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 $\chi^2$ 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

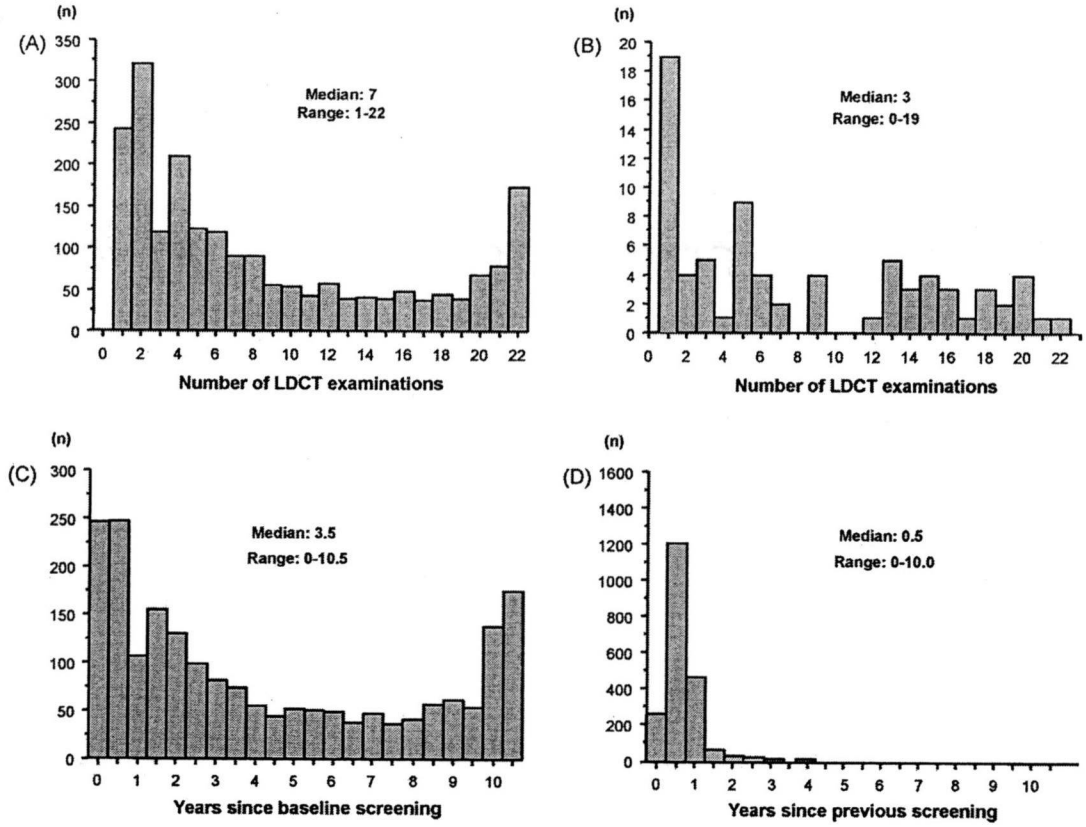


**Fig. 1.** Characteristics of repeated LDCT screening. (A) Distribution of the number of times participants underwent repeated LDCT screening (*X* axis indicates the number of LDCT examinations, and *Y* axis indicates the number of participants in each ordinal screening). (B) Distribution of the number 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.

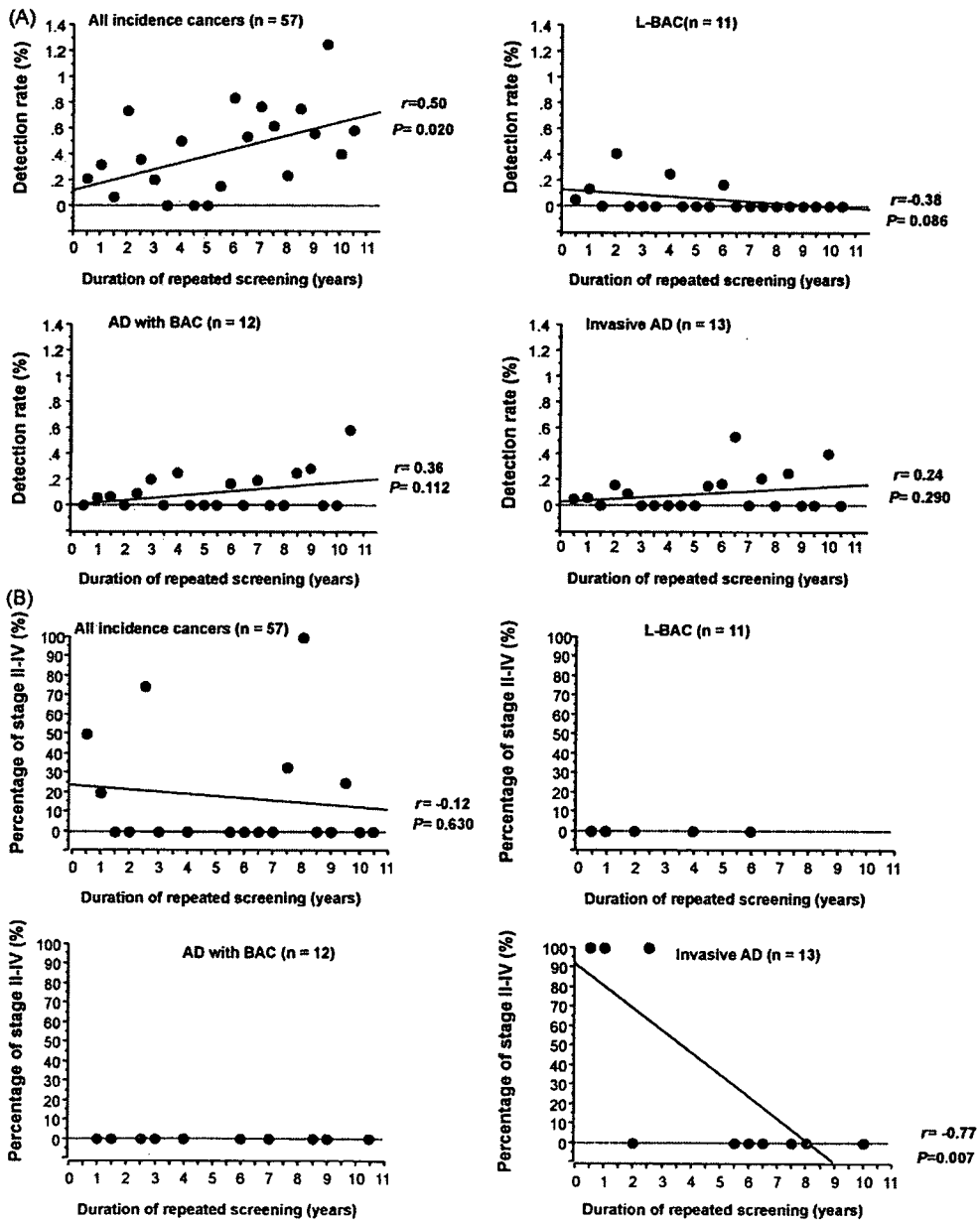


Fig. 2. Relationship between the duration of repeated screening and characteristics of incidence lung cancers. Correlations between the duration of repeated screening and the detection rate (A), the proportion of stage II–IV disease (B), and tumor size (C) were evaluated according to histological subtypes.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

