(adenocarcinoma or others), gender, age (<70 or ≥70 years old) and thin-section CT findings (solid or non-solid).

### Treatment Methods

In the standard treatment arm, lobectomy with hilar and mediastinal lymph node dissection is performed. Systemic or selective lymph node dissection is mandatory, and nodal sampling is not allowed. The distance from the dissection margin to the tumor edge must be evaluated intra-operatively. If the distance is either less than the maximum tumor diameter or <20 mm, the absence of cancer cells in the resection margin must be histologically or cytologically confirmed before finishing surgery.

In the experimental treatment arm, segmentectomy with hilar and mediastinal lymph node dissection is performed. As with lobectomy, systemic or selective lymph node dissection is mandatory, and nodal sampling is not allowed. The distance from the dissection margin to the tumor edge must be evaluated in the same manner as with lobectomy. When lymph node metastasis is present or resection margin is not cancer-free, the surgical procedure must be converted to a lobectomy.

To confirm that the randomized surgical procedures are performed properly, we review the procedures centrally by photograph in all patients.

In both arms, post-operative adjuvant chemotherapy is recommended if the pathological findings reveal a tumor diameter >2 cm or if lymph node metastasis is present.

### Follow-up

All randomized patients are followed up for at least 5 years. Tumor markers and chest X-rays are evaluated at least every 6 months, and enhanced chest CT is evaluated at least every 6 months during the first 2 years and at least every 12 months for the duration of follow-up.

### Study Design and Statistical Analysis

This trial is designed to demonstrate that segmentectomy is not inferior to lobectomy in terms of overall survival. If the non-inferiority of segmentectomy is verified and the expected reduced toxicity of segmentectomy is observed, segmentectomy will be the preferred treatment for small peripheral NSCLC.

The planned sample size is 1100 patients, with 550 cases per arm. We anticipate 5 years of follow-up after 3 years of accrual, ensuring at least 80% power with a one-sided $\alpha$ of 5% and a non-inferiority margin of 5% in terms of 5-year survival for the primary endpoint. This assumes an expected 5-year overall survival of 90% in each arm.

### Interim Analysis and Monitoring

We plan on conducting two interim analyses, taking multiplicity into account using the Lan–DeMets method with O'Brien and Fleming type alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by each Data Center to evaluate and improve study progress and quality.

### Procedure of Intergroup Study

The present study is one of the first Japanese collaborative studies between JCOG and WJOG. Patient registration, randomization, data collection, in-house monitoring and audits are performed in each data center. Each group uses a single study protocol, and protocol amendment or revision is done simultaneously. At the interim and final analyses, the data from WJOG Data Center are sent to JCOG Data Center and integrated. It is these integrated data, and not the separate data from each data center, that are used in the primary analysis.

## PARTICIPATING INSTITUTIONS (FROM NORTH TO SOUTH)

### Japan Clinical Oncology Group

Sendai Medical Center, Tohoku University Hospital, Iwaki Kyoritsu Hospital, Ibaragi Prefectural Central Hospital, Tochigi Cancer Center, Gunma Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba University Hospital, National Cancer Center Hospital, Tokyo Medical University Hospital, Cancer Institute Hospital, Juntendo University Hospital, Kanagawa Cancer Center, Niigata Cancer Center, Kanazawa University Hospital, Saku Central Hospital, Shizuoka Cancer Center, Aichi Cancer Center, Kyoto University Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka Prefectural medical Center for Respiratory and Allergic Diseases, Kinki-chuo Chest Medical Center, Osaka City General Hospital, Hyogo Cancer Center, Okayama University Hospital, Hiroshima University Hospital, Kure Medical Center, Shikoku Cancer Center, Kyushu Cancer Center, Fukuoka University Hospital, Nagasaki University Hospital, Kumamoto Chuo Hospital and Okinawa National Hospital.

### West Japan Oncology Group

Kitasato University Hospital, Kanagawa Cardiovascular and Respiratory Center, Sagamihara Kyodo Hospital, Toyama University Hospital, Ishikawa Prefectural Central Hospital, Gifu City Hospital, Hamamatsu Medical University Hospital, Seirei Hamamatsu General Hospital, Aichi Cancer Center Aichi Hospital, Nagoya Medical Center, Nagoya University Hospital, Nagoya Ekisaikai Hospital, Shiga University of Medical Science Hospital, Osaka University Hospital, Osaka City University Hospital, Kinki University Hospital, National Toneyama Hospital, Rinku General Medical Center, Suita Municipal Hospital, Kobe University Hospital, Kobe City

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Medical Center General Hospital, Hyogo Medical College University, Hyogo Prefectural Awaji Hospital, Himeji Red Cross Hospital, Kurashiki Central Hospital, Kawasaki Medical School Hospital, Hiroshima City Hospital, Hiroshima City Asa Hospital, Yamaguchi Ube Medical Center, University of Occupational and Environmental Health, Nippon Steel Yawata Memorial Hospital, Iizuka Hospital, Saga University Hospital, Kumamoto University Hospital, Kumamoto Regional Medical Center, Saiseikai Kumamoto Hospital and Oita Prefectural Hospital.

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## Conflict of interest statement

None declared.

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# Impact of positive pleural lavage cytology on survival in patients having lung resection for non–small-cell lung cancer: An international individual patient data meta-analysis

International Pleural Lavage Cytology Collaborators*

**Objectives:** Pleural lavage cytology is the microscopic study of cells obtained from saline instilled into and retrieved from the chest during surgery for non–small-cell lung cancer. The aims of this study were to collate multi-institutional individual patient data for meta-analysis to determine independence as a prognostic marker and to characterize the impact of positive results on stage-adjusted survival.

