

## PRIMARY T1G3 BLADDER CANCER: ORGAN PRESERVING APPROACH OR IMMEDIATE CYSTECTOMY?

GEORGE N. THALMANN,\* REGULA MARKWALDER, OSAMA SHAHIN,† FIONA C. BURKHARD, WERNER W. HOCHREITER AND URS E. STUDER

*From the Department of Urology and Institute of Pathology (RM), University of Bern, Inselspital, Bern, Switzerland*

### ABSTRACT

**Purpose:** In this retrospective nonrandomized study we compared the long-term outcome in patients with newly diagnosed stage T1G3 bladder cancer treated with transurethral resection and bacillus Calmette-Guerin or immediate cystectomy.

**Materials and Methods:** Of 121 patients with a median age of 67 years (range 36 to 88) diagnosed with primary T1G3 bladder cancer between 1976 and 1999, 92 were treated by transurethral resection with additional intravesical bacillus Calmette-Guerin and 29 were treated with immediate cystectomy.

**Results:** Of the 92 patients treated with an organ preserving approach 29 remained disease-free, local recurrence developed in 33 (36%) and progression developed in 30 (33%) at a median followup of 6.9 years (range 0.6 to 16.5). Of these 92 patients 27 (29%) underwent deferred cystectomy at a median of 12.9 months (range 4.8 to 136), of whom 10 (37%) with a median postoperative followup of 19 months (range 2 to 173) died of progressive disease with a median survival of 13 months (range 3 to 34) after cystectomy. The majority of patients who died of progressive disease refused cystectomy, were referred too late for cystectomy, were inoperable or had upper urinary tract disease. Six of the 29 patients (21%) undergoing immediate cystectomy had progression at a median of 13.2 months (range 5.5 to 37). Overall and tumor specific survival at 5 years in patients treated with an organ preserving approach was 69% and 80%, and in those treated with immediate cystectomy it was 54% and 69%, respectively.

**Conclusions:** The results of this analysis demonstrate that the concept of an organ preserving approach is acceptable and spares the bladder in approximately half of the patients with primary T1G3 bladder cancer. Of the patients 30% require deferred cystectomy, making meticulous, close followup mandatory.

**KEY WORDS:** bladder; carcinoma, transitional cell; cystectomy; disease progression; bladder neoplasms

When treated with transurethral bladder resection (TURB) alone, transitional cell carcinoma invading the lamina propria of the bladder wall (stage T1) is associated with a high recurrence rate of 69% to 80% and a progression rate of 33% to 48% with consequences on patient survival.<sup>1–4</sup> The optimal treatment for primary T1G3 bladder cancer remains controversial.<sup>5–9</sup> Arguments in favour of immediate cystectomy for primary T1G3 tumors are mainly provided by reports of clinical under staging in up to 40% of patients with corresponding progression and recurrence rates.<sup>10</sup> Concomitant carcinoma in situ (CIS) and/or multifocality are known negative prognostic factors for recurrence and progression, and favor recommendations of cystectomy. Although no randomized clinical phase III trials of immediate cystectomy vs organ preserving treatment exist to answer the question of whether cystectomy is warranted in T1G3 disease, they are regularly part of contemporary cystectomy series.<sup>11</sup>

Recurrence and progression rates after TURB have been reported to be decreased by adjuvant intravesical immunotherapy with bacillus Calmette-Guerin (BCG). Reported recurrence rates vary from 11% to 33% and progression rates are 8% to 19%.<sup>3, 12–14</sup> Adequate analysis of the effect of BCG on stage T1G3 tumors is limited because most existing trials of BCG for high risk, superficial bladder cancer only evalu-

ated time to first recurrence and usually contained a mixture of Ta and T1 tumors. Furthermore, patients with recurrent stage T1G3 disease, those with secondary stage T1G3 after previous resection of Ta tumors or those with other intravesical therapies prior to BCG were often included in these studies. In this retrospective, nonrandomized, single institution analysis we compared long-term results in 92 patients with primary stage T1G3 tumors treated with an organ preserving TURB approach combined with intravesical BCG therapy to those in 29 treated with immediate cystectomy according to intent to treat in terms of overall survival, tumor specific survival, progression rates, recurrence rates and ultimate organ preservation.

