Survival Outcomes of Early versus Deferred Cystectomy for High-Grade Non-Muscle-Invasive Bladder Cancer: A Systematic Review

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Abstract

Background: Studies report that survival outcomes in patients with non-muscle-invasive bladder cancer (NMIBC) are worse when cystectomy is delayed. However, no systematic evidence is available. Objective: The aim of this study was to systematically review the literature to compare the long-term survival outcomes of patients with high-grade NMIBC (T1G3, including carcinoma in situ) who have early cystectomy compared to deferred radical cystectomy post-diagnosis. Materials and Methods: A systematic review was carried out by searching MEDLINE and related databases (Google Scholar, National Health Service Evidence) for all relevant studies published from 1946 to present. Additional studies were identified through following the references of relevant papers. Studies were included if they met the following criteria: inclusion of at least 30 patients having high-grade NMIBC, 2 groups treated with either early or deferred cystectomy with a clear temporal cut-off between groups and reported data on survival rate of at least 5 years. Results: Literature was systematically reviewed, and 10 studies were included, totaling 1,516 patients who underwent either primary cystectomy or deferred cystectomy. It was found that patients who underwent early cystectomy show improved 5- to 10-year cancer-specific survival (relative risk = 0.81, p = 0.029) suggesting a significant survival benefit when compared to deferred cystectomy. Conclusions: This study provides systematically gathered evidence showing benefit of early cystectomy. Despite this result, radical cystectomy greatly impairs quality of life and represents overtreatment for a significant minority. This result highlights the importance of a decisive treatment plan to minimize treatment delay.

Introduction

Bladder cancer is the 9th most common cancer in the world, with 383,000 new cases diagnosed in 2008 [1]. In Western countries, cigarette smoking is the most highly associated risk factor, accounting for 50% of bladder cancer in males and 35% in females [2]. Worldwide age-standardized incidence is 4-fold greater in men than in women, i.e., 23.6 per 100,000 in males versus 5.4 in females [3]. Approximately 75–85% of patients will have disease limited to the mucosa [stage Ta, carcinoma in situ (CIS)] or submucosa (stage T1) [4], which is diag-
nosed based on transurethral resection (TUR) samples. Ta, T1 bladder cancers are classified as non-muscle invasive bladder cancers (NMIBC), also previously known as ‘superficial’ bladder cancer. In TaT1 bladder tumors, TUR aims to both diagnose the tumor and remove all visible lesions, though increasingly patients are opting to undergo cystectomy as early as 4 weeks post-diagnosis.

Some experts propose primary cystectomy to patients with NMIBC who are at high risk of progression, i.e., high-grade Ta, T1 tumors with or without concurrent CIS, or multiple, recurrent high-grade tumors [4]. Progression is defined by Cheng et al. [5] in 1999 as “the development of muscle-invasive or more advanced stage carcinoma, distant metastasis, or death from bladder cancer”.

For muscle-invasive bladder tumors, radical cystectomy (RC) is the standard treatment [6], and there is evidence to show that even a delay of 12 weeks in such cases can be sufficient to cause an adverse outcome [7]. Similarly, delay of cystectomy in patients with NMIBC may reduce their disease-specific survival, though currently, this is a controversial issue.

There are several advantages of primary cystectomy of T1G3 tumors. Firstly, it allows the urologist to pathologically stage the tumor and determine lymph node involvement, which are the best-known indicators of cancer outcome [8]. This enables the treatment strategy to be based on pathological staging rather than clinical staging, which is prone to understaging. In addition, cystectomy at this early stage allows for nerve-sparing treatment with ileal neobladder reconstruction, conferring high probability of restoration of sexual and urinary function. Lastly, the risk of late recurrence is greatly reduced through RC, which permits a less extensive follow-up procedure.

The prospect of a major procedure such as cystectomy carries with its significant perioperative morbidity and mortality, leading many patients to opt to preserve bladder function and maintain their quality of life (QoL). When one considers that approximately 30% of patients with T1G3 treated with TUR of bladder alone remain disease-free [9], care must be taken with decision making to avoid over-treating in this subset of patients. Currently, there is a distinct lack of accurate biomarkers for stratification of patients by the potential benefit from RC, which could facilitate decisive action. Because of these considerations, many reserve primary cystectomy only for recurrent and progressive bladder cancer [10, 11], though this paradigm is being challenged by evidence to suggest a long-term survival benefit of early RC for NMIBC. This is the first study to systematically examine the effect of early versus delayed cystectomy on cancer specific-survival (CSS) in high-grade NMIBC.

