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Anterior urethral recurrence of superficial bladder cancer: its clinical significance.

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Abstract

The aim of this study was to reveal the clinical features of anterior urethral recurrence in patients with superficial bladder cancer, and to determine the appropriate treatment. Three hundred and three patients with superficial bladder cancer, who were newly diagnosed and initially treated conservatively in our hospital between 1965 and 1990, were followed for at least 5 years and their clinical outcomes were analyzed. Clinical factors, including anterior urethral recurrence, were evaluated statistically regarding tumor progression. Eight patients (2.6%) had anterior urethral recurrence following superficial bladder cancer. Twenty-four patients (7.9%) had tumor progression and 149 (49.2%) had tumor recurrence. In a multivariate analysis using a logistic model, anterior urethral recurrence was the most important factor, followed by histological grade. Four of 5 patients who were treated for anterior urethral recurrent tumors by transurethral resection showed progression and died of the cancer within one year. Two of the remaining three patients who underwent radical cysto-urethrectomy at the time of anterior urethral recurrence survived. Anterior urethral recurrence following superficial bladder cancer is a predictor for rapid subsequent malignant progression. Once there is anterior urethral recurrence, radical intensive therapy, including radical cysto-urethrectomy, should be carried out immediately.

KEYWORDS: superficial bladder cancer, anterior urehral recurrence, prognosis, predictor

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Original Article

Anterior Urethral Recurrence of Superficial Bladder Cancer: Its Clinical Significance

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The aim of this study was to reveal the clinical features of anterior urethral recurrence in patients with superficial bladder cancer, and to determine the appropriate treatment. Three hundred and three patients with superficial bladder cancer, who were newly diagnosed and initially treated conservatively in our hospital between 1965 and 1990, were followed for at least 5 years and their clinical outcomes were analyzed. Clinical factors, including anterior urethral recurrence, were evaluated statistically regarding tumor progression. Eight patients (2.6%) had anterior urethral recurrence following superficial bladder cancer. Twenty-four patients (7.9%) had tumor progression and 149 (49.2%) had tumor recurrence. In a multivariate analysis using a logistic model, anterior urethral recurrence was the most important factor, followed by histological grade. Four of 5 patients who were treated for anterior urethral recurrent tumors by transurethral resection showed progression and died of the cancer within one year. Two of the remaining three patients who underwent radical cysto-urethrectomy at the time of anterior urethral recurrence survived. Anterior urethral recurrence following superficial bladder cancer is a predictor for rapid subsequent malignant progression. Once there is anterior urethral recurrence, radical intensive therapy, including radical cysto-urethrectomy, should be carried out immediately.

Key words: superficial bladder cancer, anterior urethral recurrence, prognosis, predictor

Clinical problems associated with superficial bladder cancer are local recurrence and progression to the advanced stage. Superficial bladder cancer itself is not a life-threatening disorder, provided it remains within the bladder mucosa. Once this type of cancer progresses to local muscle invasion or metastasis, anticancer management strategies such as radical surgery, systemic chemotherapy, or radiation therapy may have little effect, and the prognosis may be poor. Therefore, prediction of progression is a major issue in the clinical management of superficial bladder cancer. While numerous markers used to analyze the prognostic factors of superficial bladder cancer have been reported [1-6], anterior urethral recurrence of superficial bladder cancer has not been discussed as one of these prognostic factors, thus prompting our evaluation.

Materials and Methods

We statistically analyzed factors affecting progression in patients with superficial bladder cancer. From 1965 to 1990, 384 patients with superficial bladder transitional

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carcinoma (without concomitant carcinoma *in situ*; CIS) were newly diagnosed in our hospital. Among these 303, those who received conservative transurethral resection (TUR) and were followed for at least 5 years or until death, were evaluated in this study. Eighty-one patients were excluded from the analysis, since they underwent incomplete initial treatment or dropped out of follow-up treatment. In this study, malignant progression was defined as a local invasion over the muscle layer, lymph node metastasis, or distant metastasis. There were 257 male and 46 female patients whose age ranged from 19 to 88; the mean age was 61.4. The mean period of follow-up for patients was 84.0 months, ranging from 30 to 330 months. The patients were followed as described; cystoscopy was performed every 3 months for 2 years after TUR, then every 4 months from 2 to 3 years, every 6 months from 3 to 5 years, and annually after 5 years. Urine cytology was examined at the time of cystoscopy. Intravenous pyelography, pelvic computed tomography (CT), and chest radiography were performed annually. For the statistical analysis of the factors at the time of initial treatment, uni-variate and multi-variate analyses by Cox's proportional Hazards model were performed. The factors and the categories of statistical analysis were age, sex, clinical symptoms, number of tumors, tumor size, tumor shape, tumor involvement of the bladder neck, stage based on UICC 1997, and grade (highest grade in cases involving multiple grades). In 149 patients with tumor recurrence, factors related to tumor progression were analyzed using a logistic model. A P value of less than 0.05 was considered statistically significant in the uni-variate analysis.

