A STUDY OF SIDE EFFECTS & TOLERABILITY OF INTRAVESICAL 'BCG' IN SUPERFICIAL BLADDER CANCER

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CERTIFICATE

I hereby certify that this dissertation "**A Study Of Side Effects & Tolerability Of Intravesical 'BCG' In Superficial Bladder Cancer"** is the bonafide work done by **SUMIT GOYAL** who is appearing for **DM Medical Oncology Branch** examination in February 2008, under my guidance and to my satisfaction, in the College of Oncological Sciences, Cancer Institute (WIA), Adyar, Chennai.

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CONTENTS

AIMS AND OBJECTIVES

1. To study the side effects & complications following intravesical instillation of *BCG.*
2. To study the tolerability following administration of intravesical *BCG*.

MATERIALS AND METHODS

Patients

The patients of suspected ca bladder coming to our institute from March 2005 to September 2007 were evaluated. Thorough history and physical examination was done & also detailed history about addictions and co morbidities was taken.

All patients underwent complete transurethral resection of the tumor (in one or more acts), which established the tumor size, histological type, grade, stage, and absence of muscle invasion. Patients who had histologically proven superficial transitional cell carcinoma stage Ta and T1 and were eligible for intravesical BCG instillation treatment.

Tumors were staged according to the TNM classification of The Union Internationale Contre le Cancer and tumor grade by WHO grading was done. Intravesical BCG instillations were offered to all willing patients.

Methods

The protocol of immunoprophylaxis with BCG consisted of 6 weekly + 6 monthly instillations. Instillations began 2-3 weeks after transurethral resection and after obtaining

histological documentation of papillary transitional cell carcinoma for each patient. Before proceeding with instillation all patients were examined and symptoms were noted for any adverse effects and also urine routine testing was done& therapy delivered only if patient found to be fit for the therapy..

Therapy consisted of bladder instillations of 120 mg of "1331 strain" of BCG ('UROVAC' manufactured by Govt of India, Chennai), suspended in 100 mL of saline.

Instillations were performed after the bladder was catheterized and completely drained. We ensured not to insert any air or cause trauma or bleeding during catheterization.

The patients were instructed to lie down for 2 h and change position every 15 min to allow maximal contact of the suspension with the bladder mucosa. Patients were instructed to hold the urine for as long as longer minimum 2 hours.

Following instillation patients were instructed to report any side effects or any untoward adverse reactions immediately. Patients presenting were evaluated and managed as per the requirements.

Follow-up consisted of cystoscopic examinations every 3 months, urine cytology, and mucosal biopsies of all overt or suspicious areas in the bladder in the first year and at the 6-month intervals in the second year and later.

INTRODUCTION

The Ca Bladder is one of the important tumors of the genitourinary cancers and usually affects the people all around the globe. Broadly urinary bladder cancers can be divided into superficial, muscle invasive and metastatic cancers. Of which superficial cancers constitute the majority of cases. Superficial bladder cancers are the tumors confined to the mucosa and submucosa (Ta, Tis & T1). This is a heterogeneous disease with variable natural history.

At one end of the spectrum are low grade tumors (Ta) with low potential for progression & rarely represent a threat to the patient, while at the other end are the high grade (T1) tumors with high malignant potential with significant progression and death.

Although thorough endoscopic tumor resection remains the principal treatment, intravesical agents have become an important in the subgroup of tumors that are at risk of progression. Intravesical ***Bacillus Calmette-Guerin*****,** is effective treatment in preventing recurrences & delaying progression in superficial bladder cancer. It has been in use since the 1980's, and is the most proven and effective form of immunotherapy. Though therapy with BCG is generally safe, it is not completely, without side effects.

This study was done to know the various side effects, outcomes and tolerability of the therapy.

REVIEW OF LITERATURE

TCC of the bladder can be divided into 2 categories: superficial tumors and muscle-invasive tumors. Superficial TCC tumors are those that have not invaded the muscularis propria, regardless of grade. They include papillary lesions confined to the urothelium that do not penetrate the basement membrane (Ta), tumors with invasion into the lamina propria (T1), and carcinoma in situ (CIS). At the time of diagnosis, 64% to 80% of cases are superficial; of those, 70% are stage Ta and 30% are stage T1.[1] Despite complete resection, recurrence rates are 66% at 5 years and 88% at 15 years.[2] Progression from superficial bladder cancer to deep muscle invasion occurs in 15% of patients.[3]

EPIDEMIOLOGY

Approximately 80 percent of cases of bladder cancer are diagnosed in people over the age of 60.

Globally, the incidence of bladder cancer varies approximately 10-fold, with Western Europe and North America having the highest and Eastern Europe and Asian countries the lowest rates.[4] In some high incidence regions, bladder cancer is associated with specific disease states or toxin exposures (Balkan countries, Taiwan)

In United States, Cancer of the urinary bladder is the fourth most common cancer in men and the ninth in women & it is the second most prevalent cancer in men 60 years of age or older. In the United States in 2007 an estimated 67,160 new cases of bladder cancer are expected to be diagnosed (approximately 50,040 men and 17,120 women), with an overall lifetime risk of developing bladder cancer of approximately 1 in 28.[5, 6]

South East Asia No uniform data exists however in Southeast Asia; the incidence in 2002 was 2.7 per 100,000 in males and 0.8 per 100,000 in females, making it the ninth most common cancer in men.[7]

In India and in MMTR (Madras Metropolitan registry) In India the reported incidence of Ca bladder is 1.71 per 100, 000 population. In Chennai MMTR the overall incidence is 1.85 per 100,000 population.[8]

Gender – Male to female ratios are 3 to 4:1 in the United States as a whole, 7:1 in Italy, and 10:1 among American Indians.[9, 10] In India the incidence in males being 2.72 and females as 0.7 per 100,000 population. While in Chennai MMTR it is 2.9 & 0.8 in males and females respectively.[8]

Racial and ethnic variations Non-Hispanic white males are at highest risk, while the observed incidence in African-Americans and Latinos is approximately one-half of that number. [11, 12] Bladder cancer rates in Asian populations in the United States, including Chinese and Japanese-Americans, are about 40 percent those of non-Hispanic whites, while incidence rates for American Indians are about one-eighth that numbers. A possible explanation for these disparities is variations in acetylator phenotypes in different racial/ethnic groups [12]

ETIOLOGY AND RISK FACTORS

Many of the aetiological factors for the development of bladder tumours are known. Environmental exposures are thought to account for most cases of bladder cancer and occupational exposures remain a significant risk factor for bladder cancer.

The characteristic feature of urothelial carcinomas of both the urinary bladder and the upper urinary tract is multifocality ("*field cancerization*" hypothesis").[13]

However, in the majority of cases, multifocal urothelial carcinomas are monoclonal. This supports their presumed origin from a single genetically altered cell, which then spreads through the urothelium via intraluminal seeding or intraepithelial migration.[14, 15] This is referred to as the *monoclonality hypothesis.*

Chemical carcinogens —

Aromatic amines, aniline-containing dyes and arylamines, such as 2-naphthylamine, benzidine and 4-aminobiphenyl rubber, amides and azodyes have been implicated as bladder carcinogens.[16]

Occupational and environmental exposures — aluminum, dye, paint, petroleum, rubber, and textile industries are estimated to account for up to 20 percent of all bladder cancer cases.[17, 18] Other occupations at an excess risk has been described in hairdressers and barbers,

which is thought related to exposure to hair dyes.[19, 20]

Cigarette smoking —The association between cigarette smoking and bladder cancer was first established in 1956[21], and multiple studies have demonstrated a two to threefold increased risk in smokers compared to nonsmokers.[22, 23, 24]

Drinking water — the by-products of water chlorination and the concentration of arsenic in drinking water have been associated with an elevated risk of bladder cancer. Arsenic, both ingestion and inhalation of arsenic have been linked to the development of lung, skin, and bladder cancers.[25, 26]

Fluid consumption — is inversely associated with urothelial exposure to potential carcinogens.[27]

Analgesic abuse — particularly phenacetin has been linked to chronic kidney disease and cancers of the kidney, renal pelvis and bladder.[28]

Artificial sweeteners — (e.g., saccharin, cyclamates) At least 13 case-control studies have failed to convincingly demonstrate an increased risk of bladder cancer in people exposed to saccharin or cyclamates.[29] However, subgroup analysis in some reports suggests an increased risk of bladder cancer formation in non-smoking women, a group with an overall low risk for this disease.