The primary objective of this study was to compare the CSS rate of patients with high-grade T1G3 NMIBC who underwent early (also primary; immediate) cystectomy versus patients who deferred cystectomy (> 3 months from diagnosis). Secondary outcomes, such as pathological upstaging, tumor progression and lymph node metastases were also assessed where data was available. These outcomes were assessed in non-randomized trials and observational studies. A review protocol was not used.

### Materials and Methods

#### Eligibility Criteria

Observational studies and trials studying the survival benefit of early cystectomy compared to delayed cystectomy were searched for. Studies were included if they included at least 30 patients with high-grade NMIBC according to the European Association of Urology guidelines. Studies were only included if they had CSS data for at least 5 years from diagnosis, and availability of the full text in English. Participants of any age with high-grade NMIBC were considered. NMIBC was defined as clinical stage Tis/Ta/T1.

Patients grouping into immediate or deferred cystectomy groups was based on time from diagnosis. Studies were included if they stated either their cut-off time or stated the median time to cystectomy in each group. Each study’s definition of ‘early’
Table 1. An assessment of the risk of bias for each study using a standard approach with defined criteria modified from Viswanathan et al. (2012) [29]

| Study                                | Do the inclusion/exclusion criteria vary across the comparison groups of the study? | Does the strategy for recruiting participants into the study differ across groups? | Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations? | Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding? | Are any important primary outcomes missing from the results? | Are any important harms or adverse events that may be a consequence of the intervention/exposure missing from the results? | Are results believable taking study limitations into consideration? | Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores)? | Were important confounding variables not taken into account in the design and/or analysis (e.g., through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)? |
|--------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Ali-El-Dein et al., 2011 [14]        | no                                                                                | no – consecutive series                                                          | no                                                                               | yes – upstaging and CIS provided; however, several pre-cystectomy factors were missed                         | no – includes overall survival                                                                                     | no – multiple outcomes reported                     | yes – stratification too broad                        | no – multivariate analysis carried out                                                         | no – stratification too broad                                                                 |
| Kamat et al., 2006 [15]              | no                                                                                | no – consecutive series                                                          | no                                                                               | yes – comprehensive use of statistics                                                                         | no – includes overall survival                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Thalman et al., 2004 [16]            | no                                                                                | no – all patients between 1980 and 1999 with T1G3 BCa included                  | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Gupta et al., 2007 [23]              | no                                                                                | no – consecutive series                                                          | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Dalbagni et al., 2009 [18]           | no                                                                                | no – all patients restaged with a diagnosis between 1990 and 2007               | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Denzinger et al., 2007 [13]          | no                                                                                | no – consecutive series                                                          | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Dimney et al., 1998 [27]             | no                                                                                | no – consecutive series                                                          | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Hautmann et al., 2009 [22]           | no                                                                                | no                                                                               | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Jäger et al., 2011 [17]              | no                                                                                | no                                                                               | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
| Herr et al., 2001 [10]               | no                                                                                | no                                                                               | no                                                                               | yes – also use intention to treat                                                                                | no – multiple outcomes reported                                                                                     | yes – RC not indicated or refused                      | yes – bacille Calmette-Guérin was showed not to be a confounder                              | no – multivariate analysis carried out                                                         | multivariate analysis carried out                                                                 |
Early vs. Deferred Cystectomy for High-Grade NMIBC

### Information Sources and Study Selection

Studies were identified by searching Ovid MEDLINE for the period 1946 to November 2013 (n = 85), the Cochrane library (n = 1) [12], Google Scholar (n = 45, some overlapping with previous articles), NHS Evidence (n = 1) [4]. An example search strategy was shown in figure 1, which indicates the keywords used.

In addition, reference lists of relevant articles were searched to identify other relevant studies (n = 8). For articles that did not have a complete electronic version of the full text available, the article was requested from the British Library Document Supply Service; 2 articles were obtained through this means.

