24 Ajani JA, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Marabotti C and Van Cutsem E; V-325 Study Group: Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal cancer adenocarcinoma: the V-325 Study Group. J Clin Oncol *25(22)*: 3205-3209, 2007.

25 Ridwelski K, Fahlke J, Kettner E, Schmidt C, Keilholz U, Quietzsch D, Assmann M, Stauch M, Zierau K and Lippert H: Docetaxel-cisplatin (DC) *versus* 5-fluorouracil-leucovorin-cisplatin (FLC) as first-line treatment for locally advanced or metastatic gastric cancer: Preliminary results of a phase III study. Proc Am Soc Clin Oncol Abstr *26*: 4512, 2008.

26 Jin M, Lu H, Li J, Shen L, Chen Z, Shi Y, Song S, Qin S, Liu J and Ouyang X: Randomized 3-armed phase III study of S-1 monotherapy *versus* S-1/CDDP (SP) *versus* 5-FU/CDDP (FP) in patients (pts) with advanced gastric cancer (AGC): SC-101 study. Proc Am Soc Clin Oncol Abstr *26*: 4533, 2008.

27 Bang Y, Chung H, Sawaki A, Xu J, Shen L, Lipatov O, Park SR, Gangadharan VP, Advani SH and Kang YK: HER2-positivity rates in advanced gastric cancer (GC): Results from a large international phase III trial. Proc Am Soc Clin Oncol Abstr *26*: 4526, 2008.

Received September 23, 2008
Revised December 18, 2008
Accepted January 13, 2009

Lung Cancer 67 (2010) 318–324

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

The adenocarcinoma-specific stage shift in the Anti-lung Cancer Association project: Significance of repeated screening for lung cancer for more than 5 years with low-dose helical computed tomography in a high-risk cohort☆

Nobuhiko Seki[a,*], Kenji Eguchi[a], Masahiro Kaneko[b], Hironobu Ohmatsu[c], Ryutaro Kakinuma[d], Eisuke Matsui[e], Masahiko Kusumoto[f], Takaaki Tsuchida[b], Hiroyuki Nishiyama[g], Noriyuki Moriyama[d]

[a] Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan
[b] Division of Endoscopy, National Cancer Center Hospital, Tokyo, Japan
[c] Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan
[d] Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan
[e] Anti-lung Cancer Association, Tokyo, Japan
[f] Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan
[g] Division of Thoracic Surgery, Social Health Insurance Medical Center, Tokyo, Japan

ARTICLE INFO

Article history:
Received 20 January 2009
Received in revised form 25 April 2009
Accepted 27 April 2009

Keywords:
Stage shift
Size shift
Repeated screening
Low-dose helical computed tomography
High-risk cohort
Invasive lung adenocarcinoma

ABSTRACT

Background: We investigated whether a stage shift occurs during long-term repeated screening for lung cancer with low-dose helical computed tomography (LDCT) in a high-risk cohort.
Methods: A total of 2120 subjects (mean age, 63 years; 87% male and 83% smokers) were continuously recruited and underwent repeated screening with LDCT from 1993 through 2004.
Results: Nineteen lung cancers were detected at baseline examinations (prevalence cancers), and 57 lung cancers were detected at subsequent examinations (incidence cancers). For both prevalence cancers and incidence cancers, adenocarcinoma (74% and 63%, respectively), especially invasive adenocarcinoma (42% and 23%, respectively), was the most common histological diagnosis, and stage IA was the most common pathological stage (58% and 79%, respectively). The detection rate of incidence cancers other than bronchioloalveolar carcinoma became significantly higher after 5 years of LDCT examinations ($r = 0.50$, $P = 0.020$). Moreover, both the percentage of cancers of stage II–IV and tumor size became significantly lower for invasive adenocarcinoma after 5 years of LDCT examinations ($r = -0.77$, $P = 0.007$ and $r = -0.60$, $P = 0.029$, respectively).
Conclusions: Repeated screening for more than 5 years might demonstrate the efficacy of LDCT screening for lung cancer through an adenocarcinoma-specific stage shift.
© 2009 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Lung cancer is considered as an appropriate disease for screening because it is the leading cause of cancer death worldwide, symptomatic disease is generally lethal, localized disease can be managed curatively, and high-risk cohorts can be defined on the basis of tobacco consumption [1]. However, screening with chest X-ray films or sputum cytological examination has failed to reduce lung-cancer mortality rates in randomized, controlled trials [2–6].

Low-dose helical computed tomography (LDCT) is a promising screening method because a higher percentage of asymptomatic, X-ray–invisible, or stage IA lung cancers (mostly adenocarcinoma) are found with baseline or repeated computed tomography (CT) examinations than with conventional screening methods [7–11]. In fact, according to the results of the International Early Lung Cancer Action Program, the 10-year survival rate for all patients with lung cancer was 80% regardless of stage or treatment [12]. If the cancer was in clinical stage I and was promptly resected, the 10-year survival rate was 92%. However, because large, randomized, controlled trials of LDCT screening are still in progress [13,14], whether LDCT screening reduces lung-cancer mortality rates remains uncertain. Although mortality data are needed to determine whether LDCT screening is effective, indirect evidence for a possible mor-

Abbreviations: CT, computed tomography; LDCT, low-dose helical computed tomography; BAC, bronchioloalveolar cell carcinoma; ALCA, Anti-lung Cancer Association.

☆ This work was presented as an oral presentation at the 42nd Annual Meeting of the American Society of Clinical Oncology, 2006, Atlanta, GA.

* Corresponding author. Tel.: +81 3 3964 1211x1587; fax: +81 3 3964 7094.
E-mail address: nseki@med.teikyo-u.ac.jp (N. Seki).

0169-5002/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2009.04.016

tality reduction can be obtained from a "stage shift," an increase in the detection rate of putatively curable early-stage lung cancers and a concomitant decrease in incurable late-stage cancers, leading to a decrease in the lung-cancer-specific mortality rate [15], which can be used as a surrogate endpoint even in a nonrandomized, uncontrolled trial.

Results of many single-armed, uncontrolled trials of annual screening with LDCT have been published [12,16–22]. However, none of these trials has documented a stage shift, perhaps because the number of lung cancers detected with repeated screening was too small (range, 4–35 cancers) or because the duration of repeated screening (range, 1–4 years) was too short. Thus, to determine whether a true stage shift occurs, a longer-term LDCT study with a larger number of detected lung cancers is required.

Furthermore, studies performed to date have not considered the effect of histological classification on the stage shift. Recent LDCT trials suggest that an increase in early-stage lung cancer might not be accompanied by a decrease in late-stage lung cancer (i.e., overdiagnosis) [15] and that the presence of localized bronchioloalveolar cell carcinoma (BAC) and mixed adenocarcinoma with BAC component might reflect overdiagnosis bias, although adenocarcinoma without BAC component behaves as aggressively as do other non-small cell carcinomas [23].

In the present study, on the basis of an update of the Anti-lung Cancer Association (ALCA) project [16], we investigated whether a stage shift occurs when lung cancers are stratified by histological subtype during long-term repeated LDCT screening for lung cancer in a high-risk cohort comprising mostly male smokers in their 60s.

2. Patients and methods

2.1. Study population

From September 1993 through August 2004, LDCT screening was performed semiannually by the ALCA in Tokyo. The ALCA is a for-profit organization established in 1975 to thoroughly screen for lung cancer in dues-paying participants. Because the participants are continuously recruited from members of the general population 40 years or older with a history of smoking (>20 pack-years) or a single episode of hemoptysis within the past 6 months, most participants are male smokers in their 60s. Written informed consent was obtained from each participant at baseline CT screening.

2.2. Screening procedures

Screening was performed as described previously [16]. Briefly, at baseline screening a simple questionnaire about smoking history and symptoms was completed, and LDCT, chest radiography (posterior–anterior position), and sputum cytological examination pooled for 3 days were performed. Participants were invited twice a year by mail after the baseline screening to repeat the same screening procedures. The CT scanner (TCT-900S Superhelix, Toshiba Medical, Tokyo, Japan) was used under the following conditions: 120 kVp, 50 mA, 10-mm collimation, 1 rotation of the X-ray tube per second, and a table speed of 20 mm/s (pitch, 2:1). Image construction was performed with 180° linear interpolation at 1-cm intervals. All CT images were examined by 2 of 7 readers (radiologists or thoracic physicians).

2.3. Evaluation of detected lung cancers

The staging and the histological classification of detected lung cancers were performed according to the International System for Staging Lung Cancer [24] and the World Health Organization lung tumor classification system [25], respectively. Cancers were classified as adenocarcinoma, squamous cell carcinoma, other non-small cell carcinoma, or small cell carcinoma. Moreover, adenocarcinoma was subclassified on the basis of the histological growth pattern as localized BAC, mixed adenocarcinoma with BAC component, and adenocarcinoma without BAC component (invasive adenocarcinoma).

Lung cancers detected at baseline screening were considered "prevalence cancers," whereas those newly detected at subsequent repeated LDCT screening examinations were considered "incidence cancers." Furthermore, lung cancers diagnosed outside our semiannual LDCT screening procedure within a screening interval were defined as "interval cancers," whereas those diagnosed outside our screening procedure after a period longer than the screening interval (due to refusal by ALCA participants) were not classified as "interval cancers." The presence or absence of interval cancers was confirmed through questionnaire when participants were invited twice a year by mail after the baseline screening to repeat the same screening procedures.

Excluded from analysis were 6 cases of hilar lung cancer detected on sputum cytological examinations or on evaluation of hemoptysis but not with LDCT.

2.4. Statistical analysis

Statistical P values for the differences in percentages and means were evaluated with the χ^2 test and the t-test, respectively. Survival curves were estimated with the Kaplan–Meier method, with survival time defined as starting from when microscopic evidence for malignancy was first obtained to the date of death or November 25, 2005, whichever came first. Differences in survival rates between groups were evaluated with the log-rank test. Multivariate Cox proportional hazards model analysis was performed to identify significantly independent prognostic factors for overall survival. Linear regression analysis with the least-squares method was performed for the relationships between groups. All calculations were performed with Stat View 5.0J software (SAS Institute Inc., Cary, NC). P values less than 0.05 were considered to indicate statistical significance.

3. Results

3.1. Characteristics of participants

During the study period, 20,113 LDCT scans were performed for 2120 ALCA participants (mean age, 63 years; 87% male and 83% smokers), and 76 peripheral lung cancers were detected. Participants underwent LDCT screening a median number of 7 times (range, 1–22 times; Fig. 1A); a median number of 3 lung cancers were detected in each ordinal screening (range 0–9; Fig. 1B); a median of 3.5 years had passed since a participant's baseline screening (range, 0–10.5; Fig. 1C); and a median of 0.5 years had passed since a participant's previous screening (range, 0–10.0; Fig. 1D). Of the 2120 ALCA participants, 243 (11%) underwent only baseline LDCT screening, 753 (36%) underwent repeated LDCT screening for more than 5 years, and 322 (15%) underwent repeated LDCT screening for more than 10 years.

