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URO-ONCOLOGY: Bladder Tumors

RANDOM BIOPSIES AND RECURRENCE RATES IN BLADDER TUMORS*

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Transitional cell tumors of the bladder are reported, in different series, to have five-year recurrence rates of 75-85% [1-3]. Some of the factors which contribute to the high recurrence rates include: size, muscular invasion, the high grade and incomplete resection of the primary tumor[3,4].

In recent years epithelial changes occurring in the normal mucosae of bladders bearing transitional tumors have drawn increasing attention. It has been suggested that these changes in the forms of hyperplasia, metaplasia, dysplasia and carcinoma *in situ* give rise to future recurrences and/or multicentric tumors.

In this study, random biopsies from standard sites were obtained from endoscopically normal mucosae of bladders with transitional cell tumors. The same specimens were utilized to assess the degrees of blood group antigen loss. The results were correlated with recurrence rates of tumors during regular follow-up examinations of the patients.

Material and Methods

The study included 25 patients between 58 and 81 years of age. There were 22 males and 3 females. Random biopsies were taken from four standard sites:

1. The lateral side of the right ureteral orifice,
2. The lateral side of the left ureteral orifice,

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3. The posterior wall,
4. The normal appearing mucosa in the vicinity of the tumor.

Tissues were fixed in 10% formalin, embedded in paraffin and processed in the routine manner. Sections were stained with hematoxyline and eosin and evaluated blindly. Histopathologic findings were classified as:

1. Negative (normal urothelium),
2. Hyperplasia,
3. Squamous metaplasia,
4. Dysplasia,
5. Carcinoma *in situ*.

For analysis of blood group antigens, paraffin sections were treated with antiserum to blood group antigens, followed by fluorescein-labelled anti-human globulin. Staining of tumor tissue, normal urothelium and blood vessel endothelium, were recorded separately.

The patients were followed-up at least once every three months with cystoscopy. Seven patients with a benign prostatic disease undergoing cystoscopy and with no apparent bladder disease, comprised the control group.

Results

The results of an analysis of 100 biopsy samples taken from 25 patients with tumors are shown in Table I. Six samples were regarded as insufficient for diagnosis. Correlation of the grade of the tumor with the results of the random biopsies is given Table II. Statistically significant results were found between the presence of hyperplasia and grades I and IV tumors only, whereas the presence of dysplasia correlated significantly between grades I and III; I and IV; and II and IV. In other words, the chance of dysplasia occurring in mucosae was seen to increase with the

TABLE I

Histopathological Diagnosis in 100 Biopsy Samples

Diagnosis	% Observed
Dysplasia	40.49
Hyperplasia	17.35
Squamous metaplasia	9.91
Carcinoma *in situ*	4.13
Normal	28.09

TABLE II

Correlation of Intraepithelial Lesions with Grade of Tumor

Grade	Total	Dysplasia	Hyperplasia	Squamous metaplasia	Carcinoma *in situ*	Normal
I	3	2	—	1	—	7
II	12	20	9	8	2	16
III	3	8	3	2	—	4
IV	7	19	9	1	3	7
Total	**25**	**49**	**21**	**12**	**5**	**34**

TABLE III

Correlation of Intraepithelial Lesions with Stage of Tumor

Stage	Total	Dysplasia	Hyperplasia	Squamous metaplasia	Carcinoma *in situ*	Normal
T_1 (SF)	6	4	2	4	—	15
T_2, T_3, T_4 (INV)	19	45	19	8	5	19
Total	**25**	**49**	**21**	**12**	**5**	**34**

SF : Superficial, INV : Invasive

advancing grade of the tumor. There was no significant relationship between grade of tumor and occurrence of normal mucosa in the biopsy samples.

The distribution of biopsy findings in relation to the stage of the tumors is shown in Table III. The chance of encountering dysplasia between superficial (T_1) and invasive (T_2, T_3, T_4) tumors was highly significant. The occurrence of normal epithelium also decreased with advancing tumor grade. Although no statistical difference was observed between the two groups for the occurrence of carcinoma *in situ,* all carcinoma *in situ* lesions were found in patients with invasive tumors.

Analysis of the cases according to previous treatments showed no significant differences in rates of intraepithelial lesions in patients who had previously received surgical treatment as compared with those presenting for the first time.