### Data Collection and Quality Assessments

Study selection was carried out in a standardized, unblinded manner by one reviewer. Abstracts and titles were read, and if considered relevant then full papers were obtained and reviewed. After the initial screen, 23 articles were selected and their methodology reviewed. Retrospective studies were checked for using the same patient data, and the data were unique in each case.

For selected studies, the relevant outcome data were collected using a data-extraction spreadsheet in Microsoft Excel 2010. All data collected were verified for comparability and compared with the data in the publication. For each study, the time period, methodological design, duration of follow-up, number of patients, proportion of Ta/T1, proportion of concomitant CIS, CSS rate, lymph node involvement at pathological staging, pathological upstaging proportion, progression rate and associated p value were extracted. An assessment of the risk of bias for each study is given in table 1.

### Statistics

The principal summary measure was the relative risk of CSS between early and deferred cystectomy cohorts. P values, sample sizes and effect directions were entered into MetaP Java applet [30] and Stouffer’s Z-trend [31] was calculated for the 9 p values available. The study by Hautmann et al. [22] was not used for the calculation of Z-trend as no p value was given. Stouffer’s Z-score gives weight to each study according to their power. A paired t-test was used to compare the mean difference between 2 samples in table 2.

### Results

Through the literature search, 140 relevant papers were identified through the searching online databases and reference lists. From this set of papers, 123 were discarded for being not relevant from reading the abstract, e.g., not a study on RC; not a comparison between early and delayed cystectomy. The full-text papers of the remaining 17 studies’ methodology were analyzed and 7 discarded. Papers were excluded because of being: not high-grade NMIBC, or not mainly treated with primary or deferred cystectomy. After filtering, 10 studies were identified for inclusion in this review. Figure 2 shows the flow of information through this systematic review.

Table 3 shows the included trials, which totaled 1,516 patients, with data for 5-, 7- and 10-year survival; studies are grouped by the duration of their CSS data. All articles were published between 1998 and November 2013, and the data was collected between 1908 and 2005. The median percentage of patients with concurrent CIS was 28.4% and the median patient follow-up of each study ranged 32–180 months. Only 1 study was prospective [10], and none were randomized. The number of patients per study ranged 30–278. Four of the studies show that their cohorts are well-matched [13–16], and 2 stratify their results by risk factors [17, 18].

For the retrospective studies, the median 5-year survival of the shorter length studies was 69% in the early cystectomy group, compared to 60% who had deferred cystectomy. Thalman et al. [16] found a significant survival disadvantage of early RC (63 early RC vs. 75% deferred RC; p = 0.02). One study provided only a 7-year CSS, showing 75.3% survival in the early group versus.
45% in the deferred group (p = 0.21), with a median follow-up time of 33.8 months.

The studies that provide a 10-year CSS (n = 2) have a median CSS of 79% (range 78–85%) in the early cystectomy group, compared to 65% (range 51–85%) in the delayed cystectomy group. Overall, 2 studies showed a significant survival benefit of early cystectomy. The only prospective study by Herr et al. [10] showed a significant survival benefit of early cystectomy (92 vs. 55% CSS; p = 0.03).

Table 4 shows a significant increase in patients with lymph node positive cancer at the time of pathological staging in the delayed cystectomy group. There was a trend towards increased cancer progression in patients who defer treatment (p = 0.09); and there was a non-significant difference in the proportion of patients pathologically upstaged at the time of cystectomy (p = 0.39). Overall, deferred cystectomy compared to early cystectomy is associated with a hazard ratio (HR) for CSS of
1.24 (p = 0.029), indicating a poorer survival outcome with surgical treatment delay (table 2).

### Discussion

In this study, it was found that patients who underwent early cystectomy showed improved 5- to 10-year CSS (relative risk = 0.81, p = 0.029) suggesting a significant survival benefit of early cystectomy compared to deferred RC. This finding should be considered when informing patients about treatment options for high risk T1G3 bladder cancer. However, the data available are not compelling enough to warrant immediate RC for every patient with T1G3 bladder cancer without a wholehearted attempt at conservative treatment. Far from advocating RC in every case, this study highlights the necessity of a decisive treatment plan to minimize time to cystectomy should conservative treatment fail.