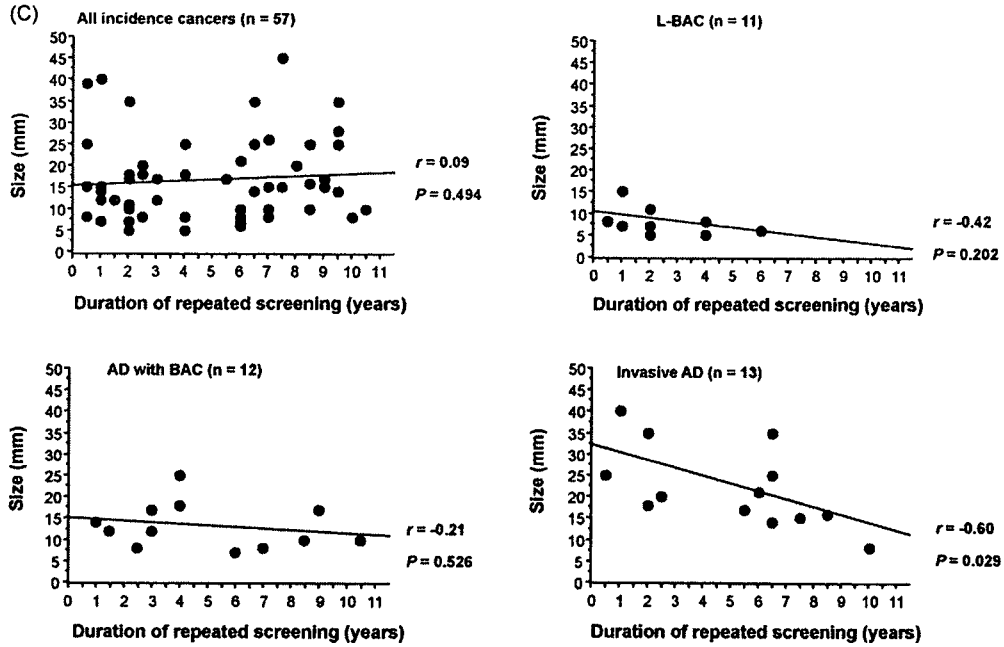


Fig. 2. (*Continued*).

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.

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ORIGINAL ARTICLE

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

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**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

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## 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 $\chi^2$ 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 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.

