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Papillary Recurrence of Bladder Cancer at First Evaluation after Induction Bacillus Calmette-Guérin Therapy: Implication for Clinical Trial Design

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Abstract

Background—Recurrence with papillary tumor(s) by 3-mo after induction bacillus Calmette-Guérin (BCG) is historically believed to be a poor prognostic indicator in patients with high-risk nonmuscle invasive bladder cancer. However, the impact of a clinical Ta (cTa) papillary recurrence at 3 mo after BCG is often debated.

Objective—To evaluate the prognostic implications of cTa papillary recurrence found 3 mo after induction BCG therapy and to evaluate its significance clinical trial design.

Design, setting, and participants—We reviewed our database of 917 patients who underwent transurethral resection and induction of BCG from 1995 to 2012. Clinical characteristics were compared between 3-mo recurrence stages.

Intervention—Transurethral resection of bladder tumor and intravesical therapy.

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Outcome measurements and statistical analysis—Chi-square analysis and Student *t* test were used to compare clinical characteristics between 3-mo recurrence stages. Kaplan-Meier method was used to determine bladder-preservation time, progression-free survival, and disease-specific survival.

Results and limitations—We identified 84 patients who met the study criteria (66 patients with cTa and 18 patients with clinical T1 [cT1]). The median follow-up for the entire cohort was 74 mo. Of the patients with cTa recurrence, 60 continued with bladder-sparing therapy. Patients with a high-grade cTa recurrence who continued bladder-sparing therapy had a 17% incidence of disease progression and a 62% incidence of recurrence within 1 yr. No patients with low-grade cTa recurrence (*n* = 13) developed disease progression or underwent radical cystectomy. Patients with an initial cTa at diagnosis had a higher 5-yr bladder preservation rate than those with an initial cT1 diagnosis (84% vs 61%; *p* = 0.041). Patients with high-grade cTa recurrence and those with cT1 recurrence had similar outcomes with respect to death rates over the entire follow-up period (10% and 15%, respectively), as well as 5-yr progression-free survival (77% vs 83%). Limitations include using a single institution and a retrospective review.

Conclusions—Patients with low-grade cTa papillary recurrence 3 mo after induction of BCG can safely continue with bladder-sparing therapy. Patients with high-grade cTa papillary recurrence at that time have risks of recurrence and progression similar to those of patients with cT1 recurrence. These are important factors to consider during clinical trial design.

Patient summary—Low-grade clinical Ta papillary recurrence following induction of bacillus Calmette-Guérin therapy can be safely managed conservatively, although a high-grade clinical Ta recurrence should be treated similar to a clinical T1 recurrence due to its comparable progression rates.

Keywords

Bladder cancer; Non-muscle invasive; Recurrence; Bacillus Calmette-Guérin; Clinical outcomes

1. Introduction

The current standard treatment for high-risk nonmuscle invasive bladder cancer is transurethral resection (TUR) and intravesical bacillus Calmette-Guérin (BCG). Although BCG therapy reduces the risk of recurrence by 32% for these patients, between 12% and 24% of the patients treated still have disease progression [1,2]. Studies have shown that if intravesical immunotherapy is unsuccessful and a patient requires radical cystectomy (RC), performing the intervention within 24 mo after diagnosis optimizes survival [3]. To this end, it has been suggested that early disease recurrence (eg, 3 mo after BCG) be considered an indication for early RC [4].

Recurrence with papillary tumor(s) by 3 mo after induction of BCG is a poor prognostic indicator in patients with high-risk nonmuscle invasive bladder cancer [5,6], with a progression rate of 47% in those with clinical T1 (cT1) disease [7]. However, the impact of a clinical Ta (cTa) papillary recurrence at 3 mo after BCG is often debated. In fact, recent trial designs have even attempted to exclude a cTa recurrence at 3 mo after BCG therapy as a significant end point, regardless of grade. To determine how to safely manage this select

group of patients, we examined the oncologic outcomes of patients who developed cTa or cT1 recurrence by 3 mo after BCG therapy induction, and compared those outcomes between recurrence stages, tumor grades, and initial clinical stages.

