However, Zimmerman *et al* and Burstein *et al* reported that GLUT-1-positive cells of RM showed equivocal-to-weak staining and were easily distinguishable from unequivocal positivity of other cell types, so that the specificity of GLUT-1 was not diminished. According to them, a number of 'false-positive' cases occurred in patients with cirrhosis. The RM resulting from cirrhosis may be prompted by glucose intake to compensate for the unfavorable environment in effusion. Our cohort of RM consisted of surgically resectable cases within the physiological range or without effusion.

Positron emission tomography (PET) measurements of fluorodeoxyglucose (FDG) accumulation in different animal tumors has shown a correlation between tracer FDG uptake and the GLUT-1 mRNA content. GLUT-1 has been found to be overexpressed in tumor cells and to promote glucose metabolism and FDG accumulation in humans.[22,24] In MPM, Carretta *et al*[36] have reported that FDG-PET can differentiate RM from MPM. These findings are consistent with the present immunohistochemical results.

In summary, GLUT-1 appears to be a sensitive and specific marker for differentiating between RM and MPM, although it is unable to discriminate between MPM and lung carcinoma.

Acknowledgement

This work is supported in part by Special Coordination Funds for Promoting Science and Technology of Japan.

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Surg Today (2009) 39:728–732
DOI 10.1007/s00595-008-3918-0

SURGERY TODAY

Simultaneous Laparoscopic Descending Colectomy and Nephroureterectomy for Descending Colon Carcinoma and Left Ureteral Carcinoma: Report of a Case

NAOTAKA NISHIYAMA[1], SEIICHIRO YAMAMOTO[2], NAOKI MATSUOKA[1], HIROYUKI FUJIMOTO[1], and YOSHIHIRO MORIYA[2]

Divisions of [1]Urology and [2]Colorectal Surgery, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

Abstract
To our knowledge, there is no case report of the synchronous resection of colon and ureteral carcinomas by laparoscopy, because of the rareness of this combination and the technical difficulties involved. We report a case of simultaneous descending colon and left ureteral carcinomas, both of which were judged to be relatively early stage carcinoma, which we resected successfully laparoscopically. The patient, a 65-year-old man, recovered uneventfully and was discharged on postoperative day 8. For simultaneous abdominal primary malignancies, laparoscopic surgery should be considered proactively if the procedure is technically feasible and judged to be curative.

Key words Synchronous resection · Laparoscopic colectomy · Laparoscopic nephroureterectomy

Introduction

Synchronous laparoscopic resections of colorectal carcinoma and procedures for coexisting benign conditions, such as cholecystectomy for cholelithiasis, are recognized as feasible without increasing postoperative morbidity.[1] Conversely, synchronous laparoscopic resections of colorectal carcinoma and coexisting malignant disorders require prolonged total operation and anesthesia times, and demanding technical requirements. Thus, there are concerns that the intraoperative and postoperative complication rate would be elevated and the oncologic safety of synchronous laparoscopic surgery (LS) for multiple malignancies has not been established.

Reprint requests to: S. Yamamoto
Received: May 2, 2008 / Accepted: July 30, 2008

Many randomized and nonrandomized studies comparing LS and conventional open surgery (OS) for colorectal or renal carcinoma have revealed short-term advantages of LS. Moreover, the long-term oncologic outcomes achieved after LS were recently reported to be comparable with those after OS.[2-6] Similarly, for patients with simultaneous colorectal and renal carcinoma requiring resection, synchronous resection by LS is considered to be technically feasible and safe, with good short-term clinical outcomes and favorable oncologic outcomes.[7-10] However, we could not find any case report on the synchronous resection of lesions of colon and ureteral carcinomas by LS, because such cases are rare and because of the increased technical requirements.

Recently, we encountered a rare case of simultaneous descending colon and left ureteral carcinoma. Preoperative examinations showed that both malignancies were at relatively early stages; therefore, synchronous laparoscopic descending colectomy and left nephroureterectomy were indicated and performed successfully. The patient is still disease-free 27 months after surgery. To the best of our knowledge, synchronous laparoscopic colectomy and nephroureterectomy have not been reported previously.

Case Report

A 65-year-old man was referred to the Division of Colorectal Surgery of the National Cancer Center Hospital, Tokyo, Japan, for the treatment of early descending colon carcinoma, diagnosed by colonoscopy findings at a local hospital after a positive fecal occult blood test performed during a medical checkup. He had no family history of hereditary nonpolyposis colorectal carcinoma (HNPCC). A colonoscopy performed at our hospital showed a shallow ulcerated lesion occupying half of the lumen, which was judged as a T1 or T2 lesion (Fig. 1).

Biopsy results confirmed that the tumor was well-differentiated adenocarcinoma. There was no evidence of metastasis on chest and abdominal computed tomography (CT) scans; however, left hydronephrosis was evident (Fig. 2a) and drip infusion pyelography confirmed a left ureteral defect (Fig. 2b), suggestive of left ureteral carcinoma. A few degenerated atypical cells were detected in his urine cytology, collected by inserting a catheter into the left ureter, and judged as class III. Cystoscopy showed no anomaly of the urinary bladder and a biopsy from around the left ureteral orifice revealed no malignant findings. Thus, we diagnosed simultaneous descending colon and left ureteral carcinomas. Both malignancies were judged as relatively early stage carcinoma, so laparoscopic resection was performed 5 weeks after initial consultation.

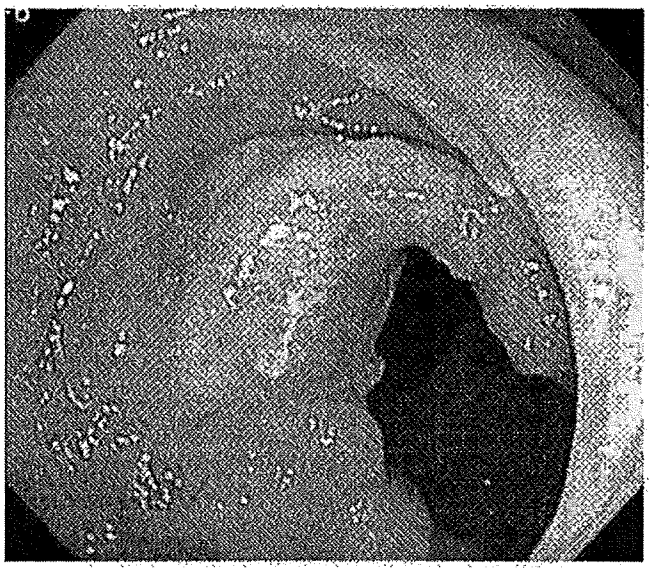

Fig. 1. Colonoscopy revealed a shallow ulcerated lesion occupying half of the lumen

At surgery, we used five trocars (Fig. 3). Pneumoperitoneum was established by the open laparotomy technique through a supraumbilical incision. Under laparoscopic guidance, three 5-mm ports and one 12-mm port were inserted. The operating table, tilted to the right, was placed in the head up or down position depending on the location of the target organs. First, the sigmoid colon, descending colon, and splenic flexure were completely mobilized along Toldt's fusion fascia. After visualizing the inferior mesenteric vessels, intracorporeal ligation of the tumor-feeding arteries (left colic artery and the first sigmoidal artery) was done at their origins, preserving the inferior mesenteric artery. Next, the anterior aspect of the left kidney was exposed after complete mobilization of the left colon with the operating table tilted to the nearly right lateral position (Fig. 4a). After identifying the left gonadal vessels and the left ureter on the left side of the aortic bifurcation, the left gonadal vessels were divided just before the inguinal canal. The left gonadal vessels and left ureter, together with the retroperitoneal adipose tissue, were dissected proximally, and the left gonadal artery was divided at the origin. Subsequently, the left gonadal vein, left renal vein, and left adrenal vein were identi-

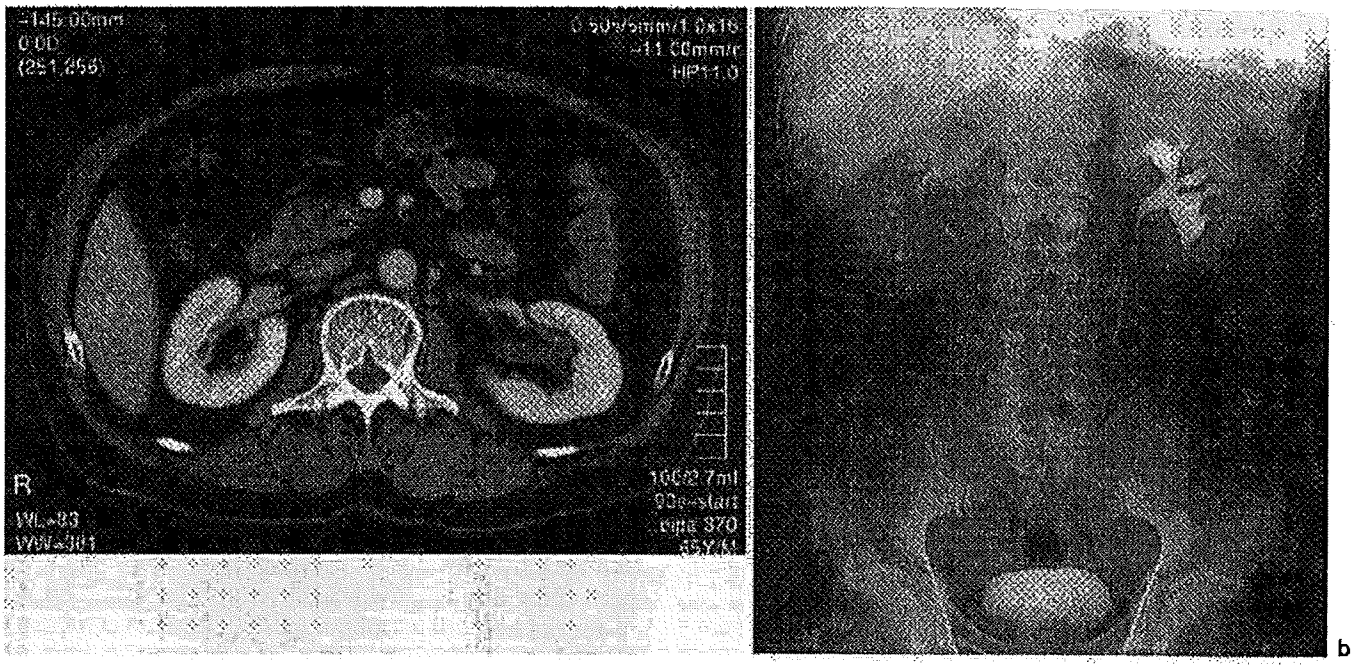

Fig. 2. **a** Preoperative enhanced computed tomography scan showing left hydronephrosis. **b** Intravenous pyelography. Drip infusion pyelography confirmed a left ureteral defect

fied at the hilum of the kidney, and the left renal artery was found to be located dorsal to them. After division of the left renal artery by endoclips, the left renal vein was divided using an endolinear stapler, preserving the left adrenal vein (Fig. 4b). En bloc removal of the left kidney with Gerota's fascia was performed, preserving the left adrenal gland. The left ureter was then dissected up to the inflow point of the urinary bladder, as the final procedure in the laparoscopic manipulation.

