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Pathological Study of Bladder Cancer

PATHOLOGIAL STUDY OF BLADDER CANCER BY MAPPLING OF UROTHELIUM

TATSURO MURASE

Department of Urology (Director: Prof. H. Mitsuya)
Nagoya University School of Medicine; Nagoya Japan

ABSTRACT

Using sixty-four cases of bladder cancer, the distribution of carcinomatous lesions, carcinoma in situ, and atypism were observed by step section of the entire urothelium. Carcinoma of the bladder was divided into four tumor types in accordance with the mapping of the disease foci, the patterns of tumor growth, and the DNA distribution pattern in the tumor cells. Type 1 was localized consisting mainly of papillary non-invastive tumors. Atypia was mild around the tumor, and neither atypia nor carcinoma in situ was seen in sites distant from the tumors. Type 2 was multifocal, non-invasive, and consisted mainly of papillary tumors. Type 3 was multifocal, invasive and multiple carcinomata in situ were present at sites distant from the tumors. Type 4 was localized and invasive with no findings suggestive of precancerous lesions in the bladder mucosa. Type 4 tumors grew very rapidly and were highly malignant.

According to the retrospective analysis of the clinical course of each type, a plan for reasonable treatment of the bladder cancer was proposed as follows. Type 1; This type of tumor may be controlled sufficiently by transurethral resection. In cases of T_2 (B_1) or more, dissection of the lymph node is necessary. Type 2; This type may basically be controlled by transurethral resection, but careful follow-up is required because of high incidence of recurrence. When T_2 (B_1) or more are diagnosed, total cystectomy is indicated. Type 3; Total cystectomy including the urethra and dissections of the lymph node are necessary. Type 4; Partial, sometimes total, cystectomy and dissection of the regional lymph node at an early stage are necessary.

INTRODUCTION

Of all tumors treated by urologists, bladder cancer has the highest incidence, but its natural history is not clear and at present no fixed treatment is available. In the case of radical surgery, the patients become urologically crippled due to the diversion of the urinary tract; consequently, great care must be exercised in total cystectomy. However, more than a few cases come to unfortunate results because of insufficient treatment. The prognosis of bladder cancer is customarily based on the assessment of histologic grade, type of tumor, and clinical pathological stage. The aim of this report was to clarify the natural history of bladder tumors and to establish a reasonable approach to the treatment of baldder tumors by type.

In recent years, increasing attention has been directed to the potential prognostic importance of abnormality in the bladder epithelium. In 1952, Melicow (1) and Melicow and Hollowell (2) reported that epithelial abnormalities, ranging from hyperplasia to carcinoma in situ, might be observed in incidental biopsy material and by histologic examination of seemingly unaffected bladder epithelium in cystectomy specimens. They pointed out the difficulty in cystoscopic identification of such lesions. Our study demonstrates the distribution of epithelial lesions in surgically-removed cancerous bladders by a complete histologic examination.

Melamed (3), Koss (4), Soto (5), Skinner, (6) and Cooper *et al.* (7) studied the continuity and discontinuity of tumor foci by means of step sectioning of total cystectomy specimens,

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and showed that the tumors were multifocal intra-epithelial carcinomas. This mapping method of disease foci showed the lesions, which multiply with time, at each stage of bladder carcinoma and therefore provided suitable material for estimating the natural history of the bladder cancer.

In our work, focal mapping of the bladder cancer was performed on 64 of the patients who underwent radical total cystectomy. The tumors were classified into four types according to the disease foci conditions as seen from mapping of the growth pattern of the tumors. Some of the tissues were subjected to Feulgen's staining. Because Feulgen reagent reacts to nuclear deoxyribonucleic acid (DNA), the DNA content in cell nuclei is easily determined. Microspectrophotometric values obtained by this method are found to be consistent with those obtained biochemically. Nuclear DNA as well as chromosomal number are constant in the same animal except for specific tissues (8). A comparative investigation was made of the histograms showing the quantities of DNA in the nuclei of the tumor cells.

MATERIALS AND METHODS

The patients were selected for cystectomy in the Nagoya University Hospital and National Cancer Center because they had failed to respond to local treatment and also because biopsy evidence indicated the presence of widespread disease of the bladder epithelium or deep invasions of the bladder wall.

Table 1 summarizes the clinical and pathological data on 64 patients prior to and after cystectomy. There were 53 men and 11 women. At the onset, the youngest patient was 33 years old, the oldest 75. At the time of cystectomy the youngest was 35 years old, the oldest 75. The duration of known carcinoma prior to cystectomy ranged from 1 to 240 months, averaging 23.9 months.