**Methods:** We identified 31 publications from 22 centers/research groups that performed pleural lavage cytology during surgery for non–small-cell lung cancer and invited submission of individual patient data. Actuarial survival was calculated using Kaplan-Meier methods, and comparisons were performed using the log-rank test. Cox proportional hazards regression was used to ascertain the covariates associated with survival.

**Results:** By January 1, 2008, submissions were received internationally from 11 centers with individual data from 8763 patients. In total, 511 (5.8%) patients had a positive pleural lavage cytology result, and this was shown to be an independent predictor of adverse survival associated with a hazard ratio of 1.465 (1.290–1.665; $P < .001$) compared with a reference hazard ratio of 1 for a negative result. On statistical modeling, the best adjustment for patients with a positive pleural lavage cytology result was a single increase in the T category assigned to the case, up to a maximum of T4. Correction for differences in survival were obtained in stages IB ($P = .315$) and IIB ($P = .453$), with a degree of correction in stage IIIA ($P = .07$).

**Conclusions:** Pleural lavage cytology should be considered in all patients with non–small-cell lung cancer suitable for resection. A positive result is an independent predictor of adverse survival, and the impact on survival suggests that it may be appropriate to upstage patients by 1 T category. (J Thorac Cardiovasc Surg 2010;139:1441-6)

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Pleural lavage cytology (PLC) is the microscopic study of cells obtained from saline instilled into and retrieved from the chest cavity (in patients without preoperative pleural effusion) during surgery for non–small-cell lung cancer. The solution is aspirated, and cytologic analysis is performed to screen for malignant cells. Results from this procedure have been published from Japan as early as 1989,[1] and internationally, an increasing number of centers have adopted this practice.

The frequency of positive results in the literature varies according to amount of solution used, timing of the procedure, and the center, but in general is less than 10% in the larger published series. Because the positive pickup rate is low, it is difficult for any single center alone to accumulate sufficient patient numbers for detailed study. As a result, its role as an independent predictor of prognosis has not been firmly established[2,3] and neither is the lung cancer community certain where to best place patients with positive results in relation to International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) stage-adjusted survival.

The aims of this study were to collate individual patient data from centers that have performed PLC to determine independence as a prognostic marker and to characterize the impact of a positive result on stage-adjusted survival.

## METHODS

A literature search was conducted by a professional medical librarian to identify publications on PLC (the full search strategy is available from Lyn Edmonds on request). From each publication, the authors were contacted by

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**Abbreviations and Acronyms**
AJCC = American Joint Committee on Cancer
PLC = pleural lavage cytology
UICC = International Union Against Cancer

E-mail or telephone or in person and invited to contribute data from their respective centers. Authors who responded were issued a data dictionary, and submissions were collated electronically in the specified standardized format. Staging was requested to follow the 6th UICC TNM Classification of Malignant Disease.[4]

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## Statistical Analyses

Continuous variables are expressed as means with standard deviations or median with interquartile ranges as appropriate to the data distribution. Nominal and categorical variables are expressed as frequency counts with percentages (%). Actuarial survival was calculated using Kaplan-Meier methods, and comparisons were performed using the log-rank test. Cox proportional hazards regression was used to ascertain the covariates associated with survival. Exploratory models were undertaken to determine the effect of upstaging of patients with positive PLC, including fixed and variable T-category assignment and stage groupings, compared with their peers at a higher stage.

Statistical analyses were performed using R 2.6.0 (R core development team, Vienna, Austria) and Stata 9.2 (StataCorp, College Station, Tex). There was no funding associated with this project.

## RESULTS

From 345 abstracts, we identified 31 publications[1-3,5-32] from 22 centers/research groups that performed PLC during surgery for non–small-cell lung cancer. All lead authors from the identified centers or research groups were contacted by E-mail or telephone or in person. By the deadline of January 1, 2008, submissions were received internationally from 11 centers with individual data from 8763 patients. The mean age (standard deviation) of the cohort was 64 (10) years, with the majority being male (66%). The demographic and follow-up details from the 11 centers and entire cohort are summarized in Table 1. The pathologic T, N, and M categories are summarized in Table 2.

In total, 511 (5.8%) patients were documented with positive PLC (evaluated on light microscopy), and the staging characteristics in 477 patients with complete staging information were 29 (6.1) in IA, 122 (25.6) in IB, 7 (1.5) in IIA, 92 (19.3) in IIB, 112 (23.4) in IIIA, 84 (17.6) in IIIB, and 31 (6.5) in IV, respectively.

## Survival

At a median follow-up time of 3.3 (1.3–5.8) years, follow-up was complete in 8213 patients (94%) with 3441 (39%) deaths. On multivariable Cox regression analysis (Table 3), positive PLC status was identified as an independent predictor of adverse survival, associated with a hazard ratio of 1.465 (1.290–1.665; $P < .001$). Increasing age, male gender, increasing UICC/AJCC staging categories of pT, pN, and M status were all independent predictors of adverse survival ($P < .001$). In addition, despite inclusion in the T categories, tumor size ($P < .001$) and breeching of the visceral

