant variable was the pathological response (P < 0.001). The median duration of survival for the 23 patients who had a pathological response was not reached at the time of the analysis whereas for the other 52 patients it was only 24 months (Figure 4). With respect to predicting the pathological response, only a tumour diameter ≤5 cm was of border-line significance (P = 0.050).

Multivariate analysis

With respect to the duration of survival for all eligible patients, and based on patient and tumour characteristics (Table 1) and the clinical response after two cycles, the clinical response (CR/PR versus others), the largest tumour diameter (≤5 cm versus >5 cm) and WHO performance status (0 versus 1–2) were retained in the final model at the 5% level of significance (the model P value <0.001). Considering that these three variables are in the model, none of the other variables were significant at the 5% level. Table 2 presents the level of significance and the death hazard ratio estimate for each of these three variables. These results are based on 139 patients for whom the values of these three variables were known. The analysis for the 75 patients who underwent surgery showed that only the G category and the pathological

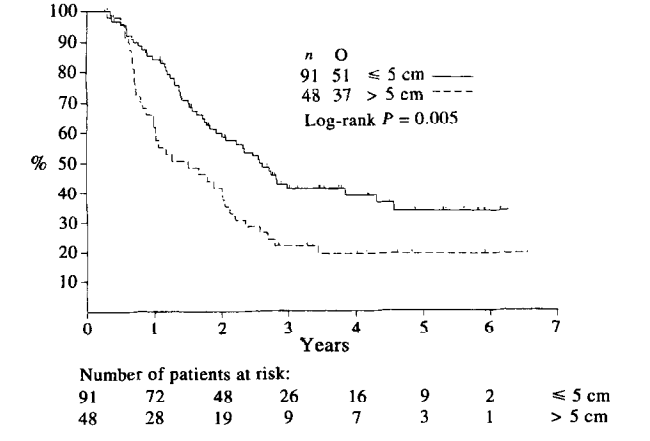

Figure 2. Survival by largest tumour diameter; ——, ≤5cm; ····, >5 cm. O = number of deaths.

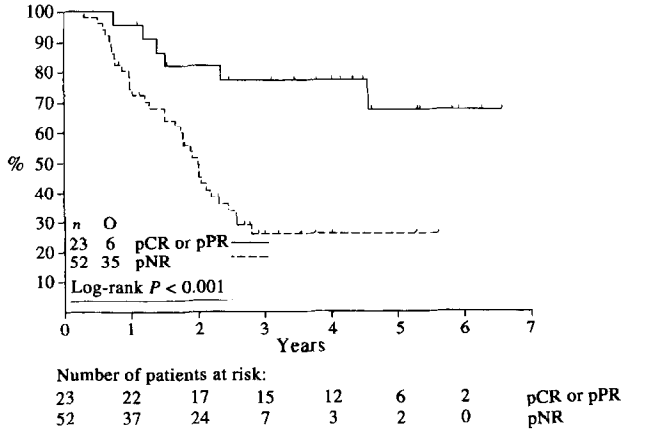

Figure 4. Survival by pathological response; ——, pCR + pPR; ····, pNR. O = number of deaths.

Table 2. Results of multivariate analysis with respect to duration of survival of eligible patients (a) and cystectomy patients (b)

Variable	Death hazard ratio	95% confidence interval	Log-rank *P*
(a) 149 eligible patients			
WHO performance status			
0*	1.0		
1–2	1.8	1.0–2.5	0.039
Largest tumour size			
≤5 cm*	1.0		
>5 cm	1.8	1.2–2.7	0.007
Clinical response			
CR/PR*	1.0		
Other	1.9	1.2–2.9	0.004
(b) 75 eligible patients who underwent cystectomy			
G-category			
G1–G2*	1.0		
G3	2.6	1.1–6.3	0.031
Pathological response			
pCR or pPR*	1.0		
No response	4.2	1.7–10.2	0.002

* Reference category.
Each variable is adjusted for the other ones.

response were significant at the 5% level of significance. Further details are presented in Table 2.

