

Neoplastic Invasion of the Connective Stalks in Transitional Cell Papillary Tumors (TCPT) of the Bladder

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Summary. Neoplastic invasion into the connective stalks of transitional cell papillary tumors of the bladder was assessed in TUR specimens from new cases. There were 21 G1 cases, none of which showed invasion of the connective tissue stalk; this compared with definite invasion in 19 of 77 G2 cases (25%) and in 16 of 17 G3 cases (94%). During a 5 year follow-up period more of the stalk invasive cases had an unfavorable course (fatal outcome or total cystectomy) than of the stalk non-invasive cases; this was statistically significant ($p < 0.01$) for the whole group of patients and for the smaller group of patients with G2 tumors ($p < 0.05$).

Key words: Bladder, Bladder tumors, Transitional cell carcinoma, Urothelioma.

Introduction

Some transitional cell papillary tumors (TCPT) behave in an unfavorable fashion with local invasion and distant metastases, whereas some do not invade and do not metastasize and run a more favorable course.

A considerable amount of research has been concerned with predicting the behaviour of TCPT; electron microscopy [6, 8], ploidy [7, 10], morphometry [3, 15], synthesis of blood isoantigens [2, 13], localization of CEA [9, 18], and expression of blood group precursor T-antigen [1, 12] have been explored. The results and their practical significance are still debated. In practice histologic grading and staging remain the criteria utilized most for prognosis and patient management [4, 16].

Well differentiated (G0 and G1) tumors usually behave favorably and are conservatively treated; poorly differentiated (G3) tumors usually behave in a more malignant fashion and may require radical surgery; however, the great majority

of TCPT show intermediate degrees of differentiation (G2) causing dilemma in management [5, 11, 14]. The above mentioned studies and the different clinical courses of the patients with moderately differentiated (G2) tumors indicate that these tumors are heterogeneous with a variable behaviour that apparently cannot be identified by histologic grading.

For the purpose of staging, invasion is assessed in the lamina propria and in the muscular coat at the base of the tumor. However, the demonstration of the infiltrative properties of TCPT is not always feasible in the specimens from transurethral resections (TUR), because specimens from the base of the tumor may be absent or may be poorly representative (scanty, cauterized, and disorientated in tissue sections). Little attention has been paid to the patterns of invasion of the connective stalks in the exophytic part of TCPT although these patterns could be of practical use because they are identifiable even in TUR specimens that do not include the base of the tumor.

In this study we looked for neoplastic invasion of the connective stalks in the exophytic part of TCPT; the aim of the present work was to investigate:

- 1) the possibility of detection of the neoplastic invasion into the stalks of TCPT in routine sections from transurethral resections;

- 2) the possible relationships between neoplastic invasion into the stalks of TCPT and unfavorable behaviour of the tumor.

Tiltman [17] has already investigated these two topics and concluded that invasion of the stromal stalks is not an indicator of subsequent behaviour of the tumor; he used protrusions and islands of epithelial cells in the stroma with incomplete lining of a silver stained basement membrane as evidence of stromal invasion and recurrence, occurring more than 4 weeks after the original biopsy, as indicator of tumor behaviour. We have used different criteria for diagnosis of invasion and as indicators of tumor behaviour.

