

## Bladder Mucosal Pathological Changes Accompany High Grade and Squamous Cell Bladder Tumors

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### ABSTRACT:

#### BACKGROUND:

Carcinoma of the bladder is the second most common cancer in Iraq. The status of the bladder urothelium other than the principal lesions can provide distinct diagnostic information with regard to treatment response and outcome. Positive mucosal biopsy results are a significant indicator of intravesical recurrence. Currently, in our urological practice, the importance of performing this step in cystoscopy is relatively underestimated.

#### OBJECTIVE:

The objective of this study is to carry out a histological assessment of 'extra-tumor' bladder mucosa for dysplasia, and correlate the resulting findings of dysplasia with the grade, the type, and the macroscopic appearance of the tumor.

#### MATERIALS AND METHODS:

A total of 350 biopsies were taken by cystoscopy from 68 patients admitted with bladder tumors, either by cold-cupped biopsy forceps or resectoscope as part of TUR of the tumor. Normal-looking mucosa of the bladder was included in each patient's biopsy in a four quadrant way. All biopsies were examined by the same histopathologist. All patients were managed according to their presentation, cystoscopic and histopathological findings.

#### RESULTS:

Statistical analysis showed that the highest significant difference was obtained in patients with tumor grade, low against high grade ( $p < 0.005$ ). However, a noticeable difference was found in the other two comparison groups, namely, the type, transitional against squamous and the macroscopic appearance, papillary against solid ( $p < 0.05$ ).

#### CONCLUSION:

The high grade, solid tumors and squamous cell carcinoma are associated with general bladder mucosal dysplastic changes which may exclude the bladder preserving procedures as an option of surgical treatment. In Iraq, more extensive studies are necessary to come out with appropriate guidelines for a better treatment and outcome of bladder carcinoma which is a major health problem.

**KEYWORDS:** bladder carcinoma, cystoscopy, dysplasia, histopathology, TCC, SCC.

### INTRODUCTION:

Urinary Bladder carcinoma is the second most common cancer in Iraq<sup>(1)</sup>. The most common histopathological type is the squamous cell carcinoma (SCC)<sup>(2)</sup> because schistosomiasis (due to *Schistosoma hematobium*) is endemic in Iraq, especially in southern provinces<sup>(3)</sup>, but transitional cell carcinoma is frequent. In this country, cystoscopic examination is the mainstay tool as a primary resort investigation in older patients presenting to urologist with intermittent painless hematuria, or those with bladder mass on ultrasonic or CT examination. It allows visualization of the lesions in terms of size, site, number, relation to

ureteric orifices, and accordingly, biopsy is taken, whether cold-cupped, or by resectoscope. The position of the patient also facilitates bimanual examination under anesthesia (EUA) for staging of the tumor. Biopsies taken from the masses are sent to the pathologist to determine the type and grade of the tumor. However, multiple biopsies are *infrequently* taken from suspicious bladder mucosa surrounding the mass, or from normally-appearing mucosa. This setting decides the final modality of treatment, whether intravesical chemotherapy, TUR of the bladder tumor (TURBT), partial cystectomy, or radical cystectomy.

Soloway et al concluded that the status of the bladder urothelium other than the principal lesions can provide distinct diagnostic information with

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regard to treatment response and outcome, TUR or cold-cup biopsy of these areas can be therapeutic and diagnostic<sup>(4)</sup>. Positive mucosal biopsy results are a significant indicator of intravesical recurrence in patients with superficial bladder carcinoma<sup>(5)</sup>. Some studies suggest that the additional value provided by biopsies from random sites of normal-appearing tissue at the time of resection appears to be minimal, and, theoretically, the process may aid tumor implantation<sup>(6, 7)</sup>. Select biopsies of suspicious areas, however, are an important part of a complete evaluation. Overlooking this point can result in a faulty work-up of the patient management since dysplastic or neoplastic changes in areas other than the principal lesion can not be overruled. Currently, in our urological practice, the importance of performing this step in cystoscopy is relatively underestimated.

The objective of this study is to carry out a histological assessment of 'extra-tumor' bladder mucosa, and correlate the resulting findings of dysplasia, with the type, the macroscopic appearance, and the grade of the tumor.

