Jpn. J. Cancer Res. 83, 1354–1358, December 1992

Analysis by Step Sectioning of Early Invasive Bladder Cancer with Special Reference to G3·pT1 Disease

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Eighty cases of cystectomized and step-sectioned pT1 transitional cell carcinomas of various grades were analyzed. During the same period, 30 consecutive cases of pT2 carcinomas were also cystectomized and examined for comparison. This is a cross-sectional study of a variety of cases of bladder cancer, designed to delineate the characteristics of G3·pT1 disease. Tumors in this series had a full set of various pathological findings; grades 1 to 3, stages Ta-T1-T2, papillary-papillonodular-nodular tumor configuration, α-β-γ type of invasion, presence of lymphatic and venous involvement, and presence of associated carcinoma *in situ*/dysplasia. There is a distinct tendency of stepwise disease progression, such as grade 1→3, stage T1→T2, papillary→nodular configuration, and $\alpha\rightarrow\gamma$ invasion, these factors being mutually related. We noted a similarity between tumor groups containing G3 component, such as G2-3·pT1, G3>2·pT1, G3·pT1, G1-3·pT2, and G3·pT2. These tumors are different from groups such as G1-2·pT1, G2·pT1 and G2>3·pT1 in terms of tumor configuration and type of invasion. As regards pT1 having G3 components, early cystectomy seems to be the surest treatment. Whenever one adopts a conservative policy in treatment of these tumors, extreme care should be taken to monitor tumor progression.

Key words: Bladder cancer — G3·pT1 tumor — Cystectomy

Bladder cancer is dually characterized by grade (G) and stage (T). T1 bladder cancers frequently are classified and treated, together with Ta and Tis, as being included in the category of superficial bladder cancers. At the same time T1 cancers, by definition, exhibit submucosal invasion and consequently represent an initial stage of invasive cancers. A particularly difficult clinical problem in the management of G3·pT1 disease is the prediction of progression, i.e., the development of muscle-invasive disease.

There are two different methods of analyzing the biological nature of G3·pT1 tumors of the urinary bladder. One is close follow-up of patients when the initial tumor is diagnosed as G3·pT1 by transurethral resection (TUR), and provision of appropriate treatment as soon as evidence of muscular invasion is obtained.[1-3] Under these circumstances, it is important to determine which types of initial tumors later become deeply invasive, and which types remain superficial,[2-4] although this is difficult, requiring a longitudinal study of the natural/treated history of G3·pT1 bladder cancers. The other method is careful examination of G3·pT1 tumors and comparison, in step-sectioned cystectomized specimens, with related pathological lesions such as pT1 without G3 components and pT2 of various grades. This involves a cross-sectional study of a variety of cases to delineate the characteristics of G3·pT1 disease. We used the latter method in this study in an attempt to establish the principles of management of G3·pT1 tumors.

MATERIALS AND METHODS

Eighty cases of pT1 transitional cell carcinomas, treated by cystectomy between 1970 and 1988, were analyzed. During this period, 9 pT1 tumors verified by biopsy were treated by intraoperative radiotherapy and 16 pT1 tumors were treated by TUR alone. These 25 cases of pT1 conservatively treated were excluded from this analysis. Cystectomy for pT1 was performed depending on the size and configuration of tumor, or number of recurrences, or presence of G3 component. In addition, 30 consecutive cases of pT2 carcinomas treated by cystectomy during the same period were included for comparison. Treatments prior to cystectomy in these patients having pT1 and pT2 were examined in the medical record (Table I).

The pT1 patients, ranging in age from 31 to 78 (mean, 60), included 62 male and 18 females (3.4:1). The pT2 patients ranged in age from 46 to 80 (mean, 59.7) and included 20 males and 10 females (2:1).

Specimens were sagittally opened from the urethra and both ureters were also opened. The specimens, pinned to a cork board, were fixed in 10% neutralized formalin. For histological examination, specimens were serially cut

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into strips approximately 7–10 mm wide. All tumor configurations were recorded by cystophotography at the time of biopsy. Based on the cystophotographic and histological findings, the tumors or mucosal lesions were classified as papillary (P), papillonodular (PN) and nodular (N) carcinomas, carcinoma *in situ* (CIS) and dysplasia.[5] Staging and grading of cancers were performed as defined in the General Rule for Clinical and Pathological Studies of Bladder Cancer[6] (Japanese Urological and Pathological Association, 1980), in which specimens are graded as recommended by the World Health Organization.[7] Grading (G) depends on both cellular and structural atypism, being classified as 1, 2 and 3: G1 indicates mild cellular and structural atypism, and G2 and G3 indicate cellular or structural atypism that is moderate or severe, respectively. When a single specimen contained tissues of different grades, it is expressed by a sign of inequality (e.g. G2>3·pT1). The pathologist was given minimal clinical information, such as history and cystoscopic findings. Pathological reports and slides were reviewed by T.K. Bladder cancers examined by step-sectioning were, on the basis of gross and histological findings, diagrammatically illustrated in the charts. Patterns of invasion were classified as α, β, and γ, in which INF α indicates expansive, solid invasion, INF γ indicates tentacular, diffuse invasion, and INF β indicates intermediate pattern between INF α and INF γ[6] (Fig. 1). When lymphatic permeation was identified, it was expressed as ly (+) and likely venous involvement as v (+).[6] These specimens were analyzed for (1) multiplicity of tumors, (2) configuration of tumors, (3) pattern of invasion, and (4) associated CIS/dysplasia on the mucosa.

