Relationship between Papillary and Nodular Transitional Cell Carcinoma in the Human Urinary Bladder

Tadao Kakizoe, Ken-ichi Tobisu, Kazuhiro Takai, Yoshinori Tanaka, Kiyozo Kishi, and Shin-ichi Teshima

Urology [T. K., K. To., K. Ta., Y. T.] and Pathology [K. K., S. T.] Divisions, National Cancer Center, Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan

ABSTRACT

A total of 186 cystectomized specimens were examined by step-sectioning to determine the relation between papillary and nodular transitional cell carcinomas of the urinary bladder. Tumors were classified as papillary (PC), nodular (NC), and carcinoma in situ (CIS) according to their gross and microscopic configurations. These cases, grouped as simple combinations of PC, NC, and CIS, namely, PC + CIS, PC + NC + CIS, PC + CIS + NC, and PC + CIS + NC + CIS, were analyzed with respect to (a) the time from the initial symptom to cystectomy, (b) the treatment before cystectomy, (c) the grade, (d) the stage of tumors, (e) the multiplicity of tumors, (f) the presence of papillary structures inside or on the surface of nodular carcinoma, and (g) data on survival after cystectomy. Of the tumors, 17 were classified as CIS and 80 as PC and NC + CIS. Studies on 57 cases suggested an early change from PC to a mixture of PC and NC through papillonodular carcinoma during development, whereas 6 showed late development of NC during repeated recurrence of PC. These courses indicate that some cases of NC developed from PC. On the other hand, 26 cases exhibited direct progression from CIS to NC. Thus nodular invasive carcinomas may develop in two ways: by emergence of a more anaplastic cell population within a preexisting low grade papillary carcinoma; and by de novo development of an invasive nodular carcinoma directly from CIS.

INTRODUCTION

Papillary and nodular transitional cell carcinomas of the urinary bladder exhibit significantly different clinical behaviors (1, 2). Papillary carcinomas usually develop in multiple forms and frequently recur elsewhere in the bladder after transurethral resection. However, these tumors usually remain superficial, and even though the patient undergoes multiple, repeated resections, the prognosis is generally fair. On the other hand, nodular carcinomas are usually deeply invasive up to or beyond the bladder wall when first observed, and the clinical outcome, even after radical cystectomy, is poor. Thus although these two types of tumors develop in the urinary bladder, their biological behaviors and clinical courses are like those of two different disease entities.

For systematic understanding of human bladder carcinogenesis, we first carefully examined 33 cases with both papillary and nodular carcinomas of the bladder simultaneously, as transitional forms of these two types of tumors (3). Then we found that for analysis of the relationship between papillary and nodular carcinomas of the bladder it was necessary to collect information about cases of pure papillary carcinoma, or nodular carcinoma, with or without carcinoma in situ. Thus this paper reports clinical and pathological analyses of 186 cystectomized specimens examined by step-sectioning. The relationship between papillary and nodular carcinomas of the bladder was analyzed based on the concept that all human bladder cancers are papillary carcinoma, nodular carcinoma, or flat carcinoma in situ, or their combinations.

MATERIALS AND METHODS

From January 1969 to August 1986, 220 patients with transitional cell carcinoma of the urinary bladder were cystectomized and specimens were examined by step-sectioning. Of these, 17 cases for which data were insufficient and 17 cases of carcinoma in situ with microinvasion were excluded; thus, a total of 186 cases were analyzed. The patients ranged from 28 to 83 years old (mean, 60.8 years old), and the male:female ratio was 143:43 (3:1). Specimens were cut serially into strips approximately 7-10 mm wide for histopathological examination. From the gross and histological findings, the tumors or mucosal lesions were classified as PC, NC, and CIS, as described in the General Rule for Clinical and Pathological Studies on Bladder Cancer (4), (Japanese Urological and Pathological Association, 1980), which was adopted from the system for tumors, nodes, and metastasis (Geneva, 1978). In this system, specimens were graded as recommended by the World Health Organization (5). On the basis of gross and histopathological patterns, bladder cancers examined by step-sectioning of cystectomized specimens were classified as PC, NC, and CIS, and their simple combinations, namely, PC + CIS, PC + NC, PC + NC + CIS, and NC + CIS. CIS indicates primary or secondary carcinoma in situ without visible tumors at the time of cystectomy. PN, defined (6) as a single tumor with short fronds showing confluent growth with neighboring fronds, giving a pattern intermediate between those of papillary and nodular carcinomas, was also included in groups PC + NC and PC + NC + CIS. For simplifying analyses, these groups were sometimes combined; namely, PC and PC + CIS as PC/PC + CIS, PC + NC and PC + NC + CIS as PC + NC/PC + NC + CIS, and NC and NC + CIS as NC/NC + CIS.