### PATIENTS AND METHODS

**Patients.** Of 121 patients with primary stage T1G3 bladder cancer treated between 1980 and 1999, 92 (male-to-female ratio 4:1) were treated with an organ preserving approach at our institution with a basically unchanged TURB technique. In these 92 patients TURB was followed by a minimum of 6 weekly intravesical BCG instillations. During the same period another 29 patients underwent immediate cystectomy for primary T1G3 bladder cancer at our institution (table 1). Indications for immediate cystectomy were multifocal disease or residual tumor at second resection. All patients in the immediate cystectomy group underwent cystectomy within 3 months of the treatment determining TURB. All histological examinations were performed at the institute of pathology at our university.

Accepted for publication February 13, 2004.

\* Correspondence: Department of Urology, University of Bern, Inselspital, CH-3010 Bern, Switzerland (telephone: +41-31-632-36-21; FAX: +41-31-632-21-80; e-mail: george.thalmann@insel.ch).

† Current address: Department of Urology, University of Basel, Liestal, Switzerland.

TABLE 1. Patient characteristics

	Immediate Cystectomy	TURB + BCG
No. pts	29	92
No. men/women	26/3	71/21
Median age (range)	66 (42–75)	69 (37–88)
No. concomitant Tis (%)	6 (21)	20 (22)
No. multifocal disease (%)	22 (76)	51 (55)

p not significant.

The median number of TURBs in patients with immediate cystectomy was 1 (range 1 to 3) and 4 (2 to 10) in patients with attempted organ preserving treatment. Patients undergoing immediate cystectomy had more multifocal disease (76%) compared to patients treated conservatively (55%) (p = 0.14). There was also no significant difference in age or concomitant CIS (21% vs 26%, p = 0.88, table 1).

**Treatment and followup.** The 92 patients with attempted organ preserving treatment received 1 course of intravesical BCG therapy a median of 1.18 months following initial TURB. This delay was due to re-resection of the primary resection site(s) in 76% of all patients. Of the 92 patients 22 (24%) received 2 or more 6-week BCG treatment cycles. Followup consisted of cystoscopy with bladder was 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. Some patients were followed by the referring urologist.

In patients undergoing radical cystectomy lymphadenectomy was performed according to a standard protocol, as recently described.<sup>15</sup> Progression was defined as muscular invasion (stage T2 or higher) or metastatic disease (M+).

**Statistical analysis.** Differences between the 2 groups in progression-free, tumor specific and overall survival as well as overall and tumor specific survival after deferred cystectomy were calculated using the Kaplan-Meier survival function and analyzed by the log rank test.<sup>16</sup> Differences in patient characteristics, and progression, recurrence and cystectomy rates between the 2 groups were calculated by Pearson's chi-square test with p <0.05 considered significant.

RESULTS

Of the 92 patients treated with an organ preserving TURB approach and histologically negative second resection followed by at least 1 cycle of BCG recurrence (stage Ta/T1) developed in 33 (36%). Median time to recurrence was 22.4 months (range 3 to 147.9). Three patients had recurrence in the upper urinary tract.

Tumor progression occurred in 30 of 92 patients (33%) at a median of 11.4 months (range 3.0 to 119.1), of whom 3 had distant metastases. A total of 27 patients (29%) underwent deferred cystectomy for progression at a median of 12.9 months (range 4.8 to 136) (table 2). Of these patients 23 underwent deferred cystectomy after the first recurrence/progression. Four patients were treated with multiple

TABLE 2. Results

	Immediate Cystectomy	TURB + BCG
No. pts	29	92
Median yrs followup (range)	3.9 (0.2–8.7)	6.9 (0.2–16.5)
No. progression (%)	6 (21)	30 (33)
Median mos to progression	13.2	11.4
Median progression free survival mos	Not achieved	134
No. overall mortality (%)	14 (48)	39 (43)
No. disease specific mortality (%)	7 (24)	21 (23)
No. pos lymph nodes at lymphadenectomy (%)	4 (14)	5 (18)*

p not significant.

\* Lymphadenectomy in 27 patients who underwent deferred cystectomy.

TURBs for up to 10 years until tumor progression. Initially 18 of these 27 patients (67%) had multifocal disease. Histopathological evaluation of the cystectomy specimen revealed that 15 of these 27 patients (56%) had tumor stage pT2 or greater.