2. Patients and methods

We performed an institutional review board-approved search of our database of patients who underwent TUR and induction BCG during the period from 1995 to 2012 and had developed papillary recurrence at the 3-mo endoscopic evaluation after starting induction BCG. We excluded patients whose initial pathology slides were not available for review, those with only carcinoma in-situ (cis) at the 3-mo evaluation, and those without at least 2-yr of follow-up. External pathology slides were all rereviewed by dedicated genitourinary pathologists to confirm clinical stage, grade, and histology. All pathologists involved during the study period were fellowship trained in genitourinary pathology.

During the time period of our study repeat endoscopic evaluation was performed on all new patients presenting for treatment of bladder cancer. If residual tumor or any abnormalities were present patients underwent restaging TUR with examination under anesthesia before starting BCG induction therapy. Patients found to have cT1 underwent a second TUR for accurate staging before BCG therapy after 2005, and on a case-by-case basis before 2005. Tumor staging was based on the TNM staging system and the 1973 and 2004 World Health Organization grading classification system. Tumors were classified as high grade (including Grade 2 and 3) and low grade. Patients usually received induction BCG 2–4 wk after TUR. All patients underwent surveillance cystoscopy about 6 wk after their last induction BCG treatment. Patients with evidence of tumor or positive cytology underwent repeat TUR. After recurrence was diagnosed and treatment options discussed between the patients and their providers, the patients received either immediate RC or bladder-sparing therapy (ie, additional intravesical therapy or surveillance). Patients were offered RC as a treatment option at every episode of recurrence and strongly encouraged to undergo definitive surgical treatment at any sign of progression of disease following their 3-mo recurrence. Intravesical treatments included maintenance BCG, (administered according to the Southwest Oncology Group schedule) [2], maintenance BCG with interferon- α (50 million U), and intravesical mitomycin-C (40 mg) for 6 wk with or without 1-mo maintenance regimen for 12 mo. Patients receiving bladder-sparing therapy were evaluated every 3 mo with cystoscopy with or without urine markers as clinically indicated. There was no difference in the treatment or surveillance strategy of patients who had concomitant cis with a papillary recurrence at 3 mo following intravesical induction BCG.

For our analysis, disease recurrence was defined as pathologic evidence of disease, whereas disease progression was defined as an increase in clinical stage or grade from the original diagnosis, new development of lymph node involvement, or visceral or bony metastasis (as proposed by the International Bladder Cancer Group) [8]. The primary endpoints included 1-yr recurrence and progression rates, disease-specific survival (DSS), progression free survival (PFS) rate, and bladder-preservation rate (ie, sparing from RC). All endpoints were determined from the time of recurrence at 3 mo. DSS was determined from the date of original diagnosis to the date of death from urothelial carcinoma.

Clinicopathological variables were compared between the cTa and cT1 groups using chi-square test and a Student *t* test. Bladder-preservation, PFS, and DSS was assessed using the Kaplan-Meier method, and initial clinical stage and recurrence histologic grade were compared using the log rank test. A *p* value of less 0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 21 (IBM, Armonk, NY, USA).