With the operating table held in a slight right lateral position, the left kidney and ureter were delivered under protection through an 8-cm incision in the left lower abdomen. The distal part of the ureter and part of the bladder were excised under direct vision, and the left kidney and ureter were completely removed. Subsequently, the bowel loop was delivered from the same incision, and division of the mesenterium with resection of the involved parts was performed, followed by extracorporeal functional end-to-end anastomosis. The total operation time was 442 min and the blood loss was 158 ml. Liquid and solid foods were started on postoperative days 1 and 3. The patient recovered uneventfully and was discharged on postoperative day 8.

Histopathologically, the descending colon carcinoma was diagnosed as a well-differentiated adenocarcinoma (pT1N0M0) (Fig. 5c). Microscopic examination of the left kidney and ureter revealed two papillary tumors, 2.5 × 0.5 × 0.5 cm and sharing the same basal point, in the upper ureter. Histopathologically, they were grade 2 transitional cell carcinomas confined to mucosa (pTaN0M0) (Fig. 5a,b). The patient remains well without any sign of recurrence 26 months after the operation.

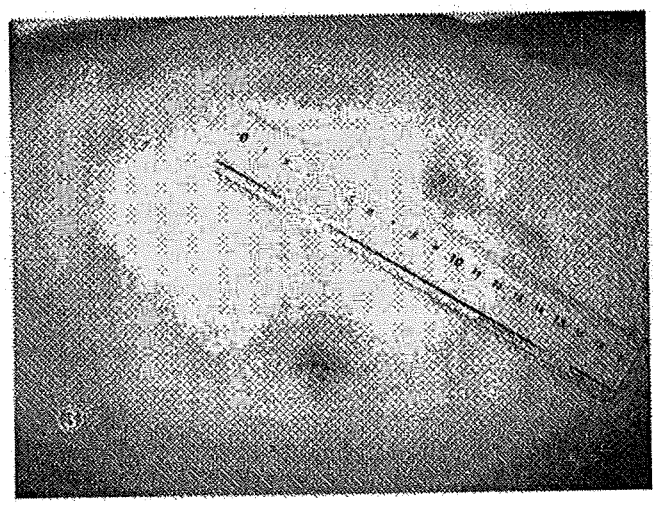

Fig. 3. Photograph taken 2 years after the operation, showing the five trocar positions and the small incision

Discussion

The effectiveness of synchronous resection of simultaneous colon and renal carcinoma by LS has been reported; however, to our knowledge the synchronous resection of simultaneous colon and ureteral carcinomas by LS has never been described before.[7–10] Our patient underwent these procedures successfully with favorable results, an uneventful recovery, and a short hospitalization.

Unlike for renal carcinoma, for ureteral carcinoma total removal of the ureter is necessary, which requires

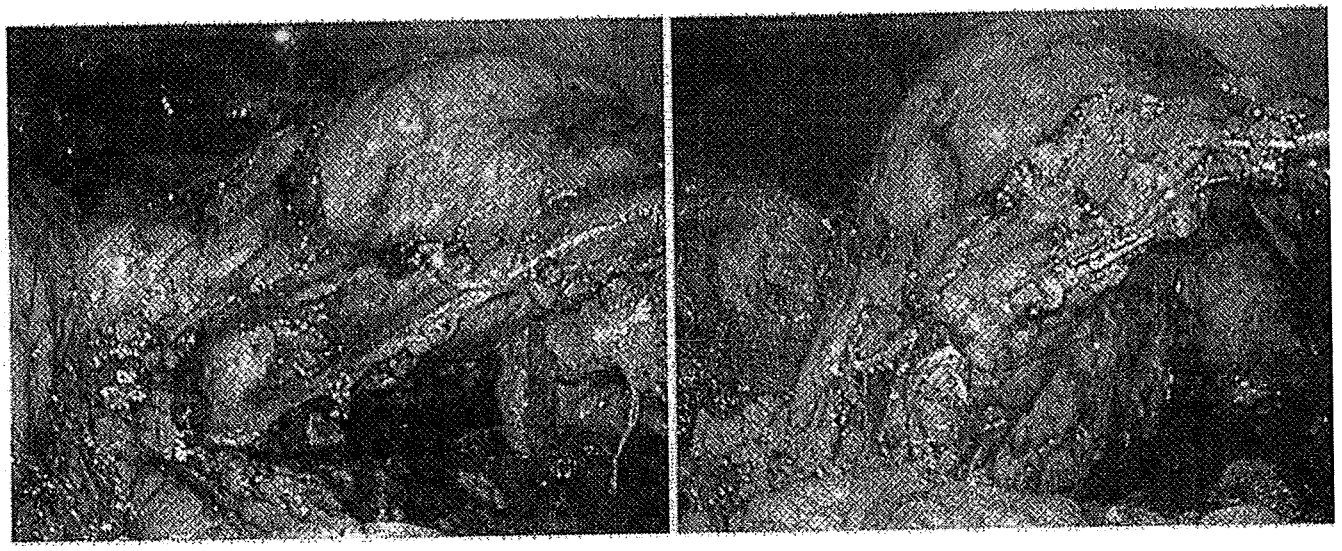

Fig. 4a,b. Intraoperative photographs. **a** The left kidney and ureter as seen laparoscopically. The anterior aspect of the left kidney was exposed after complete mobilization of the left colon. **b** After division of the left renal artery by endoclips, the left renal vein was divided using an endolinear stapler

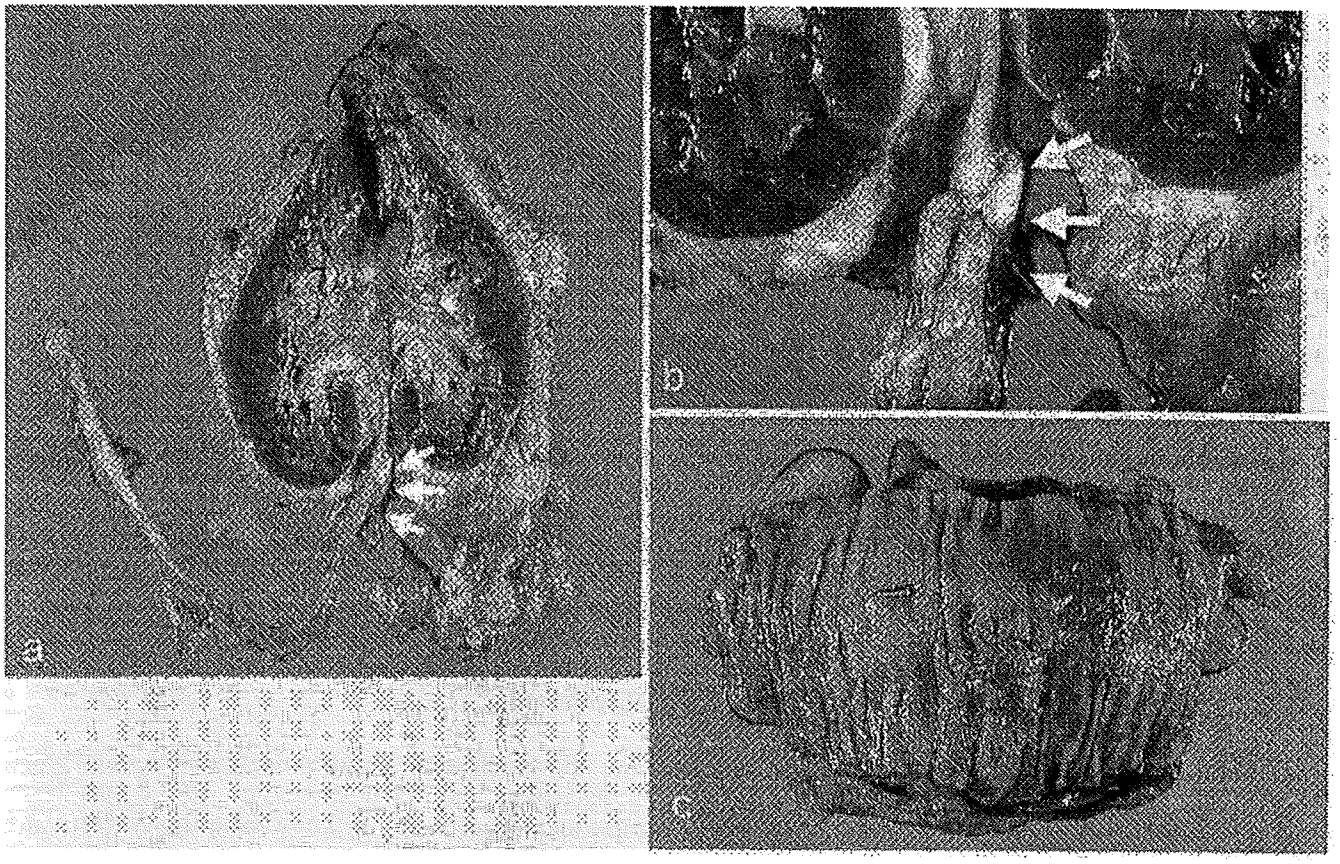

Fig. 5. a,b The left nephroureterectomy specimen. *Arrows* indicate the tumor. **c** Descending colectomy specimen

an ingenious approach. The colon and ureteral carcinomas in our patient were both located on the left side, so we successfully cuffed the bladder, and then resected and anastomosed the colon carcinoma under direct vision through a small incision in the left lower abdomen. However, if one of the carcinomas had been on the opposite side, one of the procedures would have had to be performed laparoscopically, increasing the level of technical difficulty further. Although a technique for transurethral resection of the lower ureter has been reported, we have not adopted it because suturing the resection site of the lower ureter is difficult, which increases the risk of tumor cell spillage.[11]

Regarding the treatment strategy for colorectal carcinoma, several randomized control trials in Western countries have revealed that the long-term prognosis after LS is equivalent to that after OS.[3–5] Consequently, the number of patients with colorectal carcinoma treated with LS is expected to increase. Similarly, the technical and oncologic feasibility of nephroureterectomy for ureteral carcinoma by LS or hand-assisted laparoscopic surgery has been reported, and the number of patients treated by minimally invasive surgery is also expected to increase.[6,12]

Our patient had simultaneous descending colon carcinoma and left ureteral carcinoma, and with advances in diagnostic techniques and treatment modalities, the number of patients identified with multiple primary malignancies during long-term follow-up is increasing. Aydiner et al. reported that 1% of patients with carcinoma had multiple primary malignancies, and that among patients with simultaneous colorectal and urological carcinomas, about 4% had renal carcinoma, followed by 1% with prostate carcinoma.[13] In the Japanese population, the most common site for multiple primary malignancies associated with colorectal carcinoma in men is the stomach, followed by the lung, prostate, larynx, liver, esophagus, and urinary bladder in men; and in women it is the uterus, followed by the stomach, breast, and liver. Although ureteral carcinoma is regarded as an HNPCC related malignancy, the frequency of HNPCC in Japanese is lower than that in Western countries. Reports of synchronous colorectal carcinoma and ureteral carcinoma are extremely rare in Japan.[14]

In summary, we described a case of synchronous descending colon and left ureteral carcinoma successfully treated with laparoscopic descending colectomy

and left nephroureterectomy. To expand the use of minimally invasive surgery for malignancies, advanced technical skills must be acquired, with confirmation of the oncologic safety of LS.[15] For simultaneous abdominal multiple primary malignancies, LS should be considered proactively if the procedure is judged to be curative.