3.2. Comparison of results between baseline and subsequent LDCT screenings

The characteristics of all participants and of participants who underwent at least 1 subsequent LDCT screening examination are shown in Table 1. No significant difference was observed between these groups in terms of age, sex, or smoking status at baseline. However, the detection rate of lung cancer was significantly higher

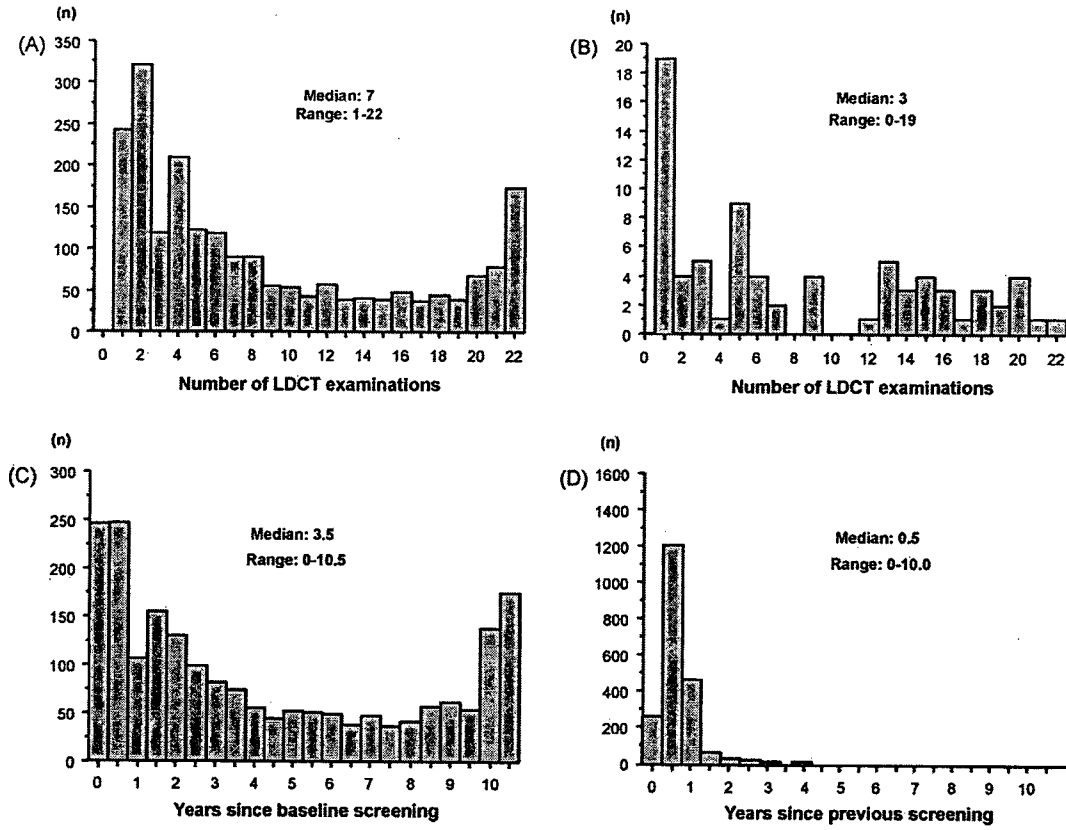

Fig. 1. Characteristics of repeated LDCT screening. (A) Distribution of the number of times participants underwent repeated LDCT screening (*X* axis indicates the number of LDCT examinations, and *Y* axis indicates the number of participants in each ordinal screening). (B) Distribution of the number of lung cancers detected in screening examinations grouped by ordinal number (*X* axis indicates the number of LDCT examinations, and *Y* axis indicates the number of lung cancers detected in each ordinal screening.). (C) Distribution of years since participants had undergone baseline screening (*X* axis indicates years since baseline screening, and *Y* axis indicates the number of participants in each ordinal screening period). (D) Distribution of years since participants had undergone previous screening (*X* axis indicates years since previous screening, and *Y* axis indicates the number of participants in each ordinal year since previous screening).

at baseline screening (0.90%: 19 prevalence cancers in 2120 participants) than at repeated screenings (0.32%: 57 incidence cancers in 1877 participants; $P<0.001$).

The characteristics of 76 patients with lung cancers detected at screening examinations are summarized in Table 2. The 19 patients with prevalence cancers and the 57 patients with incidence cancers did not differ in age, sex, or smoking status. However, both the percentage of positive chest X-ray films (53% vs. 16%, $P=0.004$) and tumor size (24 mm vs. 17 mm, $P=0.018$) were significantly less in patients with incidence cancers than in patients with prevalence cancers. Although neither histological diagnosis nor pathological stage differed significantly between patients with prevalence cancers and those with incidence cancers, in both groups of patients adenocarcinoma (74% and 63%, respectively), especially invasive adenocarcinoma (42% and 23%, respectively), was the most common histological diagnosis and stage IA was the most common pathological stage (58% and 79%, respectively).

Table 1
Characteristics of participants.

	Baseline LDCT	Repeated LDCT	*P*
No. of participants	2120	1877	
Age (years, mean ± SD)[a]	63 ± 11	64 ± 11	NS
Sex (% male)	87	88	NS
Smoking (% smokers)[a]	83	84	NS
No. of detected lung cancers	19	57	
No. of screenings	2120	17993	
Detection rate (%)	0.90	0.32	<0.001

[a] Fixed at baseline screening.

Survival rates were compared between patients with prevalence cancers and those with incidence cancers. The 5- and 10-year survival rates were 84.5% and 84.5%, respectively, in patients with incidence cancers ($n=57$) and were 68.7% and 38.1%, respectively, in

Table 2
Clinicopathological characteristics of patients with screening-detected lung cancer.

	Prevalence cancers	Incidence cancers	*P*
No. of patients	19	57	
Age (years, mean ± SD)[a]	66 ± 8	69 ± 9	NS
Sex (% male)	84	86	NS
Smoking (% smokers)[a]	89	93	NS
Positive X-ray (%)	53	16	0.004
Tumor size (mm, mean ± SD)	24 ± 15	17 ± 10	0.018
Histological type			NS
Adenocarcinoma	14 (74%)	36 (63%)	
BAC	2	11	
Adenocarcinoma with BAC	4	12	
Invasive adenocarcinoma	8	13	
Squamous cell carcinoma	4	12	
Other non-small cell carcinoma	1	5	
Small cell carcinoma	0	4	
Pathological stage			NS
IA	11 (58%)	45 (79%)	
IB	2	3	
II	0	3	
III	5	4	
IV	1	2	

BAC: bronchioloalveolar cell carcinoma.
[a] Fixed at baseline screening.

patients with prevalence cancers ($n = 19$). No significant difference was observed between the groups (log-rank test, $P = 0.208$). Multivariate analysis with the Cox proportional hazards model found that only pathological stage ($P = 0.006$) was an independent prognostic factor for overall survival. The risk of death in patients with stage II–IV disease was increased 8.26-fold (95% confidence interval, 1.85–37.03). In contrast, age, sex, smoking status, tumor size, histological subtype (presence of BAC component), and screening type (baseline vs. repeated) were not independent prognostic factors.

No interval lung cancers were detected outside our semiannual LDCT screening procedure within a screening interval. However, 3 lung cancers were detected outside our screening procedure after a period longer than the screening interval. For these 3 lung cancers, the histological classification and stage, screening period from baseline to previous screening, and time since previous screening, respectively, were: invasive adenocarcinoma, stage IV, 5 years, and 4 years; squamous cell carcinoma, stage IA, 3.5 years, and 5 years; and other non-small cell carcinoma, stage II, 5 years, and 1.5 years.

3.3. The presence of an increased detection rate, a stage shift, and a size shift

The detection rate of all 57 incidence cancers was positively correlated with the duration of repeated screening ($r = 0.50$, $P = 0.020$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2A). In contrast, the detection rate of localized BAC showed a weak negative correlation with the duration of repeated screening ($r = -0.38$, $P = 0.086$). Other histological subtypes, including invasive adenocarcinoma, showed no significant correlations.

