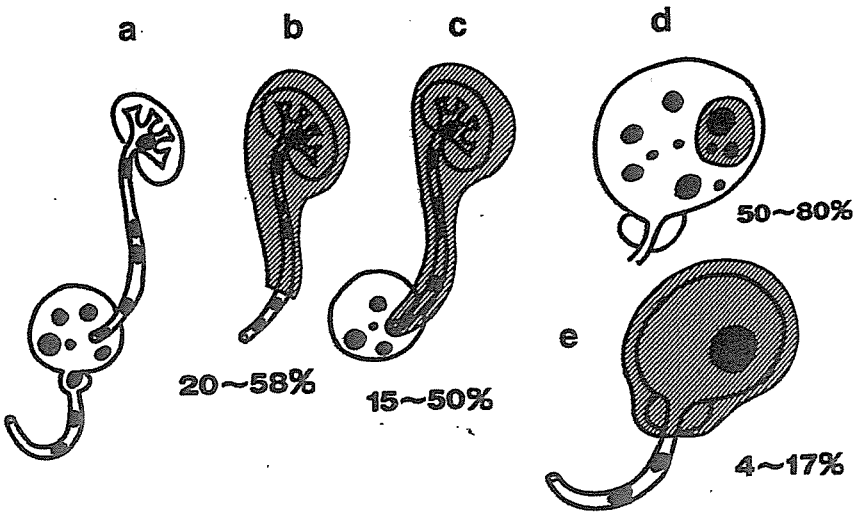

Fig. 1. Clinical findings indicating multifocal tumor development in the urinary tract. Black lesions are original tumors and red lesions are recurrent tumors.

Fig. 2. A case of renal pelvic, ureteral and vesical carcinomas who underwent right nephroureterocystectomy.

of the bladder carcinoma.[8,9] However, the risk is reported to increase to the level of 6–20% (15–22-fold) if the patients suffer from vesico-ureteral reflux.[10]

With upper urinary tract carcinomas, simultaneous bilateral lesions are rare, the estimated incidence being 1–5%.[11] Approximately 2–3% of patients with unilateral upper urinary tract carcinoma experience subsequent contralateral upper urinary tract carcinoma.[12] These clinical data should be taken into serious consideration when we decide on nephroureterectomy or cystectomy and plans for follow up after surgery, and the upper and lower urinary tract and the contralateral upper urinary tract should be assumed to constitute a single clinical unit from the renal pelvis to the urethra.

Field cancerization versus clonal expansion

To explain multifocal carcinoma development in the urinary tract, two theories have been proposed.[13,14] The first is field cancerization, proposed in 1953 by Slaughter *et al.*, which was based on observations of the multicentric development of cancers in the oral cavity, with the high impact of carcinogens and promoting agents being associated with some lifestyle factors.[15] A similar understanding is possible for the urinary tract as the entire urothelium is exposed to carcinogens contaminating the urine. The second hypothesis is that multiple carcinomas in the urinary tract are the result of intraluminal spread from a single lesion, originating from a single transformed cell, namely seeding or implantation of cancer cells at different sites. This phenomenon is also called clonal expansion of multifocal carcinomas. Debates on multiple cancer development have been similar for cancers of the oral cavity,[16] respiratory tract,[17] head and neck,[18] breast,[19] ovary[20] and cervix.[21] Recently, strong molecular evidence has been presented in support of clonal expansion in the epithelium of oral cavity and respiratory tract cases.[16,22]

Many urologists and pathologists have supported the field cancerization hypothesis in the urinary tract, but recent molecular studies have also pointed to a clonal origin for most multifocal urothelial carcinomas. Various molecular analyses have been applied. Sidransky *et al.* investigated X-chromosome inactivation in multiple bladder carcinomas of four female patients and proved that the same allele of the X-chromosome was inactivated in all lesions within the single bladder.[23] Subsequently, Lunec *et al.*[24] and Habuchi *et al.*[25] examined patients having heterotopic synchronous or recurrent urothelial carcinomas in the bladder or upper urinary tract. These carcinomas had identical mutation sites and patterns of p53 gene alteration, indicating the metachronous carcinomas to be derived from the original carcinoma cells due to clonal expansion. Habuchi also reviewed the origin of

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multifocal carcinomas of the bladder and upper urinary tract.[26] Other genetic features that can be used to assess clonal origin are loss of heterozygosity (LOH) and microsatellite alteration patterns, both commonly used as markers of neoplasia.

Stoehr *et al.* analyzed primary carcinomas in 14 cystectomy specimens for p53 protein overexpression by immunohistochemistry and p53 gene mutation by genomic sequencing.[27] They reported detection of p53-mutant cells in histologically normal adjacent or remote mucosa and in preneoplastic urothelial areas in four patients with invasive bladder carcinoma, concluding extensive intraurothelial tumor cell spread.

Evidence of a monoclonal origin and intraepithelial spread has also been provided by Simon *et al.* from comparative genomic hybridization in 32 bladder tumors originating from six cystectomy specimens.[28] Identical *TP53* mutations and protein overexpression were found in tumors from the same individual, as well as in mucosal samples from the continuous areas. The sequence of genomic changes apparently acquired during progression of bladder carcinomas was highly complex and varied within each patient and from tumor to tumor. Early changes included alterations in −17p, +20p, −9p, −9q, +2q34-qter, +12q14-q21, +1q22-q25, −8p22-pter, −5q31-qter and +17q. Subsequent tumor progression was characterized by accumulation of changes in +11q14, −21q, −5q13-q14, +8q22, +10p, −10q22qter and −11p. Cytogenetic variety in multifocal tumors has also been described in support of intraluminal tumor seeding.[29]

It is conceivable that widespread p53-mutated cells in the normal urothelium are generated in the bladder due to carcinogen exposure, and that from these, new tumors later develop with surrounding normal-appearing mucosa having p53 mutations. However, there is no mechanistic explanation for the intraepithelial spread of carcinoma cells to remote normal-appearing mucosa, and it is unrealistic to consider a mechanism due to cell motility.

Although the clonal theory now dominates in explanations of multifocality of urothelial carcinomas, there are also conflicting observations. Cheng *et al.* collected cancer cells by microdissection from 18 cystectomy specimens from female patients and analyzed the X-chromosome-linked human androgen receptor gene.[30] Only 11 of the 18 specimens were informative, with nine exhibiting non-random inactivation of the target locus and seven showing different patterns, indicating field change in these cases. Paiss *et al.* examined X-chromosome inactivation in 45 archival or fresh frozen bladder tumors obtained from 27 female patients using a polymerase chain reaction-based procedure.[31] Polyclonal patterns were observed in 16 of the 45 tumors. Stoehr *et al.* examined multiple samples from four cystectomy specimens for LOH at chromosomes 8p, 9p, 9q and 17p and they observed oligoclonality in two patients.[27] Thus, both hypotheses continue to be discussed, although clonal expansion by intraluminal spread of primary carcinoma appears the dominant explanation for multifocality.

Relationship between papillary carcinoma and nodular carcinoma

Urothelial carcinogenesis has been investigated in various species of animal. A particular focus has been on the histogenesis of lesions in rats treated with the carcinogen *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine (BHBN).[32] Normal urothelium of rats is composed of two to three layers of urothelial cells and when BHBN is given in the drinking water, the mucosal layer becomes hyperplastic at 4 weeks. If BHBN administration is stopped at this point, mild hyperplastic mucosal lesion regresses to the normal state. However, if BHBN treatment is continued, mucosal hyperplasia progresses to papillary growth and papillary carcinomas develop via papillomas (Fig. 3). Large papillary carcinomas may occasionally invade the bladder wall. Usually, papillary carcinomas are multifocal but superficial, indicating bladder carcinoma in rats to be a good model for human papillary bladder carcinoma. With progression, urinary bladders become filled with multifocal urothelial carcinomas and rats die due to massive bleeding. Papillary carcinomas are always induced in rats, irrespective of the strain of animal, the concentration of BHBN, or the carcinogen, with similar findings being reported with *N*-(4-[5-nitro-2-furyl]-2-thizolyl)formamide and *N*-methyl-*N*-nitrosourea.

Urinary bladder carcinogenesis in mice treated with BHBN in the drinking water originates in the normal mucosa (composed of two to three layers of urothelium) and progresses through mild hyperplasia, dysplasia and carcinoma *in situ*, to form large nodular invasive carcinomas[33] (Fig. 4). Bilateral ureters are frequently obstructed due to invasion of carcinomas into the bladder wall, and when advanced, mice die because of renal insufficiency due to hydronephrosis. Because of these features, the bladder carcinomas induced by BHBN in mice offer good models for human nodular invasive bladder carcinoma. Of interest, it has proven impossible to induce multiple papillary carcinomas in any strain of mouse, not with any concentration of BHBN nor any other carcinogen. Thus, there is a clear contrast between the biological and morphological characteristics of bladder carcinomas in rats and mice.

Bladder carcinogenesis in female dogs has been studied extensively by Okajima *et al.* who used these animals to periodically observe the surface of the bladder epithelium directly by cystoscopy.[34] They made capsules of BHBN (80–500 mg/capsule), which were administered once a day. After 4–5 years, papillary superficial bladder carcinomas were induced (Fig. 5), and when these were examined by cystoscopy without further BHBN treatment after more than 10 years, the bladders of the dogs were full of multifocal papillary carcinomas. When dogs were given 500 mg of BHBN daily, nodular invasive carcinomas were induced after approximately 1 year. These findings indicate that bladder carcinogenesis in dogs can be controlled by the concentration and period of BHBN administration in terms of the type of carcinoma (i.e. papillary superficial and nodular invasive bladder carcinoma). Thus, in the various animal species, rats, mice and dogs, the relationship between papillary and nodular carcinomas in the bladder appears to differ.

Morphological and pathological characteristics of human urothelial carcinomas, mainly bladder carcinomas, are a combination of papillary (P), papillonodular (PN), nodular (N) and carcinoma *in situ* (C). On careful analysis of cancerous lesions and normal-looking mucosa of 186 cystectomized specimens by step-sectioning,[35] we classified 17 as C and 80

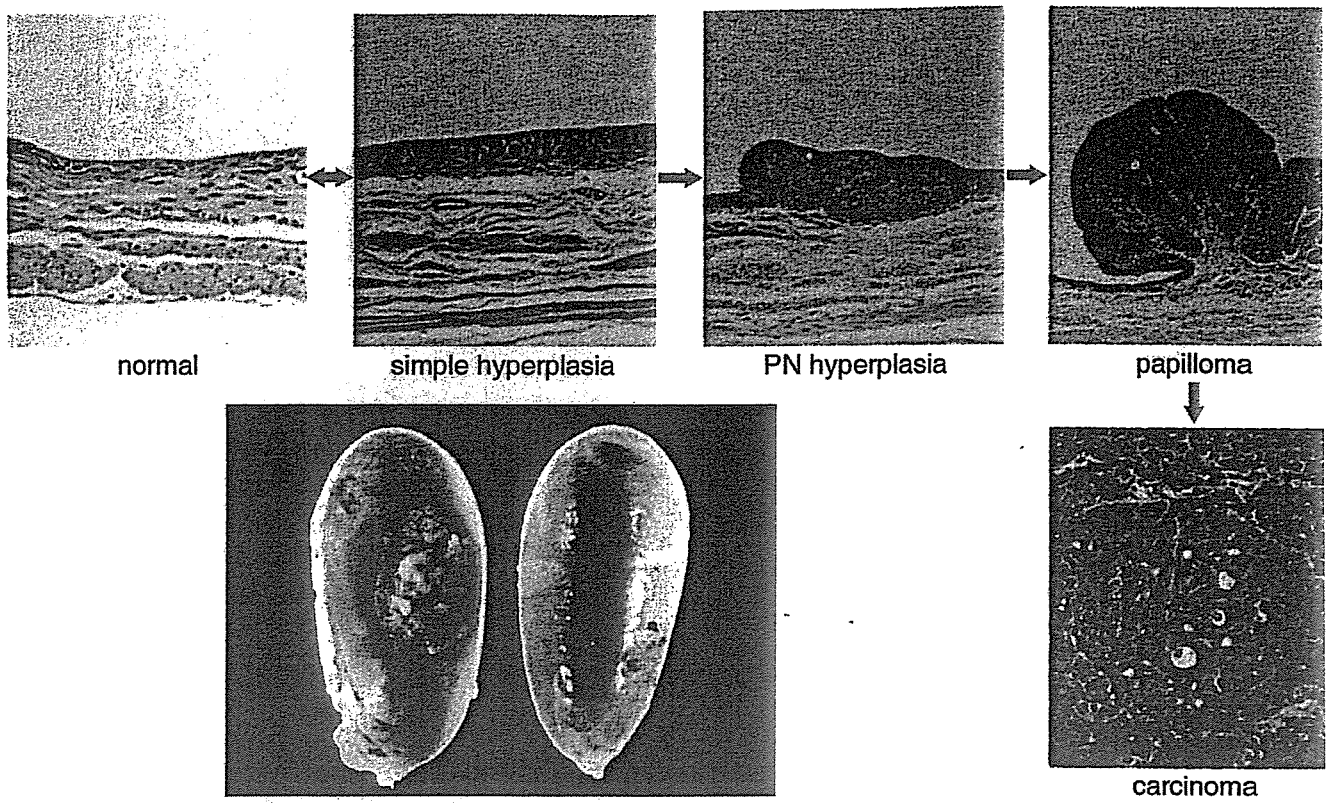

Fig. 3. Histogenesis and progession of papillary carcinomas in rats. (Reproduced with permission from Medical view Co., T. Kakizoe, Development and Progression of Bladder Cancer, 1995.)

