TREATMENT DELAY AND PROGNOSIS IN INVASIVE BLADDER CANCER

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ABSTRACT

Purpose: We studied treatment delay, and the impact on disease specific survival and stage progression in a series of patients who had undergone cystectomy.

Materials and Methods: All 141 patients underwent radical cystectomy between 1990 and 1997 due to locally advanced bladder cancer. Treatment delay was defined as time from pathological confirmation of invasive disease to performance of cystectomy, and was registered retrospectively from the patient charts. Two patients received neoadjuvant chemotherapy and were excluded from further analyses. Followup continued until April 2003 with death due to bladder cancer as the end point. Causes of death were retrieved from the Swedish Cause of Death Registry.

Results: The median treatment delay was 49 days, but was significantly longer for the 71 cases who were referred from other hospitals (63 vs 41 days, p <0.001). Treatment delay did not influence cumulative incidence of death from bladder cancer. Considering all cases, there was no significant correlation between treatment delay and stage progression. For clinical stage T2 tumors, median treatment delay was 76 days among patients with stage progression compared to 41 and 48 days for those with stage regression and stage equivalence, respectively (p=0.20).

Conclusions: Treatment delay was not found to influence disease specific survival in the present study. Furthermore, treatment delay was not significantly longer in cases that progressed compared to those with equal or lower pathological stage in the cystectomy specimen.

KEY WORDS: bladder neoplasms, disease progression, therapeutics, appointments and schedules

Striving for early diagnosis and treatment of malignant tumors is the sine qua non in oncology, and the ultimate goals are to increase the chances of achieving cures and to decrease worry and anxiety. This is no doubt particularly important in cases of invasive tumors. However, diagnosis and treatment are often delayed in uro-oncology as in many other areas of medicine. Studies of bladder cancer have reported a median diagnostic delay (ie time from first symptom to diagnosis) in the range of 105 to 144 days which can be ascribed primarily to health care routines.[1–3] Treatment delay (ie time from diagnosis to treatment with cystectomy or radiotherapy) is also largely due to hospital routines, and median delays of 42 to 63 days have been reported.[4–8]

Muscle invasion in bladder cancer has been characterized "as a major signal of an impending lethal event."[9] Even in cases in which there is only early invasion, as in T1 disease, delayed treatment with radical cystectomy might reduce survival.[10,11] Three current publications suggest that a long interval between diagnosis of invasiveness and performance of cystectomy influences pathological tumor stage[6] and probably also disease specific survival.[5–7] Such reports are alarming because they suggest that slow hospital routines influence patient prognosis. If these results are confirmed, reallocation of resources and changes in hospital practices should be strongly considered. Therefore, we investigated the effects of treatment delay on cancer specific survival and on stage migration from the time of diagnosis of invasive bladder cancer to the performance of radical cystectomy in a well-defined series of hospital cases.

MATERIALS AND METHODS

In all 141 patients with locally advanced bladder cancer underwent radical cystectomy between 1990 and 1997 at the Department of Urology of Lund University Hospital. Lymphadenectomy was limited to the obturator fossa, and in 18 patients lymphadenectomy was omitted according to individual surgeon preferences (9 of these 18 patients were thought to have organ confined disease, ie clinical stage T2 or less). A total of 46 patients with locally advanced tumors received preoperative radiation of 20 Gy for 1 week immediately before surgery. The criteria for preoperative radiation were T3 (palpable after transurethral resection) or T4a tumors, however some nonpalpable tumors (11 stage T2 or less) were also selected based on tumor size and surgeon preference. Two patients with clinical stage T4b (TNM 2002) were given 4 courses of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin. Treatment delay was defined as the interval between the pathology report confirming invasive disease and performance of cystectomy, and was ascertained retrospectively from the charts. Thus, for those patients who received preoperative radiation the week before surgery, this time was included in treatment delay. The 2 patients who obtained neoadjuvant chemotherapy were excluded from study since this therapy increased treatment delay by 16 weeks at the same time as it reduced the tumor. Reasons for treatment delay were also retrieved from the charts. Followup ended in April 2003. Death from bladder cancer was the primary end point, causes of death were obtained from the Swedish Cause of Death Registry until December 2000, and after that further followup information was retrieved from clinical records until April 2003. Those records also substantiated data from the Cause of Death Registry.

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Comparisons of treatment delay in groups determined by referral status and by stage progression were done using Wilcoxon's rank sum test and a nonparametric rank based trend test, respectively. The relative hazard of death from bladder cancer was determined by Cox regression analysis. Survival was calculated from the date of diagnosis, but patient followup time was not included in the analysis until the date of cystectomy ("delayed entry")[12] since this event was a prerequisite study inclusion. The main purpose was to analyze the effect of treatment delay. This factor was dichotomized at 60 days, a point that is close to the median in this study and may represent a clinically relevant limit that should not be exceeded. The analysis was also adjusted for potentially confounding factors such as clinical stage, age, sex, preoperative radiation and cases referred from other hospitals. Cumulative incidence curves were used to illustrate the risk of dying of bladder cancer.[12] Time was then calculated from cystectomy and death due to other causes was considered a competing event. The statistical program STATA® version 8.2 was used in all analyses.

