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Original Article

Efficacy of Intravesical BCG in Patients with Bladder Cancer in the Tobruk City Population

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ABSTRACT

Background: The particular pathophysiology of tumors makes it difficult to treat cancer successfully, The survey's goal was to assess the predictive risk factors for bladder cancer and the efficiency of intravesical BCG as a local example of bacterial cancer therapy in reducing tumor recurrence rates The participants in this study were drawn from Tobruk City and the surrounding area, From January 2022 to June 2022, the study was conducted. Result: Overall, there were 47 patients in our statistical data had 47 patients with bladder cancer and was carried out in Tobruk City, Libya, from January 2022 to June 2022. Only 3.6% of the patients were female, with men making up the majority (93.6%). The study's participants' ages ranged from 2 to 87, with a mean of 59. 18 (38.2%) of the 47 individuals received care, compared to 29 (61.7%) who did not. 17 (94%) of the 18 patients who received BCG were men, and only one patient (0.5%) was a woman. 16 (34.0%) of the 47 patients had tumor recurrences, and 3 passed away. Four (25%) of the patients had conditions related to hypertension, diabetes, or the prostate, and 75% of them received BCG. The remaining 31 patients, with an average age of 50 and 6 (1.9%) undergoing BCG, were all in stable condition. Conclusion: The study found that BCG-immunotherapy effectively reduced NMIBC in 18 out of 47 patients in Tobruk City, with minimal side effects. However, specific risk factors reduced the effectiveness of BCG immunotherapy.

Keywords: Bacterial therapy, BCG, TURBT, bladder cancer. NMIBC, MIBC

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Introduction

Cancer remains the leading cause of disease deaths all over the world. According to the statistics of the Worldwide Cancer Society, cancer resulted in 9.6 million deaths in 2018, accounting for 20% of all deaths (1). By 2030, it is

estimated that there will be 26 million new cases and 17 million cancer deaths worldwide(2). These statistics underline exceptional challenges in the treatment of cancer and shed light on the urgency of discovering novel effective antitumor therapies(3). Conventional anticancer therapies like chemotherapy, radiation therapy, and immunotherapy have been used for cancer treatment. Due to the potential of cancer cells in the generation of resistance to traditional therapies, these treatments have failed to completely eradicate tumor cells. Moreover, the long-term sequelae and side effects significantly impair the therapeutic efficacy of patients treated with traditional therapies (4). Not all cancerous tissue can be targeted with a scalpel and physical and chemical methods in general do not distinguish between healthy and malignant tissues(5).

The role of bacteria as an anticancer agent was recognized almost a hundred years back. The German physicians W. Busch and F. Fehleisen separately observed that certain types of cancers regressed following accidental erysipelas (Streptococcus pyogenes) infections that occurred whilst patients were hospitalized. Independently, the American physician William Coley noticed that one of his patients suffering from neck cancer began to recover following an infection with erysipelas. He began the first well-documented use of bacteria and their toxins to treat end-stage cancers. He developed a safer vaccine in the late 1800s composed of two killed bacterial species, S.pyogenes, and Serratia marcescens to simulate an infection with the accompanying fever without the risk of an actual infection. The vaccine was widely used to successfully treat sarcomas, carcinomas, lymphomas, melanomas, and myelomas (6) Recently, bacterial strains with therapeutic characteristics against cancer have been discovered. Mycobacterium bovis (BCG) is considered a prototype. It is an obligate anaerobic, acid-alcohol-resistant, facultative intracellular, and non-motile bacterium that has been employed in the past for tuberculosis vaccine manufacturing For more than 30 years it has been utilized in bladder cancer patients as immunotherapy (7,8)

(6) long clinical experience with BCG, the mechanism of its therapeutic effect is still under investigation. Available evidence suggests that urothelial cells (including bladder cancer cells themselves) and cells of the immune system both have crucial roles in the therapeutic anti-tumor effect of BCG(9).

BCG immunotherapy is the gold-standard treatment for non-muscle-invasive bladder cancer at high risk of recurrence or progression. Preclinical and clinical studies have revealed that a robust inflammatory response to BCG involves several steps: attachment of BCG; internalization of BCG into resident immune cells, normal cells, and tumor urothelial cells; BCG-mediated induction of innate immunity, which is orchestrated by a cellular and cytokine milieu; and BCG-mediated initiation of tumor-specific immunity. As an added layer of complexity, variation between clinical BCG strains might influence the development of tumor immunity. However,

more than 40 years after the first use of BCG for bladder cancer, many questions regarding its mechanism of action remain unanswered. A better understanding of the mechanisms underlying BCG-mediated tumor immunity could lead to improved efficacy, increased tolerance of treatment, and identification of novel immune-based therapies. Indeed, enthusiasm for bladder cancer immunotherapy, and the possibility of combining BCG with other therapies, is increasing owing to the availability of targeted immunotherapies, including checkpoint inhibitors. Understanding of the mechanism of action of BCG immunotherapy has advanced greatly, but many questions remain, further basic and clinical research efforts are needed to develop new treatment strategies for patients with bladder cancer (10).