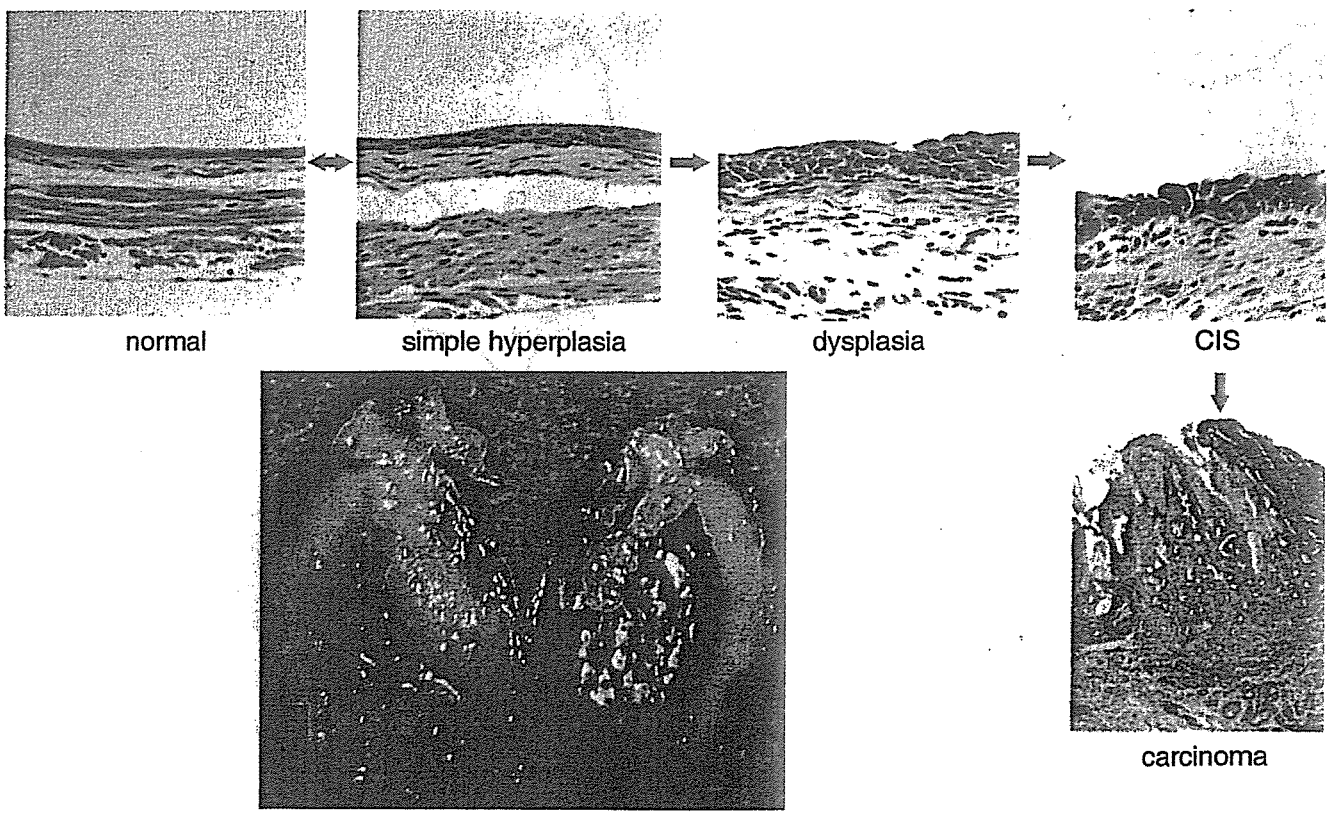

Fig. 4. Histogenesis and progression of nodular invasive carcinoma in mice. (Reproduced with permission from Medical view Co., T. Kakizoe, Development and Progression of Bladder Cancer, 1995.)

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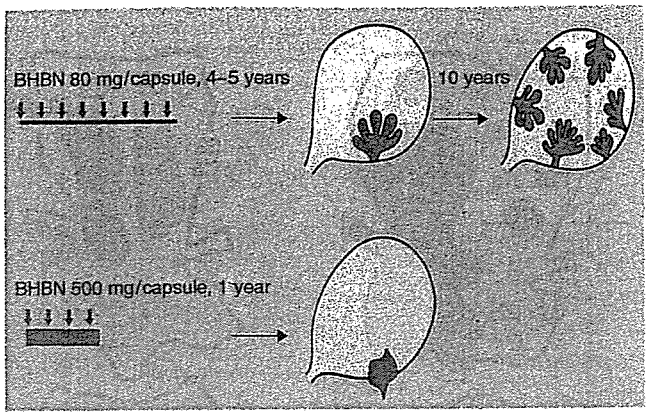

Fig. 5. Development and progression of papillary and nodular carcinomas depending on the concentration and period of administration of *N*-butyl-*N*-(4-hydroxybutyl) nitrosamine (BHBN) in female dogs.[34] (Reproduced with permission from Medical view Co., T. Kakizoe, Development and Progression of Bladder Cancer, 1995.)

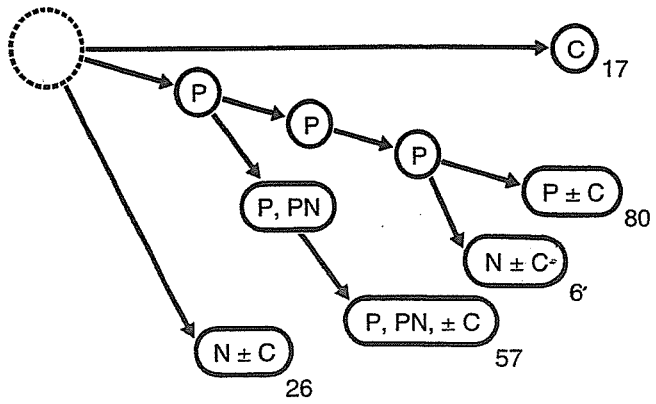

Fig. 6. Conceptual progression routes of papillary (P), papillonodular (PN) and nodular (N) carcinoma, and carcinoma *in situ* (C), in 186 cystectomized specimens examined by step-sectioning.[35]

as P and P + C. Fifty-seven cases featured apparent early changes from P to a mixture of P and N, whereas six showed late development of N with repeated recurrence of P. The findings thus indicated some N to have developed from P as more anaplastic cell populations within a pre-existing low-grade lesion, whereas others arose directly *de novo* from C (Fig. 6). Topographic relationships between P and N in the pT3 group are illustrated in Fig. 7. Figure 8 demonstrates findings for patients having a previous history of repeated recurrence of papillary carcinomas treated by TUR. At the time of cystectomy, all the cystectomized specimens showed a variable degree of coexistence of P, N and C.

Molecular pathways of urothelial carcinogenesis

With papillary superficial and nodular invasive carcinomas, there appear to be differences in molecular pathways as well

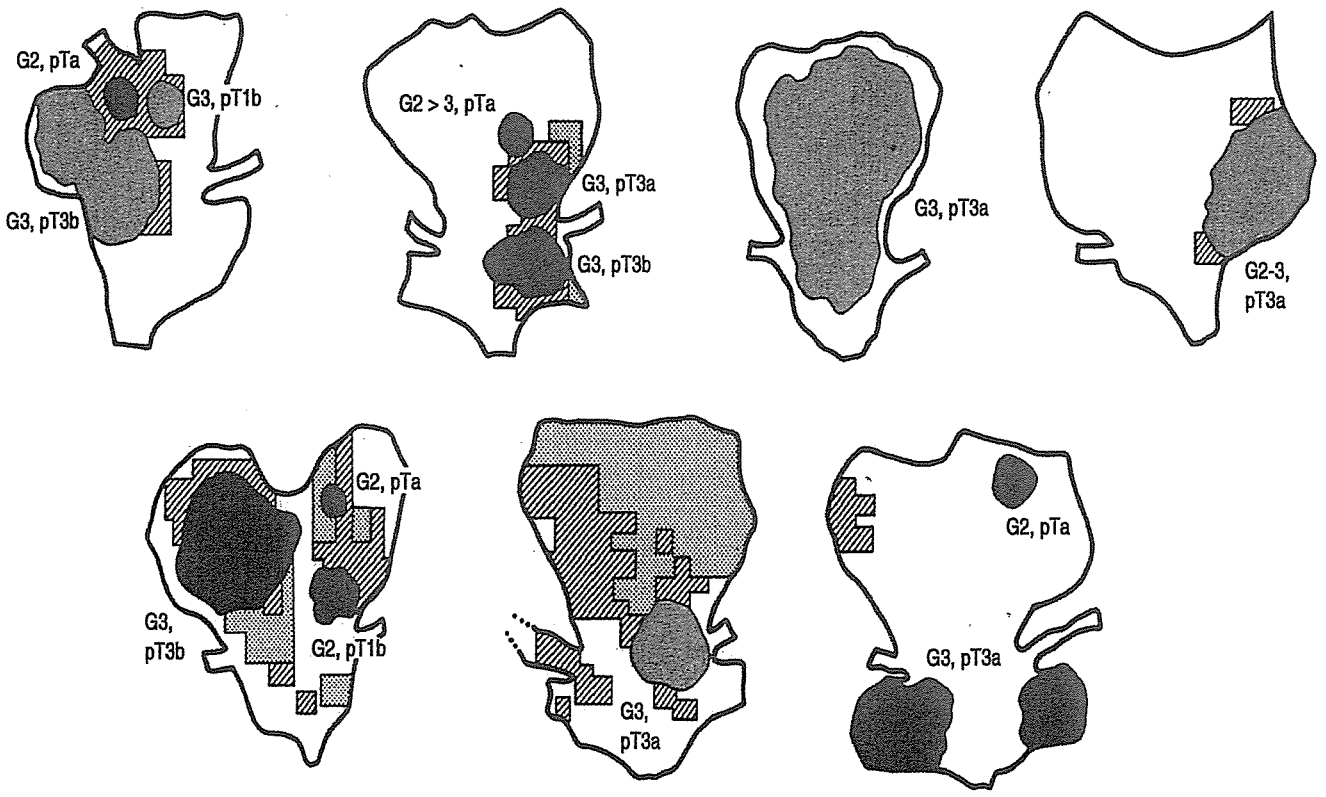

Fig. 7. Cases of pT3 cystectomized specimens indicating coexistence of papillary (P; blue), papillonodular (PN; yellow) and nodular (N; red) carcinoma together with oblique line area (C) and shaded area (dysplasia).[35]

