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Original article

Clinical and Pathological Features, and Cancer Behaviors of Non-Muscle Invasive Bladder Cancer

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Abstract

Background and aims*. Bladder cancer is the second most frequent genitourinary malignancy. Urothelial carcinoma makes up to 90 % of initial bladder tumors, and non-muscle invasive bladder cancer (NMIBC) makes the most common type of urothelial bladder cancer. Patients with NMIBC generally have an excellent prognosis, with a 5-year relative survival rate of 80–90%. Only 20 to 40 % of cases of bladder cancer manifest with or progress to muscle-invasive bladder cancer (MIBC). To determine the diagnosis and implement a strategic management plan for the disease, clinical and pathological assessments as well as cancer behavior of NMIBC are crucial. The aim of the present study was to determine the clinical and pathological features as well as cancer behaviors of NMIBC.* ***Patients and Methods****. A total of 32 NMIBC patients who were admitted to National Center Institution, Misurata, Libya between 2013 to 2017 were evaluated and followed up for at least 3 years.* ***Results****. Young and elderly NMIBC patients did not exhibit any appreciable differences in tumor behavior, prognosis, progression, or recurrence. In the examined instances with NMIBC, a statistically significant connection between smoking and hematuria was found (p- value < 0.015). A total of 23 samples of the NMIBC tissues (72%) were staged as T1, and 9 cases were staged as Ta (28 %). At the first transurethral resection of the bladder tumor (TURBT), 19 patients (59%) were grade I, 11 patients (35%) were grade II, and 2 patients (6%) were grade III. Majority (29/32) of the cases received adjuvant intravesical chemo- or immuno-therapy therapy. In a minimum 3-year follow-up, only 6 cases (19%) experienced disease progression or recurrence.* ***Conclusion****. NMIBC had a good prognosis with TURBT and adjuvant intravesical chemo- or immune-therapy as recommended treatment strategies. High grade NMIBC requires specific management, demonstrating that early cystectomy as a possible disease treatment strategy.*

Keywords: *Bladder Cancer, NMIBC, TURBT, Clinical and Pathological Behaviors, Grading, Staging, Therapy.*

Introduction

In 2020, there were 573,278 cases of urinary bladder cancer reported globally. The Asian nations (China, Japan, and Korea) and Central Africa showed the lowest incidence rates. However, North America and Western Europe had the highest incidence rates (1). Additionally, urothelial carcinoma is thought to make up about 90% of initial bladder tumors.

Bladder cancer is considered the second most frequent genitourinary urologic malignancy. The majority of them have non-muscle invasive bladder cancer (NMIBC) (2). The clinical course of urothelial bladder carcinoma is uncertain (3). Muscle invasive bladder cancer (MIBC) and NMIBC are classified based on the degree of bladder wall penetration (4). NMIBC patients have an average prognosis with a 5-year relative survival of 80% to 90% (3). MIBC is present in or will occur in between 20 and 40 % of bladder cancer cases (2).

If treated with a transurethral resection of the bladder tumor (TURBT) without additional therapy, it is predicted that 40 to 80% of NMIBC non-muscle-invasive bladder malignancies will return within 6 to 12 months (5). The recommended course of treatment for NMIBC is TURBT, followed by adjuvant chemotherapy or "Bacillus Calmette-Gue'rin" (BCG) immunotherapy intravesical injections. Adjuvant instillations are required to lower the chance of NMIBC recurrence and to slow the development of muscle invasive illness (4). Mitomycin C, and epirubicin are the two adjuvant chemotherapeutic drugs for NMIBC that are most frequently prescribed and utilized (4). For individuals with NMIBC, six cycles of intravesical chemotherapy instillations are recommended to lower the chance of recurrence in the

near future. Mitomycin C is given once a week for roughly six weeks in dosages of 20 to 60 mg. Epirubicin is administered using the same manner at doses of 30-80 mg. Both medications are generally safe and well-tolerated by patients (4).
The intravesical bacillus Calmette-Gue'rin (BCG) was first used to treat NMIBC by Morales et al. in 1976. High grade urothelial bladder cancer is thought to respond well to intravesical (BCG) therapy (7). The BCG treatment focuses on eliminating existing subclinical tumors, preventing the development of new tumors, and delaying the progression of the illness (8).
Finding the elements that affect the progression of bladder cancer requires studying clinical and pathological features as well as cancer behavior. This assessment will help determine the disease's prognosis and planned management. Patients with bladder cancer are most concerned on reducing and delaying recurrences in order to delay the development of invasive disease (9). The clinical and pathological features as well as cancer behaviors of 32 NMIBC patients who were monitored for 3 years in the urology department of National Cancer Institute (NCI)-Misurata, Libya, were examined for this report.