3. Results

3.1. Entire cohort

We identified 917 patients who underwent TUR and BCG at our institution during the evaluation period. After applying our exclusion criteria, we identified 84 patients who had developed papillary recurrence 3 mo after BCG induction (cTa: 66 patients; cT1: 18 patients). Most of these patients ($n = 51$) initially presented with cT1 bladder cancer and 33 with cTa disease. Of the 51 patients with cT1 disease, 39 patients underwent restaging TUR (four with cT0, 14 with cT1, 18 with cTa, and three with cTis). Only one patient underwent restaging TUR for cTa disease due to large volume disease. All biopsy/resection specimens contained muscularis propria. There were no major differences in common parameters between those with cTa recurrence and those with cT1 recurrence (Table 1). The median follow-up for the entire cohort was 74 mo (range, 22–194 mo), and the median follow-up for those alive without disease at last follow-up was 94 mo (range, 28–194 mo). The pathologic results of patients who underwent immediate RC and delayed RC for both cTa and cT1 recurrence at 3 mo are listed in Supplementary Table 1. Two patients who underwent immediate RC for cTa disease at 3 mo had $> pT2$ disease (one with prostatic stromal invasion), while all patients who underwent immediate RC for cT1 recurrence at 3 mo had $< pT2$. The 5-yr bladder preservation rate for the 73 patients that had a 3-mo recurrence (both cTa and cT1) who did not undergo immediate RC is 72%. The 5-yr PFS for all 73 patients that had a 3-mo recurrence (both cTa and cT1) who did not undergo immediate RC is 82%. The 5-yr DSS for the entire cohort (84 patients) is 95%. The presence of concomitant cis at the 3-mo evaluation did not affect the outcomes of patients with a cTa recurrence (Supplementary Fig. 1).

3.2. Patients with cTa recurrence at 3 mo

Of the 66 patients who had cTa recurrence 3 mo after induction BCG, 57 (86%) had high-grade disease at diagnosis and 53 (80%) had high-grade disease at recurrence. Six patients with cTa recurrence underwent immediate RC; one of these patients subsequently developed disease recurrence (distal recurrence in a supraclavicular node). For the remaining 60 patients who received bladder-sparing therapy, the 1-yr recurrence rate was 55%, the 1-yr progression rate was 13%, and the 5-yr bladder preservation rate was 65% (Fig. 1A).

When patients with cTa recurrence at 3 mo were stratified by grade of recurrence, those with high-grade cTa recurrence ($n = 47$) who underwent bladder-sparing therapy had a 1-yr recurrence rate of 62% (29/47 patients), and disease progression rate of 17% at 1 yr and 19% at 2 yr (21% over the entire follow-up period). The delayed RC rate was 36% (17/47) over the entire follow-up period. The 5-yr PFS rate in patients with high-grade cTa recurrence

was 77% (Fig. 1B). Of the 10 patients with high-grade cTa recurrence who progressed, six developed muscle-invasive disease (cT2–4), and three had evidence of metastasis at the time of progression. Overall, five (11%) patients with a high-grade cTa recurrence died from urothelial cancer over the entire follow-up period. The 5-yr DSS rate of all patients with high-grade cTa recurrence (both those treated with immediate RC and bladder-sparing therapy) was 95% (Fig. 1C).

When patients with a cTa recurrence who underwent bladder-sparing therapy were stratified according to their initial clinical stage, patients with cTa disease at their initial diagnosis ($n = 24$) had a significantly higher bladder preservation rate than those with an initial cT1 diagnosis ($n = 36$; 84% vs 61%; $p = 0.041$; Fig. 2A), while PFS rates (Fig. 2B) and DSS rates (Fig. 2C) were similar between the initial clinical stages of cTa and cT1.

Thirteen (20%) patients had low-grade cTa recurrence at 3 mo; one patient underwent immediate RC, and the remaining 12 opted for bladder-sparing therapy. While the recurrence rate for this group was 33% at 1 yr with a median follow-up of 66 mo (range, 33–186 mo), not a single patient had disease progression or required delayed RC (Fig. 3A and 3B). There was no difference in outcomes in patients based on their initial clinical stage and their 3-mo recurrence stage (Supplementary Table 2).

3.3. Patients with cT1 recurrence at 3 mo

Of the 18 patients who had cT1 recurrence 3 mo after induction BCG, all (100%) had high-grade disease at diagnosis and at recurrence. Five patients with cT1 recurrence underwent immediate RC; none of those patients subsequently developed disease progression. For the remaining 13 patients, the 1-yr recurrence rate was 31%, the 1-yr progression rate was 8%, and the 5-yr bladder-preservation rate was 76% (Fig. 1A). Two patients with cT1 recurrence who underwent bladder-sparing therapy died from urothelial carcinoma. The 5-yr PFS rate for patients with cT1 recurrence was 83%. The overall 5-yr DSS rate for all patients with cT1 recurrence at 3 mo, regardless of treatment, was 93%.