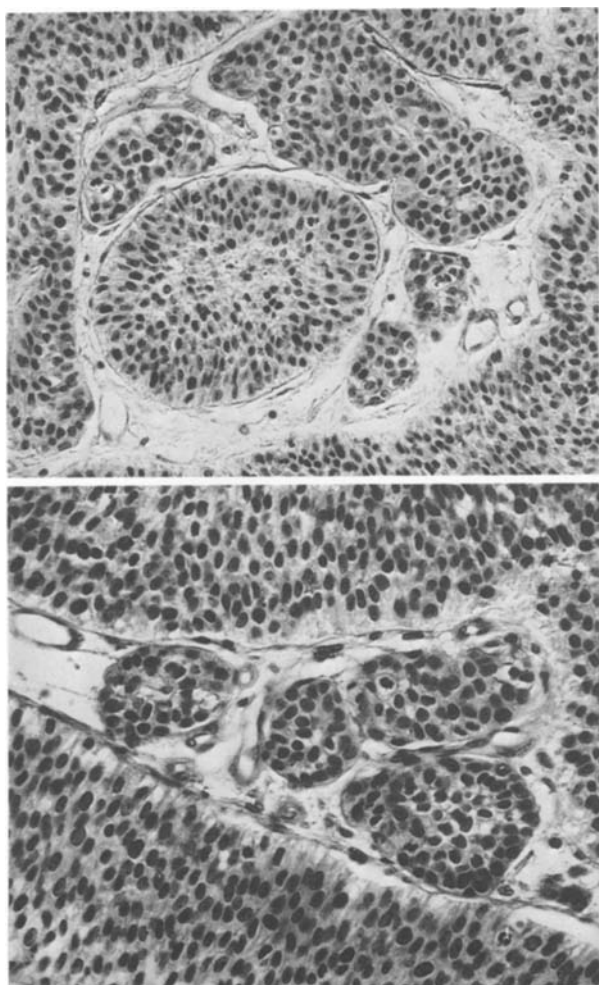


Fig. 1. Patterns negative for invasion of the stalks (2 different cases): the cellular nests in the connective stalks are large, with rounded sharp edges; the cells of the nests closely resemble the cells of the overlying epithelium

Material and Methods

Histological slides from 244 consecutive new cases of transitional cell tumors of the bladder, seen between January 1, 1970 and December 31, 1980 were taken from the files of the surgical pathology department of Magenta Hospital (Milan, Italy). 50 cases with non-papillary tumors, 15 cases with inadequate material (small biopsies, cauterized specimens), 19 cases of total or partial cystectomy and 45 cases lost to follow-up were discarded. The remaining 115 cases were clinically non-infiltrating tumors and were judged to be suitable for our study. Only slides of the first TUR from newly detected tumors were reviewed. An average of four slides (paraffin sections, H & E) per case were available. A few sections were stained with silver methenamine, but we were unable to utilize these sections to identify invasion because occasionally the basement membrane was interrupted by apparently non-invasive epithelial buds, and was present around single cells and cords that definitely did invade the stroma.

The diagnosis and grading of TCPT were carried out according to the WHO classification (1973). For the purpose of staging we only considered small infiltrating nests as evidence of neoplastic invasion, because, in our judgement, large pushing nests can easily be mistaken for patterns of inverted growth that have nothing to do with invasion

and that are frequently observed in the subepithelial connective tissue of TCPT; the following histologic criteria defined the invasiveness of tumor cells:

- *Negative Patterns:* 1) tumor cells grouped in nests of large size (more than 20 cells), either isolated or continuous with the superficial neoplastic epithelium; 2) nests of regular shape, usually round or oval; 3) rounded sharp borders of the nests; 4) nests similar in cells and structure to the overlying neoplastic epithelium (Fig. 1).
- *Positive Patterns:* 1) single cells or small clusters (fewer than 20 cells) either isolated in the connective tissue or budding from the superficial neoplastic epithelium; 2) irregular shape of the cell clusters and buds; 3) indented angulated borders of the cellular clusters; 4) structural irregularities and atypicality of the cells, usually more pronounced in the clusters than in the overlying superficial neoplastic epithelium (Fig. 2).

Results

Of the 115 cases of TCPT, 80 were classified as negative and 35 as positive for neoplastic invasion of the connective stalks. Invasion was usually evident in the areas of branching of the papillae where the connective stalks were thicker. Invasion could be seen in more than one field; only a few cases showed diffuse patterns of invasion. The percentage of cases with neoplastic invasion of the stalks varied for the different tumor grades. None of the 21 well differentiated (G1), 19 (25%) of the 77 moderately differentiated (G2) and 16 (94%) of the 17 undifferentiated (G3) tumors were positive for invasion. The percentages of positivity would probably increase if a greater number of sections at different levels of the blocks had been examined. Specimens from the base of the tumor were available in 69 (62%) cases; specimens were inadequate for histologic examination (scanty or cauterized) in 2 cases. Of the remaining 67 (58%) cases 12 were positive and 43 were negative for invasion either at the base or in the papillary stalks, 12 were negative at the base and positive in the papillary stalks, no cases were positive at the base but negative in the stalk.

