A CLINICO-PATHOLOGICAL SURVEY OF EXOPHYTIC TUMORS OF THE URINARY BLADDER

I. An Analysis of the Structure of the Fibro-vascular Cores With Special References to the Clinical Prognosis

BY

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ABSTRACT

In this paper the results of the clinicopathological study on a total of 79 bladder tumor cases are presented. They are principally related to the stromal proliferation or branching of the tumors. The tumor cases consist of those with a good prognosis as well as those with a poor prognosis.

In the former category there are 61 cases with a long survival history (with or without recurrence); the remainder (18 cases) had a history of a short survival (dying within 2 years).

Histologically there was a marked difference in the regularity of the stromal branching of the tumor between those cases with a long survival history and those cases with a short survival history. In the former group the regular type of stromal branching was predominant; in the latter group the irregular type was predominant.

INTRODUCTION

In the literature many morphological criteria for determining the malignancy of the urinary bladder tumor have been suggested1-41. However, they do not always guarantee an accurate clinical prognosis. Thus it is preferable to find some additional criteria for the malignant grading of urinary bladder tumor, which relates the clinical prognosis as exactly as possible. In this paper, an attempt is made to elucidate the malignancy grading of urinary bladder tumor by analysing the stromal pattern as well as to elucidate the interrelation between the proliferation of the tumor cells and the tumor stroma.

MATERIALS AND METHODS

Seventy-nine urinary bladder tumor cases were analysed histopathologically. They included those cases with a good prognosis (surviving more than 5 years) as well as those cases with a poor prognosis (dying within 2 years). The slides were reviewed and the pathological diagnosis was confirmed in all instances from the point of cell differentiation, tumor invasion and pat-
tern of stromal proliferation (branching). The differentiation of the tumor cells was analysed into four degrees, e.g. highly, well moderately and poorly differentiated. The invasion of the tumor was classified microscopically into three stages, i.e. no invasion-submucosal invasion, muscular invasion and beyond the muscular layer.

First of all, proliferation of the fibrovascular cores (tumor stroma) was confirmed microscopically under a low power magnification or under a loop (Table 1, Fig. 7, 8). The proliferation pattern was estimated as being of a regular type when the fibrovascular cores in the tumor (hereafter abbreviated as F-V cores) branched regularly or uniformly from the base to the periphery like the regular and uniform branching of a tall cedar tree (Fig. 8). Next, the slenderness or breadthness of the F-V cores was estimated as being of a regular slender type or of a regular broad type. When the proliferation of the F-V cores was irregular or not uniform from the base to the periphery, these patterns were defined as being of an irregular type (Fig. 7). The scattered type is defined as the proliferation of the tumor stroma which still shows continuity, but loses regularity or uniformity (Fig. 5). The chaotic type is defined as the stroma losing continuity in branching, having an irregularly shaped fibro-vascular core, and with the tumor cells and tumor stroma intermingling irregularly (Fig. 6). The intermediate pattern is defined as that in which

<table>
<thead>
<tr>
<th>Regular Type</th>
<th>Irregular Type</th>
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<tbody>
<tr>
<td>Slender</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Broad</td>
<td>Scattered</td>
</tr>
<tr>
<td>Mixed</td>
<td>Chaotic</td>
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Table 1. Identifiable Stromal Proliferation of the Exophytic Tumors

Fig. 1(a), 300×*

Fig. 1. A highly differentiated tumor. Each papillae is separated and tumor cells are freely proliferating.

* This photo was printed white on black being reversed from the original film to make the print in sharp contrast.
Fig. 2 (a), 100 \times

Fig. 2 (b), 1.9 \times

Fig. 2. A highly differentiated tumor with the regular and slender type of tumor stroma.

Fig. 3 (a), 20 \times

Fig. 3 (b), 1.6 \times

Fig. 3. A well differentiated tumor with regular and broad type of tumor stroma.
both the regular and irregular stromal proliferation is confirmed in the tumor (Fig. 4, 7).