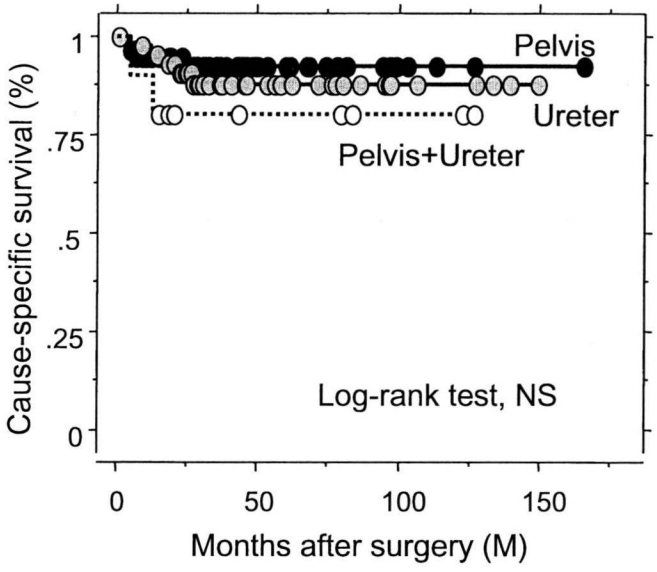


**Fig. 1.** Kaplan-Meier curve of cause-specific survival stratified by tumor location. *NS*, not significant

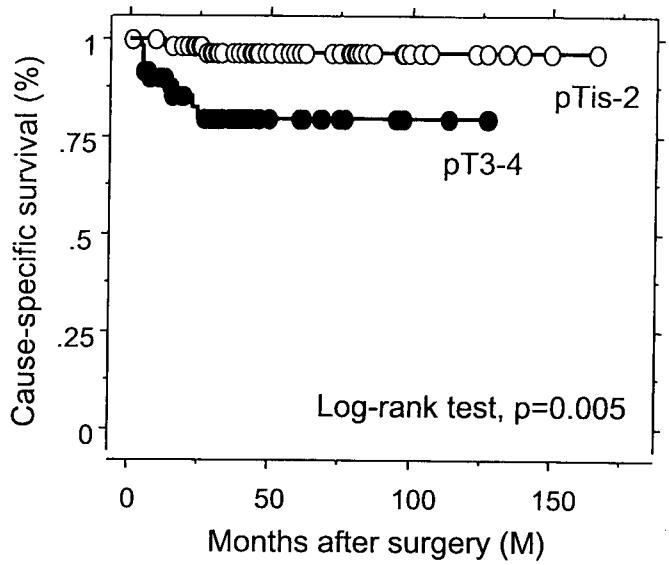


**Fig. 2.** Kaplan-Meier curve of cause-specific survival stratified by pathological stage

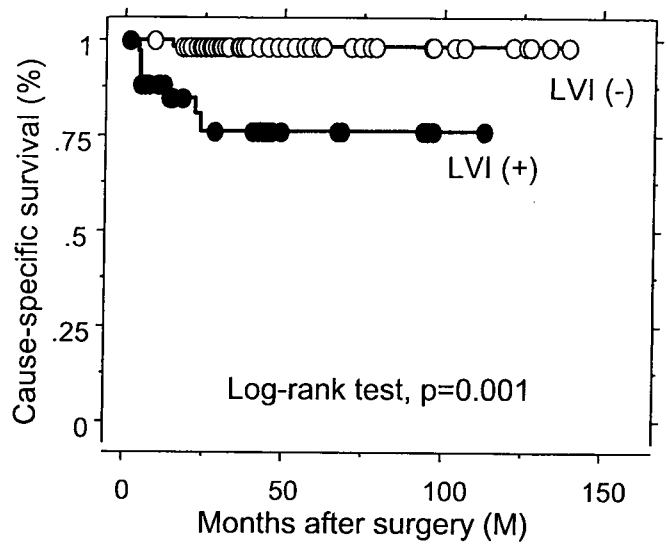


**Fig. 4.** Kaplan-Meier curve of cause-specific survival stratified by lymphovascular invasion (*LVI*)

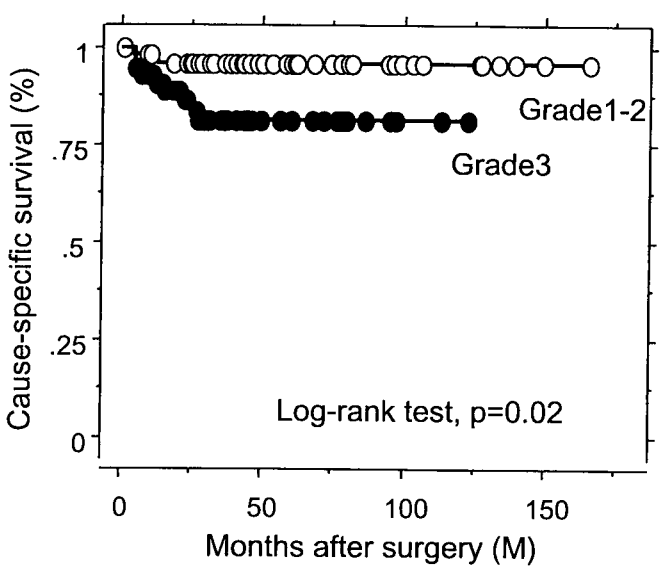


**Fig. 3.** Kaplan-Meier curve of cause-specific survival stratified by tumor grade

**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 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.

### 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<br>Grade<br>DNA ploidy |
| Hall et al.[8] | 252 | Median, 64 | CSS 5Y Ta/is, 100<br>T1, 91.7<br>T2, 72.6<br>T3, 40.5 | Age<br>Stage<br>Surgical procedure |
| Ozsahin et al.[9] | 126 | Median, 39 | OAS 5Y, 29; 10Y, 19 | Stage<br>Residual tumor<br>Tumor location (pelvis vs ureter ± pelvis) |
| Kikuchi et al.[13] | 173 | Median, 43 | CSS 5Y, 72.3; 10Y, 65.1 | Stage<br>Grade<br>LVI |
| Present study | 114 | Median, 39 | OAS 5Y, 84.8; 10Y, 76.0 | Stage<br>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.

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原著論文

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# 腹腔鏡下根治的膀胱摘除術の初期経験

**要旨**　【目的】膀胱癌に対する，腹腔鏡下根治的膀胱摘除術の当科における初期経験ならびに開腹術式との比較について報告する．

【対象と方法】2005年7月から2008年9月までの間に当科において腹腔鏡下根治的膀胱摘除術（LRC）を施行した24例と，ほぼ同時期に施行された開腹による根治的膀胱摘除術（ORC）16例を対象とした．LRCでの尿路変向術式は体外で行なった．また，尿路変向については，LRC，ORC双方ともに腸管を利用した術式（回腸導管または回腸新膀胱）を施行したものを対象とした．LRC群とORC群との比較を行い，LRC群の有用性について検討した．

【結果】術前因子（年齢，性別，Grade，臨床病期）はLRC群とORC群間に有意差を認めなかった．手術関連項目（手術時間，出血量，輸血率，術後イレウス発生率，術後経口摂取開始までの期間，術後合併症発生率，歩行開始までの期間，退院までの期間，術翌日の血中白血球数，CRP値）の比較においても今回の検討ではLRC群での明らかな優位性は認められなかった．病理学的所見，生存率（全生存率，非再発生存率）においても2群間の差を認めなかった．

【結論】尿路変向までを含めた場合，統計学的に明らかなLRCの有用性は確認できなかった．しかし，術中の拡大視野による正確な解剖の把握，良好な操作性，気腹による出血量の減少など，この術式の有用性は充分に期待できる．他の外科手技と同様，ラーニングカーブの影響をも鑑み，今後とも有用性についての検討をすすめる必要があると考えられた．

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**Abstract**　Objectives：Our initial experience in laparoscopic radical cystectomy or cystoprostatectomy (LRC) for bladder carcinoma in comparison with open radical surgery is reported.

Patients and Methods：Between July 2005 and September 2008, 24 patients underwent LRC followed by open urinary diversion. We compared peri- and postoperative findings of the 24 cases with those of 16 open radical cystectomy or cystoprostatectomy (ORC) conducted during the same time period. Urinary diversions in these patients were either ileal conduit (IC) or ileal neobladder (NB).

Results：There was no significant difference between LRC group and ORC group in terms of preoperative paramters (age, gender, tumor grade, clinical stage). Neobladder was more commonly chosen in LRC than in ORC. Statistically significant advantage was not evident in LRC group with regard to peri- and postoperative findings. Pathological findings and survival (overall, recurrence-free) were the same between two groups.

Conclusion：The advantage of LRC over ORC was not substantiated in our initial experience. Nevertheless, we consider this procedure as promising, which needs to be further pursued in terms of practical utility after learn-

ing curve being reached.

**Key words**：膀胱癌，腹腔鏡下根治的膀胱摘除術，周術期成績

## 緒　言

根治的膀胱摘除術は，膀胱癌（浸潤性癌，ハイリスク表在性癌）に対する標準治療である．開腹によるアプローチが標準術式であるが，泌尿器科領域における他臓器手術と同様，腹腔鏡下手技も取り入れられ，その短中期成績も検討されている．さらに最近ではロボット手術の経験も報告されている[1]ものの，改善の余地も多く，手技の標準化が期待されている．

本邦においても，徐々に報告[2-5]が増えてきており，今後，発展してゆくであろう分野の一つであると考える．

今回，我々の施設におけるLRCの初期経験と，同時期に施行されたORCとの比較検討につき報告する．

## 対象と方法

### 患者背景

2005年7月から2008年9月までの間に当科においてLRCを施行した症例で，腸管を利用した尿路変向術（回腸導管または回腸新膀胱造設）をおこなった24例と，同時期に施行されたORCの16例（同様に尿路変向については腸管を利用したもの）を対象とした．症例の詳細はTable 1に示す．