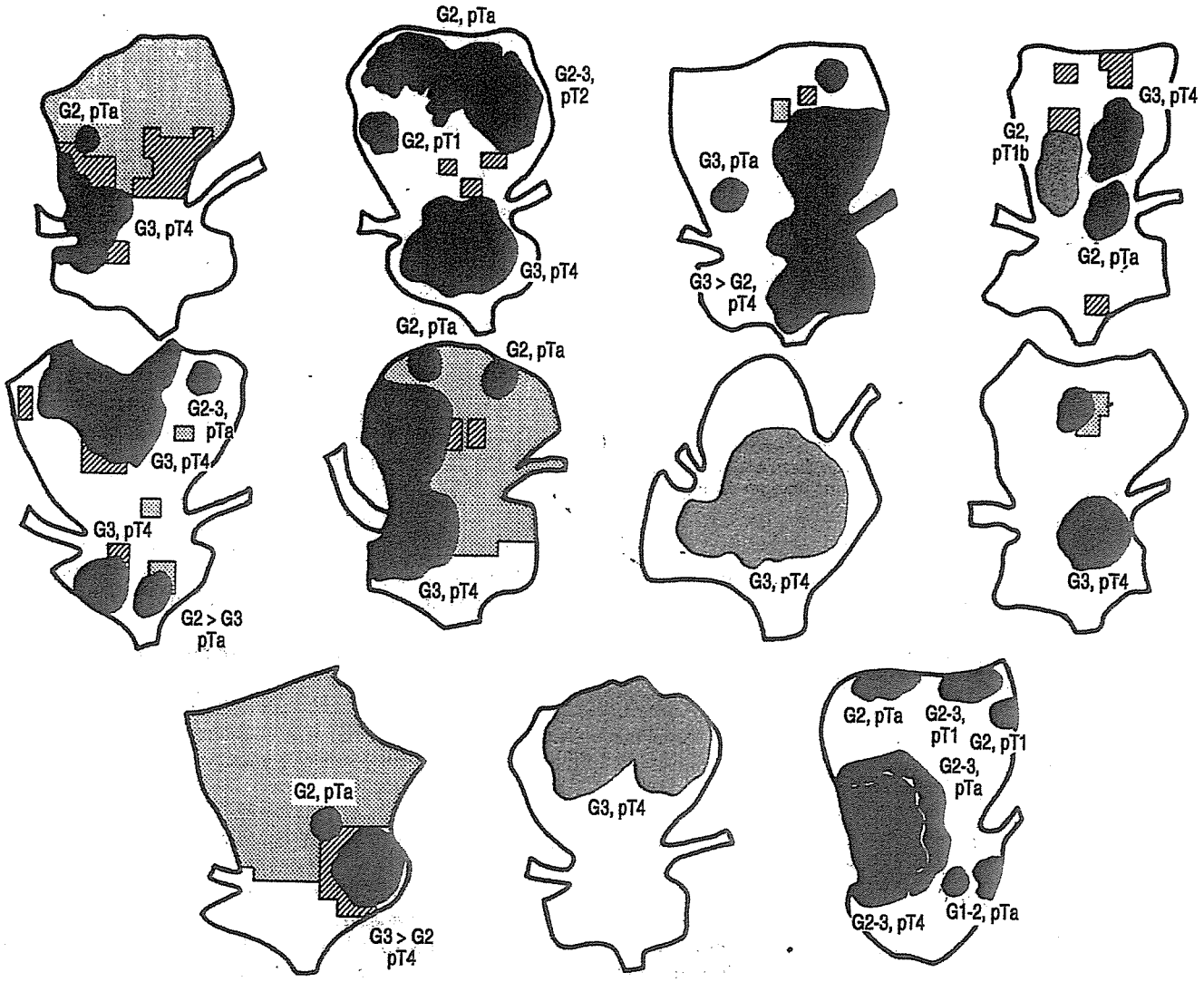

Fig. 8. Eleven cases of cystectomized specimens having histories of multiple transurethral resection for papillary recurrent carcinomas showing variety of stages and morphology in a single bladder.[35]

as morphology[36–38] (Fig. 9). The most common genetic alterations in low-grade papillary urothelial carcinomas are LOH of chromosome 9 and activating mutations of fibroblast growth factor receptor 3 (FGFR3).[39,40] Over 70% of low-grade papillary carcinoma exhibit FGFR3 mutations, but only 10–20% of high-grade invasive carcinomas have FGFR3 mutations, implying a key role for FGFR3 together with mutations of 9p and 9q, specifically for the induction of low-grade papillary carcinomas. Invasive carcinoma is frequently associated with p53 mutations.[41–43]

In addition to the above-mentioned genomic abnormalities associated with urothelial carcinoma, epigenetic alterations also occur during urothelial carcinogenesis. Almost all cells in the human body contain the same sequence of DNA, but cells in different organs during different developmental stages express different genes by epigenetic control of cellular function. This expression control of DNA is achieved by DNA methylation, chromatin structure and transcription factors. DNA can be methylated at cytosine residues adjacent to guanine residues (CpG) and CpG sites are distributed non-randomly throughout the genome, being found as islands in the promoter and exonic regions. Inactivation of tumor suppressor genes is known to occur via promoter hypermethylation, frequently due to DNA methyltransferase 1 (DNMT1). Expression of DNMT1 is increased in tumors and even during the precancerous stages of the urothelium with the development of flat carcinomas *in situ*.[44] Hypermethylation in urothelial carcinogenesis has also been observed in the promoter region of the E-cadherin gene, indicating an association with carcinoma *in situ* and detachment of cells or clusters of carcinoma cells in the urine.[45]

Development and progression of urothelial carcinoma

As is shown in Fig. 1, multifocal transitional cell carcinomas may develop in any region of the urinary tract, from the renal pelvis/ureter to the bladder/urethra.[4,46] Whereas upper urinary

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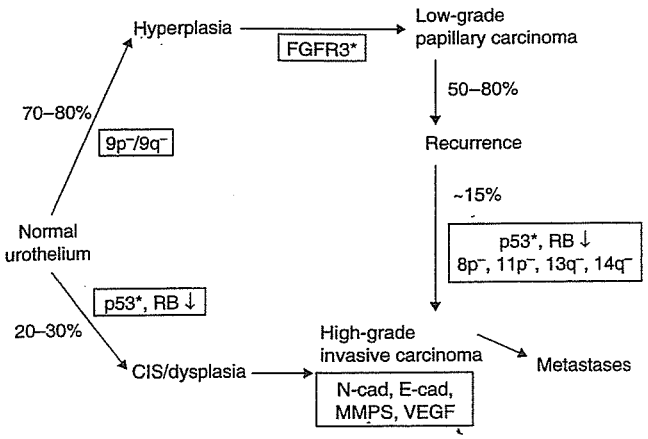

Fig. 9. Presumed molecular pathways of development of papillary and nodular carcinoma. (Modified from Wu.[38]) CIS, carcinoma *in situ*; FGFR3, fibroblast growth factor receptor 3; MMPS, matrix metal proteinases; RB, retinoblastoma gene; VEGF, vascular endothelial growth factor.

tract carcinomas occur infrequently after transurethral management of bladder carcinomas, the incidence is much greater in patients with vesico-ureteral reflux,[10] suggesting seeding or implantation of primary urothelial carcinoma cells after spread via the urine rather than field cancerization. In addition, recent molecular analyses using X-chromosome inactivation,[23] p53 mutation,[24–28] LOH[27,28] and comparative genomic hybridization[29] have provided compelling evidence that multifocal urothelial carcinomas are monoclonal in origin, despite some discrepancies.[30,31]

Comparing the basic morphological patterns of urothelial carcinomas, namely low-grade, superficial papillary carcinomas and high-grade, invasive nodular carcinomas, these two patterns of urothelial carcinomas are clearly separated in rats[32] and mice.[33] However, in dogs,[34] papillary carcinomas and nodular carcinomas can both be induced, depending on the concentration and period of carcinogen administration. In humans, papillary carcinomas and nodular carcinomas may originally develop separately, but coexistence of the two types is occasionally observed in a single bladder together with dysplasia and carcinoma *in situ*.[35] During the process of repeated recurrence, progression from papillary carcinoma to nodular carcinoma may be observed and molecular analysis of bladder carcinogenesis indicates the presence of two pathways: LOH of 9p/9q loss and FGFR3 mutation resulting in papillary carcinoma, and if p53 mutation occurs, nodular carcinoma. If p53 mutations occur initially, nodular carcinoma develops via dysplasia and carcinoma *in situ*. The available data clearly indicate that multiple genetic alterations are associated with the development and progression of bladder cancer.[36–38]

In the normal-appearing mucosa of the renal pelvis, ureter and bladder, dysplasia and carcinoma *in situ* may be frequently observed.[46] As mucosal dysplasia is not malignant, a derivation by implantation from primary carcinomas is not conceivable. In normal-appearing mucosa in remote areas from tumors, p53 mutation may be observed.[27] Intraepithelial spread[27,28] has been proposed as an explanation but this would appear unlikely. The phenomenon of coexistence of dysplasia, carcinoma *in situ* and p53 mutation in normal-appearing mucosa can be far more readily explained by the field cancerization theory. Differences in growth patterns of papillary and nodular carcinomas, and carcinoma *in situ*, as well as in cellular polarity and grade of malignancy make a single origin by seeding unreasonable. Finally, on detailed analysis of recurrent patterns of papillary carcinomas after TUR with or without intravesical instillation therapy, Akaza *et al.* concluded that recurrence patterns are biphasic, with an initial peak due to seeding or implantation of cancer cells during therapy and a second peak due to a new tumor occurrence from a background of field changes.[47] Thus, multifocal bladder recurrence of urothelial carcinomas is due to a combination of seeding and field changes. This is directly relevant to the condition for reconstruction of the urinary tract after cystectomy, inhibition and control of multiple recurrences after TUR, and the frequency and timing of follow-up for upper tract malignancies after treatment of bladder carcinoma. However, such clinical issues will be covered elsewhere.

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Staging performance of carbon-11 choline positron emission tomography/computed tomography in patients with bone and soft tissue sarcoma: Comparison with conventional imaging

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The present study was conducted to compare the diagnostic accuracy between carbon-11 choline (^{11}C-choline) positron emission tomography (PET)/computed tomography (CT) and conventional imaging for the staging of bone and soft tissue sarcomas. Sixteen patients who underwent ^{11}C-choline PET/CT prior to treatment were evaluated retrospectively for staging accuracy. Conventional imaging methods consisted of ^{99m}Tc-hydroxymethylene diphosphonate bone scintigraphy, chest CT and magnetic resonance imaging of the primary site. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using hard-copy films and multimodality computer platform. Tumor stage was confirmed by histological examination and/or by an obvious progression in number and/or size of the lesions on follow-up examinations. Reviewers examining both ^{11}C-choline PET/CT and conventional imaging classified T stage in all patients. Interpretation based on ^{11}C-choline PET/CT, the Node (N) stage was correctly diagnosed in all patients, whereas the accuracy of conventional imaging in N stage was 63%. Tumor Node Metastasis (TNM) stage was assessed correctly with ^{11}C-choline PET/CT in 15 of 16 patients (94%) and with conventional imaging in eight of 16 patients (50%). The overall TNM staging and N staging accuracy of ^{11}C-choline PET/CT were significantly higher than that of conventional imaging ($P < 0.05$). ^{11}C-choline PET/CT is more accurate than conventional imaging regarding clinical staging of patients with bone and soft tissue sarcomas. A whole body ^{11}C-choline PET/CT might be acceptable for imaging studies of tumor staging prior to treatment. (*Cancer Sci* 2006; 97: 1125–1128)

The general diagnostic tools for staging bone and soft tissue sarcomas are clinical examination, magnetic resonance imaging (MRI) and X-ray of the primary tumor site, chest X-ray or computed tomography (CT), and bone scintigraphy.[1]

Positron emission tomography (PET) with [18F]-fluoro-2-deoxy-D-glucose (FDG) has been used in the evaluation of patients with bone and soft tissue sarcomas for grading and therapy monitoring.[2–7] Most of these studies reveal that ^{18}FDG-PET is superior in the assessment of grading and therapy monitoring compared with conventional imaging.