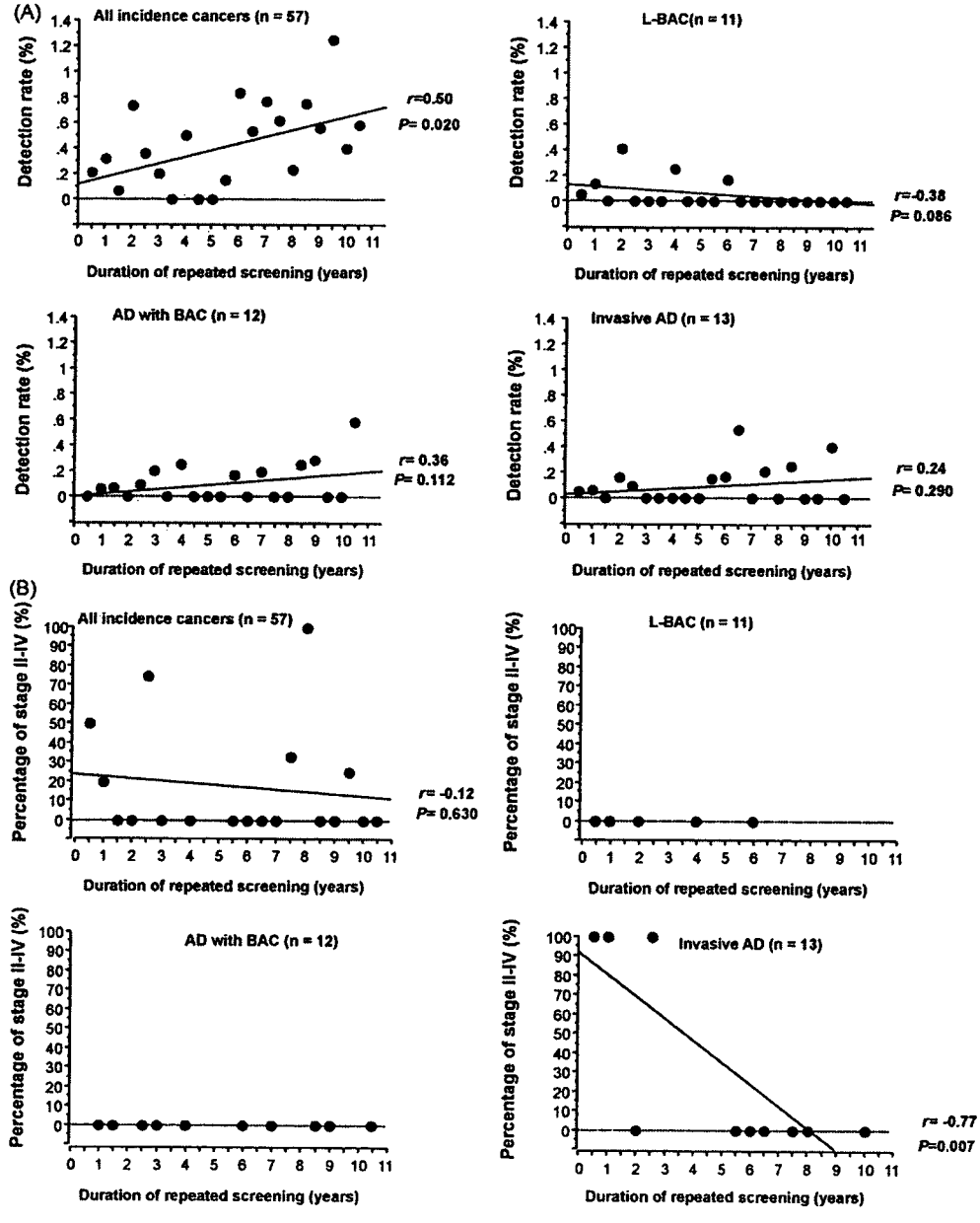

Fig. 2. Relationship between the duration of repeated screening and characteristics of incidence lung cancers. Correlations between the duration of repeated screening and the detection rate (A), the proportion of stage II–IV disease (B), and tumor size (C) were evaluated according to histological subtypes. L-BAC, localized bronchioloalveolar carcinoma; AD, adenocarcinoma.

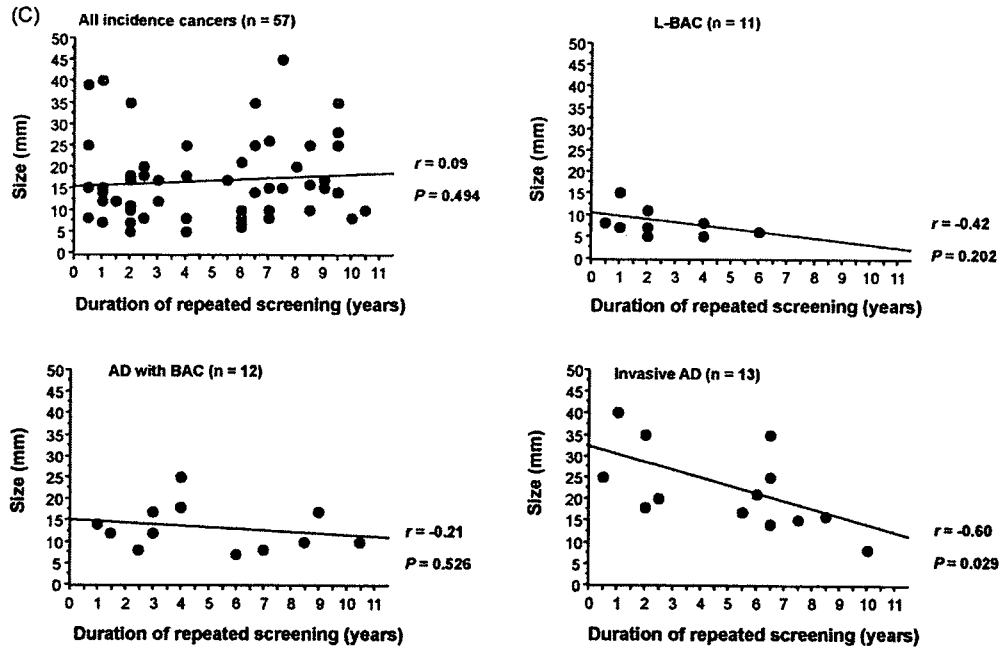

Fig. 2. (*Continued*).

Although the percentage of stage II–IV disease among all 57 incidence cancers was not correlated with the duration of repeated screening ($r=-0.12$, $P=0.630$), the percentage of stage II–IV disease among invasive adenocarcinoma was negatively correlated with the duration of repeated screening ($r=-0.77$, $P=0.007$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2B). In contrast, the percentage of stage II–IV disease among both localized BAC and mixed adenocarcinoma with BAC component remained 0% regardless of the duration of repeated screening. Neither squamous cell carcinoma ($r=-0.12$, $P=0.767$) nor small cell carcinoma ($r=-0.67$, $P=0.999$) showed a significant correlation between the percentage of stage II–IV disease and the duration of repeated screening.

Similarly, although tumor size among all 57 incidence cancers was not correlated with the duration of repeated screening ($r=-0.12$, $P=0.630$), the tumor size of invasive adenocarcinoma was negatively correlated with the duration of repeated screening ($r=-0.60$, $P=0.029$) but remained uncorrelated if the duration of repeated screening was 5 years or less (Fig. 2C). In contrast, other histological subtypes showed no significant correlations.

4. Discussion

In the present study involving 10 years of semiannual LDCT screening in a continuously recruited cohort comprising mostly male smokers in their 60s, increased detection rates were observed for lung cancers other than localized BAC. Moreover, both a stage shift and a size shift were observed for invasive adenocarcinoma of the lung. This report is, to our knowledge, the first to document the significance of long-term repeated screening for lung cancer with LDCT in a high-risk cohort.

Recently, Bach et al. have demonstrated that screening for lung cancer with LDCT may not meaningfully reduce the risk of advanced lung cancer or death from lung cancer [26]. Their conclusion was based on a model predicting deaths from lung cancer applied to 3 studies of LDCT screening in asymptomatic population at risk for lung cancer [20–22]. However, most importantly, the screening period of each of the 3 studies was less than 5 years. If each screening period had been 5 years or longer, Bach et al. might have instead confirmed a decrease in the lung-cancer-specific mortality rate. The screening period is important for other cancers for which the efficacy of screening has already been demonstrated; for example, the period of screening with fecal occult blood for colorectal cancer has been shown to be the important factor in a large randomized, controlled trial [27]. The initial protocol of the study specified 5 years of screening; however, the Policy and Data Monitoring Group recommended that screening be reinstituted because of the lack of statistical power regarding the mortality rate through 5 years of screening in the population. Screening then continued for 10 years, resulting in the finding of a lower mortality rate in screened subjects. Furthermore, meta-analysis of 8 randomized, controlled trials of screening mammography has demonstrated a statistically significant reduction in mortality rate among women aged 40–49 years at entry through screening for 10 years [28]. In particular, in 1 of these studies, the mortality rate from breast cancer was similar in screened group and the control group during the first 8 years but then became lower in screened group after 8 years [29]. Therefore, the efficacy of repeated screening for lung cancer might be demonstrated only with a long screening period.

To determine whether LDCT screening can reduce the mortality rate from lung cancer, a large, randomized, controlled trial has been started in the United States (National Lung Screening Trial) [13]. In this trial, 50,000 subjects at high risk for lung cancer were randomly assigned to undergo screening with chest radiography or LDCT at baseline and then annually for 2 additional years with annual telephone follow-up thereafter. Accrual was completed in February 2004, and final analyses are scheduled to be completed in 2009. In addition, a Dutch-Belgian randomized trial (NELSON trial) comparing CT screening with no screening at baseline and then 2 repeated screenings within 3 additional years in almost 20,000 subjects at high risk for lung cancer should be completed by 2010 [14]. However, if only long-term, repeated LDCT screening produces a stage shift, these 2 trials of short-term, repeated LDCT screening might fail to show any benefit. In fact, we should note that the detection rate of incidence lung cancers of all types remained unchanged if the duration of repeated screening was 5 years or less. Furthermore, neither a stage shift nor a size shift in invasive adenocarcinoma occurred if the duration of repeated screening was 5

years or less. Therefore, considering our present findings that the detection rate of incidence lung cancers in a cohort of mostly male smokers increased after 5 years of repeated LDCT screening and that the stage shift was observed for at least invasive adenocarcinoma after long-term, repeated LDCT screening for 5 years, we believe that proving the efficacy of LDCT screening would be difficult if the screening period is less than 5 years.

In the present study both a stage shift and a size shift were observed for invasive adenocarcinoma of the most common histological diagnosis. Considering direct evidence exists for a stage-size relationship in LDCT screen-diagnosed lung cancers [30], the fact that the stage shift was followed by a simultaneous size shift supports the occurrence of a stage shift in invasive adenocarcinoma. However, we wonder why this phenomenon was observed for only invasive adenocarcinoma. This question is difficult to answer, considering that invasive adenocarcinoma behaves as aggressively as do other non-small cell carcinomas. A possible explanation might simply be that the number of incidence lung cancers detected in our study lacks sufficient statistical power. However, some adenocarcinomas have higher volume-doubling times, grow more slowly, and are, therefore, diagnosed more easily at an early stage; another explanation could be length-time-biased sampling inherent to single-armed, uncontrolled trials. Thus, large, randomized, controlled trials on the basis of long-term repeated screening will be necessary to answer this question.

In the present study, we have performed semiannual LDCT screening to detect aggressive, fast-growing lung cancers at an early stage. However, no interval lung cancers were detected in our screening population. On the other hand, an interesting phenomenon is shown by the characteristics of 3 patients with lung cancers detected outside our screening procedure after a period longer than the screening interval. These lung cancers were detected after the patients had stopped undergoing semiannual LDCT screening because no abnormality was observed during the screening periods, which were 3.5 years in 1 patient and 5 years in 2 patients. Therefore, these facts suggest the efficacy of long-term repeated LDCT screening for more than 5 years.

We have several concerns about our study. The first concern is that, in addition to the stage shift caused by long-term repeated screening, we estimated the efficacy of long-term repeated screening could also be shown indirectly if the overall survival of patients with incidence cancers would be significantly longer than that of patients with prevalence cancers. So, we compared baseline screening with subsequent screening. However, multivariate Cox proportional hazard model analysis showed that the screening type (baseline vs. repeated screening) was not an independent prognostic factor for overall survival. A possible reason for this finding is the small number of participants and, therefore, the small number of deaths from lung cancer in both groups. Thus, larger studies involving larger numbers of participants are needed to investigate whether the overall survival of patients with incidence cancers is, in fact, significantly longer than that of patients with prevalence cancers because of the efficacy of long-term repeated screening. A second concern is that the partial-volume effect might affect the ability of screening CT images to demonstrate small nodules because only thick-section screening CT with image construction at 1-cm intervals was available during the screening period. Therefore, in a second ALCA study still in progress we have performed both chest radiography and LDCT to evaluate the detection power of LDCT in terms of the partial-volume effect. A third concern associated with long-term semiannually repeated LDCT screening is that a large number of healthy persons would be exposed to radiation and have an increased risk of radiation-induced lung cancer, although the risk of radiation-induced cancers other than lung cancer would be far lower [31,32]. According to one estimate, LDCT screening at a rate of 1.5 examinations per year would induce 4.5 lung cancers per year in 100,000 persons aged 60–70 years [33]. According to another estimate, annual LDCT screening would induce approximately 6.7 lung cancers per year in 100,000 persons if male current smokers aged 60 years undergo annual screening until age 75 years with a compliance rate of 50% [34]. In contrast, because our population with a median age of 64 years undergoes LDCT screening twice a year, the risk of radiation-induced malignancy would be slightly higher. However, assuming that our semiannual screening yielded 57 lung cancers in 1877 participants during a median follow-up period of 3.5 years, the yearly incidence of lung cancer in 100,000 participants would be 868. Furthermore, because the 13 incidence invasive adenocarcinomas detected with the benefits of a stage shift and a size shift in our study suggest an incidence of 198 cancers per year per 100,000 persons, which is far larger than that of radiation-induced lung cancers, we maintain that semiannually repeated LDCT screening is beneficial despite the potential harm of the radiation exposure.