Coffee consumption — the results of epidemiologic studies have been inconsistent, and those that do show a weak association probably reflects the confounding influence of smoking.[30] Although the best available data do not support a clinically important association between the regular use of coffee and bladder cancer, the consumption of ten or more cups per day is suspected to be associated with a slightly increased risk, independent of the influence of smoking [71]

Genetic factors — the Swedish Cancer Registry identified families with a parental-offspring bladder cancer concordant history. These families exhibited a high sibling to offspring risk and a greater prevalence within female offspring, suggesting the possibility of an X chromosome-linked gene defect.[32]

A study from MD Anderson evaluated the impact of smoking and bladder cancer development among individuals with a familial history of bladder cancer. A five fold increased risk of developing bladder cancer was observed among those individuals with both a family history of bladder cancer and a prior history of smoking. This risk increased to nearly sevenfold when the family member was diagnosed with bladder cancer at younger than 65 years of age. [33]

Chronic cystitis — Individuals with recurrent or chronic bladder infections and those who have an ongoing source of bladder inflammation (eg, prolonged indwelling catheters, bladder calculi, gonorrhea) have a higher risk of bladder cancer compared to the general population.[34, 35] The frequency of SCC as opposed to TCC is higher in this setting.

Schistosomiasis — Infection with S. haematobium, also known as bilharzial bladder

disease, has been linked to hyperplasia, metaplasia, dysplasia and overt invasive carcinoma in the bladder.[36]

Treatment-related carcinogenesis

Radiation — an increased risk for developing secondary bladder cancer has been associated with pelvic radiation for cervical, ovarian, and prostate cancers.[37-40] The relative risk ranges from 1.5- to fourfold, and is proportional to dose. Radiation-related bladder cancer has a relatively short latency period (five to ten years), and is characteristically high-grade and muscle-invasive at diagnosis.[41-43]

Chemotherapy — Patients treated with cyclophosphamide as an antitumor or immunosuppressive agent have up to a nine-fold increased risk of bladder cancer, and the latency period is generally short (less than 10 years). [44 - 47]

PATHOLOGY AND GRADING OF TUMORS

The cells comprising the lining of the urinary tract are transitional cells. The most common histology is

- Transitional cell cancers (TCCs), > 90%
- Squamous cell cancers (SCCs), 3 to 5%
- Adenocarcinomas, 0.5 to 2 %
- Small cell carcinomas, <1%

HISTOLOGIC GRADE — Bladder tumors are now classified as either low or high grade. This replaces the previous system of classification in which tumors were designated as low (G1), intermediate (G2), or high (G3) grade. The histologic grade varies in noninvasive tumors, while almost all invasive neoplasms (tumor stage T1) are high grade. The histologic grade is based upon the degree of resemblance to the normal tissue architecture. The normal urothelium has a thickness of less than five to seven cell layers, normal polarity of nuclei, and no pleomorphism.

WHO/ ISUP grading

In 2004, members of the WHO and International Society of Urologic Pathologists published and recommended a revised consensus classification for papillary neoplasms.[48] A new category of papillary urothelial neoplasm of low malignant potential was created to describe lesions with an increased number of urothelial layers when compared with papilloma but without cytologic features of malignancy.[48] Although they have a negligible risk for progression, they are not completely benign and still have a tendency to recur.

WHO/ International Society of Urologic Pathologists2004:

Classification of Nonmuscle Invasive Urothelial Neoplasia[48]

Hyperplasia (flat and papillary)

Reactive atypia

Atypia of unknown significance

Urothelial dysplasia

Urothelial carcinoma in situ

Urothelial papilloma

Papillary urothelial neoplasm of low malignant potential

Nonmuscle invasive low-grade papillary urothelial carcinoma

Nonmuscle invasive high-grade papillary urothelial carcinoma

CLINICAL PRESENTATION —

The diagnosis of bladder cancer is often delayed due to the similarity of symptoms to those of benign disorders (eg, urinary tract infection, interstitial cystitis, prostatitis, and the passage of renal calculi). Furthermore, symptoms are often intermittent. The symptoms also depends on the occurrence of the three clinical presentations of bladder cancer (ie, superficial, invasive, and metastatic).

Hematuria — The most common presenting symptom is hematuria, which is typically intermittent, gross, painless, and present throughout micturition.

The degree of blood in the urine is not predictive of the probability of cancer. The prevalence of asymptomatic hematuria in the general population is estimated at 2.5 percent.[49] Microscopic hematuria is present in up to one-fifth of the general population and predominant cause is usually benign. In one population-based study, asymptomatic microscopic hematuria was present in 13 percent of the population, but attributed to urothelial cancer in only 0.4 percent.[50]

Pain — Pain usually indicates locally advanced or metastatic tumor. Its distribution is

related to the size and location of the primary tumor or its metastases. Flank pain may result when a tumor obstructs the ureter at any level (bladder, ureter or renal pelvis). Although usually a sign of a muscle-invasive disease, large superficial tumors located at the ureteral orifice may also cause symptomatic obstruction. The pain is similar to that experienced with the passage of urinary stones, and may or may not be associated with hematuria. Suprapubic pain is usually a sign of a locally advanced tumor that is either directly invading the perivesical soft tissues and nerves, or obstructing the bladder outlet and causing urinary retention. Hypogastric and perineal pain are ominous signs of advanced disease invading the obturator fossa, presacral nerves, or the urogenital diaphragm. Bone pain may indicate the presence of metastases.

Voiding symptoms — Irritative voiding symptoms (e.g., daytime and/or nocturnal frequency, urgency, dysuria, or urge incontinence) occur in approximately one-third of patients with bladder cancer. Voiding symptoms are most common in patients with carcinoma in situ, and may result from a functional decrease in the bladder capacity, detrusor overactivity, invasion of the trigone, or obstruction of the bladder neck or urethra. In particular, the complex of dysuria, frequency, and urgency is highly suggestive of bladder CIS. Obstructive voiding symptoms are less common, and may be due to tumor location at the bladder neck or prostatic urethra. Symptoms include straining, an intermittent stream, nocturia, decreased force of stream, and a feeling of incomplete voiding. On occasion, gross hematuria may result in "clot retention".

Constitutional symptoms — Symptoms such as fatigue, weight loss, anorexia, and failure to thrive are usually signs of advanced or metastatic disease and denote a poor

prognosis.

DIAGNOSTIC APPROACH

The goal of the diagnostic evaluation is to determine the diagnosis, site, and extent of cancer, and the presence or absence of muscle-invasive disease.

The presence of otherwise unexplained hematuria denotes an urothelial cancer in individuals over the age of 40 until proven otherwise and requires a full urologic evaluation of the entire urinary tract.

Recommendations for assessment of TaT1 bladder tumours (EAU, 2006)[51]:

The European Association of Urology recommends the following investigations for assessment of superficial bladder cancers.

- Urine analysis (microscopic and gross examination)
- Urine cytology
- Renal and bladder USG and/or IVU in selected cases (grade 3 tumours)
- Cystoscopy with description of the tumour: site, appearance
- TUR in one piece for small tumours, including a part from the underlying bladder wall
- TUR in fractions (including muscle tissue) for larger tumours
- Selected biopsies of abnormal-looking urothelium

- Biopsy of the prostatic urethra in case of bladder neck tumour, or suspicion of CIS.

Urine analysis –

Urine color can be affected by its concentration, ingestion of certain foods or drugs, and the presence of bacteria.

Urinary pigments that can mimic hematuria include

- Betalaine contained in beets (beeturia)
- Phenazopyridine, a urinary analgesic
- Vegetable dyes
- Urates
- Myoglobin
- Serratia marcescens
- Phenolphthalein, component of many over-the-counter laxatives

Microhematuria is usually not considered significant unless there are more than 3 RBCs per HPF. RBC morphology may also suggest the etiology of the hematuria; cells of glomerular origin are often dysmorphic or formed in casts, indicating intrinsic renal disease, while isomorphic RBCs are more likely from an extrinsic source such as calculi, tumor, obstruction, or infection.

Urine cytology — the sensitivity of urine cytology is greatest for CIS, about 90 percent. In contrast, sensitivity for upper tract TCC is limited; the reported false negative rate overall is

65 percent, and may be as high as 96 percent for low-grade tumors.[52, 53]

Urine flow cytometry — the role of flow cytometry in screening patients for urothelial malignancies is unclear. Evaluation of abnormal tumor DNA ploidy (aneuploidy) by flow cytometry may be more accurate than cytology for detecting the presence or absence of exfoliated malignant cells. Compared to cytology, which is labor intensive, flow cytometry is an automated screening procedure. One drawback is that a catheterized specimen rather than voided urine is required.