Materials And Methods

A retrospective study was carried out on a sample of Libyan patients from Tobruk City and its surrounding area who visited a government hospital (Tobruk Medical Centre), The goal of the current investigation was to determine whether bacterial products (BCG) are effective against urinary bladder cancer and to link these results with other demographic parameters. In this study, forty-seven individuals with urinary bladder cancer who were between the ages of 2 and 87were included, Results of Transurethral Bladder tumor Resection (TURBT) were gathered from the Tobruk Medical Centre for the study that was conducted from January 2022 to June 2022. Age, gender, and the date of the test for each individual were collected and documented as demographic data, The history, clinical, and pathological characteristics of individuals with newly diagnosed bladder cancer were all included in the register After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems Finally, a database with information on recently discovered non-muscle invasive bladder cancer was created. Then, the clinical result following the initial diagnosis and BCG therapy was obtained and analyzed. Statistical analysis: was performed using Excel 2010. Categorical variables mean and correlation between males and females were presented using bar charts. Before performing the research, Ethical approval: It was authorized to extract data from registries and records. The data collected did not contain the patient's name or any other personal identifying information to ensure confidentiality.

TURBT Procedure The patient is given anesthesia, either general or spinal, the surgeon inserts a cystoscope through the urethra into the bladder, the cystoscope is a thin, tube-like instrument with a camera and light at the end, this allows the surgeon to see inside the bladder, the surgeon uses a resectoscope, which is a small, wire loop attached to the cystoscope, to remove the tumor, the surgeon may also take a biopsy of the tumor, which is a small piece of tissue that is removed for testing, the surgeon will irrigate the bladder with saline solution to remove any blood or debris, the cystoscope is then removed and the urethra is closed, the entire procedure

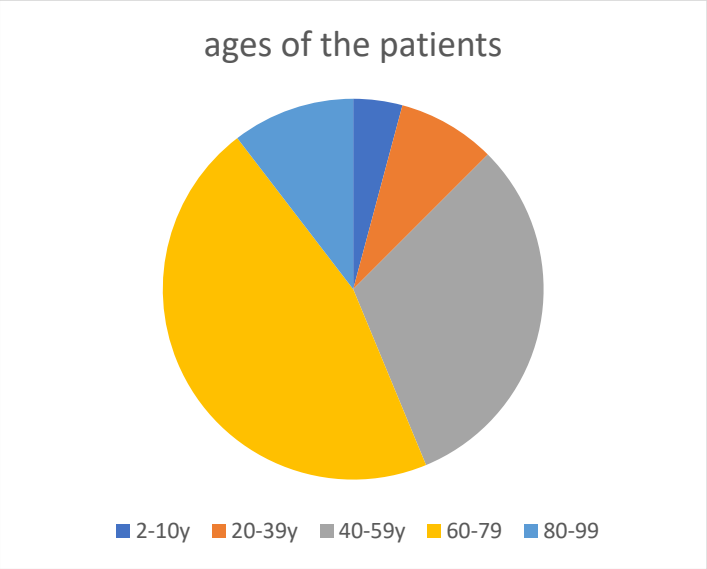
usually takes about 15-40 minutes, after the procedure, you will be taken to a recovery room where you will be monitored, a patient may have some pain or discomfort, which can be managed with medication, may also have some bleeding or blood clots in the urine, this is normal and should subside within a few days.

Must verify that bleeding has stopped (there is no hematuria) and put BCG dosage via a catheter, the patient has to hold the urine, rotate to the right and left sides, and lay horizontally while being instructed to sanitize the restroom to prevent the distention of bacteria, a cystoscopy check must be performed six weeks after the last dose of NMIBC.

RESULT

The age range of the study group, which included individuals with urinary bladder cancer who had gotten an official diagnosis, ranged from 2 to 87 years, with a mean age of 59. Additionally, 42 (89.3%) of the study participants were older than 30 years old, compared to 6 (10.6%) of them. This is shown in Figure 1.

Figure 1: Shows the incidence rate of bladder cancer in the sample.