Freshly removed bladders were cut open the front surface of the bladders extirpated during surgery together with the prostate gland in males and the urethra in females, then spread stretched, and pinned down on a piece of stiff wooden board, and fixed in 10% buffered formal dehyde solution. Following a 48-hour fixation, the entire epithelium of the bladder was cut into appropriately identified tissue blocks measuring about 3.5 x 0.5 cm and about 1 cm in thickness. Approximately 100 blocks were required to process the bladder in toto. Mapping was performed on the parts of the bladder with atypical hyperplasia (hereafter referred to as ATP) and carcinoma in situ. The criteria of Koss were used in diagnosis of the ATP. carcinoma in situ, and grade of cancer (4). The stages of the bladder cancer were classified according to Jewett (9) and the UICC (10). A schematic diagram was adopted to show the distribution of cancer lesions, carcinoma in situ, and atypical hyperplasia. Growth patterns, of turmor, carcinoma in situ, and non-papillary invasive carcinoma were investigated. The presence or absence of lymph node metastasis was also checked in each case. Analysis of the foregoing pathological study of carcinoma of the bladder was divided into the following four types.

Type 1 tumors were unifocal, localized and papillary. They were mainly non-invasive, but when invasive, they showed a rpedominantly broad fron invasion. ATP was present in the area surrounding the tumors, but there was no ATP or carcinoma in situ at sites distant from the tumors. The grade was 1 or 2 in almost all cases. Type 2 tumors were multifocal and papillary. In the mapping, there were many ATP and microscopic papillary projections not only in the vicinity of the tumors but also at sites distant from them. The grade of malignancy was 1-2 in almost all cases.

Table 1. Clinical and pathological findings before and after cystectomy

No.	Age	Sex	Symtoms	Cystoscopic findings	Past treatment	Duration of cystectomy from first symptom	Stage	grade	lymph node meta
1	61	M	Hematuria	papillary	—	18M	PT_1 A	1-2	—
2	53	M	Burning Hematuria	papillary sessile non papillary	TUC × 4	51M	PT_3 B_2	3	—
3	58	M	Hematuria	papillary sessile	segmental resection	6M	PT_3 B_2	3	—
4	68	F	Burning	non papillary	—	7M	PT_1 A	2	—
5	43	M	Hematuria	papillary	—	18M	PTa 0	1	—
6	63	M	Hematuria	non papillary	radiation	7M	PT_4 D	3	+
7	62	M	Hematuria	non papillary	Tumorectomy by section alta	60M	PT D	3	+
8	74	M	Hematuria	non papillary	TUR	1M	PT_3 B_2	3	—
9	73	M	Hematuria	non papillary	segmental resection	19M	PT_3 B_2	3	—
10	39	F	Frequency	non papillary	—	16M	PT_3 B_2	3	+
11	57	M	Burning	papillary	—	16M	PT_3 B_2	3	+
12	46	M	Hematuria	papillary	TUC segmental resection	60M	PTa 0	2	—
13	55	M	Hematuria	papillary	—	13M	PT_1 A	2	—
14	64	M	Hematuria	papillary	TUC × 3	20M	PTa 0	2	—
15	52	M	Hematuria	papillary	TUR × 3	35M	PT_1 A	2	—
16	59	M	Hematuria	papillary	TUR × 3	24M	PT_1 A	1-2	—
17	65	M	Hematuria	papillary	—	4M	PT_2 B_1	2	—
18	66	M	Hematuria	non papillary	segmental resection	13M	PT_1 A	2	—
19	66	M	Hematuria	non papillary	Tumorectomy by section alta	25M	PT_3 B_2	2-3	—
20	66	M	Hematuria	papillary	Tumorectomy by section alta	18M	PT_2 B_1	1	—
21	67	M	Hematuria	papillary	Tumorectomy by section alta	29M	PT_1 A	3	+
22	46	M	Micro hematuria	non papillary	segmental resection	12M	PT_3 B_2	3	—
23	75	F	Hematuria	papillary	—	2M	PT_2B_1	2	0
24	72	M	Turbia urine	non papillary	—	2M	PT_3 D	3	+