Urine immunocytochemistry and proteomics assays — the limitations of cytology and the invasiveness of cystoscopy for detecting bladder cancer have generated interest in other non-invasive diagnostic tools, such as urine immunocytochemistry (ImmunoCyt test) and proteomics assays for the nuclear matrix protein NMP22 (NMP22 BladderChek test).[54, 55]

These assays are most promising as tools to improve the detection rate for low-grade tumors. Compared to cytology, the ImmunoCyt test appears to be more sensitive for low-grade tumors.[56] Although it is more sensitive for detecting low-grade cancer than urine cytology, the ImmunoCyt test is not sensitive enough to replace cystoscopic examination. Urine cytology is a better test for detecting high-grade disease.

NMP22 proteomics assay — Proteomics refers to the analysis of protein expression in tissues, serum, and other biologic samples in order to identify and/or characterize malignant tumors on the basis of unique protein expression patterns. The NMP BladderChek test is

approved in the United States for diagnosis of bladder cancer.

Other urinary biomarkers - Intense evaluation of multiple other urinary biomarkers including DNA ploidy and qualitative fluorescence image analysis, molecular cytogenetics, telomerase expression, tumor associated intracellular or secreted products, oncogene mutations, micro satellite alterations, and markers of apoptosis is underway.[57-61] Several are approved in the United States (eg, BTA Stat, BTA TRAK, UroVysion tests) for the detection of recurrent bladder tumors, but none is approved for widespread screening, initial diagnosis, or risk assessment[62] None of these tests has shown sufficient diagnostic reliability to eliminate the need for cystoscopy for either primary or recurrent bladder tumors[63]

Radiographic imaging (including the upper tract)

The purpose of the radiographic evaluation is to identify the tumor location, and assess the possibility of multifocal disease.

- USG KUB
- CT scan of abdomen & pelvis
- Intravenous pyelography

Ultrasound — USG is not very useful for the diagnosis or staging of bladder cancer. It

can confirm a soft tissue mass, but usually cannot determine depth of invasion, the presence of extravesical extension, or nodal status. However, it is useful in evaluating the upper tracts for renal parenchymal disease, hydronephrosis, and to differentiate a non-radiopaque stone from a soft tissue mass by differences in echogenicity.[64]

IVP — IVP is more sensitive for detection of small lesions of the ureter or renal pelvis, while CT scan or renal ultrasound (US) are better tests for the evaluation of renal parenchymal disease.

The cystogram phase of the IVP detects 60 to 85 percent of large bladder tumors; however, smaller tumors may be missed. The classic urographic findings of an upper tract TCC is a meniscus-shaped ureteral filling defect known as the "goblet" or "Bergmann" sign, and the "stipple sign" produced by contrast being trapped in the fronds of a papillary tumor.

About 50 percent of patients with a filling defect either in the renal pelvis or ureter will have associated hydronephrosis, hydroureter, or nonvisualization of the kidney secondary to obstruction. Invasive bladder tumors may cause distal ureteral obstruction and secondary hydronephrosis.

CT scan — IVPs are gradually being replaced by helical CT scanning. CT may demonstrate extravesical extension, nodal involvement in the pelvis or retroperitoneum, visceral, pulmonary or osseous metastasis, and upper tract function, tumor involvement, or obstruction. Although CT provides better visualization of tumors than US, it may also miss tumors <1 cm in size, particularly those in the bladder trigone or dome, and cannot differentiate

depth of bladder wall invasion (ie. mucosal versus lamina propria or muscularis propria). [65] Although a thickened bladder wall on CT suggests the presence of muscle invasive disease, tissue is required for diagnosis.

CT is about 80 percent accurate in differentiating locally advanced tumors involving extravesical adipose tissue or surrounding structures from less invasive tumors. It may be difficult to distinguish inflammatory or iatrogenic edematous changes from true extravesical tumor extension if CT is performed after a transurethral resection.

The sensitivity of CT for identification of nodal involvement is relatively low (false negative rate 68 percent, false positive rate 16 percent), and requires a needle or excisional biopsy for confirmation.[65]

Cystoscopy – Cystoscopy forms the mainstay of diagnosis and staging of bladder cancer. The bladder is inspected visually, and a detailed description of the size, number, location, and growth pattern (papillary or solid) of all lesions is recorded. The status of the uninvolved mucosa is also noted.

TURBT – Biopsy specimens are taken from visible tumors, or the tumors are resected transurethrally in stages to determine the histologic subtype and depth of invasion into the submucosa and muscle layers of the bladder. For patients undergoing repeat diagnostic cystoscopy after a prior TURBT, repeat biopsy should be obtained from areas that were previously resected, even if they appear clinically uninvolved, since about one-third of areas

involved with prior superficial disease will be upstaged by the detection of muscle invasive disease.[66]

Completion of the staging workup – Once the diagnosis of cancer is made, other imaging studies may be appropriate to evaluate for extravesical extension and other sites of disease (eg, metastatic lesions). The decision whether or not to perform additional diagnostic studies is based upon the results of the physical and bimanual examination, cystoscopy and the histologic/cytologic evaluation.

Chest X ray — Chest x rays are used as an initial screening tool and for periodic monitoring in patients at risk for pulmonary metastasis, although they are insensitive for lesions <1 cm. Metastatic lesions are typically non-calcified soft tissue densities. If the chest film is suspicious, a chest CT is warranted.

MRI — Magnetic resonance imaging (MRI) is as reliable as CT for staging of invasive or locally advanced disease, and may better evaluate tumors at the base and dome of the bladder. Contrast (gadolinium-enhanced) MRI may be superior to CT particularly in detecting superficial and multiple tumors, extravesical tumor extension, and surrounding organ invasion.[67-69]

Transvesical needle biopsy — CT-guided transabdominal fine needle aspirate biopsy of the bladder wall may be potentially useful for staging, since it permits full thickness transmural evaluation of bladder masses.[70]

Bone scan — Radionuclide bone scans to assess the presence of bone metastasis are recommended only in patients with invasive or locally advanced tumors and either skeletal symptoms or unexplained elevations in serum alkaline phosphatase. Plain radiographs, CT, or MRI of suspicious areas may be necessary to confirm a metastasis. Bone biopsy should be performed to document metastatic disease if necessary

CLINICAL STAGING — The most commonly used staging system is the TNM (tumor, node, metastasis) system, developed from pathologic studies of cystectomy specimens, in which the association between depth of invasion and clinical course was first identified. [71]

2002 TNM classification of urinary bladder cancer[71]

Table 1. TNM classification of bladder tumours

Tumour type	Description
Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*, flat tumour
Ta	Noninvasive primary tumour
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle
T2b	Tumour invades deep muscle
T3	Tumour invades perivesical fat
T3a	Microscopically
T3b	Macroscopically
T4	Tumour invades any of the following: prostate, uterus, vagina, pelvic wall or abdominal wall
T4a	Tumour invades prostate, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
Regional lymph nodes (N)	
Nx	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node measuring ≤ 2 cm in greatest dimension
N2	Metastasis in a single lymph node measuring > 2 cm but not > 5 cm in greatest dimension or multiple lymph nodes, none measuring > 5 cm in greatest dimension
N3	Metastasis in a lymph node measuring > 5 cm in greatest dimension
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M1	No distant metastasis
M2	Distant metastasis

Table 2. Patient risk classification

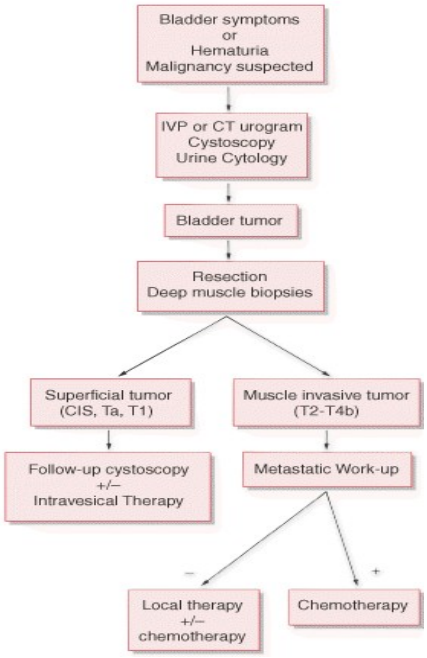
Risk status	Description
Low	Single, Ta, G1, < 3 cm in diameter
High	T1, G3, multifocal or highly recurrent CIS
Intermediate	All other tumours, Ta, Ta-1, G1-2, multifocal, > 3 cm in diameter

G = grade of tumour and refers to the differentiation of the tumour; G1 = tumours that have least degree of anaplasia compatible with the diagnosis of malignancy, i.e. well differentiated; G3 = tumours with the most severe degree of anaplasia, i.e. poorly differentiated; G2 = tumours in between; CIS = carcinoma *in situ*.