LRC群の年齢は平均64.3歳（48-84歳），男性21例，女性3例であった．臨床病期（T stage）ならびにgradeは，T1以下14例，T2：7例，T3：2例，T4（T4a）：1例，G1：1例，G2：4例，G3：17例，不明2例であった．尿路変向は回腸導管（Ileal conduit：IC）：7例，回腸新膀胱（Neobladder：NB）：17例であった．男性症例21例のなかで神経温存術を施行したものは2例，尿道摘除術を施行したものは4例（男性でIC6例中）であった．

ORC群の平均年齢は64.9歳（39-79歳），男性12例，女性4例であった．臨床病期（T stage）ならびにgradeは，T1以下5例，T2：10例，T3：0例，T4（T4a）：1例，G1：0例，G2:3例，G3:12例，不明1例であった．尿路変向はIC:13例，NB：3例であり，神経温存術施行例はなかった．男性でのIC 9例中，尿道摘除術は4例に施行された．

尿路変向は体外にて行い，NBは全例Studer 法で施行した．高齢，高度の合併症などのため，5例ではリンパ節郭清を施行せず原疾患の摘除にとどめた．術前補助化学療法（MEC療法）はORC群のT4症例（1例）のみで施行されていた．LRC群の1例では同時に腹腔鏡下での右腎摘除術が施行された．

LRC群とORC群について，臨床病理学的所見，また，手術関連項目として，手術時間，出血量，輸血率，術後イレウス発生率（イレウス管挿入やイレウス解除術を施行したもの），術後経口摂取開始（水分，食事）までの期間，術後合併症発生率（Minor：創哆開ならびに腎盂腎炎，発熱を伴うその他の炎症等で軽症なもの，Major：腸管吻合不全，重症感染症など，再手術，集中管理を要するような重症なもの），歩行開始までの期間，退院までの期間，術翌日の血中白血球数，CRP値などについて比較を行った．

統計処理はDr SPSS II®を用い，LRC群とORC群の2群間の比較を$\chi 2$検定（全生存率ならびに非再発生存率についてはlog-rank test）にて行なった．p値は0.05未満を有意

**Table 1** Comparison of clinicopathological parameters between LRC and ORC

| | LRC (%) | ORC (%) | p-value |
|---|---|---|---|
| Number pts | 24 | 16 | |
| Age (yo, mean ± SD) | 64.3 ± 10.2 | 64.9 ± 11.2 | NS |
| Gender | | | NS |
| male | 21 (87.5) | 12 (75) | |
| female | 3 (12.5) | 4 (25) | |
| Grade* | | | NS |
| 1 | 1 (4.7) | 0 (0) | |
| 2 | 4 (19.0) | 3 (20.0) | |
| 3 | 17 (80.1) | 12 (80.0) | |
| T stage | | | NS |
| ≦2 | 21 (87.5) | 15 (93.7) | |
| ≧3 | 3 (12.5) | 1 (6.2) | |
| Diversion | | | p=0.01 |
| IC | 7 (29.2) | 13 (81.2) | |
| NB | 17 (70.8) | 3 (18.7) | |
| Nerve sparing** | 2 (10.5) | 0 (0) | NS |
| Urethrectomy*** | 4 (66.7) | 4 (44.4) | NS |

LRC：Laparoscopic radical cystectomy or cystoprostatectomy
ORC：Open radical cystectomy or cystoprostatectomy
IC：Ileal conduit　NB：Neobladder
NS；not significant, SD；standard deviation
*：Unassigned in 3cases（LRC：2, ORC：1）
**：excluding female cases　***：Male pts, ileal conduit group

差ありとした.

### LRC手術方法

手術は全身麻酔下に，頭低位，軽度開脚位（適時，切石位がとれるようにレビテーター®を使用）にて施行．まず，腹部にFig. 1のように5本のポートをおき，経腹膜的，順行性に膀胱摘除術を行う．以下，実際の手術方法につき概説する．

まず，腹腔内の観察を行い，操作に支障をきたすような癒着があれば，適時剥離しておく．次に，膀胱内に生理食塩水を約150ml注入し，腹膜越しに膀胱の輪郭を確認し，膀胱外側より約1cm外側で腹膜を縦切開する（Fig. 2）．下方に切開を進めると，この切開線に対し横切るように精管が確認されるので，この時点で切断する．さらに下方で，尿管が確認されるので，これを膀胱側に向かい剥離し（Fig. 3），尿管を切断し，断端は迅速病理診断に提出する．両側の尿管切断後，両側の腹膜の切開線をつなげるように，腹膜の横切開をおき，ここで，精嚢を確認し剥離する（Fig. 4）．lateral pedicleは超音波凝固切開装置（LCS）など用いて切断する．この後，直腸と前立腺の間の剥離，ならびに前立腺外側の処理を進める（この処理は腹腔鏡下前立腺全摘除術に準じて行う）．次に正中臍索を切断し，膀胱前腔を展開し，DVCの結紮を行う．神経温存は，当科では腹腔鏡下前立腺摘除術と同様にintra-fascial nerve sparing法にて施行している．尿道の切断は本検討では前立腺全摘除術と同様に行い，切断部をあらかじめ結紮する処理などは施行していない．また，尿道の処理は当初，開腹（下腹部正中切開）の後，膀胱を摘出する直前に行って

