

# A RETROSPECTIVE ANALYSIS OF 153 PATIENTS TREATED WITH OR WITHOUT INTRAVESICAL BACILLUS CALMETTE-GUERIN FOR PRIMARY STAGE T1 GRADE 3 BLADDER CANCER: RECURRENCE, PROGRESSION AND SURVIVAL

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## ABSTRACT

**Purpose:** We retrospectively evaluated the long-term outcome in patients with newly diagnosed stage T1 grade 3 bladder cancer treated with transurethral resection with or without intravesical bacillus Calmette-Guerin (BCG).

**Materials and Methods:** Of 153 patients with a median age of 67 years (range 36 to 88) and a male-to-female ratio of 4:1 we treated 92 with transurethral bladder resection and additional BCG, and 61 with transurethral bladder resection alone. BCG was administered intravesically as 120 mg. BCG Pasteur F dissolved in 50 ml. saline, retained for up to 2 hours weekly for 6 weeks and repeated as necessary.

**Results:** Median followup was 5.3 years (range 0.4 to 18.2). Disease recurred in 70% of the patients treated with BCG and in 75% treated with transurethral resection alone. Median time to recurrence was 38 and 22 months for BCG and resection alone ( $p = 0.19$ ). Tumor progressed in 33% of patients with BCG and in 36% with resection alone. Deferred cystectomy was performed in 29% of the patients with BCG and in 31% with resection alone. Overall and disease specific survival did not differ significantly.

**Conclusions:** Our results suggest that intravesical BCG therapy after transurethral bladder resection for stage T1 grade 3 bladder cancer may delay the time to recurrence and cystectomy but it does not substantially alter the final outcome. Our findings reflect the rule of 30% for stage T1 grade 3 cancer, namely approximately 30% of patients never have recurrence, 30% ultimately die of metastatic disease and 30% require deferred cystectomy.

**KEY WORDS:** bladder; *Mycobacterium bovis*; carcinoma, transitional cell; bladder neoplasms

The ideal treatment for primary stage T1 grade 3 bladder cancer remains controversial. The main therapeutic options after initial transurethral resection are observation, repeat resection, intravesical therapy with immunomodulatory or chemotherapeutic agents (or a combination of these options)<sup>1</sup> and cystectomy.<sup>2</sup> Concomitant carcinoma in situ and/or multifocality are known negative prognostic factors for recurrence and progression.<sup>3</sup> Reports of clinical under staging in up to 40% of patients with stage T1 bladder tumors after primary resection also led to a cautious therapeutic approach to primary stage T1 bladder tumors.<sup>4</sup>

After transurethral bladder resection alone the recurrence rate for stage T1 grade 3 bladder tumors is 69% to 80%<sup>3,5-7</sup> and the progression rate is 33%<sup>3</sup> to 48%.<sup>5</sup> Brake et al evaluated 44 patients with stage T1 grade 3 bladder cancer who received adjuvant intravesical immunotherapy after complete transurethral resection. There was superficial recurrence in 11% of cases and muscle invasive progression in 16% after a median followup of 28 months.<sup>8</sup> Cookson and Sarosdy reported a progression rate of 19% after a median followup of 59 months in 86 cases managed with adjuvant bacillus Calmette-Guerin (BCG).<sup>9</sup> Pansadoro et al evaluated 81 patients with stage T1 grade 3 tumors after a median followup of 76 months and noted a recurrence rate of 33% and a progression rate of 15%, which they attributed to the beneficial effect of BCG.<sup>10</sup>

Analysis of the effect of BCG on stage T1 grade 3 tumors is limited in existing trials since in most only time to first

recurrence was evaluated and they included a mixture of stages Ta and T1 disease. Stage Ta tumors are known to have a low progression rate and a low impact on survival, making assessment of stage T1 grade 3 subgroups difficult. Furthermore, patients with recurrent stage T1 grade 3 disease, secondary stage T1 grade 3 disease after previous resection of stage Ta tumors or another intravesical therapy before BCG are often included in analysis.

In this retrospective study long-term results in 92 patients with primary stage T1 grade 3 tumors who were treated with adjuvant intravesical BCG therapy after transurethral resection were compared with results in a predominantly historical control group of 61 treated with transurethral resection alone for primary stage T1 grade 3 disease. All cases were treated at a single institution. We determined whether only time to recurrence is favorably influenced by BCG or whether BCG also exerts a long-lasting effect in patients treated with BCG with an organ conserving approach.