4. Discussion

Our study demonstrated that high-grade cTa papillary recurrence at 3 mo after induction BCG portends a similar risk as that of high-grade cT1. These patients had a recurrence rate of 62% at 1 yr and a disease progression rate of 17% at 1 yr and 19% at 2 yr following their 3-mo recurrence. However, patients with low-grade cTa recurrence at 3 mo had a very good prognosis, with no disease progression noted in those patients in our cohort. Thus, both for management as well as clinical trial design, a cTa low-grade lesion can be considered a “nonevent” while a high-grade papillary lesion should be considered a significant finding regardless of whether it is cT1 or cTa.

The management of cases treated with intravesical BCG can be complex, especially when patients develop recurrence after induction BCG. In fact, patients who have papillary disease recurrence at the 3-mo evaluation are often referred to as “BCG refractory,” although some experts have suggested that to be considered truly unresponsive to BCG as the disease should have been treated with at least one additional 3-wk course of BCG [9]. Nonetheless,

patients with papillary recurrence after induction BCG at the 3-mo cystoscopic evaluation present a treatment quandary, as well as being a matter of discussion during clinical trial designs in the BCG failure population.

Treatment options for patients with papillary recurrence after induction BCG generally revolve around a discussion of early RC, continued intravesical BCG, switching to an alternative intravesical therapy, or a clinical trial. Many experts believe that RC is the standard treatment for patients with high-grade recurrence following BCG induction [4]. In our cohort, where cystectomy was generally offered to patients as a treatment option following recurrence after induction BCG, only 9% of patients with cTa recurrence and 28% of patients with cT1 recurrence chose this mode of therapy. Interestingly, when patients with cTa recurrence after induction BCG chose bladder-sparing therapy, the 5-yr DSS was 95%, which suggests that with adherence to maintenance treatment, routine endoscopic surveillance, and prudent clinical judgment, bladder-sparing therapy can safely prolong the need for definitive surgery.

Nonetheless, a high-grade cTa tumor after induction BCG should not be taken lightly. In our series, patients who elected to undergo bladder-sparing therapy following a high-grade cTa recurrence at 3 mo had a 21% incidence of disease progression over the entire follow-up period, and 36% of patients with high-grade cTa recurrence underwent delayed RC over the entire follow-up period. Notably, most progression events occurred within the first 2 yr following recurrence at 3 mo.

Interestingly, in a study by Solsona et al [7], of the eight patients who had cTa recurrence 3 mo after induction BCG, five developed disease progression. This progression rate is higher than that seen in our series (10% overall progression for cTa recurrence at 3 mo), which could be attributed to the definition of progression used by Solsona et al [7], which included subsequent prostatic mucosal/duct involvement and any spread to the upper urinary tracts.

Of interest from the viewpoint of counseling patients, the initial clinical stage did not appear to affect outcomes in our patients. Although the 5-yr PFS rate in patients with initial cTa disease was higher than in those with initial cT1 disease (88% vs 75%), this difference was not statistically significant. There was also no difference in DSS between patients with initial cT1 and those with initial cTa urothelial cancer. Historical reports preceding the widespread implementation of maintenance BCG have shown similar long-term outcomes in patients with cTa and those with cT1 urothelial cancer [10]. In our series, patients who had an initial cT1 diagnosis had a significantly higher rate of delayed RC than those with an initial cTa diagnosis. At our institution the threshold for performing a timely RC in patients managed with bladder-sparing therapy with a history cT1 disease is a lot lower than those with an initial cTa diagnosis. RC is offered at every episode of recurrence during intravesical therapy, with the goal of performing definitive surgical treatment prior to progression of disease. Hence, we believe the similar PFS outcomes in patients with cT1 and cTa disease is due to our stringent management of patients with an original cT1 diagnosis.