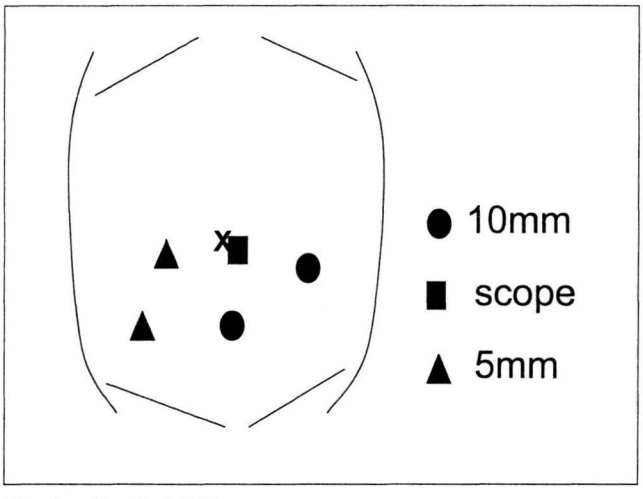


**Fig. 1** ポートの位置

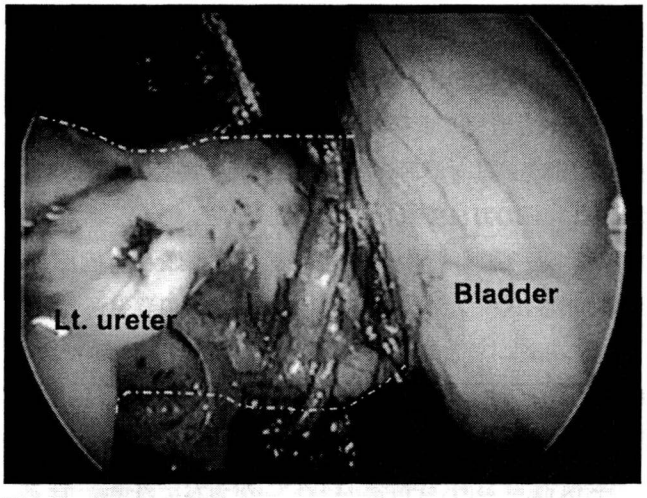


**Fig. 3** 左尿管の剥離

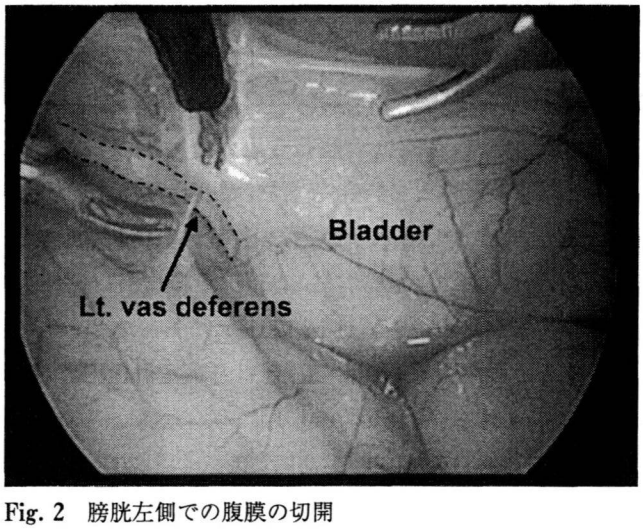


**Fig. 2** 膀胱左側での腹膜の切開

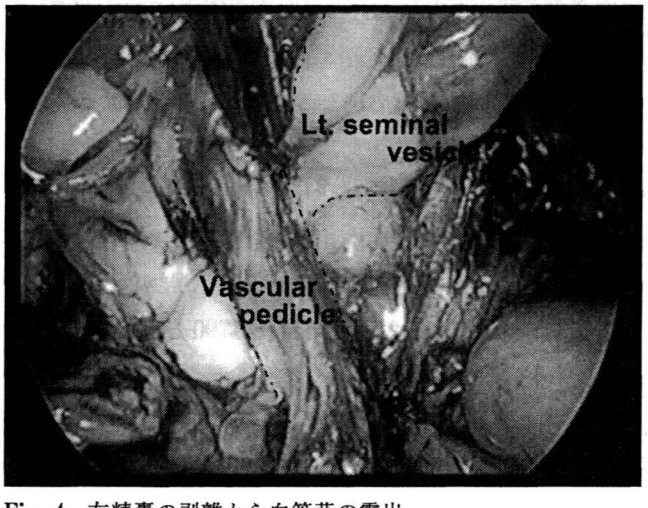


**Fig. 4** 左精嚢の剥離から血管茎の露出

**Table 2** Peri- and postoperative findings of LRC and ORC

| | LRC | ORC | p-value |
|---|---|---|---|
| Number pts | 24 | 16 | |
| Operative time (min) | 620±122 | 477±68.5 | NS |
| Blood loss* (ml) | 1683±812 | 2350±1321 | NS |
| Transfusion** (%) | 62.5 | 75.0 | NS |
| Transfusion*** (%) | 37.5 | 68.7 | p=0.053 |
| Ileus (%) | 16.7 | 18.7 | NS |
| Oral intake | | | |
| Fluid (d) | 6.0±4.1 | 4.0±0.8 | NS |
| Diet (d) | 8.6±6.4 | 6.8±2.6 | p=0.02 |
| Postop. complication | | | |
| Minor (%) | 58.3 | 56.2 | NS |
| Major (%) | 12.5 | 6.2 | NS |
| Ambulation (d) | 2.8±1.2 | 2.6±0.9 | NS |
| Hospital stay (d) | 26.8±13.4 | 30.5±24.7 | NS |
| WBC**** (/mm$^3$) | 9996±2765 | 10219±3208 | NS |
| CRP **** (mg/l) | 8.61±1.90 | 9.70±2.02 | NS |

*: including urine
**: including autologous blood transfusion
***: excluding autologous blood transfusion
****: Data from day 1 following surgery
Figures are mean±standard deviation.

**Table 3** Pathological findings and survival in LRC and ORC

| | LRC | ORC | p-value |
|---|---|---|---|
| Number of pts | 24 | 16 | |
| Grade* | | | NS |
| G2 (%) | 5 (25.0) | 3 (23.1) | |
| G3 (%) | 15 (75.0) | 10 (77.9) | |
| pT stage | | | NS |
| ≦2 (%) | 15 (62.5) | 8 (50.0) | |
| ≧3 (%) | 9 (37.5) | 8 (50.0) | |
| Number of lymph nodes (mean±SD) ** | 14.6±6.0 | 17.8±10.3 | NS |
| Lymph node mets. (%) ** | 5 (22.7) | 4 (30.8) | NS |
| Pos. surgical margin (%) | 0 (0) | 1 (6.25) | NS |
| Follow- up (d, mean±SD) | 504±297 | 311±293 | NS |
| Survival | | | |
| Overall (%) | 21 (87.5) | 14 (87.5) | NS |
| Recurrence-free (%) | 21 (87.5) | 12 (75.0) | NS |

pT0 were 5 cases (LRC : 4, ORC1) in this study.
* : excluding 2 cases (ORC : 2) of non-urothelial carcinoma
** : excluding 5 cases (LRC : 2, ORC : 3) without lymph node dissection.
SD, standard deviation

いた．（下腹部正中切開はカメラのポートと正中の10mmのポートを結び，さらに恥骨上までの皮膚切開とした．）組織の摘出，リンパ節郭清，尿路変向は開腹後に通常の開腹術と同様の方法で施行した．

