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GRADE 3 BLADDER CANCER WITH LAMINA PROPRIA INVASION (pT1): CHARACTERISTICS OF TUMOR AND CLINICAL COURSE

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ABSTRACT

To determine the clinical characteristics of grade 3 tumors with lamina propria invasion (pT1), we reviewed the data of 217 patients with superficial bladder cancer who had initially been treated by transurethral resection (193 patients) and fulguration (4), supravesical resection (13) or partial cystectomy (7). We classified the patients into four groups according to histological grade and stage of disease: group 1) grade 0 or 1, pTa tumors (n=58); group 2) grade 2, pTa tumors (n=106); group 3) grade 2, pT1 tumors (n=30); and group 4a) grade 3, pT1 tumors (n=23). Grade 3, pT1 tumors were significantly related to nonpapillary growth (p=0.0002), multiple tumors (p=0.005) and irritative bladder symptoms (p=0.01). The 5-year progression rates were 0% for group 1, 5% for group 2, 8% for group 3, and 18% for group 4a. The respective 5-year survival rates were 97%, 91%, 83% and 79%. All five patients with grade 3, pT1 tumors who had originally undergone total cystectomy (group 4b) remained alive free of disease for a median follow-up 57 months, establishing a far better survival rate than that for group 4a. These findings show that patients with grade 3, pT1 tumors face a high probability of progression and poor chance of survival. Immediate radical treatment is indicated when tumors recur after initial transurethral resection.

Key Words: Superficial bladder cancer, Progression, Survival

INTRODUCTION

Serious problems in superficial bladder cancer (Ta and T1) are intravesical recurrence and disease progression. Intravesical recurrence develops in 50% to 70% of the patients with superficial bladder cancer,[1)] and disease progression in about 10% of them.[2–5)] Progression, which is defined as the development of muscle invasion or distant metastasis, is closely linked to poor prognosis. To find useful indicators for progression, several adjuncts have been investigated, including flow cytometry,[6,7)] chromosomal analysis[8,9)] and immunohistochemistry of ABH blood group antigens.[9,10)] Recent studies revealed that patients with initial grade 3, stage T1 tumors face a high risk of progression and a low prospect of survival.[11,12)]

We related clinical and pathological findings at presentation to grade 3, pT1 tumors, and we compared grade 3, pT1 tumors with other superficial tumors in respect of frequency of progression, number of total cystectomies, survival, and intravesical recurrence to clarify what treatment would be most appropriate for patients with initial grade 3, pT1 tumors.

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PATIENTS AND METHODS

From January 1973 to December 1987, 454 patients with primary bladder epithelial tumors were admitted to Nagoya University Hospital. Of these, 359 (79%) received diagnosis and treatment for the first time. In a total of 220, superficial transitional cell tumors (pTa and pT1), including papilloma and inverted papilloma (grade 0) were diagnosed histologically, and the patients were first treated conventionally without total cystectomy. Tumors were graded by the criteria of the Armed Forces Institute of Pathology[13] and staged according to the UICC classification.[14] Some tumors were found to be of mixed grade and were arbitrarily classified as of highest grade. According to the predominant pattern, the histological pattern of growth was classified into two groups: papillary and nonpapillary growth. Table 1 shows the relation between histological grade and stage. Two patients with carcinoma *in situ* (CIS) and one with grade 3, pTa tumor were excluded from the present analysis because such cases were too few in number. Consequently, we reviewed and analyzed the data of the remaining 217 patients. Their mean age was 61.5 ± 12.4 (SD) years, 179 being male (82%) and 38 being female (18%). Initial surgical treatment was transurethral resection (TUR) in 193 patients, transurethal fulguration in 4, supravesical tumor resection in 13, and partial cystectomy in 7. The median follow-up for the 217 patients was 50 months. According to histological grade and stage, the 217 patients were classified into four groups: group 1) grade 0 or 1, pTa (n=58); group 2) grade 2, pTa (n=106); group 3) grade 2, pT1 (n=30); and group 4a) grade 3, pT1 (n=23). Group 4a comprised 11% of the 217 patients with superficial tumors. In addition, we surveyed five patients with grade 3, pT1 tumors who had initially undergone total cystectomy (group 4b) in the same period. Disease progression was defined as the development of muscle invasion or distant metastasis after initial tumor resection, as described previously.[4]

Relative risks were calculated with a logistic regression model.[15] Cumulative progression-free, survival, and recurrence-free curves were drawn using the Kaplan-Meier method,[16] and data were compared in a generalized Wilcoxon test.[17] We expressed progression rates as 100% minus the percent of progression-free rates, and recurrence rates as 100% minus the recurrence-free rates. All statistical analyses were performed at the Nagoya University Computer Center using the Statistical Analysis System (SAS).