## MATERIALS AND METHODS

**Patients.** Between January 1976 and January 1996, 186 consecutive patients were treated for primary stage T1 grade 3 bladder cancer with transurethral bladder resection at our institution. Accrual in the 2 treatment arms was evenly distributed in the 20-year observation period. All patients were treated with a basically consistent resection technique aimed at deep and complete resection across the presumed healthy outer bladder wall. All histological examinations were performed at the institute of pathology at our hospital.

Excluded from study were 15 patients with secondary stage T1 grade 3 disease who had a history of stage Ta bladder tumors. A total of 13 patients with multifocal disease and concomitant Tis who underwent primary cystectomy within 3 months after transurethral resection were also excluded from analysis. An additional 5 patients were excluded from study, including 2 with progressive disease within 3 months who were considered to have received inadequate treatment and 3 who were lost to followup after primary resection. Results in the remaining 153 patients are presented, including those in 20 with multifocal disease combined with carcinoma in situ who did not undergo primary cystectomy because of medical contraindications for surgery or because they elected a conservative approach. No patient in the transurethral resection alone group received BCG at a later stage. Of the 153 patients 83 (54%) underwent repeat transurethral resection of the tumor site within 3 months with no difference between the 2 treatment groups. Disease persisted after initial resection in 31 of these cases (37%), with stage Ta and T1 disease in 13 and 18, respectively. Of the 153 patients 39 (26%) underwent repeat resection between 3 and 12 months, and 25 (16%) underwent repeat transurethral resection 12 months or later after primary transurethral resection. There was no additional transurethral resection in 6 cases (4%). At initial presentation 27 patients (18%) had concomitant Tis and 71 (46%) had multifocal disease. Patients treated with BCG had a significantly higher incidence of concomitant Tis than those without BCG (23% versus 10%,  $p = 0.04$ ). There was no difference for multifocal disease (49% versus 43%,  $p = 0.45$ , table 1).

**Treatment and followup.** In 92 patients BCG was administered a median of 2 months after initial transurethral resection because more than 50% underwent repeat transurethral bladder resection. Of the 92 patients 22 (24%) received 2 or more BCG treatment cycles. Followup consisted of cystoscopy with urine barbotage cytology every 3 months for 2 years and every 6 months thereafter. Excretory urography was performed every 12 months for 3 years and then at 2 to 3-year intervals. Progression was defined as muscular invasion (stage T2 or higher) or metastatic disease (M+). Patients with recurrent stage T1 grade 3 and those with progressive disease underwent radical cystectomy.

**Statistical analysis.** Differences in treatment types (transurethral bladder resection with BCG versus transurethral bladder resection alone), recurrence-free, progression-free, disease specific and overall survival as well as time to cystectomy and survival after cystectomy were calculated using the Kaplan-Meier survival function and evaluated by the log rank test.<sup>11</sup> Differences in patient characteristics, progression, recurrence and cystectomy rate in the 2 groups were calculated by Pearson's chi-square test.

## RESULTS

Median followup was 5.3 years (range 0.4 to 18.2) with no difference between the treatment groups. Recurrence was observed in 64 of the 92 patients (70%) treated with BCG and in 46 of the 61 (75%) treated with transurethral bladder resection alone. Median recurrence-free survival was 38 months (range 1 to 120) for BCG compared with 22 months (range 1 to 87) for resection alone. The 10-year recurrence-free survival rate was 22% in patients with and without BCG treatment ( $p = 0.19$ , fig. 1).

Tumor progressed in 30 of 92 patients (33%) with BCG therapy and in 22 of 61 (36%) with transurethral resection alone. Median time to progression was 38 months after BCG and 28 months without BCG ( $p = 0.7$ ). Median progression-free survival was not achieved (fig. 2).

Overall survival was 42% with BCG and 48% without BCG at 10 years of followup (fig. 3). Disease specific survival was 77% and 79%, respectively (fig. 4). These parameters showed no statistical difference.

Deferred cystectomy was performed in 29% of the patients treated with BCG and in 31% treated with transurethral resection alone ( $p = 0.73$ ). Median time to cystectomy was 42 (range 5 to 148) and 22 months (range 3 to 180), respectively ( $p = 0.53$ , fig. 5). Overall survival after cystectomy was 56% and 63% in patients with and without BCG, respectively ( $p = 0.15$ ). There was no advantage in terms of disease specific survival after cystectomy at 63% and 79%, respectively ( $p = 0.2$ , table 1).