尚，本手術は，学内の倫理委員会の承認を得て実施している．

## 結　果

本検討における術者は4名であった．年齢，性別，grade，臨床病期（T stage）についてLRC群とORC群間に有意差を認めなかったが，尿路変向術式についてはLRC群において回腸新膀胱が，ORC群において回腸導管がより多く選択（p=0.01）されていた（Table 1）．

LRC群とORC群別の手術関連項目，病理学的所見，生存率の結果について示す（Table 2, 3）．手術時間はLRC群が平均620分（337－800分），ORC群が477分（360－585分）であった（p=0.3）．出血量はLRC群が平均1683ml（380-3295ml），ORC群が平均2350ml（790-5700ml）であった（p=0.4）．自己血輸血を含む輸血を要したものはLRC群が15例（62.5%），ORC群が12例（75.0%）であり（p=0.4），同種血輸血をおこなったものはLRC群が9例（37.5%），ORC群が11例（68.7%）であった（p=0.053）．術後イレウスをLRC群では4例（16.7%）に，ORC群では3例（18.7%）に認めた（p=0.8）．経口摂取開始（飲水，食事）までの期間は，それぞれLRC群で平均6.0日（3－23日），8.6日（6－37日），ORC群が平均4.0日（3－5日），6.8日（4－13日）であった（各p=0.3, 0.02）．Minor，Majorな術後の合併症発生率は，それぞれLRC群が14例（58.3%），3例（12.5%），ORC群が9例（56.2%），1例（6.2%）であった（各p=0.4, 0.8）．腸管吻合不全に伴うイレウスはイレウス発生と術後合併症（Major）ともに「あり」と分類した．合併症の種類と症例の背景をTable 4（a, b）に示す（症例は手術施行順に記した）．創哆開については，軽度のものもすべて含めた．今回の検討ではMajorなものは4例（ORC群1例，LRC群3例）で，すべて腸管吻合不全であった．4例中3例（ORC群1例，LRC群2例）は手術にて修復した．LRC群の1例は保存的に治療しえたが，食事の開始まで37日を要した．術後歩行開始までの期間はLRC群が平均2.8日（1－6日），ORC群が平均2.6日（1－5日）であった（p=0.1）．退院までの期間はLRC群が平均26.8日（14－83日），ORC群が平均30.5日（16－120日）であった（p=0.5）．手術翌日の血中白血球数，CRP値はそれぞれLRC群が平均9996/mm$^3$（5600－16400/mm$^3$），平均8.61mg/l（5.81－13.27mg/l），ORC群が平均10219/mm$^3$（4200－18600/mm$^3$），平均9.70mg/l（5.27－12.61mg/l）であった（各

**Table 4a** Complication in ORC group

| Age (yo) | Gender | Stage | Diversion | Op. time (min.) | Blood loss (ml) | Complication |
|---|---|---|---|---|---|---|
| 70 | M | T1 | IC | 505 | 790 | WI |
| 76 | M | T2 | IC | 425 | 1232 | WD |
| 66 | F | T2 | IC | 490 | 2120 | WD |
| 75 | M | T1 | IC | 520 | 2810 | WD |
| | | | | | | ABL* |
| 66 | M | T4 | IC | 360 | 1900 | PN |
| 39 | M | T2 | NB | 540 | 4420 | PN |
| 77 | F | T2 | IC | 510 | 2250 | PN |
| 59 | F | T2 | IC | 480 | 3880 | WD |
| 67 | M | T2 | IC | 509 | 1790 | WD |

*: Major complication
WI: Wound infection WD: Wound dehiscence
ABL: Anastomotic bowel leak PN: Pyelonephritis

**Table 4b** Complication in LRC group

| Age (yo) | Gender | Stage | Diversion | Op. time (min.) | Blood loss (ml) | Complication |
|---|---|---|---|---|---|---|
| 56 | M | T1 | NB | 800 | 2695 | PN |
| 58 | M | T2 | NB | 740 | 1430 | PN |
| 62 | M | T2 | NB | 760 | 2000 | WD |
| | | | | | | PN |
| 75 | M | T3 | NB | 615 | 2810 | WD |
| 60 | M | T1 | NB | 655 | 2680 | WD |
| 76 | M | T1 | IC | 610 | 2317 | WD |
| 48 | M | T1 | NB | 480 | 1560 | WD |
| 63 | M | T2 | NB | 630 | 1712 | PN |
| 58 | M | T2 | NB | 540 | 1790 | EP |
| 79 | M | T1 | IC | 632 | 1550 | FUO |
| 54 | M | T2 | NB | 580 | 610 | WD |
| | | | | | | ABL* |
| 84 | M | T1 | IC | 337 | 380 | PN |
| 64 | M | T3 | IC | 395 | 1170 | ABL* |
| 61 | M | T1 | IC | 680 | 1420 | WD |
| | | | | | | ABL*,** |
| 58 | F | T1 | NB | 622 | 1560 | WD |

*: Major complication
**: Treated conservatively
PN: Pyelonephritis WD: Wound dehiscence EP: Epididymitis
FUO: Fever of unknown origin ABL: Anastomotic bowel leak

p=0.4, 0.4).

上述のように，食事の開始についてはORC群で有意(p=0.02)に短かった．同種血輸血を行った率では有意差は得られなかったがLRC群で少ない（LRC群では自己血のみでコントロール可能な率が高い）傾向があった(p=0.053)．そのほかの項目については2群の間に有意差は認めらなかった．

両群の病理学的所見（Grade，pT stage，リンパ節転移陽性率，切除断端陽性率）に有意差を認めなかった（各p=0.9, 0.4, 0.3, 0.2)． pT0 は5例（LRC：4例，ORC：1例）に認めた．悪性度（Grade）の比較においては腺癌（ORC：1例)，扁平上皮癌（ORC：1例）は除外した．

シスプラチンを用いた術後補助化学療法（MEC療法）はLRC群7例，ORC群2例に対して行われたが有意差は認めなかった（p=0.2)．

術後観察期間はLRC群が平均504日（19－1089日)，ORC群が平均311日（50－1128日）で有意差を認めず（p=0.4)，観察期間は短いが，生存率（全生存率，非再発生存率）においてもこの2群間に差を認めなかった（p=0.4, 0.08)．

なお，LRC群において2例で術中に直腸損傷を認めたが，術中に修復し得た．術後，直腸損傷による合併症は認めなかった．

## 考　察

ORCとLRC＋体外での尿路変向術の周術期成績に関する比較について，Haberら[1]はLRC＋体外での尿路変向術では出血量やイレウスの発生がより少なく，入院期間が短いことを報告している．また，Basillotelら[6]はORCに比較してLRC＋体外での尿路変向術は術後の鎮痛剤の使用量が少なく，術後経口摂取開始までの期間が短く，入院期間や軽作業への復帰までの期間が短いこと，さらにPropigliaら[7]はLRCのグループでは鎮痛剤使用がより少なく，術後経口摂取可能となるまでがより短いことを報告している．そして，手術時間や合併症については両者の間に有意な差を認めなかった[1,6]としている．