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Cancer Science
The official journal of the Japanese Cancer Association JCA

Characteristics of prostate cancers found in specimens removed by radical cystoprostatectomy for bladder cancer and their relationship with serum prostate-specific antigen level

Tohru Nakagawa,[1,3] Yae Kanai,[2] Motokiyo Komiyama,[1] Hiroyuki Fujimoto[1] and Tadao Kakizoe[1]

[1]Urology Division, National Cancer Center Hospital; [2]Pathology Division, National Cancer Center Research Institute, Tokyo, Japan

(Received April 13, 2009/Revised June 18, 2009/Accepted June 22, 2009/Online publication July 30, 2009)

Prostate cancer mass screening using serum prostate-specific antigen (PSA) has been conducted widely in the world. However, little is known about the true prevalence of prostate cancer in the 'normal' PSA range (4.0 ng/mL or less). The aim of the present study was to elucidate the clinicopathological features of prostate cancer occurring in men with a wide range of PSA levels. The study comprised 349 male patients who underwent radical cystoprostatectomy for bladder cancer. Patients who had had treatment for known prostate cancer were excluded. Tissue specimens were reviewed microscopically. Ninety-one patients (26.1%) were found to have prostate cancer, and 68 (74.7%) of these 91 cancers were considered to be clinically significant. Both increasing patient age and PSA level were significantly correlated with an increased incidence of both all and significant prostate cancers. Sixty-five (21.9%) among 297 patients with PSA < 4.0 ng/mL had prostate cancer, and 45 (69.2%) of the 65 cancers were significant cancers. Eighteen patients had prostate cancers 0.5 mL or more in volume. Among the 18 patients, the PSA level was 4 ng/mL or more in 11, and 3 ng/mL or more in 15. Our study shows that prostate cancer is a common finding in radical cystoprostatectomy specimens excised because of bladder cancers, and a significant proportion of these cancers are clinically significant. PSA still appears to be a useful screening tool for detecting prostate cancers with significant volume. (*Cancer Sci* 2009; 100: 1880–1884)

Prostate cancer is one of the leading causes of mortality and morbidity in developed countries.[1] Screening of serum PSA followed by systematic prostate biopsy has enabled detection of prostate cancer at an earlier stage,[2] although it is still debatable whether mass screening using PSA contributes significantly to reduction in mortality from prostate cancer.[3]

Historically, 4.0 ng/mL PSA has been used as the threshold to prompt prostate biopsy. Although it is known that prostate cancers do exist even in the low PSA range (4.0 ng/mL or less),[4] until recently little was known about the true prevalence of prostate cancer in the low PSA range because most men in this category do not undergo prostate biopsy.[5] In 2004, Thompson *et al.* reported data from the PCPT showing that biopsy-detectable prostate cancer is not rare among men with a low PSA level (4.0 ng/mL or less).[6] This result provoked a discussion about the optimal threshold of PSA for recommending biopsy, although no definitive agreement has been reached so far.[7,8] Although the PCPT demonstrated the prevalence of biopsy-detectable prostate cancer in the low PSA range, there is still a notable lack of data based on thorough histological evaluation of the whole prostate in relation to PSA level in a large general population.

It is possible to microscopically examine the whole prostate of autopsied individuals in whom prostate cancer had not been suspected before death.[9] Although most latent prostate cancers observed in autopsy cases are small lesions, their histology is not different from clinical cancers, and they may be merely in the early phase of progression.[10,11] Usually, however, PSA levels are not available in autopsy cases.

Radical cystoprostatectomy (RCP) is a gold-standard treatment for invasive bladder cancer.[12] Even though some researchers have reported an epidemiological association between bladder cancer and prostate cancer,[13] the specimen obtained from this operation represents a fairly random sample of whole prostate tissue from asymptomatic men. Several studies have examined the incidence and histopathological characteristics of prostate cancer found incidentally in RCP specimens.[14–18] They showed that incidental prostate cancer is not rare in RCP specimens (incidence, 4–60%).[14–18] However, only a few of them examined its relationship with PSA value.[15–18]

In order to elucidate the incidence and histopathological features of prostate cancers occurring in men with a wide range of PSA levels, we reviewed 349 whole prostate tissues in RCP specimens excised because of bladder cancer in Japanese men.

Patients and Methods

Medical records of 354 consecutive men who underwent RCP for bladder cancer at the National Cancer Center Hospital between July 1995 and April 2008 were reviewed retrospectively. The study was approved by the institutional review board.

Three men were excluded from the study because they had undergone pelvic irradiation for bladder cancer before RCP. Two were also excluded because they had been diagnosed as having prostate cancer and treated with androgen ablation and/or radiation therapy before RCP. Thus, 349 men were included in the present study.

A routine pathological examination was conducted on all RCP specimens by sectioning the prostate and bladder every 5 mm. A single pathologist (YK) reviewed the specimens microscopically. Each prostate cancer was staged and graded based on the 2002 International Union Against Cancer (UICC) TNM system[19] and 2005 modified International Society of Urological Pathology (ISUP) Gleason grading system.[20] Tumor volume was calculated using the formula:

$$\text{volume} = (\text{width} \times \text{height} \times \text{length}) \times \pi/6 \times 1.5,$$

in which length is calculated from 0.5 cm multiplied by the number of slices containing tumors and 1.5 is a tissue shrinkage factor.[21]

[3]To whom correspondence should be addressed. E-mail: trnakaga@ncc.go.jp

doi: 10.1111/j.1349-7006.2009.01267.x

Table 1. Status and pathology of prostate biopsy and prostate-specific antigen (PSA) levels before radical cystoprostatectomy (RCP) in the 349 patients

PSA	Prostate biopsy before RCP		
	Yes		No biopsy
	Prostate cancer proved	Benign prostatic tissue	
<4 ng/mL	1	0	296
≥4 ng/mL	3	2	44
Unknown	0	0	3

Table 2. Characteristics of prostate cancers found in radical cystoprostatectomy specimens

Characteristic	Patients	
	n	%
Gleason score		
6 or less	24	26.4
7 (3 + 4)	54	59.3
7 (4 + 3)	9	9.9
8–10	4	4.4
pT stage		
pT2	85	93.4
pT3a	3	3.3
pT3b	1	1.1
pT4	2	2.2
Lymph node status		
pN0	89	97.8
pN1	1	1.1
pN2	1	1.1
Surgical margin status		
Not involved by tumor	87	95.6
Involved by tumor	4	4.4
Perineural invasion		
Negative	69	75.8
Positive	22	24.2

The serum PSA level was determined routinely before RCP at the outpatient clinic. Measurement of PSA levels was carried out using the Delfia-PSA assay (Pharmacia Diagnostics Co., Tokyo, Japan) until September 1997, the Lumipulse PSA assay (Fujirebio, Tokyo, Japan) until July 2004, and the Lumipulse PSA-N assay (Fujirebio) thereafter.

Correlations of clinicopathological parameters between groups were analyzed by Mann–Whitney *U*-test or Kruskal–Wallis test. Differences with *P*-values < 0.05 were considered significant.

Results

The median patient age was 65 years (range, 27–89 years). Preoperative PSA levels were not evaluated in 3 of the 349 men. The median preoperative PSA level was 1.28 ng/mL (range, 0.03–20.603 ng/mL) for the 346 patients.

In 6 of the 349 patients, prostate biopsy had been carried out before RCP. The presence or absence of prostate biopsy, pathology of the biopsy specimen, and serum PSA levels in the 349 patients are summarized in Table 1.

Ninety-one patients (26.1%) were found to have prostate cancer. Of these, four (1.1%) had been preoperatively diagnosed as having prostate cancer by needle biopsy, but had not been treated before RCP. Eighty-seven (24.9%) were found to have incidental prostate cancer.

The pathological features of these 91 prostate cancers are shown in Table 2. The distribution of the prostate cancer volumes

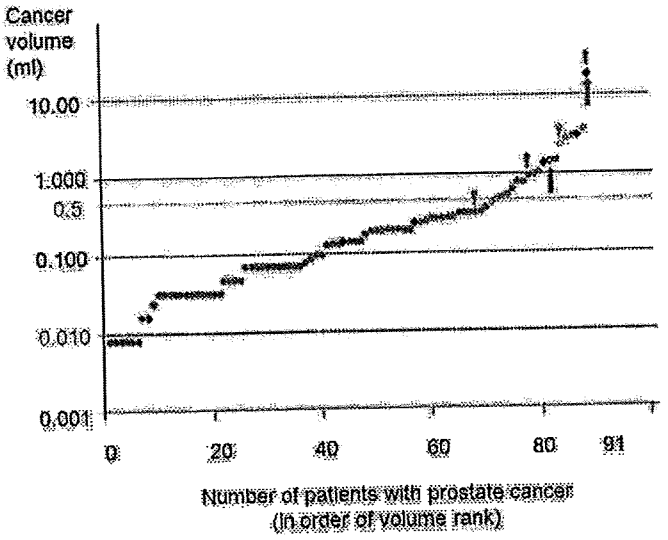
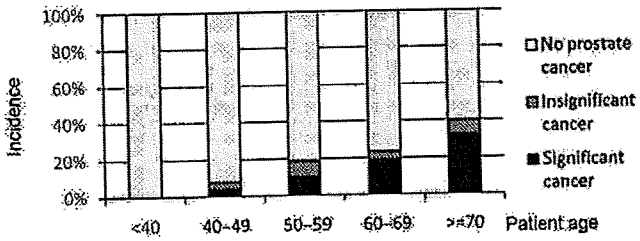


Fig. 1. Volume distribution of prostate cancers. All 91 prostate cancers are plotted in order of volume rank. Each circle and square indicates one prostate cancer. Squares indicate pT3 or pT4 cancers. Clear circles and squares indicate cancers diagnosed by biopsy before cystoprostatectomy. Arrowheads indicate cancers with a Gleason score of 8 or more. Arrows indicate cancers with lymph node metastasis.