Table 1. Relation Between Histological Grade and Stage in 220 Patients with Superficial Bladder Cancer

	G0	G1	G2	G3	Total
pTis				2	2
pTa	12	46	106	1	165
pT1			30	23	53
Total	12	46	136	26	220

RESULTS

1. Clinical and Pathological Factors Related to Grade 3, pT1 Tumors

Table 2 shows the proportions in eight categories of clinical and pathological factors. The dividing marks for these categories were set arbitrarily. Patients in group 1 were younger and

Table 2. Proportions (%) in Eight Categories for the Four Groups

Factor	(Category)	Group 1	2	3	4a
Age	(70 or more)	17[a]	26	47	43
Sex	(Male)	84	79	90	83
Irritative symptoms	(Yes)	7[b]	19	23	39
Time from onset	(> 3 months)	50	42	37	48
Location	(other than RUO)	55	48	70	70
Size	(> 1 cm)	47	52	60	43
Number	(multiple)	33	38	43	70[c]
Growth pattern	(nonpapillary)	14	0	20	35[d]

RUO = Region adjacent to ureteral orifices.

a Significantly lower than group 3 ($p < 0.01$) and group 4 ($p < 0.05$).

b Significantly lower than group 2 ($p < 0.05$) and group 3 and group 4 ($p < 0.01$).

c Significantly higher than group 1 and group 2 ($p < 0.01$).

d Significantly higher than group 2 ($p < 0.01$).

Table 3. Results of Univariate Analysis of Factors Related to Grade 3, pT1 Tumors

Variables	Associated subgroup	Less strongly associated subgroup	Relative risk	p
Growth pattern	nonpapillary	papillary	6.9	0.0002
Number	multiple	solitary	3.9	0.0045
Irritative symptoms	yes	no	3.4	0.0096
Age	≥ 70 years	< 70 years	2.1	0.0997
Location	Other sites	Near ureteral orifices	2.0	0.151
Size	> 1 cm	≤ 1 cm	1.4	0.466
Time from onset	> 3 months	≤ 3 months	1.2	0.714
Sex	male	female	1.0	0.987

had less frequent irritative symptoms than those in groups 2 to 4a. On the other hand, patients in group 4a had by far more multiple tumors and nonpapillary tumors.

Table 3 shows the relative risks for the clinical and pathological factors by logistic regression analysis. Grade 3, pT1 tumors were significantly associated with nonpapillary growth ($p=0.0002$), multiple tumors ($p=0.005$) and irritative bladder symptoms ($p=0.01$).

2. Frequencies of Progression, Survival Rates and Intravesical Recurrence Rates

Figure 1 shows the progression-free curves for each group. The overall 5-year and 10-year progression rates were 5.3% and 11%, respectively. Disease progression developed in 12 of the 217 patients (5.5%): invasion of the bladder wall muscle in 11, and lung metastasis in one. Five (22%) of 23 patients with grade 3, pT1 tumors encountered progression. The median interval between first treatment and occurrence of progression was 11.5 months, ranging from 4 to 108 months. The 5-year progression rates were 0%, 5%, 8% and 18%, and the 10-year ones were 0%, 12%, 8% and 34% for the four groups, respectively. Patinets of group 4a experienced progression more frequently than all those of groups 1 to 3 ($p=0.003$).

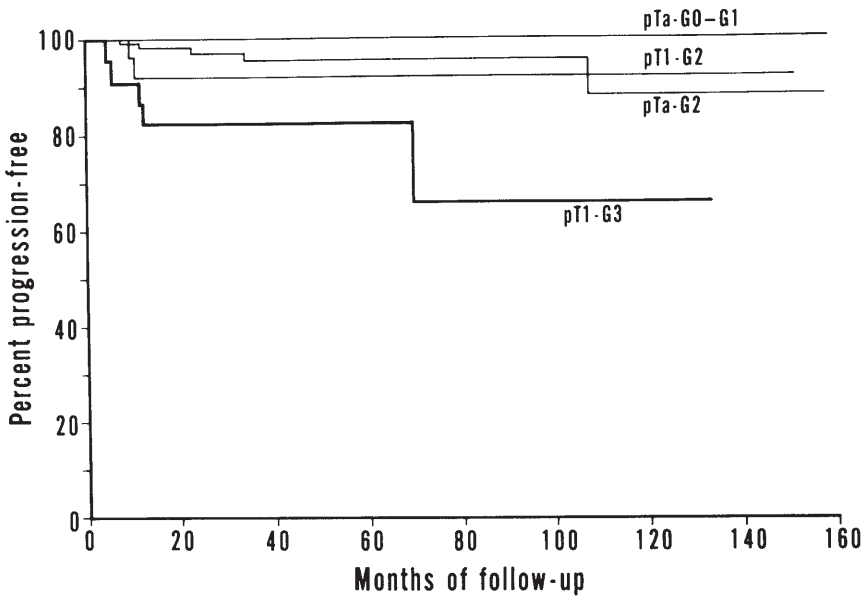

Fig. 1. Cumulative progression-free curves for the four groups. Patients with pT1, grade 3 tumors are dexposed to higher progression than those with other tumors.