## DISCUSSION

The results of this retrospective nonrandomized analysis show that approximately 30% of patients with primary stage T1 grade 3 bladder cancer treated with transurethral bladder resection alone remain disease-free, approximately 30% ultimately die of metastatic disease and about 30% require deferred cystectomy. This 30% rule has also been noted by other groups managing stage T1 bladder tumors by transurethral bladder resection alone (table 2). Our results in patients receiving additional intravesical BCG treatment after transurethral bladder resection are also comparable to previously published data, especially those in trials with a long followup of more than 5 years (table 2). Institutional differences may have various causes, such as differences in tumor staging by different pathologists, as described by Coblenz et al,<sup>12</sup> completeness and technique of transurethral resection and repeat resection, various indications for cystectomy and followup (table 2). In our series patients with recurrence before 3 months and those who underwent immediate cystectomy were excluded from analysis.

Based on published results in prospective randomized

TABLE 1. Patient characteristics and results

	BCG	No BCG	p Value
No. pts.	92	61	
No. men/women	71/21	48/13	
Median age (range)	69 (37–88)	65 (36–88)	
No. concomitant Tis (%)	21 (23)	6 (10)	0.04
No. multifocal disease (%)	45 (49)	26 (43)	0.45
Median yrs. followup (range)	5.3 (0.4–18.2)	5.4 (0.5–8.2)	
No. recurrence (%)	64 (70)	46 (75)	0.26
No. progression (%)	30 (33)	22 (36)	0.66
Median mos. recurrence-free survival (range)	38 (1–120)	22 (1–87)	0.19
Median mos. to progression	36	28	0.70
No. overall deaths (%)	39 (42)	39 (48)	0.93
No. disease specific deaths (%)	21 (23)	13 (21)	0.72
No. deferred cystectomy (%)	27 (29)	19 (31)	0.73
No. overall deaths after cystectomy (%)	12 (44)	7 (37)	0.15
No. disease specific deaths after cystectomy (%)	10 (37)	4 (21)	0.20
No. median mos. to cystectomy (range)	42 (5–148)	22 (3–180)	0.53

Median progression-free survival was not achieved.

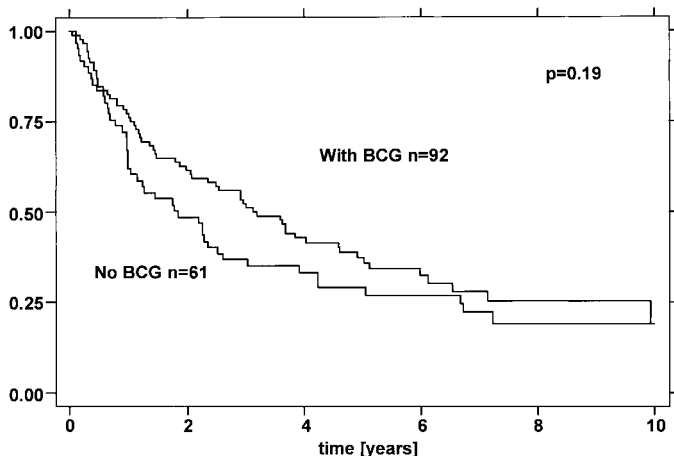


FIG. 1. Recurrence-free survival of primary stage T1 grade 3 bladder cancer in 61 patients with transurethral bladder resection alone versus 92 with transurethral bladder resection and adjuvant BCG therapy. Although median time to recurrence appeared to be 1 year longer in BCG group, with prolonged observation overall recurrence rate was approximately 75% in each group.

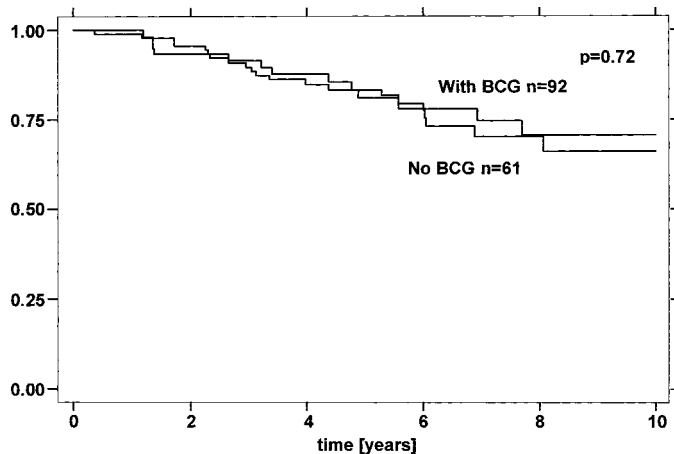


FIG. 3. Disease specific survival of primary stage T1 grade 3 bladder cancer in 61 patients with transurethral bladder resection alone versus 92 with transurethral bladder resection and adjuvant BCG therapy. Approximately 30% of patients die of progressive disease with or without of BCG therapy.