Materials and Methods

Patients: The NCI-Misurata registry office provided the medical records of patients with bladder cancer. Patients with bladder cancer selected for this study were admitted to NCI-Misurata between 2013 and 2017. These individuals had been received medical care for at least three years from time of diagnosis. In this study, we examined 73 newly diagnosed bladder cancer patients in total. Adenocarcinoma was seen in two cases, squamous cell carcinoma in three, a rare mesenchymal tumor in one, and metastatic and muscle-invasive bladder cancer in 35 cases. In addition, 32 cases involved bladder cancer that was non-muscle invasive and urothelial. The cases were assessed and studied by a renowned pathologist. Using a 26 French storz resectoscope, every case received a full transurethral resection of bladder tumor (TURBT) intended to remove every gross tumor.
Treatment: Patients received adjuvant therapy every week for six weeks by having either Mitomycin C (50 mg) or doxorubicin (50 mg), or BCG dissolved in 50 ml of saline implanted intravesicaly after emptying the bladder, and lying 30 minutes on each side for a total of two hours. Six out of 32 cases (or 19%) involved intravesical chemotherapy, while 23 out of 32 cases involved intravesical BCG therapy (72 %). The three remaining cases were not given any adjuvant treatment. All of the participants in this study had a histologically confirmed diagnosis of NMIBC and had been monitored for the next three years at intervals of 3 to 4 months by recurrent cystoscopy and TURBT when needed.

Statistical analysis

Microsoft Excel 2013 was used to analyze all the data, create the graphs, and get the p-value.

Ethical approval

The ethical approval for the study was received, and the consents were signed by the patients.

Results

The mean age of the 32 patients diagnosed with NMIBC was 60.5 year, and the median age was 64 years. A total of 28 cases were older than 40 years of age (88%), and only 4 cases were younger than 40 years of age (12%). The age distribution of the patients was illustrated in Figure 1. Young and elderly NMIBC patients who participated in this study did not exhibit significantly different tumor behavior, prognosis, or progression or recurrence (P-value = 0.43). Only 3 cases out of 32 (9.4%) were females while 29 cases were males (90.6 %).
The majority of the patients in this study were from the city of Misurata, which is located in the Midland region of Libya. There were other patients from Liby's west, east, and south regions.
The NMIBC patients under study displayed a range of clinical symptoms. Hematuria was the primary symptom in 22 cases (69%), lower urinary tract symptoms (LUTS) were the primary symptom in 8 cases (25%), and the malignancy was unintentionally discovered in 2 patients (6%) while being evaluated for another illness. A total of 25 out of 32 cases with NMIBC (78%) were current or former smokers and a statistically significant relationship between smoking and hematuria was found in our cohort (P=0.01). Two cases of synchronous cancers of the ovary and rectum got chemotherapy among the seven nonsmoking pa-

tients. The two patients who passed away during this investigation from synchronous metastatic non-urological cancers. They were being followed up when the bladder urothelial cancer was unintentionally found.

A total of 23 cases (72%) were in the T1 stage, according to the staging of the NMIBC tissues that were examined. Ta was only found in 9 cases (28%) of the total. At the first TURBT, the cases were graded, with 19 patients classified as a grade I (59%), 11 cases as a grade II (35%), and 2 case grade III (6 %), which is substantially correlated with the disease's reported T stage (P value < 0.039), as shown in Table 1.

In a minimum 3-year follow-up, 6 cases (19%) experienced disease progression or recurrence. Two patients passed away during the follow-up period, and the causes of death in both cases were synchronous rectal and ovarian cancer. None of the individuals in the study passed away as a result of bladder cancer. Only one patient got a radical cystectomy after developing MIBC. The symptoms, pathological T stage, tumor grade, and smoking habit did not show a statistically significant correlation to future disease development or recurrence (table 2).