The clinical outcomes of patients with anterior urethral recurrence of superficial bladder cancer were also analyzed. A total of 8 patients suffered from anterior urethral recurrence during this period. In this study, anterior urethral recurrence was defined as follows: tumor recurrence at the anterior urethra excluding the prostatic urethra and bladder neck in males, and tumor recurrence at the urethra excluding the bladder neck in females.

Results

During the follow up period, there were recurrences in 149 patients and among these, there was progression in 24 patients. These recurrent cases were analyzed according to the factors and categories shown in Table 1. The factors were evaluated in terms of their impact on

Table 1 Tumor characteristics in 149 recurrent cases

	Progression Cases (n = 24)		Non-Progression Cases (n = 125)	
	Initial	Accumulated*	Initial	Accumulated*
Urethral Tumor (+)	0	4 (18.7%)	0	1 (0.8%)
Tumor No.				
1	13	5	51	20
2–4	6	6	38	38
5 or more	5 (20.8%)	13 (54.2%)	36 (28.8%)	67 (53.6%)
Tumor Size				
< 1 cm	4	3	21	14
1–3 cm	16 (66.7%)	16 (66.7%)	73 (58.4%)	75 (60.0%)
3 cm <	4 (16.7%)	5 (20.8%)	31 (24.8%)	36 (28.8%)
Tumor Shape				
Pap. Stalk	10	5	84	55
Pap. Broadbased	7 (29.2%)	12 (50.0%)	29 (23.2%)	55 (44.0%)
Non-Pap.	7 (29.2%)	7 (29.2%)	12 (9.6%)	15 (12.0%)
Neck Tumor (+)	7 (29.2%)	15 (62.5%)	39 (31.2%)	71 (56.8%)
Stage Ta	7	4	63	55
T1	17 (70.8%)	20 (83.3%)	61 (48.8%)	70 (56%)
Unknown			1	0
Grade G1	3	0	36	26
G2	16	14	75	78
G3	4 (16.7%)	10 (41.7%)	11 (8.8%)	21 (16.8%)
Unknown	1		3	0

*Worst feature among the factors at each recurrence without progression.

malignant progression. In the uni-variate analysis, anterior urethral recurrence, and tumor shape, grade, and stage all had a statistically significant correlation with progression. In the multivariate analysis using a logistic model, anterior urethral recurrence was the most important predictor of progression, followed by histological grade (Table 2). There was anterior urethral recurrence in 8 patients at 14 to 148 months (median: 47.5) after the initial diagnosis, with no obvious sub-mucosal invasion apparent upon pre-operatural examinations such as urethroscopy and CT. All of these patients had concomitant bladder recurrence. In 6 of the 8 patients, pre-operatural examination revealed concomitant bladder cancer without and 2 cases with muscle infiltration. Five of the 6 patients with concomitant bladder cancer and without muscle infiltration were treated by transurethral resection without additional chemo- or radiation therapy; the latter 2 patients with muscle infiltration underwent radical cysto-urethrectomy. The remaining patient underwent cysto-urethrectomy for multiple tumor recurrence, although no obvious sub-mucosal invasion had been observed before surgery. Histo-pathological findings in the urethrectomy specimens of these 3 patients revealed micro-invasion into the prostate and/or into the deep muscle wall. After additional adjuvant systemic chemotherapy was performed on these 3 patients, 2 patients showed no evidence of recurrence, and one died of the cancer 2 months after the surgery. Malignant progression (3 patients with local invasive recurrence and 1 patient with a distant metastasis) was revealed during the follow-up treatment period as described above. Thus, Malignant progression was observed in 4 of the 5 patients who were treated conservatively, 9 to 37 months after the transurethral management. These 4 patients received intensive therapy, including radical cysto-urethrectomy and systemic chemotherapy. However, each patient had a poor prognosis and died within 1 year. Transurethral management succeeded in controlling the disease in only one patient with anterior urethral recurrence. The summaries and clinical courses of these 8 cases are shown in Table 3.

On the other hand, among the five cases involving progression without urethral recurrence, had lymph node metastasis with local progression, two had distant metastasis without local progression, and one had distant metastasis with lymph node metastasis and local progression.

Discussion

Numerous factors that are prognostic of superficial bladder cancer have been reported for use as markers. However, there is no definite marker for determining the treatment of superficial bladder cancer. Recent advances in molecular biological techniques have revealed many factors such as oncogenes and onco-supressor genes that may affect the clinical course of superficial bladder cancer. Intensive studies have shown that among the several identified prognostic markers, the status of suppressor gene p53 mutation, the Ki-67 labeling index, and EGFr are very useful. Detection of malignant phenotypes, especially those related to local invasion and metastasis, are the major subjects of cancer research. However, the suggested impact of these factors (*e.g.*, prognostic molecular markers, tumor number, tumor size, tumor grade, and CIS varies among reports [1–6]. Moreover, there have been no definitive clinical evaluations to date, and it remains difficult to predict global clinical courses according to minute molecular biological changes. In addition, the standard treatment strategy for patients with concomitant CIS differs from that for patients without

Table 2 Univariate and multivariate analysis of recurrent cases (n = 149)

Factors	Category	Univariate *P*-Value	Multivariate *P*-Value
Urethral Tumor	(−)/(+)	0.0008**	0.017*
Tumor Number	1/2–4/5 <	0.764	0.492
Tumor Size	< 1/1–3/3 <	0.738	0.859
Tumor Shape	Stalk/Broadbased/Non-Pap.	0.032*	0.433
Neck Tumor	(−)/(+)	0.577	0.887
Grade	1/2/3	0.006**	0.094
Stage	Ta/T1	0.012*	0.191

*$P < 0.05$, **$P < 0.01$.