MANAGEMENT

For patients with superficial bladder cancer, the initial treatment generally is a complete

transurethral resection of all visible bladder tumors (TURBT) which is followed by adjuvant treatment. The choice between chemotherapy and immunotherapy largely depends on the risk that needs to be reduced, recurrence or progression. Adjuvant chemotherapy bladder instillations are effective in preventing recurrence in low-grade tumours. In high-grade tumours, bacillus Calmette-Guerin (BCG) therapy has proven to be superior to intravesical chemotherapy. A brief overview of treatment plan is as per the algorithm below.



Two meta-analyses demonstrated that BCG therapy prevents, or at least delays, tumour progression[72, 73] (level of evidence: 1a).

History: Development of BCG[74]

In **1904,** Nocard isolated Mycobacterium bovis.

In **1908**, Calmette and Guérin, obtained a special avirulent special M. bovis strain, after 231 subcultures over a period of 13 years, which was named Bacillus of Calmette and Guérin, or BCG. Storage was a problem at that time so it was necessary to subculture, which led to genetic variability and the emergence of various sub strains.

In **1929**, Pearl observed that patients who suffered from tuberculosis had lower frequency of cancer, and BCG as a cancer therapy was first suggested, but it was only in the 1960s that it was taken up.

In **1969**, Mathe et al showed promising results in treating lymphoblastic leukaemia with BCG.

In **1974**, Zbar and Rapp formulated conditions necessary for antitumour effect with BCG:

- Ability to develop an immune response to mycobacteria antigens;
- Adequate number of living bacilli;
- Close contact between BCG and tumour cells;
- The tumour burden must be small.

In **1976**, Morales et al noted that all the conditions were present in superficial bladder cancer and was able to show a decrease in recurrence rate in the nine patients he initially treated. After Lamm et al confirmed these findings in a larger study, BCG has been widely

used in the treatment of superficial bladder cancer.

Indications for Intravesical BCG **Therapy** [51]

The 3 main objectives that guide the use of intravesical therapy of superficial bladder cancer are:

1. to treat existing tumor or carcinoma in situ,
2. to prevent recurrence in a bladder rendered free of tumor, and
3. to prevent progression of disease.

Prior to initiating intravesical therapy, an attempt to minimize the extent of disease by resection and fulguration should be made, since a low tumor burden increases the chances of therapeutic success.

Although BCG is considered to be a very effective treatment, consensus exists that not every patient with superficial bladder cancer should be treated with BCG due to its increased risk of toxicity.

BCG can delay or prevent progression to muscle-invasive disease. The use of BCG will not alter the natural course of the disease in low-risk patients and may be considered to be over-treatment for this category.

Ultimately, the choice of treatment will depend upon the patient's risk of recurrence and progression.

In patients with high-risk tumours for whom a cystectomy is not carried out, no controversy exists about how to treat these patients. In multiple T1G2 tumours, Ta-T1G3 tumours with or without CIS, and CIS alone, where 15% or more of the patients will progress, the advantages of intravesical BCG are more pronounced than in intermediate-risk patients, who are at a lower risk of progression (level of evidence: 1).

The treatment of the remaining intermediate-risk tumours (multifocal T1G1, TaG2 and single T1G2 tumours) is more controversial. It consists of complete TUR followed by intravesical chemotherapy or intravesical BCG. The major issue in intermediate-risk tumours is to prevent recurrence and progression, of which recurrence is by far the most likely. Millan-Rodriguez et al. found that, while tumour will recur in about 45% of these patients, the likelihood of progression to muscle-invasive disease is low in these patients at approximately 1.8%.

Although BCG is superior to chemotherapy in preventing recurrences, controversy existed until recently as to whether BCG could delay or prevent progression to muscle-invasive disease. A meta-analysis carried out by the EORTC has provided a clinically relevant answer to this question (level of evidence: 1). A total of 24 randomized trials were identified with follow-up information on progression for 4,863 patients. A total of 3,967 (81.6%) patients had only papillary tumours and 896 (18.4%) had primary or concomitant CIS.

Five different BCG strains were used, and in 20 out of the 24 trials some form of BCG

maintenance was used. In four trials only, a 6-week induction course was used. Based on a median follow-up of 2.5 years and a maximum of 15 years, 260 out of 2,658 patients (9.8%) on BCG progressed compared to 304 out of 2,205 (13.8%) in the control groups (TUR alone, TUR plus intravesical chemotherapy, or TUR plus another immunotherapy). This result is a reduction of 27% in the risk of progression with BCG treatment (p =0.0001). The size of the reduction is similar in patients with Ta,T1 papillary tumours and in those with CIS.

Mechanism of action[74, 75]

The exact antitumour mechanism of BCG is not clear but it is known that a complex cascade of immuno modulating processes is involved. The importance of an intact immune system in the antitumour activity of BCG was first demonstrated by Ratliff and colleagues.[75] T lymphocytes and cell mediated immunity are important in the immune response to BCG.

After intravesical instillation, live mycobacteria attach to the urothelial lining. This binding is facilitated by fibronectin, which is a component of the extracellular matrix and BCG undergoes endocytosis.

The contact between BCG and the epithelium is important as BCG induced antitumour activity is localized to the site of contact.[76, 77] This process leaves bacterial cell surface glycoprotein attached to the epithelial cell membrane and this interaction of BCG leads to the activation of urothelial and antigen presenting cells (APC). The APC include macrophages, B lymphocytes, dendritic cells and Langerhans cells. The APC process and present antigens

which are then linked to major histocompatibility (MHC) class II molecules for recognition by T helper cells.

Intravesical BCG therapy has been noted to induce local production of various cytokines including interleukin- 1 (IL-1), IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-18, interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α).[52]

These cytokines are known to be involved in the initiation or maintenance of the inflammatory process.[78]

It is thought that the initial production of cytokines, after BCG instillation, is by macrophages and urothelial cells and further production is by activated T cells.[78] The cytokines produced after intravesical BCG have been identified in the urine of patients. The majority of the cytokines produced are mainly the T helper type 1 (TH1) cytokines like IFN-γ, IL-2 and IL-12. It has also been shown that the production of cytokines associated with TH2, like IL-4, are decreased and patients who have a high level of TH2-associated cytokines are more likely to have BCG failure.[79, 80]

A few studies have shown that cytokine levels can be used to predict the long-term response to BCG treatment with higher levels indicating a lower recurrence rate and a longer recurrence-free interval.

The main mechanism by which BCG stimulates the immune system to overcome the

tumour is by playing a role, either directly or indirectly, in the production of effector cells. These include the stimulation of cytotoxic T lymphocytes (CTL), natural killer (NK) cells; lymphokine activated killer (LAK) cells and BCG-activated killer cells (BAK). BAK cells are similar to NK and LAK cells but have some differences, as the effects are believed to last longer than those of the other killer cells.[78] The production of effector cells is stimulated by cytokines. The cytokines, especially IFN-γ, also induce the expression and upregulation of MHC class II and intracellular adhesion molecular 1 by the tumour cells. This helps in the recognition and destruction of the tumour by the effector cells.[77]

The peak immune response is usually noted around 6–24 hours after instillation and there is a cumulative increase in response up to the fifth or sixth cycle. The response slowly continues to wane over a period but the exact duration of response is not clear as cytokine-producing infiltrates have been identified up to 21 months after treatment.[81] This is the rationale for maintenance therapy.

Maintenance therapy is necessary for optimal efficacy

In the EORTC meta-analysis,[51] only patients receiving maintenance BCG benefited. In the four trials where no maintenance was given, no reduction of progression was observed. In the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the risk of progression was observed ($p = 0.00004$). The metaanalysis was unable to determine which BCG maintenance schedule was the most effective. In their metaanalysis, Bohle et al. concluded that at least 1 year of maintenance BCG was required to show the superiority of BCG over mitomycin C in preventing recurrence.

BCG toxicity

Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. Due to the more pronounced side-effects of BCG compared to intravesical chemotherapy, reluctance still exists about BCG use. Early publications reporting deaths due to BCG sepsis and indicating that BCG induced cystitis occurs in up to 90% of patients have strongly compromised the use of BCG.