Recently, carbon-11 choline (^{11}C-choline) has been introduced as a new oncological positron-emitting radiopharmaceutical for evaluation of a variety of malignant tumors.[8–11] Choline is an essential component of the cell membrane, and choline uptake may be via a choline-specific transporter protein.[12] Choline kinase, which catalyzes the phosphorylation of choline, is upregulated in malignant cells. Some studies have demonstrated additional gains in diagnostic accuracy using ^{11}C-choline.[13] ^{11}C-choline uptake is significantly higher in malignant tumors than in benign tumors and correlates well with the degree of ^{18}FDG accumulation with the lesion, while the high background activity owing to excretion via urinary tract interferes with evaluation on ^{18}FDG-PET.[14,15] However, the role of ^{11}C-choline PET scan in the staging of bone and soft tissue sarcomas has not been clarified. To fully elucidate the role of ^{11}C-choline PET, the comparison with ^{18}FDG-PET and conventional imaging modalities are needed.

A new-modality PET/CT can improve the localization of tumors and accuracy of staging in patients because anatomic and molecular information can be coregistered precisely.[16] The aim of the current study was to compare the diagnostic accuracy between ^{11}C-choline PET/CT and conventional imaging for the staging of bone and soft tissue sarcomas.

Materials and Methods

Patient. We retrospectively reviewed ^{11}C-choline PET/CT results from September 2005 to March 2006 for patients with bone and soft tissue sarcomas, who subsequently underwent surgical resection, chemotherapy and/or radiotherapy within 2 weeks. ^{11}C-choline PET/CT was performed for initial staging in 12 patients and for restaging of recurrent disease in four patients. The study population consisted of 13 men and three women with a mean age of 44 years (range, 13–75 years). The clinical records of all of the patients were available for review. This study was conducted in accordance with the amended Helsinki declaration and the protocol was approved by the Institutional Review Board (National Cancer Center, Research Center for Cancer Prevention and Screening). All of the patients provided their written informed consent to participate in the present study and to review their records and images.

Radiopharmaceuticals. Carbon-11 choline was synthesized with a commercial module essentially using the method described by Hara and Yuasa.[17] $^{11}CO_2$ was converted to ^{11}C-methyl iodide by $LiAlH_4$/HI reaction. ^{11}C-methyl iodide was trapped in dimethylaminoethanol. After a washing step with ethanol and water, ^{11}C-choline retained on a cation exchange resin was eluted with saline. Radiochemical purity of the solution was evaluated by liquid chromatography radiodetector. The organic solvents were analyzed by gas chromatography. Endotoxin was assayed by the lysosomal acid lipase method.

PET/CT. Scans were acquired with a PET/CT device (Aquiduo; Toshiba Medical Systems, Tokyo, Japan) that consisted of a PET scanner (ECAT HR+; CTI, Knoxville, TN, USA) and 16-section CT scanner (Aquilion V-detector; Toshiba Medical Systems) with a whole-body mode implemented as the standard software. Prior to the ^{11}C-choline PET/CT study, the patients fasted for at least

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Table 1. Summary of patients and confirmed staging

Patient no.	Diagnosis	SUV	Size (mm)	Staging type	Location	TNM	Metastasis	Grade	Stage
1	Leiomyosarcoma	4.63	110	Initial	Retroperitoneum	T2bN0M1	Soft tissue	High	IV
2	Rhabdomyosarcoma	3.03	60	Initial	Perineum	T2bN1M0	Lymph node	High	IV
3	Pleomorphic malignant Fibrous histiocytoma	15.05	133	Initial	Chest wall	T2bN0M1	Bone, pleura, lymph node	High	IV
4	Leiomyosarcoma	4.10	80	Initial	Retroperitoneum	T2bN0M,P	Lung	Low	IV
5	Osteosarcoma	6.70	110	Initial	Iliac bone	T2N0M1b	Bone, lung	High	IVB
6	Clear cell sarcoma	13.03	80	Initial	Chest wall	T2bN0M1	Bone, lung, pleura, lymph node	High	IV
7	Myxoid liposarcoma	2.15	50	Initial	Leg	T1aN1M0	Lymph node	Low	IVB
8	Osteosarcoma	5.31	110	Initial	Tibia	T2N1M0	Lymph node	High	IV
9	Ewing sarcoma	3.46	95	Initial	Leg	T2bN0M0	N/A	High	III
10	Ewing sarcoma	9.86	102	Initial	Shoulder	T2N0M0	N/A	High	IIB
11	Ewing sarcoma	6.14	16	Initial	Spine	T1N0M0	N/A	High	IA
12	Chondrosarcoma	5.99	110	Initial	Iliac bone	T2N0M1b	Bone	High	IVB
13	Leiomyosarcoma	3.18	50	Restaging	Thigh	T1bN1M1	Bone, soft tissue, lymph node	High	IV
14	Osteosarcoma	4.95	75	Restaging	Jaw	T1N0M1a	Lung	High	IVA
15	Osteosarcoma	3.60	50	Restaging	Femur	T1N0M1b	Lung, bone	High	IVB
16	Alveolar soft part sarcoma	3.60	25	Restaging	Shoulder	T2N0M1	Bone	High	IV

N/A, not applicable; SUV, standardized uptake value; TNM, Tumor Node Metastasis.

6 h. CT was performed from the head to the mid-thigh according to a standardized protocol with the following setting: axial 3.0-mm collimation × 16 modes; 120 kVp; 100 mAs; and a 0.5-second tube rotation, pitch 11.0. Patients maintained normal shallow respiration during the three-dimensional acquisition of CT scans. No iodinated contrast material was administered. Emission scans from the base of the skull to the leg were obtained starting 5 min after the intravenous administration of 350–573 MBq of ^{11}C-choline. The acquisition time for PET was 2 min per table position. Images were reconstructed with attenuation-corrected ordered-subset expectation maximization with two iterations and eight subsets using emission scans and CT data.

Positron emission tomography, CT and coregistered PET/CT images were analyzed with dedicated software (e-soft; Siemens). The initial review of the attenuation-corrected PET images was performed using transaxial, coronal and sagittal planes. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using a multimodality computer platform. ^{11}C-choline uptake was considered to be abnormal when it was substantially greater than the surrounding normal tissue. For ^{11}C-choline PET/CT, tumor sizes and T staging were determined by the CT part of PET/CT. ^{11}C-choline-avid lymph nodes or distant metastases on PET/CT were interpreted as positive for metastases regardless of size. Lymph nodes with abnormal uptake were deemed positive for metastases even when they were smaller than 10.0 mm in short axis nodal diameter. Lung nodules without abnormal uptake but highly suggestive of lung metastases on ^{11}C-choline PET/CT were considered to be positive for metastases. A pixel region of interest (ROI) was outlined within regions of increased ^{11}C-choline uptake and measured on each slice. For quantitative interpretations, standardized uptake value (SUV) was determined according to the standard formula, with activity in the ROI given in Bq per mL/injected dose in Bq per weight (kg). However, time decay correction for whole-body image acquisition was not conducted. A SUV of more than 2.5 was considered to characterize malignancy.

Conventional imaging. Conventional imaging methods, performed within 2 weeks of ^{11}C-choline PET/CT, either before or after, were ^{99,m}Tc-hydroxymethylene diphosphonate (HMDP) bone scintigraphy, chest CT and MRI of the primary site. ^{99,m}Tc-HMDP bone scintigraphy was performed 2 h after intravenous injection of 740 MBq of ^{99,m}Tc-HMDP. Both anterior and posterior whole-body planar images were obtained simultaneously with a dual-headed gamma camera (E.CAM; Siemens). Chest CT was performed using a multidetector scanner (Aquilion V-detector; Toshiba Medical Systems) with the following setting: axial 4.0-mm × 4 modes; 120 kVp, automated electric current; 0.5-second tube rotation; and pitch 5. Images were reconstructed with 10.0-mm slice thickness by means of a standard algorithm. MRI of the primary site was performed using a 1.5 Tesla system (Signa Horizon; GE Medical Systems, Milwaukee, WI, USA or Visart; MRI produced by Toshiba Medical Systems, Tokyo, Japan). Pulse sequences comprised T1-weighted spin echo (SE) images, T2-weighted fast spin echo (FSE) images, as well as post-contrast T1-weighted SE images with fat suppression after injection of contrast material. Pulse sequence parameters and slice orientation varied with the examined anatomic site. The images were reviewed and a consensus was reached by two board-certified radiologists who were unaware of any clinical or radiological information using hard-copy films and multimodality computer platform. The two readers for ^{11}C-choline PET/CT and those for conventional imaging were not the same persons.

Each tumor was staged according to the Tumor Node Metastasis (TNM) classification of the International Union Against Cancer for sarcoma of bone and the American Joint Committee staging protocol for sarcoma of the soft tissue.[18,19] T, N and M stages were assigned for both PET/CT and conventional imaging. T staging was confirmed by pathological evaluation using specimens obtained from surgical resection of the primary tumors. N staging was confirmed by pathological examinations in two patients using specimens obtained from sampling of regional nodes. In terms of extraregional nodes in two patients, nodal staging was confirmed by an obvious progression in number and/or size of the lesions on follow-up examinations. The mean follow-up period was 172 days (range, 44–322 days).

Statistical analysis. All valuables were assessed on a patient-by-patient basis. The McNemar test was used for paired comparisons between ^{11}C-choline PET/CT and conventional imaging. Statistical analysis was performed with the SPSS version 11 software program (SPSS, Chicago, IL, USA).

Results

There were eight bone sarcomas and eight soft tissue sarcomas (Table 1). The primary sites included shoulder ($n = 2$), chest wall

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Table 2. Staging of bone and soft tissue sarcoma

Variables	^{11}C-choline PET/CT	Conventional imaging	*P*-value
Overall stage			0.023
Correct	15 (94)	8 (50)	
Understaged	1 (6)	8 (50)	
Overstaged	0	0	
N stage			0.041
Correct	16 (100)	10 (63)	
Understaged	0	6 (38)	
Overstaged	0	0	
M stage			0.617
Correct	15 (94)	13 (81)	
Understaged	1 (6)	3 (19)	
Overstaged	0	0	

Note: Data are presented as number (*n*). Numbers in parentheses are percentages. CT, computed tomography; PET, positron emission tomography.

($n = 2$), retroperitoneum ($n = 2$), iliac bone ($n = 2$), leg ($n = 2$), thigh ($n = 1$), perineum ($n = 1$), tibia ($n = 1$), femur ($n = 1$), mandible ($n = 1$) and spine ($n = 1$). Pathological diagnoses were osteosarcoma ($n = 4$), Ewing sarcoma ($n = 3$), leiomyosarcoma ($n = 3$), clear cell sarcoma ($n = 1$), chondrosarcoma ($n = 1$), pleomorphic malignant fibrous histiocytoma ($n = 1$), myxoid liposarcoma ($n = 1$), rhabdomyosarcoma ($n = 1$), and alveolar soft part sarcoma ($n = 1$). Histological grade of tumors was grade 1 ($n = 1$), grade 2 ($n = 1$), grade 3 ($n = 11$) and grade 4 ($n = 3$).