In the research from 2020 to 2022, the number of incidents was represented as follows: the proportion of male cases was 44 (93.6%), the proportion of female cases was 3 (6.4%), and the sum of all causes was 47.

From January 2022 to June 2022, this study was conducted in Tobruk City, Libya,

involving patients who worked at the Tobruk Medical Centre Number of individuals participating in research per year during the study period.

The number of subjects varied depending on the study period, with the highest population numbers being recorded in the years 2020 and 2021, 21 (44.7%) and 20 (42.6%), respectively, and 6 (12.7%) in 2022. The study population, which included people with urinary bladder cancer who were diagnosed, ranged in age from 2 to 87 years, with a mean age of 59. Furthermore, 6 (10.6%) of the persons in the study were younger than 30 years old, whereas 42 (89.3%) were older than that age.

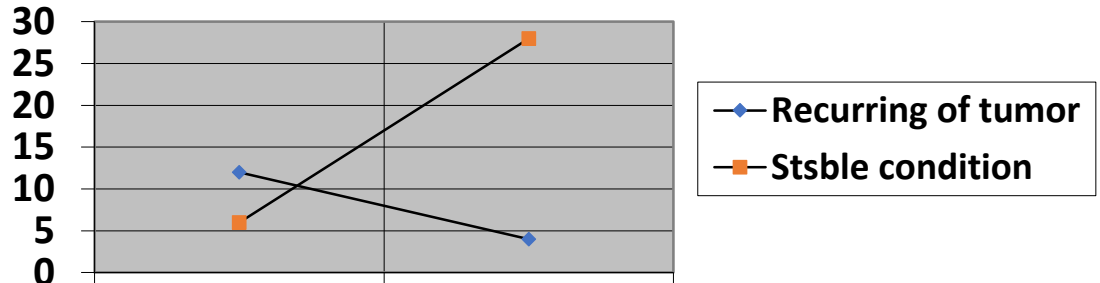
Table 1: Demographic and Clinicopathologic characteristics of 47 patients with bladder cancer

Demographic variables		Number (%)
Diabetes mellitus	Yes	13 (27.6%)
	No	34(72.3%)
HTN (Full name)	Yes	11(23.4%)
	No	36(76.5%)
Smoking	Yes	8(17%)
	No	37(79%)
	Stop	2(4.2%)
Recurrence	Yes	14(29.78%)
	no	30(36.82%)
BCG therapy	Yes	18(38.2%)
	No	29(61.7%)
Others	MIBC (full name)	2(4.2%)
	More than one course of BCG	4(8.5%)
	Other diseases	14(41%)

Therapies were recorded, out of 47 patients, 18 (38.2%) were treated while 29(61.7%) were not treated Figure 2. The people who received more BCG therapy were 4 (8.5%), Tumor recurring was reported for 16(34.0%)out of 47 patients, and 3 died

Out of 18 patients that received BCG treatment, 17 (94%) were men and 1 (0.5%) was female, Of the 18 patients, 7 (36.8%) were over 50, and 11 (61.11%) were under 50. Out of 47 patients, 16 (34%) had tumor recurrences; of these, 12 (75%) had received BCG, 4 (25%) had received more than one course, and their average age was 63. Additionally, 4 (25%) had hypertension, 3 (18.7%) had diabetes, and 2 (12.5%) had prostate diseases, while the remaining 31 (65.9%) patients were in stable condition; of these, 6 (1.9%) had received BCG, and their average age was 50. Two (33.3%) of them had high blood pressure, two (33.3%) had diabetes, and two (33.3%) were smokers.

Figure 2: Demonstrates the status of the patients in the BCG-received group compared to the BCG-non-received group.



	receiving BCG.	non receiving BCG
Recurring of tumor	12	4
Stsble condition	6	28

DISCUSSION

This scientific study aimed to characterize the clinical outcome of newly diagnosed non-muscle invasive bladder cancer (NMIBC) in a series of patients from Tobruk Medical Center. The effectiveness of adjuvant intravesical BCG immunotherapy as a treatment for high-risk NMIBC after transurethral resection of bladder tumor (TURBT) was analyzed, the study also investigated the association between NMIBC and various risk factors such as diabetes mellitus (DM), hypertension (HTN), prostate diseases, and demographic variables including gender, age, smoking, mortality, recurrence, and invasive bladder cancer (MIBC).

Regarding gender and age, the study observed a higher incidence of bladder cancer in men compared to women. Out of the 47 patients, 44 (93.61%) were men, while only 3 (6.38%) were women. The study also found that older age was associated with a higher risk of developing bladder cancer, with 27 (55.31%) out of 47 patients being aged ≥60 years (11).