The 186 patients and specimens were analyzed with respect to the following 7 factors: (a) the period from the initial development of symptoms to cystectomy. In this analysis the significances of difference among groups were analyzed by multiple comparison by the method of Wallenstein (7); (b) the treatment before cystectomy; (c) the grade; (d) the stage; (e) the multiplicity of tumors in the cystectomized specimens. When tumors were a mixture of different grades or stages, the highest grade or stage was recorded. (f) In nodular carcinomas, the presence of papillary structures inside or on the surface of nodular carcinoma was carefully examined histologically, because we thought that the presence of papillary structures was suggestive evidence for development of nodular carcinoma from papillary carcinoma. (g) Data on survival of patients after cystectomy were computed by the Kaplan-Meier method, and the significances of difference in survivals of subgroups were evaluated by the generalized Wilcoxon test. The follow-up period after cystectomy ranged from 6 to 200 months (median, 40 months). No patients received postoperative intrapelvic radiotherapy. Some of the patients who had invasive carcinomas received postoperative prophylactic chemotherapy by 1 to 3 courses of a combination of cis-platinum, doxorubicin, and cyclophosphamide or 10 to 20 courses of a combination of neocarzinostatin, vincristine, and cyclophosphamide, namely, 7 of 23 patients (30%) in group NC, 6 of 11 (55%) in group NC + CIS, 7 of 15 (47%) in group PC + NC + CIS, and 3 of 18 (17%) in group PC + NC.

By analyses of the clinical courses before and after cystectomy and histopathological findings in step-sections, we tried to determine the

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To whom requests for reprints should be addressed.
RESULTS AND DISCUSSION

The clinical histories of all cases were reviewed and the time from the initial symptom such as gross hematuria to cystectomy was calculated. Patients with CIS were excluded from this analysis, because in many of them the time of onset of disease was uncertain. This time tended to shorten in transition from group PC to group NC, but values for each group showed marked standard deviations. Time from initial symptom to cystectomy for PC/PC + CIS, PC + NC/PC + NC + CIS, and NC/NC + CIS groups were 32 ± 31, 22 ± 24, and 18 ± 20 months, respectively. In the PC and PC + CIS groups, about one-half of the patients initially received bladder-preserving therapy at other institutions and were later referred to this hospital. Consequently the difference in the duration of symptoms did not simply reflect the speed of progression of each type of tumor. However, the data indicated a general tendency for papillary tumors to grow relatively slowly, although differences were not statistically significant.

Treatment before Cystectomy (Table 1). Before cystectomy, patients received various treatments, mainly at other institutions. "Instillation" in Table 2 means intracavitary injection of anticancer drugs.

Grades of Tumors (Table 2). The mean ages of the patients in each group at the time of cystectomy were not significantly different. Patients in group CIS were not graded, because world consensus has not yet been reached on a suitable grading system and we wanted to avoid a discussion of the differentiation of CIS from dysplasia. In the combined group PC/PC + CIS, two-thirds of the cases had G2 tumors, whereas when NC was added to the group as a tumor element, 80–90% of the cases had G1 tumors.

Stage of Tumors (Table 3). There were 17 cases of CIS with microinvasion that were excluded from this analysis, because this entity is contradictory to the definition of CIS and it is hard to classify these cases as either PC or NC. Comparison of PC and PC + CIS showed that the association of CIS indicated more invasion than PC alone. When NC was combined with PC in the group PC + NC/PC + NC + CIS, a clear tendency for invasive growth was observed. Of the 75 cases of invasive carcinomas of more than pT1 in groups PC + NC/PC + NC + CIS and NC/NC + CIS, 17 cases (22%) had a previous history of papillary carcinoma treated by transurethral resection or partial cystectomy. This is suggestive evidence that in some cases NC developed from PC, although the number of cases was small.