No.	Age	Sex	Symtoms	Cystoscopic findings	Past treatment	Duration of cystectomy from first symptom	Stage	grade	lymph node meta
25	71	M	Burning	non papillary	—	8M	PT_3 B_2	3	0
26	63	M	Hematuria	non papillary	rediation	36M	PT_3 D	3	+
27	42	F	Hematuria Burning	papillary	—	1M	PT_1 A	2-3	—
28	33	M	Hematuria	non papillary	Tumorectomy by section alta	6M	PT_3 D	3	+
29	72	F	Hematuria	non papillary	—	1M	PT_3 D	3	+
30	71	M	Hematuria	non papillary	—	10M	PT_3 D	3	+
31	46	M	Micro hematuria	non papillary	radiation	26M	PT_4 D	3	—
32	70	F	Burning Hematuria	non papillary	—	36M	PT_4 D	3	+
33	52	F	Hematuria	non papillary	—	120M	PT_4 D	3	+
34	75	M	Hematuria	papillary	segmental resection TUR × 4	60M	PT_4 D	3	+
35	62	M	Hematuria	non papillary	TUC × 1	16M	PT_3 D	3	+
36	68	M	Hematuria	non papillary	—	4M	PT_3 D	2-3	+
37	70	F	Hematuria	non papillary	TUC × 4 segmental resection	240M	PT_1 A	2-	—
38	44	M	Hematuria	non papillary	segmental resection	12M	PT_3 D	3	+
39	72	M	Frequency	non papillary	—	24M	PT_1 A	2	—
40	58	M	Frequency	non papillary	—	38M	PT_3 B_2	3	—
41	65	M	Hematuria	papillary	TUR × 1	12M	PTa 0	2	—
42	44	M	Hematuria	papillary	—	30M	PTa 0	1-2	—
43	59	M	Hematuria	papillary	—	24M	PTa 0	2	—
44	62	M	Hematuria	papillary	—	3M	PT_1 A	2	—
45	70	M	Hematuria	non papillary	—	2M	P_iS 0	3	—
46	73	M	Hematuria	papillary	TUC × 3	60M	P_1 A	2	—
47	46	M	Frequency	non papillary	—	4M	P_1 B_1	3	—
48	57	M	Hematuria	non papillary	radiation	26M	P_3 C	3	—

No.	Age	Sex	Symtoms	Cystoscopic findings	Past treatment	Duration of cystectomy from first symptom	Stage	grade	lymph node meta
49	53	M	Burning	non papillary	TUR × 1	26M	P_3 C	3	—
50	58	M	Hematuria	non papillary	—	4M	P_2 B_1	3	—
51	35	M	Hematuria	papillary	radiation	20M	PTa 0	2	—
52	46	M	Hematuria	papillary	—	40M	PT_1 A	2	—
53	49	M	Frequency Burning	papillary	TUC × 1 segmental resection	8M	PTa A	2	—
54	38	M	Hematuria	papillary	—	8M	PTa 0	2	—
55	71	M	Hematuria	papillary	—	3M	PT_1 A	2	—
56	69	M	Hematuria	non papillary	—	4M	PT_3 C	3	+
57	63	F	Hematuria	non papillary	TUR × 1	6M	PT_2 B_1	3	—
58	64	M	Burning	non papillary	TUR × 1	4M	PT_2 B_1	3	—
59	71	M	Hematuria	papillary	TUR × 1	96M	PT_1 A	2	—
60	64	F	Hematuria	non papillary	—	6M	PT_3 D	2-3	+
61	63	M	Hematuria	papillary	—	10M	PT_1 A	2	—
62	57	M	Hematuria	papillary	—	4M	P_1 A	2	—
63	67	M	Hematuria	papillary	TUR × 1	6M	PT_1 A	2	—
64	58	M	Hematuria	non papillary	—	3M	PT_1 A	3	—

TUC: transurethral cagulation
TUR: transurethral resection

Type 3 tumors were non-papillary, invasive, or a mixture of papillary, non-invasive, and invasive tumors, mostly graded 2 or 3. They were multifocal, with ATP and carcinoma in situ found not only around the tumors but also in sited distant from them. Type 4 consisted of localized, non-papillary invasive tumors deeply invading the muscle layer at an early stage. The invasion was tentacular. No carcinoma in situ or ATP was seen at sited distant from the tumor.

Some tissues were subjected to Feuglen's staining and the amount of DNA in 100 cancer cells was measured. As a control, lymphocytes in the same tissue were measured. In order to describe these DNA distribution patterns the following terms have been employed. The modal value has been called "2C" if it coresponds to a normal diploid population and "4C" if it corresponds to a normal tetraploid population. The DNA value most frequently foud in the lymphocytes was 2C. Olympus florescent measuring system was used as the measuring equipment. A MH SP-1F green filter was used with a wave length of 610 nm.

RESULTS

Table 2 shows four types of bladder cancer. Only 5 cystectomies were performed for type 1 tumors, which were mainly of the giant papaillary type. Cases up to B_1(PT_2) were all that were observed and there was no case of lymph node metastasis nor any case of grade 3 malinancy.

Type 2 was observed in 24 cases. They were also cases of early stage up to stage 0-stage B_1 (PTa-PT_2). Most cases were graded 1 or 2, and no metastasis to the lymph node was observed. Type 3 was present in 27 cases including those from stage 0 (P_{TIS}) to stage D (PT_4). In advanced stage cases, there was lymph node metastasis. Five cases of recurrence in the urethra after total cystectomy were found. There were cases with a mixture of grades 2 and 3 or those with only grade 3 and some with only grade 2. Tyep 4, though relatively rare, was observed in seven cases. The stage ranged from stage 0 (P_{TIS}) to stage D (PT_4), and lymph node metastasis was seen in advanced stage cases. Figures 1, 2, 3, 4, show the mapping from types 1 to 4 with each starting from the early stage and may serve as a tool to surmised the natural history of each type of bladder cancer. The DNA distribution pattern was also obtained.