**Results**

Of the 61 long survival cases, 55 (90.2%) were of the regular stromal proliferation type, whereas 4 (6.6%) were of the irregular proliferation type. Of the 18 short survival cases, 16 (88.9%) were of an irregular pattern, whereas 2 (11.1%) were of regular pattern.

Histologically, highly and well differentiated lesions (47 cases) showed a regular pattern in 97.9% of 46 cases, whereas there was only one case (2.1%) showing an irregular pattern (Table 8). Histologically, malignant lesions of moderately and poorly differentiated type (32 cases) showed an irregular pattern of stromal proliferation in 19 cases (59.3%), whereas those showing the regular pattern were 10 cases (31.3%).

Twenty-two cases were of the moderately differentiated tumor type. Of the eleven cases of regular stromal pattern, ten (90.0%) were the long survival cases and one (9.1%) was the short survival case. Of the nine cases with an irregular stromal pattern, six (66.7%) were the short survival cases and three (33.3%) the long survival cases.

Of the fifteen cases in the long survival group, ten (66.7%) were of the regular type in stromal proliferation and three cases (20%) were of the irregular type. Of the seven cases in the short survival group, one

![Fig. 4](image)

**Fig. 4.** A moderately differentiated tumor with stroma regularly and irregularly intermingled (Intermediate Type).

Table 2. Correlation of the Patterns of Stromal Proliferation to the Differentiation of Tumor Cells

<table>
<thead>
<tr>
<th>Cell Differentiation</th>
<th>Regular Type</th>
<th>Intermediate Type</th>
<th>Irregular Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total 79</td>
<td>Slender</td>
<td>Broad</td>
<td>Mixed</td>
</tr>
<tr>
<td>Highly Differentiated</td>
<td>15 (18.7)</td>
<td>6 + 4</td>
<td>3 + 1</td>
</tr>
<tr>
<td>Well Differentiated</td>
<td>32 (41.3)</td>
<td>7 + 8</td>
<td>5 + 6</td>
</tr>
<tr>
<td>Moderately Differentiated</td>
<td>22 (27.5)</td>
<td>1 + 1</td>
<td>1 + 4</td>
</tr>
<tr>
<td>Poorly Differentiated</td>
<td>10 (12.5)</td>
<td>0 + 0</td>
<td>0 + 0</td>
</tr>
</tbody>
</table>

Upper figure in each column: (left) Tumor cases with long survival (with no recurrence)

Lower figure in each column: Tumor cases with short survival
Fig. 5. A moderately differentiated tumor, the stromal branching of which is irregular scattered.

Fig. 6. A poorly differentiated tumor. The tumor stroma is diffusely and irregularly intermingled with tumor cells (Irregular Chaotic Type).
case (14.2%) was of the regular type and six cases (85.7%) were of the irregular type. Of the 57 cases of the regular type of stromal proliferation, 96.5% (55 cases) were in the long survival group, whereas 3.5% (2 cases) were in the short survival group. Of the 20 cases of the irregular type of tumor stroma, 80.0% (16 cases) were in the short survival group, whereas 20% (4 cases) were in the long survival group. Tumor cases of the highly differentiated type numbered fifteen (18.7%) and those of the poorly differentiated type ten (12.5%), whereas those of intermediate malignancy (well and moderately differentiated group) numbered fifty-four (68.8%). On the other hand, tumors with a regular stromal proliferation were seen in 57 cases (72.2%) and those with an irregular proliferation in 20 cases (25.3%), and only two cases (2.5%) were of the intermediate type.

Out of the 42 cases with a shallow invasion or no invasion, 40 cases (95.2%) were of the regular pattern type. Of the 8 cases with a deep invasion, 7 cases (87.5%) were of the irregular pattern type (Table 3).

**DISCUSSION**

It appears that there has been no study on the analysis of the morphological changes of the stromal proliferation of bladder tumors in relation to the clinical prognosis.

In the excellent illustration of Duke's report this delicate difference in the stromal proliferation between the papilloma and the less differentiated types of tumors has not been pointed out.

In those tumors with a morphologically benign appearance, the tumor stroma is reported to be slender or thin, and in those of the less differentiated types of tumors, the tumor stroma is reported to be broad.