	<40	40–49	50–59	60–69	≥70
Number of patients	6	25	80	128	110
All prostate cancer	0	2	15	30	44
	0%	8.0%	18.8%	23.4%	40%
Significant cancer	0	1	8	24	35
	0%	4.0%	10.0%	18.8%	31.8%

Fig. 2. Incidence of prostate cancer in each age group. The definition of significant cancer is given in the Results section.

is shown in Figure 1. Larger cancers were more likely to have a higher Gleason score and to have lymph node metastasis (Fig. 1). As for the relationship between cancer volume and pT stage, even small cancers could be at high pT stage: a cancer 0.23 mL in volume showed extracapsular extension (pT3a). A cancer 0.13 mL in volume arose in the prostatic base and invaded to the bladder neck (pT4).

The incidence of prostate cancer increased with patient age (Fig. 2). The median age of the patients with prostate cancer was 69 years (range, 43–81 years), and was significantly higher than that of patients without prostate cancer (median, 63.5 years; range, 27–89 years) ($P < 0.0001$, Mann–Whitney *U*-test).

The incidence of prostate cancer increased with the PSA level (Fig. 3). The median PSA level in the patients with prostate cancer was 1.90 ng/mL (range, 0.26–20.60) and was significantly higher than in those without prostate cancer (median 1.20 ng/mL, range 0.03–13.27 ng/mL) ($P < 0.0001$, Mann–Whitney *U*-test).

Prostate cancer was considered clinically significant if any of the following criteria were present: total tumor volume ≥ 0.5 mL,

Table 3. Relationship between prostate cancer and patient age

Prostate cancer	No. patients	Median age (years)	P-value			
No prostate cancer	258	63.5 (range 27–89)	$P < 0.0001$*			
Prostate cancer	91	69 (range 43–81)		$P = 0.2340$*	$P < 0.0001$†	$P < 0.0001$*
Insignificant	23	67 (range 43–78)				
Significant	68	70 (range 46–81)		$P = 0.1216$*		

*Mann–Whitney *U*-test, †Kruskal–Wallis test.

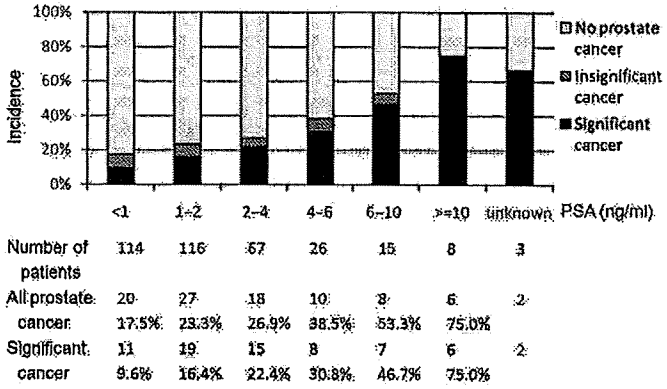


Fig. 3. Incidence of prostate cancer in each prostate-specific antigen (PSA) range. Definition of significant cancer is given in the Results section.

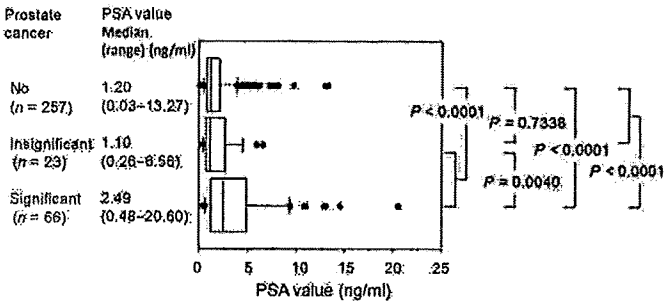


Fig. 4. Relationship between prostate cancer and prostate-specific antigen (PSA) value. The boxes show a range of 25–75 percentiles, and the whiskers a range of 10–90 percentiles. The vertical bars in each box indicate median values. Correlation was calculated using the Mann–Whitney *U*-test.

Gleason grade ≥ 4, ECE, SVI, or lymph node metastasis. Sixty-eight patients (74.7%) had significant prostate cancer. The reasons for designating these cancers as 'significant' were: tumor volume ≥ 0.5 mL in 18 patients (19.8%), Gleason grade ≥ 4 in 67 patients (73.6%), ECE in five patients (5.5%), SVI in one patient (1.1%), and lymph node metastasis in two patients (2.2%).

The incidence of significant prostate cancer increased with patient age (Fig. 2). The median age of the patients with significant prostate cancer was 70 years (range, 46–81 years), and was significantly higher than that of patients without significant prostate cancer (median, 64 years; range, 27–89 years) ($P < 0.0001$, Mann–Whitney *U*-test) (Table 3).

The incidence of significant prostate cancer increased with the PSA level (Fig. 3). Figure 4 shows the distribution of PSA levels in the patients with significant, insignificant, or no prostate cancer. The median PSA level in the patients with significant prostate cancer was 2.49 ng/mL (range, 0.48–20.60 years) and was significantly higher than in those with insignificant cancer (median, 1.10 ng/mL; range, 0.26–6.56 ng/mL) ($P = 0.0040$) and in those without cancer (median, 1.20 ng/mL; range 0.03–13.27 ng/mL) ($P < 0.0001$). The PSA level in the patients with insignificant prostate cancer was not significantly different from that in patients without cancer ($P = 0.7338$) (Fig. 4).

The median follow-up period was 36 months (range, 1–128 months) for the 91 patients with prostate cancer. None of the patients died of prostate cancer during follow-up. One patient, who had a preoperative PSA level of 5.0 ng/mL and a Gleason grade 4 + 3 prostate cancer 2.96 mL in volume, developed biochemical recurrence (PSA recurrence; PSA > 0.2 ng/mL) at 36 months after surgery without any detectable mass lesion. His serum PSA level was 0.583 ng/mL, and no additional therapy has yet been started at 42 months of follow-up.

Discussion

The incidence of prostate cancer varies among races; East Asians have a lower cumulative incidence than white and black people in the USA and Europe.[22] However, the incidence of latent prostate cancer does not differ between Japanese and white and black people in the USA.[9] Latent cancer is not different from clinical cancer in terms of histology.[10,11] The proportion of Japanese men who undergo PSA screening remains at only 5%,[23] whereas 75% of men aged 50 years or older have had a PSA test in the USA.[24] In Japan, however, the morbidity and mortality of prostate cancer have been increasing,[22] and its incidence will increase further as more men undergo PSA mass screening. Our study shows that the incidence of prostate cancer in RCP specimens from Japanese men is consistent with previous reports from the USA and Western Europe,[14–18] and similar to the reported incidences (22.5–34.6%) in Japanese autopsy cases.[9]

With regard to the age distribution of prostate cancer, Ashley showed that there is a linear relationship between the frequency of prostate cancer and age when plotted double logarithmically, and that its slope is 3.[25] In other words, the age-specific incidence of prostate cancer increases approximately with the third power of age.[25] Our present data are consistent with Ashley's classic paper (Fig. 5). Although Ashley considered that the development of prostate cancer requires three (epi)genetic events, based on the Armitage and Doll multistage carcinogenesis model,[26] our data should not be interpreted so simply; the number of (epi)genetic events required for prostate carcinogenesis cannot be determined solely on the basis of incidence data. However, we were able to confirm that prostate carcinogenesis is highly age dependent. Moreover, when we plotted the incidence of significant cancer on the same graph, the plot was linear with a slope of 4 (Fig. 5), indicating that progression to significant prostate cancer requires additional (epi)genetic events.

The PCPT revealed that a considerable proportion of men with low PSA values have prostate cancer.[6] Consequently, it has been suggested that the 'normal' PSA threshold should be discarded.[8] Moreover, there has been an argument that the significance of PSA as a tumor marker has been lost, and that PSA is better regarded as a marker of benign prostatic hyperplasia.[27] Thus, the significance of PSA in screening and prognostication

doi: 10.1111/j.1349-7006.2009.01267.x

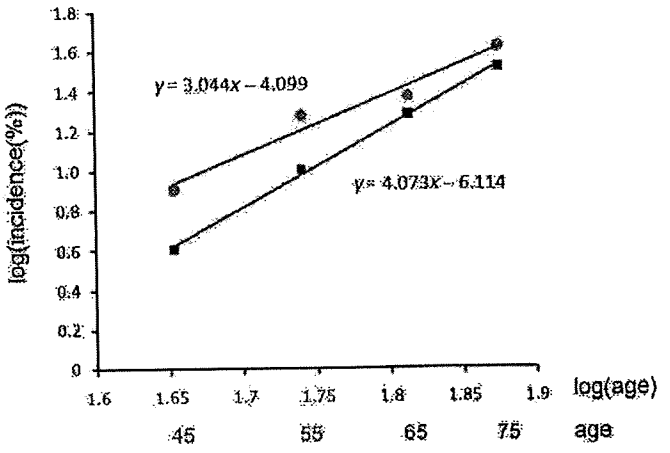


Fig. 5. Incidence of all (circles) and significant (squares) prostate cancers in every decade of patient age presented as a double logarithmic graph. Approximate lines are shown.

has recently been questioned. However, our present study indicates that increasing PSA levels are certainly associated with a higher incidence of all and significant prostate cancers. For example, the incidence of prostate cancer in patients with a PSA level ≥3 ng/mL (35/74, 47.3%) was significantly higher than in patients with a PSA level <3 ng/mL PSA (54/272, 19.9%) ($P < 0.0001$, χ^2-test). Thus, our data suggest that PSA would still be a useful screening tool for prostate cancer, at least in Japan where PSA screening is less prevalent than in Western countries.