**TABLE 1. Demographic and follow-up details**

| Centre | Institution | Location | Number, n | Mean age (SD) | Males, n (%) | Positive PLC, n (%) | Median follow up, y (IQR) | Deaths, n (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | National Cancer Center Hospital East | Chiba, Japan | 2950 | 65 (10) | 1866 (63) | 117 (4.0) | 3.0 (1.4–6.1) | 982 (33) |
| 2 | Osaka Medical Centre for Cancer and Cardiovascular Diseases | Osaka, Japan | 507 | 63 (9) | 363 (72) | 73 (14.4) | 4.5 (2.1–6.4) | 249 (49) |
| 3 | Taichung Veterans General Hospital | Taichung, Taiwan | 36 | 64 (8) | 29 (81) | 15 (41.7) | 1.5 (0.4–5.2) | 28 (78) |
| 4 | The Royal Brompton Hospital | London, UK | 292 | 64 (10) | 196 (67) | 13 (4.5) | 1.25 (0.1–3.3) | 94 (32) |
| 5 | Hopital European Georges Pompidou | Paris, France | 194 | 62 (12) | 140 (72) | 24 (12.3) | 2.7 (1.3–3.7) | 84 (43) |
| 6 | Osaka Prefectural Medical Center for Respiratory and Allergic Diseases | Osaka, Japan | 1522 | 64 (10) | 1081 (71) | 92 (6.0) | 2.3 (1.0–5.5) | 839 (55) |
| 7 | Kurashiki Central Hospital | Okayama, Japan | 1025 | 67 (10) | 627 (61) | 45 (4.3) | 2.2 (0.8–4.8) | 253 (25) |
| 8 | Hyogo Cancer Centre | Akashi, Japan | 1192 | 64 (10) | 833 (70) | 52 (4.3) | 4.5 (2.4–6.4) | 517 (43) |
| 9 | Cancer Institute Hospital | Tokyo, Japan | 853 | 63 (10) | 500 (59) | 41 (4.8) | 4.4 (2.9–6.2) | 272 (32) |
| 10 | Second University of Naples | Naples, Italy | 107 | 65 (9) | 97 (91) | 31 (29.0) | 4.9 (1.9–5.8) | 43 (40) |
| 11 | Chest Diseases Hospital | Athens, Greece | 85 | 60 (8) | 77 (91) | 8 (9.4) | 3.4 (1.4–4.9) | 80 (94) |
| Total | | | 8763 | 64 (10) | 5809 (66) | 511 (5.8) | 3.3 (1.3–5.8) | 3441 (39) |

*IQR*, Interquartile range; *PLC*, pleural lavage cytology; *SD*, standard deviation.

TABLE 2. Pathologic T, N, and M status

| | T category | | | | | | | N category | | | | | | M category | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Center | T0, n (%) | T1, n (%) | T2, n (%) | T3, n (%) | T4, n (%) | Tx, n (%) | N/A, n (%) | N0, n (%) | N1, n (%) | N2, n (%) | N3, n (%) | Nx, n (%) | N/A, n (%) | M1, n (%) | Mx, n (%) | N/A, n (%) |
| 1 | 8 (<1) | 1279 (43) | 1039 (35) | 272 (9) | 268 (9) | 7 (<1) | 77 (3) | 1915 (65) | 421 (14) | 399 (14) | 14 (<1) | 110 (4) | 91 (3) | 36 (1) | 0 (0) | 97 (3) |
| 2 | 0 (0) | 180 (36) | 239 (47) | 70 (14) | 18 (4) | 0 (0) | 0 (0) | 324 (64) | 83 (16) | 95 (19) | 5 (1) | 0 (0) | 0 (0) | 22 (4) | 0 (0) | 0 (0) |
| 3 | 0 (0) | 1 (3) | 24 (67) | 5 (14) | 5 (14) | 0 (0) | 1 (3) | 14 (39) | 8 (22) | 13 (36) | 0 (0) | 0 (0) | 1 (3) | 3 (8) | 0 (0) | 1 (3) |
| 4 | 0 (0) | 76 (26) | 190 (65) | 8 (3) | 18 (6) | 0 (0) | 0 (0) | 198 (68) | 48 (16) | 39 (13) | 0 (0) | 1 (<1) | 6 (2) | 4 (1) | 0 (0) | 6 (2) |
| 5 | 0 (0) | 36 (19) | 131 (67) | 24 (12) | 3 (2) | 0 (0) | 0 (0) | 122 (63) | 31 (16) | 41 (21) | 0 (0) | 0 (0) | 0 (0) | 6 (3) | 0 (0) | 0 (0) |
| 6 | 12 (1) | 476 (31) | 693 (46) | 200 (13) | 138 (9) | 0 (0) | 3 (1) | 855 (56) | 290 (19) | 338 (22) | 23 (2) | 13 (1) | 3 (<1) | 104 (7) | 0 (0) | 5 (1) |
| 7 | 0 (0) | 599 (58) | 309 (30) | 59 (6) | 58 (6) | 0 (0) | 0 (0) | 756 (74) | 97 (9) | 121 (12) | 5 (1) | 46 (4) | 0 (0) | 21 (2) | 8 (1) | 0 (0) |
| 8 | 15 (0) | 535 (45) | 487 (41) | 107 (9) | 48 (4) | 0 (0) | 0 (0) | 784 (66) | 198 (17) | 182 (15) | 21 (2) | 7 (<1) | 0 (0) | 48 (4) | 0 (0) | 0 (0) |
| 9 | 4 (<1) | 387 (45) | 307 (36) | 47 (6) | 108 (13) | 0 (0) | 0 (0) | 584 (68) | 122 (14) | 127 (15) | 18 (2) | 2 (<1) | 0 (0) | 20 (2) | 0 (0) | 0 (0) |
| 10 | 0 (0) | 29 (27) | 47 (43) | 30 (28) | 1 (1) | 0 (0) | 0 (0) | 77 (72) | 13 (12) | 17 (16) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| 11 | 0 (0) | 10 (12) | 44 (52) | 31 (36) | 0 (0) | 0 (0) | 0 (0) | 33 (39) | 30 (35) | 22 (26) | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 0 (0) |
| Total | 39 (<1) | 3608 (41) | 3510 (40) | 853 (10) | 665 (8) | 7 (<1) | 81 (1) | 5662 (65) | 1341 (15) | 1394 (16) | 86 (1) | 179 (2) | 101 (1) | 265 (3) | 8 (<1) | 109 (1) |