### **PATIENTS AND METHODS:**

Sixty eight (68) patients with bladder carcinoma presenting to the urology department in Al-Karama Teaching Hospital, a general tertiary hospital, during the period between 2002 and 2007, were included in this study. Most of them were admitted to the ward one to two days prior to cystoscopy. Some were referred from other departments in the hospital. Complete hematological and blood chemistry assessment was done to them, the bladder tumor for each one, was basically confirmed by ultrasonic examination in the same hospital.

Cystoscopy was done under G/A by rigid 20 F cystoscope, with 25° telescope lens. The irrigant fluid was sterilized distilled water. Resection of the tumor was done by a 26 F non-continuous flow resectoscope sheath.

The tumor mass was dealt with according to its size, site, and macroscopic appearance. Small to moderate size tumors were completely resected, other tumor foci were fulgurated by roller-ball electrode. While huge tumors with multiple masses were de-bulked to the minimum size feasible. The stage of the disease, accomplished by bimanual EUA, decided whether the tumor site was totally resected or biopsied or more radical intervention

would be necessary. Bleeding was dealt with by coagulation.

Multiple cold-cup biopsies were taken from normal-looking sites in the urinary bladder in a four quadrant plan as close as possible to the ureteric orifices. They were covered with appropriate antibiotics during the postoperative period. There were no complications during and after the biopsies and the urethral catheter was removed on the third postoperative day.

A total of 350 biopsies were sent for histopathological examination, after being preserved in a physiological solution. Both specimens, i.e. from tumor and from normal-looking mucosa were studied histologically by the same pathologist.

The data collection was made by a 'Patient Data Sheet' form that recorded the complete profile of each patient including: name, age, sex, date of admission, presentation, ultrasonic findings, and main laboratory investigation findings; in addition to the operative findings: stage of the tumor and macroscopic appearance, and histopathological results in regard to type and grade of the tumor as reported by the histopathologist.

Statistical analysis of the data was made by the computer software Microsoft Office 2010 and double-checked by the SPSS.

### **RESULTS:**

Patients' age ranged between 55 and 80, with an average of 66 years: 42 of them were males and 26 were females; a male: female ratio of 1.6:1. Average patients' stay in hospital was 24 hours. Postoperative period was uneventful.

Data was analyzed by the  $\chi^2$ -test, with the subgroups of each comparison category taken against the incidence of dysplasia or 'no dysplasia'. The level of significance (p value) < 0.05 was selected to decide significant differences.

Staging of the tumor revealed that muscle-invasion, whether superficial or deep, is a significant feature in the patients undergoing the study: most of them (45%) had stage T2a-T2b, while 5% of them only had stage Ta-T1.

The histo-pathological pattern of the biopsies taken from the tumors was predominated by transitional cell carcinoma: 54 patients (79%). Squamous cell carcinoma was found in 12 patients (18%), adenocarcinoma in 2 patients (3%). As shown in Table 1.

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**Table 1: Histopathology of tumor site biopsies:**

Histopathology pattern	Number (patients)
TCC	54 (79%)
Squamous Cell Ca.	12 (18%)
Adenocarcinoma	2 (3%)
Total	68

Biopsies taken from the adjacent normal-looking mucosa revealed dysplasia in 30 (56%) patients with TCC, 10 (83%) patients with squamous cell carcinoma, and none of the patients with

adenocarcinoma, i.e., a total of 40 of the 68 patients (59%) had dysplastic changes in the 'extra-tumor mucosa' (Table 2).

**Table 2: Histopathology of extra-tumor mucosa**

Histopathology pattern	Number of patients with dysplasia
TCC	30/54 (56%)
Squamous Cell Ca.	10/12 (83%)
Adenocarcinoma	0/2 (0%)
Total	40/68 (59%)
$X^2 = 6.1$ / P-value = 0.04804 ( P < 0.05)	

Study of the macroscopic appearance of the tumor on cystoscopy showed that 47 patients (70%) had papillary tumor, while 19 patients had sessile (solid) appearance (28%). Ulcerative tumors were

found in 2 patients (2%). Dysplasia was detected in 24 of the papillary group (51%), 16 of the sessile group (84%), and in none of the ulcerative group. Table 3 shows the above results.