However, with increased experience in applying BCG, the side-effects now appear to be less prominent and few, if any, deaths due to BCG therapy have been reported in recent literature. Serious side effects are encountered in less than 5% of patients and can be effectively treated in virtually all cases[51, 82] (level of evidence: 2).

The optimal schedule for BCG

Although some modifications have been tried, induction BCG instillations are classically given according to the empirical 6-weekly induction schedule introduced by Morales 30 years ago. Maintenance therapy involves continuous treatment with BCG after successful induction therapy. However, there is no standard maintenance therapy schedule, many different maintenance schedules have been used, ranging from a total of 10 instillations given in 18 weeks, to 30 instillations given over 3 years.[83] The optimal number of induction instillations and the optimal frequency and duration of maintenance instillations remain unknown. The main concern regarding maintenance therapy has been the side effects associated with BCG

The optimal dose of BCG

To reduce BCG toxicity, a number of authors have proposed one-third and one-quarter dose instillations of BCG. Comparing one-third dose to full-dose BCG in 500 patients, the Spanish Oncology Group (CUETO) found no overall difference in efficacy. However, there was a suggestion that a full dose of BCG may be more effective in multifocal disease[84] (level of evidence: 2). Although fewer patients reported toxicity with the reduced dose, the incidence of severe systemic toxicity was similar in the standard and reduced dose groups. Further research is required to determine the optimal dose of BCG, both for induction instillations and for maintenance. Kelley et al measured the CFU in each batch of BCG vials and noted that the batch with 6×10^6 CFU had a higher recurrence rate compared to another batch with 300 billion CFU.

Treatment of failures of instillation therapy

Failure of adjuvant intravesical therapy is poorly defined. While progression to muscle-invasive disease is the trigger for cystectomy in most cases, there are other features that may indicate the failure of intravesical instillations.

The treatment can be considered to fail when

- Higher grade or T category or carcinoma in situ (Tis) appear during therapy.
- If a recurrence (even of the same grade and T category) is present at both 3 months and 6 months, the therapy can also be considered to be a failure because only a few

patients will respond to further intravesical therapy (51) (level of evidence: 3).

- A recurrence at 3 months is not considered to be a failure because additional treatment provokes complete remission in about one-fifth of patients.

Changing from BCG to chemotherapy can give further remissions in selected cases.

The time to response to intravesical therapy is not defined. Although it is known that BCG immunotherapy needs some time to evoke an immune response, it is unknown how long the clinician may wait for a response without jeopardizing the patient. Delaying cystectomy might lead to progression, metastases and death from bladder cancer. Patients with no response to BCG at 6 months after starting BCG should be offered radical cystectomy. Furthermore, the appearance of new superficial tumours every 3 months, the consequent TUR, the ongoing intravesical instillations, etc., may lead to a bladder of such low quality in terms of capacity, urge, pain, etc., that, in selected cases, a patient should undergo a cystectomy.

Follow-up of patients with TaT1 bladder tumours[51]

Recommendations for follow-up cystoscopy

• Patients with low-risk (TaG1) tumours (50% of all patients) should have a cystoscopy at 3 months. If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years

High-risk patients (15% of all patients) should have a cystoscopy at 3 months. If negative, the following cystoscopies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly IVU should be recommended

Patients with intermediate-risk factors (about one-third of all patients) should have an in-between follow-up scheme, adapted according to personal and subjective factors.

Prophylactic treatment

One of the main aims of treating patients with intravesical BCG is to reduce the recurrence and progression rate.

CIS

CIS in the bladder is a high-grade noninvasive disease with a progression rate of more than 50%. The complete response rate to intravesical BCG varies between 60% and 79% based on 41 studies with a total of 1,496 patients.

Lamm et al showed a complete response rate of 70% with a median duration of response of 39 months when BCG was used in the treatment of CIS; 45% of patients were disease free after 5 years and 64% of patients who had a complete response remained disease-free for 5 years or more.

In another South West Oncology Group (SWOG) study, an additional 3-week course of BCG at 3 months resulted in a further 25% increase in the complete response rate at 6 months, and with further maintenance every 6 months for 3 years, there was an estimated 5-year disease-free rate of more than 75%. With these impressive results, BCG has replaced radical cystectomy as the treatment of choice in the management of patients with CIS.

Residual disease

Eradication of residual disease is another indication for using intravesical BCG. This group of patients forms a very small proportion of patients who have BCG treatment and are usually patients who are not fit to undergo endoscopic resection or patients with very extensive Ta or T1 disease. The response rate is usually around 60% to 70%.

BCG vs. intravesical chemotherapy

BCG has been shown to be superior to many of the intravesical chemotherapy agents used. However, very few studies have shown it to be better than mitomycin C (MMC) in terms of recurrence. One of the main reasons for this is that in many of the studies, patients of varying risk groups were analysed together.

In the Cochrane review, when BCG was compared to mitomycin C, it was noted that tumour recurrence was significantly reduced with BCG only in the subgroup of patients at high risk of tumour recurrence. However, there was no difference in terms of disease progression or survival. However, others have shown a survival benefit with BCG treatment.

Herr et al in their review reported that in high risk and recurrent superficial bladder cancer, patients treated with intravesical BCG had superior disease-free survival. Lamm et al also showed that maintenance BCG improved disease-free survival.

SIDE EFFECTS

While generally well-tolerated, both local and systemic infectious complications can arise. The primary side effects of BCG are increased urinary frequency, dysuria, hematuria, and flu-like symptoms. Systemic symptoms can include arthralgia/arthritis, rash, fatigue, fever, and systemic BCG infection.

PATHOGENESIS OF TOXICITIES —

The mechanism by which BCG leads to the development of infectious complications is not adequately understood. Its mechanism of action as an immunotherapeutic agent in cancer is not fully known but recent evidence suggests that elaboration of a particular helper T cell cytokine profile known as the "Th1 response" is an integral part of its mechanism. [85]

Considerable debate exists in the literature about whether infectious complications due to BCG represent a hypersensitivity response or actual ongoing infection. The hypersensitivity hypothesis gained early credence based upon the presence of granulomas and the absence of recoverable organisms.[86, 87] A response to corticosteroids, administered along with antituberculous drugs, has also supported the notion of a hypersensitivity response.

In contrast, other case reports have demonstrated viable organisms in a variety of tissues, including lung, psoas abscess contents, mycotic aneurysm, bone marrow, and vitreous fluid. The fastidious growth nature of BCG in culture and a doubling time of 24 to 48 hours contribute to the difficulty in its isolation. M. bovis has also been demonstrated by PCR in

some cases, although in other reports these studies have been negative.

Both viewpoints about the pathogenesis of complications due to BCG have merit and both probably play a role in the manifestations of disseminated infection. Organisms are most likely to gain access to lymphatics and blood through disruption of uroepithelial cells and, as with other mycobacterial infections, disseminate to a variety of sites. Manifestations at these distant sites may reflect initial dissemination or even reactivation of infection following alteration in the immune status of the host, hypersensitivity responses, or a combination of both.

EPIDEMIOLOGY — severe adverse events due to local instillation of BCG are uncommon. In a retrospective analysis of 2602 patients reported in 1989, the overall rate of serious complications was less than five percent. The most common complication was fever >103ºF in 2.9 percent followed in decreasing frequency by:

Significant hematuria (1%), Granulomatous prostatitis (0.9%) Pneumonitis and/or hepatitis (0.7%) Arthralgia (0.5%) Epididymitis (0.4%) Sepsis (0.4%) Rash (0.3%) Ureteral obstruction (0.3%) Contracted bladder (0.2%) Renal abscess (0.1 %) Cytopenia (0.1%). No differences in the incidence of complications were observed comparing different BCG preparations or doses.[88] A Cochrane review identified six randomized trials of intravesical BCG including 585 patients; local complications included urinary frequency, cystitis, fever, and hematuria in 71, 67, 25, and 23 percent, respectively.[89] No cases of BCG sepsis or deaths occurred in this review.