Multiplicity of Tumors (Table 4). The numbers of tumors in cystectomized specimens of combinations of PC and PC + CIS, PC + NC and PC + NC + CIS, and NC and NC + CIS are summarized in Table 4. In the PC + NC/PC + NC + CIS group, 33% of the cases that had a solitary tumor had a large single papillonodular carcinoma. On the contrary, groups with NC showed a tendency for development of solitary, but deeply invasive tumors. Analyses, such as grades, stage, and multiplicity of tumors (see above) showed that tumor patterns such as PC and NC and the grade, stage, and number of tumors are closely correlated.

Presence of Papillary Structures in Nodular Carcinoma (Table 5). We examined whether residual microscopic papillary structures could be observed inside or on the surface of nodular carcinomas. As will be discussed later, the presence of papillary structures in the nodular carcinoma appears to be further suggestive evidence that some nodular carcinomas developed from papillary carcinomas. In this respect, the multiplicity of tumors is also indicated in Table 5, because it appears to be another relevant factor in speculating on the developmental pathway of nodular carcinomas. In the NC/NC + CIS group, 26 of 55 (47%) of the nodular carcinomas did not have any papillary structures, whereas in group PC + NC/PC + NC + CIS 32 of 33 (97%) of the nodular carcinomas had papillary structures. Typical photographs indicating papillary structures in nodular carcinoma are presented later. Schematic illustrations of 11 examples of the coexistence of PC, NC, and CIS in a bladder are presented in Fig. 1. Of 26 cases of NC in which no papillary structures were demonstrated, 12 cases had a single tumor without concomitant CIS, and 10 cases had a single tumor with concomitant CIS. These data suggest that nodular carcinoma develops by two routes, via papilliferous carcinoma and de novo from CIS.

Survival after Cystectomy (Figs. 2 and 3). The survival rates calculated by the Kaplan-Meier method are illustrated in Fig. 2 for groups CIS, PC/PC + CIS, PC + NC/PC + NC + CIS, and NC/NC + CIS. Significant differences were found in the survival rates of groups PC/PC + CIS and PC + NC/PC + NC + CIS (P < 0.01) and groups PC/PC + CIS and NC/NC + CIS (P < 0.01) by the generalized Wilcoxon test. Similar trends of differences in survival were observed between CIS and PC + NC/PC + NC + CIS and between NC and NC/NC + CIS. However, there was no significant difference between the survivals of groups PC + NC/PC + NC + CIS and NC/NC + CIS. These results are closely correlated with the high grades and high stages of tumors in the groups associated with NC.

Papillary carcinomas associated with CIS are reported to have a higher probability of later development of invasive carcinomas than papillary carcinomas without CIS (9). As mentioned previously, in our series, PC + CIS was slightly more invasive than PC alone (Table 3), but the survival rates of groups PC and PC + CIS were not significantly different (Fig. 3).

Relation between Papillary Carcinoma and Nodular Carcinoma. It is now controversial whether cystectomy is beneficial, and if so, when it should be done, in patients with superficial bladder cancer, such as primary or secondary carcinoma in situ.
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Table 3 Tumor types and stages

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of patients</th>
<th>Stage (I.C.P.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIS</td>
<td>17</td>
<td>T1: 15 (50)</td>
</tr>
<tr>
<td>PC</td>
<td>30</td>
<td>T2: 19 (38)</td>
</tr>
<tr>
<td>PC + CIS</td>
<td>50</td>
<td>T3: 6 (34)</td>
</tr>
<tr>
<td>PC + NC</td>
<td>18</td>
<td>T4: 2 (13)</td>
</tr>
<tr>
<td>PC + NC + CIS</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>NC</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>NC + CIS</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>PC/PC + CIS</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>PC + NC/PC + NC + CIS</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>NC/NC + CIS</td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in parentheses, percentages.

Table 4 Multiplicity of tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC/PC + CIS</td>
<td>11 (14%)*</td>
</tr>
<tr>
<td>PC + NC/PC + NC + CIS</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>NC/NC + CIS</td>
<td>38 (69%)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses, percentages.

