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Intravesical BCG: Current Results, Natural History and Implications for Urothelial Cancer Prevention

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Abstract Bacillus Calmette-Guerin (BCG) has been shown in randomized trials to be the most effective agent against superficial bladder tumors. BCG therapy prevents or reduces tumor recurrences, abrogates tumor progression and improves survival over surgery alone. The optimal BCG schedule varies among patients, reflecting a heterogeneous tumor population. Multifocality, high grade (G2,3) and T1 tumors are risk factors for tumor recurrence or invasion. Patients presenting with such features are most likely to benefit from BCG. An incomplete response to BCG portends a high risk of tumor progression. Non-responders have a 40–60% risk of developing muscle invasion or metastases within 10 years, compared with 10–15% for BCG responders. Further, 80% of non-responders progress in the bladder within 3–5 years. After 5 years, relapses are more common in the prostate (13–35%) and upper collecting system (15–33%); one-half of these are invasive tumors. This suggests that intense therapy directed at premalignant and early bladder lesions coupled with a chemoprevention strategy designed to protect the whole urothelium will be required to reverse a panurothelial tumor diathesis.

Key words: BCG, carcinoma *in situ*, chemoprevention, intravesical therapy, superficial bladder tumors, urothelial neoplasia

The majority of urothelial neoplasms display field cancerization, forming multiple primary tumors at different times and at different sites within the urinary tract. Most initial tumors are superficial, but up to one-third of recurrent tumors become invasive cancers. Urothelial neoplasms most commonly originate in the bladder.

Intravesical Bacillus Calmette-Guerin (BCG) is currently the most active agent against superficial bladder tumors [1]. BCG is used prophylactically against new tumor occurrences and therapeutically for carcinoma *in situ* (CIS). The aim of BCG therapy is to prevent bladder tumor recurrence and progression to muscle invasion or metastasis.

Superficial bladder tumors provide an optimal target for intravesical therapy since they are localized, low volume and occur in immune-competent patients. Further, the entire mucosa including premalignant or early malignant neoplasms is exposed directly to high concentrations of BCG organisms.

The present report details current results achieved with BCG therapy. Long-term follow-up of BCG-treated versus untreated patients provides valuable insight into the natural history of superficial bladder tumors and has implications for future therapeutic strategies and prevention of urothelial cancers.

INDICATIONS FOR BCG

Superficial bladder tumors constitute a spectrum of neoplasms with different biologic potential for recurrence and progression (Table I). Primary tumors are recognized as papillary or flat CIS. Papillary tumors are further characterized as noninvasive (papilloma, Ta carcinoma) or superficially invasive (T1) tumors; low (G1) or high (G2,3) grade; and single or multiple. CIS is a high grade lesion that may be focal or diffuse and is usually associated with multicentric papillary tumors.

Individual tumors are uncommon and most are mixed in space and time (polychronotropism). In a mixed tumor population there are conservatively over 400 possible combinations of tumor types, grades, and extent of mucosal involvement. Since tumors differ in their potential for invasiveness and are unlikely to be phenotypically identical, an agent active against a variety of tumor types might be more effective in the population at risk than would specific

TABLE I. Superficial Bladder Tumors

Tumor Type	Grade	No. of Tumors	CIS
Papilloma	Benign	1 or ≥2	+ or –
Ta	Low or high	1 or ≥2	+ or –
T1	Low or high	1 or ≥2	+ or –
CIS	High	Focal or diffuse	

TABLE II. Multivariate Analysis for Recurrence and Progression of Superficial Bladder Tumors

		Tumor Characteristics			
Author	No. of Pts.	Stage (Ta vs. T1)	Grade (G1 vs. G2,3)	Multi-focality (CIS)	Other
Recurrence					
Kurth [2]	240	0.006	0.064	0.016	
Dalesio [3]	308	NS	0.03	0.001	Rec. Rate
Herr [4]	228	NS	NS	0.01	
Invasion					
Torti [5]	252	NS	0.009	NS	
Herr [6]	221	0.03	0.06	NS	Duration <1 Yr.
Kalish [7]	249	0.01	0.07	--	