In conclusion, we have demonstrated that both a stage shift and a size shift occur for invasive lung adenocarcinoma during long-term repeated LDCT screening in a high-risk cohort. Long-term repeated screening for more than 5 years might disclose the potential efficacy of LDCT screening for lung cancer as the truth has been disclosed for other types of cancers, including colorectal cancer and breast cancer.

Conflicts of interest

The authors indicated no potential conflicts of interest.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Cancer Research (17-2) from the Ministry of Health, Labor, and Welfare of Japan, and supported in part by a Grant-in-Aid for the Third-term Comprehensive 10-Year Strategy for Cancer Control (Category: Japanese General Screening Study for Asbestos-related Diseases) from the Ministry of Health, Labor, and Welfare of Japan.

We thank the physicians and technical staff of the ALCA.

References

[1] Mulshine JL, Smith RA. Lung cancer. 2. Screening and early diagnosis of lung cancer. Thorax 2002;57:1071–8.
[2] Melamed MR, Flehinger BJ, Zaman MB, et al. Screening for early lung cancer. Results of the Memorial Sloan-Kettering study in New York. Chest 1984;86:44–53.
[3] Frost JK, Ball Jr WC, Levin ML, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 1984;130:549–54.
[4] Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. Am Rev Respir Dis 1984;130:561–5.
[5] Marcus PM, Bergstralh EJ, Fagerstrom RM, et al. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. J Natl Cancer Inst 2000;92:1308–16.
[6] Kubik A, Polak J. Lung cancer detection. Results of a randomized prospective study in Czechoslovakia. Cancer 1986;57:2427–37.
[7] Kaneko M, Eguchi K, Ohmatsu H, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. Radiology 1996;201:798–802.
[8] Sone S, Takashima S, Li F, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. Lancet 1998;351:1242–5.
[9] Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99–105.
[10] Swensen SJ, Jett JR, Sloan JA, et al. Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 2002;165:508–13.
[11] Diederich S, Wormanns D, Semik M, et al. Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 2002;222:773–81.
[12] International Early Lung Cancer Action Program InvestigatorsHenschke CI, Yankelevitz DF, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763–71.

[13] Gohagan J, Marcus P, Fagerstrom R, et al. Baseline findings of a randomized feasibility trial of lung cancer screening with spiral CT scan vs chest radiograph: The Lung Screening Study of the National Cancer Institute. Chest 2004;126: 114–21.
[14] Xu DM, Gietema H, de Koning H, et al. Nodule management protocol of the NELSON randomized lung cancer screening trial. Lung Cancer 2006;54: 177–84.
[15] Bepler G, Goodridge Carney D, Djulbegovic B, et al. A systematic review and lessons learned from early lung cancer detection trials using low-dose computed tomography of the chest. Cancer Control 2003;10:306–14.
[16] Sobue T, Moriyama N, Kaneko M, et al. Screening for lung cancer with low-dose helical computed tomography: Anti-lung Cancer Association project. J Clin Oncol 2002;20:911–20.
[17] Sone S, Li F, Yang ZG, et al. Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 2001;84:25–32.
[18] Nawa T, Nakagawa T, Kusano S, et al. Lung cancer screening using low-dose spiral CT: results of baseline and 1-year follow-up studies. Chest 2002;122:15–20.
[19] Diederich S, Thomas M, Semik M, et al. Screening for early lung cancer with low-dose spiral computed tomography: results of annual follow-up examinations in asymptomatic smokers. Eur Radiol 2004;14:691–702.
[20] Swensen SJ, Jett JR, Hartman TE, et al. CT screening for lung cancer: five-year prospective experience. Radiology 2005;235:259–65.
[21] Pastorino U, Bellomi M, Landoni C, et al. Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results. Lancet 2003;362:593–7.
[22] Zhukov TA, Johanson RA, Cantor AB, et al. Discovery of distinct protein profiles specific for lung tumors and pre-malignant lung lesions by SELDI mass spectrometry. Lung Cancer 2003;40:267–79.
[23] Manser RL, Irving LB, de Campo MP, et al. Overview of observational studies of low-dose helical computed tomography screening for lung cancer. Respirology 2005;10:97–104.
[24] Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710–7.
[25] Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and genetics of tumours of the lung, pleura, thymus and heart (World Health Organization Classification of Tumours). Lyon: IARC Press; 2004. pp. 9–124.
[26] Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953–61.
[27] Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365–71.
[28] Hendrick RE, Smith RA, Rutledge 3rd JH, et al. Benefit of screening mammography in women aged 40–49: a new meta-analysis of randomized controlled trials. J Natl Cancer Inst Monogr 1997;22:87–92.
[29] Nyström L, Rutqvist LE, Wall S, et al. Breast cancer screening with mammography: overview of Swedish randomised trials. Lancet 1993;341:973–8.
[30] Henschke CI, Yankelevitz DF, Miettinen OS, International Early Lung Cancer Action Program Investigators. Computed tomographic screening for lung cancer: the relationship of disease stage to tumor size. Arch Intern Med 2006;166:321–5.
[31] Berrington de González A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. Lancet 2004;363:345–51.
[32] Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.
[33] Diederich S, Wormanns D. Impact of low-dose CT on lung cancer screening. Lung Cancer 2004;45:S13–19.
[34] Brenner DJ. Radiation risks potentially associated with low-dose CT screening of adult smokers for lung cancer. Radiology 2004;231:440–5.

一次予防と二次予防

がん検診の役割と意義

金子昌弘
国立がんセンター中央病院内視鏡部　部長

プライマリ・ケアにおけるポイント

がん検診には行政側の職員から検診・精検・治療機関の職員，技師，医師などさまざまな職種の人々が関与している．しかし，それぞれの部門で最善の努力が行われていても，部門ごとの連携が不十分であったり，検診結果の意味が正確に受診者に伝わらなかったりすると，その効果を十分に発揮することはできない．現在の検診システムの場合，個々の受診者に対して適切に対応しているかどうかの総合的な監視が十分には行われていない問題がある．

一方，受診者側の問題としては，検診結果の意味が十分に理解されず，異常を指摘されても種々の理由で精検を受診しない場合や，逆に精査不要の所見にもかかわらず，いたずらに不安を感じて医療機関を受診する場合，検診で異常が指摘されなかった場合に，多少の症状があっても医療機関を受診せず診断が遅れるなどの危険も存在する．

プライマリ・ケア医の先生方には，各人の生活様式やリスクに応じた適切な検診受診を勧め，その結果を正確に受診者に伝え，必要な場合には適切な精検機関を確実に受診するよう勧めていただきたい．さらに，異常が認められない場合においても，検診受診を各人のライフスタイルの見直しの機会として捉え，禁煙や食事，運動などの生活指導を行い，がん検診を単にがんの早期発見の場だけではなく，がん発生の予防の場とするようにも努めていただきたい．

はじめに

現在，ほとんどの地方自治体や職場で胃・子宮頸部・肺・乳房・大腸のがん検診が行われ，前立腺や肝臓についても一部で行われているが，受診率は必ずしも高くなく，2006年の厚生労働省の発表では胃癌：12.1%，子宮頸癌：18.6%，肺癌：22.4%，乳癌：12.9%，大腸癌：18.6%と報告されており，それぞれの検診の都道府県ごとの格差も50%前後から5%程度と10倍以上の差が認められる[1]．どのように精度の高い検診が行われていても，その検診を必要とする多くの住民が受診し，要精検者が確実に精密検査機関を受診し，確実な治療が行われなければその効果を発揮することはできない．わが国は検診大国といわれ，がんに限らず各種の検診が行われているが，個々の検診に限ってみるとその受診率はむしろ諸外国よりも低いのが現状である．プライマリ・ケア医の方々は，**個々の患者やその家族のライフスタイルやリスクに応じたがん検診を確実に受診するように指導していただきたい．**

がん検診を実施する側は，できるだけ多く早期のがんを発見・治療し，がんによる死亡者を減らそうと考えているが，受診者側はむしろその時点ではがんのないことを証明してもらおうとして受診する場合が少なくない．したがって多くの場合，多少の自覚症状があっても異常なしの判定をもらえば安心してしまうし，逆に要精密検査といわれても自覚症状がないから大丈夫などと思って，受診しなかったり，先延ばししてしまったりする場合も少なくない．検診受診を勧めた受けもちの患者に対しては，その検診結果も把握し，その結果

に応じた対応が確実に行われているかどうかを確認し，行われていなければそれを強く勧めることが必要と思われる．

検診を実施する側の関心はどうしても要精検者，あるいはがんを発見した患者のほうに向いてしまいがちで，その時点で異常が発見されなかった受診者に対しては無関心，あるいは無駄な検査を行ってしまったという意識が働いてしまう．しかし，**がん検診の一番の目的は受診者全体のがん死亡減少であり**，これに最も効果のあるのは，がんの罹患者を減らすことである．

受診者側には検診を定期的に受診していれば，がんには罹らないのではないかという期待が伺えるが，現実のがん検診に予防効果はなく，この点で住民の期待と大きく乖離が存在する．検診にがんの予防効果をもたせ，多少とも受診者の期待に応えるためには，たとえ検診で異常所見が指摘されなかった場合にも，問題のあるライフスタイルの受診者には，それを続けさせるのではなく，がんの発生を予防する意味でも，禁煙指導・食生活改善・運動指導が重要である．とくに喫煙は，肺癌はもちろん，食道癌，胃癌，子宮頸癌とも関連が認められており，強力な禁煙指導はこれらのがんのすべての予防につながると思われる．

検診受診は個々の住民の生活環境を見直すよい機会である．**プライマリ・ケア医の先生方には，受診者側の視点に立って，がんの早期発見だけでなく，がんを予防できる生活指導を行っていただきたい．**