TABLE 3. Multivariable predictors of survival

| Covariate | Hazard ratio | 95% confidence interval | *P* value |
|---|---|---|---|
| Positive lavage cytology | 1.465 | 1.290–1.665 | <.001 |
| Age, per year | 1.023 | 1.019–1.027 | <.001 |
| Female gender | 0.683 | 0.625–0.746 | <.001 |
| pT category | | | |
| T1 | 1.000 | N/A | N/A |
| T2 | 1.422 | 1.277–1.583 | <.001 |
| T3 | 1.340 | 1.116–1.610 | .002 |
| T4 | 1.511 | 1.292–1.767 | <.001 |
| pN category | | | |
| N0 | 1.000 | N/A | N/A |
| N1 | 1.897 | 1.723–2.088 | <.001 |
| N2 | 3.133 | 2.864–3.427 | <.001 |
| N3 | 4.758 | 3.680–6.153 | <.001 |
| M1 status | 2.169 | 1.854–2.539 | <.001 |
| Size of primary tumor, cm | 1.091 | 1.069–1.113 | <.001 |
| Visceral pleural invasion | 1.289 | 1.183–1.404 | <.001 |
| Parietal pleural invasion | 1.344 | 1.150–1.571 | <.001 |

($P < .001$) and parietal pleura ($P < .001$) remained stage-independent predictors of adverse survival.

The overall 1- and 5-year survivals of the 511 patients who were PLC-positive were 80% and 31%, respectively. Stage for stage, patients with positive PLC results had poorer survival compared with their peers with a negative result (Figure 1, *A–C*). When overall survival was plotted for stage groupings I to III, patients with positive PLC result had similar overall survival to patients in UICC/AJCC stage III (Figure 1, *D*).

Using exploratory statistical modeling, the best adjustment for patients with a positive PLC result was to increase the T category assigned by a single numerical category (upstage). This had the effect of upstaging patients into designated groups and retaining the independent effects of nodal status on patients who were PLC-positive. The differences in adjusted survival by increasing the T stage by 1 category for patients who were PLC-positive (up to a maximum of T4 status) are presented in Figures 2 and 3 for stages IB, IIB, IIIA, and IIIB. The results were not presented for stages IA and IIA, as no comparative group remains when patients in T1 who were PLC-positive are reassigned to T2. Good correction is visible in stages I to II, and the differences are somewhat reduced in stage IIIB. No correction is present in stage IIIB as the T4 designation remains unaltered.

## DISCUSSION

Although a number of studies have reported positive PLC result as a predictor of poor prognosis, there have been conflicting opinions if it is independent to UICC/AJCC stage.[2] A principle difficulty in evaluating prognostic independence on multivariable analyses is the relatively small number of

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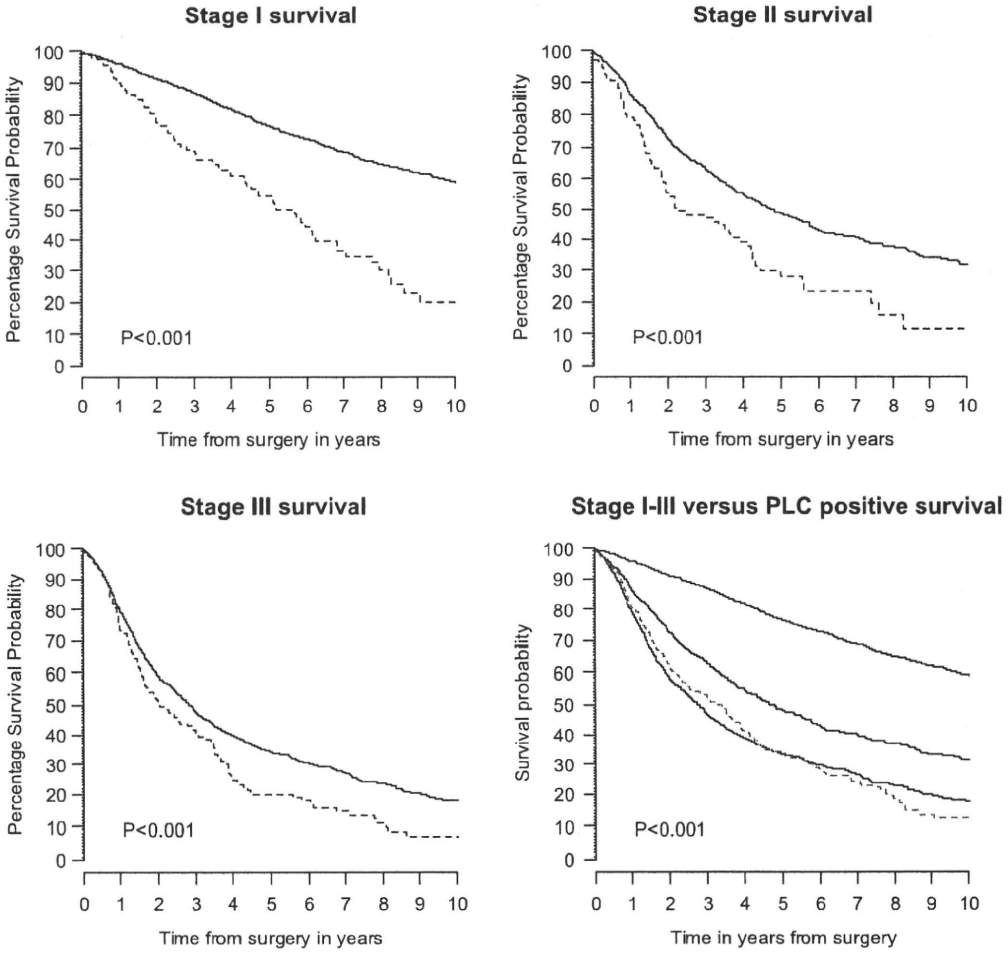