**Table 3: Correlation between appearance of the tumor and dysplasia**

Tumor cystoscopic appearance	Number of patients	Patients with dysplasia
Sessile (solid)	19 (28%)	16 (84%)
Papillary	47 (70%)	24 (51%)
Ulcerative	2 (2%)	0 (0%)
Total	68	40 (59%)
$X^2 = 9.1$ / P-value = 0.010667 ( P < 0.05)		

High grade tumors were found in 36 patients (53%), while 26 patients had grade II, and 9 patients had grade I tumors. Assessment of the grade of the tumor as related to the dysplastic

changes found in normal-looking mucosa showed that 26 of 36 patients with grade III, 14 of 26 patients with grade II, and none of the six patients with grade I; had dysplasia, as shown in Table 4.

**Table 4: Correlation of dysplasia with grade of the tumor**

Grade of the tumor	Number of patients	Patients with dysplasia (%)
Grade III	36 (53%)	26 (72%)
Grade II	26 (38%)	14 (54%)
Grade I	6 (9%)	0
Total	68	40 (59%)
$X^2 = 11.32$ / P-value = 0.003174 ( P < 0.005), very significant.		

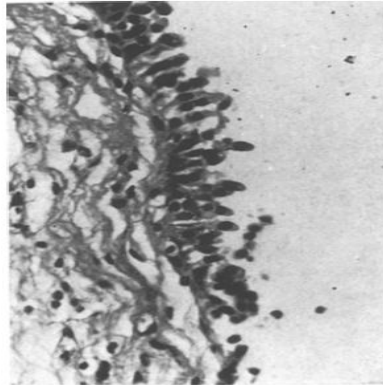
Statistical analysis showed that the highest significant difference was obtained in relation to tumor grade (p<0.005). However, a noticeable

difference was found in the other two comparison groups, namely, the type and the macroscopic appearance (p<0.05).

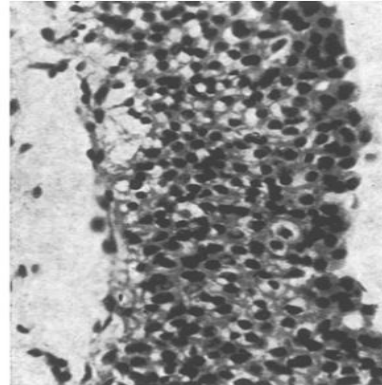
### DISCUSSION:

The term *dysplasia* denotes epithelial changes that are intermediate between normal urothelium and carcinoma in situ (CIS). Dysplastic cells have large, round, notched, basally situated nuclei that

do not exhibit the normal epithelial polarity (Fig. 1). Dysplastic epithelium does not have an increased number of cell layers or mitotic figures (Murphy & Soloway, 1982<sup>(8)</sup>). (Fig. 2)



**Fig 1: Dysplasia**



**Fig 2: Normal Urothelium**

Random biopsy of the vesical mucosa is a widely used approach to assess the underlying risk potential of the bladder mucosa since neoplastic recurrences could be attributed to sub-endoscopic lesions of the bladder which could be easily missed if biopsy is taken from the tumor mass only. It was reported that 4 of 26 patients (15%) with moderate dysplasia develop high-grade urothelial cancer (median follow-up, 3.5 years), 3 with muscle invasion (Cheng et al). A positive biopsy is an alarming sign that has a great prognostic value<sup>(9)</sup>. Schade and Swinney concluded that bladder cancer is a gross manifestation of a diffuse neoplastic diathesis of the urothelium.<sup>(10)</sup>

This conclusion applies to the three parameters mentioned in our study, namely: grade, type and macroscopic appearance.

In our study the most significant statistical relation ( $p < 0.005$ ) was found between the grade of the tumor and the presence of dysplastic changes of the normal-looking mucosa (72%). This is in accordance with other series which stated that dysplasia, and other mucosal abnormalities, were reported in association with high grade bladder tumors<sup>(11, 12)</sup>.

The life history of *Schistosoma haematobium* in Iraq is described for the first time in 1936 by Mills et al<sup>(3)</sup>. Squamous cell carcinoma is a dreadful complication of vesical bilharziasis. This disease is of multi-focal nature, since the contents of the ova trapped in the tissues and the death of the

organisms cause a severe local reaction, with infiltration of round cells, monocytes, eosinophils, and giant cells that form tubercles, nodules, and polyps leading eventually to fibrosis or metaplasia resulting in squamous cell carcinoma<sup>(13)</sup>.

In our study, a very significant statistical relation, ( $p < 0.05$ ), is evident between patients with squamous cell carcinoma (SCC) and dysplasia of the apparently normal mucosa (83%). Lesions of SCC are often nodular and invasive at the time of diagnosis. Histologically, they appear as poorly differentiated neoplasms<sup>(14)</sup>. This could explain the high incidence of atypia associated with this type of tumor.