All patients of initial staging had increased ^{11}C-choline uptake of the primary lesion (average maximal SUV ± SD: 5.92 ± 3.68 [range, 2.15–15.05]). Pathological T stages available in patients with initial staging are as follows: T1 ($n = 1$), T1a ($n = 1$), T1b ($n = 1$), T2 ($n = 4$) and T2b ($n = 5$). T stages in patients with restaging were T1 ($n = 2$), T1b ($n = 1$) and T2 ($n = 1$). Tumor size of patients for initial staging was 78.5 ± 34.0 mm (mean ± SD [range, 16.0–133.0 mm]). Both ^{11}C-choline PET/CT and conventional imaging classified the T stage correctly in all patients. Twelve (75%) of the 16 patients had N0 disease. Using ^{11}C-choline PET/CT, the N stage was correctly assigned in all patients, whereas the accuracy of conventional imaging in N stage was 63% ($P = 0.041$, Table 2). Understaging occurred in six patients (38%). Three of these patients (19%) had metastasis of inguinal node whose largest diameter was less than 10.0 mm (Fig. 1). The incidence of distant metastases was high in our study population. Both ^{11}C-choline PET/CT and conventional imaging detected bone metastases in seven patients (44%), lung metastases in five (31%) and pleural dissemination in two (18%, Fig. 2). Using ^{11}C-choline PET/CT, the M stage was correctly assigned in 15 patients (94%), whereas the accuracy of conventional imaging in M stage was 81% ($P = 0.617$, Table 2).

The complete stages of all patients were stage IA ($n = 1$), stage IIB ($n = 1$), stage III ($n = 1$) and stage IV ($n = 13$). TNM stage was correctly assessed with ^{11}C-choline PET/CT in 15 of 16 patients (94%) and with conventional imaging in eight of 16 patients (50%, $P = 0.023$, Table 2). ^{11}C-choline PET/CT assigned an incorrect TNM stage in a patient. This patient was understaged due to small metastatic lung tumor which was not clearly visualized by CT part of ^{11}C-choline PET/CT. Eight patients were understaged by conventional imaging (50%). Of these, skip metastases of soft tissues were identified in two (25%) and small nodal metastases in six (75%). ^{11}C-choline PET/CT correctly determined TNM stage in seven patients (44%) in whom stage derived from conventional imaging was incorrect.

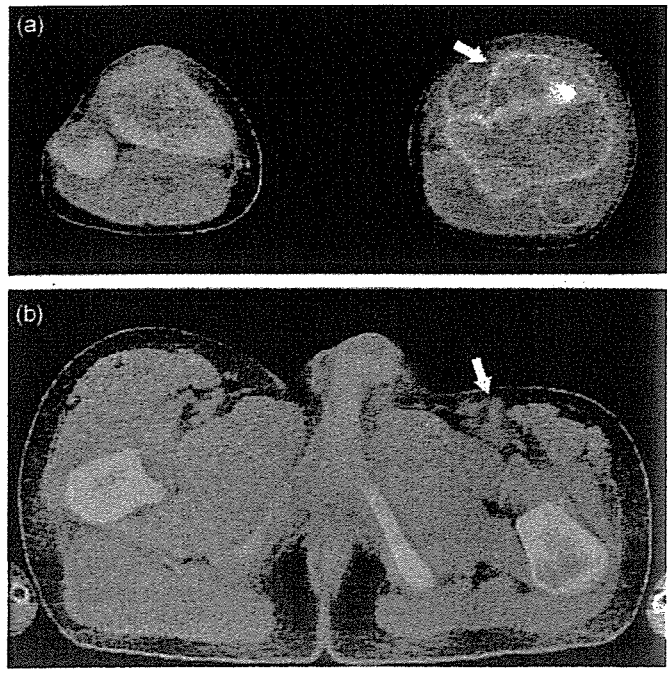

Fig. 1. A 13-year-old boy with osteosarcoma. (a) Transverse ^{11}C-choline positron emission tomography (PET)/computed tomography (CT) image revealed hypermetabolic focus in the proximal portion of the left tibia (arrow). PET/CT findings were verified at histopathological analysis. (b) Abnormal uptake of ^{11}C-choline was also noted in the left inguinal lymph node, which was interpreted as highly suspicious for malignancy (arrow). Subsequent resection revealed metastasis from osteosarcoma.

Discussion

The results of the present study show that ^{11}C-choline PET/CT improves the accuracy of staging in patients with bone and soft tissue sarcomas compared to conventional imaging. Specifically, ^{11}C-choline PET/CT has potentially significant implications for detecting nodal and distant metastases at overall staging. Reports about the efficacy of ^{11}C-choline in the localization and detection of bone and soft tissue sarcomas are still limited.[15] To our knowledge, no study regarding ^{11}C-choline PET/CT for staging bone and soft tissue sarcomas was found. In our study, seven of the 16 patients had skip metastases of soft tissue or nodal metastases detected by ^{11}C-choline PET/CT that were not identified by routine clinical and conventional radiological evaluation.

The ability of PET to depict increased metabolism in malignancies has greatly improved the accuracy in detecting neoplasms.[4] However, compared with conventional imaging studies, use of PET alone results in a lack of substantial detail.[20] The PET/CT device permits sequential acquisition of anatomic CT and functional PET images in a single scanning session. Morphological characterization of scintigraphic lesions by PET/CT resulted in a lower percentage of equivocal interpretations compared with that of conventional imaging. Tumor-detecting PET/CT technology is growing rapidly. However, there are only limited data available on staging of bone and soft tissue sarcomas with PET/CT.

Carbon-11 choline uptake was significantly higher in malignant soft tissue tumors and was due to the high utilization of cell membranes of these lesions. ^{11}C-choline uptake is observed physiologically in the liver, pancreas, kidney and duodenum. ^{11}C-choline is also secreted into phospholipid-rich pancreatic juice in a non-fasting state. A potential advantage of ^{11}C-choline PET/CT might be the assessment of tumors in the skull or retroperitoneum. Blood clearance of ^{11}C-choline is rapid and radioactive distribution

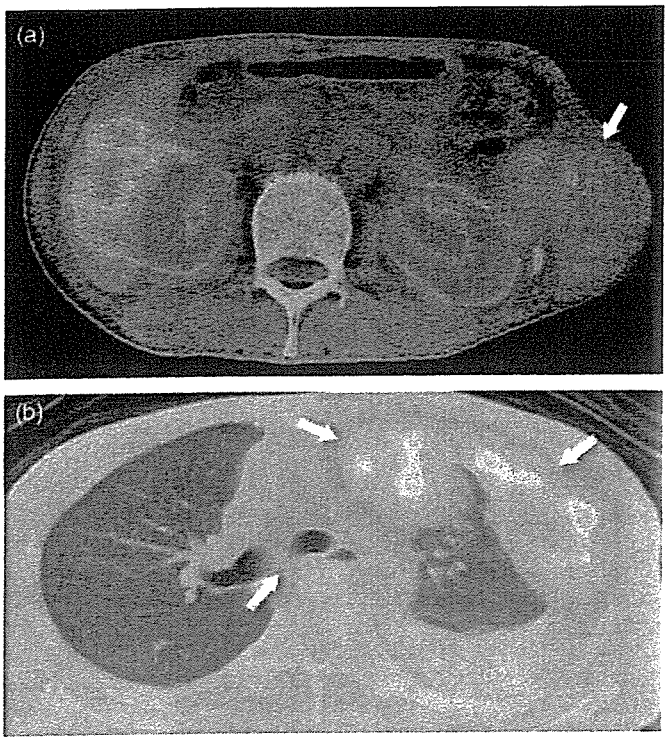

Fig. 2. A 34-year-old man with clear cell sarcoma. (a) Transverse ^{11}C-choline positron emission tomography (PET)/computed tomography (CT) image depicting abnormal uptake in the tumor arising from the left lateral chest wall (arrow). (b) PET/CT image also depicts pleural dissemination and mediastinal lymph node (arrows). Follow-up findings in this patient confirmed the diagnosis.

in tissues is constant in 5 min. The accumulation of ^{11}C-choline in the skull or retroperitoneum is hardly affected by background within the limits of short uptake time. In comparison to ^{18}FDG, physiological background level in the urinary tract is low. This may be due to incomplete tubular reabsorption of the intact tracer, or enhanced excretion of labeled oxidative metabolites like betaine.[12]

Limited resolution of the present generation of ^{11}C-choline PET/CT and the partial volume effect result in failure to detect small lesions. In our study, one patient was understaged due to small metastatic lung tumor, which was not visualized clearly by the CT part of ^{11}C-choline PET/CT. Faint increase in tracer uptake and motion artifact caused by breathing contribute to false negative results. However, the advantage of ^{11}C-choline PET/CT is that the whole-body can be visualized in a single examination. In our study, 50% of patients were understaged by conventional imaging. The inaccuracy of conventional imaging in assessing skip metastases of soft tissues is due to the field of view.

We reported the accurate modality of ^{11}C-choline PET/CT as a non-invasive method for staging in patients with bone and soft tissue sarcomas compared to conventional imaging. Choline is an essential component of the cell membrane, and choline uptake may be via a choline-specific transporter protein. Choline kinase, which catalyzes the phosphorylation of choline, is upregulated in tumor cells.[12] In some types of tumor cells, overexpression of choline-specific transporter protein and choline kinase were identified by *in situ* hybridization.[21] ^{11}C-choline will be phosphorylated by choline kinase as a choline analog and retained in tumor cells.[21] However, the precise pathway of metabolic trapping by tumor cells has not been elucidated, and further studies to clarify the mechanism of imaging by ^{11}C-choline are needed.

Our study has limitations. Most patients in this study had high-grade tumors (88%) and may differ from the patient population of previous studies. Our study was intended to examine the staging prior to treatment; therefore, patient population of high-grade tumors may explain the significant accuracy in overall staging compared to conventional imaging. A study with a larger patient population would clarify the influence of ^{11}C-choline PET/CT on staging. ^{11}C-choline is clearly a sensitive PET tracer for staging patients with bone and soft tissue sarcomas. The short half-life of ^{11}C-choline necessitates the availability of an on-site cyclotron, which causes practical restriction. More specific radiotracers will help overcome this limitation in the future.

In summary, the use of ^{11}C-choline PET/CT in patients with bone and soft tissue sarcomas increases the accuracy of overall staging and N staging compared to conventional staging. Our study suggests that whole-body ^{11}C-choline PET/CT should be the preferred modality for staging in patients with bone and soft tissue sarcomas.