**FIGURE 1.** Overall survival by stage and pleural lavage cytology *(PLC)* status. *Solid lines* are patients with negative PLC; *dashed lines* are patients with positive PLC.

patients with a positive result. To address this problem, a collaborative effort was undertaken by 11 centers from around the world contributing individual data from over 8700 patients.

The results of our study confirm the independence of positive PLC as an adverse prognostic predictor in patients (without preoperative malignant effusion) deemed suitable for lung resection for non–small-cell lung cancer. The effect is the upstaging of patients by 1 T category (up to a maximum of T4). Although patients with T4 disease had poorer survival associated with a positive PLC status, this remained better than the M1a designation of the International Association for the Study of Lung Cancer proposals for stage grouping in the 7th edition of TNM in lung cancer.[33]

PLC is inexpensive and simple to perform and does not require specialized equipment or facilities for analysis. Techniques, however, differ from center to center, and there is a need to standardize this practice internationally, to minimize differences in the positive results that may arise from differences in technique. We recommend 100 mL of saline irrigated over the lung surface immediately after thoracotomy and prior to lung resection. The saline is aspirated and the sample sent for cytologic screening for malignant cells. The UICC recommends that cytologic results of pleural and peritoneal washings be considered separate to the classification of isolated tumor cells and micrometastasis. In addition, identification of patients with positive PLC results can be recorded with the suffix of (cy+).[34]

The effect of upstaging patients with early stage disease will shift a proportion of patients from stage I to II, the threshold for consideration of postoperative chemotherapy. It would be ideal for further trials to be conducted to specifically evaluate the utility of postoperative chemotherapy in the setting of positive PLC status. In the absence of such evidence, the implications for the change in stage and the potential benefits for adjuvant chemotherapy should be carefully considered.

The inferences from this work were based on the availability of the submitted data and on the assumption that

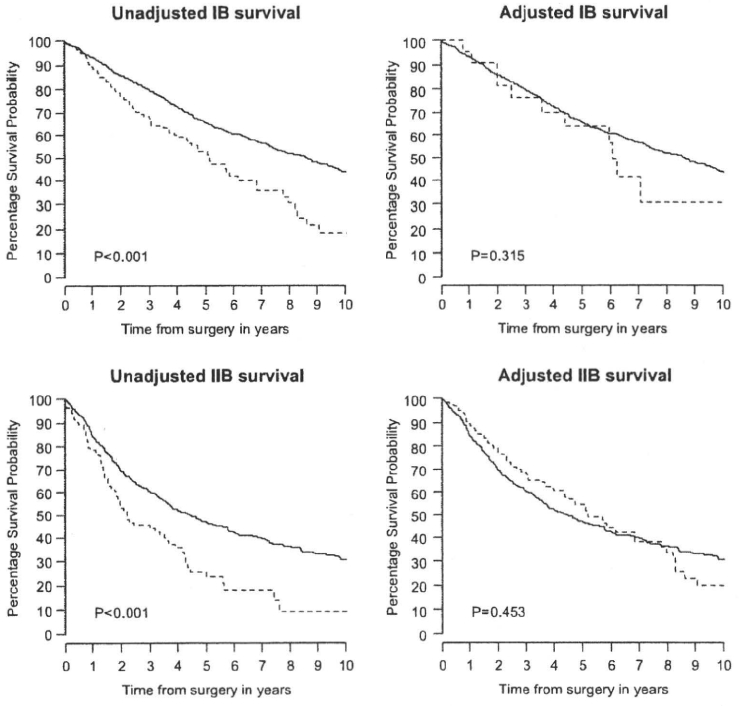


**FIGURE 2.** Survival by pleural lavage cytology (PLC) status with adjusted T stage for patients with positive PLC in stage I to II. *Solid lines* are patients with negative PLC; *dashed lines* are patients with positive PLC.