In an attempt to evaluate the prognostic significance of the patterns classified as positive for invasion of the papillary stalks, the cases were grouped according to their clinical courses. We divided the cases in two groups; those which progressed unfavorably (fatal outcome or total cystectomy), and those with a favorable course (alive with conservative transurethral resections) within a five year period of follow-up. None of the cases had been treated with radio- or chemotherapy. The distribution into these two groups according to the presence or lack of stalk invasion is summarized in Table 1 for all cases and in Table 2 for the cases with moderately differentiated (G2) tumors. The difference in outcome for the positive and negative cases was statistically significant for the group as a whole ($p < 0.01$). Even for the smaller group of patients with moderately differentiated (G2) tumors, we noticed a statistically significant difference in outcome for the positive and negative cases ($p < 0.05$).

The presence of nests of tumor cells that we interpreted as non significant for invasion of the stalks was related to

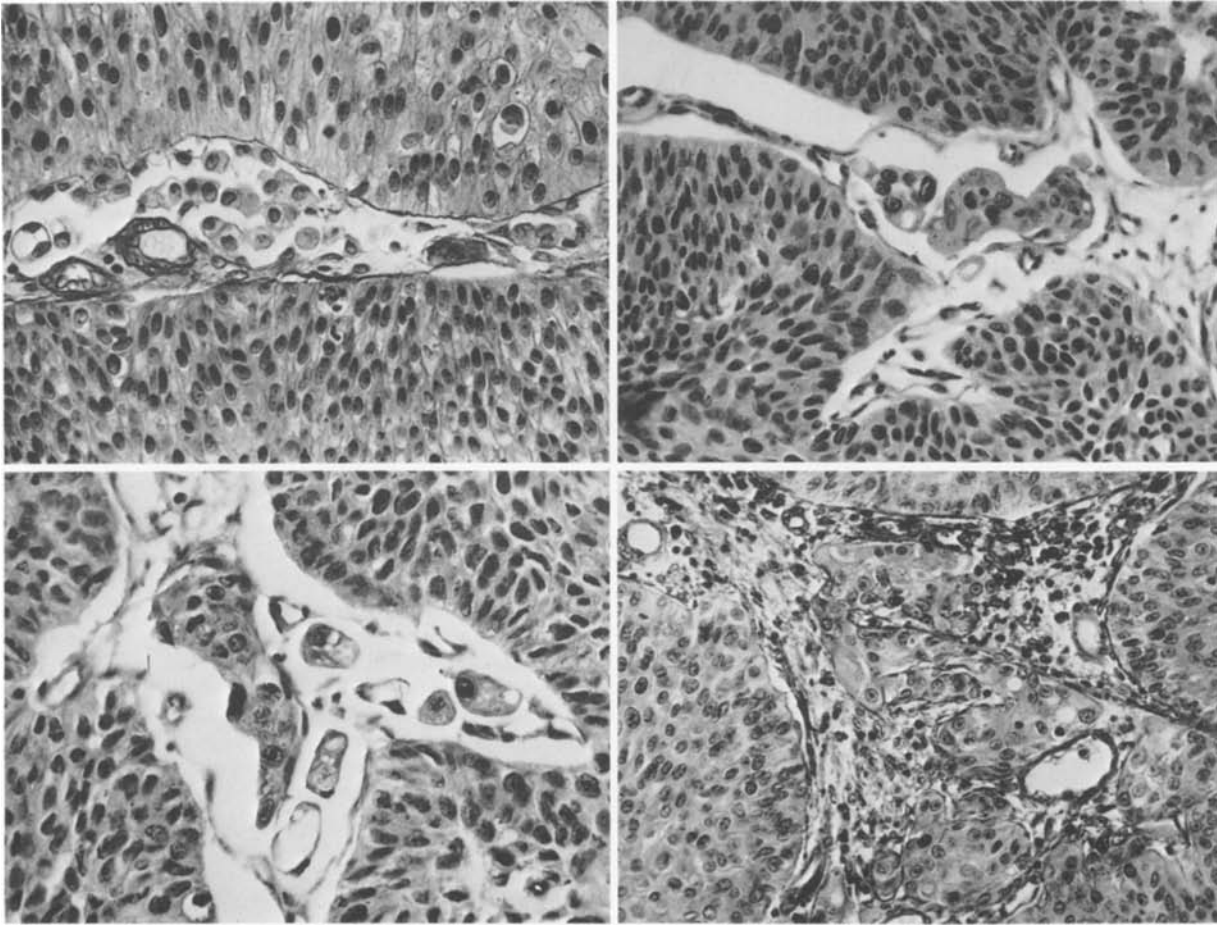


Fig. 2. Patterns positive for invasion of the stalks (4 different cases): the cells in the connective stalks are isolated or in small groups with angulated borders and irregular shapes; the arrangement of the cells is more uneven in the infiltrating groups than in the overlying epithelium

Table 1. Invasion of the stalks (all patients): clinical outcome of 35 positive and 80 negative cases

Invasion of the stalks	favorable outcome	unfavorable outcome
Positive	16	19
Negative	65	15

Table 2. Invasion of the stalks (patients with G2 tumors): clinical outcome of 19 positive and 58 negative cases

Invasion of the stalks	favorable outcome	unfavorable outcome
Positive	9	10
Negative	47	11

tumor grade. We found such nests in 12 (57%) of the 21 well differentiated (G1), in 62 (81%) of the 77 moderately differentiated (G2), in 16 (94%) of the 17 undifferentiated (G3) tumors.

Discussion

Transurethral resection of TCPT of the bladder is practiced as a diagnostic or therapeutic procedure on many patients who do not have clinical evidence of invasion; a pathologic staging is not always possible because TUR material may not be representative of the base of the tumor, so that

grading remains the standard prognostic indicator. However, tumor cells in the connective stalks of TCPT are easily recognizable by light microscopy in routine slides (paraffin sections, H & E) of transurethral resections. The presence of tumor cells in the connective stalks of TCPT has been regarded by us as "significant" or "not significant" for neoplastic invasion in relation to definite histologic criteria (see above). Using these criteria, the presence in the stalks of tumor cells interpreted as significant for neoplastic invasion seemed to be related to tumor grade and to an unfavorable clinical course. In fact, stalk tumor cells were present in 94% of the G3, 25% of the G2 and in none

