Journal of the Egyptian Society of Parasitology, Vol. 51, No. 2, August 2021
J. Egypt. Soc. Parasitol. (JESP), 51(2), 2021: 417 - 422
(Online: 2090-2549)

TRANSURETHRAL BLADDER BIOPSY AFTER POST INTRAVESICAL BCG THERAPY FOR SUPERFICIAL BLADDER CANCER PATIENTS

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Abstract

This study evaluated the role of routine biopsy from the site of previously resected superficial bladder tumor three months following resection and intravesical BCG therapy in the presence of negative urine cytology and cystoscopy. Thirty-two patients (21males and 11 females) with high-risk superficial transitional cell carcinoma (TCC) of the bladder were followed prospectively. All patients received a single six weeks course of intravesical Bacillus Chalmette-Guerin (BCG). Three months following resection, urine cytology was done. Cystoscopy was then performed and a routine biopsy from the previous resection site was taken. All patients included in the study had negative urine cytology and cystoscopy at the time of biopsy. Four (12.5%) patients were having TCC although they had negative urine cytology and cystoscopy at the time of biopsy. The histological recurrence was corresponded to T1G1 in two patients and T1G2 in the other two patients and the pathology after BCG treatment for the four patients was the same as before instillation. There were no statistically significant differences between patients with positive and negative biopsies with regard to the stage and grade of the tumor before resection, or the number of resected lesions.

Keywords: Egypt, Patients, BCG, Tumor bladder, Superficial.

Introduction

Generally, the stage T1 bladder cancers invade the lamina propria of the bladder and, despite sharing many of genetic features of muscle-invasive bladder cancers, were classified as non-muscle-invasive or superficial tumors (Jordan and Meeks, 2019). The initial treatment is transurethral resection with the attempt to remove all tumors. This must provide an accurate histological grade and stage, and from this information a prognosis can be determined (Herr, 1997). The important predictive factors that correlated with a new occurrence or true recurrence and development of a subsequent tumor with muscle invasion (high risk group) are a high tumor grade, lamina propria invasion T1, a positive cytology following resection, multifocal tumors, dysplasia, or carcinoma in situ (CIS) from mucosal biopsies of normal appearing urothelium, and a prior history of bladder cancer (Amling, 2001. The recurrence rate varied from 30 to 80% and progression with the muscle invasive tumor up to 30% (Stapp *et al,* 2000).

The intravesical Bacillus Chalmette-Guerin (BCG) instillation is recommended as the first choice to treat high-risk group patients (Van Der Meijden *et al*, 2003). After BCG treatment, high-grade carcinomas are cured in long term in one third of the cases, with recurrence in the same form in one third of the cases, and in second one third, evolved into an infiltrating form (Lebert, 1998). An accurate diagnosis of recurrence of the high-grade tumor was of the utmost importance, since it implied the major worsening of prognosis and led to the decision to perform cystectomy (Herr, 1992).

To assess response of intravesical BCG, urologists evaluated patients after intravesical therapy with transurethral bladder biopsies at time of 3-month cystoscopy (Skemp and Fernandes, 2002). This practice of routine bladder biopsy at 3-6 months; but many authors suggested instead that biopsies only to be carried out in selected patients based on initial pathology or 3-month cystoscopy and cytology (Highshaw *et al,* 2003; Murakami, 2007; Chen *et al,* 2018).

The study aimed to evaluate routine biopsy role from the site of resected superficial bladder tumor 3 months after resection and intravesical BCG therapy in patients with negative urine cytology and cystoscopy.

Subjects and Methods

Thirty-two patients with high-risk bladder superficial transitional cell carcinoma were prospectively studied over the year 2018.

The patients were examined by urine analysis, serum creatinine (Callens and Bartges, 2015), abdominal and pelvic US (Babjuk *et al,* 2017) and intravenous urography (IVU). Diagnosis was done by cystoscopy & complete lesion transurethral resection. All received a course of 6-weeks BCG. Dose was (90mg) diluted in (50ml) normal saline solution instilled by a urinary catheter, 2 weeks elapsed after the TURT before BCG treatment (Lamm *et al,* 2000). Post-BCG instillation, patients were asked to hold the fluid in their bladders for about 2hrs, & frequently change their positions to distribute treatment throughout urinary bladder. Follow up was done 3 months after lesion trans-urethral resection by urine cytology and scheduled for check cystoscopy where a routine biopsy was taken from resected tumor site. All patients showed negative urine cytology and cystoscopy at biopsy time.

Results

Details were given in tables (1, 2 & 3).