TABLE III. BCG vs. Surgery-Prophylaxis

		No. of Tumor-Free Pts.		
Author	No. of Pts.	BCG	TUR[a]	Follow-up (Months)
Herr [8]	86	27/43 (63%)	2/43 (5%)	60
Lamm [9]	57	24/30 (80%)	13/27 (48%)	60
Pagano [10]	133	52/70 (74%)	11/63 (17%)	12
Rubben [11]	67	24/27 (89%)	24/40 (60%)	18
Melekos [12]	94	42/62 (68%)	13/32 (41%)	24
Totals	437	169/242 (70%)	63/205 (31%)	

[a] Transurethral resection

tumor-targeted therapy in individual patients. BCG is a nonspecific biologic response modifier that partially fulfills this promise.

Patients with superficial bladder tumors can be considered as low or high risk for recurrence and progression. Table II [2–7] shows results of multivariate analyses indicating that multifocality is the most significant prognostic variable for superficial recurrences, whereas T1 tumor stage and high grade are more significant predictors of invasion.

Patients at risk for progression are most likely to benefit from intravesical therapy. These include multifocal TaG2–3 tumors, T1G1–2 tumors associated with CIS, T1G3 tumors with or without CIS and multifocal (≥ 3 lesions), diffuse (25% or more bladder mucosa involved) or symptomatic (dysuria) CIS, with or without prior or concomitant papillary tumors. Patients who do not need BCG are those with a solitary Ta, T1 tumor and papillary tumors of low (G1) grade; such tumors have a low risk of recurrence and a negligible risk for progression.

A single six week induction course of BCG suffices to eradicate disease in 40–60% of patients but another 20–30% may benefit from periodic retreatment regimens to prevent recurrent papillary tumors and to control CIS.

BCG PROPHYLAXIS

Table III shows the results of BCG prophylaxis in randomized clinical trials [8–12]. BCG significantly ($p = 0.001$) reduces tumor recurrences and prolongs the tumor-free interval over surgery [transurethral resection (TUR)] alone. Such data also show that surgery to remove the primary and recurrent tumor(s) contributes less to long-term cure rates than does adjuvant topical therapy directed to the remaining bladder mucosa at risk for new tumor development.

TABLE IV. BCG Therapy—Carcinoma *in Situ* (Tis)†

Series	No. of Pts.	Complete Response
Herr (1983)	23	17 (74%)
Morales (1984)*	26	20 (77%)
Lamm (1985)	43	35 (81%)
Brosman (1984)	33	31 (94%)
DeKernion (1985)	19	15 (79%)
Herr (1986)*	47	34 (72%)
Schellhammer (1986)	28	20 (71%)
Catalona (1986)	19	13 (68%)
Badalament (1987)	33	22 (67%)
Herr (1989)*	111	76 (68%)
Lamm (1989)	52	37 (71%)
Reitsma (1989)	119	78 (66%)
Brosman (1989)	48	34 (71%)
Steg (1989)	54	43 (80%)
Dejager (1990)*	123	90 (73%)
Totals	676	488 (72%)

† For additional or complete references, see [13].
* Disease-free interval >5 years

BCG THERAPY

Table IV shows the therapeutic effect of BCG against CIS [13]. Collectively, a complete response (negative biopsy and urine cytology) is achieved in 72% of patients. Moreover, this response rate has been maintained during the 10 years that BCG has been used to treat CIS; many favorable responses have been sustained beyond 5 years.