Figure 1 shows the type 1 cases according to stage. Figure 1-1 illustrates a stage 0 (PTa) tumor with no ATP at other sites. Figure 1-2 shows a case of a giant papillary tumor in which the patient was initially diagnosed as having bladder cancer but refused to undergo cystectomy. After 8 years, hematuria became severe and total cystectomy was performed. The stage was A (PT_1). Figure 1-3 shows preservation of the papillary morphology and invasion of the tumor up to the middle of the muscle layer. The invasion was of the broad fron invasion type. In figures 1-2 and 1-3, the ATP and carcinoma in situ in the other epithelium were observed only in the vicinity of the neoplasm. Figure 1-1 represents grade 1 and the DNA distribution mode is 2C. Figure 1-2 and 1-3 show modes in 3c. It is possible for type 1 tumors to remain at an early stage over long periods of time. Figure 2 shows type 2 cases according to stage. Figure 2-1 is a small papillary tumor with multiple ATP. The stage is stage 0 (PTa) and the grade is 2. Figure 2-1 shows a tumor which may change into one such as presented in Figure 2-2 after a certain degree of growth. The tumor in Figure 2-2 is also graded 2. Figure 2-3 depicts a giant papillary tumor mixed with a small papillary tumor and ATP being observed extensively. The stage was A (PT_1) and the grade 2. Figure 2-4 shows tumors one year and six months after onset. These were multifocal tumors including a 5 x 5 cm giant papillary tumor

Table 2. Post surgical stage and 4 types of bladder cancer

	PTa (PT_{is})	PT_1	PT_2	PT_3	PT_4
Type 1	0	3	2	0	0
Type 2	88	15	1	0	0
Type 3	0 (1)	12	9	5 (3)	1 (1)
Type 4	0	1	2 (1)	3 (3)	1 (1)

( ) : cases of lymph node metastases.

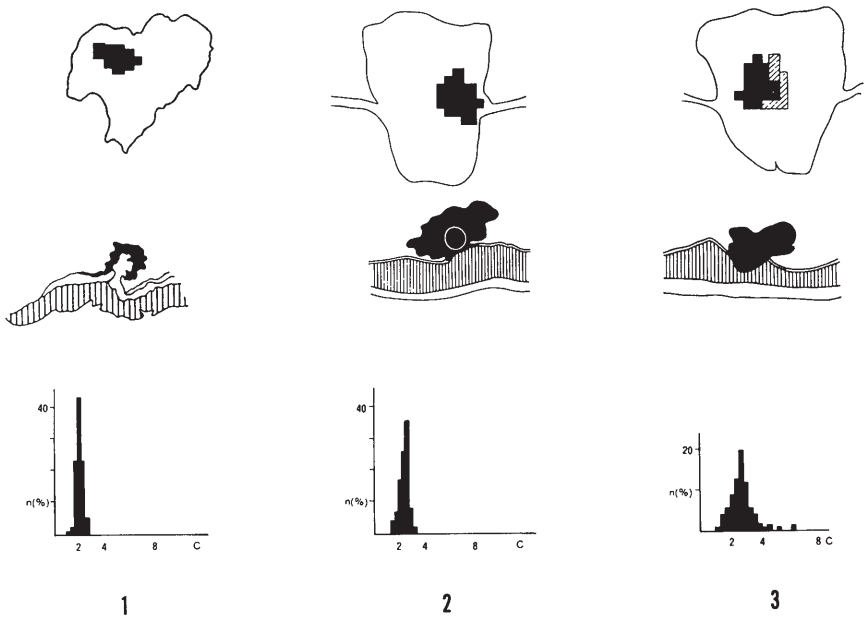

Fig. 1 Mapping of bladder cancer and DNA values in Type 1

ca in situ and atypical hyperplasia
cancer

Figure 1-1 A stage 0 (PTa), grade 1 papillary tumor. No ATP in other sites was found by mapping. The DNA histogram of the tumor showed a mode in the vicinity of 2C.

Figure 1-2 A stage A (PT_1), grade 2 tumor with an 8-year course from the initial symptoms until total cystectomy. A giant papillary tumor, it has remained at stage A (PT_1). There is no ATP or microscopic papillary elevations anywhere else on the bladder. No carcinoma in situ is noted. The DNA histogram showed a mode near 3C. n = number of cell nuclei measured.

In evaluation of continuous changes estimated from figure 1-1 to figure 1-3, no cases in Figure 1 evidenced lymph node metastasis.

with slight invasion of the muscle layer; the stage was B_1 (PT_2) and the grade 2. Type 2 tumors were considered to be a multifocal variation of type 1. This kind of tumor can also become giant, but even when the entire bladder was occupied by many tumors, there was only slight invasion of the muscular layer. Such tumors appear to remain at an early stage for a long period of time.