In our study 73.5% of 'significant' cancers were small (less than 0.5 mL). Haas *et al.* reported that only 11% of cancers with a volume of less than 0.5 mL, which was estimated by computerized planimetry using an image analysis program, were detectable by 12-core biopsy in autopsy cases.[28] Therefore, most of the small 'significant' cancers in the present study would not have been detectable with current biopsy techniques. However, it is unlikely that all of these small 'significant' cancers need to be detected at such an early stage: McNeal reported that the probability of metastasis is correlated with cancer volume and grade.[11] In our present cohort of prostate cancers, we observed that most cancers with a Gleason score of ≥8 or with nodal metastasis had a volume of 0.5 mL or more (Fig. 1). Overlooking small 'significant' cancers would not compromise prognosis if patients were undergoing periodic PSA screening.

Eighteen of our patients had prostate cancers of 0.5 mL or more, which corresponds to a tumor approximately 1.0 cm in diameter. If PSA = 3.0 ng/mL were used as a threshold for recommending prostate biopsy, then 15 men with prostate cancers of 0.5 mL or more would have been included (sensitivity, 15/18 = 83.3%; specificity, 269/328 = 82.0%; positive predictive value, 15/74 = 20.3%). If PSA = 4.0 ng/mL were applied as a threshold, then an additional four men with prostate cancers of 0.5 mL or more would have been missed, resulting in lower sensitivity (11/18 = 61.1%). In addition, prostate biopsy does not always guarantee detection of all cancers with a volume of 0.5 mL or more. The threshold PSA level for prompting prostate biopsy needs to be determined carefully bearing these issues in mind.

Schröder *et al.* have reported that men with a PSA level of 3.0 ng/mL or less do not require immediate biopsy:[29] according to their analysis of data from the European Randomized Screening for Prostate Cancer Trial, which adopted 3.0 ng/mL PSA as a threshold to prompt biopsy, only six deaths from prostate cancer might have been prevented if all 15 773 eligible men with a PSA level of 3.0 ng/mL or less had undergone biopsy.

In summary, prostate cancer is a common finding in RCP specimens, with a significant proportion having the characteristics of clinically significant prostate cancer. Increasing patient age and PSA value are associated with a high incidence of all and significant prostate cancers, and PSA still appears to be a useful tool for prostate cancer screening

Disclosure Statement

The authors have no conflict of interest.

Abbreviations

ECE	extracapsular extension
PCPT	the Prostate Cancer Prevention Trial
PSA	prostate-specific antigen
RCP	radical cystoprostatectomy
SVI	seminal vesicle invasion

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doi: 10.1111/j.1349-7006.2009.01267.x

International Journal of Urology (2009) 16, 64–69 doi: 10.1111/j.1442-2042.2008.02194.x

Original Article: Clinical Investigation

Bladder cancer develops 6 years earlier in current smokers: Analysis of bladder cancer registry data collected by the cancer registration committee of the Japanese Urological Association

Shiro Hinotsu,[1] Hideyuki Akaza,[1] Tsuneharu Miki,[2] Hiroyuki Fujimoto,[3] Nobuo Shinohara,[4] Eiji Kikuchi,[5] Yoichi Mizutani,[6] Hirofumi Koga,[7] Eijiro Okajima[8] and Akihiko Okuyama[9], The Japanese Urological Association

[1]Urology and Andrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, [2]Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, [3]Department of Urology, National Cancer Center, Tokyo, [4]Department of Renal and Genitourinary Surgery, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, [5]Department of Urology, Keio University, Tokyo, [6]Department of Urology, Kyoto Prefectural University of Medicine, Kyoto, [7]Department of Urology, Harasanshin Hospital, Fukuoka, [8]Department of Urology, Nara Medical University, Kashihara, Nara, [9]Department of Urology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Objectives: It is generally recognized that cigarette smoking is the most important risk factor for bladder cancer. The present study was undertaken to examine the relationships between smoking history of bladder cancer patients and the age of onset of bladder cancer and tumor characteristics.

Methods: The present study examined the data for 5959 cases (4728 males and 1231 females) collected in the bladder cancer database of the Japanese Urological Association from 1999 to 2001. Patients were divided by smoking history into three categories as current non-smokers, current smokers and unknown smoking history. Relationship between smoking history and the age at diagnosis of bladder cancer, gender, T stage, grade, tumor size, tumor number and initial symptoms was analyzed

Results: In both males and females the onset of bladder cancer is about 6 years (6.1 years in males and 5.9 years in females) earlier for current smokers than for current non-smokers. At the time of diagnosis, tumor stage was significantly higher in the current smokers group. The current smokers group tended to have larger tumor size.

Conclusions: The finding of 6-year-earlier onset of bladder cancer among current smokers is of great importance to both health care and medical economics. It is essential to make people better informed concerning the need to quit smoking.

Key words: age at diagnosis, bladder cancer, smoking.

Introduction

There is a well-known relationship between smoking and bladder cancer. In the large-scale survey in the European prospective investigation into cancer and nutrition, the risk of bladder cancer was 2.70 to 5.52 times higher in the current smokers as compared with never smokers. This risk was shown to have a dose-response relationship with smoking intensity.[1] Many other studies have detected an association between smoking and the onset of bladder cancer.[2–6] However, most were case-control studies or cohort studies, and few published studies have been designed to examine the relationship between the smoking history of patients with bladder cancer and the biological characteristics of their bladder cancer. The present study was undertaken to examine the relationships between smoking history of bladder cancer patients and the age of onset of bladder cancer and tumor characteristics on the basis of data collected in the bladder cancer database of the Japanese Urological Association (JUA).

Methods

The JUA bladder cancer database program was started in 1982 on the initiative of the JUA. In this program, background variables of patients with first primary bladder cancer diagnosed in each year are registered with the database. The program covers nationwide urological facilities certified by the JUA. The present study examined the data for all 5959 cases (4728 males and 1231 females) registered during the period approved by the JUA for data access (i.e., the 3-year period from 1999 to 2001).

The patients were divided by smoking history into three categories as current non-smokers (CNS), current smokers (CS) and unknown smoking history (UK). Current non-smokers (CNS) included current and past non-smokers (CPNS) those who had never smoked, past smokers (PS), past unknown (PUK) smoking history. This program did not collect information on duration of smoking. Smoking level is divided in this database simply into two categories with a cut-off level set at 20 cigarettes per day, and no further information on amount of smoking is available. Relationships between smoking history and age at first diagnosis, background variables at the time of first examination (tumor size, tumor number, T classification, histological grade), and gender were examined.

For statistical analysis, Student's t-test was used for analysis of inter-group differences in means, and the χ^2 test was used for inter-group comparison of tumor stage, grade, size, and number.

Results

Table 1 summarizes the characteristics of the 5959 cases analyzed. In terms of smoking history, there were 2384 (40.0%) CNS including 1741 current and CPNS, 380 PS, and 263 PUK, 1612 (27.1%) CS, and 1963 individuals (32.9%) with UK. When smoking history was analyzed separately for the male group and the female group, the male

Corresponding author: Hideyuki Akaza MD, Urology and Andrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tennodai 1-1-1, Tsukuba City, Ibaraki 305-8575, Japan. Email: akazah@md.tsukuba.ac.jp

Received 12 August 2008; accepted 23 September 2008.
Online publication 27 November 2008

Table 1 Patients characteristics and smoking history

Factor	Gender	Current non-smoker									Current-smoker			Current non-smoker vs. current smoker
		Current and past non-smoker			Past-smoker			Past unknown-smoker						
		n	Mean age	SD	*n*	Mean age	SD	*n*	Mean age	SD	*n*	Mean age	SD	*P*-value
All	Both	1741	71.1	11.6	380	70.3	10.9	263	73.7	10.2	1612	65.0	11.8	<0.0001
Gender	Male	989	70.8	11.3	357	70.5	10.6	213	73.4	10.2	1512	65.0	11.8	<0.0001
	Female	752	71.4	12.0	23	67.5	14.1	50	74.8	10.5	100	65.6	11.5	<0.0001
Symptom	Gender	Category	*n*	%	Category	*n*	%	Category	*n*	%	Category	*n*	%	
Hematuria	Both	+	1347	77.4	+	291	76.6	+	198	75.3	+	1308	81.2	
		−	382	21.9	−	86	22.6	−	60	22.8	−	289	17.9	
		Unknown	12	0.7	Unknown	3	0.8	Unknown	5	1.9	Unknown	15	0.9	
Pain on urination	Both	+	285	16.4	+	42	11.1	+	36	13.7	+	248	15.4	
		−	1395	80.1	−	329	86.5	−	214	81.4	−	1295	80.3	
		Unknown	61	3.5	Unknown	9	2.4	Unknown	13	4.9	Unknown	69	4.3	
Pollakisuria	Both	+	420	24.1	+	91	24.0	+	61	23.2	+	367	22.8	
		−	1266	72.7	−	283	74.4	−	187	71.1	−	1179	73.1	
		Unknown	55	3.2	Unknown	6	1.6	Unknown	15	5.7	Unknown	66	4.1	
Factor	Gender	Category	*n*	%	Category	*n*	%	Category	*n*	%	Category	*n*	%	*P*-value
T stage	Both	Tis	100	6.0	Tis	30	8.3	Tis	21	8.4	Tis	67	4.3	
		Ta,T1	1203	71.7	Ta,T1	243	67.5	Ta,T1	177	70.8	Ta,T1	1091	69.9	
		T2,T3	328	19.5	T2,T3	81	22.5	T2,T3	43	17.2	T2,T3	342	21.9	
		T4	47	2.8	T4	6	1.7	T4	9	3.6	T4	61	3.9	0.0017
	Male	Tis	67	7.1	Tis	28	8.3	Tis	15	7.4	Tis	63	4.3	
		Ta,T1	700	73.8	Ta,T1	232	68.6	Ta,T1	150	74.2	Ta,T1	1029	70.1	
		T2,T3	157	16.6	T2,T3	72	21.3	T2,T3	30	14.9	T2,T3	316	21.6	
		T4	24	2.5	T4	6	1.8	T4	7	3.5	T4	58	4.0	<0.0001
	Female	Tis	33	4.5	Tis	2	9.1	Tis	6	12.5	Tis	4	4.2	
		Ta,T1	503	68.9	Ta,T1	11	50.0	Ta,T1	27	56.2	Ta,T1	62	65.2	
		T2,T3	171	23.4	T2,T3	9	40.9	T2,T3	13	27.1	T2,T3	26	27.4	
		T4	23	3.2	T4	0	0.0	T4	2	4.2	T4	3	3.2	0.902
Grade	Both	G1	262	15.5	G1	53	14.4	G1	38	14.9	G1	234	14.9	
		G2	751	44.6	G2	157	42.7	G2	106	41.6	G2	762	48.6	
		G3	672	39.9	G3	158	42.9	G3	111	43.5	G3	572	36.5	0.011
	Male	G1	144	14.9	G1	50	14.4	G1	32	15.4	G1	219	14.9	
		G2	441	45.7	G2	152	43.8	G2	88	42.3	G2	718	48.7	
		G3	379	39.3	G3	145	41.8	G3	88	42.3	G3	536	36.4	0.067
	Female	G1	118	16.4	G1	3	14.3	G1	6	12.8	G1	15	15.8	
		G2	310	43.0	G2	5	23.8	G2	18	38.3	G2	44	46.3	
		G3	293	40.6	G3	13	61.9	G3	23	48.9	G3	36	37.9	0.727
Size	Both	<1 cm	424	27.7	<1 cm	89	26.5	<1 cm	48	20.9	<1 cm	326	23.0	
		1–3 cm	728	47.6	1–3 cm	173	51.5	1–3 cm	120	52.2	1–3 cm	742	52.5	
		3 cm or over	376	24.6	3 cm or over	74	22.0	3 cm or over	62	27.0	3 cm or over	347	24.5	0.031
	Male	<1 cm	253	29.3	<1 cm	87	27.5	<1 cm	39	20.7	<1 cm	306	23.1	
		1–3 cm	421	48.8	1–3 cm	161	50.9	1–3 cm	99	52.7	1–3 cm	705	53.1	
		3 cm or over	189	21.9	3 cm or over	68	21.5	3 cm or over	50	26.6	3 cm or over	316	23.8	0.021
	Female	<1 cm	171	25.7	<1 cm	2	10.0	<1 cm	9	21.4	<1 cm	20	22.7	
		1–3 cm	307	46.2	1–3 cm	12	60.0	1–3 cm	21	50.0	1–3 cm	37	42.1	
		3 cm or over	187	28.1	3 cm or over	6	30.0	3 cm or over	12	28.6	3 cm or over	31	35.2	0.389
Number	Both	Solitary	798	51.3	Solitary	173	51.3	Solitary	120	51.3	Solitary	763	52.5	
		Multiple	758	48.7	Multiple	164	48.7	Multiple	114	48.7	Multiple	690	47.5	0.474
	Male	Solitary	444	51.3	Solitary	164	51.7	Solitary	103	54.2	Solitary	716	52.5	
		Multiple	422	48.7	Multiple	153	48.3	Multiple	87	45.8	Multiple	648	47.5	0.711
	Female	Solitary	354	51.3	Solitary	9	45.0	Solitary	17	38.6	Solitary	47	52.8	
		Multiple	336	48.7	Multiple	11	55.0	Multiple	27	61.4	Multiple	42	47.2	0.667