Of the 29 patients undergoing immediate cystectomy 12 (41%) had tumor stage pT2 or greater and 6 (21%) progressed at a median of 13.2 months (range 5.5 to 37) (table 2). There was no statistical significant difference in time to progression after initial diagnosis between patients treated with early cystectomy and patients with BCG (p = 0.09, table 2, fig. 1). Positive lymph nodes were found in the 2 groups in 19% and 14% of cases, respectively (p = 0.40, table 2).

Median followup in all patients was 6.9 years (range 0.2 to 16.5). Overall survival at 5 years was 69% in patients treated with the organ preserving approach and 54% in patients treated with immediate cystectomy. At 10 years 45% of patients treated with an organ preserving approach were dead, as were all with immediate cystectomy (fig. 2). The difference between the 2 treatment arms was not significant (p = 0.1243).

Tumor specific survival at 5 years in the 2 groups was 80% and 69%, respectively (p = 0.33, fig. 3). Analysis of the 30 patients who died of disease after treatment with an organ preserving approach showed that 11 (37%) were inoperable for medical reasons, 7 (23%) refused cystectomy, 7 (23%) were referred for cystectomy by the treating urologist after multiple resections of invasive recurrences and 2 (7%) died of progressive upper urinary tract disease. Of the remaining 3 patients (10%) 1 had early, highly aggressive recurrence at 3 months, 1 died of metastatic rectal and bladder cancer, and 1 died of metastatic disease. Ten of the 27 patients (37%) who underwent deferred cystectomy at a median of 12.9 months (range 4.8 to 136) then died of disease at a median of 12.5 months (range 3 to 34). In the group of patients treated with immediate cystectomy 14 (48%) died, including 7 of bladder cancer and 7 of other causes. There was no significant difference in overall survival between patients undergoing early vs deferred cystectomy (p = 0.62, fig. 4). For tumor specific survival the difference was significant in favor of deferred cystectomy (p = 0.02, fig. 5).

DISCUSSION

This retrospective, nonrandomized study demonstrates that T1G3 disease is potentially lethal even after immediate cystectomy. Micrometastases may be present at initial diagnosis due to vascular and/or lymphatic tumor invasion of the lamina propria. In other series in which basically all patients with T1G3 underwent cystectomy approximately 20% died of disease.<sup>17, 18</sup> Thus, even immediate radical surgery could not prevent cancer death in these patients.

An organ preserving TURB approach with a negative second TURB followed by at least 1 cycle of BCG is an acceptable alternative in patients with primary T1G3 bladder cancer. Of the patients 30% require deferred cystectomy and, thus, this approach allows us to spare the bladder in approximately 50%. Regular and stringent followup is mandatory. Because approximately 30% of patients with T1G3 bladder cancer never have recurrence and another 30% never have progression,<sup>19</sup> these patients would be over treated with cystectomy. Based on our results, albeit in a retrospective, nonrandomized study, bladder preservation in patients with primary stage T1G3 bladder cancer seems to be a valid treatment option.

The question remains whether patients treated with an organ preserving approach who died of disease might have been saved by immediate cystectomy. The majority of such patients who died of bladder cancer in our series were inoperable, refused cystectomy, had progressive upper urinary tract disease or were treated too long with an organ preserv-