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Screening for Lung Cancer With Low-Dose Helical Computed Tomography: Anti-Lung Cancer Association Project

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Purpose: **Because efficacy of lung cancer screening using chest x-ray is controversial and insufficient, other screening modalities need to be developed. To provide data on screening performance of low-dose helical computed tomography (CT) scanning and its efficacy in terms of survival, a one-arm longitudinal screening project was conducted.**

Patients and Methods: **A total of 1,611 asymptomatic patients aged 40 to 79 years, 86% with smoking history, were screened by low-dose helical CT scan, chest x-ray, and 3-day pooled sputum cytology with a 6-month interval.**

Results: **At initial screening, the proportions of positive tests were 11.5%, 3.4%, and 0.8% with low-dose helical CT scan, chest x-ray, and sputum cytology, respectively. In 1,611 participants, 14 (0.87%) cases of lung cancer were detected, with 71% being stage IA disease and a mean tumor diameter of 19.8 mm. At repeated screening, the proportions of positive tests were 9.1%, 2.6%, and 0.7% with low-dose helical CT, chest x-ray, and sputum cytology, respectively. In 7,891 examinations, 22 (0.28%) cases of lung cancer were detected, with 82% being stage IA disease and a mean tumor diameter of 14.6 mm. The 5-year survival rate for screen-detected lung cancer was 76.2% and 64.9% for initial and repeated screening, respectively.**

Conclusion: **Screening with low-dose helical CT has potential to improve screening efficacy in terms of reducing lung cancer mortality. An evaluation of efficacy using appropriate methods is urgently required.**

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LUNG CANCER IS THE most common cause of cancer death not only in Japan but in most developed countries. In 1998, 36,880 males and 13,991 females died of lung cancer in Japan, which ranked first among males and third among females in the number of cancer deaths.[1] Lung cancer screening using chest x-ray and sputum cytology was introduced by the Japanese government in 1987 as one lung cancer control strategy, and 7,030,639 people were screened under this program in 1998.[2] This approach has not been recommended for the asymptomatic general population in other countries.[3] Although the efficacy of lung cancer screening using chest x-ray remains controversial,[4-6] it seems to be insufficient. This is underscored by the low survival rate among patients with screen-detected lung cancer compared with patients with cancer at other sites[7]; therefore, more effective screening modalities need to be developed. Low-dose helical computed tomography (CT) scanning is one candidate for this because of its great ability to detect small peripheral nodules.[8,9]

There have been several projects in which low-dose helical CT scanning was used as a screening modality. Kaneko et al[10] reported the results from the Anti-Lung Cancer Association (ALCA) project from September 1993 to April 1995, in which 3,457 low-dose helical CT examinations were conducted for 1,369 participants, and 15 (0.4%) cases of lung cancer were detected. Of these, 14 (93%) were stage I disease, and the mean tumor diameter was 16 mm. Sone et al[11,12] reported that in 1996 to 1998, population-based annual lung cancer screening using low-dose helical CT scanning was provided for 5,483 people (13,786 examinations), and 60 cases of lung cancer (0.4%) were detected. Among them, 55 (92%) were stage I, and the mean tumor diameter was 13.4 mm. Henschke et al[13] reported the baseline findings from the Early Lung Cancer Action Project (ELCAP), in which 1,000 high-risk male patients were screened by low-dose helical CT scan and 27 (2.7%) cases of lung cancer were detected. Of these, 23 (85%) were stage I disease. These studies have consistently indicated that CT screening can detect lung cancer in an earlier stage than conventional chest x-ray, which may bring

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greater efficacy in terms of a reduction in mortality from lung cancer. In the present study, we provide an update on the findings from the ALCA project, including the survival data for patients with screen-detected lung cancer.

PATIENTS AND METHODS

Study Population

The ALCA is a for-profit organization established in 1975 to thoroughly screen dues-paying participants for lung cancer. Participants are continuously recruited from the general population who smoke cigarettes and are 40 years of age or older, although some exceptions have been allowed in practice. The participants underwent chest x-ray and sputum cytology twice a year until August 1993. From 1975 to 1993, 26,338 examinations were conducted for 2,529 participants, and 43 cases of lung cancer were detected, as reported elsewhere.[10]

In September 1993, low-dose helical CT scanning was introduced in addition to the above two modalities. By December 1998, 742 participants who had been members of this project since before the introduction of CT screening and 940 new participants who entered into the project after the introduction of CT screening had undergone screening using low-dose helical CT scanning at least once. In total, 9,847 screening examinations for 1,682 participants were conducted from September 1993 to December 1998.

In this analysis, we excluded 233 examinations for 70 participants who were aged 39 years or younger or 80 years or older at the initial CT screening and one examination for one member whose smoking status was unknown at the initial CT screening. Also, data for 29 participants who reached 80 years of age during the study period were not used afterward (111 examinations). These exclusion criteria left 9,502 examinations for 1,611 participants in the analysis. Of these, 3,355 examinations for 1,320 participants conducted from September 1993 to April 1995 and 14 cases of lung cancer detected by helical CT scanning (10 at initial screening and four at repeated screening) overlapped with the previous study.[10]

Screening Procedures

Screening was conducted at one clinic (ALCA) located in central Tokyo. At initial screening, a simple questionnaire regarding smoking history and symptoms was completed, and helical CT scan, chest x-ray (posterior-anterior position), and sputum cytology pooled for 3 days were conducted after obtaining informed consent from each participant. A TCT-900S Superhelix (Toshiba Medical, Tokyo Japan) was used for helical CT scanning, with parameters as follows: 120 kVp, 50 mA, 10-mm collimation, one rotation of the x-ray tube per second, and a table speed of 20 mm/sec (pitch, 2:1). A thoracic area spanning 30 cm was scanned from a level 2 cm superior to the apex to the level of the diaphragm with a 15-second breath hold. Image construction was performed with 180-degree linear interpolation at intervals of 1 cm.

All CT images were checked by two of seven readers (radiologists or thoracic physicians; M.K., M.K., R.K., H.O., H.N., E.M., and K.E), one using hard-copy film and the other using a cathode ray tube (CRT) monitor. Display conditions were a window width of 2,000 HU and a window level of −700 HU. When using hard-copy film, CT images taken at previous examination were also referred to, if available. The two readers classified the images independently into five categories according to the classification tentatively developed by this study group at the beginning of the project and later authorized by the Japan Lung Cancer Society, as follows: (A) inadequate image; (B) normal; (C) scar lesion caused by a previous inflammatory episode; (D) benign tumor or an active inflammatory disease; and (E) suspected lung cancer.[14] Chest x-ray films were read by two readers using the classification of the Japan Lung Cancer Society,[14] and the second reader, who was aware of the first reader's judgment, made a summary judgment. From 1993 to August 1996, cases classified as D or E either by helical CT scan or chest x-ray were considered for additional diagnostic workup, and a third reader determined the necessity of thin-section CT (TSCT) scanning when the findings showed a solitary nodule without calcification, a nodule greater than 4.9 mm in diameter, or an area of localized opacification increasing in size with sequential comparison. In September 1996, the checking procedure was changed with the introduction of a computer-aided diagnosis (CAD) system.[15] The first reader checked the helical CT on a CRT monitor using the CAD system. Then the second reader made the summary judgment using hard-copy display, referring to the findings by the first radiologist on CRT and hard-copy film of previous CT images in cases with repeated screening. Checks by the third reader were no longer conducted. Participants with positive helical CT scan tests were defined as those who were asked to undergo TSCT, and participants with positive chest x-ray tests were defined as those who were classified as D or E regardless of the judgment based on helical CT scan.

TSCT was conducted at the same clinic (ALCA) with the following parameters: 120 kVp, 250 mA, 2-mm collimation, one rotation of the x-ray tube per second, table speed of 2 mm/sec (pitch, 1:1), and thin-section algorithm. If lung cancer was suspected, the participant was referred to the National Cancer Center Hospital or National Cancer Center Hospital East for diagnostic procedures, such as CT fluoroscopy-guided transbronchial biopsy, CT fluoroscopy-guided percutaneous needle biopsy (CTPNB), or video-assisted thoracoscopic surgery (VATS).

Sputum specimens were processed by the Sacomanno method and checked by trained cytoscreeners. Abnormal findings were confirmed by a certified cytopathologist and classified as follows: (A) inadequate sample; (B) normal or squamous metaplasia with mild atypia; (C) squamous metaplasia with moderate atypia; (D) squamous metaplasia with severe atypia; or (E) lung cancer according to the classifications of the Japan Lung Cancer Society.[14] Test positives for sputum cytology were defined as patients who were classified as having D or E. For these patients, sputum cytology was repeated at an ALCA clinic. If lung cancer was still suspected, participants were referred to the National Cancer Center Hospital or National Cancer Center Hospital East for bronchoscopy. Participants were invited twice a year by mail after the initial screening to repeat the same screening procedures.

Statistical Analysis

Statistical P values for the difference in proportions and means were evaluated by χ^2 test and t test, respectively, with a two-sided level. The cumulative survival rate for lung cancer cases was calculated with the Kaplan-Meier method, with survival time defined as starting from the date of diagnosis, when microscopic evidence for malignancy was initially obtained, until the date of death or February 1, 2000, whichever came first.

RESULTS

Screening Tests at Initial CT Screening

Participants were mainly middle-aged males with a smoking history and had initial CT screening in 1993 or

Table 1. Characteristics of Participants, Proportion of Test Positives, and Detection Rate of Lung Cancer at Initial CT Screening

	Participants		Test Positives (%)			Lung Cancer	
	No.	%	Helical CT Scan	X-Ray	Cytology	No.	%
Sex							
Male	1,415	88	11.4	3.3	0.8	13	0.92
Female	196	12	12.2	4.6	0.5	1	0.51
Age at screening							
40-49 years	258	16	8.9	1.9	0.0	0	0.00
50-59 years	521	32	11.1	2.7	0.6	2	0.38
60-69 years	630	39	11.6	3.8	1.1	9	1.43
70-79 years	202	13	15.8	5.5	1.5	3	1.49
Smoking status							
Never smoked	225	14	15.1	1.3	0.4	1	0.44
Former smoker	395	25	11.1	3.3	0.8	4	1.01
Present smoker	991	62	10.9	3.9	0.9	9	0.91
Year of screening							
1993	640	40	5.8	3.8	0.3	5	0.78
1994	615	38	11.1	3.3	1.1	4	0.65
1995	156	10	18.6	3.8	2.6	2	1.28
1996-1998	200	12	26.0	2.5	0.0	3	1.50
Total	1,611	100	11.5	3.4	0.8	14	0.87

1994 (Table 1). Of 1,611 participants, 186 (11.5%), 55 (3.4%), and 13 (0.8%) tested positive on helical CT scan, chest x-ray, and sputum cytology, respectively, approximately three times higher for helical CT than for chest x-ray. The proportion of test positives for chest x-ray and sputum cytology varied according to age and smoking status, whereas the proportion for helical CT scan varied by age and year at screening, although none of the differences were statistically significant ($P > .05$). Variation for test positives in helical CT scan with the year of screening ($P = .001$) indicates that the checking criteria were not constant throughout the study period.

Screening Tests at Repeated CT Screening

Two or more examinations were repeated for 1,180 participants (Table 2). Participants were instructed to come to the clinic at 6-month intervals, but some did not. For simplicity, once an examination was conducted with an interval of less than 5 months or more than 7 months, then all the examinations conducted afterward were considered to be examinations at irregular intervals (1,897 examinations). Of 7,891 examinations, 721 (9.1%), 202 (2.6%), and 52 (0.7%) were positive by helical CT scan, chest x-ray, and sputum cytology, respectively. The proportion of test positives was slightly lower among those undergoing repeated screening than those undergoing initial screening by helical CT scan ($P = .003$) and chest x-ray ($P = .054$). The proportion of test positives for helical CT scan varied according to screening round ($P = .004$), but there were no clear trends. For chest x-ray, the proportion of test positives did not change with screening round ($P > .05$), whereas for sputum cytology, it decreased with screening round ($P = .003$). Similar to the initial CT scan screening, the proportion of test positives was higher in the older age group for all three modalities ($P = .001$, .006, and .02 for CT scan, x-ray, and cytology, respectively), but there was no substantial difference by sex and smoking status ($P > .05$). The proportion of test positives on helical CT scans was higher in later periods ($P = .001$), whereas the proportion for sputum cytology was lower in later periods ($P = .001$).