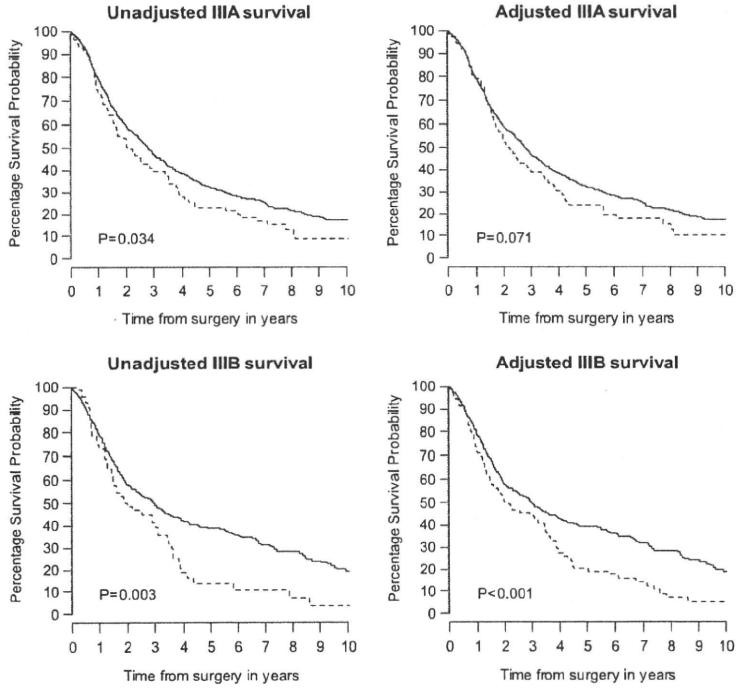


**FIGURE 3.** Survival by pleural lavage cytology (PLC) status with adjusted T stage for patients with positive PLC in stage III. *Solid lines* are patients with negative PLC; *dashed lines* are patients with positive PLC.

the estimates would not be significantly altered if data were submitted by all centers that published on this topic.

## CONCLUSIONS

PLC should be considered in all patients with early stage lung cancer suitable for resection. A positive result is an independent predictor of adverse survival and carries a prognosis that suggests it may be appropriate to upstage patients by 1 T category.

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# Automated assessment of malignant degree of small peripheral adenocarcinomas using volumetric CT data: Correlation with pathologic prognostic factors

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ABSTRACT

*Purpose:* To evaluate a custom-developed software for analyzing malignant degrees of small peripheral adenocarcinomas on volumetric CT data compared to pathological prognostic factors.
*Materials and methods:* Forty-six adenocarcinomas with a diameter of 2 cm or less from 46 patients were included. The custom-developed software can calculate the volumetric rates of solid parts to whole nodules even though solid parts show a punctate distribution, and automatically classify nodules into the following six types according to the volumetric rates of solid parts: type 1, pure ground-glass opacity (GGO); type 2, semiconsolidation; type 3, small solid part with a GGO halo; type 4, mixed type with an area that consisted of GGO and solid parts which have air-bronchogram or show a punctate distribution; type 5, large solid part with a GGO halo; and type 6, pure solid type. The boundary between solid portion and GGO on CT was decided using two threshold selection methods for segmenting gray-scale images. A radiologist also examined two-dimensional rates of solid parts to total opacity (2D%solid) which was already confirmed with previous reports.
*Results:* There were good agreements between the classification determined by the software and radiologists (weighted kappa = 0.778–0.804). Multivariate logistic regression analyses showed that both 2D%solid and computer-automated classification were significantly useful in estimating lymphatic invasion ($p = 0.0007$, 0.0027), vascular invasion ($p = 0.003$, 0.012), and pleural invasion ($p = 0.021$, 0.025).
*Conclusion:* Using our custom-developed software, it is feasible to predict the pathological prognostic factors of small peripheral adenocarcinomas.

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## 1. Introduction

Adenocarcinoma is the most common histopathologic subtype of lung cancer, and its incidence has been increasing [1,2]. Recent advances in CT scanning technology have enabled the detection of small pulmonary nodules, most of which are peripherally located adenocarcinoma. Such early detection using CT may alter the course of treatment of adenocarcinomas and subsequently improve the prognosis [3,4]. Although there is general consensus regarding the pathologic diagnosis of early pulmonary adenocarcinoma [5–8], the clinical and radiologic diagnosis of early adenocarcinoma with favorable prognosis remains controversial. Many reports [8,9] have demonstrated that the size of the central collapse/fibrosis and the percentage of the bronchioloalveolar carcinoma (BAC) component can be used as prognostic indicators for small lung adenocarcinomas. The BAC component is commonly detected on CT as ground-glass opacity (GGO); defined as a hazy increase in lung attenuation that does not obscure the underlying vascular markings [10]. However, there is no generally accepted method for measuring the area of GGO.

A new radiologic classification of small pulmonary adenocarcinoma on thoracic thin-section CT has already been proposed [11]. This classification, which is significantly associated with pathological prognostic factors, is based on the findings of thin-section CT

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scans, such as the presence of solid and GGO parts, the distribution of solid parts, and the rate of solid parts to the whole nodule. However, because this classification can only be evaluated visually on CT, observers may differ in their assessment regarding the presence of solid and GGO parts. The purpose of the present study was to evaluate the ability of our custom-developed software to automatically analyze the malignant degree of small peripheral adenocarcinomas on quantitative volumetric CT data compared to pathological prognostic factors.

## 2. Materials and methods

### 2.1. Patients and diagnoses

The present study was approved by the institutional review board. Informed consent was waived for retrospective review of patient records and images. The study population consisted of consecutive patients who had undergone surgery at one hospital from January 2001 through July 2005 for primary pulmonary adenocarcinomas with a diameter of 2 cm or less. CT scans were performed in all patients before surgery. In all patients, the pulmonary nodules with a diameter of 2 cm or less in the longest diameter had areas with GGO and/or solid parts on CT, and were completely surrounded by the lung or visceral pleura at surgery. Patients who had previous adenocarcinomas in the lungs or other organs and who had undergone chemotherapy before surgery were excluded from the study. Moreover, patients were also excluded if their thin-section CT data was not available. Forty-six patients (22 men, 24 women; age range, 43–78 years; mean age, 61 years) were included in the present study.