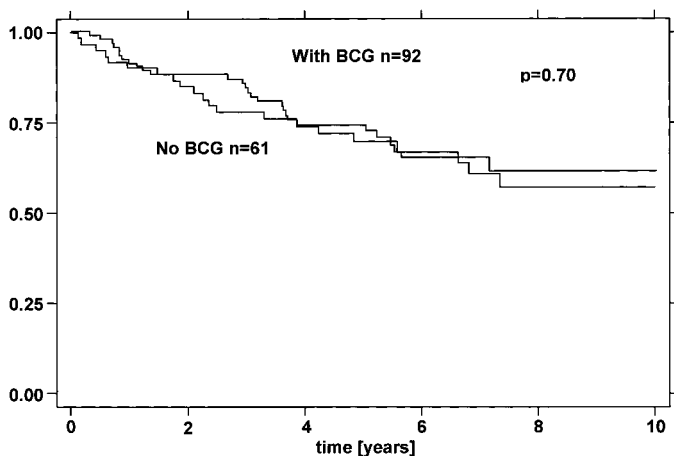


FIG. 2. Progression-free survival of primary stage T1 grade 3 bladder cancer in 61 patients with transurethral bladder resection alone versus 92 with transurethral bladder resection and adjuvant BCG therapy. No difference in 30% to 35% progression rate was observed at 10 years.

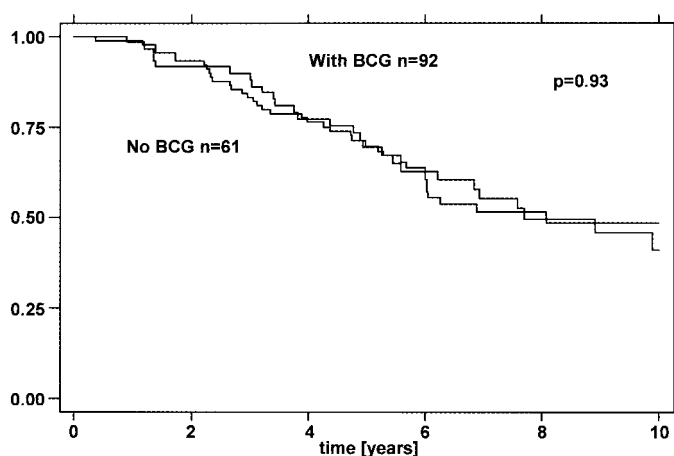


FIG. 4. Overall survival of primary stage T1 grade 3 bladder cancer in 61 patients with transurethral bladder resection alone versus 92 with transurethral bladder resection and adjuvant BCG therapy. No difference was observed and at 10 years approximately 50% of patients in each group had died.

studies it is evident that BCG significantly delays time to recurrence and progression compared with transurethral surgery alone.<sup>9,10,13</sup> Our findings are consistent with these reports, and baseline patient and tumor characteristics are comparable. The difference in our 2 groups in median time to recurrence was more than 12 months with a median of 38 months in the group treated with BCG. These values are comparable to those of Lamm et al in a Southwest Oncology Group trial comparing maintenance BCG versus no maintenance therapy.<sup>14</sup> In that series median recurrence-free survival was 35.7 months in the arm without maintenance. Hurle et al reported 18% progression and 14% mortality rates in 51 patients, of whom 44 received maintenance BCG therapy.<sup>15</sup> These results seem somewhat better but not all patients had primary stage T1 grade 3 tumors and there were fewer with concomitant Tis than in our series. In addition, 7 patients (14%) had extravesical disease, of whom 4 died of metastatic disease. By adding these 4 patients to those with progressive disease (18%) this progression rate was also around 30%.