Ⅰ 胃癌検診

胃癌は男女とも最も罹患数の多いがんであるが，近年の検診の効果などもあり，死亡数は減少傾向にあり，子宮癌とともにその効果がよく現れているがんの一つである．

胃癌検診は，通常はバリウムによる造影の間接撮影で行われているが，撮影枚数の限られた検診の場合には，盲点になる場合も少なくなく，また微小な病巣の描出は困難な場合もある．したがって内視鏡での検診も一部では行われていたが，被験者の苦痛も多く普及はしなかった．しかし，最近では経鼻的な細経内視鏡による観察も行われるようになり，苦痛も軽減し人間ドックなどを中心に普及している．ただし，医師が直接行わなくてはならないので，施行できる数には限界がある．

一方，ピロリ菌の発見により，この菌が胃癌の発生に大きく関与してきていることも明らかになってきた．また，血液中のペプシノーゲンを測定することで，一種の前がん状態とも考えられる萎縮性胃炎の診断が可能になり，ハイリスク症例の絞り込みが可能になった．ペプシノーゲンの測定は，造影や内視鏡のような主観的な判断ではなく，定量的な判定なので専門医でなくても行うことが可能という利点もある．したがって，検診を希望する住民に**一律に同じ検査を行うのではなく，ピロリ菌の有無と萎縮性胃炎の程度に応じて検査の方法や間隔も変えることにより，効率のよい検診を行うことが可能になってきた．**

一方，生活習慣としては喫煙と塩分の多い食事をとることはリスクを高め，野菜や果実を多くとる場合はリスクを下げることが国際的にも認められている[2]．したがって，これらのリスクにすべて当てはまるような住民に対しては，その生活習慣を改めさせることはもちろんであるが，一般的な間接造影による検診ではなく，年に1回程度は内視鏡を行うべきであり，逆にこれらのリスクのほとんどない住民にはバリウムによる造影検査を定期的に受診するように勧めていただきたい．

さらに，食道癌や胃癌の場合には，病巣が粘膜

内にとどまる状態で発見できれば，外科的な切除を行わず，経口的な内視鏡切除で全く機能を損なうことなく短期間で治療が可能になってきた．治療後に高い生活の質を維持させるためにも，ハイリスクの住民に対しては定期的な内視鏡での観察が重要と思われる．

Ⅱ 子宮頸癌検診

子宮頸癌も，以前は最も重要な女性のがんであったが，発生数の減少に加えて，検診の効果により早期の発見例も増えたことにより，死亡数は急激に減少しつつある．

子宮頸癌の原因も，ある種のヒトパピローマウイルス（HPV）の感染によることが明らかになってきており，感染後10年程度で浸潤癌になるとされている[3]．しかしまだ，ウイルスの治療による発がん予防の効果は証明されていないので，アメリカでは12歳頃に予防注射を受けることが推奨されているが，わが国でも検討されているものの一般的ではない．

子宮頸癌のハイリスクとしては，一般的には多産，若年の妊娠・出産などがあげられており，これらはパピローマウイルスの感染の機会の多いこととも関連しているとも考えられる．

子宮頸癌の検診は，婦人科医が局所を直接観察して細胞診を行うので，その診断精度はきわめて高い．また，最近では早期に発見すれば部分的な切除のみで済み，その後の妊娠も可能な場合も少なくない．全体的には減少傾向にあるものの，性行動の変化によって比較的若年者での発症も増えている傾向もある．婦人科以外の先生方も，ハイリスクと思われる患者には積極的に検診を受診し適切な治療を受けるように勧めていただきたい．

一方，喫煙もリスクを高める要因とされている．その理由として，喫煙により肺から血中に取り込まれた発がん物質が子宮頸管粘液のなかにも含まれ，これが刺激することによると考えられている．現在，日本人全体の喫煙率は減少しているが，若年女性では増加傾向にあり，JTでも女性向けのタバコの開発に力を入れている．喫煙女性の出産には多くのリスクも伴うので，**喫煙女性には子宮癌検診の受診を勧めるとともに，禁煙指導を強力に行っていただきたい．**

Ⅲ 肺癌検診

肺癌検診は，戦後まもなくから始まった間接写真による結核検診が，疾病構造の変化からその対象が，結核から肺癌へと移行するのに伴って，その中心が肺癌へと変化して行われるようになった．現在の一般的な肺癌検診は，100mm幅の間接高圧撮影と，喫煙指数（一日の喫煙本数×喫煙年数）600以上の重喫煙者，あるいは半年以内の血痰自覚者には3日間の蓄痰による喀痰細胞診を行うことが義務づけられている．

喫煙歴などで検診方法が異なる理由は，肺癌のなかでも肺門部にできる扁平上皮癌はX線では発見しにくいが，喀痰細胞診で比較的容易に発見でき，しかもこの部位に癌ができるのはヘビースモーカーにほぼ限定されているため，このように定められている．自治体によっては，喀痰細胞診を行う場合，別料金が発生する地域もあり，喀痰細胞診の受診率は必ずしも高くはない．プライマリ・ケア医の方々には，対象者には確実に喀痰検査も受けるように勧めていただきたい．

一方，**最近はX線の検診の精度を高めるために，**

低線量CTの導入が人間ドックを中心に進められている．通常のX線写真とCTを比較すると，CTのほうが心臓や横隔膜などによる盲点が少ない，濃度分解能が高く微妙な濃度の差が指摘できるなどにより，肺のあらゆる部位の5mm程度以上の結節であればすべて拾い上げられるという利点はあるものの，X線の被曝が多い，撮影に時間がかかる，費用が高いなどの欠点も存在した．しかし，低線量ヘリカルスキャン撮影が開発され，これらの問題もある程度解決されることにより検診への導入が可能になった．**小病変の発見能は高く，発見された肺癌の病期は早く予後は良好であることは認められているが**，受診者全体の肺癌死亡率低減にどの程度寄与しているかがまだ明確に証明されていないので，いわゆる対策型の検診としては推奨されていないが，任意型の人間ドックなどではむしろ標準的な検査になりつつある[4]．

CT検診のメリットとしては，肺癌以外の多くの疾患も発見できる点がある．呼吸器疾患として肺気腫や線維化も早期に指摘でき，これらの疾患は喫煙との関連も高いので，CT画像を示しながら禁煙指導を行うとその効果も高いといわれている．呼吸器以外では，心筋梗塞との関連の強い冠動脈の石灰化や，時に胸部大動脈瘤，縦隔腫瘍や，甲状腺，乳腺の腫瘍も指摘できることがある．また，上腹部も撮影範囲に含まれるので，最近話題の内臓脂肪の指摘も容易で，これも食生活や運動指導の効果判定にも有効とされている．

40歳以上のヘビースモーカーや，一度CT撮影を受け，微小な結節や淡いすりガラス陰影（ground glass opacity：GGO）が指摘された場合には，年に1回程度はCTを定期的に受けることを勧めていただきたい．また，喫煙者には禁煙指導を強力に行うのはもちろんであるが，禁煙後に肺癌のリスクが非喫煙者と同等になるには20年はかかるといわれており，禁煙後もしばらくは喫煙者と同等のリスク管理が必要である．

Ⅳ 乳癌検診

乳癌は欧米では最も頻度の高い女性のがんであるが，**マンモグラフィー（MMG）による検診の普及もあり，死亡率は減少傾向にある**．一方，わが国では，欧米に比べると罹患率は低いものの，依然として罹患率・死亡率ともに上昇傾向にあり，最も対策の急がれるがんの一つと考えられる．乳癌はほかのがんに比べ発生年齢が比較的若く，妊娠・出産経験の少ない女性に罹患しやすいとされている．肥満との関係では，閉経前ではむしろ発がんを抑制する因子として働き，閉経後は促進する因子として働くと考えられている[5]．ただし，これらの条件に合致する例はむしろ少なく，これらの条件で絞り込むことはできない．

乳癌検診は，以前は外科医や婦人科医による視触診で行われていたが，この方法では死亡率低減の効果のないことが証明された．一方，X線撮影によるMMGでの検診の効果は証明されたので，現在ではMMGで検診を行うことが義務づけられている．MMGの場合，最近導入されたこともあり，精度管理中央委員会の審査が全国的に確実に行われているので，ここでの審査に合格した施設での検診を受診するように一般住民にはお勧めしていただきたい．

乳癌も最近は早期に発見されれば局所切除や放射線治療の組み合わせで，ほとんど形態を損なわず治療も可能になってきているので，早期発見の意義は非常に大きい．

V 大腸癌検診

大腸癌の検診は便の潜血反応によって行われている．これは人間のヘモグロビンを直接測定するので感度は高く，数値化したデータとして表示されるので，全国どこで受けても同じ結果が出るという安心感は大きい．しかも，受診者の肉体的・時間的な負担も少ないため，一般的に対象者中の受診率は比較的高い．

しかし，便潜血陽性と判断されると，精密検査には大腸鏡または注腸造影が必要になる．これらの検査は上部消化管の検査に比べると被験者の肉体的・時間的な負担が大きいので，精検受診率がほかの臓器の検診に比べ低いことが問題になっている．いかに多くが受診しても，潜血陽性者が確実に精密検査を受診しなくてはその成果を発揮することはできない．

大腸鏡は受けたくないが，潜血陽性は心配というような受診者に対して，再度便潜血検査だけを行い，再現性がないから大丈夫としたり，直腸鏡だけを行い痔があるのでそこからの出血であったろうなどと安心させたりしてしまう施設も皆無ではない．**大腸癌があっても毎回必ず便潜血が陽性になるとは限らないし，たとえ痔はあっても，その口側にがんがないという保証はないので，積極的に大腸鏡を受けるように勧める必要がある．**

大腸鏡については，最近は自宅で前処置を行うシステムを採用する施設も増え，多少受診者の時間的な負担の軽減は行われており，また，鎮静剤の使用などで検査の苦痛も非常に軽減している．内視鏡検査を専門に開業しているクリニックも増えているので，ホームページなどで楽な検査を行うことを標榜している施設を探して受診させるほうがよい．

大腸癌については，そのほとんどが多発するポリープなどから段階的に発がんするとされている．したがって複数のポリープの認められる症例でも，その時点ですべて取り去るとしばらくは発がんの危険性は著しく低下するとされているので，理想的には便潜血の有無にかかわらず，**40歳以降は数年に1回程度は大腸鏡を行うのが理想的と考えられる．**

さらに大腸癌に関しては，体をよく動かすことや野菜の摂取はリスクを下げ，赤身肉や加工肉の摂取が多く，多量の飲酒や肥満はリスクを上げることが証明されている[6]．これらに該当する患者には積極的に大腸癌検診を受診させるとともに，定期的な運動と食生活の改善，節酒を勧め，大腸癌の罹患を予防するように指導していただきたい．

VI その他の臓器のがん検診

前述のいわゆる5大がんのほかに，地域によっては前立腺癌や肝臓癌などの検診も行われている．

前立腺癌は，いわゆる5大がんには入っていないが，近年の増加傾向が著しく，欧米で多いことから，今後の食生活の欧米化に伴い更なる増加が危惧されている．前立腺癌自体は泌尿器科の扱う疾患なので，プライマリ・ケア医の方々が直接診療する機会は少ないと思われるが，**その検診は血液中のPSAの測定で行われ，泌尿器的な知識・技術も必要としない．**一般に，腫瘍マーカーはある程度の進行がんにならないと上昇しないので，早期がんの発見を目的とする検診には用いられないが，PSAだけは早期の時期から上昇するので，検診に用いることができる．**各種の慢性疾患で通院中の中高年男性には年に1回程度測定することで，早期発見が可能になる**ので，ぜひ行っていただき

たい.