The DNA distribution was investigated for the tumors in figures 2-3 and 2-4, but the mode was found to be approximately 3C, which was almost the same as that of type 1. There were also many cells with 4C or more. Type 3 tumors were invasive, multifocal, and sometimes there was a mixture of invasive and non-invasive tumors. In the mapping, many carcinomas in situ were seen. Figure 3 shows type 3 cases ranging from stage 0 (PTis) to stage D (PT_4). It was possible to estimate continuous changes from carcinoma in situ to stage D (PT_4). Figure 3-1 shows the case of a patient who came to the hospital with the symptoms of cystitis. Cystoscopy revealed no tumor. The cytology was continuously positive and total cystectomy

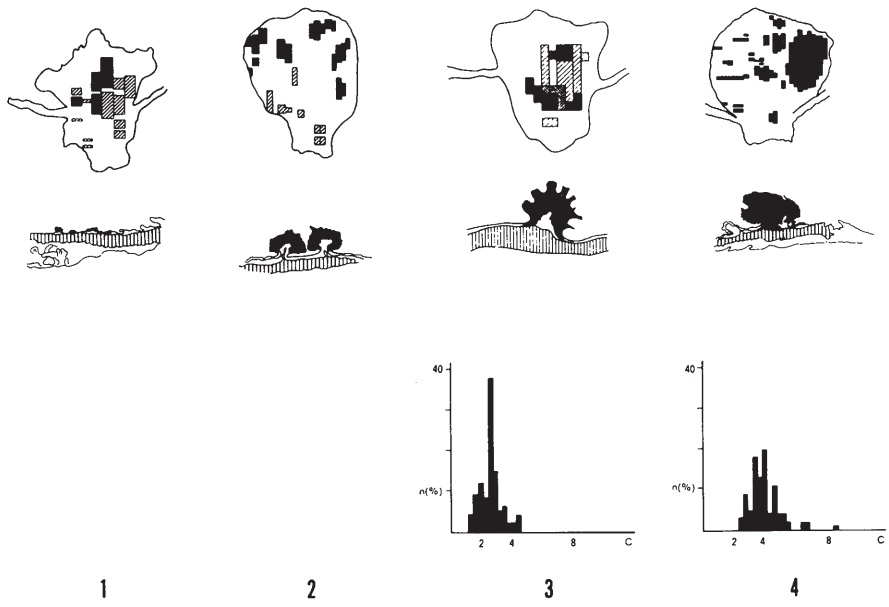

Fig. 2 Mapping of bladder cancer and DNA values in Type 2

Figure 2-1 A case with many stage 0 (PTa), grade 1-2 multifocal small papillary tumors with considerable ATP and many microscopic papillary elevations. The DNA histogram showed a mode near 3C.

Figure 2-2 A tumor type of stage A (PT_1) and grade 2 considered to be an advanced form of the tumor type in figure 2-1. Note the many papillary tumors.

Figure 2-3 A giant papillary tumor of stage A (PT_1) and grade 2 present together with a small papillary tumor. ATP and microscopic papillary elevations were also found at sites distant from the tumor.

Figure 2-4 Bladder carcinoma consisting of a single stage B_1 (PT_2), grade 2 giant papillary tumor and many papillary tumors. The giant papillary tumor has begun to invade the muscle layer. The mode of DNA distribution is near 3C.

Continuous changes are inferred from figure 2-1 → figure 2-2 → figure 2-3 → figure 2-4. No cases in Figure 2 indicated lymph node metastasis.

was performed. Multiple carcinoma in situ was observed. Figure 3-2 indicates a small non-papillary tumor with submucosal invasion. The stage was A (PT_1) with grade 3 malignancy. Figure 3-3 shows multiple carcinoma in situ in a non-papillary tumor with invasion of the cancer into the lymphatic vessels of the muscle layer. The stage was B_1 (PT_2) with grade 2 and grade 3.

Figure 3-4 illustrates a non-papillary tumor of stage C (PT_3) and grade 3 with a wide ranging carcinoma in situ. After total cystectomy, recurrence of the cancer was noted in the urethra. Type 3 was found to be multiple from the focal mapping with the possibility of carcinoma in situ existing in the urethra. This type is considered liable to have recurrence in the urethra. Figure 3-5 represents an advanced case of the tumor shown in Figure 3-4. Cancer was also found in the fatty tissue surrounding the bladder. Metastasis in the lymph nodes was also noted. The stage was D (PT_4).