of the G1 tumors; moreover the rates of death and total cystectomy within five years from the time of diagnosis, were significantly higher for the cases with evidence of invasion of the stalks.

G3 tumors usually run an unfavorable course; G1 tumors behave favourably; the high percentage (94%) of invasion of the stalks found in G3 tumors and the absence of patterns of invasion in all of the G1 tumors indirectly support the correctness of our study. On the other hand, G2 tumors show an unpredictable course; data from the literature concerning their biological and structural characteristics indicate that they are a non-homogeneous group of tumors. The group of G2 tumors is not homogeneous even in terms of invasion of the stalks; in our material 25% of the cases were positive and 75% were negative for invasion.

The presence in the connective stalks of nests of tumor cells that we interpreted as not significant for neoplastic invasion does not seem to be related to the clinical course. We found these nests in a high percentage (57%) of well differentiated (G1) tumors; all these tumors had a favorable course.

Out of the 67 cases with specimens from the base of the tumor, invasion of the stalks corresponded to invasion at the base of the tumor in 82% of the cases; in the remaining 18% the discordance was exclusively due to cases positive for invasion in the stalks, but negative at the base. This fact suggests either that invasion of the stalks somehow precedes invasion of the base, or that in TUR material invasion of the stalks is more readily recognizable than invasion at the base of the tumor, or both.

As a conclusion, we can say that while the finding of tumor cells significant for neoplastic invasion of the stalks of TCPT most likely does not increase our information about G1 and G3 tumors, it could be of some help for the interpretation of the nature of G2 tumors and to the prognostic evaluation of the patients bearing these tumors. Further studies are required to decide whether or not invasion of the stalks may be relevant to the staging of TCPT. We therefore suggest that invasion into the connective stalks be included in histological reports of TCPT, provided invasion is diagnosed with definite histologic criteria. Our data suggest that invasion of the stalks could have a meaning analogous to invasion of the lamina propria at the base of the tumor.

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