There are conflicting data on the safety of steroids in patients treated with BCG. In one series of 24 patients who had concomitant treatment with steroids or were immuno compromised the incidence of side effects was comparable to that of patients without evidence of immuno suppression.[90] In contrast, a fatal case of BCG reactivation and sepsis three years after uneventful BCG treatment for bladder cancer was documented following several months of oral prednisone therapy.[91]

Systemic sepsis and even death can also develop early following local instillation of BCG. During the initial clinical experience with BCG as an intravesical agent, most cases of sepsis could be traced back to recognized errors in BCG administration such as traumatic catheterization, administration too early after transurethral surgery, or instillation during a concomitant UTI. All these conditions result in physical disruptions in the urothelial blood barrier. Nowadays, sepsis has been estimated to occur in approximately one in every 15,000 patients treated with intravesical BCG.[88]

LOCAL COMPLICATIONS — Symptoms of bladder irritation, such as dysuria and frequency, develop in the majority of patients within two to four hours of BCG instillation; a low grade fever and malaise may accompany these symptoms, especially in patients who have received prior intravesical instillations.[86] Such manifestations generally resolve within 48 hours.

Infection can also spread locally to involve structures within the genitourinary tract. Such infections include granulomatous prostatitis, epididymitis, ureteral obstruction, bladder

contracture and renal abscess.[92, 93] Granulomatous prostatitis may be quite common although symptomatic disease is not. In one series of 12 patients undergoing cystoprostatectomy following BCG instillation, nine had evidence of granulomatous prostatitis.[94]

Symptoms from BCG infection of any of these structures cannot be distinguished from infection due to other organisms. This is particularly problematic as up to 20 percent of patients receiving intravesical BCG develop a conventional bacterial UTI at some point during treatment.[95] Occurrence in proximity to local instillation of BCG can be helpful, but cases of epididymo-orchitis arising years after the BCG therapy have been described.[96] Thus, a level of clinical suspicion must be maintained once this treatment has been administered. In one report of eight cases with a review of the literature, the authors describe both early and late (>1 year) presentations of BCG infection; the late disease involved local granulomatous infection in the genitourinary tract usually with positive cultures for M. bovis.[97]

SYSTEMIC COMPLICATIONS — The most serious complications of BCG intravesical instillation relate to disseminated infection.

Sepsis — A classic sepsis syndrome can occur, complete with fever, rigors, hypotension, disseminated intravascular coagulation, and respiratory failure.[93] These manifestations are probably due to high levels of cytokines released directly into the bloodstream as part of the hypersensitivity response (so called cytokine storm).[98] This rare event typically develops soon after the BCG instillation. Delayed cases have been reported years after an apparently uncomplicated treatment; the administration of systemic corticosteroids may have caused reactivation of a dormant focus in one of these latter cases.[91]

Granulomatous hepatitis — Granulomatous hepatitis can rarely arise as either an early or late complication of BCG intravesical instillations. Patients with granulomatous hepatitis present with symptoms and signs of hepatitis, including fever, anorexia, and jaundice. Non-caseating granulomas are found on liver biopsy; eosinophils can also be seen in these specimens.[86] Three cases have been reported in which renal insufficiency accompanied granulomatous hepatitis; epithelioid granulomas were found on renal biopsy in two of these patients.[99] A progressive mycotic abdominal aneurysm was also noted in one case of granulomatous hepatitis, which occurred a year after the last BCG instillation.[100]

Pneumonitis — A miliary nodular or interstitial pattern on routine chest radiography and CT scanning develops in some patients with disseminated BCG infection, most often in association with sepsis.[87] Dyspnea, accompanied by fever and malaise, has been described. Progression to respiratory compromise can occur.

Osteomyelitis — Osteomyelitis is another rare complication of disseminated BCG infection. The majority of the handful of reported cases involves the spine, [101, 102] presumably due to spread from the urinary tract through Batson's plexus.

Other — Other sites of infection may be caused by BCG.

- A fever of unknown origin
- Granulomas in bone marrow.
- Mycotic aneurysms.
- Endophthalmitis.

DIAGNOSIS — Specimens should be obtained for staining for acid-fast bacilli, culture,

and PCR testing for mycobacterial DNA in any patient with suspected disseminated BCG infection, even though all of these procedures can be negative in some cases[85],[86].

Empiric therapy may be instituted when the clinical suspicion is high. Despite concerns about cases in which M. bovis cannot be demonstrated, organisms have been recovered or demonstrated by PCR in an increasing proportion of cases.

The presence of breaks in the urogenital epithelium is known to be a risk factor for the development of disseminated infection.[87] Thus, patients with difficult bladder catheterizations, preexisting cystitis, or persistent gross hematuria following transurethral resection of the bladder tumor (TURBT) should have BCG instillation deferred for a minimum interval of several weeks.

Reduction of BCG-related local side effects and fever can be achieved by BCG dose reduction to one-half to one-fourth of the typical dose.

While many studies have shown that BCG regimens using lower doses have similar efficacy, at least one trial showed a significantly reduced cancer response rate.[103] For this reason titration of the BCG dose to a level where symptoms are acceptable is becoming a preferred alternative to automatic dose reduction. Other regimen modifications that improve BCG tolerance include reducing the dwell time to 30 minutes or applying treatments on an every other week schedule as needed.[104, 105]

Intravesical BCG is an effective and well established immunotherapy for superficial

TCC of the bladder. However, the optimum dose and schedule of treatment is yet to be defined. The other important aspect that needs to be established is the prognostic or predictive factors of treatment response. This is important for selecting patients who will benefit from the treatment to avoid unnecessary radical treatment and toxicities, at the same time to identify nonresponders early on so that they can be offered alternative treatment without compromising their prognosis. The BCG therapy is associated with toxicities but most are mild and resolve after discontinuation & symptomatic treatment. The life threatening complications may occur with such therapy, so high clinical suspicion and prompt treatment may be helpful. Currently the studies testing lower doses have shown lesser toxicities with equal efficacy, such therapies need to be explored further, to reduce complications and improve compliance.

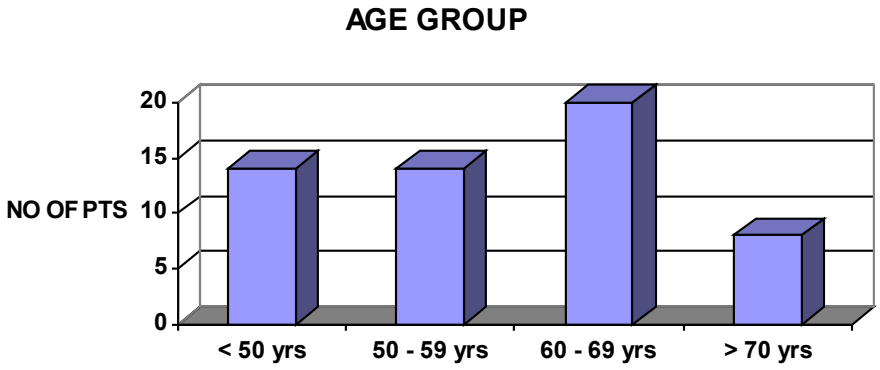
RESULTS

A total of 56 patients diagnosed as superficial bladder cancers were treated with intravesical BCG from March 2005 to September 2007.

Patient characteristics

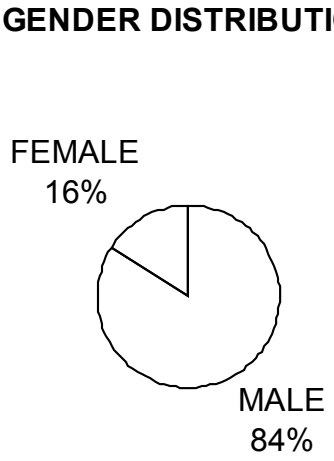
The age of the patients ranged from 25 yrs to 86 years, with maximum 35.7% presenting in the seventh decade and 25% in the sixth decade, 25% were younger than 50 years and 14.3% were above 80 years, age group distribution is shown in Chart 1.

Chart 1: AGE GROUP DISTRIBUTION



There were 47 males (83%) and 9 females in this study as shown in Chart 2.

Chart 2 : GENDER DISTRIBUTION



Only 12.5% were from city, 44.6% from the various parts of the state, 43% from neighbouring states and 37.5% of patients were illiterates and 41% of total patients were labourers. On asking about addictions, 24(43%) patients were smokers and 13% took alcohol socially.

All patients were in good physical health of which 33(60%) patients had comorbidities of which only 25(75%) were on medication. 36% patients were Hypertensive with 16% patients also having Ischemic Heart Disease, 26% were diabetics and additional 12.5% having other comorbidities which included hypothyroidism and bronchial asthma.

Presentation

The most common presentation was Painless hematuria 46(82%) either alone or with dysuria 7(12.5%), other presentations included Pain during voiding & flank pain in 3 patients, 2 patients had increased frequency, whereas 1 patient had Pyuria and one had Retention of urine.