The proportion of cases with concurrent CIS varied between studies which must be taken into account when interpreting the results, as concomitant CIS has been reported to confer significantly worse outcome [13, 19]; for example, Denzinger et al. [13] report a 2.55 HR for CIS (p = 0.02). This effect is especially marked in deferred cystectomy cohorts, which could make delayed cystectomy appear as a worse option.

Unfortunately, there is no level I evidence to definitively guide the urologist in the decision-making process for T1G3 bladder cancer. Only observational and non-randomized studies were found for inclusion. The lack of randomization in any study introduces selection bias as patients that undergo deferred cystectomy are selected alternatively, some studies instead stratify data according to other risk factors [17, 18].

Studies varied in their definition of ‘early’ or ‘delayed/deferred’ cystectomy. The cut-off time varied between 90 days and 2 years. None of the studies selected explicitly state their reasoning behind the determination of their time-based cut-off, though Sanchez-Ortiz et al. state that they use a threshold of 12 weeks so that patients

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**Table 3.** All the studies included in this systematic review (the time-based cut-off points for defining early versus delayed cystectomy, the median follow-up, cancer stage/grade, and CIS percentage)

| Source                        | Date       | Patients, | Early, | Deferred, | Time of RC post-diagnosis (early vs. delayed) | Median follow-up, months | Proportion of initial stage/grade | CIS, % |
|-------------------------------|------------|-----------|--------|-----------|--------------------------------------------|--------------------------|----------------------------------|--------|
| Ali-El-Dein et al., 2011 [14] | 1990–2004  | 204       | 134    | 70        | < 2 vs. > 2 years                           | 77.66 (early vs. deferred groups, respectively) | T1G1 (9.3%), T1G2 (77%), T1G3 (13.7%) | 28.4   |
| Kamat et al., 2006 [15]       | 1989–2004  | 30        | 12     | 18        | deferred RC = after disease progression to cT2 or higher | 32.1 | Ta (11%), T1 (80%), micropapillary (100%) | 13.4   |
| Thalman et al., 2004 [16]     | 1980–1999  | 56        | 29     | 27        | < 3 vs. > 3 months                          | 82.8 (range: 2.4–198)    | T1G3 (100%)                       | 21.0   |
| Gupta et al., 2007 [23]       | 1984–2003  | 167       | 89     | 34        | < 3 vs. > 3 months                          | 33.8 (0.4–177.1)         | T1G3 (100%)                       | 45.6   |
| Dalbagni et al., 2009 [18]    | 1990–2007  | 333       | 274    | 59        | < 3 vs. > 3 months                          | 51.6 | T1 (100%), high grade (97%)              | 23.0   |
| Denzinger et al., 2007 [13]   | 1995–2005  | 105       | 54     | 51        | median: 4 weeks vs. 11.2 months             | 120 | pT1G3 (100%)                          | 46.0   |
| Dinney et al., 1998 [27]      | 1992–1994  | 34        | 20     | 14        | median: 22 vs. 421 days                     | 48 (range: 12–239)       | T1G2/3 (100%)                     | –      |
| Hautmann et al., 2009 [22]    | 1908–1986  | 274       | 124    | 99        | < 90 vs. > 90 days                         | 180 | T1G3 (100%)                           | –      |
| Jäger et al., 2011 [17]       | 1989–2006  | 278       | 141    | 77        | < 1 vs. > 1 year                           | 79 (0–242)               | pTaG3 (7%), pT1G3 (72%)           | 21.0   |
| Herr et al., 2001 [10]        | 1979–1984  | 35        | 26     | 9         | < 2 vs. > 2 years                           | 180 | TaG3 (100%)                          | 81.0   |
may be grouped by similar HRs. This is based on Fahmy et al. [20] reporting that the safe period of delay for any kind of treatment for invasive bladder cancer is 3 months. For NMIBC, this period is likely to be longer due to the lower rate of progression and recurrence [21], assuming cases are staged correctly.

Many of the studies included in this analysis acknowledge their rate of understaging as between 20.4 [22] and 50% [23], introducing a degree of heterogeneity into the cohorts. It is known that upstaging is associated with statistically worse disease specific and recurrence-free survival due to the drastic reduction in survival conferred by progression to muscle-invasive cancer [24]. The proportion of pathologically upstaged patients was greater in the delayed cystectomy group, though the difference was non-significant. The inaccuracy of current staging of T1G3 bladder cancers delays decisive therapy.