DISCUSSION

Despite 10 years of investigations of adjuvant and neoadjuvant chemotherapy and surgery or radiotherapy in invasive bladder cancer, its effect on survival remains unanswered [1]. However, when neoadjuvant chemotherapy is shown to improve survival in invasive bladder cancer, the improvement will probably be very modest and careful selection of patients by pre- and post-treatment prognostic variables will be needed. Multivariate analysis of prognostic factors in a small group of 40 patients with T2–T4 N0 M0 bladder cancer, who were treated with neoadjuvant cisplatin, methotrexate and vinblastine (CMV) plus radiotherapy, showed that tumour size (<5 cm and ≤5 cm), clinical response to chemoradiotherapy and vascular invasion were independent predictors of distant metastases and therefore survival [6]. Recently, a multivariate analysis was performed on 111 patients with T2–4 N0 M0 bladder cancer, who had been treated with neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC), followed by different locoregional treatment modalities to determine prognostic factors for survival. Median follow-up was 5.8 years. 14 patients were not evaluable for reponse because, in 13 patients, tumours had been completely resected endoscopically prior to treatment and 1 patient died in CR prior to surgery. In the remaining 97 patients, the initial tumour stage and clinical response to chemotherapy were significant predictors of survival. In a subgroup of 81 patients, who underwent late surgery (more than 90 days after completion of chemotherapy) or surgery on time (an interval of less than 90 days), prechemotherapy clinical stage and postchemotherapy pathological stage were the only two important prognostic factors. An association between pathological response and survival was only observed for patients with advanced stages (≥3B) at the start of chemotherapy. The 5-year survival rate of all patients was 52%. This study was a single centre study at the Memorial Sloan Kettering Cancer Centre (MSKCC, New York, U.S.A.) [7]. Our study was performed by 23 different centres. The median follow-up was 42 months, maximum follow-up 79 months. The 5-year survival rate was 29%. Multivariate analysis of pretreatment variables and postchemotherapy clinical response showed that clinical response, tumour size and performance status were significant prognostic factors. In our study, 75 of the 149 patients underwent a partial or radical cystectomy within 6 weeks after completion of chemotherapy. Prognostic factor analysis of the subgroup showed that the pathological response (pCR an pPR) and, to a much lesser degree, tumour grading had significant prognostic value. The 5-year survival rate of patients with a pCR or pPR was 62% and 26% for pathological non-responders. These data are very similar to an earlier reported retrospective study of 147 patients in which patients with a pCR or pPR and patients with a pNR had a 5-year survival rate of 70% and 20%, respectively [4].

The three multivariate analyses by Fung and colleagues [6], Schulz and associates [7] and our own have all shown that the prognostic factors for all patients are the clinical response to chemo(radio)therapy and pretreatment T-category or tumour size. The difference between T-category and tumour size probably reflects differences in thoroughness of clinical staging and patient selection. In the MSKCC series, 16 patients had T2 tumours, whereas in the EORTC study the lowest T-category was T3a. Moreover, the 5-year survival rates of both studies were 52% and 29%, respectively, indicating a significant difference in prognosis between the two study populations. Finally, performance status, which was an important prognostic factor in the EORTC study, was not significant in the MSKCC series, since only very few patients

had a performance score <70%. Therefore, it seems justified to conclude that, for patients with invasive bladder cancer, who receive neoadjuvant chemotherapy, followed by either surgery or radiotherapy, the most important prognostic factors are the clinical response to chemotherapy and T-category or tumour size, depending on the selection of patients and probably the thoroughness of staging.

The multivariate analysis by Schulz and colleagues [7] of the subgroup of 81 patients, who underwent surgery, showed that pretreatment T-category and postchemotherapy pT-category were the only two important prognostic factors. Downstaging and survival were only associated in patients with T-category ≥3B. However, the interval between completion of chemotherapy and surgery was less than 90 days in 69 patients and considerably longer in 11 patients, who initially refused surgery, but eventually underwent definitive surgery at the time of documented local progression. The latter group probably contained patients with a better initial response than at the time of surgery. It is unclear how much these rather long intervals may have influenced the association between pathological response and survival. In our multivariate analysis of 75 patients, who underwent surgery, the postchemotherapy pathological response was the main prognostic factor, consistent with an earlier report [4]. Considering the aforementioned difference in 5-year survival rates between both studies, indicating the presence of more advanced stages in the EORTC study in comparison with the MSKCC series, the conclusion seems justified that, for patients with invasive bladder cancer, who receive neoadjuvant chemotherapy followed by surgery, the most important prognostic variable is the pathological response in more advanced stages. The pretreatment T-category is probably a second important prognostic factor, when less advanced stages such as T2 and some T3a tumours are involved.

In conclusion, the response to neoadjuvant chemotherapy in invasive bladder cancer is a strong and independent prognostic factor in addition to other independent variables, such as pretreatment T-category, tumour size and performance status. This prognostic value does not indicate that chemotherapy is an effective method to improve survival in invasive bladder cancer. However, the prognostic value of the clinical response to neoadjuvant chemotherapy is not strong enough to delineate patients who have no chance of cure and should therefore receive palliative treatment. Moreover, the inaccuracy of clinical repsonse evaluation [5] does not make neoadjuvant chemotherapy a suitable method for decision-making on subsequent therapeutic strategies, such as bladder preservation. The use of the prognostic value of the response to neoadjuvant chemotherapy in invasive bladder cancer seems, therefore, only warranted when the ongoing randomised trials have shown a survival benefit.

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