また，尿路変向についてHaber[8]らは，体外で行うOpen-assistedの方が，腹腔鏡下で行う方法（Pure laparoscopic）よりも手術時間が短く，出血量と輸血率が少なく，術後の経口摂取可能となるまでの期間，入院期間が短いとしている．小さな合併症についてはPure laparoscopicの方が多く，再手術を要するような合併症の発生率はPure laparoscopicでは29％，Open-assistedでは11％（p=0.08）と報告している．現時点では，LRCはORCよりもメリットがあるが，尿路変向については体外で行うほうがよいという結論である．

今回のわれわれの検討では上に挙げた報告例のような明らかな有用性は認められなかった．今回の検討ではLRC

とORCの症例において選択された尿路変向法に差があったことが要因となった可能性もある．出血量に関しては，LRCでは膀胱全摘（気腹終了時）までの平均値は217.5ml（30-650ml）と比較的少量にコントロールされていた．しかし，開腹術に移行してからのoozingなどにより全体の出血量が増加してしまったと考えられる．食事開始までの期間について，今回の検討ではORC群の方が短期間であったが，LRC群においては腸管吻合不全により37日を要した症例もあり，少ない症例数での比較において影響が大きかった可能性もある．低侵襲性の評価については，今回の検討では術翌日の血中白血球数とCRP値，歩行開始までの期間を指標としたが，いずれも有意差を認めなかった．今後は海外での報告例のように術後鎮痛剤の投与量や投与期間などについても評価を行う必要があると考える．

尿路における他臓器の腹腔鏡下手術と同様に，この術式においても，腹腔鏡下での拡大視野のもとでの操作，気腹による出血量の軽減，低侵襲化などのメリットが期待される．さらに腸管を利用した尿路変向において，腸管の浮腫の軽減も期待でき，術後の消化管機能回復期間の短縮が期待される．また，今回の検討では，術者が4名で，症例数も24例と少なく，データには示していないが明らかなラーニング効果は認められなかった．しかし，他の外科手術と同様に，今後ラーニングカーブが立ちあがり，安定することも十分に期待できる．このような点からも，さらに症例を増やし，この術式と開腹術との比較検討を進めていく予定である．

## 結　語

当科で施行したLRCの初期経験ならびに，同時期に施行された開腹による根治的膀胱摘除術との比較について報告した．今回の検討では，諸種所見の数値上，海外での報告のような有用性は認められなかったものの，十分に今後が期待できる手術手技であると考えられた．

## 文　献


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Research Article

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# Association between mutations in the core region of hepatitis C virus genotype 1 and hepatocellular carcinoma development

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**Background & Aims:** To determine whether amino acid mutations in the core region of hepatitis C virus (HCV) genotype 1 are associated with response to interferon (IFN) therapy and development of hepatocellular carcinoma (HCC).

**Methods:** We followed up 361 patients (median duration, 121 months), and IFN monotherapy was administered to 275 (76%) [sustained virological response (SVR) rate, 26.5%]. Using pretreatment sera, mutations at core residues 70 and 91 were analyzed [double wild (DW)-type amino acid pattern: arginine, residue 70; leucine, residue 91].

**Results:** A low aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio and low HCV load were independently associated with SVR, but core mutations were not. During follow-up, 12 of 81 (14.8%) patients with the DW-type pattern and 52 of 216 (24.1%) patients with non-DW-type pattern developed HCC ($p = 0.06$, Breslow–Gehan–Wilcoxon test). Multivariate analysis with the Cox proportional-hazards model revealed the following independent risk factors for HCC: male gender [$p < 0.0001$; risk ratio (RR), 3.97], older age ($p < 0.05$; RR, 2.08), advanced fibrosis ($p < 0.0001$; RR, 5.75), absence of SVR ($p < 0.01$; RR, 10.0), high AST level ($p < 0.01$; RR, 2.08), high AST/ALT ratio ($p < 0.01$; RR, 2.21), and non-DW-type pattern ($p < 0.05$; RR, 1.96). In patients with F0–F2 fibrosis at entry, non-DW-type was likely to lead to cirrhosis ($p = 0.051$).

**Conclusions:** In HCV genotype 1 patients, HCC risk could be predicted by studying core mutations, response to IFN, and host factors like age, gender, and liver fibrosis.



## Introduction

Hepatitis C virus (HCV) infection is a global health problem and the number of chronic carriers worldwide is estimated at 170 million [1]. HCV causes chronic hepatitis, which may progress to liver cirrhosis and hepatocellular carcinoma (HCC); the speed of disease progression, though, varies among patients [2,3]. Age, gender, steatosis, liver fibrosis, and response to interferon (IFN) therapy are reported to be associated with disease progression and HCC development [4–7]. HCV has six major genotypes, of which genotype 1 is most common in Japan and reported to be associated with increased severity and progression of chronic liver disease [8,9]. HCV contributes to HCC by directly modulating the pathways promoting the malignant transformation of hepatocytes [10–13]. Studies on transgenic mice revealed that the HCV core protein has oncogenic potential [14], but other studies yielded conflicting results [15,16]. Recently, mutations at amino acids 70 and 91 in the core region were shown to predict virological response to therapy with IFN plus ribavirin and also HCC development [17–19]. However, few studies support these results, and hence, the clinical impact of core mutations on HCC development is still unclear. In order to determine the viral factors associated with HCC development, we performed a retrospective cohort study on 361 patients with chronic liver disease caused by HCV genotype 1 infection and analyzed the amino acids present at core residues 70 and 91. Additionally, we evaluated whether these mutations were associated with IFN treatment, cirrhosis development, or host factors like age and gender.

## Patients and methods

### *Study population*

We enrolled 361 consecutive HCV genotype 1-infected patients who had undergone liver biopsy between August 1986 and June 1998 at Chiba University Hospital. At the enrollment time, the absence of HCC was proven by abdominal ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI). All the patients tested positive for anti-HCV antibody, determined by second-generation enzyme-linked immunosorbent assay. Patients with chronic hepatitis B, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, Wilson disease, or alcoholic liver disease were excluded, as were patients with a history of alcoholism, drug abuse, or IFN therapy. Written informed consent was obtained from all patients before performing liver biopsy.

