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Review – Bladder Cancer

Delay in the Surgical Treatment of Bladder Cancer and Survival: Systematic Review of the Literature

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Abstract

Objectives: Eighty per cent of the newly diagnosed invasive bladder tumours are invasive from the outset. Half of these patients already have occult distant metastases reflecting the rapid nature of progression. The aim of the current study was to review the literature to determine if delay in cystectomy leads to worse prognosis and to determine if a possible cutoff point for delay exists, after which a worse outcome would be expected.

Methods: We performed a systematic review of publications indexed in Medline and other scientific databases by analyzing types and causes of delay in performing radical cystectomy. Information on the impact of such delays on tumour recurrence and survival was collected and summarized. Papers that described only delay without any outcome correlation were excluded from the study.

Results: A total of 13 papers published from 1965 to 2006 were included in this study. Three (23%) papers did not find any correlation between pretreatment delays and survival. Two (15%) papers reported a trend towards worse survival with delay. Eight (62%) papers documented significant association between delay and worse prognosis. Delay influenced survival as an independent variable in two (25%) of these eight papers. In the remaining six (75%) manuscripts, delay was significantly associated with a higher pathologic stage.

Conclusions: Although studies on bladder cancer failed to show a linear relationship between delay and prognosis, the majority confirmed that delays are associated with worse outcome. Studies suggested a window of opportunity of less than 12 weeks from diagnosis of invasive disease to radical cystectomy.

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1. Introduction

Bladder cancer is the sixth most common noncutaneous cancer in Canada. It is the 8th most common cause of cancer death in males and the 13th in females [1]. While only 20% of muscle invasive bladder tumours present initially as superficial disease and progress with time into invasive tumours, the majority (about 80%) are already invasive tumours at initial presentation. Furthermore, about 50% of bladder tumour patients have occult distant metastases at the time of presentation [2]. These statistics demonstrate the aggressive nature of bladder cancer.

Radical cystectomy with urinary diversion remains the gold standard for the treatment of invasive bladder tumours. It has been suggested that delaying radical cystectomy in organ-confined disease is associated with poorer survival [3]. Even though it is well accepted that treatment should be instituted once a diagnosis of cancer has been made, several factors play a role in delaying such treatment. Some of these factors are linked to the health care system [4], while others are patient related [5,6]. The question of whether there is a window of opportunity for the treatment of invasive bladder cancer remains unanswered. We conducted a systematic review of the scientific literature to (1) determine if delay in cystectomy leads to a worse prognosis and (2) determine if a possible cutoff point for delay exists, after which a worse outcome would be expected.

2. Methods

We identified relevant studies and abstracts by searching PubMed and Ovid gateway for studies published before January 2006. We also searched the Web of Science and the Cochrane Collaboration Controlled Trials Register. We used the following search terms: ''bladder'', ''urological tumours'', ''survival'', ''death'' and/or ''delay''. In addition, we screened the bibliographies of identified publications for additional citations. Studies were included if they met the following criteria: (1) The article describes a delay in treatment of bladder cancer by radical cystectomy, and (2) the article includes information on the effect of delay on prognosis.

For publications studying the delay in relation to multiple management modalities, if shown, only data concerning radical cystectomy were included. We excluded published abstracts and papers published in languages other than English. Since the goal of this study was to assess association of delay with prognosis, all papers that described only delay without any outcome correlations were excluded. Relevant data were extracted into custom-made spreadsheets. Given the heterogeneity of the reported study populations and the differences in the way delay was described in each study, we could not perform a meta-analysis.

Studies were divided on the basis of delay type into the following groups:

1. Delay A = onset of complaints to first general practitioner (GP) referral (Patient and GP delays)
2. Delay B = first GP referral to first hospital appointment (Hospital and Urologist delays)
3. Delay C = first hospital appointment to transurethral resection of bladder tumor (TURBT)/first treatment (Diagnostic delay)
4. Delay D = TURBT to cystectomy/definitive treatment (Treatment delay)
5. Delay E = B + C (Hospital diagnostic delay)
6. Delay F = B + C + D (Hospital treatment delay)

The following reported end points were summarized:

1. Pathologic stage
2. Five-year progression-free survival
3. Five-year cancer-specific survival
4. Five-year overall survival

3. Results

Results of our search yielded 23 articles, 2 editorial comments [7,8], and 2 letters to the editors [9,10]. Ten papers were excluded from our study, because they did not examine prognosis in relation to delay. The remaining 13 articles [5,6,11–21] described investigations conducted between 1958 and 2002, and were published from 1965 to 2006. They featured a total of 7700 patients aged 22 to 92 years. There were no randomized controlled trials. Nine (69%) of these studies were European, three (23%) North American, and one (8%) Japanese. Baseline patient characteristics from the 13 included studies are shown in Tables 1 and 2. The different types of delay investigated with their corresponding minimum and maximum reported values are shown in Fig. 1 and Table 3. There was only one prospective study (Wallace et al. [20]); the remaining 12 papers were retrospective studies. Data used in these studies were obtained from billing databases, cancer registries, and death registries or collected from doctor offices and hospitals. Sample sizes ranged from 50 [14] to 3000 patients [21]. Reported mean follow-up ranged from 33.9 [6] to 50 months [14]. Delay was reported as a categorical variable by all studies. Only one manuscript [18] studied delay as a continuous variable, but there was no significant association with survival. The presence of associated comorbidity has been reported by only five studies [5,6,11,13,15] and has ranged from 15.8% [6] to 25% [13] of their studied cohorts.