**Table 4.** The results on cancer progression, proportion of pathologically upstaged patients, percentage of patients with lymph node positive disease at pathological staging

|                | Cancer progression, % |       |          |       |          |       |          |       |
|----------------|-----------------------|-------|----------|-------|----------|-------|----------|-------|
|                |                       | Early  | Deferred |      |          | Early  | Deferred |      |
| Thalman et al., 2004 [16] | 21                  | 33     |          |      |          |        |          |      |
| Denzinger et al., 2007 [13] | 8                   | 24     |          |      |          |        |          |      |
| Dinney et al., 1998 [27] | 15                  | 57     |          |      |          |        |          |      |
| Mean           | 14.7                 | 38.0   |          |      |          |        |          |      |

**B**

|                | Upstaged patients, % |       |          |       |          |       |          |       |
|----------------|----------------------|-------|----------|-------|----------|-------|----------|-------|
|                |                       | Early  | Deferred |      |          | Early  | Deferred |      |
| Gupta et al., 2007 [23] | 52              | 71     |          |      |          |        |          |      |
| Denzinger et al., 2007 [13] | 14            | 18     |          |      |          |        |          |      |
| Hautmann et al., 2009 [22] | 29         | 64     |          |      |          |        |          |      |
| Mean           | 31.7                 | 51.0   |          |      |          |        |          |      |

**C**

|                | Upstaged patients, % |       |          |       |          |       |          |       |
|----------------|----------------------|-------|----------|-------|----------|-------|----------|-------|
|                |                       | Early  | Deferred |      |          | Early  | Deferred |      |
| Ali-El-Dein et al., 2011 [14] | 1.5          | 5.7    |          |      |          |        |          |      |
| Kamat et al., 2006 [15] | 25              | 39     |          |      |          |        |          |      |
| Thalman et al., 2004 [16] | 19              | 14     |          |      |          |        |          |      |
| Gupta et al., 2007 [23] | 2               | 8.70   |          |      |          |        |          |      |
| Dinney et al., 1998 [27] | 15             | 20     |          |      |          |        |          |      |
| Hautmann et al., 2009 [22] | 9.1           | 20.2   |          |      |          |        |          |      |
| Jäger et al., 2011 [17] | 9               | 18     |          |      |          |        |          |      |
| Mean           | 11.5                | 17.9   | 0.03      |      |          |        |          |      |

**Conclusion**

This study provides systematically gathered evidence showing a significant survival benefit of early RC for T1G3 bladder cancer. This finding is in line with the work of Varca et al. [25], who suggests that delaying RC gives time to allow lymph nodal dissemination and progress in stage and grade, resulting in a worse outcome as the risk of non-organ confined disease is increased [15, 26]. Moreover, performing the cystectomy as early as possible is thought to save the lives of 15–20% of T1G3 patients [22], and Denzinger et al. [13] quantify the HR of delaying treatment as 5.13 (p < 0.01).

Despite this result, RC greatly affects QoL and could be overtreatment for some. Also, even with early RC a significant proportion (up to 50%) appear not to be cured of their disease. This could be due to micrometastases present at initial diagnosis as a result of invasion through the lamina propria. Stein et al. [11] found that of patients with T1G3 bladder cancer undergoing RC, about 20% die of disease regardless, indicating that not even immediate RC is enough to prevent cancer-related death in this proportion.

The majority of studies analyzed found that the improved CSS was non-significant and suggest that RC should be reserved for patients with progression or disease refractory to local therapies. This approach is the current standard for treatment and allows a greater number of patients to maintain bladder functionality, independence, and QoL. Thalmann et al. [16] suggest that an organ-preserving approach is acceptable because it spares the bladder in approximately half of the patients with T1G3 cancer. Conservative treatment first would avoid the risk of overtreatment, though one must be mindful of the outlined results to show that even a delay of 3 months post-diagnosis can confer a worse survival outcome.

Although the above data are generally supportive of early cystectomy, they are not robust enough to warrant immediate RC without at least a vigorous attempt at conservative therapy. The results presented here highlight the importance of a decisive treatment plan to minimize treatment delay should conservative treatment fail.
Early vs. Deferred Cystectomy for High-Grade NMIBC

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