Table 5 Papillary structures in nodular carcinoma

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC + NC/PC + NC + CIS</td>
<td>33</td>
</tr>
<tr>
<td>NC/NC + CIS</td>
<td>55</td>
</tr>
</tbody>
</table>

Fig. 2. Survival data calculated by the Kaplan-Meier method in terms of CIS and combined tumor patterns PC/PC + CIS, PC + NC/PC + NC + CIS, and NC/NC + CIS. P, papillary; N, nodular; C, CIS.

Fig. 3. Comparison of survival data for PC (P) and PC + CIS (C). Differences were not statistically significant.

Fig. 1. Topographic relations between PC and NC in the pT4 group. P. carcinoma (P, papillary; N, nodular); N. carcinoma in situ; D, dysplasia (from Ref. 3, used with permission).

and multiple recurrent papillary carcinomas. Depending upon the indications of cystectomy used in cases of superficial bladder cancer, the total composition of the tumor in cystectomized cases varies from series to series (10). Based upon the present data, tumor progression in the 186 cases in our series were classified into the hypothetical pathways shown in Fig. 4. Unfortunately, the initial status of human bladder cancer, i.e., the histogenesis of bladder cancer, has not yet been delineated. Consequently, this status is shown by a dashed circle in Fig. 4. Of the 186 cystectomized patients, 17 had primary or secondary CIS, and 5 of these (29%) had a history of resected papillary carcinoma. Most of the cases of PC continued to be PC, in spite of multiple recurrences. However, it is reported that about 10–20% of papillary carcinomas later progress to nodular invasive carcinomas (11, 12). In our series, 6 cases later exhibited a higher grade of invasion than pT3, which was confirmed by cystectomy. The initial tumor patterns of the 57 cases in groups PC + NC/PC + NC + CIS and NC/NC + CIS were presumably PC, judging from the treatment before cystectomy (Table 1), the presence of papillary structures in NC (Table 5), or the distributions of PC, NC, and CIS in the bladders shown in Figs. 1 and 5 which have already been published in Ref. 3. The final patterns observed in cystectomy specimens were PC + NC with NC predominance. This developmental course from PC to NC was probably through PN, since as shown in Fig. 6, papillary fronds sometimes grow confluently, together with downward growth at the very beginning of tumor formation. The extreme pattern of this type of progression from papillary carcinoma to nodular carcinoma is shown in Fig. 7, in which remaining...
papillary structures can be observed by microscopic examination.

Of 55 cases in groups NC/NC + CIS, 26 cases seemed to have developed directly from CIS to NC. As discussed previously, in these 26 cases no papillary structures were observed in nodular carcinomas, and there was no history of papillary tumor. Probably in these cases tumors developed directly from very rapidly growing CIS to the pattern shown in Fig. 8, in which no papillary structures can be found inside the tumor even by the careful microscopic examination.

The 80 cases of PC and 26 cases of NC in Fig. 4 were indeed like different disease entities, as mentioned in the “Introduction.” However, there were many intermediate types of tumors, such as those in the 57 cases in groups PC + NC/PC + NC + CIS and NC/NC + CIS. NC in these groups presumably developed from PC through PN. Thus, we think that the relation between PC and NC is not fixed and that depending on some unknown factors, conversion of PC to NC can take place. Clearly, it is necessary to determine what kind of factors are involved in this process.

There are some reports that only a small number of patients with invasive bladder carcinoma had a history of papillary carcinoma (13, 14), indicating that papillary neoplasms of the bladder may not be common precursors of invasive carcinoma, although details of the invasive carcinomas were not described in these reports. This was also apparently true in our series. As discussed in relation to stages of tumors (Table 3), only 17 (22%) of the 75 cases in groups PC + NC/PC + NC + CIS and NC/NC + CIS with invasive carcinomas of more than pT2 had a previous history of papillary carcinoma. However, of 88 cases of NC-mixed tumors (Table 3), 62 cases, excluding 26 cases supposed to have developed from CIS, were speculated to have emerged from papillary carcinomas. As Oyasu et al. (15) reported from their experiments using rats, there are at least two ways in which high grade, deeply invasive carcinomas develop: one is by the emergence of a more anaplastic cell population.
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Fig. 8. Nodular carcinoma supposed to have developed directly from very rapidly growing CIS. H & E, × 2 (original magnification).

within a preexisting low grade carcinoma; and the other is by the direct de novo development of an invasive carcinoma from a carcinoma in situ.

REFERENCES

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