Among the 47 studied patients, 13 (27.60%) had both diabetes and NMIBC and underwent TURBT. Out of these diabetic patients, 5 (38.4%) received BCG therapy courses, this finding supported the association between diabetes and bladder cancer risk, which has been reported in

other studies (12) (13)Furthermore, 4 (8.51%) patients had both hypertension and diabetes, the study suggested that hypertension might be a consequence of metabolic disorders, contributing to increased cancer risk (14)

The study observed that 12 patients had prostate diseases, such as enlargement, obstruction, or prostate cancer, and underwent transurethral resection of the prostate (TURP), among the 44 male patients, a relationship of 27.20% was found between non-invasive bladder cancer and prostate diseases. Additionally, the study investigated the effect of bladder tumor (BT) location on prostate cancer (PCa) and found three patients with elevated prostate-specific antigen (PSA) levels. The study suggested that the location of the bladder tumor, particularly in the neck of the bladder might be associated with elevated PSA levels (15)

While previous studies have not examined PCa detection based on BT location in NMIBC patients undergoing intravesical BCG instillation, this study provided insights. However, due to the small study population and lack of follow-up after PSA elevation, it was not determined whether the elevation occurred before or after BCG therapy.

Among the 10 smokers, two patients (4.20%) who quit smoking showed improvement in their(16)recovery, consistent with previous studies. However, eight patients (17.00%) continued to smoke, highlighting smoking as a significant risk factor for cancer and recurrence. Different studies have presented conflicting opinions regarding the relationship between smoking and tumor recurrence after BCG treatment (17).

The study also observed that patients who had recurrence after a long period were those who required injections as part of their treatment. Hypertension and smoking were prevalent among patients with tumor recurrences, suggesting a potential negative effect of hypertension or antihypertensive drugs on treatment effectiveness However, some studies have reported that antihypertensive drugs improve recurrence-free survival in NMIBC patients after BCG therapy (18).

Similarly, patients with diabetes showed a higher recurrence rate after treatment, suggesting a potential association between diabetes and recurrence (19).

Age was identified as an influencing factor in treatment outcome, with older patients having a higher recurrence rate. The average age of patients with tumor recurrence was 63 years, while those with stable conditions had a younger average age of 50 years (20).

Finally, the study confirmed that chemotherapy with surgical bladder removal is the treatment for invasive bladder cancer, while BCG therapy has only been proven effective for non-invasive bladder cancer at all stages. Two patients in the study were diagnosed with invasive bladder cancer and were treated with BCG. One patient responded well to the treatment, showing improvement without tumor recurrence, while the other patient experienced tumor recurrence after BCG therapy and required additional surgeries and doses of BCG (21,22)

Overall, this study provided insights into the clinical outcome of newly diagnosed

NMIBC and the effectiveness of adjuvant intravesical BCG immunotherapy. It also explored the association between NMIBC and various risk factors, such as diabetes, hypertension, prostate diseases, age, and smoking. The findings contribute to the existing body of knowledge on bladder cancer and its treatment, emphasizing the importance of considering these factors in patient management and treatment decisions.

Study limitation

-Through the local study, the study can be completed for long-term follow-up of patients to determine the extent of tumor recurrence

- The sample size is not satisfactory

Conclusion:

The results showed that the majority of patients diagnosed with non-muscle invasive bladder cancer were male. The correlation between gender and tumor stage was also analyzed, revealing that males were more likely to have higher-stage tumors than females. BCG therapy was found to be effective in reducing tumor recurrence rates, with a success rate of 33.3%. However, there were some cases where BCG therapy was not successful, and further treatment options needed to be explored. Overall, this study provides valuable insights into the diagnosis and treatment of non-muscle invasive bladder cancer, highlighting the importance of early detection and personalized treatment plans for each patient. Future research should focus on identifying biomarkers that can predict response to BCG therapy and developing new treatment options for patients who do not respond well to current therapies.

RECOMMENDATION:

1 .Experimenting with the effect of non-BCG bacteria treatments on patients in the city .

2 .Continue genetic modification of bacteria, especially salmonella.

3. Finding other synergistic factors with bacteria treatments.

ABBREVIATIONS:

BCG	Bacillus Calmette-Guérin
TURBT	Trans urethral resection of bladder tumor
NMIBC	Non-muscle invasive bladder cancer
MIBC	Muscle-invasive bladder cancer
UC	Urothelial carcinoma
HTN	Hypertension

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