RESULTS

Median patient age at surgery was 66 years (range 26 to 82), 116 of the 139 subjects (83%) were men and half of the patients (71) were referred from other hospitals. After the pathology report confirming muscle invasive bladder cancer, 129 of 139 patients were sent for further diagnostic evaluation such as computerized tomography of the abdomen, chest x-ray, urography, renal clearance and split function test. Preoperative radiation was given to 46 patients selected due to locally advanced disease. Of the cystectomies 108 (78%) were performed for muscle invasive disease (clinical stage T2a or higher, tables 1 and 2).

Of the 122 patients 25 (20%) who underwent regional lymphadenectomy had lymph node positive disease. The types of urinary reconstructions performed were ileal conduit in 52 patients (37%), continent cutaneous diversion in 44 (32%) and orthotopic neobladder in 43 (31%). The pathological stage distribution in the patients is shown in table 3.

Median treatment delay was 49 days. It was significantly longer for the 71 patients who were referred from other hospitals (63 days vs 41 days for nonreferred patients, p <0.001). In patients who received preoperative radiation, median treatment delay was 48 days compared to 53 days for patients not given radiation (p=0.28).

Stage migration from clinical tumor stage to pathological tumor stage in cystectomy specimens and treatment delay according to clinical stage are presented in tables 2 and 4, respectively. Considering all patients there was no significant correlation between treatment delay and stage progression (table 5), and median treatment delay was approximately 50 days regardless of stage progression status. The patients with clinical stage T2 tumors are of special interest because such lesions are presumably still confined to the bladder wall. Median treatment delay was 76 days among patients showing stage progression compared to 41 days for those with stage regression. The delay was 48 days for those with stage equivalence (table 6) but this difference was not

statistically significant (p=0.20). No difference in treatment delay (p=0.49) was found between patients with and without lymph node metastases.

During followup 84 patients died, 56 of whom due to bladder cancer. Median treatment delay was 48 days (range 20 to 201) among those alive at the end of followup, 52 days (range 0 to 424) among those who died due to bladder cancer and 53 days (range 13 to 1,258) among patients who died of other causes. The incidence of death from bladder cancer was strongly related to pathological stage as shown in figure 1 (trend test p <0.001). Univariate analysis demonstrated that the likelihood of dying of that disease was not affected by other potential risk factors such as sex, age, noncontinent versus continent urinary tract reconstruction, preoperative radiation, or referral versus nonreferral (table 7). Nor was the risk of death from bladder cancer increased in 24 cases of a superficial tumor progressing to muscle invasive disease compared with 84 de novo muscle invasive cases (relative risk [RR] 0.88, 95% CI 0.43 to 1.79, p=0.72). Treatment delay did not influence the incidence of death from bladder cancer (fig. 2 and table 7). For instance, the cumulative incidence of death from bladder cancer was 0.39 (95% CI 0.29 to 0.49) at 5 years for those with a treatment of 60 days or less and 0.36 (95% CI 0.23 to 0.49) for those with a treatment delay greater than 60 days. Nor was the RR changed in multivariate analysis when adjusting for the potential risk factors known at diagnosis (RR 1.02, 95% CI 0.56 to 1.87, p=0.94). We did not adjust for pathological stage because that variable might also depend on treatment delay and, thus, mediate a potential negative impact on the analysis. Some investigators have chosen to group patients according to treatment delay shorter or longer than 3 months but this cutoff had no effect on the results of our analysis. The RR was 0.76 (95% CI 0.37 to 1.56) comparing patients with treatment delay greater than 90 days versus 90 days or less in a univariate analysis and 0.72 (95% CI 0.35 to 1.51) in a multivariate analysis adjusting for factors known at diagnosis.

DISCUSSION

The median treatment delay in our study was 49 days, which is comparable to data from the United Kingdom concerning patients with a median treatment delay of 9 weeks from transurethral resection of the bladder to definitive treatment with radiotherapy or radical cystectomy.[8] In our series of patients as in 2 other series[6,8] the results of the analyses indicated that a long treatment delay had no influence on disease specific survival. Wallace and Harris were the first to suggest that treatment delay may result in a worse prognosis,[13] and thus far that conclusion has only been confirmed by Sanchez-Ortiz[5] and May et al.[7] The latter investigators compared patients with short and long treatment delays, but those 2 groups comprised different proportions of extravesical disease (48% and 84%, respectively). Consequently some authors believe that there is not yet sufficient evidence to suggest that early treatment will translate into improved survival.[14] All studies that have concerned treatment delay and prognosis, including the present investigation, have been rather small and hence have only had the

TABLE 1. *Baseline characteristics of the study group*			
	No. Pts	Treatment Delay 60 Days or Less	Treatment Delay Longer Than 60 Days
Male/female	116/23	71/15	45/8
Age 65 or older/younger than 65	76/63	46/40	30/23
De novo muscle invasive disease/progression to muscle invasion	84/24	52/13	32/11
Noncontinent/continent urinary tract diversion	52/87	26/60	26/27
Preop radiation yes/no	46/93	31/55	15/38
Referred: yes/no	70/69	31/55	39/14