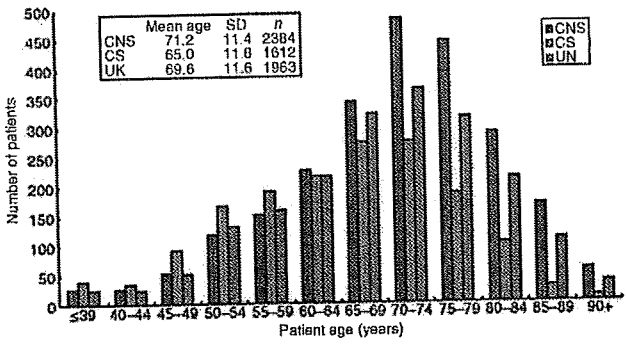

Fig. 1 Patients age distribution at diagnosis and smoking history (male and female). CNS, current non-smoker; CS, current smoker, UK, unknown.

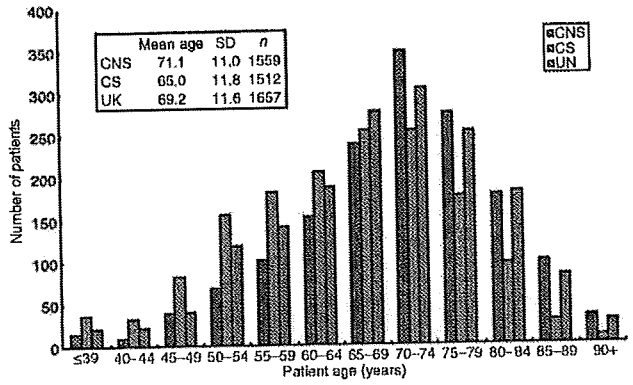

Fig. 2 Patients age distribution at diagnosis and smoking history in male. CNS, current non-smoker; CS, current smoker; UK, unknown.

group was composed of 1559 (32.9%) CNS including 989 CPNS, 357 PS, and 213 PUK, 1512 (32.0%) CS and 1657 individuals (35.1%) with UK. The female group was composed of 825 (67.5%) CNS including 752 CPNS, 23 PS, and 50 PUK, 100 (8.1%) CS and 306 individuals (24.9%) with UK.

Initial symptoms

As shown in Table 1, the most frequent initial symptom was macroscopic hematuria. No correlation was noted between smoking history and symptoms.

Comparison between smoking history and age at onset of bladder cancer

Table 1 shows mean age at diagnosis, and Figure 1 shows the distribution of age at diagnosis of bladder cancer. Figures 2 and 3 illustrate the distribution of the same parameter by gender. When males and females were analyzed together, the mean age (±SD) at diagnosis of bladder cancer was 71.2 (±11.4), 65.0 (±11.8) and 69.6 (±11.6) years for CNS, CS and UN, respectively. The ages at diagnosis in the PS group and the PUK group differed little from that in the CPNS group. Thus, we compared the CNS group and the CS group according to the current smoking status. The mean age at diagnosis was 6.2 years lower in the CS group than in the CNS group. In each group, age exhibited an approximately normal distribution, then we carried out statistical tests for the age at diagnosis, and mean age at diagnosis in the CS group was

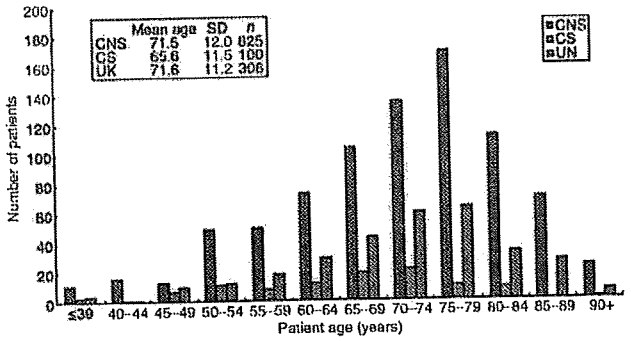

Fig. 3 Patients age distribution at diagnosis and smoking history in female. CNS, current non-smoker; CS, current smoker; UK, unknown.

significantly lower than in the CNS group. Similar findings were obtained when males and females were analyzed separately. The mean age at diagnosis was 71.1 for the male CNS and 71.4 for the female CNS group, and it was 6.1 years and 5.9 years lower for the male CS and female CS group, respectively.

Relationship between smoking history and bladder cancer stage

At the time of diagnosis, clinical T stage was significantly higher in the CS group when the entire population or only males were analyzed (Table 1). When analyzed in relation to the T stage, the age at tumor onset was 5–6 years lower in the CS group both among the males and the females (Fig. 4, abcd). This difference in mean age at tumor onset was statistically significant in both the male and the female groups (Table 2).

Relationship between smoking history and histological grade of bladder cancer

When the entire population was analyzed, Grade 2 tumor was significantly more frequent in the CS group. However, when males and females were analyzed separately, no significant differences were noted in this parameter (Table 1). On analysis of the age distribution in each histological grade, the CS group exhibited a deviation toward the 4–5 years lower for both males and females (Fig. 5, abcdef), and significant differences were noted for all grades in males and for grade 2 in females (Table 2).

Relationships of smoking history to tumor number and size

The CS group tended to have larger tumor size on analysis of the entire population and the male group. No notable differences were observed among groups or genders in tumor number (Table 1).

Discussion

A new finding of this analysis is that in both males and females the onset of bladder cancer is about 6 years (6.1 years in males and 5.9 years in females) earlier for current smokers than for current non-smokers. In initial symptoms at the urological clinic, there were no differences between smokers and non-smokers. This suggests that the findings of this study are probably not due to differences in age at