肝臓癌も男性に多いがんの一種であるが，発症はほとんどC型肝炎の罹患者に限られている．肝炎の病歴のある人や，輸血の経験者でC型肝炎ウイルスの抗体を有する症例には，定期的な腹部エコーなどにより肝臓癌の有無をチェックしていただきたい.

おわりに

がんの原因に関して不明な部分もあるが，胃癌における萎縮性胃炎やピロリ菌感染，子宮頚癌におけるHPV感染，あるいは肺癌における喫煙など，かなり原因が明らかになりつつある．また，乳癌や大腸癌のようにリスクの高いグループも明らかになってきた.

がん検診の受診者を増やすことは大事であるが，**とくにこれらのリスクの高い人々には重点的に検診受診を勧めるとともに，さらにハイリスクのグループには内視鏡やCTなど精密検査の手法を初めから用いての定期的なチェックが必要と考える.**

最近は多くのがんにおいて**超早期に発見できれば，機能的にも外観的にも治療前と変化のない状態での治療が可能**になってきているので，その意味からのがん早期発見の意義は大きい.

一方，がんに限らず検診の受診は自らのライフスタイルの見直しのよい機会である．**検診の結果説明の場を健康指導の場とすることにより，**より積極的な発がんを予防する検診へと脱皮を図る必要がある．プライマリ・ケア医の先生方は単に結果を説明するだけでなく，ライフスタイルの改善にぜひ努めていただきたい.

参考文献

1) 濃沼信夫：がん検診の現状と問題点. 日本医師会雑誌, 138：S43-46, 2009.
2) 島津太一, 辻　一郎：生活習慣と胃がん. BIO Clinica, 23：19-24, 2008.
3) 小西郁生, 万代昌紀：子宮頸がん. 日本医師会雑誌, 138：S254-257, 2009.
4) 江口研二：肺癌検診は有効か. 臨床と研究, 86：900-904, 2009.
5) 永田知里：生活習慣と乳がん. BIO Clinica, 23：36-42, 2008.
6) 溝上哲也：生活習慣と大腸がん. BIO Clinica, 23：25-30, 2008.

Int J Clin Oncol (2009) 14:213–218
DOI 10.1007/s10147-008-0837-4

© The Japan Society of Clinical Oncology 2009

ORIGINAL ARTICLE

Tatsuya Shimomura · Norishige Ohtsuka · Hiroki Yamada
Jun Miki · Norihiro Hayashi · Takahiro Kimura
Hidetoshi Kuruma · Shin Egawa

Patterns of failure and influence of potential prognostic factors after surgery in transitional cell carcinoma of the upper urinary tract

Received: January 23, 2007 / Accepted: September 7, 2008

Abstract
Background. We investigated the long-term outcome of upper urinary tract transitional cell carcinoma (TCC) after surgery.
Methods. The study population comprised 114 surgically treated patients with upper urinary tract TCC treated at Jikei University Hospital between March 1990 and December 2004. All these patients underwent radical surgery without any type of neoadjuvant therapy. Patterns of failure and patient survival were compared with clinicopathological parameters.
Results. The 5- and 10-year overall survival (OAS) rates for the patients were 85% (95% confidence interval [CI], 81%-89%) and 76% (95% CI, 69%-83%). To date, 19 patients (16.7%) have experienced distant or lymph node metastasis at a mean of 13.3 months following surgery (range, 1 to 50 months). The site of the primary tumor did not affect patient survival ($P > 0.05$). Both lymphovascular involvement (LVI) and positive lymph nodes were found to have poor prognosis in univariate analysis ($P = 0.004$ and $P < 0.0001$). Multivariate analysis indicated pathological stage and bladder recurrence (bladder recurrence being a better prognostic factor) to be independent predictors of metastasis-free survival, but not of OAS or cause-specific survival (CSS).
Conclusion. Pathological stage and bladder recurrence were found to be the predictors of metastasis-free survival in this study. Further searching for reliable biomarkers is needed to accurately predict the prognosis of this malignancy.

Key words Transitional cell carcinoma (TCC) · Upper urinary tract · Prognostic factors

T. Shimomura (✉) · N. Ohtsuka · H. Yamada · J. Miki · N. Hayashi · T. Kimura · H. Kuruma · S. Egawa
Department of Urology, Jikei University School of Medicine, 3-25-8 Nishi-shimbashi, Minato-ku, Tokyo 105-8461, Japan
Tel. +81-3-3433-1111 (ext. 3561); Fax +81-3-3437-2389
e-mail: shimomura@jikei.ac.jp

Introduction

Transitional cell carcinoma (TCC) of the upper urinary tract is relatively uncommon. It is estimated that renal pelvic TCC accounts for approximately 5% of all urothelial tumors in the United States.[1,2] Ureteral TCC is even less common than renal pelvic TCC, by a ratio of 1:3 to 1:4.[3,4] In Japan, in 2000, renal pelvic and ureteral carcinomas accounted for 0.2%–0.3% of all malignant neoplasms, respectively.[5]

The limited number of patients with upper urinary tract tumors makes the organization of randomized, prospective trials unlikely. There have been a few studies which have systematically analyzed patterns of relapse and the influence of potential prognostic factors such as extent of surgery, adjuvant chemotherapy, and pathological findings.[6–10] Retrospective review of data is thus of the utmost importance to determine potential prognostic factors and the role of adjuvant therapy.

We reviewed our experience with patients surgically treated for upper urinary tract TCC to define patterns of failure and prognostic factors, as well as the role of adjuvant chemotherapy.

Patients and methods

Patients

The study population comprised 114 surgically treated patients with upper urinary tract TCC treated at Jikei University Hospital between March 1990 and December 2004. All these patients underwent radical surgery without any type of neoadjuvant therapy.

Preoperative evaluation and treatment

All patients underwent pretreatment evaluation with urine cytology, chest X-ray, intravenous pyelography, retrograde

pyelography, computerized tomography or magnetic resonance imaging scan of the abdomen, and bone scanning. Clinical stage was determined according to the 2002 version of the unified tumor node metastasis (TNM) system.[11] Tumor extent and grade was determined histologically by board certified pathologists according to the *General rule for clinical and pathological studies on renal pelvic and ureteral cancer.*[12]

Initial treatment of all patients was surgery. Nephroureterectomy with removal of a bladder cuff was conducted in 110 patients. Lymph node dissection of the hilar and regional nodes adjacent to the ipsilateral great vessel or sampling biopsy was implemented in patients who had enlarged nodes on preoperative examination or were suspected of having enlarged nodes on intraoperative examination. The remaining 4 patients underwent radical nephrectomy under the diagnosis of renal cell carcinoma without lymph node dissection. But their final pathology revealed TCC.

Adjuvant therapy was conducted postoperatively in 44 patients (38.6%). The therapy was implemented at the discretion of the attending physician based on the pathological findings; cisplatinum-based systemic chemotherapy was used in 29 patients, fluorouracil-based chemotherapy in 13, and chemo (cisplatinum-based, systemic) -radiation therapy in 2 patients.

Follow up and endpoints

After surgery, patients were evaluated at 3- to 6-month intervals, by urine cytology, cystoscopy, and imaging studies, including chest X-ray, abdominal ultrasonography, computed tomography scans, and bone scanning. Recurrence was defined clinically as the appearance of new lesions on any of these studies. Causes of death were determined based on hospital records and/or death certificates. Patterns of failure and patient survival were compared with clinicopathological parameters.

Statistical analysis

The χ^2 test was used to evaluate the relationship between comparisons of variables, with $P < 0.05$ as significant. Survival curves of the patients were compared using the Kaplan-Meier method and analyzed by the log-rank test; the level of significance was again set at 5%. Cox proportional hazards models were used to assess the hazard ratio (HR) with the 95% confidence interval (95% CI) in univariate or multivariate analysis. All statistical analyses were conducted using StatView 5.0 (SAS Institute, Cary, NC, USA)

Results

Patient characteristics

The mean (± SD) follow-up period of the 114 patients was 47.9 ± 36.5 months after surgery (Table 1). The male-to-female ratio was 4:1, with the mean age being 64.4 ± 9.0 years.

Table 1. Demographic data of patients with transitional cell carcinoma of the upper urinary tract

	No. of patients	%
Sex		
Male	91	79.8
Female	23	20.2
Age (years; mean ± SD)	64.4 ± 9.0	
Follow-up (months; mean ± SD)	47.9 ± 36.5	
Location		
Pelvis	58	50.9
Ureter	46	40.4
Both	10	8.8
Laterality		
Right	53	46.5
Left	61	53.5
Pathological stage		
pTis	1	0.9
pTa	13	11.4
pT1	28	24.6
pT2	22	19.3
pT3	45	39.5
pT4	5	4.4
Grade		
G1	4	3.5
G2	53	46.5
G3	57	50.0
LVI		
Positive	35	38.9
Negative	55	61.1
NA	24	
Nodal status		
Positive	8	7.0
Other	106	93.0

NA, not available; LVI, lymphovascular invasion

Clinicopathological findings

The primary tumor was located in the renal pelvis, ureter, or both in 58 (50.9%), 46 (40.4%), and 10 patients (8.8%), respectively. No bilateral tumors were found, with left-side predominance in 61 patients (53.5%) and right in 53 (46.5%).

Pathological stage was distributed as pTis in 1 patient (0.9%), pTa in 13 (11.4%), pT1 in 28 (24.6%), pT2 in 22 (19.3%), pT3 in 45 (39.5%), and pT4 in 5 patients (4.4%). Pathological grade was distributed as G1 in 4 patients (3.5%), G2 in 53 (46.5%), and G3 in 57 (50.0%). Eight (7.0%) patients were found to have metastatic lymph nodes. Lymphovascular invasion (LVI) was diagnosed as positive in 35 patients (38.9%; 35/90), negative in 55 patients (61.1%; 55/90), and unknown in 24 patients.