Table 1: Pathology of lesions pre-BCG instillation

Pathology	Number (%)
Tis (CIS)	2 (6.3)
Ta G2	6 (18.8)
Ta G3	2 (6.3)
T1G1	11 (34.4)
T1G2	9 (28.1)
T1G3	2 (6.3)
Lesion number =1	25 (78.1)
Lesion number =2	5 (15.6)
Lesion number =3	2 (6.3)

Thirty-two patients (21 males & 11 females) with ages 32-75 years (mean 55.6) were enrolled. Lesions pathology before BCG instillation showed Tis (CIS) in 2 (6.3%) patients, Ta in 8 (25%), and T1 in 22 (68.7%), with majority of single lesion in 78.1%.

Table 2.Biopsy results after BCG course

Pathology	Number (%)
Cystitis	14 (43.8%)
Cystitis with dysplasia	7 (21.9%)
Cystitis cystica & cystitis glandular	3 (9.4%)
Polyposis cystitis	4 (12.5%)
TCC	4 (12.5%)

Biopsy was done after six weeks of BCG course, four patients showed TCC, although with negative urine cytology and cystoscopy at the biopsy time.

Table 3: Comparison between patients with negative or positive biopsies

Pathology	Negative biopsy No. (%)	Positive biopsy No. (%)
T stage : Tis	2 (7.1%)	00
: Ta	8 (28.6%)	00
:T1	18 (64.3%)	4 (100%)
Total	28	4
Grading: G1	9 (34.6%)	2 (50%)
: G2	13 (50%)	2 (50%)
: G3	4 (15.4%)	00
Total	26	4
Lesions: 1	21 (75%)	4 (100%)
: 2	5 (17.8%)	00
: 3	2 (71.4%)	00
Total	28 (87.5%)	4 (12.5%)

In four positive biopsied patients, histological recurrence compared to T1G1 in two patients & T1G2 in another two patients. Pathology did not change as before instillation, without significant differences between patients with positive or negative biopsies, as to tumor stage and grade before resection, or resected lesions number.

Discussion

Bladder cancer is among the top ten most common cancer types in the world, with approximately 550,000 annual new cases (Richters *et al,* 2020). Bladder cancer is the commonest urogenital malignancy, after prostate cancer (Bray *et al*, 2018). It is the commonest genitourinary cancer in USA with symptoms mimics those of a urinary tract infection that time delayed diagnosis (Farling, 2017). The major risk factors for bladder cancer are environmental and occupational factors (Kiiluk *et al*, 2012), tobacco smoking besides, from lung cancer (Sasco *et al*, 2004), exposure to toxic industrial chemicals and gases, bladder inflammation due to microbes, parasites, and some medications side-effects as well as some adverse side-effects of medications (Zhang and Zhang, 2015). Among the parasites encountered in Egypt and cause the bladder cancer are *Schistosoma haematobium* (Gaber *et al,* 2020), and chronic *Trichomonas vaginalis* was associated with prostate cancer (Saleh *et al,* 2021). Othman and Soliman (2015) considered that schistosomiasis was plagued the Egyptians since the ancient time.

Boyd (2003) in USA reported that bladder cancer still the leading risk of malignant neoplasm in men. The Bacillus Calmette-Guerin (BCG) was a accepted treatment for superficial bladder malignancy. Khaled (2005) in Egypt found that bladder cancer was the commonest malignancy among the Egyptian males (16%), with >7900 annual deaths, strikingly higher than many countries worldwide. Fedewa *et al.* (2009) in Egypt added that the bladder cancer was the commonest malignancy among Egyptian males due to *S. haematobium*, a major risk factor for squamous cell carcinoma (SCC), but, transitional cell carcinoma (TCC) incidence increased, while SCC declined. Salem and Mahfouz (2012) in Egypt reported that the incidence pattern of various histologic types of bladder cancer were changed, with most cases now transitional cell carcinoma, in contrast to the findings in the earlier Egyptian series. Antoni *et al.* (2017) in France found that the recorded patterns and bladder cancer incidence worldwide reflected the prevalence of tobacco smoking, but infection with *S. haematobium* and other risk factors were major cause nearly among all Arabian populations. Amin *et al.* (2019) in Egypt reported that the old concept that schistosomiasis associated with SCC must be re-evaluated as many cases were associated with TCC. They added that based on histopathological proved schistosomiasis was not accurate and led to irrelevant data. Hatta *et al.* (2021) in Malaysia correlated between *S. haematobium* and bladder cancer.

Moreover, BCG instillation treatment reduced the risk of progression of high-grade bladder cancer and carcinoma in situ (Van Der Meijden *et al,* 2005). However, as about 50% of complete responders may eventually experience recurrences with a risk of invasion and/or extravesical recurrence, early and precise detection of cases resistant to BCG instillation is necessary (Jakse *et al,* 2001). Lenis *et al.* (2020) in USA reported that the bladder cancer being a common malignancy in women and the 4th most common malignancy in men. They added that while intravesical BCG remained the mainstay of therapy for intermediate & high-risk non-muscle-invasive bladder cancer, therapeutic options for muscle-invasive and advanced disease included immunotherapy with checkpoint inhibition, targeted therapies, & antibody-drug conjugates.