Pathological changes were observed more frequently in biopsies taken from either ureteral orifice and the vicinity of the tumor, as compared to those from the posterior wall.

No attempt was made to analyze a relationship between the location of the primary tumor and the presence of epithelial lesions because numbers in each group were too small.

The rate of recurrence of tumors within a minimum follow-up period of 3 months is shown in Table IV. There was a significant correlation between the presence of dysplasia and the rate of recurrence. No correlation was observed for hyperplasia, or carcinoma *in situ*.

TABLE IV

Distribution of Intraepithelial Lesions between Primary and Recurrent Tumors

	No. of patients	Dysplasia	Hyperplasia	Squamous metaplasia	Carcinoma in situ	Normal
Recurrent	14	27	12	3	2	21
Primary	11	22	9	9	3	13
Total	25	49	21	12	5	34

None of the biopsies taken from the 7 control patients without bladder disease showed hyperplasia, dysplasia or carcinoma *in situ*. One sample contained areas of squamous metaplasia.

Immunofluorescence studies in 7 tumors revealed loss of blood group antigen A in all. Blood vessel endothelia stained positive in all of these tissues, as expected. In 4 random biopsy (+) staining of epithelial cells (less than 5%) was observed.

Discussion

High rates of recurrence and multicentricity of urothelial bladder tumors are well known[1-3,5]. Numerous studies have suggested that microscopic intraepithelial changes in bladders harboring transitional cell tumors might be one factor contributing to recurrences[6-8]. As a result, transitional tumors are now generally being regarded as manifestations of widespread disease of the urothelium which has undergone microscopic changes of a malignant or premalignant nature[9].

In the present study, random mucosal biopsies from standard sites revealed 40.49% dysplasia, 17.35% hyperplasia, and 4.13% carcinoma *in situ*. Various studies have reported intraepithelial abnormalities ranging from 25-56% [10-12]. Although dysplasia

is the most commonly encountered change and carcinoma *in situ* the least, ratios appear to vary according to patient group, classification of lesions, grades of tumors etc.

Localization of abnormal lesions in the bladder as seen in this study, is also consistent with the literature, the most frequent sites being the vicinity of the tumor and the ureteral orifices[11,13].

The grade of the primary tumor also appears to bear some relation to the occurrence of intraepithelial changes in the mucosa. We observed a rate of dysplasia of 16% associated with Grade I tumors while 63% of Grade IV tumors were associated with dysplasia. Similar results were obtained by Heney et al[12] and the National Bladder Cancer Collaborative Group A studies[10].

Few studies in the literature report any relationship between dysplasia rates and the stage of the tumor. Cooper and co-workers[7] found different rates of dysplasia, hyperplasia and carcinoma *in situ* between superficial and invasive tumors. In the present study the occurrence of dysplasia and hyperplasia was found to be more frequent where there were invasive tumors.

No differences in the rates of occurrence of intraepithelial lesions were detected between recurrent lesions and primary (untreated) tumors.

This study showed a highly significant correlation between the presence of dysplasia and recurrence risk within the follow-up period. This is in agreement with the literature[8,12-15].

All 7 tumors examined in this investigation showed loss of blood group antigen A, whereas 4 random biopsy samples from these cases showed weak positive staining. Although immunofluorescence staining of paraffin sections has generally been used to detect loss of blood group antigens, the use of cryostat sections appears to increase the sensitivity of the assay and is preferred[16].

In conclusion, in this study of random biopsies in bladders harboring transitional cell tumors of the bladder, significantly higher rates of intraepithelial changes were found to be associated with the advancing grade and stage of the primary tumor as well as an increased risk of recurrence. This is in agreement with the current literature and adds further support to the view that urothelial neoplasia is a generalized disease of the epithelium. Treatment strategies must take this view into account in the future.

Summary

Random mucosal biopsies were taken from standard sites of the bladder in 25 patients with transitional cell tumors and 7 patients with benign prostatic disease. The tissues were examined for the presence of intraepithelial lesions, particularly

hyperplasia, metaplasia, dysplasia and carcinoma *in situ*. The same biopsy specimens were used in an immunofluorescence assay to detect loss of blood group antigens. There was a significant correlation between the grade and stage of the tumor and the presence of intraepithelial lesions. In the follow-up period there was a higher rate of recurrence among patients with dysplasia and hyperplasia in mucosal biopsies.

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