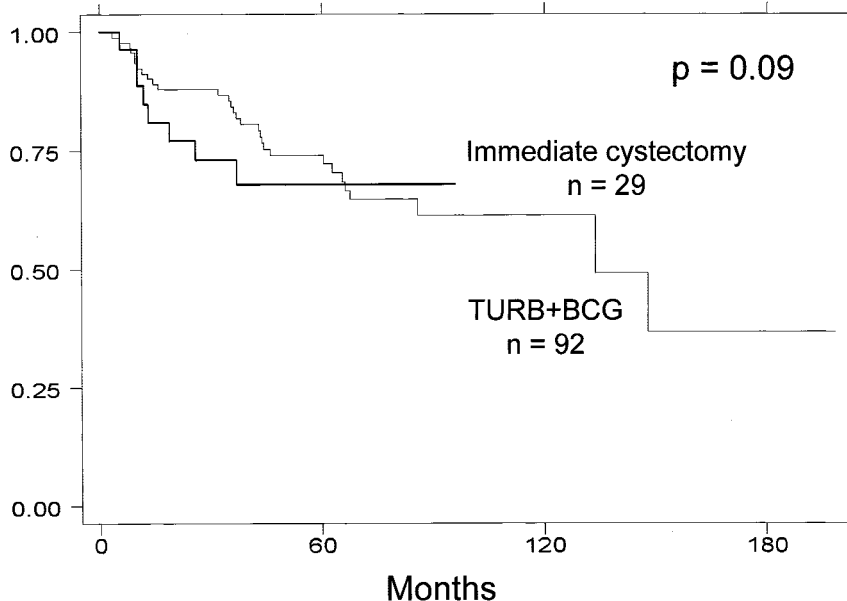


FIG. 1. Kaplan-Meier analysis of progression-free survival in 29 patients undergoing immediate radical cystectomy and 92 treated with TURB plus BCG organ preserving approach available for followup. There was no statistically significant difference between groups ( $p = 0.09$ ).

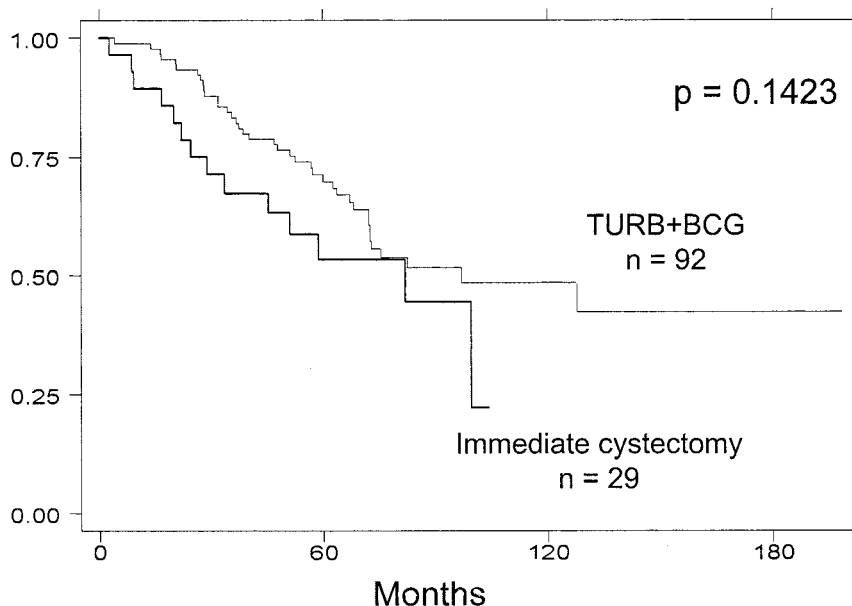


FIG. 2. Kaplan-Meier analysis of overall survival after immediate cystectomy or primary conservative TURB plus BCG treatment. There was no statistically significant difference between groups ( $p = 0.14$ ).

ing approach by the referring urologist. One patient had early recurrence at 3 months with metastatic disease and would have died of disease regardless of treatment. Another patient had concomitant metastatic rectal cancer. In retrospect only 1 patient might have avoided the fatal outcome by immediate cystectomy.

Patients with multifocal stage T1 bladder cancer combined with CIS were usually advised to undergo immediate cystectomy unless they were unfit or unwilling to undergo surgery. Despite this, 55% of our patients with multifocal disease elected an organ preserving approach. This 55% incidence is comparable to that reported in contemporary cystectomy series.<sup>9, 11, 17, 20–22</sup> Second resection of the tumor base performed in 76% of our patients prior to BCG instillation therapy may corroborate the value of re-resection for consolidating local tumor control, as suggested by Herr.<sup>23</sup> In addition, adjuvant

immunotherapy with BCG significantly delays time to recurrence. However, the probability of recurrence does not seem to be substantially altered in patients with primary T1G3 disease, as reported recently by a group from our institution.<sup>19</sup> The value of immediate postoperative mitomycin C instillation for stage T1 bladder cancer, as suggested by Soloway et al,<sup>6</sup> should be confirmed in prospective clinical trials.