Table I. Treatment before Cystectomy

Classification	No. of patients	Patients having histories of TUR, partial cystectomy, intravesical chemotherapy, BCG therapy, radiotherapy
G1-2·pT1	5	3
G2·pT1	23	13
G2>3·pT1	5	1
G2-3·pT1	10	4
G3>2·pT1	6	1
G3·pT1	13	7
CIS→pT1	18	10
G1-3·pT2	9	5
G3·pT2	21	6

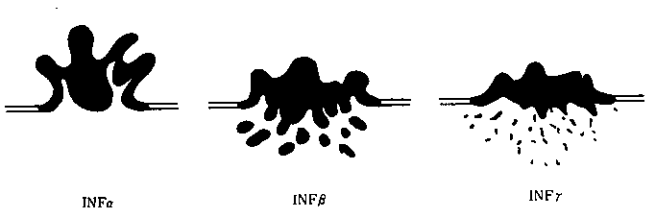

Fig. 1. Diagram of patterns of invasion. INF α indicates expansive, solid invasion, INF γ indicates tentacular, diffuse invasion, and INF β indicates an intermediate pattern between α and γ (used by permission[6]).

RESULTS

Treatment before cystectomy (Table I) and interval between diagnosis and cystectomy (Table II) Many of the patients were treated by multiple TUR. Some were referred to this hospital after treatment elsewhere with various modalities such as partial cystectomy, radiotherapy, intravesical chemotherapy, or BCG instillation. Some, having either large tumors in the bladder or tumors of aggressive appearance, underwent immediate cystectomy after biopsy. The interval between first diagnosis of bladder cancer and cystectomy consequently differed greatly, depending upon the type of tumor (Table II).

Pathological findings The types of tumors, number of patients, multiplicity of tumors, configuration, type of invasion, lymphatic and venous involvement and coexistence of CIS/dysplasia are summarized in Table III. With increase in grade and stage, there was a general pathological tendency for tumor configuration to change from P to N, and type of infiltration from α to γ. There also was a tendency for lymphatic and venous involvement to increase from low grade T1 to high grade T2.

Schema of tumor distribution, configuration and mucosal changes The distribution of tumors, tumor configuration and such mucosal changes as CIS/dysplasia in relation to type of tumors are schematically illustrated in Fig. 2.

Table II. Interval between Diagnosis of Bladder Cancer and Cystectomy

Classification	Interval (months)
G1-2·pT1	29±34*
G2·pT1	24±27
G2>3·pT1	11±13
G2-3·pT1	7±11
G3>2·pT1	7±9
G3·pT1	11±17
CIS→pT1	8±5
G1-3·pT2	7±5
G3·pT2	3±3

* Mean±SD.

Fig. 2. Diagram of G1-2·pT1 (A), G2·pT1 (B), G2>3·pT1 (C), G2-3·pT1 (D), G3>2·pT1 (E), G3·pT1 (F), G1-3·pT2 (G) and G3·pT2 (H) bladder cancer. Blue spot, papillary cancer; yellow spot, papillonodular cancer; red spot, nodular cancer; ▨ dysplasia; ▨ CIS.

Only 15 consecutive cases of 23 in types G2·pT1 are shown because of limited space. As observed in Table III, the relations between grade/stage and other pathological findings tended to be similar.

DISCUSSION

There are many reports on the natural history of treated superficial bladder cancer. Heney *et al.*,[2] with a mean follow-up of 39 months, reported that progression in relation to stages Ta and T1, and grades I, II and III was 4, 30, 2, 11 and 45%, respectively. Transitional cell carcinoma of the bladder is a disease of wide spectrum, and superficial cancer can progress to muscular layer invasion with a wide variety of time courses.[8]

We have analyzed G1-3, pT1 cystectomy specimens together with G1-3, pT2 specimens for comparison. There is a variety of pathological findings: grades 1-3;