Nearly half (53%) of our newly diagnosed patients had high grade tumor which is slightly higher than other series. Messing et al stated that 40 to 45 percent of newly diagnosed bladder cancers are high-grade lesions, more than half of which are muscle invading or more extensive at the time of diagnosis<sup>(15)</sup>. The higher number of patients with squamous cell carcinoma, in our country, could be a reason behind this observation. 'Grade II disease' was detected in 38% of our patients. Although, clinical evidence dictates that transitional cell carcinoma has two major variants, low grade and high grade,<sup>(16, 17)</sup> while the intermediate grade (grade II) could only be a mixed variety of grade I and grade III. This sharp cut classification of bladder tumors could be of great prognostic benefit as shown in the following Table:

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**Table 5: Relation of World Health Organization/International Society of Urological Pathologists (WHO/ISUP) grades to progression<sup>(18)</sup>.**

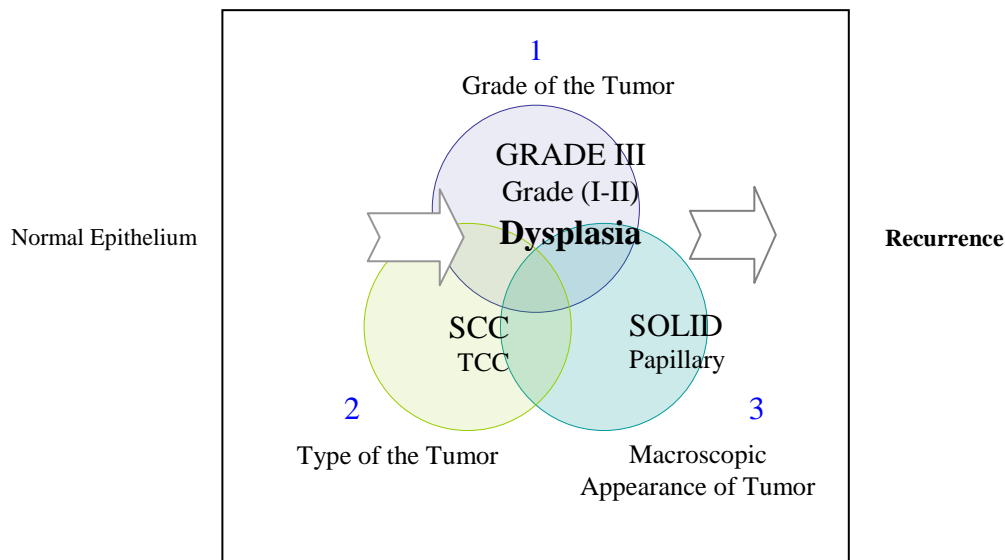
Fate	Low Grade (n = 42)	High Grade (n = 62)
Recurrence	64.1%	56.4%
Any stage progression	10.5%	27.1%
Lamina propria invasion	2.6%	8.3%
Detrusor muscle invasion	5.3%	6.3%
Metastases/death	10.6%	25.0%

A recent study suggested that the oncoprotein bcl-2 which is activated in bladder tumorigenesis was restricted to the basal cell compartment in normal urothelium and mild dysplasia, while in moderate and severe dysplasia its expression was detectable also in the upper regions. Excess bcl-2 expression was found in 50% of carcinomas, and a larger proportion of high-grade TCCs showed bcl-2 expression compared with that of low-grade TCCs.<sup>(19)</sup> An Expert Panel on Urologic Imaging by the American College of Radiology (ACR)

concluded that the likelihood of recurrent or metastatic disease increases with the presence of adjacent or remote bladder mucosal changes.<sup>(20)</sup>

### CONCLUSION:

The high grade, solid tumors and squamous cell carcinoma are associated with general bladder mucosal dysplastic changes which may exclude the bladder preserving procedures as an option of surgical treatment. All in all, the interplay of the three parameters tackled in our study can be diagrammed in Figure 3.



**Fig. 3 : Dysplasia as a common manifestation of tumor features.**

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Carcinoma of the bladder continues to be a major health problem in Iraq and needs to be addressed properly by re-evaluating its size. Further, more extensive studies are necessary to come out with appropriate guidelines for a better treatment and outcome.

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