In 32 patients undergoing radical cystectomy for stage T1 transitional cell cancer Siref and Zincke reported a progression-free survival rate of 67% and 57% at 5 and 10 years, respectively.<sup>20</sup> These results are comparable to those in our patients undergoing immediate cystectomy and not substantially different from those in our series undergoing deferred cystectomy, representing secondary negative selection with tumor progression. It is noteworthy that deferred

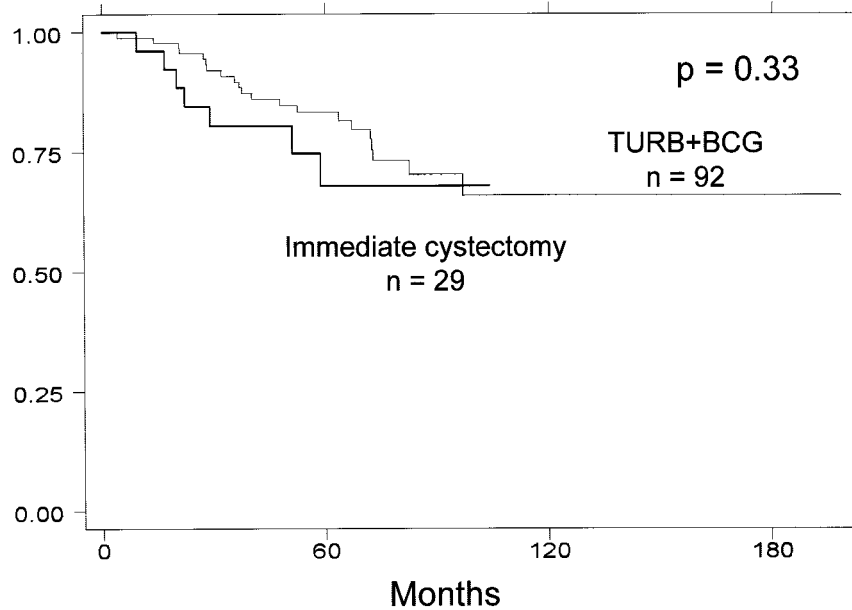


FIG. 3. Kaplan-Meier analysis of tumor specific survival after immediate cystectomy or primary conservative TURB plus BCG treatment. There was no statistically significant difference between groups ( $p = 0.33$ ).

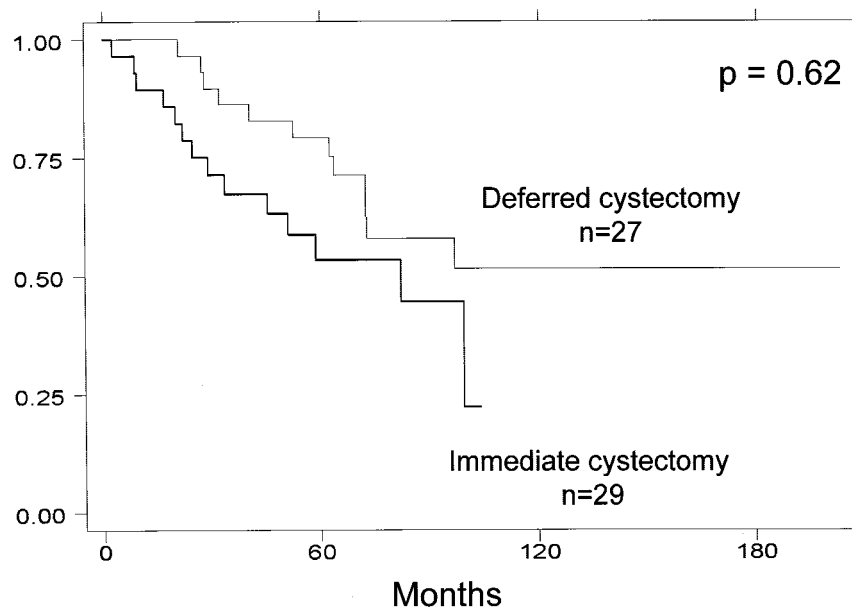


FIG. 4. Kaplan-Meier analysis of overall survival after primary or deferred cystectomy. There was no statistically significant difference in overall mortality between patients undergoing early cystectomy and those treated with organ conserving approach requiring deferred cystectomy ( $p = 0.62$ ).

cystectomy might be required even after 10 years or more, as in our series and that of others.<sup>12</sup>

Stockle et al described a poorer outcome in patients with deferred vs immediate cystectomy.<sup>21</sup> However, comparison with the results in this retrospective study is difficult because patients with primary muscle invasive tumors were also included in the immediate cystectomy group. In addition, second resection of the tumor base was not performed in all patients in the deferred cystectomy group, nor did they receive BCG or any other intravesical therapy.