Diagnostic Workups at Initial Screening

At initial screening, 192 (11.9%) of 1,611 participants were asked to submit to additional diagnostic workups on the basis of various combinations of positive test results from three screening modalities (Table 3). No participants were asked for additional diagnostic workup solely on the basis of chest x-ray. One hundred eighty-six participants who had positive test results on helical CT scan were asked to have TSCT, and 181 participants underwent TSCT at an ALCA clinic, but five participants refused. Six participants had positive test results on sputum cytology alone, and for these six participants, sputum cytology was repeated at an ALCA clinic. On the basis of TSCT and repeated sputum cytology, 26 participants were referred to the National Cancer Center Hospital or National Cancer Center Hospital East because of suspected lung cancer lesions. Three of these cases were diagnosed as benign by repeated TSCT (including one thymoma operated afterward), one participant rejected additional diagnostic workup, and 22 partici-

Table 2. Characteristics of Participants, Proportion of Test Positives, and Detection Rate of Lung Cancer at Repeated CT Screening

	Examinations		Test Positives (%)			Lung Cancer	
	No.	%	Helical CT Scan	X-Ray	Cytology	No.	%
Screening round							
2nd	1,180	15	7.1	3.1	1.0	3	0.25
3rd	891	11	6.5	2.1	1.6	5	0.56
4th	774	10	9.8	2.8	0.9	2	0.26
5th	669	8	10.2	3.0	0.4	4	0.60
6th	595	8	8.7	2.4	0.5	2	0.34
7th	507	6	8.7	2.4	0.0	2	0.39
8th	445	6	10.1	1.6	0.0	0	0.00
9th-11th	933	12	9.3	2.3	0.5	1	0.11
Irregular	1,897	24	10.9	2.6	0.4	3	0.16
Sex							
Male	7,209	91	9.0	2.5	0.7	20	0.28
Female	682	9	10.7	2.8	0.4	2	0.29
Age at screening							
40-49 years	725	9	6.1	1.4	0.0	3	0.41
50-59 years	1,993	25	7.9	2.0	0.5	2	0.10
60-69 years	3,508	44	9.5	2.7	0.7	12	0.34
70-79 years	1,665	21	11.2	3.5	1.1	5	0.30
Smoking status*							
Never smoked	753	10	10.4	2.7	0.4	2	0.27
Former smoker	2,321	29	9.0	3.2	0.7	4	0.17
Present smoker	4,817	61	9.0	2.2	0.7	16	0.33
Year of screening							
1994	1,440	18	6.3	3.1	1.0	5	0.35
1995	1,830	23	9.2	3.0	1.3	5	0.27
1996	1,685	21	9.0	2.6	0.4	5	0.30
1997	1,524	19	10.0	2.1	0.1	2	0.13
1998	1,412	18	11.1	2.0	0.4	5	0.35
Total	7,891	100	9.1	2.6	0.7	22	0.28

*Fixed at initial screening.

pants had biopsies. For 16 patients who had positive findings on helical CT and no abnormality on sputum cytology at screening, the final diagnosis was based mainly on transbronchial lung biopsy (TBLB, CTPNB, or VATS), whereas in six patients who had positive test results on sputum cytology at screening, bronchoscopy was mainly used. Fourteen (61%) of 22 participants who had biopsies were diagnosed as having lung cancer. The final diagnosis was made by supraclavicular lymph node biopsy in one case (one cancer), biopsy through bronchoscopy in four cases (two cancers and two noncancers), biopsy through bronchoscopy in nine cases (five cancers and four noncancers), and CTPNB in two cases (two cancers). In the remaining six cases, VATS or open thoracotomy was performed solely on the basis of findings from TSCT; four cases were proven to be lung cancer and two cases to be benign lesions (one atypical adenomatous hyperplasia and one focal fibrosis). Predictive value for test positives was 7.0%, 9.1%, and 30.8% for helical CT scan, chest x-ray, and sputum cytology, respectively.

In total, 14 (0.87%) cases of lung cancer were detected among 1,611 participants (Table 1). The detection rate of lung cancer was higher in male participants, the older age group, and smokers than in female participants, the younger age group, and nonsmokers, but only the difference according to age group was marginally significant ($P = .08$). The detection rate seemed to be higher after 1995 than before 1994, but the difference was not statistically significant ($P > .05$).

Diagnostic Workups at Repeated Screening

At repeated screenings, 770 (9.8%) participants from 7,891 examinations were asked to undergo additional diagnostic workups on the basis of various combinations of test results (Table 3). Among 721 participants who had positive helical CT findings and were asked to have TSCT, 719 participants underwent TSCT at the ALCA clinic and two participants refused. For 49 participants who had positive findings for sputum cytology alone, sputum cytology was repeated at the ALCA clinic. On the basis of TSCT and repeated sputum cytology, 72 participants were referred to

Table 3. Additional Diagnostic Processes for Test Positives According to Screening Round and Combination of Test Results

	Initial CT Screening					Total	Repeated CT Screening					Total
Test results												
Helical CT scan	+	+	+	+	−		+	+	+	+	−	
X-ray	−	+	+	−	−		−	+	+	−	−	
Cytology	−	−	+	+	+		−	−	+	+	+	
Test positives	161	18	5	2	6	192	630	88	1	2	49	770
TSCT at ALCA	158	18	4	1	0	181	628	88	1	2	0	719
NCC referral	14	5	4	2	1	26	48	6	1	2	15	72
TSCT	2	1	0	0	0	3	18	3	0	0	0	21
Reject	0	0	0	1	0	1	1	0	0	0	1	2
Biopsy*	12 (8)	4 (2)	4 (3)	1 (0)	1 (1)	22 (14)	29 (16)	3 (2)	1 (1)	2 (0)	14 (3)	49 (22)
LN	0	0	1 (1)	0	0	1 (1)	0	0	0	0	0	0
BS	0	0	2 (1)	1 (0)	1 (1)	4 (2)	3 (0)	1 (1)	1 (1)	2 (0)	14 (3)	21 (5)
TBLB	4 (2)	4 (2)	1 (1)	0	0	9 (5)	1 (0)	2 (1)	0	0	0	3 (1)
CTTBLB	0	0	0	0	0	0	7 (4)	0	0	0	0	7 (4)
PNB, CTPNB	2 (2)	0	0	0	0	2 (2)	3 (1)	0	0	0	0	3 (1)
VATS	6 (4)	0	0	0	0	6 (4)	14 (10)	0	0	0	0	14 (10)
OPEN	0	0	0	0	0	0	1 (1)	0	0	0	0	1 (1)

Abbreviations: NCC, National Cancer Center; LN, Lymph node biopsy; BS, bronchoscopy; TBLB, transbronchial lung biopsy; CTTBLB, CT fluoroscopy-guided transbronchial lung biopsy; PNB, percutaneous needle biopsy; OPEN, open thoracotomy.

*Numbers in parenthesis indicate number of detected lung cancer cases.

the National Cancer Center Hospital or National Cancer Center Hospital East because of suspected lung cancer lesions. Of these, 21 participants were diagnosed with benign lesions by repeated TSCT, two participants rejected additional diagnostic workup, and 49 participants had biopsies. For those who had positive findings on helical CT scan and no abnormality on sputum cytology at screening, the final diagnosis was based mainly on VATS and CT fluoroscopy-guided transbronchial biopsy. For 15 cases, VATS or open thoracotomy was performed solely on the basis of findings from TSCT, 11 cases were proven to be lung cancer, and four cases were proven to be other lesions (two atypical adenomatous hyperplasias, one focal fibrosis, and one metastasis from colon cancer). Twenty-two (45%) of the 49 participants who had biopsies had lung cancer. Predictive value for test positives was 2.6%, 1.5%, and 7.7% for helical CT scan, chest x-ray, and sputum cytology, respectively.

In total, 22 (0.28%) cases of lung cancer were detected out of 7,891 examinations (Table 2). The detection rate of lung cancer became slightly lower with additional screening rounds, but no substantial difference in sex, age, or smoking status was observed.

Characteristics of Screen-Detected Lung Cancer

Table 4 lists the distribution of characteristics for screen-detected lung cancers by screening round and method of detection. Of the 14 lung cancer cases detected at initial screening, eight (57%) were detected by helical CT scan alone, two (10%) by both helical CT and chest x-ray, one (7%) by sputum cytology alone, and three (21%) by all three methods. At repeated screenings, 16 (73%) cases were detected by helical CT scan alone, two (10%) by helical CT scan and chest x-ray, three (14%) by sputum cytology alone, and one (5%) by all three methods. The proportion of cases detected by helical CT scan alone tended to be higher and the proportion detected by all three methods tended to be lower in repeated screenings than in initial screenings, but the difference was not statistically significant ($P > .05$).

For both initial and repeated screenings, cases detected by helical CT scan alone were predominantly peripherally located adenocarcinomas of less than 2 cm in diameter and stage IA, whereas those detected by sputum cytology alone were centrally located squamous cell carcinomas of stage IA. Those detected by both helical CT scan and chest x-ray were peripherally located tumors of various histologic types, and those detected by all three methods tended to be larger in diameter and of more advanced stage. When compared with initial screening, tumors detected at repeated screenings tended to include fewer adenocarcinomas and be smaller in diameter and earlier in stage distribution, although all the differences were not statistically significant ($P > .05$). The mean diameter was smaller for tumors detected at repeated screening (14.6 mm) than initial screening (19.8 mm), but this was also not statistically significant ($P > .05$). Tumors of less than 9 mm in diameter were detected only at repeated screening. On the contrary, theproportion of tumors treated surgically was slightly lower among those detected at repeated screening, although the difference was not significant ($P > .05$).

Table 4. Characteristics of Screen-Detected Lung Cancer by Screening Round at Detection and Combination of Test Results

	Initial CT Screening				Total		Repeated CT Screening				Total	
					No.	%					No.	%
Test results												
Helical CT scan	+	+	+	−			+	+	+	−		
X-ray	−	+	+	−			−	+	+	−		
Cytology	−	−	+	+			−	−	+	+		
Location												
Hilar	0	0	1	1	2	14	0	0	0	3	3	14
Peripheral	8	2	2	0	12	86	16	2	1	0	19	86
Histologic type												
Adeno	8	1	1	0	10	71	14	0	0	0	14	64
Squamous cell	0	1	2	1	4	29	2	2	0	3	7	32
Small cell	0	0	0	0	0	0	0	0	1	0	1	5
Tumor diameter												
≤ 9 mm	0	0	0	0	0	0	5	0	0	0	5	23
10-19 mm	6	1	1	0	8	57	10	1	0	0	11	50
20-29 mm	2	1	0	0	3	21	0	1	0	0	1	5
≥ 30 mm	0	0	2	0	2	14	1	0	1	0	2	9
NA	0	0	0	1	1	7	0	0	0	3	3	14
Stage												
IA	7	2	0	1	10	71	15	0	0	3	18	82
IB	0	0	1	0	1	7	0	0	0	0	0	0
IIA	0	0	0	0	0	0	0	1	0	0	1	5
IIIA	1	0	1	0	2	14	0	1	0	0	1	5
IIIB	0	0	1	0	1	7	1	0	0	0	1	5
IV	0	0	0	0	0	0	0	0	1	0	1	5
Treatment												
Surgery	8	2	2	0	12	86	16	1	0	0	17	77
Pneumonectomy	0	0	1	0	1	7	0	0	0	0	0	0
Lobectomy	8	1	1	0	10	71	7	1	0	0	8	36
Segmentectomy	0	1	0	0	1	7	4	0	0	0	4	18
Partial resection	0	0	0	0	0	0	5	0	0	0	5	23
Endoscopic therapy*	0	0	0	1	1	7	0	0	0	2	2	9
Cx or Rx+	0	0	1	0	1	7	0	1	1	1	3	14
Total	8	2	3	1	14	100	16	2	1	3	22	100

Abbreviations: NA, not applicable; Cx or RX, chemotherapy or radiotherapy.
*Radiation or hyperthermal therapy via endoscopy.

Survival for Screen-Detected Lung Cancer

Of 36 lung cancer cases detected in the screening, eight patients died before February 1, 2000. Of these eight patients, three with stage III or IV disease died of lung cancer, two with stage IA disease died of pulmonary infection 6 months and 9 months after surgery without recurrence, two with stage IA disease died of hepatic failure attributable to liver cirrhosis and an unknown cause (the patient was 82 years of age at the time of death) without recurrence, and one with stage IIIa disease died suddenly, probably because of a cardiac event, without recurrence. The mean follow-up duration for censored cases was 3.7 years. The overall 5-year survival rate was 71% (95% confidence interval [CI], 52.4% to 89.6%). If three deaths attributable to other causes are treated as censored, the 5-year survival rate becomes 85.5% (95% CI, 73.7% to 97.2%). When cases were additionally divided by screening round, the overall 5-year survival rate seemed to be higher for those detected at initial screening (76.2%; 95% CI, 52.2% to 100%) than repeated screening (64.9%; 95% CI, 33.5% to 96.3%), although the difference was not statistically significant ($P > .05$) (Fig 1).