EFFECT OF BCG ON TUMOR PROGRESSION

We recently reported on the long-term follow-up of patients entered into our first randomized BCG protocol determining the effect of BCG on disease progression [14]. Three parameters were selected for this analysis: (1) local progression, defined as recurrent or persistent superficial disease involving bladder or prostate which necessitated therapy in addition to repeat TUR (*i.e.*, cystectomy, repeat or alternative intravesical therapy); (2) development of pathologically confirmed muscle invasion and/or metastatic disease; and (3) disease-specific survival.

Progression, either local, muscle invasive or metastatic, occurred in 95% (41/43) of the control and 53% (23/43) of the BCG patients, with median progression-free intervals of 12 and 60 months, respectively (Fig. 1).

Local bladder progression or prostatic involvement was seen in 11 patients after BCG as compared with 21 after TUR. Of 32 total patients who developed muscle invasion, 12 had BCG and 20 were controls. The median time to invasion, 48 months after TUR, was not reached in the BCG group (Fig. 2). Cystectomy was ultimately required in 18 (42%) control patients (12 because of muscle invasion) and 11 (26%) BCG-treated patients (6 for muscle invasion). The median time to operation was 8 months for controls and 24 months for the BCG patients. Disease-specific survival was improved by BCG therapy as compared to the control group (86% vs. 60%). Cancer deaths occurred in 5 patients after BCG compared with 14 of the TUR group (Fig. 3). This study

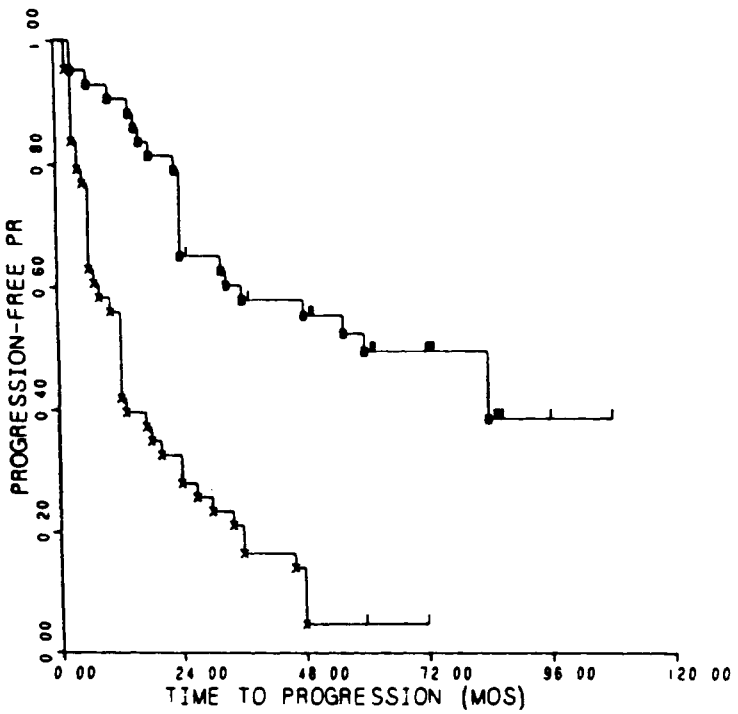

Fig. 1. Overall progression (local/invasive/metastatic) following transurethral resection, BCG ("O" 43 patients, 20 censored) versus control ("×" 43 patients, 2 censored), p = 0.00001. Tick mark indicates last follow-up.