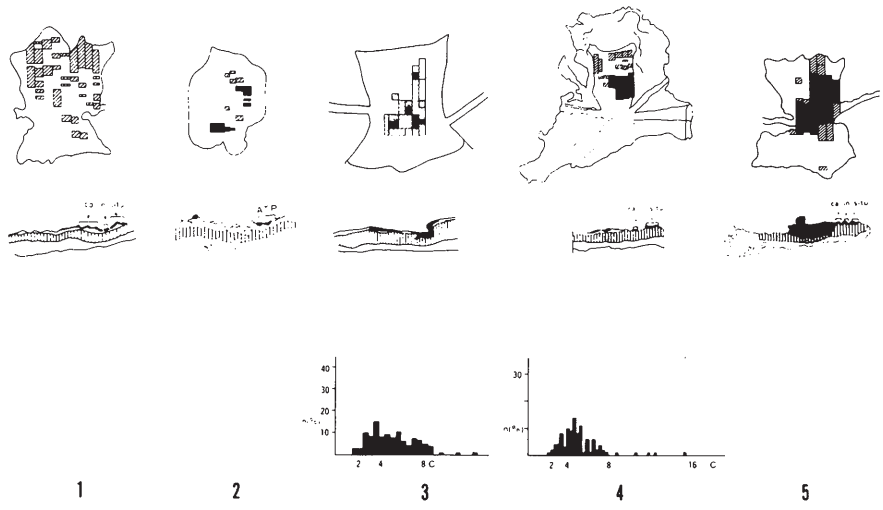

Fig. 3 Mapping of bladder cancer and DNA values in Type 3

Figure 3-1 A case of total cystectomy with many carcinoma in situ.

Figure 3-2 Multifocal stage A (PT_1), grade 2-3 non-papillary tumors with partial submucosal invasion in some foci. Carcinoma in situ and ATP are also present at sites distant from the tumor. DNA was in a mode near 5C. The mode was dispersed.

Figure 3-3 A mixed stage B_1 (PT_2), grade 2-3 non-papillary and papillary tumors. There are many carcinoma in situ. Cancer cells were found in the lymphatic vessels of the muscle layer at the site of the non-papillary tumor. The DNA showed mode dispersion with a mode near 5C.

Figure 3-4 A stage B_2 (PT_3), grade 3 non-papillary tumor showing invasion of the muscle layer. There are many carcinoma in situ. Recurrence in the urethra was observed one year after total cystectomy.

Figure 3-5 A stage C (PT_3), grade 3 non-papillary tumor together with many carcinoma in situ. There are metastases to the lymph nodes of the internal iliac artery.

The DNA histogram of many cells showed 4C or more and a mode of about 5C with the distribution pattern of tumor cells becoming larger (Figures 3-1 and 3-3). Type 4 was the most malignant and rapidly progressing; the grade was 3 in all cases. Figure 4 represents cases from stage A (PT_1) to D (PT_4). This type had a localized focus with no carcinoma in situ in the area far from the tumor. Figure 4-1 shows a non-papillary carcinoma with a small focus. The stage was A (PT_1) and the grade high. Figure 4-2 illustrates a stage B_1 (PT_2) tumor with single metastasis to the lung. The lung was partially resected. Figure 4-3 shows tentacular invasion to the fatty tissue around the bladder and lymph node metastasis. The stage was C (PT_3). Figure 4-4 shows a case which reached stage D (PT_4) in two years from the initial symptoms. During surgery, tumor cells were found in the ascites. The stage was D (PT_4) and the grade 3. There were no stage B_2 (PT_3) patients who survived for more than five years. The DNA histograms in Figures 4-1, 4-3 and 4-4 showed many cells with DNA of 8C or more. The dispersion of mode was remarkable.

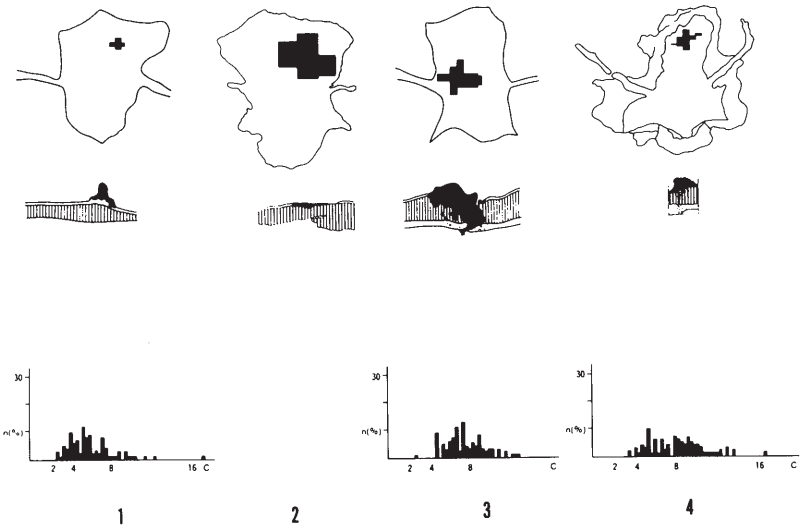

Fig. 4 Mapping of bladder cancer and DNA values in Tyep 4

Figure 4-1 A stage A (PT_1), grade 3 non-papillary tumor with no submucosal invasion or carcinoma in situ. The DNA distribution reveals a dispersed mode with many cells of 8C or more.