Herr and Sogani analyzed 90 cases of high risk superficial bladder cancer (T1G2–3) for survival after immediate or deferred cystectomy with a followup of 15 years.<sup>7</sup> The survival rate in patients with immediate cystectomy was 69% compared to 26% in patients with deferred cystectomy. These data seem to favor immediate cystectomy. However, in this

study patients undergoing deferred cystectomy again represented a secondarily negative selection of those with progression under primarily conservative treatment, whereas those with a favorable course without recurrence after conservative treatment were excluded from analysis. Furthermore, patients who may have had a favourable outcome even without cystectomy were included in the early cystectomy group.

Another group reported a 5-year actuarial survival rate of 80% in patients with immediate cystectomy for pT1G3 tumors and 78% in those with concomitant CIS.<sup>22</sup> In a report of a more recent series of patients with a median followup of 7.2 years overall survival at 5 years was 72% and recurrence-free survival was 83%.<sup>8</sup> Comparable results with 5 and 10-year cancer specific survival rates of 76% and 62%, respectively, were reported in a more recent series of Amling et al.<sup>9</sup> These results are similar to those in our series. In contrast, in a



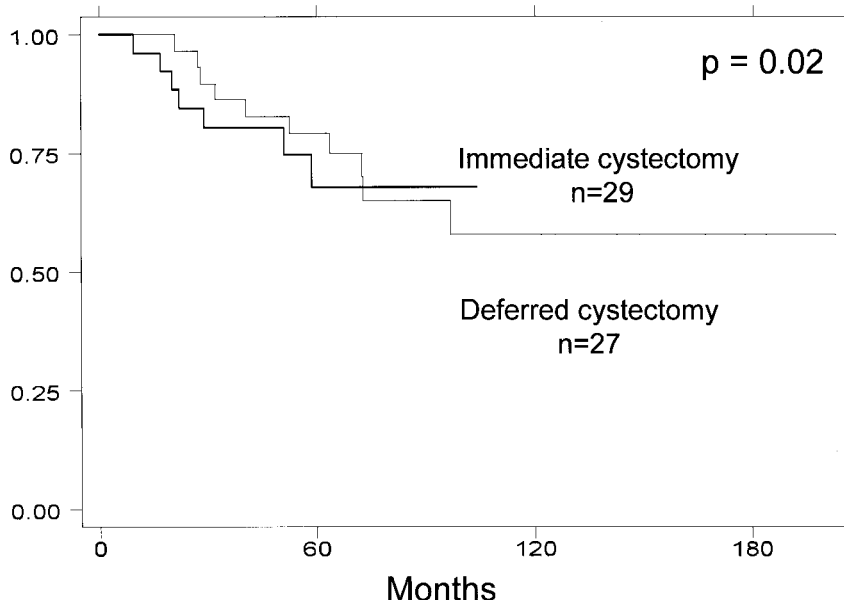


FIG. 5. Kaplan-Meier analysis of tumor specific survival after immediate or deferred cystectomy. There was significant difference in tumor specific survival in favor of patients treated with organ conserving approach requiring deferred cystectomy over those undergoing immediate cystectomy ( $p = 0.02$ ).

retrospective analysis of 88 patients at M. D. Anderson Cancer Center Dinney et al concluded that immediate cystectomy did not improve patient outcome and suggested reserving radical cystectomy for patients with progression or disease refractory to local therapy.<sup>24</sup> Institutional differences may have various causes, such as differences in tumor staging between different pathologists, as described by Coblenz et al,<sup>25</sup> the completeness and technique of TURB and second resection, varying indications for cystectomy and the duration of followup.