Table III. Pathological Findings

Type	No. of pts.	No. tumors		Configuration			Infiltration			Ly	V	CIS/dysplasia	
		S[a]	M	P	PN	N	α	β	γ	(+)	(+)	adjacent	remote
G1-2·T1	5	3	2	4	1	0	5	0	0	0	0	2 (40)[b]	2 (40)
G2·T1	23	7	16	15	8	0	9	6	0	3	3	12 (52)	11 (48)
G2>3·T1	5	2	3	3	2	0	2	2	0	0	0	4 (80)	4 (80)
G2-3·T1	10	3	7	3	6	1	4	5	0	4	1	3 (30)	3 (30)
G3>2·T1	6	3	3	0	3	3	2	4	0	3	1	4 (67)	3 (50)
G3·T1	13	9	4	5	4	4	5	5	1	2	1	8 (62)	9 (69)
CIS→G3T1	18						8	11	0	8	5	18 (100)	18 (100)
G1-3·T2	9	5	4	2	1	6	5	4	2	7	2	5 (56)	5 (56)
G3·T2	21	15	6	0	5	16	3	8	3	15	6	12 (57)	13 (62)

a) S: single, M: multiple.
b) (%)

stages Ta-T1-T2; tumor configuration P-PN-N; α-β-γ type of invasion, presence of lymphatic and venous involvement, and presence of associated CIS/dysplasia adjacent to and remote from the main tumor(s). If we analyze these cases at a fixed time, i.e., at the time of cystectomy, we can obtain a cross-sectional image of bladder cancer having various natural courses along the time axis. Table III and Fig. 2 indicate there is a distinct, stepwise disease progression, such as grade 1→3, stage T1→T2, configuration P→N, and invasion α→γ, these factors being mutually related. There was no clear tendency concerning tumor classification and associated CIS/dysplasia. We particularly note a similarity between G1-3·pT2, G3·pT2 (Fig. 2, G, H) and G2-3·pT1, G3>2·pT1, G3·pT1 (Fig. 2, D–F). On the other hand, G1-2·pT1, G2·pT1 and G2>3·pT1 (Fig. 2, A–C) diseases differ a little from other tumor groups, mainly because of either the absence or very small amount of G3 component and the absence of nodular tumors. As far as treatment policy is concerned, some of the cases in Fig. 2 (A–C) should be treated more conservatively at the initial stage, which we have been doing since 1985.

About 30–50% of G3·pT1 disease is reported to invade the muscular layer or to metastasize[4, 9–11] during follow-up. One possible reason for this progression, because of the high rate of recurrence at the same site as that of the initial tumor, is inadequate initial resection. Kläne *et al.*[12] reported the results in 46 stage T1 patients of a second TUR routinely performed within two weeks of the initial TUR. Residual disease was found in 50% despite the surgical report of complete resection. A second clinical problem concerning progression of G3·pT1 disease is prediction of the later course on the basis of the nature of the initial tumor. Heney *et al.*[2] and Jakse *et al.*[3] reported a careful analysis of risk factors. It is clear that grade III, T1, moderate to severe mucosal dysplasia, and tumor size of more than 5 cm are significant risk factors of progression.[2] In Jakse's report,[3] which lists the characteristics of G3·pT1 disease patients who had or did not have tumor progression, we note differences with regard to number of tumors, recurrence rate, mean interval to first recurrence, and type of tumor invasion. Kaubisch *et al.*[13] recently reported that among 51 patients with stage T1 transitional cell carcinoma of the bladder who were treated by TUR alone, a total of 14 (27%) experienced deep muscle invasion during the median follow-up of 78 months. None of the patients with grade 1, 5 (22%) with grade 2 and 9 (50%) with grades 3 to 4 tumors suffered deep muscle invasion. Kaubisch *et al.* therefore claimed that tumor grade is the most important biological predictor of progression to muscle-invasive cancer. Similar observations have been reported by others.[14–16] Our data (Table III and Fig. 2) also support the view that, in the presence of muscle invasion, tumor configuration changes from papillary to nodular with a gradual shift in grade.

The third problem is the indication for cystectomy. The results of early cystectomy are impressive, as reported in the literature.[4] Bracken *et al.*[17] reported that 29 G3, pT1 patients who underwent cystectomy after a median 2 TUR had an 88% uncorrected 5-year survival rate. In a large series of pT1 patients reported by Stockle *et al.*,[18] 55 patients predominantly with G3 disease who had undergone cystectomy upon diagnosis had a 90% 5-year survival rate. They were compared with 18 patients for whom the operation did not take place until one or two recurrences had taken place, and who had only a 62% 5-year survival rate. Reports by Anderstrom *et al.*[19] and Malmstrom *et al.*[10] also support this observation. As it is well known that TUR alone has an inherent problem of diagnostic accuracy, it is clear from these studies that early cystectomy saves lives.

In our series, as discussed earlier, some of the cases in the G1-2·pT1, G2·pT1 and G2>3·pT1 groups and some of the solitary tumor cases without mucosal changes may

be treated more conservatively by a combination of a second TUR at the T1 site and intravesical instillation of BCG.

For pT1 having G3 components, cystectomy is the surest method of treatment. In cases where we adopt a conservative policy for treatment of these tumors, we should be extremely careful to ensure early detection of progression. A longitudinal study has a diagnostic limitation concerning initial tumor or tumors appearing in the later course, whereas a cross-sectional study as described here has the limitation of static analysis of the resected specimens, although pathological diagnosis is very accurate. It is likely that molecular markers will be developed in the near future as factors predicting the prognosis of initial tumors having G3·pT1.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid from the Ministry of Health and Welfare for the Comprehensive 10-Year Strategy for Cancer Control, Japan.

(Received August 6, 1992/Accepted September 2, 1992)

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