Figure 4-2 A stage B_1 (PT_2), grade 3 non-papillary tumor with invasion of the muscle layer. Lung metastasis was found and the lung was resected.

Figure 4-3 A stage C (PT_3), grade 3 non-papillary tumor showing tentacular invasion. There is no carcinoma in situ. Lymph node metastasis is evident. There is remarkable dispersion of the DNA distribution and many cells of 8C or over.

Figure 4-4 A small non-papillary tumor of stage D (PT_4), grade 3 with islet-type invasion. There is no concomitant carcinoma in situ, but many lymph node metastases are observed.

CHOICE OF TREATMENT

Selection of the method for the treatment of bladder cancer can be made for each type to some extent in accordance with the lesion or the expansion of the epithelium of the bladder and growth patterns and the depth of invasion in the above-mentioned four types of bladder cancer.

Type 1 can be controlled by transurethral resection (TUR). In the case of giant papillary tumors, resection or partial resection of the tumor rather than TUR may be indicated. There are many cases where ATP is present in the vicinity of the tumor and some foci cannot be detected by cystoscopy, to which attention should be paid. Even if giant tumors reach the muscle layer, they are localized and, therefore, partial resection is sufficient depending on the site. Type 2 tumors are multifocal and often recur, so that transurethral resection is usually done over again. Hoewever, too frequently a transurethral resection involves th risk of foci extending deeper into the tissue. Moreover, when recurrence is frequent after observations on the clinical course for sometime and if invasion of the muscle layer is confirmed by transurethral resection, total cystectomy is indicated. Dissection of the regional lymphatics is

not always necessary, but resection of the urethra is needed since the tumors are multifocal and there is a possibility of recurrences in the urethra. Type 3 tumors are multiple and invasive, so that controlling the tumor by transurethral resection is impossible. Total cystectomy and dissection of the regional lymphatics are indicated. Resection of the urethra is also necessary since the tumors are multifocal and there is a possibility of carcinoma in situ in the urethra. Since a type 4 tumor progresses rapidly, total cystectomy, in case partial cystectomy should be performed without delay. dissection of the regional lymphatics is also necessary.

DISCUSSION

It has been repeatedly stressed that the prognosis of bladder cancer is greatly influenced by the depth the cancer has reached and the accompanying lymph node metastasis, but the natural history of the bladder cancer advancing from a surface tumor or carcinoma in situ to an invasive tumor, is not always clear. In clarifying the natural history of bladder cancer, studies on the carcinoma in situ, the original form of bladder cancer, are useful and significant.

Melicow (2) was the first to recognize the histological similarities between carcinoma of the bladder and Bowen's disease and to introduce the concept of carcinoma in situ in carcinoma of the bladder as subclinical preinvasive carcinoma and intraurethelial cancer. He investigated the seemingly normal epithelium of the bladder separated from the main tumor in specimens of total cystectomies and frequently found carcinoma in situ. After that, Eisenberg (16) and Simmon *et al.* (17) reported similar findings. Shade *et al.* (18) found precancerous lesions or severe atypia in 80% of biopsy specimens of bladder mucosa which was unrelated to the tumor. Carcinoma in situ delt with in the reports hitherto published was one accompanying carcinoma of the bladder, clearly observable macroscopically, and not discussed in connection with the course of growth of carcinoma of the bladder.

However, Melamed (19) reported cases which were negative for cystoscopy but positive for urinary cytology, subsequently mentioning that cancer became invasive in eight out of 25 cases of carcinoma in situ. Farrow *et al.* (20) also made follow-up investigations of carcinoma in situ in 69 cases, reporting that the carcinoma became invasive within five years in 37 cases and within three years in most cases. Koss (21) and Yate *et al.* (22) noted the possibility of carcinoma in situ developing into non-papillary or papillary carcinoma and showed the natural history of baldder cancer. Althausen *et al.* (23) reported that 42% of accompanying carcinoma in situ developed into invasive carcinoma within 5 years. The reports above have clarified the history from carcinoma in situ to invasive cancer, but the natural history of papillary tumors is not clear. Papillary type cancer does not always follow the growth patterns as described by WHO (24) or Pugh's diagram (25).

While the above-mentioned reports were taken into consideration, the mapping and growth patterns of many foci were investigated simultaneously and the natural hisory of carcinoma of the bladder was divided into four types for study. It became clear that the way the carcinoma spread was not always the same, and that the rate of spread varied with expansion in the epithelium of the bladder and the growth pattern.

The difference between types 1 and 2 according to the authors' classification arises from the presence of unifocal localized tumors and multifocal tumors. Investigations of the mapping of overall specimens of the multifocal type (type 2) reveal that ATP and low grade carcinoma in situ cannot always be confirmed by cystoscopy. This suggests that the ATP and low grade

carcinoma in situ become the focus of "recurrence" even in a tumor-free state. On the other hand, there are cases which have no recurrence whatsover after one transurethral resection and the recurrence rate after transurethral resection is reported as 40-70% (26) (27) (28). The problem of recurrence appears to depend on whether the bladder cancer is of the localized or multifocal type.