It was suggested that in the era of nerve sparing cystectomy and orthotopic neobladder reconstruction the option of early radical cystectomy may be discussed with the patient as an alternative in the treatment of stage T1G3 bladder cancer before initiating intravesical therapy.<sup>26</sup> However, patients should be equally informed that the bladder can be preserved by TURB in approximately 50% if re-resection is negative and followed by intravesical BCG therapy, while 30% require deferred cystectomy with no substantial risk of a poorer outcome. This was substantiated by Davis et al, who noted favorable results with an organ preserving approach at a minimum followup of 10 years.<sup>27</sup>

A randomized study of immediate cystectomy vs conservative, organ preserving management would be difficult to perform and would lead to a large number of unnecessary cystectomies until a survival advantage in patients undergoing immediate cystectomy could be proved. Help to decide which patients should undergo surgery might come from biological marker studies with gene array analysis, proteomics and high throughput analysis. Novel markers detectable by immunohistochemistry or in serum might help us decide which patients with T1G3 tumors require aggressive treatment with immediate cystectomy and which may be treated with TURB and BCG. Until we have such tools a certain approach based on our results may be suggested. Patients with multifocal T1G3 and CIS in the upper urinary tract or prostatic urethra should undergo primary cystectomy. In patients with unifocal or multifocal T1G3 with or without CIS and negative histology after second TURB an organ preserving approach with BCG may be attempted. In cases of positive cytology tumor recurrence at 3 months or T1G3 relapse during followup cystectomy is warranted.

Direct comparison of these 2 nonrandomized populations

may be questioned. However, all patients had primary T1G3 disease and the 2 groups were comparable in terms of multifocality, concomitant CIS and age. It may be argued that the relatively small number of patients in our immediate cystectomy group as well as differences in followup may represent a potential selection bias and patients who died of progressive bladder cancer after deferred cystectomy might have been saved. Nevertheless, the number of patients who died of progressive disease after deferred cystectomy is not higher than is to be expected for the natural course of the disease.

The results of this retrospective analysis suggest that after excluding a high risk population with multifocal disease and extravesical involvement bladder conserving management of primary stage T1G3 bladder cancer seems to be acceptable without a substantial survival disadvantage as long as second TURB is negative and close, meticulous followup is provided. If these guidelines had been respected in our study, probably only 1 patient treated with an organ preserving approach would have had progressive disease, which might have been prevented by immediate cystectomy. Nevertheless, rigorous long-term surveillance and continuous reconsideration of radical cystectomy is mandatory in these patients because they are at life long risk of recurrence and progression.<sup>1</sup> Most of our failures occurred because this was not done. It is evident that recurrent T1G3 or progressive disease should be treated aggressively with radical cystectomy.

#### CONCLUSIONS

The results of this retrospective, nonrandomized analysis demonstrate that an organ preserving TURB approach, re-resection and intravesical BCG in patients with T1G3 bladder cancer does not place patients at substantially higher risk for tumor progression or significantly decrease their chances of survival. Of patients 30% require deferred cystectomy. Thus, cystectomy may be prevented in approximately 50% of a select group of patients with stage T1G3 bladder cancer. Regular life long followup in these patients is warranted and deferred cystectomy for recurrent T1G3 or progressive disease should be aggressively considered.