Detailed clinicopathological findings according to the site of the tumor (renal pelvis vs ureter) are shown in Table 2. Of these upper urinary tract tumors, a more advanced pathological stage (≥pT3) was found in the renal pelvic than in the ureteral tumors, 58.6% vs 28.3% ($P = 0.002$), respectively. No difference was found in tumor grade. LVI was more frequent in pelvic tumors (48.9% vs 24.3%; $P = 0.02$)

Table 2. Clinicopathological findings according to the site of primary tumor

	Renal pelvis	Ureter	*P* value
Age (years; mean ± SD)	64.2 ± 8.7	66.5 ± 7.7	NS
Sex			
Male	45	39	NS
Female	13	7	NS
Follow-up (months, mean ± SD)	45.6 ± 33.5	49.9 ± 38.4	NS
Laterality			
Right	23	26	NS
Left	35	20	NS
Pathological stage			0.002
pT≤2	24	33	
pT≥3	34	13	
Grade			NS
G1,2	32	21	
G3	26	25	
LVI			0.02
Positive	22	9	
Negative	23	28	
Bladder recurrence	25	25	NS
Distant metastasis	8	7	NS
Adjuvant therapy	19	18	NS

LVI, lymphovascular invasion; NS, not significant

Recurrence and patient survival

The 5- and 10-year overall survival (OAS) rates for the patients were 85% (95% CI, 81%-89%) and 76% (95% CI, 69%–83%).

Bladder recurrence was found in 54 patients (47.4%) during follow-up (renal pelvic tumor: 25 patients; ureteral tumor: 25 patients; pelvic with ureteral tumor: 4 patients). Mean time to bladder recurrence was 9.1 months (range, 1 to 43 months). Local recurrence occurred in 1 patient with pelvic tumors. Those with bladder recurrence fared better in terms of survival than those without recurrence (5- and 10-year cause-specific survival [CSS], 96% vs 83% and 96% vs 83%; $P = 0.02$). Distant metastasis or lymph node metastasis occurred in 19 patients (16.7%; paraaortic lymph node in 8, liver in 5, bone in 5, lung in 3, Virchow node in 1, intraperitoneal in 1; with some patients having multiple recurrences). Mean time to metastasis was 13.3 months (range, 1 to 50 months).

During the study period, 18 patients (15.8%) died from all causes combined (renal pelvic tumor: 7 patients; ureteral tumor: 8 patients; pelvic with ureteral tumor: 3 patients). Cancer was the cause of death in 11 patients (9.6%), at a mean time of 12.6 months following surgery (range, 4 to 27 months). The site of the primary tumor did not affect patient survival (Fig. 1; $P > 0.05$).

Higher-stage and -grade tumors had poor CSS, as illustrated in Figs. 2 and 3 ($P = 0.005$ for pathological stage; $P = 0.02$ for G1, 2 vs G3). The 5- and 10-year OAS and CSS for patients with ≤pT2 and ≥pT3 disease were 90% (95% CI, 86%–95%) vs 78% (95% CI, 71%–84%; 5-year OAS; $P = 0.02$) and 82% (95% CI, 74–91%) vs 67% (95% CI, 55–78%; 10-year OAS, $P = 0.02$), and 96% (95% CI, 94–99%) vs 80% (95% CI, 74–92%; 5-year CSS, $P = 0.005$) and 96% (95% CI, 94–99%) vs 80% (95% CI, 74–86%; 10-year CSS , $P = 0.005$), respectively. These figures for patients with ≤G2 and G3 disease were 91% (95% CI, 87–96%) vs

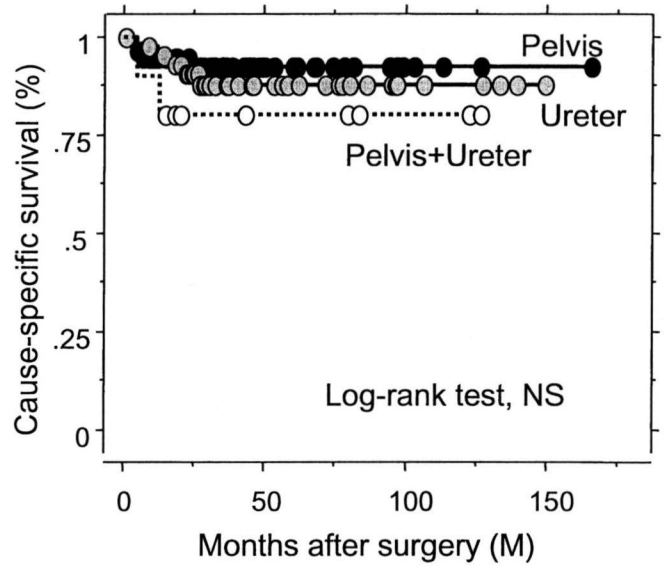

Fig. 1. Kaplan-Meier curve of cause-specific survival stratified by tumor location. *NS*, not significant

78% (95% CI, 72–84%; 5-year OAS, $P = 0.03$) and 83% (95% CI, 74–86%) vs 69% (95% CI, 59–79%; 10-year OAS, $P = 0.03$), and 96% (95% CI, 94–99%) vs 81% (95% CI, 76–87%; 5-year CSS, $P = 0.02$) and 96% (95% CI, 94–99%) vs 81% (95% CI, 76–87%; 10-year CSS, $P = 0.02$), respectively. Both findings of LVI (Fig. 4) and positive lymph nodes were found to have a poor prognosis ($P = 0.001$ and $P < 0.0001$). The 5- and 10-year OAS and CSS rates for those with negative and positive LVI were 96% (95% CI, 94–99%) vs 73% (95% CI, 65–82%; 5-year OAS, $P = 0.01$) and 87% (95% CI, 77–96%) vs 73% (95% CI, 65–82%; 10-year OAS, $P = 0.01$), and 98% (95% CI, 96–100%) vs 76% (95% CI, 68–84%; 5-year CSS, $P = 0.001$) and 98% (95% CI, 96–100%) vs 76% (95% CI, 68–84%; 10-year CSS, $P = 0.001$), respectively.

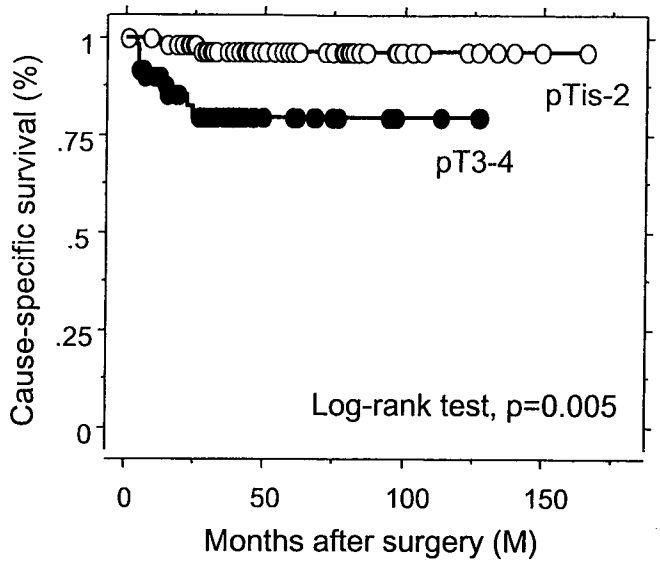

Fig. 2. Kaplan-Meier curve of cause-specific survival stratified by pathological stage

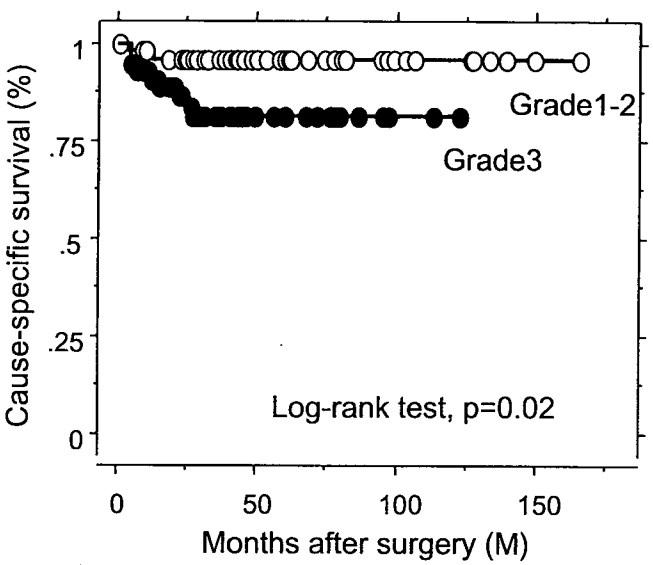

Fig. 3. Kaplan-Meier curve of cause-specific survival stratified by tumor grade

Results of univariate analysis

To date, 19 patients (16.7%) have experienced distant or lymph node metastasis at a mean of 13.3 months following surgery (range, 1 to 50 months). Table 3 tabulates the results of univariate analysis of the effect of each parameter on patient outcome. Grade, stage, LVI, nodal involvement, and bladder recurrence were found to be predictors of metastasis-free survival (MFS), CSS, and OAS ($P < 0.05$). Age was found to be predictive of CSS and OAS ($P < 0.05$). Adjuvant therapy failed to show a predictive value for any of these outcomes.

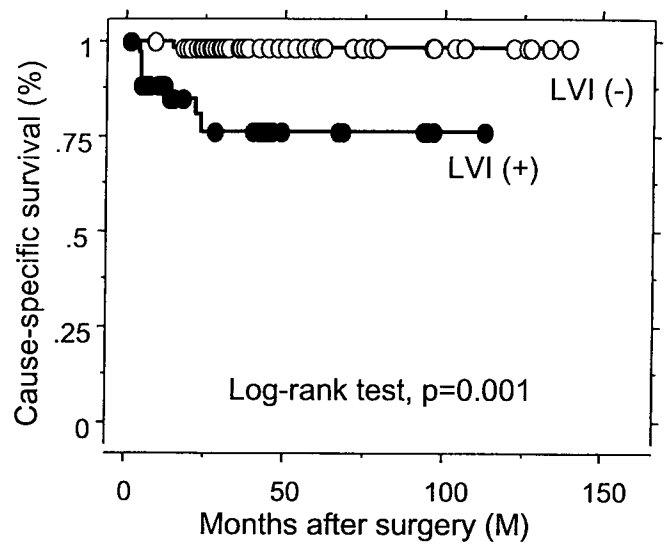

Fig. 4. Kaplan-Meier curve of cause-specific survival stratified by lymphovascular invasion (*LVI*)

Table 3. Results of univariate analysis of clinicopathological variables to predict patient outcome after radical surgery for transitional cell carcinoma of the upper urinary tract

	MFS	CSS	OAS
Sex	0.69	0.42	0.29
Age (≤59 vs 60–69 vs ≥70)	0.16	0.01	0.04
Location	0.16	0.38	0.39
Grade (G1,2 vs G3)	0.01	0.02	0.03
Pathological stage (pT ≤ 2 vs pT ≥ 3)	0.003	0.005	0.02
LVI	0.01	0.001	0.01
Positive nodal status	<0.0001	<0.0001	<0.0001
Adjuvant therapy	0.32	0.72	0.85
Bladder recurrence	0.04	0.02	0.01

MFS, metastasis-free survival; CSS, cause-specific survival; OAS, overall survival; LVI, lymphovascular invasion

Results of Cox proportional hazards multivariate analysis for survival

The Cox proportional hazards regression model, including age, gender, site of primary tumor, grade, pathological stage, LVI, nodal involvement, finding of bladder recurrence, and adjuvant therapy indicated pathological stage ($P = 0.04$ pT ≤ 2; HR, 0.078 [95% CI, 0.006–0.975]) and bladder recurrence ($P = 0.01$ bladder recurrence(–); HR, 10.36 [95% CI, 1.57–68.46]) to be independent predictors of MFS (Table 4).