Types 1 and 2 are papillary. In almost all of the cases under study, the stage did not advance beyond A (P_1). Four cases advanced to stage B_1 and no tumor developed to stage B_2 (P_3) or beyond. Nor was there any lymph node metastasis. Grade 3 papillary tumors existed but were rare. According to Koss (4), Grade 3 papillary tumors is often present as a complication with invasive cancers in other sites. No grade 3 cases were present among types 1 and 2 papillary tumors in this study. All of the tumors which had developed to stage B_1 were cases of broad front invasion. As the method of treatment, transurethral resection is basically employed both for types 1 and 2 tumors. When transurethral resection is difficult, as in the case of a giant tumor occasionally observed with type 1, highly radical effects can be obtained by tumor resection or by partial resection of the bladder. Cases of type 2 are similar to type 1 in the DNA distribution pattern, are graded 1 or 2, and are not high in biological potential. Since considerable time is required to reach stage B_2, it is preferable to follow such cases with transurethral resection for a while and then to perform total cystectomy when invasion of the muscle layer has been confirmed. For tyep 2, partial resection runs the risk of the tumor being embedded in the muscle layer. A detailed examination by multiple biopsies is necessary to differentiate between types 1 and 2.

Type 3 is the one most frequently observed in bladder mapping by Melamed, (3) Koss (4) and others. Both type 3 and type 2 are similar in being multifocal but differ in that the former is invasive. With type 3, there are many carcinomas in situ not only near the invasive tumor but also at sites distant from it as confirmed in many investigation hitherto made on total cystectomy specimens. Skinner (6) found carcinoma in situ in. 44% of total cystectomy specimens from 59 patient. Cooper *et al.* (7) found severe atypia (carcinoma in situ) in 39% of sites distant from the foci of carcinoma of the bladder. There have also been reports that carcinoma in situ and ATP are found in the ureter (29) (30) (31) or urethra (32) (33) as lesions concomitant with bladder cancer. Carcinomas of the bladder are basically considered multifocal. This has been supported by investigations using mapping or giant sections. However, it does not mean that carcinoma of the bladder on the whole is multifocal since type 3 accounts for most of the cases of total cystectoymy.

In the mapping of 64 cases in the present study, 27 were of type 3. There were not so many multifocal invasive cases as compared with the reports of Koss (4) and others using giant sections. Tyep 3 appeared to represent one type of bladder cancer, which is both multifocal and invasive. Needless to say, multiple biopsies are necessary for diagnosis of type 3.

Generally, type 3 is said to have a poor prognosis; hence, the largest number of cases of total cystectomies are of type 3. Also, since the possibility of type 3 having recurrences in the urethra is considered to be high, resection of the urethra simultaneously with total cystectomy is indicated. Richies (34) mentioned the presence of intraepithlial carcinoma in the neck of the bladder and the urethra as an indication for urethral resection in cases of total cystectomy. However, it is difficult to find carcinoma is situ in the urethra preoperatively.

The presence of type 4 was most conspicuous in this focal mapping. This type showed the tentacular invasion described by Mostofi (35) and lymphatic invasion at an early stage. Soto *et al.* (5) have reported broad front invasion in papillary tumors and tentacular type invasion in solid types. Types 1 and 2 show broad front invasion and type 3 shows both broad front and tentacular invasion. Tyep 4 generally shows only tentacular invasion and is considered a type

of cancer which is concentrated at one point and becomes invasive at an early stage. There have been few reports on type 4. Soto (5) has reported a case, although rare, in which the tumors are localized without carcinoma in situ or ATP and in which tentacular invasion is observed. Mitani (36) has classified morphologically an irregular-type tumor in which death occurs within two years. Such a tumor considerd to be equivalent to type 4. Most of the type 4 tumors are grade 3 or undifferentiated carcinoma.

Various investigators (37) (38) (39) have stated that the bladder epithelial cells of normal human subjects and mice are polypoid, consisting of tetraploid and octaploid cells as well as diploid cells.

In this study DNA values of the normal bladder were diploid. The DNA histograms revealed the same dispersion for tyeps 1 and 2 tumor histograms. Type 3 showed more dispersion, which agrees with reports of various authors (40) (41) (42) that the mode of a histogram of nuclear DNA values becomes flat and that the incidence of polypoid cells becomes higher with an increase in the grade of cancer. With type 4 the histogram is flatter than that of type 3 and there is a higher degree of atypia in the cancer cells. This type is different from type 3, likewise an invasive type, in the rate of invasion of the muscle and lymphatic vessels. Treatment requires immediate radical extirpation even at an early stage. Treatment by partial cystectomy is also possible because the focus is localized. Resnick *et al.* (43) and Novick *et al.* (44) have reported that the survival rate after partial cystectomy is high in the case of unifocal tumros.

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