The histopathologic diagnosis of all nodules was non-mucinous adenocarcinoma. On the basis of the histologic growth pattern, the adenocarcinomas were classified into the following three subtypes: localized BAC ($n = 16$), adenocarcinoma with BAC component ($n = 29$), and adenocarcinoma without BAC component ($n = 1$). The 16 cases of BAC included 3 cases associated with atypical adenomatous hyperplasia.

### 2.2. Acquisition of thin-section CT images

Chest CT scans were conducted using a 4-detector row LightSpeed QXi Scanner (General Electric Medical Systems, Milwaukee, WI, USA), an 8-detector row LightSpeed Ultra Scanner (GE Healthcare Technologies, Milwaukee, WI, USA), or a 4-detector row Aquilion V-detector Scanner (Toshiba Medical Systems, Tokyo, Japan). The parameters used for the scans depended on the indication: collimation was 0.5 or 1.25 mm, pitch was 0.625–1.5, the rotation time was 0.5–0.8 s per rotation, exposure parameters were 120 kV and 200 mA, and the field of view was 200 mm. All image data were reconstructed with a high spatial frequency algorithm at a 0.5- or 1.25-mm interval. All CT scans were displayed on a monitor at lung window settings (level, −700 Hounsfield units [HU]; width, 1200 HU).

### 2.3. Development of software

#### 2.3.1. Definition of GGO, semiconsolidation, and solid component

Radiologic classifications of small pulmonary adenocarcinomas were classified into six subgroups (types 1–6) according to malignant degree of the tumor, and were in agreement with a previous report [11] (Table 1). Generally, opacity of peripheral adenocarcinomas on CT can be visually broken down into three parts, such as GGO, semiconsolidation, and solid part. GGO was defined as an area exhibiting a slight, homogeneous increase in density, which did not obscure underlying vascular markings. Semiconsolidation was defined as an area exhibiting an intermediate homogeneous increase in density, which did not obscure underlying vascular markings. The solid part was defined as an area of increased opacification that completely obscured underlying vascular markings. Prior to the present study, we determined threshold CT values between GGO and semiconsolidation and between semiconsolidation and solid parts in an additional six cases with adenocarcinomas, other than those in the present study, in order to automatically segment the three parts using our custom-developed software. By consensus, two radiologists assessed whether the tumor was GGO, semiconsolidation, or solid part from CT images of these additional six adenocarcinomas.

Two automatic threshold selection methods for segmenting gray-level images were used in the present study, 1: Method-1, Otsu's method [12], and 2: Method-2, Kittler's method [13]. Method-1 is a nonparametric and unsupervised method of automatic threshold selection for picture segmentation [12]. This simple method enables the division of gray images into two separate images through the selection of a threshold from gray-level histograms. Utilizing only the zeroth- and the first-order cumulative moments of the gray-level histogram, extending this method to multithreshold problems is straightforward. Method-2 is based on "minimum error thresh-holding" [13]. A computationally efficient solution to the problem of minimum error thresholding is derived under the assumption that both object and pixel gray-level values are normally distributed. The thresholds between GGO and semiconsolidation were −547 HU using Method-1 and −534 HU using Method-2; those between semiconsolidation and solid part were −291 HU using Method-1 and −188 HU using Method-2 (Figs. 1 and 2).

#### 2.3.2. Decision of cut-off value of rate of solid part to total tumor (% solid) for the three-dimensional classification of tumors

According to radiologic classifications used in the present study (Table 1), the two-dimensional % solid (2D%solid) of type 3 or 4 was less than 50%, and 2D%solid of type 5 was 50% or more on transverse CT images [11]. In expanding the classifications on two-dimensional images to those on three-dimensional images, the cut-off value of three-dimensional % solid (3D%solid) between types 3 and 5 was 35.4% [$=(0.5)^{3/2} \times 100\%$].

In contrast, nodules from a previous experiment conducted using ten adenocarcinomas, different from those used in the present study, were classified based on visual assessment, as only

**Table 1**
Radiologic classifications of small pulmonary adenocarcinomas on CT images.

| Classification | Radiologic Findings |
|---|---|
| Type 1 | Pure GGO |
| Type 2 | Semiconsolidation (an area of an intermediate homogeneous increase in density, which did not obscure underlying vascular markings) |
| Type 3 | Small solid part with a GGO halo (an area that consisted of a solid part and a surrounding GGO halo; the area of solid part should be less than 50% on transverse CT image) |
| Type 4 | Mixed type (an area that consisted of GGO and solid parts that have air-bronchogram or that show a punctate distribution; the area of solid part should be less than 50% on transverse CT image) |
| Type 5 | Large solid part with a GGO halo (the area of solid part should be 50% or more on transverse CT image) |
| Type 6 | Pure solid type (a nodule visually appeared to consist of only solid components) |