Keywords: Hepatitis C virus; Core region; Hepatocellular carcinoma; Interferon; Sustained virological response.

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*Abbreviations:* HCV, hepatitis C virus; IFN, interferon; HCC, hepatocellular carcinoma; SVR, sustained virological response; DW-type, double wild-type; RR, risk ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; OR, odds ratio.

**Table 1. Baseline characteristics of 361 hepatitis C (HCV) genotype 1-infected patients according to hepatocellular carcinoma (HCC) development.**

| Patients | $n = 361$ | HCC development | | |
|---|---|---|---|---|
| | | (+), $n = 82$ | (−), $n = 279$ | $p$ value |
| Gender (male/female) | 219/142 | 56/26 | 163/116 | 0.1 |
| Age (years) | 50.5 ± 12.2 | 56.8 ± 7.1 | 48.6 ± 12.7 | <0.0001 |
| BMI (kg/m$^2$) | 23.1 ± 2.9 | 23.1 ± 2.8 | 23.1 ± 3.3 | 0.82 |
| Staging of fibrosis (F0–1/F2/F3/F4) | 197/59/52/53 | 13/18/23/28 | 184/41/29/25 | <0.0001 |
| *IFN treatment and response* | | | | |
| SVR/non-SVR/non-IFN | 73/202/86 | 4/55/23 | 69/147/63 | 0.0004 |
| *Laboratory data* | | | | |
| AST (IU/L) | 87 ± 62 | 109 ± 59 | 80 ± 61 | 0.0001 |
| ALT (IU/L) | 125 ± 93 | 139 ± 80 | 121 ± 96 | 0.13 |
| AST/ALT | 0.75 ± 0.26 | 0.84 ± 0.28 | 0.73 ± 0.25 | 0.0003 |
| Platelets (10$^4$/mm$^3$) | 17.7 ± 6.7 | 13.0 ± 3.3 | 18.2 ± 6.9 | <0.0001 |
| Albumin (g/dL) | 4.2 ± 0.36 | 4.1 ± 0.39 | 4.3 ± 0.35 | <0.0001 |
| Total bilirubin (mg/dL) | 0.8 ± 0.6 | 0.9 ± 0.3 | 0.8 ± 0.6 | 0.39 |
| Core protein (pg/mL) | 201 ± 245 | 283 ± 273 | 177 ± 231 | 0.001 |
| *Amino acid pattern* | | | | |
| 70 Wild/non-wild/ND | 168/129/64 | 32/32/18 | 136/97/46 | 0.23* |
| 91 Wild/non-wild/ND | 139/158/64 | 28/36/18 | 111/122/46 | 0.58* |
| DW/non-DW/ND | 81/216/64 | 12/52/18 | 69/164/46 | 0.08* |

BMI, body mass index; DW, double wild (arginine at residue 70 and leucine at residue 91 in the core region); ND, not detected; ND cases were excluded.

The clinical backgrounds of the patients are shown in Table 1. The study population was predominantly male (59% men), and the mean age of the patients was 50.5 ± 12.2 years, with 15% patients having liver cirrhosis.

*Laboratory examination*

Serum samples were obtained and stored at −30 °C until analysis. We assumed that genotype 1 corresponds to group 1 when determining the HCV RNA genotypes by serologic grouping of serum antibodies [20]. The serum HCV load of the patients was determined at the time of liver biopsy, using the HCV core protein detection kit (Eiken Chemical, Tokyo, Japan; detection limit, 8 pg/mL) [21].

*Histopathological examination*

Percutaneous liver biopsy was performed, and specimens were histopathologically assessed as described previously [22]. According to the criteria of Desmet et al. [23], the staging of fibrosis was defined as F0 (no fibrosis), F1 (mild fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis).

*Core nucleotide sequences*

HCV RNA was extracted from the serum samples obtained at the time of liver biopsy, and it was reverse-transcribed using SuperScript III reverse transcriptase (Invitrogen, Carlsbad, CA, USA). Nucleic acids were amplified by PCR with the

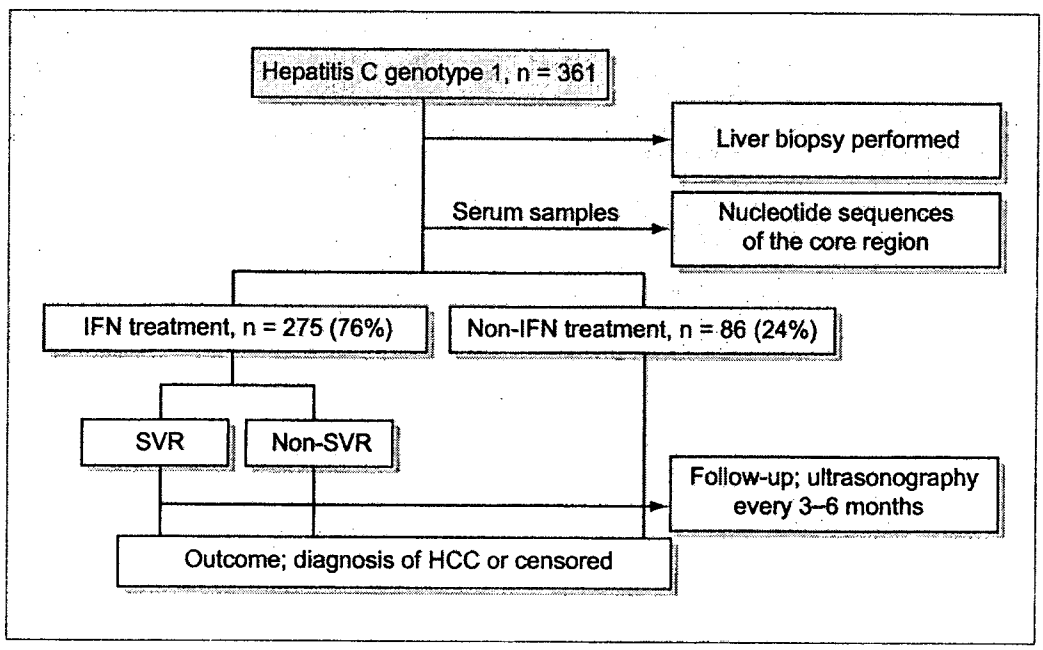


**Fig. 1. Clinical courses after enrollment and the evaluation methods.** IFN, interferon; SVR, sustained virological response; HCC, hepatocellular carcinoma. [This figure appears in colour on the web.]