Table 4. Frequency and Reason for Total Cystectomy for All Four Groups

Group	No. of patients	No. (%) of cystectomies	Reason for cystectomy (No. of patients)	
			Progression	Recurrent multiple tumors
1 (G0-G1, pTa)	58	0 (0%)	0	0
2 (G2, pTa)	106	8 (8%)	3	5
3 (G2, pT1)	30	6 (20%)	1	5
4a (G3, pT1)	23	6 (26%)	5	1
Total	217	20 (9%)	9	11

Twenty patients (9.2%) underwent total cystectomy after the first treatment because of progression (9 patients) or recurrent multiple tumors (11 patients, Table 4). No patient in group 1 underwent total cystectomy. In contrast, total cystectomy was performed in 8% of the patinets in group 2, 20% in group 3, and 26% in group 4a. Table 4 shows the causes for total cystectomy in each group and their frequency. Patients in group 4a more frequently underwent total cystectomy because of progression than those in other groups.

Figure 2 depicts the cumulative survival curves for groups 1 to 4a. All causes of death were regarded as endpoints in the evaluation of the survival curves. The overall 5-year and 10-year survival rates were 90% and 86%, respectively. Eighteen (8.3%) of the 217 patients died, 10 of bladder cancer and 8 of unrelated causes; the latter figure includes secondary neoplasm in 4, heart disease in 2, cerebral hemorrhage in 1, and peritonitis in 1 patient. Those five patients of group 4a who died, died of bladder cancer. The 5-year survival rates were 97%, 91%, 83% and

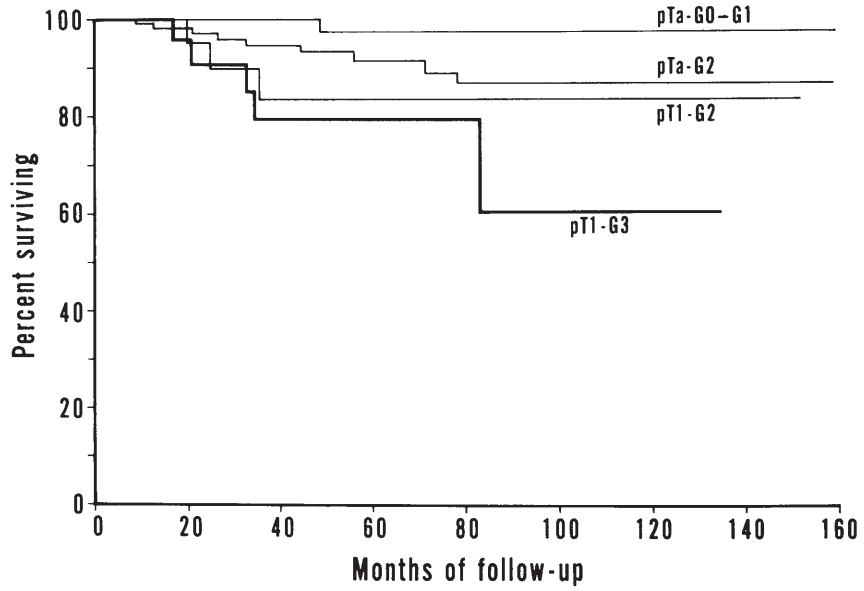

Fig. 2. Cumulative survival curves for the four groups. Patients with pT1, grade 3 tumors have a poorer prognosis than those with other tumors.