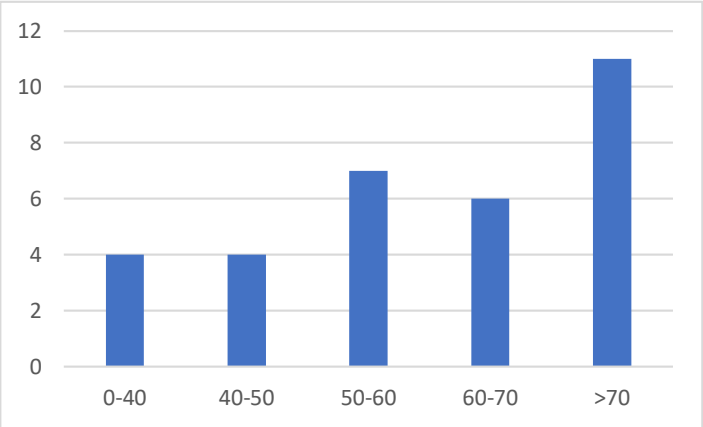

Figure 1. Age (year) distribution of the studied NMIBC patients

Table 1. The distribution of cases according to the T- stage and grade of the disease at time of diagnosis.

Grade	Ta	T1
Grade I	8	11
Grade II	1	10
Grade III	0	2
Total	9	23

Table 2. Summary of the studied parameters of NMIBC patients: age, sex, smoking, stage, grade, progression, and recurrence

Category	Number of cases	Percentage
Age		
> 40	28	44%
< 40	4	12%
Sex		
Female	3	10%
Male	29	90%
Smoker or ex-	25	78%
smoker	7	22%
Non-smoker		

Stage	23	72%
T1	9	28%
Ta		
Grade	9	32%
GI	13	13%
GII	2	6%
GIII	6	19%
Progression or recurrence of the disease	2	6.25%
Died		

Discussion

NMIBC is a condition that mainly affects elderly persons and strongly linked to smoking with variable behaviors (11). The molecular evolution of low-grade NMIBC and high-grade disease correlates with their clinical and biological behavior. This is consistent with the notion that high-grade and low-grade NMIBC may be viewed as fundamentally different illnesses (12). In our study, we noticed that patients with NMIBC had a disease with a varied biologic potential. Other than T stage and disease grading, the behavior of the disease varies depending on a variety of circumstances. According to van Rhijn et al. (2009), the three main factors influencing recurrence are multiplicity, tumor size, and past recurrence rate. The most crucial factors for progression are grade, stage, and CIS (11). Since there were no high grade instances in Ta stage, we were able to clearly demonstrate the relationship between T- stage and grade of the NMIBC. One of the two individuals in our study with T1 and grade III was the only one to advance to MIBC. This outcome can point to a unique, serious scenario.

A total of 212 patients with NMIBC had their disease histories described by Zieger et al. in 2000. They were initially identified as having Ta Grade I, II tumors, and 20 years of follow-up were conducted. In the trial, intravesical instillation was administered to just 14 participants; ten patients (4.7%) developed Ta Grade III or CIS, 18 patients (8.5%) T1, and 23 patients (10.8%) displayed muscle invasion or distant metastases (13).

In the present study, TURBT combined with adjuvant therapy had a very high prognosis in the management of NMIBC. At a minimum of three years after short-term follow-up, all of our patients were disease-free.

Raj et al. (2007) compared a historical cohort of 307 NMIBC patients to a more recent cohort of 589 individuals. Both groups received initial TURBT and adjuvant BCG therapy. DSS at 5 years improved in the current cohort (48% versus 31 %). The use of cystectomy for BCG failures, was credited by the authors as the cause of this improvement (15).

Age was not included in our investigation as a factor influencing the pathological behavior of the disease. Kurth et al.(1995) showed no correlation between numerous variables, including age, sex, and prior recurrence rate, and survival (16). This outcome is consistent with our observation that the aforementioned parameters do not correlate with the disease.

We concluded that NMIBC had a very good prognosis with TURBT and adjuvant intravesical chemo or immunotherapy as recommended treatment strategies. Additionally, NMIBC exhibited diverse behaviors and cannot be diagnosed based solely on clinical presentation due to a variety of factors influencing the disease's recurrence and progression. High grade NMIBC requires specific management, demonstrating that early cystectomy as a possible disease treatment strategy.

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