Figure 2 illustrates the survival curve when cases are classified by stage, tumor diameter (four cases detected by sputum cytology alone were excluded), histologic type, and mode of detection. A higher survival rate was observed for earlier stage ($P = .01$), smaller diameter ($P = .005$), and adenocarcinomas ($P = .02$). With regard to mode of detection, cases detected by all three methods had a lower survival rate than those detected by other modes of detection, but the difference was not statistically significant.

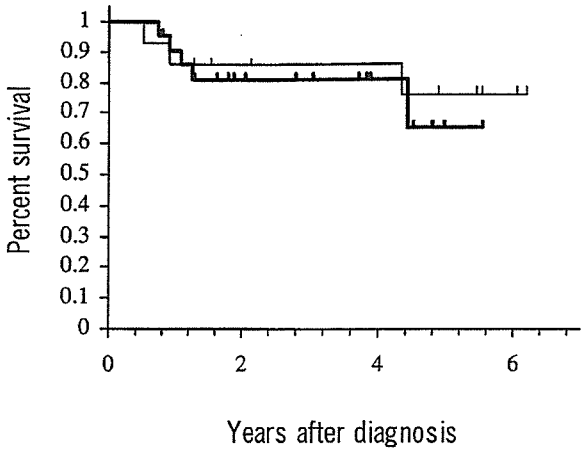

Fig 1. Cumulative survival curves for patients with lung cancer detected at initial screening (thin line; n = 14)and repeated screening (thick line, n = 22).

DISCUSSION

This study presents the findings from both initial and repeated screenings for lung cancer using low-dose helical CT scanning, conventional chest x-ray, and sputum cytology simultaneously. Among 14 cases detected at initial screening, proportion of stage I disease was 78.6% and mean tumor diameter was 19.8 mm, which are consistent with previous studies.[11-13] The detection rate at initial screening in the present study (0.9%) was lower than in the ELCAP study (2.7%) but higher than in the study by Sone (0.4%). Because the lung cancer incidence is approximately 2 times higher in the United States than in Japan and half of the participants in Sone's study were female, these differences seem to be within a reasonable range. In the present study, the detection rate by helical CT scan was 2.6 times higher than by chest x-ray (13 *v* five), which is almost the same as in the ELCAP study (four times higher) but lower than in Sone's study (19 times higher). This may be partly because miniature chest fluorophotography was used in Sone's study, whereas in ELCAP and the present study, direct chest x-ray was used.

When screenings were repeated, detection rate (0.3%) was one third that of initial screening (0.9%), and the proportion of stage I disease was 81.8% and mean tumor diameter was 14.6 mm, which seemed better than in initial screening, although the difference was not statistically significant. In Sone's study, no difference was observed for detection rate between initial (0.4%) and repeated screening (0.4%), and the proportion of stage I was lower in repeated screening (86%) than initial screening (100%), which is not consistent with the present study, but mean tumor diameter appeared smaller in repeated screening (12.0 to 12.1 mm) compared with initial screening (15.1 mm), which is consistent with the present study.[12]

The 5-year survival rate for 36 patients with screen-detected lung cancer was 71%, clearly higher than that of patients detected by conventional chest x-ray, which is reported to be around 30% to 40%.[7] When divided into initial and repeated screening, the 5-year survival rate was

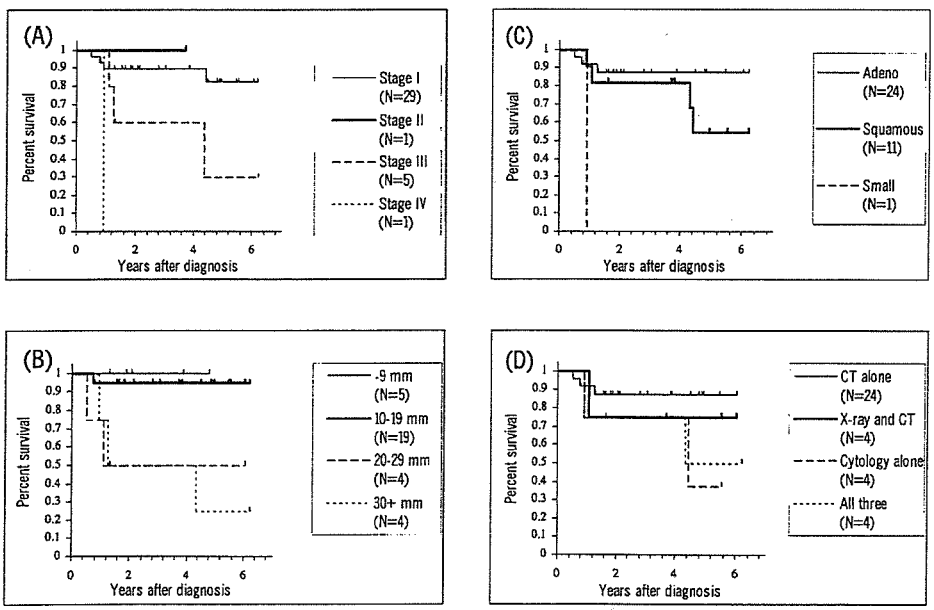

Fig 2. Cumulative survival curves for patients with screen-detected lung cancers by stage (A), tumor diameter (B), histologic type (C), and mode of detection (D).

76.2% and 64.9%, respectively, slightly lower among those detected at repeated screening, although the difference was not statistically significant. Theoretically, lung cancer detected at initial CT screening inevitably included some cases that were already advanced, but slow-growing tumors with a long preclinical detectable phase tend to be oversampled. On the other hand, cases detected at repeated screening will include less advanced cases, but the proportion of rapidly growing cancers will be higher than at initial screening. Survival will be affected by the balance of these factors, and the slightly better survival for patients detected at initial screening may indicate that growth speed is more influential. However, we should remember that because approximately half of the participants in this study had already been screened twice a year by chest x-ray and sputum cytology before initial CT screening, cases of advanced cancer were already less prevalent at the initial screening.

The proportion of test positives with helical CT scan was three to four times higher than the proportion with chest x-ray for both initial and repeated screenings. Although the proportion of test positives with helical CT scan is expected to be much lower at repeated screening than initial screening, this was not the case in this study. When the proportion of test positives at initial screening was divided by calendar year, it became higher in the later period. This indicates that the criteria for test positives with helical CT scan had changed during the study period. In 1993, when CT screening was introduced, there was limited knowledge as to what characteristics of CT images were related to malignancy for small nodules of less than 2 cm. Thereafter, through review of previous CT images for accumulated series of screen-detected cases, more subtle abnormalities that seemed to be related to malignancy came to be checked in the later screenings. The reasons for detection failures were retrospectively evaluated and reported in detail elsewhere.[16] In this case series, in a review of screening CT images from before the detection for 19 cases of lung cancer that were detected at repeated screening from abnormalities on helical CT scan, nodules were identified for 15 cases (82%) in the previous screening CT images; these were from the initial screening in eight cases and the second or later screening in seven cases. Therefore, comparisons of test positive and detection rates between the initial and repeated screenings should be interpreted with caution in the present study. Preferably, these should be reevaluated in another series using fixed criteria for test positives. The proportion of test positives with helical CT screening varied to the great extent in other studies, 23% in ELCAP,[13] 3.5% to 5.1% in the study by Sone,[12] and 9.1% to 11.5% in the present study, which clearly indicates that standardized criteria for test positives are urgently needed.

Of 186 participants who had positive findings on helical CT scan at initial screening, 21 participants (11.3%) underwent biopsies in this study. In the ELCAP study, 31 (13.3%) of 233 patients who had positive findings on helical CT scan had biopsies, which is almost the same level as in this study. Of 13 cases of lung cancer that were detected at initial CT screening based on positive findings on helical CT scan in this study, four (31%) cases were diagnosed by VATS. In the ELCAP study,[13] nine (33%) of 27 cases of lung cancer were diagnosed by VATS, whereas in Sone's study,[11] 10 (53%) of 19 lung cancers were diagnosed by VATS or open thoracotomy. Of the cases detected at repeated CT screenings in the present study, 11 (58%) of 19 lung cancer cases for which there were positive findings on helical CT scan were diagnosed by VATS or open thoracotomy. The choice of diagnostic procedure for small peripheral nodules varies by institution, and future research is needed to standardize the procedures.

Regarding the choice of treatment in this study, 10 (83%) of 12 patients with lung cancer detected at initial screening and treated surgically underwent lobectomy, whereas for those detected at repeated screening, eight (47%) of 17 patients treated surgically underwent lobectomy and the remaining nine (53%) underwent limited resection. These nine patients had peripherally located tumors that were less than 2 cm (seven adenocarcinomas and two squamous cell carcinomas), and six of seven adenocarcinomas were classified to be Noguchi's type A or B, which are considered in situ peripheral adenocarcinoma.[17] On the other hand, in the ELCAP study, 24 (96%) of 25 patients with lung cancer treated surgically underwent lobectomy. This reflects the different treatment options between the United States and Japan; ie, Japanese surgeons may intentionally choose limited resection for T1N0M0 small-cell lung cancer,[18] whereas in the United States, lobectomy is the treatment of choice even for small-cell lung cancer.[19] This is another point that should be standardized through additional research.

This study showed that the survival rate of patients with lung cancer detected by CT screening was high, which strongly indicates that CT screening has great potential for mortality reduction. However, because the preclinical detectable phase for lung cancers detected by helical CT scan must be longer than that for cancers detected by chest x-ray, the survival analysis will be influenced to a greater extent by lead-time bias and length-biased sampling. This indicates that the magnitude of mortality reduction estimated simply from survival comparison is inevitably overestimated, and studies that directly measure lung cancer mortality are essential. We are planning to measure lung cancer mortality rates among all screening participants, taking into account

deaths from lung cancer that could not be detected by screening as well as deaths from lung cancer detected by screening.

On the other hand, there are several potential harmful events attributable to helical CT screening. First, a higher proportion of test positives with helical CT scan (9.1% to 11.5%) than with chest x-ray (2.6% to 3.4%) was observed in this study, which leads to a higher proportion of false positives and results in unnecessary diagnostic workups. Moreover, 35 of 71 patients who had biopsies in this study had negative results. Of these, 17 patients had biopsies because of an abnormality on helical CT scan alone. Although there were no severe adverse events attributable to biopsy in this series, the procedure itself tends to be aggressive and cause discomfort and anxiety. Because this is a preliminary project, however, the frequency of negative biopsy tended to be high, and less aggressive workups should be developed in the future studies. Second, among patients who were diagnosed as having stage I lung cancer, two patients died of postsurgical infection 6 and 9 months after diagnosis. Because death attributable to postsurgical infection among patients with lung cancer is reported to be less than .5% in routine practice in the National Cancer Center Hospital, this experience may be accidental because of the small number of cases in this series and not applicable to other situations. Finally, the high detection rate and high proportion of adenocarcinoma imply overdiagnosis. Although we cannot identify these overdiagnosed cases at the individual level, it is possible that a certain proportion of screen-detected cases were overdiagnosed and received unnecessary treatment. These benefits and harmful events should be evaluated in a quantitative manner in larger trials before deciding whether lung cancer screening using helical CT scan can be recommended for the general population.

The accumulated evidence indicates that the major cause of lung cancer is cigarette smoking. Considering the fact that the prevalence of present smokers is still high (57.5% in 1996) among males and is now increasing in younger females,[20] it is evident that controlling smoking should be the first priority in any lung cancer control strategy. Additional measures should be taken, however, because the risk of lung cancer remains at a high level even after cessation of smoking for a long time,[21] the attributable risk percent due to cigarette smoking is low in Japan mainly because of the high proportion of adenocarcinoma,[22] and the proportion of adenocarcinoma is now increasing in Japan similar to other countries.[20] Low-dose helical CT screening has potential to improve screening efficacy in terms of reducing lung cancer mortality. It is urgent that its efficacy in terms of reducing mortality or incidence of advanced lung cancer should be evaluated with appropriate research methods.

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