We did, however, find that low-grade cTa recurrence after induction BCG can be considered a relative “nonevent” since no patient with low-grade cTa recurrence experienced

progression or required a RC, even with a median follow-up of more than 5 yr. To identify whether the prognosis of patients with low-grade cTa recurrence at 3 mo after start of induction BCG was different from those without a recurrence, we queried our database for patients with nonmuscle invasive papillary urothelial carcinoma at diagnosis who had no tumor at their 3-mo endoscopic evaluation. Of these, 123 (99%) patients went on to start maintenance therapy. Interestingly, the overall recurrence rate for the cohort was 44.3%, with a median time to recurrence of 352 d; both of which were comparable to that of patients with low-grade cTa recurrence at 3 mo (46% recurrence rate). This result has immense implications for clinical trial endpoints in BCG-refractory or BCG-unresponsive cases. The favorable oncologic outcomes for patients with low-grade cTa recurrence are in agreement with that shown by Herr et al [11] in their study, which looked at 215 patients diagnosed with a low-grade noninvasive papillary bladder tumor. With a median follow-up of 8 yr, the authors noted an 8% incidence in histologic grade or stage progression and only one death (0.5%) from bladder cancer. Hence, our results further support the use of conservative management for low-grade papillary noninvasive bladder tumors.

The limitations of this study include all those inherent to a retrospective review. Because our institution is a tertiary referral center, we restricted our analysis to patients who had outside tumor tissue evaluable by our pathologist and who had complete follow-up data available for extraction. These restrictions did limit the size of our cohort, and, hence, we were unable to perform any inferential statistical analysis to determine clinical predictors of progression, RC, or DSS. Also, we acknowledge that the sample size is relatively small; however, these events (cTa recurrences) after BCG therapy are not frequent and even in large multi-center trials, are not well captured and to date, have not been studied. Additionally, since our manuscript is focused on the 3-mo time point for the papillary recurrences, we cannot make the same conclusions about patients who have low-grade cTa recurrences after two BCG inductions or BCG induction plus maintenance.

5. Conclusions

High-grade papillary cTa tumors 3 mo after induction BCG therapy carry the same prognosis as papillary cT1 tumors found at the same time point, and hence must be considered a significant event, placing the patient at high risk of recurrence (62%) and progression (17%) within 1 yr. However, patients with low-grade cTa papillary recurrence 3 mo after induction BCG are at very low risk of progression and may safely continue with bladder-sparing therapy. These factors must be considered while designing clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take Home Message

Low-grade clinical Ta papillary recurrence following induction bacillus Calmette-Guérin therapy can be safely managed conservatively, although a high-grade clinical Ta recurrence should be treated similar to a clinical T1 recurrence due to its comparable progression rates.

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A.

5-yr Bladder Preservation: cTa = 65%; cT1 = 76%; p = .767

Number at Risk

Time (months)	0	24	48	72	96	120	144	168	192
cTa	47	32	25	16	12	6	3	1	0
cT1	13	9	6	5	3	0	0	0	0

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

B.

5-yr PFS: cTa = 77%; cT1 = 83%; p = .624

Number at Risk

Time (months)	0	24	48	72	96	120	144	168	192
cTa	47	36	28	20	18	10	6	2	0
cT1	13	12	10	6	3	0	0	0	0

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

C.

5-yr DSS: cTa = 95%; cT1 = 93%; $p = .762$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168	192
cTa	53	52	43	31	24	14	7	6	1
cT1	18	17	12	11	7	1	0	0	0

^aIncludes patients treated with bladder-sparing therapy and immediate radical cystectomy at 3 month recurrence

Figure 1.

Oncologic outcomes for 3-month high-grade papillary recurrence (cTa vs. cT1). (a.) Time to radical cystectomy.* (b.) Progression-free survival (PFS).* (c.) Disease-specific survival (DSS).

A.

5-yr % Bladder Preservation; cTa = 84%; cT1 = 61%; $p = .041$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168
cTa	24	21	15	11	10	5	3	1
cT1	36	23	18	7	4	2	1	0

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

B.

5-yr PFS; cTa = 88%; cT1 = 75%; $p = .308$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168
cTa	26	22	17	12	11	6	3	1
cT1	33	25	19	10	9	5	4	2

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

C.