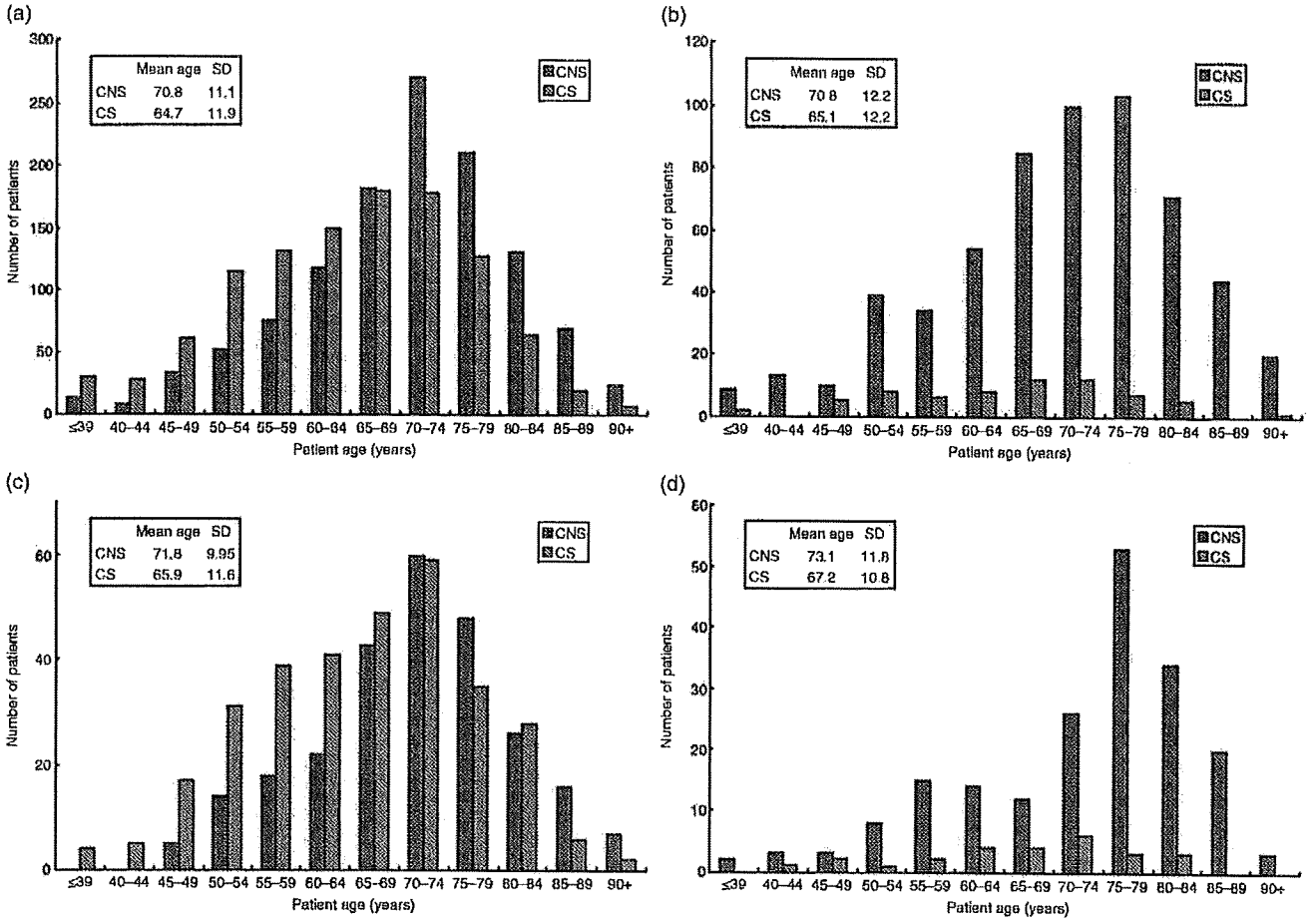

Fig. 4 Relations between patients age distribution at diagnosis and T stage. (a) Tis, Ta, T1 and Male (b) Tis, Ta, T1 and Female (c) T2, T3 and Male (4) T2, T3 and Female. CNS, current non-smoker; CS, current smoker.

Table 2 Relationship between mean age at diagnosis and T stage, grade by smoking history

Factor	Gender	Category	Current non-smoker									Current-smoker			Current-non smoker vs. current smoker
			Current and past non-smoker			Past-smoker			Past unknown-smoker						
			n	Mean age	SD	*n*	Mean age	SD	*n*	Mean age	SD	*n*	Mean age	SD	*P* value
T stage	Male	Tis,Ta,T1	767	70.4	11.3	260	70.3	10.8	165	73.1	10.6	1092	64.7	11.9	<0.0001
		T2,T3	157	71.9	10.3	72	70.4	9.5	30	74.2	8.5	316	65.9	11.6	<0.0001
	Female	Tis,Ta,T1	536	70.7	12.2	13	62.4	14.4	33	75.2	10.6	66	65.1	12.2	0.0004
		T2,T3	171	73.1	11.9	9	73.3	11.4	13	73.0	11.2	26	67.2	10.8	0.0165
Grade	Male	Grade1	144	67.3	11.8	50	70.5	11.3	32	71.2	10.0	219	63.3	12.6	<0.0001
		Grade2	441	70.8	11.2	152	70.4	10.7	88	72.9	10.1	718	64.9	11.7	<0.0001
		Grade3	379	72.5	10.4	145	70.7	10.2	88	74.3	10.3	536	65.8	11.2	<0.0001
	Female	Grade1	118	68.3	13.4	3	69.6	17.0	6	77.8	6.5	15	63.7	9.6	0.1552
		Grade2	310	71.6	11.5	5	59.8	19.2	18	74.2	13.7	44	63.4	12.7	<0.0001
		Grade3	293	72.3	119	13	70.7	12.0	23	74.6	9.1	36	69.4	10.1	0.1493

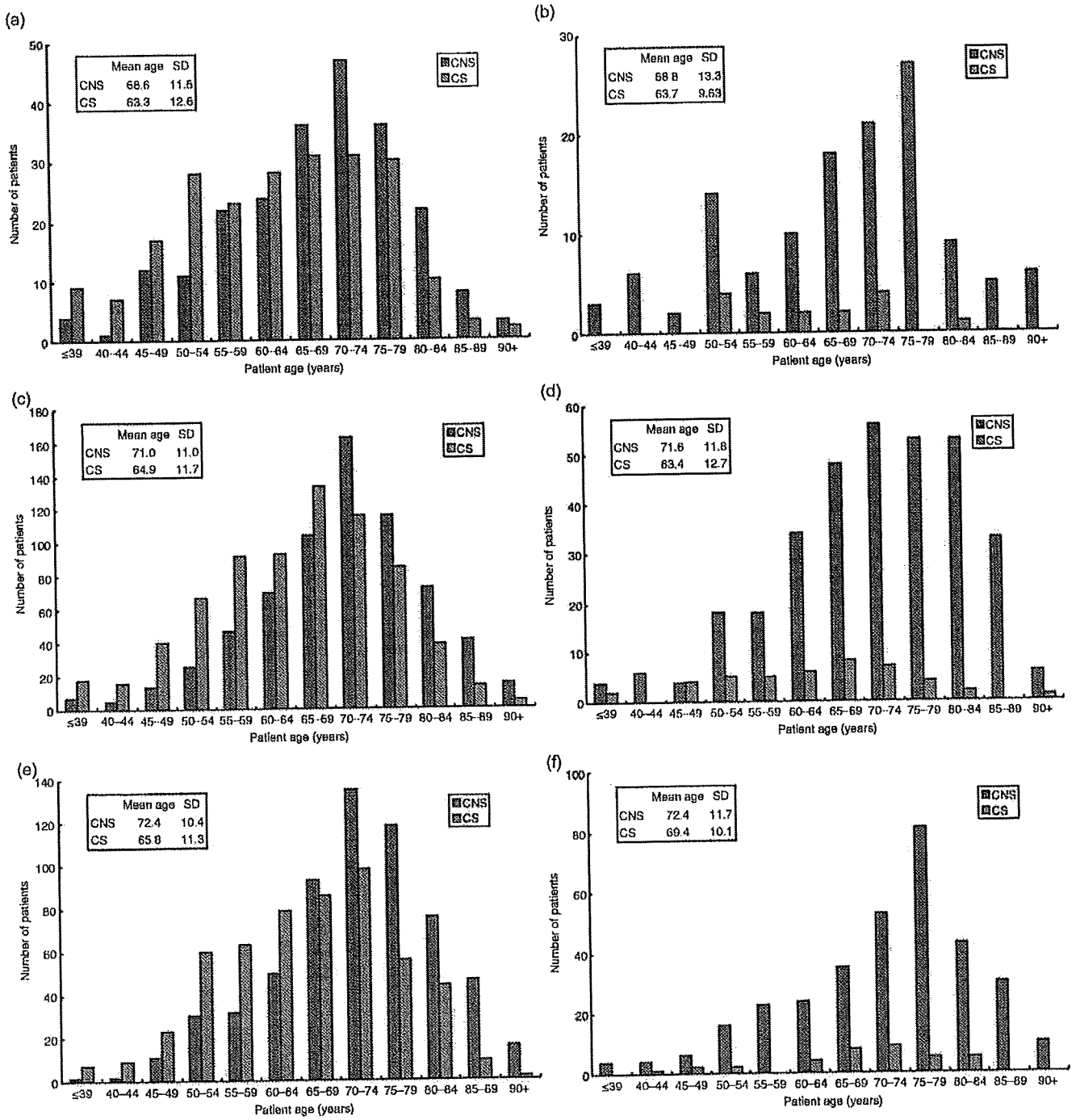

Fig. 5 Relations between patients age distribution at diagnosis and historical grade. (a) Grade 1, Male (b) Grade 1, Female (c) Grade 2, Male (d) Grade 2, Female (e) Grade 3, Male (f) Grade 3, Female. CNS, current non-smoker; CS, current smoker.

diagnosis due to lead time bias (earlier presentation of smokers to urological clinics). As noted above, the JUA bladder cancer register program was started in 1982 on the initiative of JUA. Every year, more than about 2000 newly diagnosed cases of bladder cancer are registered from about 300 facilities with urologists. Due to procedures for amendment of the public rules related to personal information management, permission to access the data collected under this program was delayed. The present study covered only the data from 1999 to 2001, since access to data was permitted only for this period. The data pertaining to smoking habits available in this database are confined to the presence/absence of smoking at present and in the past and whether the number of cigarettes consumed by smokers per day was less than 20 or at least 20. Unfortunately, the database does not provide more detailed information on amounts or duration of smoking. Furthermore, there was often lack of information on smoking history (UK cases; 32.9% of all cases). It was therefore not possible to calculate Brickman indexes in the present study, and analysis of data was carried out by dividing the patients into CPNS, PS, PUK and CS groups. When males were

analyzed, PS did not exhibit a deviation in age at diagnosis to the lower range compared with CPNS, suggesting that the risk of onset of bladder cancer can be reduced by discontinuation of smoking at some point in time. In females, on the other hand, a 3.9-year deviation was noted. This finding is difficult to explain. Careful interpretation of this finding seems essential, in view of the many published studies demonstrating differences in bladder cancer biology between males and females. Chen *et al.* reported that discontinuation of smoking reduced the incidence of tumor recurrence within the urinary bladder,[7] suggesting that recent smoking may significantly elevate the risk of onset of bladder cancer. This may explain why males exhibited no effect of past smoking on age at diagnosis of bladder cancer.

As shown in Table 1, the male/female ratio of patients with bladder cancer in this database was 3.8:1.0. This ratio is common to almost all countries in the world. According to the nationwide smoker survey reported by Japan Tobacco Inc. in 2007,[8] the overall percentage of smokers among adult Japanese males decreased from 83.7% to 40.2% during the 40-year period until 2007, while the same parameter among adult Japanese females exhibited no tendency toward decrease, remaining at 12.7% in 2007. Interestingly, the male/female ratio of smokers in 2007 was closer to that of bladder cancer patients (2.95:1.00) than previously. In addition, the percentage of smokers among young females (age 20–39) began to increase a quarter of a century ago, reversing the tendency observed in the percentage of smokers among middle-aged and elderly individuals (age 50–69).

When clinical T stage and histological grade were compared at the time of diagnosis of bladder cancer, significant differences between current smokers and current non-smokers were noted in T stage, grade and size. However, no difference between these groups was noted in tumor number (multiplicity). Mohseni *et al.* reported that bladder cancer in smokers was characterized by significantly greater tumor size, number, and histological grade than that in bladder cancer of non-smokers.[9] Our results endorse their findings. It is known that bladder cancer usually increases in histological grade with increase in size. It thus appears that the mechanism of carcinogenesis is activated earlier or is stronger in smokers.