The question remains whether BCG merely delays disease recurrence or whether recurrence is prevented. In our series, although not randomized, ultimately the same percent of pa-

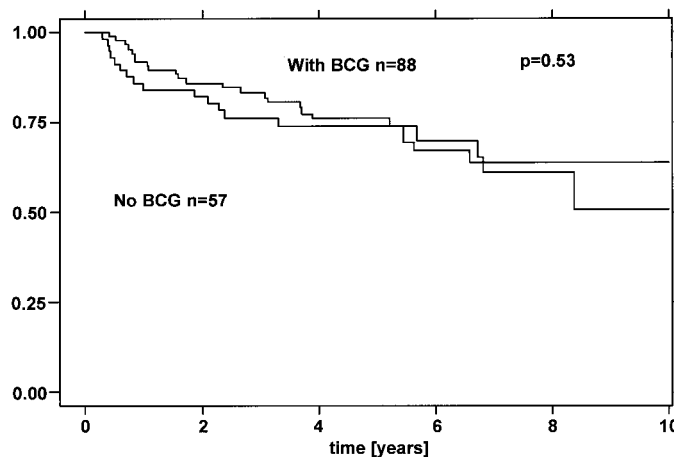


FIG. 5. Time to cystectomy for primary stage T1 grade 3 bladder cancer in 61 patients with transurethral bladder resection alone versus 92 with transurethral bladder resection and adjuvant BCG therapy. Latter treatment initially seems to prolong time to cystectomy but with prolonged observation approximately 30% of patients require cystectomy in each group.

TABLE 2. Recurrence and progression in patients with stage T1 bladder tumors after transurethral resection alone and transurethral resection with BCG bladder treatment

References	No. Stage T1 Disease	% Recurrence	% Progression	Mos. Followup
Resection only:				
Jakse et al <sup>3</sup>	31	80	33	60
Heney et al <sup>5</sup>	33	79	48	36
Mulders et al <sup>6</sup>	48	75	36	48
Lutzeyer et al <sup>7</sup>	28	69	34	36
Present series	61	75	36	64
Resection, BCG:				
Pansadoro et al <sup>10</sup>	81	33, 0	0, 15	76, 16
Cookson and Sarosdy <sup>9</sup>	86	44	19	59
Hurle et al <sup>15</sup>	51	45	18	85
Present series	92	70	33	64

tients with primary stage T1 grade 3 tumors had recurrence with or without BCG (fig. 1). Due to our small study numbers we lacked the statistical power to exclude slight differences in patients with sufficient followup for survival analysis. Furthermore, our findings suggest that the protection provided by BCG wanes with time and patients with primary stage T1 grade 3 bladder cancer remain at risk for recurrent disease regardless of the therapeutic approach. These findings are consistent with those of Cookson et al.<sup>16</sup> At an observation time of 15 years they observed that these patients remained at lifelong risk for tumor progression and death, and the risk increased with the duration of observation. This finding raises the issue of whether maintenance therapy may decrease this lifelong risk, as suggested by Lamm et al.<sup>14</sup> However, additional toxicity was associated with additional therapy and only 16% of the 243 patients on maintenance underwent all 8 scheduled maintenance courses.<sup>14</sup> It also remains to be determined whether repetitive BCG instillations, as in 24% of our patients, starting at the time of recurrence would be inferior to prophylactic maintenance treatment. Furthermore, a substantial number of patients are at risk for over treatment with maintenance therapy and would be subjected to significant side effects since a third never have recurrence even without BCG and those with superficial recurrence can be treated adequately with transurethral resection. An initial answer was provided by Palou et al, who randomly assigned 131 patients with high risk superficial bladder cancer 6 months after primary treatment to a control or a maintenance therapy group.<sup>17</sup> They detected no advantage in the maintenance arm compared with the group that received repeat intravesical therapy at the time of recurrence.

Early cystectomy for stage T1 grade 3 bladder cancer has been discussed and remains controversial. While it is generally accepted that patients with multifocal disease combined with carcinoma in situ require early cystectomy, at many centers such as ours an organ sparing approach is preferred for solitary stage T1 grade 3 tumors when repeat transurethral resection is negative. Siref and Zincke reported the Mayo Clinic experience with radical cystectomy for pT1 transitional cell cancer.<sup>18</sup> The progression-free survival rate in 32 patients at 5 and 10 years was 67% and 57%, respectively. The 66% incidence of concomitant Tis in these patients may have contributed to this rather high progression rate despite cystectomy. These and other results after early cystectomy for stage T1 grade 3 bladder cancer are similar to ours with a primarily organ preserving strategy but the 2 populations may not be comparable based on the inherent potential limitations when comparing nonrandomized groups. Nevertheless, it seems evident that even early radical surgery cannot prevent progression and cancer death in a specific group of patients, of whom some must have had microscopic metastases at diagnosis and cystectomy. Stockle et al reported a poorer outcome in cases of deferred versus immediate cystectomy after the diagnosis of invasive bladder cancer.<sup>19</sup> However, in this retrospective study patients with primary muscle invasive tumors were also included in the early