5-yr DSS; cTa = 92%; cT1 = 100%; p = .925

Number at Risk

Time (months)	0	24	48	72	96	120	144	168
cTa	28	27	22	17	13	7	3	3
cT1	38	37	31	17	13	8	5	4

Figure 2.

Three month cTa oncologic outcomes by initial clinical Stage. (a.) Time to radical cystectomy.* (b.) Progression free survival (PFS).* (c.) Disease specific survival.

A.

5-yr Bladder Preservation; Low grade = 100%; High grade = 65%; $p = .030$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168	192
Low grade	12	11	8	2	2	1	1	1	0
High grade	47	32	25	16	12	6	3	1	0

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

B.

5-yr PFS; Low grade = 100%; High grade = 77%; $p = .094$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168	192
Low grade	12	11	8	2	2	1	1	1	0
High grade	47	35	28	20	18	10	6	2	0

* Excludes patients treated with immediate radical cystectomy following 3 month recurrence.

C.

5-yr DSS; Low grade = 100%; High grade = 95%; $p = .361$

Number at Risk

Time (months)	0	24	48	72	96	120	144	168
Low grade	13	12	10	3	2	1	1	1
High grade	53	51	43	31	24	14	7	6

Figure 3. Three month cTa oncologic outcomes by recurrence grade

(a.) Time to radical cystectomy.* (b.) Progression free survival (PFS).* (c.) Disease specific survival.

Table 1

Patient Characteristics for cTa and cT1 papillary recurrence. (a) Demographic variables (b) Recurrence characteristics and treatments

A.			
Variable			
	cTa	cT1	p-value
No. patients (%)	66 (79)	18 (21)	
Male (%)	52 (78.8)	14 (77.8)	1.000
Median age, (range), years	67 (29 – 92)	68 (36 – 75)	.597
Median follow up, (range), months	71.1 (8.1 – 194)	93.6 (22 – 139)	.485
Initial Clinical stage, (%)			.593
cTa	27 (40.9)	6 (33.3)	
cT1	39 (59.1)	12 (66.7)	
Initial Clinical high grade disease, (%)	57 (86.4)	18 (100)	.194
Initial Concomitant carcinoma in-situ, (%)	11 (16.7)	7 (38.9)	.055
Multiple initial tumors, (%)	35 (53.0)	13 (72.2)	.184

B.			
Variable			
	cTa	cT1	p-value
Median time to recurrence after induction BCG, (range), days	119 (54 – 238)	123 (76 – 182)	.831
Complication/or delay in Induction BCG, (%)	12 (18.2)	3 (16.7)	1.000
Clinical high-grade recurrence, (%)	53 (80.3)	18 (100)	.061
Recurrence Concomitant carcinoma in-situ, (%)	9 (13.6)	10 (55.6)	< 0.001
Treatment after 3-month recurrence, (%)			n/a
Surveillance	2 (3.0)	0 (0)	
Repeat Induction BCG	12 (18.2)	2 (11.1)	
BCG + INF induction + Maintenance	8 (12.1)	10 (55.6)	
BCG + INF Maintenance	6 (9.1)	0 (0)	
BCG Maintenance	28 (42.4)	1 (5.6)	
Mitomycin C	4 (6.1)	0 (0)	
Radical Cystectomy	6 (9.1)	5 (27.8)	
*Recurrence 1-year after BCG failure, (%)	33 (55.0)	4 (30.8)	.136
*Delayed Radical Cystectomy, (%)	17 (25.8)	3 (23.1)	1.000
*Mean TURBTs after 3-month recurrence, (STD)	2.0 (1.7)	0.8 (.9)	.017
*Mean recurrences since initial 3-month recurrence, (STD)	1.4 (1.5)	0.5 (.7)	.032

* Excludes patients treated with immediate radical cystectomy [Bacillus Calmette Guerin (BCG), Interferon- α (INF), Transurethral resection of bladder tumor (TURBT), Standard deviation (STD)]