## REFERENCES

1. Cookson, M. S., Herr, H. W., Zhang, Z.-F., Soloway, S., Sogani, P. C. and Fair, W. R.: The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol*, **158**: 62, 1997
2. Heney, N. M., Ahmed, S., Flanagan, M. J., Frable, W., Corder, M. P., Hafermann, M. D. et al: Superficial bladder cancer: progression and recurrence. *J Urol*, **130**: 1083, 1983
3. Jakse, G., Loidl, W., Seeber, G. and Hofstädter, F.: Stage T1, grade 3 transitional cell carcinoma of the bladder: an unfavorable tumor? *J Urol*, **137**: 39, 1984
4. Lutzeyer, W., Rübber, H. and Dahm, H.: Prognostic parameters in superficial bladder cancer: an interim analysis of 315 cases. *J Urol*, **127**: 250, 1982
5. Brake, M., Loertzer, H., Horsch, R. and Keller, H.: Recurrence and progression of stage T1, grade 3 transitional cell carcinoma of the bladder following intravesical immunotherapy with bacillus Calmette-Guerin. *J Urol*, **163**: 1697, 2000
6. Soloway, M. S., Sofer, M. and Vaidya, A.: Contemporary management of stage T1 transitional cell carcinoma of the bladder. *J Urol*, **167**: 1573, 2002
7. Herr, H. W. and Sogani, P. C.: Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol*, **166**: 1296, 2001
8. Freeman, J. A., Esrig, D., Stein, J. P., Simoneau, A. R., Skinner, E. C., Chen, S. C. et al: Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer*, **76**: 833, 1995
9. Amling, C. L., Thrasher, J. B., Frazier, H. A., Dodge, R. K., Robertson, J. E. and Paulson, D. F.: Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. *J Urol*, **151**: 31, 1994
10. Dutta, S. C., Smith, J. A., Jr., Shappell, S. B., Coffey, C. S., Chang, S. S. and Cookson, M. S.: Clinical under staging of high risk nonmuscle invasive urothelial carcinoma treated with radical cystectomy. *J Urol*, **166**: 490, 2001
11. Gschwend, J. E., Fair, W. R. and Vieweg, J.: Radical cystectomy for invasive bladder cancer: contemporary results and remaining controversies. *Eur Urol*, **38**: 121, 2000
12. Cookson, M. S. and Sarosdy, M. F.: Management of stage T1 superficial bladder cancer with intravesical bacillus Calmette-Guerin. *J Urol*, **148**: 797, 1992
13. Pansadoro, V., Emiliozzi, P., de Paula, F., Scarpone, P., Pansadoro, A. and Sternberg, C. N.: Long-term follow-up of G3T1 transitional cell carcinoma of the bladder treated with intravesical bacille Calmette-Guerin: 18-year experience. *Urology*, **59**: 227, 2002
14. Baniel, J., Grauss, D., Engelstein, D. and Sella, A.: Intravesical bacillus Calmette-Guerin treatment for stage T1 grade 3 transitional cell carcinoma of the bladder. *Urology*, **52**: 785, 1998
15. Mills, R. D., Turner, W. H., Fleischmann, A., Markwalder, R., Thalmann, G. N. and Studer, U. E.: Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. *J Urol*, **166**: 19, 2001
16. Peto, R. and Pike, M. C.: Conservatism in the approximation sigma (O-E)2-E in the logrank test for survival data or tumor incidence data. *Biometrics*, **129**: 579, 1973
17. Stein, J. P., Lieskovsky, G., Cote, R., Groshen, S., Feng, A. C., Boyd, S. et al: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*, **19**: 666, 2001
18. Hautmann, R. E. and Simon, J.: Ileal neobladder and local recurrence of bladder cancer: patterns of failure and impact on function in men. *J Urol*, **162**: 1963, 1999
19. Shahin, O., Thalmann, G. N., Rentsch, C., Mazzucchelli, L. and Studer, U. E.: 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. *J Urol*, **169**: 96, 2003
20. Siref, L. E. and Zincke, H.: Radical cystectomy for historical and pathologic T1 N0, M0 (stage A) transitional cell cancer. Need for adjuvant systemic chemotherapy? *Urology*, **31**: 309, 1988
21. Stockle, M., Alken, P., Engelmann, U., Jacobi, G. H., Riedmiller, H. and Hohenfellner, R.: Radical cystectomy—often too late? *Eur Urol*, **13**: 361, 1987
22. Malkowicz, S. B., Nichols, P., Lieskovsky, G., Boyd, S. D., Huffman, J. and Skinner, D. G.: The role of radical cystectomy in the management of high grade superficial bladder cancer (PA, P1, Pis, and P2). *J Urol*, **144**: 641, 1990
23. Herr, H. W.: The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol*, **162**: 74, 1999
24. Dinney, C. P. N., Babkowski, R. C., Antelo, M., Perrotte, P., Liebert, M., Zhang, H.-Z. et al: Relationship among cystectomy, microvessel density and prognosis in stage T1 transitional cell carcinoma of the bladder. *J Urol*, **160**: 1285, 1998
25. Coblenz, T. R., Mills, S. E. and Theodorescu, D.: Impact of second opinion pathology in the definitive management of patients with bladder carcinoma. *Cancer*, **91**: 1284, 2001
26. Esrig, D., Freeman, J. A., Stein, J. P. and Skinner, D. G.: Early cystectomy for clinical stage T1 transitional cell carcinoma of the bladder. *Semin Urol Oncol*, **15**: 154, 1997
27. Davis, J. W., Sheth, S. I., Doviak, M. J. and Shellhammer, P. F.: Superficial bladder carcinoma treated with bacillus Calmette-Guerin: progression-free and disease specific survival with minimum 10-year followup. *J Urol*, **167**: 494, 2002