However, there have been no studies on the delicate changes of the stromal pattern in relation to the clinical prognosis.

The authors have been interested in this fact and analysed whether there is a delicate difference in the stromal proliferation of the tumor among the patients with different survival period.

In these findings it should be emphasized that the identification of the stroma was done more objectively than on the cell atypism.

New additional criteria for the classification of the bladder tumors based on the interrelation between the tumor cells and the F-V cores was also suggested by the authors.

For the definition of cell differentiation, various gradings have been presented, i.e. grading in two, four or more degrees, but the definition of cell atypia tends to be rather subjective.

<table>
<thead>
<tr>
<th>Tumor Invasion</th>
<th>Total Cases (%)</th>
<th>Regular Type</th>
<th>Intermediate Type</th>
<th>Irregular Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submucosal</td>
<td>42 (53.8)</td>
<td>Slender 21</td>
<td>Broad 13</td>
<td>Mixed 6</td>
</tr>
<tr>
<td>Muscular</td>
<td>18 (23.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beyond Muscular Layer</td>
<td>8 (10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (12.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Correlation of the Patterns of Stromal Proliferation to the Tumor Invasion
The estimation of the depth of invasion may be objective.

Routine sectioning is not a reliable method to find the deepest lesion of invasion, because serial sectioning is not always performed in routine laboratory procedure.

From the morphological analysis of the tumors in the two groups, i.e. patients of the long survival group (more than 5 years) and patients of the short survival group (dying within 2 years), it is clear that mainly two types of stromal pattern of proliferation or branching can be recognized, that is the regular pattern and irregular pattern. The result of the stromal survey showed that most of the cases surveyed in this series fell into one of these two groups, e.g. 57 cases (71.3%) in the regular group and 20 cases (25%) in the irregular group, only 2.5% being of the intermediate type.

However, according to the criteria of malignancy from cell atypism, 68.8% of those showed intermediate malignancy (well and moderately differentiated type).

According to the criteria of malignancy from the stromal proliferation, as shown in Table 2, it definitely suggests that in the case of tumors with regular and uniform stromal proliferation, the prognosis is good (Fig. 1).

On the contrary, in the case of tumors of irregular stromal proliferation, the prognosis is poor (Fig. 5, 6).

Furthermore, analysis of the stroma seems to be very useful in analyzing moderately differentiated tumors (intermediate malignancy), which show varied clinical prognoses; in this group clinical prognosis is unpredictable, some having a good prognosis and some very poor. Here, tumor patients with a regular stromal pattern definitely showed a good prognosis and
those with an irregular pattern showed a poor prognosis.

From the point of carcinogenesis, where uniformity or regularity exist in both stromal proliferation and cell arrangement, a harmonized tumor proliferation might be suggested (Fig. 1).

Where there is evidence of disharmony between the rate of proliferation of the tumor cells and of the tumor stroma (i.e. in the case of a malignant tumor) we can predict that there is an acceleration in the potency of tumor proliferation and the prognosis will be poor (Fig. 5, 6).

Up to now the authors discussed this subject from the pathohistological point of view.

From the clinical point of view, it would be beneficial in further defining the malignancy of the tumor to use clinical methods which have recently been developed, e.g. cytology under direct vision\(^9\) and a fluorescent cystoscope assembly\(^10\), by which the tumor lesion is able to be identified very accurately.

In addition to the conventional method of histological definition, that is the method of defining cell atypism and invasion, the observation of the stromal pattern in the tumor would be a more effective and helpful method of defining tumor malignancy; especially the interrelation between morphological analysis of the tumor and its clinical prognosis.

Acknowledgement

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References

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"Gengo Mitani, Toshio Inada, Shigeru Suzuki, Fumio Owada, Iwao Fukui,"
read

"Gengo Mitani, Toshio Inada, Shigeru Suzuki, Fumio Owada, Iwao Fukui,"

"山田 信: Department of Pathology (Chief: Prof. Takashi Yamada), Tokyo University,"
read

"山田 信: Department of Pathology (Chief: Prof. Takashi Yamada), Dokkyo University,"