cystectomy group, making the comparison for stage T1 grade 3 alone difficult. Furthermore, resection of the tumor ground was not repeated in all patients in the deferred cystectomy group, nor did they receive BCG or any other intravesical chemotherapy. Herr and Sogani analyzed the records of 90 patients with high risk superficial bladder cancer to determine survival after early or deferred cystectomy with a followup of 15 years.<sup>20</sup> They noted a 69% versus 26% survival rate in patients with early versus deferred cystectomy. These data seem to favor early cystectomy. However, patients undergoing deferred cystectomy represent a second negative selection of those in whom disease progressed during primarily conservative treatment, whereas patients with a favorable course without recurrence after conservative treatment were excluded from analysis. On the other hand, cases that would have had a favorable outcome even without cystectomy were included in the early cystectomy group.

Although our study was retrospective and nonrandomized, our results suggest that when the highest risk population with multifocal stage T1 grade 3 plus Tis plus possible involvement of the distal ureters or prostatic urethra undergo primary cystectomy, a primary organ preserving approach is feasible in the remainder with no increased risk if they undergo close and meticulous followup, and receive aggressive treatment when there is progression or multifocal recurrence. Furthermore, our results and those of others confirm the stage T1 grade 3 rule of 30% since approximately 30% of patients never have recurrence, 30% require cystectomy and 30% die of disease regardless of treatment choice. Identifying patients at high risk for progressive disease by molecular markers is a challenging task for the future.

#### CONCLUSIONS

The results of our nonrandomized analysis suggest that intravesical BCG therapy after transurethral bladder resection for stage T1 grade 3 bladder cancer delays time to recurrence and cystectomy but ultimately does not alter the final outcome. Furthermore, findings confirm the stage T1 grade 3 rule of 30% that approximately 30% of patients never have recurrence, 30% require deferred cystectomy and 30% die of disease regardless of the therapy that they receive.

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## EDITORIAL COMMENT

These authors describe similar 5-year outcomes in 153 patients with stage T1 grade 3 bladder tumors with or without BCG therapy. Worth emphasizing is that they had primary (newly diagnosed) as opposed to recurrent stage T1 disease, few (18%) had associated carcinoma in situ and the majority (80%) underwent repeat contemporary transurethral resection after the first resection or after the initial course of BCG. Because the study was not randomized and data were collected and analyzed retrospectively, case selection undoubtedly contributed to the results, warranting cautious acceptance of the findings.

The value of this study is that it reaffirms transurethral resection (surgery) rather than BCG as the primary and most effective treatment for a stage T1 grade 3 tumor and it shows that repeat resection helps consolidate local control of the invasive tumor and surgery is the primary treatment for tumor recurrences. BCG is given as an adjunct to surgery for residual carcinoma in situ after the invasive tumor has been (or should have been) completely and reliably removed by surgery. Put another way, BCG is used to treat the malignant bladder, whereas surgery is used to control the malignant tumor.

The study also corroborates other reports that a significant proportion of patients with stage T1 grade 3 bladder cancer who are treated with bladder sparing strategies have tumor progression and many die of bladder cancer. A 30% death rate for a newly diagnosed nonmuscle invasive bladder tumor seems too high a price to pay to save the bladder for long. Although these data do not address the issue of early versus later (salvage) cystectomy, earlier cystectomy, albeit it is over treatment in some patients, is likely to decrease the current unacceptably high mortality due to stage T1 grade 3 bladder tumors.

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## REPLY BY AUTHORS

We agree with the importance of surgical control in the management of stage T1 grade 3 bladder tumors and share the concern that any death due to stage T1 grade 3 bladder cancer should be avoided. However, it should be stressed that we presented overall survival data and that approximately 50% of patients died of cancer and the other 50% of other causes. Therefore, the 5-year cancer specific survival for stage T1 grade 3 bladder tumors lies in the range of 85% in our series, which is not substantially different compared to contemporary radical cystectomy series.<sup>1</sup> This rate corroborates that primary nonmuscle invasive bladder tumors have metastatic potential and may progress early independent of treatment choice. Thus, our results suggest that after exclusion of the high risk population with multifocal disease and extravesical involvement, bladder conserving management of stage T1 grade 3 bladder cancer seems acceptable without apparent survival disadvantage, provided followup is close and meticulous. Progressive disease should be treated aggressively by radical cystectomy.

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