In the present study, no cystoscopy biopsies were positive in patients with mucosal erythema and negative cytology. Dalbagni *et al.* (1999) in USA reported that bladder biopsy is not necessary in patients 3 months after receiving BCG who have a normal office cystoscopy or an erythematous bladder and normal urine cytology. Skemp and Fernandes (2002) in USA also found that patients with papillary TCCB with negative cystoscopic and negative urine cytologic results

were safely be spared routine transurethral bladder biopsy with its associated cost and morbidity. But, patients with carcinoma in situ were very likely to have persistent abnormal cytologic or abnormal cystoscopic results warranting investigation with biopsy and benefited from routine scheduled biopsy. Highshaw *et al.* (2003) didn't do cytology examinations, but recommended limiting biopsies to patients with suspicious cystoscopy findings. Guy *et al.* (2006) in France found that this tactic resulted in four false negatives out of 84 patients with a negative cystoscopy, and the four false-negative patients presented high-grade tumors on histology. Murakami *et al.* (2007) in Japan did not recommend the routine bladder biopsy in patients with negative cystoscopy and negative urine cytology. They found that of 1/48 patients with negative cystoscopy and urine cytology had a positive bladder biopsy.

In the present study, only 4/32 (12.5%) patients with negative urine cytology and cystoscopy showed positive bladder biopsies with high-risk superficial urothelial tumor. Hara *et al.* (2009) reported that false-negative cytology was attributed to the intravesical BCG therapy effect, which decreased urine cytology sensitivity.

The sensitivity of urine cytology for recurrence of high-risk tumors was a parameter varied from 44% up-to 97% (Bastacky *et al*, 1999). The sensitivity was reduced by its inability to detect low-grade tumors whose risk of progression was very low, and therefore do not require early diagnosis. Otherwise, interpretation of urine cytology findings after BCG treatment was difficult without an expert pathologist (Molinie *et al,* 2003). Guy *et al.* (2006) found that the sensitivity of cytology was 56%, and its specificity was 92% and cystoscopy and urine cytology combined had a sensitivity of 100% for the detection of bladder recurrence after BCG treatment. They concluded that the negativity of these two examinations therefore makes it possible to avoid systematic biopsies and, consequently the usefulness of cystoscopy as an additional procedure. But, Lightfoot *et al.* (2012) reported that the previous studies that did not recommend biopsy with a negative cystoscopy and cytology had limitations. A variable number of biopsies (3-7) and location sites limited study (Skemp and Fernandes (2002).

Nevertheless, Guy *et al.* (2006) carried out thorough and systematic biopsies; and did not carry out biopsies on all patients undergoing treatment with a history of CIS or Ta disease, thereby limited their results. Murakami *et al*. (2007) in Japan found that routine transurethral biopsy of bladder for evaluating the response to BCG intravesical therapy was not indicated in patients who have no visible tumor on cystoscopy and negative urinary cytology. Lightfoot *et al.* (2012) concluded that patients with thorough and consistent biopsies of the bladder and prostate are more likely to have bladder cancer recognized, even in the negative cystoscopy and negative cytology.

Hara *et al.* (2009) in Japan reported that performing routine bladder biopsy and urine cytology helped in the early detection of the BCG-resistant cancer in 10/63 (16%) patients with a normal appearing bladder mucosa on cystoscopy and negative cytology. May *et al.* (2003) in Germany prospectively carried out six random bladder biopsies on normal appearing urothelium in 1033 patients with bladder cancer, and in 128 (12.4%) cancer was in areas of normal appearing urothelium. Improved understanding of the molecular biology and genetics of bladder cancer has evolved the way localized and advanced disease is diagnosed and treated.

While the intravesical BCG has remained the mainstay of therapy for the intermediate and high-risk non-muscle-invasive bladder cancer, the therapeutic options for muscle-invasive and advanced disease has expanded to include immunotherapy with checkpoint inhibition, targeted therapies, and antibody-drug conjugates (Peyrottes *et al,* 2021).

Conclusion

Generally, bladder cancer ranged from unaggressive and noninvasive tumors that recur and commit patients to long-term invasive surveillance, to aggressive and invasive tumors with high specific mortality.

The present data which did not recommend biopsy in a negative cystoscopy and cytology showed limitations. The presence of controversies regarding whether to perform a routine transurethral bladder biopsy at the time of the first follow up after BCG instillation, it is better to combine routine biopsy with cytology and cystoscopy to increase the sensitivity of early detection of BCG failures and tumor recurrences.

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