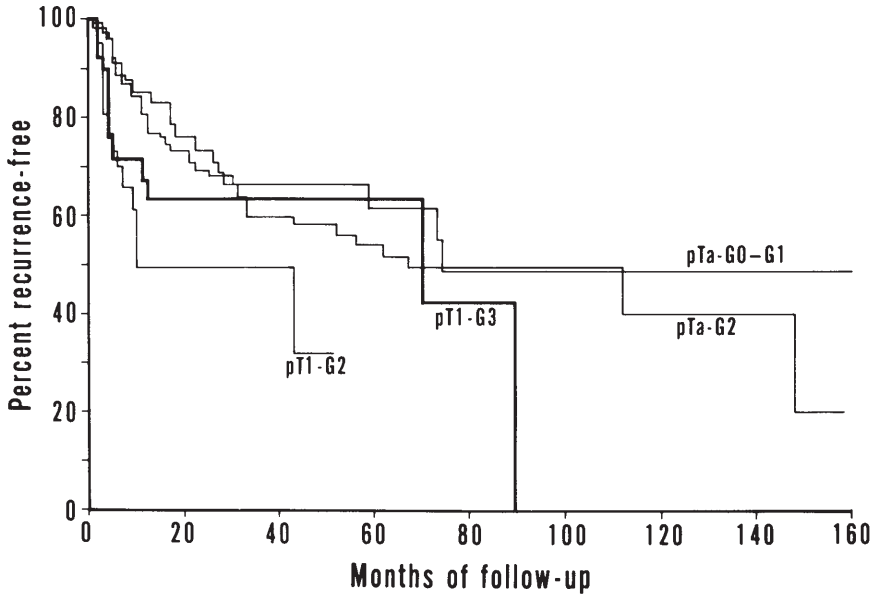

Fig. 3. Cumulative recurrence-free curves for the four groups showing no significant differences.

79%, and the 10-year survival rates were 97%, 86%, 83% and 59% for the four groups, respectively. Fewer patients in group 4a survived than in the other groups (p=0.03). All five patients with grade 3, pT1 tumors who originally underwent total cystectomy (group 4b) remained alive without disease with a median follow-up of 57 months, ranging from 34 to 84 months.

Figure 3 shows the cumulative recurrence-free curves for groups 1 to 4a. The overall 5-year recurrence rate was 45%, and the 10-year recurrence rate was 65%. The 5-year recurrence rates were 38%, 45%, 67% and 37%, respectively. No statistical difference was found among the four groups in respect of the interval between first treatment and first recurrence.

DISCUSSION

Progression is an ominous problem for patients with superficial bladder cancer. Several investigators showed that grade, stage, size, number, lymphatic invasion, concomitant CIS or dysplasia, and frequency of recurrence are all factors affecting progression.[2,4,11,18–21] Recent studies revealed that grade 3, stage T1 tumors were closely associated with progression and poor prognosis.[11,12] We confirmed this finding and we believe that immediate radical treatment would be the most appropriate for patients with initial grade 3, pT1 tumor and subsequently progressive disease.

The clinical (T) stage differs sometimes from the accurate pathological (pT) stage; tumors may be understaged or overstaged.[22] In addition, it has been pointed out that pathologists do not always agree on the pathological stage and grade.[23,24] In this series, grade 3, pT1 tumors accounted for 11% out of all superficial bladder cancers surveyed. Heney *et al.* reported a similar proportion of 12% for grade 3, T1 tumors,[11] whereas, Jakse *et al.* reported a higher incidence of 23%.[12] This inconsistency may in part be attributed to the different grading and staging. A properly performed TUR is the crucial prerequisite for an accurate diagnosis of the histopathological materials.

We closely related grade 3, pT1 tumors to nonpapillary growth, multiple tumors and irritative bladder symptoms. Jakse *et al.* reported that patients with stage T1, grade 3 tumors were different from patients with other superficial tumors with regard to age at presentation, number, morphology and size of tumors.[12] Other researchers found that high-grade tumors more often accompanied CIS and severe dysplasia than low-grade tumors[25] We could not evaluate concomitant CIS and dysplasia in our study because we performed a selected mucosal biopsy in only a limited number of patients. Irritative bladder symptoms, however, which we noted to be frequently accompanied by grade 3, pT1 tumors, might represent the presence of concomitant CIS and dysplasia.[26]

We reviewed slides of the 23 patients with grade 3, pT1 tumors to find histopathological factors differentiating the progression group from the nonprogression group. Most cases contained the muscle layer for an accurate diagnosis of pT1 tumors. No significant difference was found between the two groups in infiltration pattern, vascular invasion, or lymphocytic infiltration. Further prospective studies, including flow cytometry and immunohistochemistry, are needed to identify a high-risk group for progression among patients with grade 3, pT1 tumors.

Skinner showed that muscle invasion, together with the presence of CIS, is the crucial determinant for total cystectomy.[22] In patients with grade 3, pT1 tumors the presence of CIS and dysplasia would also affect the choice of treatment. We believe at present that patients with initial grade 3, pT1 tumors and concomitant CIS as well as severe dysplasia are prime candidates for total cystourethrectomy, considering the high risk of subsequent progression and poor prospects of survival. Recent studies showed that bacillus Calmette Guérin (BCG) intravesical

therapy is effective in treating CIS[27] and preventing progression.[28] Further studies are required here to determine the most appropriate treatment of grade 3, pT1 tumors with or without CIS and dysplasia.

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