Analyses are based on accumulated characteristics evaluated by Cox's Proportional Hazards Model.

Table 3 Detailed clinical features of patients with anterior urethral recurrence

	Frequency before urethral recurrence	Period from onset to urethral recurrence (months)	Treatment for urethral recurrence	Pathological bladder findings at urethral recurrence	Period from urethral recurrence to progression (months)	Treatment after progression	Prognosis	Survival duration after urethral recurrence	Survival duration after progression
1	3	40	TUR	T1, G3	9	Radical	Dead	17	8
2	2	18	TUR	T1, G2	37	Radical	Dead	49	12
3	4	55	TUR	T1, G2	31	In-ope.	Dead	34	3
4	4	76	TUR	Ta, G3	10	Radical	Dead	11	1
5	11	148	TUR	Ta, G2	No progression		Alive	51	
6	6	80	Radical	T3b, G2	Synchronous		Alive	12	12
7	1	14	Radical	T4, G3	Synchronous		Dead	2	2
8	4	21	Radical	T1, G3	No progression		Alive	108	

Radical, radical cysto-urethrectomy.

concomitant CIS. Our results suggest that anterior urethral recurrence following superficial bladder cancer is a significant predictor of malignant progression. Although some clinical reports [7–12] have described urethral recurrence after cystectomy for advanced bladder cancer, as well as the occurrence of primary anterior urethral cancer, there have been few clinical studies on urethral recurrence following superficial bladder cancer. Erckert *et al*. [12] reported the clinical features of urethral tumor involvement in 910 male patients with bladder cancer at all stages; although the patient number is large, the criteria for urethral recurrence included both the anterior and posterior urethra, without distinguishing between the 2 types of tumor. Our retrospective study is one of the few that deal specifically with the clinical significance of anterior urethral recurrence following superficial bladder cancer.

It has been a long-term matter of debate whether such metachronous tumors represent the unrecognized direct extension of bladder cancer, the seeding of cancer cells from the bladder, metastasis, or a second manifestation of a multicentric defect of the transitional cell mucosa that caused the original bladder cancer. Freeman *et al*. [9] supported the latter theory in cases of post-radical cystectomy, since urethral tumors occur variably throughout the length of the anterior urethra as skip lesions and in the absence of a positive surgical margin. The results of that study did not support the theory of mechanical implantation, since urethral tumors tend not to occur in areas of stricture, which presumably represent sites of mucosal trauma and thus the most fertile ground for seeding. If this speculation is true across the board, conservative treatment may be feasible, provided the tumor is superficial. However, such speculation is based on the results of urethral recurrence after radical cystectomy. It is important to consider the circumstance in which continuous urinary flow from upstream lesions may contain cancer cells that are then transported to the urethra. These conditions differ radically from those of a post-radical cystectomy, in which mechanical implantation from a superficial bladder cancer seems primary. Mechanical implantation may lead to more invasive tumors of the anterior urethra than would be expected among second-manifestation tumors due to multicentric defects of the transitional cell mucosa; this would be the case because the injured urethral mucosa into which the cancer cells are implanted is thin, as is the muscle wall, and is adjacent to cavernous tissue with abundant blood flow. Cancer cells may easily migrate into the blood stream and cause distant metastasis in such circumstances. In fact, histopathological examination of our patients with urethral recurrence who had undergone radical cysto-urethrectomy immediately revealed micro-invasion to deep sites, and 4 of the 5 patients who were treated conservatively for anterior urethral recurrences had poor prognoses. These findings indicate the potent ability of cancer cells to migrate and eventually form local invasions and distant metastases at the time of anterior urethral recurrence. Since urethral recurrence of superficial bladder cancer can be regarded as a sign of the high malignancy of cancer cells, immediate radical and systematic therapy, including cysto-urethrectomy, chemotherapy, or radiation therapy, should be performed as soon as recurrence is diagnosed. To prevent tumor seeding, the urethral mucosa should be

protected during any transurethral maneuver. Although this was not a randomized prospective study, the following conclusions can be drawn from the present results: 1] anterior urethral recurrence of superficial bladder cancer could be a significant prognostic factor; 2] immediate radical systematic intensive therapy should be performed in such cases; 3] precise urethroscopic examination should also be performed during the routine follow-up treatment for superficial bladder cancer.

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