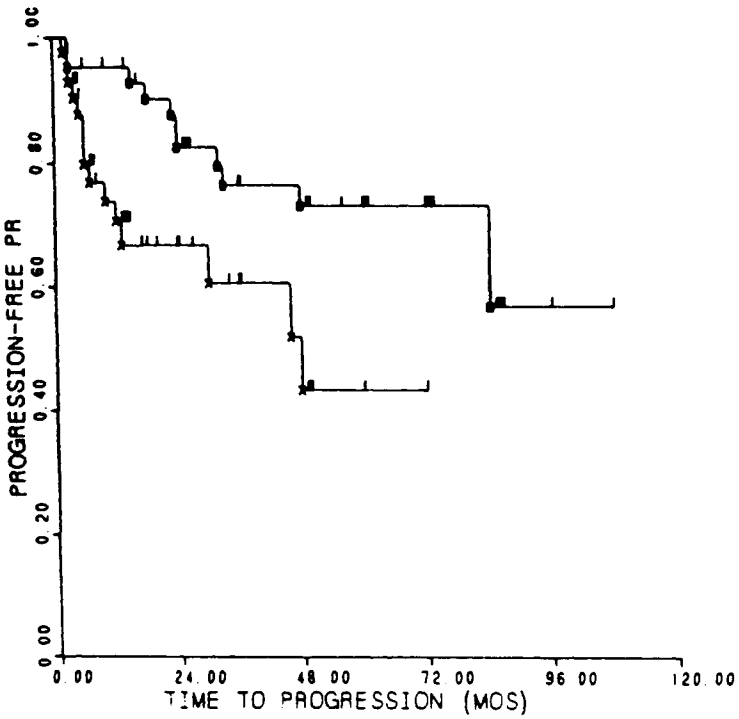

Fig. 2. Time to invasive and/or metastatic progression following transurethral resection, BCG ("O" 43 patients, 31 censored) versus control ("×" 43 patients, 28 censored), p = 0.012. Tick mark indicates last follow-up.

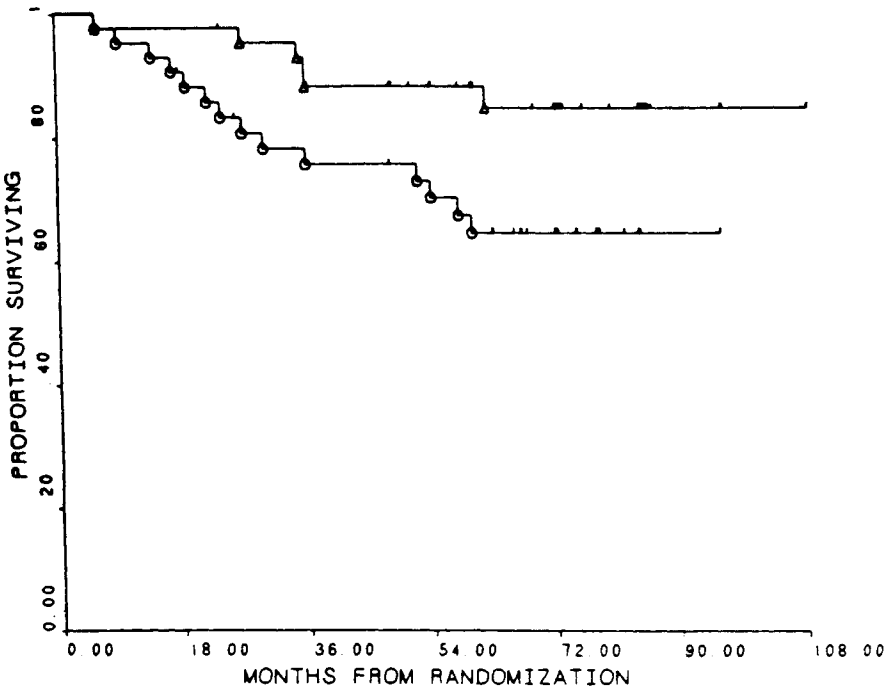

Fig. 3. Survival based on initial treatment, BCG ("Δ" 43 patients, 38 censored) versus control ("O" 43 patients, 29 censored), p = 0.032. Tick mark indicates last follow-up.