Discussion

Stage, tumor grade, size, multifocality of TCC, and existence of carcinoma in situ are currently the most useful findings for making therapeutic decisions and evaluating prognosis in bladder cancer patients. However, the paucity of data in TCC of the upper urinary tract makes accurate prediction more challenging.

Previous retrospective studies indicated stage, grade, LVI, and lymph node status to be prognostic for patient survival.[6–10,13,14] Hong et al.[14] reported the 5-year disease-specific and recurrence-free survival rates were 98% and 94% in the absence of LVI ($P = 0.0005$), and 70% and 60% in the presence of LVI ($P = 0.0007$), respectively, in patients without lymph node involvement or stage T4 disease (Ta-T3N0M0; $n = 62$). In multivariate analysis, LVI was the only significant predictor of recurrence-free survival, and no factor was significant for disease-specific survival. On the other hand, Kikuchi et al.[13] found LVI, pathological T stage, and tumor grade to be independent predictors of disease-specific survival in multivariate analysis. They could stratify patients into low-risk (grade 1 or 2, LVI-negative, stage pT2 or lower), high-risk (any tumor grade, LVI-positive, stage pT3 or greater), and intermediate-risk (all others) groups with significant differences in survival. Though LVI was a significant predictor of metastasis and patient survival in univariate analysis, in our study, our multivariate analysis indicated pathological stage and bladder recurrence (bladder recurrence being a better prognostic factor) to be independent predictors of metastasis-free survival (MFS), but these factors were not independent predictors of OAS or CSS (statistics processing of OAS and CSS was impossible because each factor affected the other). This finding (pathological stage or bladder recurrence was not an independent predictor of OAS or CSS) may be due to the relatively few such events in our study. These findings thus need further validation and more investigation. The reason why patients with bladder recurrence had a better prognosis than bladder recurrence-free patients is not clear. Hasui et al.[15] suggested a potential role of vascular invasion in the prediction of an unfavorable outcome in patients with upper urinary tract cancers. Such morphological findings may be a manifestation of a more aggressive phenotype of this malignancy.

Table 4. Results of multivariate analysis of clinicopathological variables to predict patient outcome after radical surgery for transitional cell carcinoma of the upper urinary tract

	MFS
Sex	0.95
Age (≤59 vs 60–69 vs ≥70)	0.48
Location	0.27
Grade (G1,2 vs G3)	0.12
Stage (pT ≤ 2 vs pT ≥ 3)	0.04
LVI	0.90
Nodal status	0.22
Adjuvant therapy	0.12
Bladder recurrence	0.01

MFS, metastasis-free survival; LVI, lymphovascular invasion
Statistical processing was impossible for OAS and CSS because each factor affected the other

The location of the primary tumor in upper urinary tract carcinoma has been suggested to be predictive of prognosis by some[6,7] and questioned by others.[5] Park et al.[10] found pelvis and ureteral TCC not to be the same disease in terms of invasion and prognosis. Ureteral TCC was found to be associated with a higher local or distant failure rate than renal pelvis TCC. Hall et al.,[8] however, showed that tumor location did not affect recurrence and CSS in a Cox proportional hazards regression model. In our study, tumor location was not found to be a predictor of patient outcome, either ($P > 0.05$; Fig. 1).

Table 5 shows a summary of clinical series of TCC of the upper urinary tract with patient populations of more than 100. Though pathological stage was universally found to be a significant prognostic factor, the value of other clinicopathological parameters was inconsistent among studies.

In circumstances in which conservative resection is performed, postoperative therapy is considered. In bladder cancer, three randomized trials have suggested that adjuvant systemic chemotherapy after radical cystectomy improves relapse-free survival compared with that in patients undergoing surgery alone.[16–18] But the role of adjuvant therapy in TCC of the upper urinary tract is not well established. Ozsahin et al.[9] failed to show any benefit of postoperative radiation therapy in a multicenter retrospective study. Brookland and Richter[19] reported that the incidence of local recurrence was lower, but that of distant failure was about the same with postoperative radiation therapy. Adjuvant chemotherapy may have a role, because good objective responses have been observed in palliative settings.[20,21] Adjuvant therapy was not found to be

Table 5. Summary of clinical series (patient populations of more than 100) of transitional cell carcinoma of the upper urinary tract

Authors	No. of patients	Follow-up (months)	% Survival	Prognostic factors
Corrado et al.[6]	127	1 to 172	OAS 5Y, 67; 10Y, 52	Stage Grade DNA ploidy
Hall et al.[8]	252	Median, 64	CSS 5Y Ta/is, 100 T1, 91.7 T2, 72.6 T3, 40.5	Age Stage Surgical procedure
Ozsahin et al.[9]	126	Median, 39	OAS 5Y, 29; 10Y, 19	Stage Residual tumor Tumor location (pelvis vs ureter ± pelvis)
Kikuchi et al.[13]	173	Median, 43	CSS 5Y, 72.3; 10Y, 65.1	Stage Grade LVI
Present study	114	Median, 39	OAS 5Y, 84.8; 10Y, 76.0	Stage Bladder recurrence

CSS, cause-specific survival; OAS, overall survival; LVI, lymphovascular invasion; Y, year

an independent predictor of MFS, CSS, or OAS in the present study. Because the true impact of adjuvant therapy for TCC of the upper urinary tract will not be known until a well-designed randomized study is accomplished, its application must be balanced between its expected efficacy and its adverse events.

Noninvasive, highly accurate diagnostic tests capable of predicting the probability of disease recurrence and progression have long been desired in the field of urologic oncology. Further efforts need to be made in searching for new, more powerful biomarkers in TCC of the upper urinary tract. The development of treatment algorithms based on upcoming evidence will lead the way to defining the place of multimodal therapy such as radical surgery together with adjuvant therapy. Further study is warranted.

Conclusion

In univariate analysis of patients with TCC of the upper urinary tract, pathological stage and grade, lymph node status, and LVI were found to be significant predictors of patient survival. Multivariate analysis indicated pathological stage and bladder recurrence to be predictors of MFS.

Further research is needed to investigate new biomarkers that will accurately predict the outcome of this malignancy.

References

1. Landis SH, Murray T, Bolden S, et al. (1998) Cancer statistics, 1998. CA Cancer J Clin; 48:6–29
2. Guinan P, Vogelzang NJ, Randazzo R, et al. (1992) Renal pelvic cancer: a review of 611 patients treated in Illinois 1975–1985. Cancer Incidence and End Results Committee. Urology; 40:393–399
3. Huben RP, Mounzer AM, Murphy GP (1988) Tumor grade and stage as prognostic variables in upper tract urothelial tumors. Cancer; 62:2016–2020
4. Murphy DM, Zincke H, Furlow WL (1980) Primary grade 1 transitional cell carcinoma of the renal pelvis and ureter. J Urol 123:629–631
5. Oshima A, Kuroiwa T, Tajima K (2004) Number of deaths from malignant neoplasms by site and its proportion of all malignant neoplasms in Japan (2000) Gan Toukei Hakusho 2004 (in Japanese) (Cancer Statistics 2004) Shinoharashuppanshinsha, Tokyo, pp 9
6. Corrado F, Ferri C, Mannini D, et al. (1991) Transitional cell carcinoma of the upper urinary tract: evaluation of prognostic factors by histopathology and flowcytometric analysis. J Urol 145:1159–1163
7. Heney NM, Nocks BN, Daly JJ, et al. (1981) Prognostic factors in carcinoma of the ureter. J Urol 125:632–636
8. Hall MC, Womack S, Sagalowsky AI, et al. (1998) Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. Urology 52:594–601
9. Ozsahin M, Zouhair A, Villa S, et al. (1999) Prognostic factors in urothelial renal pelvis and ureter tumors: a multicenter Rare Cancer Network study. Eur J Cancer 35:738–743
10. Park S, Hong B, Kim C, et al. (2004)The impact of tumor location on prognosis of transitional cell carcinoma of the upper urinary tract. J Urol 171:621–625
11. Sobin LH, Wittekind Ch (2002) TNM Classification of Malignant Tumours. International Union Against Cancer (UICC). Wiley-Liss, New York, pp 196–198
12. Japanese Urological Association, The Japanese Society of Pathology (2002) General rule for clinical and pathological studies on renal pelvic and ureteral cancer. Kanehara, Tokyo
13. Kikuchi E, Horiguchi Y, Nakashima J, et al. (2005) Lymphovascular invasion independently predicts increased disease specific survival in patients with transitional cell carcinoma of the upper urinary tract. J Urol 174:2120–2123
14. Hong B, Park S, Hong JH, et al. (2005) Prognostic value of lymphovascular invasion in transitional cell carcinoma of upper urinary tract. Urology 65:692–696
15. Hasui Y, Nishi S, Kitada S, et al. (1992) The prognostic significance of vascular invasion in upper urinary tract transitional cell carcinoma. J Urol 148:1783–1785
16. Skinner DG, Daniels JR, Russel CA, et al. (1991) The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 145:459–464
17. Stöckle M, Meyenburg W, Wellek S, et al. (1992) Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and three adjuvant cycles of chemotherapy. Results of a controlled prospective study. J Urol 148:302–306
18. Freiha F, Reese J, Torti FM (1996) A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 155:495–499
19. Brookland RK, Richter MP (1985) The postoperative irradiation of transitional cell carcinoma of the renal pelvis and ureter. J Urol 133:952–955
20. Loehrer PJ, Einhorn LH, Elson PJ, et al. (1992) A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastin, and doxorubicin in patients with metastatic urothelial carcinoma; a Cooperative Group study. J Clin Oncol 10: 1066–1073
21. Stenberg CN, Yagota A, Scher HI, et al. (1989) Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Cancer 64:2448–2458