Patients had symptom duration ranging from less than 1 month to 24 months before seeking any medical attention. 3 patients had symptoms for 3, 8 & 12 years & were diagnosed previously & had undergone TURBT as previous therapy. Mean duration of symptoms was 3.6 months (range < 1 to 120 months)

Patients were grouped according to the risk groups as per AJCC staging as shown in table 1.

Table 1: Risk group stratification according to stage & grade.

RISK GROUP	No of pts	%	SUB GROUPS
LOW RISK	2	3.6%	TaG1
INTERMEDIATE	34	58.9%	T1G1, T1G2, TaG2
HIGH	17	32.1%	TaG3, T1G3
DYSPLASIA	3	5.4%	DYS

Only 2 patients presented with low stage low grade disease, 34 (59%) had intermediate risk group, 31% were in high risk advanced stage disease and while 5.4% had dysplasia.

The time gap between the last TURBT and BCG administration was less than 2 weeks in 7(12.5%) patients only and majority received after 2 weeks of intervention.

Patients undergoing and completing the therapy while on weekly and monthly schedules is as per shown in table 2.

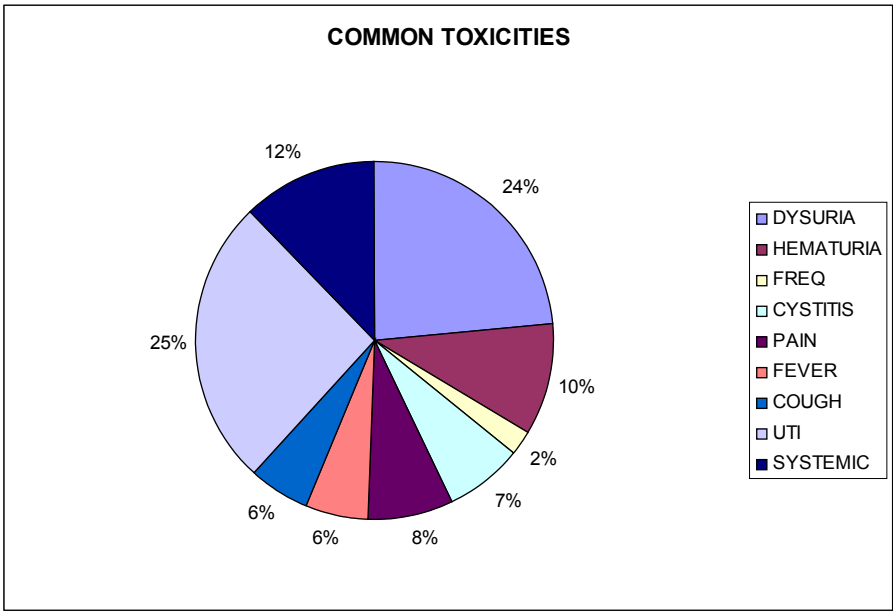
Table 2: Therapy completion rates

	WEEKLY (n 56)	MONTHLY (48)
Completed	48 (85%)	28 (58%)
Defaulted	4 (7%)	6 (12.5%)
stopped	2(3.5%)	6 (12.5%)
On treatment	2 (3.5%)	8 (16.6%)

During therapy 38 (65.4%) patients experienced some form of toxicity, of which 60% experienced during weekly schedule, 40% on monthly and 15.7% experienced both on weekly and monthly schedules.

The common side effects experienced by the patients were dysuria, hematuria, UTI, pain on and after administration of BCG, cystitis and are as depicted in the chart 3.

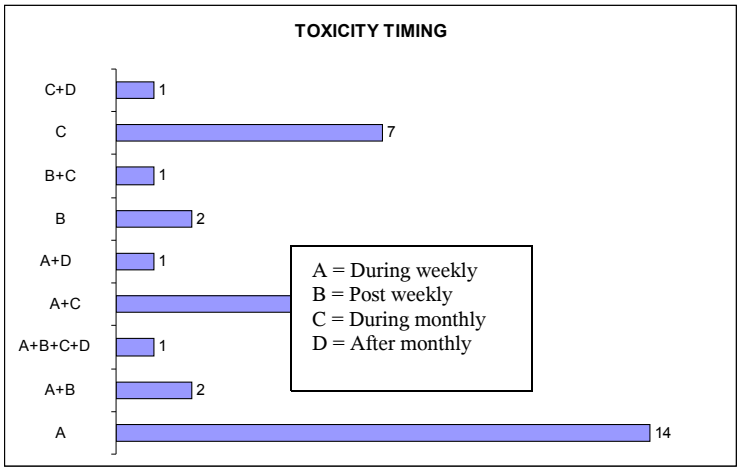
Chart 3: Incidence Of Common Toxicities



Most patients experienced toxicities during weekly instillations as compared to the

monthly administration, the timing of toxicity with respect to BCG instillation is as shown in chat 4

Chat 4: Toxicity with respect to timing of BCG administration



The most common systemic symptoms included fatigue & bodyache. Others symptoms were arthralgia which was present in 2 patients.

One patient had ARF requiring dialysis, which recovered with supportive care and is doing well.

In our study another 2 patients had deranged blood sugars, first patient had no history of Diabetes Mellitus, he also had significant weight loss > 10 kgs and constitutional symptoms. Another patient a known diabetic had deranged blood sugars which were however attributed to poor drug compliance. Both the patients recovered fully after completion of the treatment.

In patients developing UTI most common organism isolated was Klebsiella followed by E. fecalis. Stricture of urethera and meatal stenosis usually more common following instillation after procedural trauma, though there were no procedural complications in this study, Uretheral stricture or Meatal stenosis was noted in 6 patients.

Cough and upper respiratory tract infection like features were present in 12 patients. One patient had presented with symptoms suggestive of disseminated disease with predominantly lung symptoms, systemic 'BCGosis' was thought but all the infectious work up was negative. No anti tubercular treatment was given and patient responded after stopping the treatment and with supportive care. Another patient had upper respiratory tract infection with fever however work up was negative for any systemic BCG infection, the patient recovered with supportive therapy

One patient each had documented Granulomatous prostatitis and epididymo-orchitis while on follow up.

On follow up or during therapy 15 (26.7%) had recurrence, the intervention done and outcome & status of which is as per the table 3.

Table 3: Recurrence, intervention and status

RECURRENCE (n 15 PATIENTS)		
Intervention	**No of patients**	**Status**
TURBT (n = 7)	**6**	NAD
	1	Expired (defaulted)
CYSTECTOMY	**3**	NAD

Not Willing for Rx	**2**	LFU (defaulted)
RT	**1**	LFU (defaulted)
On evaluation	**2**	On W/U

At the time of analysis of this study 30 patients were without any symptoms of disease, 10 were still on maintenance treatment, 9 had defaulted out of which 1 patient had died of progressive disease, 3 patients underwent Radical cystectomy, 2 are on re-BCG and 2 patients are on further evaluation for recurrence.

DISCUSSION

Since the initial report in 1976 that intravesical instillation of BCG reduced the rate of recurrence of superficial transitional cell carcinoma, the superiority to chemotherapy and the safety of BCG immunotherapy have been repeatedly confirmed The mechanism of action is thought to be BCG-mediated modulation of the immune response in the bladder, resulting in inflammation and subsequent elimination of the tumor. However inoculating a viable infectious agent into the bladder raises the potential risk of local or generalized infection, just as has been described following intradermal BCG vaccination for prevention of tuberculosis

A review of literature regarding the complications reported with the treatment of superficial bladder cancer with intravesical BCG was done including the Pubmed and Internet resources.

As opposed to treatment efficacy comparisons available, comparing complications rates from different studies was problematic as most studies have not particularly looked at the complications and study variables are not uniform.

In the Cochrane review of 2007 for intravesical BCG, the mean age was 64 in the TUR plus BCG group, with the male to female ratios of 3.5. The mean percentage of patients with Ta and T1 tumours were 41 and 59% (TUR plus BCG).[109] In our study the mea age at presentation was 57 years and male to female ratio was 5.2 :1. The % of Ta & T1 tumours was

41 & 52% respectively.

In the Cochrane review of intravesical therapy complications (2007) the main toxicities associated with BCG were cystitis (67%), haematuria (23%), fever (25%) and urinary frequency (71%). No BCG sepsis or deaths were reported.[109]

In review of literature in relation to complications of BCG by American Urological Association reported incidence of Hematuria (29%), LUTS (57 – 71%), Urethral infections (4%), systemic symptoms (22 – 30%) and bladder contracture in 3% patients.[106] The incidence of BCG side effects have been reported to be BCG cystitis in 57 – 91%, Hematuria (26 – 55%) and Fever (28 – 73%) in studies reported by Lamm, Morales, and Sasaki et al.