It is known that non-muscle invasive bladder cancer frequently recurs after transurethral resection, that the likelihood of progression to muscle invasive cancer increases with repetition of recurrence, and that although radical cystectomy is a standard treatment for muscle invasive bladder cancer, its outcome is unsatisfactory. In this context, the finding of 6-year-earlier onset of bladder cancer among smokers is of great importance to both health care and medical economics. This problem becomes more serious if we note that the bladder cancer developing in smokers tends to have a poor prognosis (high stage, high grade, and of larger size).

Nieder *et al.* have pointed out that information on the role of smoking as a bladder carcinogen has not been extensively disseminated extensively in society.[10] It is essential to make people better informed concerning the need to quit smoking.

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International Journal of Urology (2009) 16, 279–286 doi: 10.1111/j.1442-2042.2008.02235.x

Original Article: Clinical Investigation

Clinical outcome of tumor recurrence for Ta, T1 non-muscle invasive bladder cancer from the data on registered bladder cancer patients in Japan: 1999–2001 report from the Japanese Urological Association

Eiji Kikuchi,[1,2] Hiroyuki Fujimoto,[1,3] Yoichi Mizutani,[1,4] Eijiro Okajima,[1,5] Hiroshi Koga,[1,6] Shiro Hinotsu,[1,7] Nobuo Shinohara,[1,8] Mototsugu Oya,[2] Tsuneharu Miki[1,4] and the Cancer Registration Committee of the Japanese Urological Association*

[1]Working Group of the Bladder Cancer Registration Committee of the Japanese Urological Association, [2]Department of Urology, Keio University School of Medicine, Tokyo, [3]Urology Division, National Cancer Center Hospital, Tokyo, [4]Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine, Kyoto, [5]Department of Urology, Nara Medical University, Nara, [6]Department of Urology, Faculty of Medical Sciences, Kyushu University, Fukuoka, [7]Urology and Andrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaragi, and [8]Department of Urology, Graduate School of Medicine, Hokkaido University, Sapporo, Hokkaido, Japan

Objective: To characterize the clinical outcome in a large contemporary series of Japanese patients with newly diagnosed Ta, T1 non-muscle invasive bladder cancer who underwent transurethral bladder tumor resection with or without intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) therapy.

Methods: We developed a database incorporating newly diagnosed non-muscle invasive bladder cancer data and outcomes from a Japanese bladder cancer registry between 1999 and 2001 and identified a study population of 3237 consecutive patients who had complete data based on pathological features. Median patient age was 69.9 years.

Results: The 1-year, 3-year, and 5-year overall recurrence-free survival rates were 77.0%, 61.3%, and 52.8%, respectively. In multivariate analyses, the multiplicity of bladder tumors, tumor size greater than 3 cm, pathological stage T1, tumor grade G3, and the absence of adjuvant intravesical instillation were independent risk factors for tumor recurrence. Overall, 1710 patients (52.8%) received intravesical instillation; chemotherapy in 1314 (76.8%) and BCG treatment in 396 (23.2%). In patients treated with intravesical chemotherapy in which an anthracycline chemo-agent was used in 90.5% of the cases, multivariate analyses demonstrated that male gender, multiple bladder tumors, a tumor size greater than 3 cm, and pathological stage T1 were associated with tumor recurrence.

Conclusions: The accumulation and analysis of data from the Japanese National Bladder Cancer Registry made it possible to determine the clinical characteristics, management trends, and survival rates for the period studied. Further study with a dataset created from longer follow-up data would be warranted to analyze tumor progression and disease survival.

Key words: bladder, carcinoma, non-muscle invasive, recurrence, transitional cell.

Introduction

Transurethral bladder tumor resection (TUR-BT) with or without intravesical therapy is the primary treatment modality in individuals with non-muscle invasive Ta, T1 bladder cancer. Some patients with risk factors, such as a high grade, lamina propria infiltration, multiplicity, a large tumor, and concomitant carcinoma *in situ* (CIS) still have a lifelong frequency of multiple recurrences and a probability of stage progression.[1–4] To date, several contemporary single center series of patients treated with intravesical chemo- or immunotherapy after TUR-BT for Ta, T1 non-muscle invasive bladder cancer have been published to evaluate the prognostic indicators for tumor recurrence in Japan.[5–8] These studies had relatively small patient populations and single center bias. Data compiled from multiple institutions may offer the benefit of understanding and generalizing the diagnosis, patient selection, staging, pathological evaluation, treatment, and follow-up protocol. In addition, a contemporary series of a large number of patients with Ta, T1 non-muscle invasive bladder cancer has the potential benefit of identifying bladder cancer recurrence as an outcome measure.

We developed a database incorporating comprehensive non-muscle invasive bladder cancer data and outcomes from data collected by multiple centers in Japan in retrospective fashion under the program of the Japanese National Bladder Cancer Registry. The aim of the present study was to characterize the clinical outcome in a large contemporary series of Japanese patients with newly diagnosed Ta, T1 non-muscle invasive bladder cancer who underwent TUR-BT with or without

Correspondence: Eiji Kikuchi MD, Department of Urology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. Email: eiji-k@kb3.so-net.ne.jp

**Members of the Cancer Registration Committee of the Japanese Urological Association:* Tsuneharu Miki, Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine; Tomoaki Fujioka, Department of Urology, Iwate Medical University; Tomohiko Ichikawa, Department of Urology, Graduate School of Medicine, Chiba University; Seiji Naito, Department of Urology, Faculty of Medical Sciences, Kyushu University; Kenjiro Kohri, Department of Urology, Graduate School of Medical Sciences, Nagoya City University; Hideyuki Akaza, Urology and Andrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba; Hiroyuki Fujimoto, Urology Division, National Cancer Center Hospital; Yoichi Mizutani, Department of Urology, Graduate School of Medical Sciences, Kyoto Prefectural University of Medicine; Tadao Kakizoe, National Cancer Center; Akihiko Okuyama, Department of Urology, Graduate School of Medicine, Osaka University.

Received 3 September 2008; accepted 19 November 2008.
Online publication 21 January 2009

intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) therapy for preventing tumor recurrence. In addition, we determined the association of established clinical and pathological characteristics with tumor recurrence.

Methods

Patient population

Data sets from multiple centers in Japan were collected in retrospective fashion under the program of the Japanese National Bladder Cancer Registry. The Registry was sponsored by the Japanese Urological Association. The registration included the background of newly diagnosed bladder cancer patients, their clinical and pathological characteristics, and their 3-year clinical outcome after the initial diagnosis. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Ultimately we developed a database incorporating newly diagnosed non-muscle invasive bladder cancer data and outcomes between 1999 and 2001.

A total of 4036 patients with newly diagnosed non-muscle invasive bladder cancer (Ta, T1) N0M0 who were treated with initial TUR-BT from the database were identified. Exclusion criteria included the main histological component of non-urothelial carcinoma ($n = 37$), a non-curative operation was carried out ($n = 703$), the presence of a concomitant CIS ($n = 32$), or incomplete data ($n = 27$). We identified a study population of 3237 consecutive patients for whom there were complete data sets based on pathological features. After complete tumor resection, intravesical chemotherapy or BCG treatment was carried out in 1314 (40.6%) or in 396 (12.2%) patients, respectively for the purpose of preventing bladder tumor recurrence.

Clinical outcomes

Pathological specimens were reviewed by the genitor-urinary pathologist at each institution. Pathological staging and grading were classified according to the 2nd and 3rd edition of the General Rule for Clinical and Pathological Studies on Bladder Cancer.[9,10] In the study we combined the pT1a and pT1b according to the 2nd edition and treated them as pT1. Recurrence was defined as a new tumor appearing in the bladder after initial clearance. Tumor progression was not analyzed in the present study because of the shorter follow-up period of our study. The time until tumor recurrence was calculated as the time from TUR-BT to the date of the first documented bladder tumor recurrence. Patients who had not experienced bladder tumor recurrence were censored at the last follow-up. Patients who died before bladder cancer recurrence were censored at the time of death.

Statistical analysis

Bladder tumor recurrence-free survival curves were constructed using the Kaplan–Meier method, and were compared with the log-lank test. Cox proportional hazards regression analysis was used to assess the prognostic indicators for recurrence. A *P*-value less than 0.05 was considered to indicate statistical significance. These analyses were carried out with the STATA version 7.0 statistical software package (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics of overall patient population

Of the 3237 patients (Table 1), 80.3% were men with a median age of 69.9 years (mean; 68.3, range, 18–103). Multiple tumors were found in

Table 1 Clinicopathological characteristic in all patients ($n = 3237$)

	No. patients (%)
Age (years)	
≤70	1660 (51.3)
>70	1577 (48.7)
Gender	
Male	2600 (80.3)
Female	637 (19.7)
Papillary type	
Yes	2938 (90.8)
No	212 (6.6)
Unknown	87 (2.7)
Tumor stalk	
Yes	2251 (69.5)
No	785 (24.3)
Unknown	201 (6.2)
Multiplicity	
Yes	1312 (40.5)
No	1810 (55.9)
Undetected	33 (1.0)
Unknown	82 (2.5)
Tumor size	
<1 cm	1013 (31.3)
1–3 cm	1681 (51.3)
>3 cm	374 (11.6)
Uncountable	45 (1.4)
Unknown	124 (3.8)
Pathological T category	
pTa	1651 (51.0)
pT1	1586 (49.0)
Grade	
G1	782 (24.2)
G2	1850 (57.2)
G3	605 (18.7)
Intravesical treatment	
Chemotherapy	1314 (40.6)
BCG	396 (12.2)
No treatment	1527 (47.2)

BCG, Bacillus Calmette-Guerin.

1312 cases (40.5%) and a tumor size greater than 3 cm was observed in 374 (11.6%). Disease was grade 1 in 24.2%, 2 in 57.2%, and 3 in 18.7%. Pathological tumor stage was Ta in 51% and T1 in 49%. There were 608 TaG1, 919 TaG2, 124 TaG3, 174 T1G1, 931 T1G2, and 481 T1G3 cases, respectively. Tumor grade was significantly associated with pathological stage ($P < 0.001$). A total of 1710 patients (52.8%) received intravesical instillation, consisting of chemotherapy in 1314 and BCG treatment in 396.

Tumor recurrence in overall patient population

The 1-year, 3-year, and 5-year overall recurrence-free survival rates were calculated to be 77.0%, 61.3%, and 52.8%, respectively. Kaplan–Meier analysis (Table 2) and univariate Cox proportional hazards regression analysis (Table 3) revealed the presence or absence of tumor stalk, tumor multiplicity, tumor size, pathological stage, tumor grade, and with or without adjuvant intravesical therapy to be significant predictors of tumor recurrence. According to the intravesical instilla-