TABLE V. Multivariate Analysis of Risk Factors for Tumor Progression Before and After Intravesical BCG (n = 221)

Prognostic Variable	p-Value		
	Before BCG	3 Months	6 Months
CIS	0.26	0.0003	<0.0001
Multifocality	0.96	0.002	<0.0001
T1	0.03	0.0001	0.002

TABLE VI. Carcinoma *in Situ* Risk of Progression by Response to BCG

Response	No. of Pts.	Type of Progression	Probability of Progression (%)		
			1 Year	3 Years	5 Years
Complete	105	Overall	2	11	19
		Local	1	7	11
		T2+	1	3	7
		Mets	0	1	1
Incomplete	75	Overall	23	60	95
		Local	20	43	65
		T2+	3	15	25
		Mets	0	2	5

TABLE VII. Outcome of BCG-Treated Patients Followed for 10 Years (n = 61)

Site of Relapse	No. of Pts.	Time of Relapse	
		0–5 Years	5–10 Years
None	19 (31%)	--	--
Bladder			
Superficial	17 (28%)	15 (8)*	9 (4)
Invasive T2+	12 (20%)	10	2
Extravesical			
Prostate	8 (13%)	3	5
UTI	14 (23%)	3	11
M+	5 (8%)	5	0

* Ave. no. of tumors per patient

showed that BCG can prevent or delay progression, preserve bladders and increase overall survival.

Lamm *et al.* [15] have recently reported the results of 391 patients with superficial bladder cancers randomized to intravesical BCG induction therapy only or retreatment with BCG over 3 years. This study confirmed that BCG improved ($p = 0.04$) patient survival.

NATURAL HISTORY OF BCG-TREATED PATIENTS

We did a multivariate analysis of prognostic variables for tumor progression in 221 patients treated with intravesical BCG and followed for 5 years [6]. T1 tumor category was the only significant adverse variable predictive of progression before BCG therapy, whereas nonresponding patients (3 and 6 months after BCG) with residual or persistent multifocal papillary tumors and CIS were at increased risk for stage progression (Table V). Recurrent T1 tumors have the highest risk (57%) of developing muscle invasion [16]. Table VI shows the nature of progression among patients with CIS relative to their BCG response. Most incomplete responders progressed to uncontrolled local disease, but 30% developed muscle invasion or metastases within 5 years.

We have now followed 61 of these patients for more than 10 years [17] (Table VII). After BCG therapy for superficial bladder tumors, relapses within 5 years were more common in the bladder; urothelial tumors that recur after 5 years usually involve either prostatic or upper tract uroepithelium. Further, one-half of these tumors (4 of 8 in the prostate and 7 of 14 in the upper collecting system) were invasive. In the entire series of 221 patients, 34 (15%) have developed upper urinary tract tumors, with 19 (56%) of these involving the distal ureter and the remaining 15 (44%) within the renal pelvis. The frequency of supravesical urothelial tumor is projected to increase with longer follow-up. The incidence of upper tract relapse is independent of bladder recurrence, primary bladder stage, grade, prior tumor recurrence rate, duration of bladder disease and presence of CIS. Of the 160 patients who have not developed upper tract tumors, 85% are alive >5 years later compared with 22 (65%) who have panurothelial disease.

IMPLICATIONS FOR FUTURE STRATEGY

The results with intravesical BCG show that clonal evolution of intraepithelial neoplasms occurs increasingly over time throughout the urinary tract. Transitional cell carcinomas are commonly recognized initially in the bladder, but subsequent risk of recurrence or progression appears to diminish within the bladder over time in treated patients. This exposes the extravesical urothelium as a potential site for clinical disease owing to the emergence of dormant cells unexposed to topical BCG. Whether the apparent decreasing risk of bladder tumors over time is the result of BCG therapy (protected bladder mucosa) or of the natural history of the disease will require additional patients, longer follow-up and better understanding of the local antitumor effect of BCG.

In designing future therapeutic strategies, a combination of intense therapy directed to the bladder early in the course of tumor evolution, coupled with a systemic chemoprevention strategy designed to protect the urothelium as a whole, will be required to prevent a panurothelial tumor diathesis.

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