In another Japanese study by Suzuki et al [107] the incidence of BCG- induced side effects was more than 80%, but major side effects that required treatment and postponement or discontinuation of BCG instillation occurred in 50% courses or less reported in 41.8%.

In another study by Gonzalez et al[108] reported symptoms of BCG infection after treatment with instilled BCG were Fever & malaise, Urinary symptoms (62%) Chills, Sweats, Weight loss, Shortness of breath (37.5%), Arthralgia/arthritis, Nausea/vomiting, testicular or prostatic mass (25%), Ascites (12.5%)

BCG induced toxicities (Cochrane review 07) in comparison with our study[109]

	Krege 1990	**Lamm 1985**	**Melekos 1990**	**Pagano 1990**	**Pinsky 1985**	**Yamamoto 1990**	**Mean (%)**	***Our study***
cystitis	34	93	84	27	88	76	67	***7***
Haematuria	6	34	21	3	58	14	23	***10***
Fever	18	28	27	16	44	14	25	***6***
Frequency	-	90	-	-	51	-	71	***2***
Flu-like	-	7	10	-	28	-	15	***6***
Nausea	-	11	7	-	5	-	8	***-***
Malaise	-	10	7	-	26	-	14	***2***
Prostatitis	5	1	1	2	2	-	3	***1***
Epididymitis	10	1	-	2	-	-	6	***1***
Allergic	3	-	-	-	19	-	10	***-***
Contracted bladder	-	0	-	1	0	10	2	***1***
BCG-Sepsis	-	0	-	0	0	-	0	***0***
Deaths	0	0	0	0	0	0	0	***0***

In our study the most common symptom was UTI followed by Dysuria (24%), Hematuria occurred in 10% and cystitis occurred in 7% patients. The incidence of Cystitis is much less in our study as compared to the other studies, which is minimal as compared to studies in Cochrane review. The lowest incidence is in the study by Pagano et al (27%). The high incidence in the other studies is probably due to overlapping symptoms of cystitis with LUTS or probably may also be related to different strains of BCG vaccine used in different studies. Also in various studies there is no uniformity in the description of Cystitis. Also in our study we had UTI in 25% patients.

In our patients incidence of Hematuria was 10% which was also less as reported in the Cochrane review (mean 23%) and other studies. In a metaanalysis of 9 trials by Madhusudan P. Koya et al, incidence of hematuria was reported ranging from 1 to 9% of patients.[111]

Most of studies have not looked at increased frequency or allergic reactions & few studies have reported malaise and flu like symptoms. In our patients only 2% had increased frequency as compared to mean 71% of patients which was looked into in only 2 of the studies. In our study no allergic reactions were noted.

Arthralgia was present in 2 patients, in the literature arthritis is usually

regarded as a rare event but *Andreas Bohle et al* in their study "QOL assessment during intravesical therapy" observed that a no of patients had complained about arthralgia/ arthritis.[112]

In our study one patient had ARF requiring Dialysis, the renal functions returned to normal after discontinuation of therapy. On literature review a case report describing similar toxicity (ARF) was reported with uneventful recovery of the patient. It was found that although renal complications are uncommon, several cases of interstitial nephritis (with or without granulomas) and mesangial glomerulonephritis have been reported and underlying interstitial nephritis may be the underlying factor.[113] the other toxicities such as Granulomatous prostatitis, Epididymo-orchitis, bladder contracture are comparable as reported in the metaanalysis. In our patient 10% had meatal or ureteral stenosis, though described in the literature, the incidence in other studies is not known.

In our patient group only 1 patient had significant weight loss (>10kgs) & 11(19.6%) had systemic symptoms as compared to 37.5% patients as reported by Gonzalez et al.[108]

In our study there were no systemic BCG infections and no death was reported while on treatment, as shown in other studies, though anecdotal

reports are published.

Patients usually have overlapping symptom complexes and differentiating predominant symptoms from others may help explain the differences in reported toxicities. Also there is no uniformity in describing the various symptoms resulting in wide variation in incidences of various toxicities.

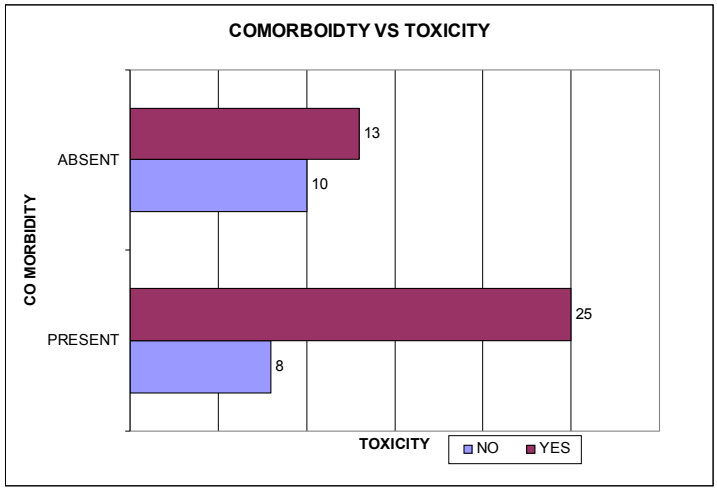
In the literature the toxicities associated with BCG are reported in up to 95% of patients[110] but most are transient and self limiting requiring no specific intervention.

In our study 38 (68%) patients had some form of toxicity out of which 8 (14%) had significant toxicity requiring therapy to be stopped. Whereas in SWOG trial 25% patients and Grade 3 toxicity or above and only 16% patients were able to complete planned treatment. In our study 85% completed induction therapy and 58% completed maintenance therapy and 18% are still on treatment. In another Polish study 7% of patients had grade III toxicity and required cessation of therapy.[114]

In our study statistically no significant association was found when the toxicity group was compared with various variables like stage distribution

with toxicity (p = 0.6), toxicity with comorbidities(as per chart 5, p = 0.6), toxicity with addictions (smoking: p = 0.06; alcohol, p = 0.9), toxicity with age group, toxicity with time gap between TURBT & intravesical therapy, toxicity and relation with comorbidities or toxicity with recurrence rates (p = 0.8).

Chart 5 Relation of Comorbidity Group with Toxicity



CONCLUSIONS

1. Intravesical BCG is an effective and well established immunotherapy for superficial TCC of the bladder. However, the optimum dose and schedule of treatment is yet to be defined.

2. BCG doses were well tolerated and the patient compliance was good with 70% of the patients completing the therapy and 17 % still on therapy.

3. The common toxicities reported were dysuria, hematuria, cystitis, UTI and systemic symptoms. Incidences of which are comparable to those reported in the literature.

4. Majority of toxicities were mild and self limiting requiring no intervention. 68% patients experienced some form of complications however 14% had significant toxicities requiring treatment to be stopped. There were no BCG sepsis and no deaths were reported due to the therapy.

5. In our study no statistically significant factors or subgroups were found to be related to the development of side effects.

6. There is need for larger uniform multicentric studies looking at tolerance and complications in our subset of patients as there are no reported studies addressing the issue from our country. Also the QOL issues needs to be addressed in such larger studies.

7. The role of low dose BCG vs. standard doses needs to be addressed as various recent studies report equal efficacy with less toxicity.

8. Overall intravesical BCG is well tolerated therapy that can be safely administered as day care treatment.

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PROFORMA

Name Age / Sex O/No DOA

Address

EDUCATION

Presenting complaints

DURATION

Personal Hx

Drug Hx

Family hx

Occupation

Prev intervention

Cystoscopy (baseline)

Diagnosis: T G

Urine (R/M)

Date of TURBT Date of starting BCG time gap

BCG weekly

1st 2nd 3rd 4th 5th 6th

Delay

Cause

Intervention

Cystoscopy

BCG monthly

1st	2nd	3rd	4th	5th	6th
Delay					
Cause					
Intervention					
Side effects/ complications			weekly		monthly
Fever					
Chills rigors					
Pain					
UTI					
'Bcg' osis					
Hematuria					
Dysuria					
Cystitis					
Increased frequency					
Systemic symp					
Procedural					
Others					
Infections: UTI/ systemic/					
Culture report					
Antibiotics					
Timing of toxicities					
Recurrence					
If yes intervention & outcome					
Last Follow up					
Status at last follow up					