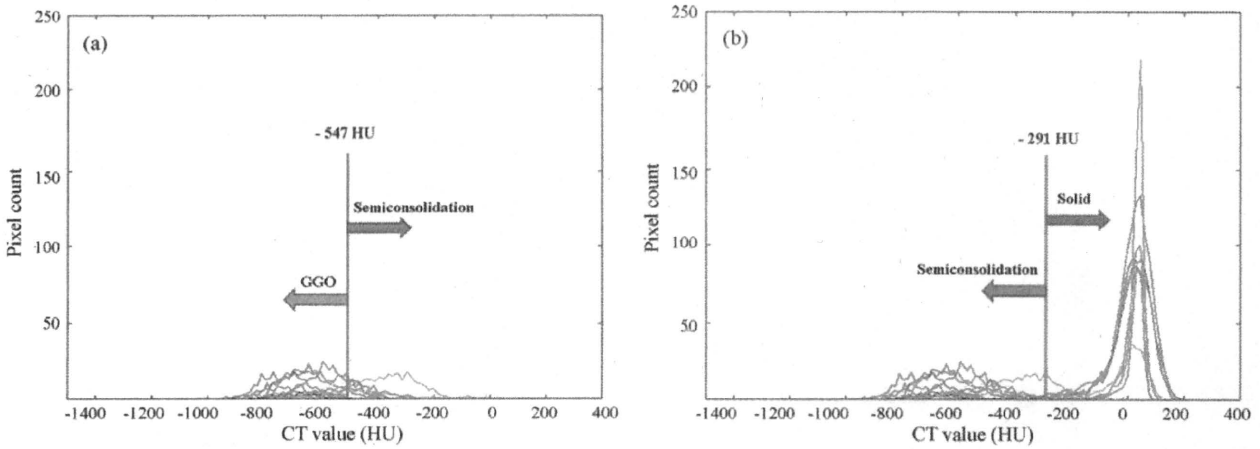


**Fig. 1.** (1) Threshold selection methods for segmenting gray-level images (Method-1, Otsu's method): the threshold between GGO and semiconsolidation. The gray-level histogram was generated using cases of type 1 (GGO) and 2 (semiconsolidation). The threshold (red line) between GGO and semiconsolidation was −547 HU using Method-1. (2) Threshold selection methods for segmenting gray-level images (Method-1, Otsu's method): the threshold between semiconsolidation and solid. The gray-level histogram was generated using cases of type 2 (semiconsolidation) and 6 (solid). The threshold (blue line) between semiconsolidation and solid was −291 HU using Method-1.

**Table 2**
Modified radiologic classifications on 3D-CT images.

| Classification | Radiologic findings by Method-1 or Method-2 |
|---|---|
| Type 1 | Tumor with a CT value less than *x* HU. |
| Type 2 | Tumor with a CT value from *x* HU to *y* HU. |
| Types 3–6 | Tumor including a solid part with a CT value more than *y* HU. |
| Type 3 | The volume rate of solid part should be less than 35.4%. |
| Type 4 | The volume rate of solid part should be less than 35.4%. Solid parts have air-bronchogram or show a punctate distribution. |
| Type 5 | The volume rate of solid part should be from 35.4 to 71.5%. |
| Type 6 | The volume rate of solid part should be greater than 71.5%. |

Method-1 (Otsu's method): $x = -547$, $y = -291$.
Method-2 (Kittler's method): $x = -534$, $y = -188$.

solid part (type 6). This experiment revealed that 2D%solid on transverse CT images calculated using Method-1 or Method-2 was equivalent to about 80%. Therefore, the cut-off value of 3D%solid between types 5 and 6 was 71.5% [$=(0.8)^{3/2} \times 100\%$]. The modified radiologic classifications on 3D images are summarized in Table 2.

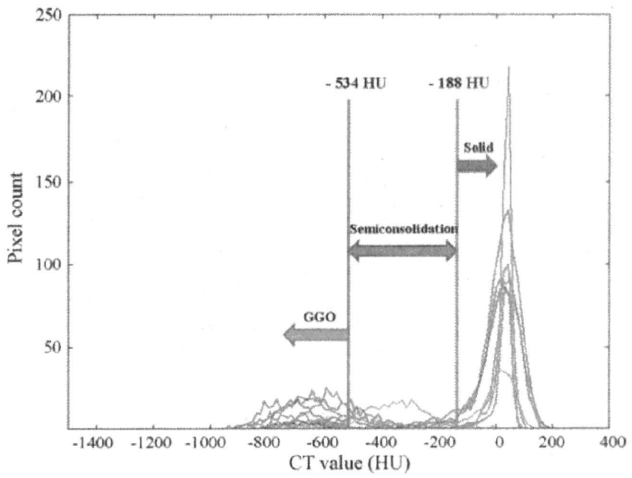


**Fig. 2.** Threshold selection methods for segmenting gray-level images (Method-2, Kittler's method): the thresholds among GGO, semiconsolidation and solid. Method-2 is based on "minimum error thresh-holding", which can decide more than two thresholds. The gray-level histogram was generated using cases of type 1 (GGO), 2 (semiconsolidation) and 6 (solid). The threshold (red line) between GGO and semiconsolidation was −534 HU and that (blue line) between semiconsolidation and solid was −188 HU using Method-2.

### 2.3.3. *Outline of custom-developed software*

Our software was developed using Microsoft Visual C++ 6.0 (Microsoft Corporation, Redmond, WA, USA) on a commercially available personal computer. It was a plug-in for the software used to segment the nodules on volumetric CT data, and used the following algorithm. First, by manually highlighting the boundary between the tumor and normal lung parenchyma on every CT slice, each volume of GGO, semiconsolidation, and solid part included in the highlighted area is automatically segmented. Next, the 3D%solid of the tumor is also automatically calculated. Finally, the tumors are automatically classified into the subgroups (types 1–6) (Fig. 3). Computer-automated classification according to malignant degree of the tumor on 3D-CT images is summarized in Fig. 4.

## 2.4. *Image analysis*

Three independent chest radiologists (with 8, 20 and 21 years of experience, respectively) visually classified tumors into the six subgroups (types 1–6) according to a previous report [11]. Final visual classification of the subgroup was decided by consensus.

The chest radiologist with 8 years of experience also manually examined 2D%solid on the maximum cross-section of the CT images directly on the monitor using a caliper, because the utility of a prognostic prediction using 2D%solid on CT images was already confirmed with previous reports [14].

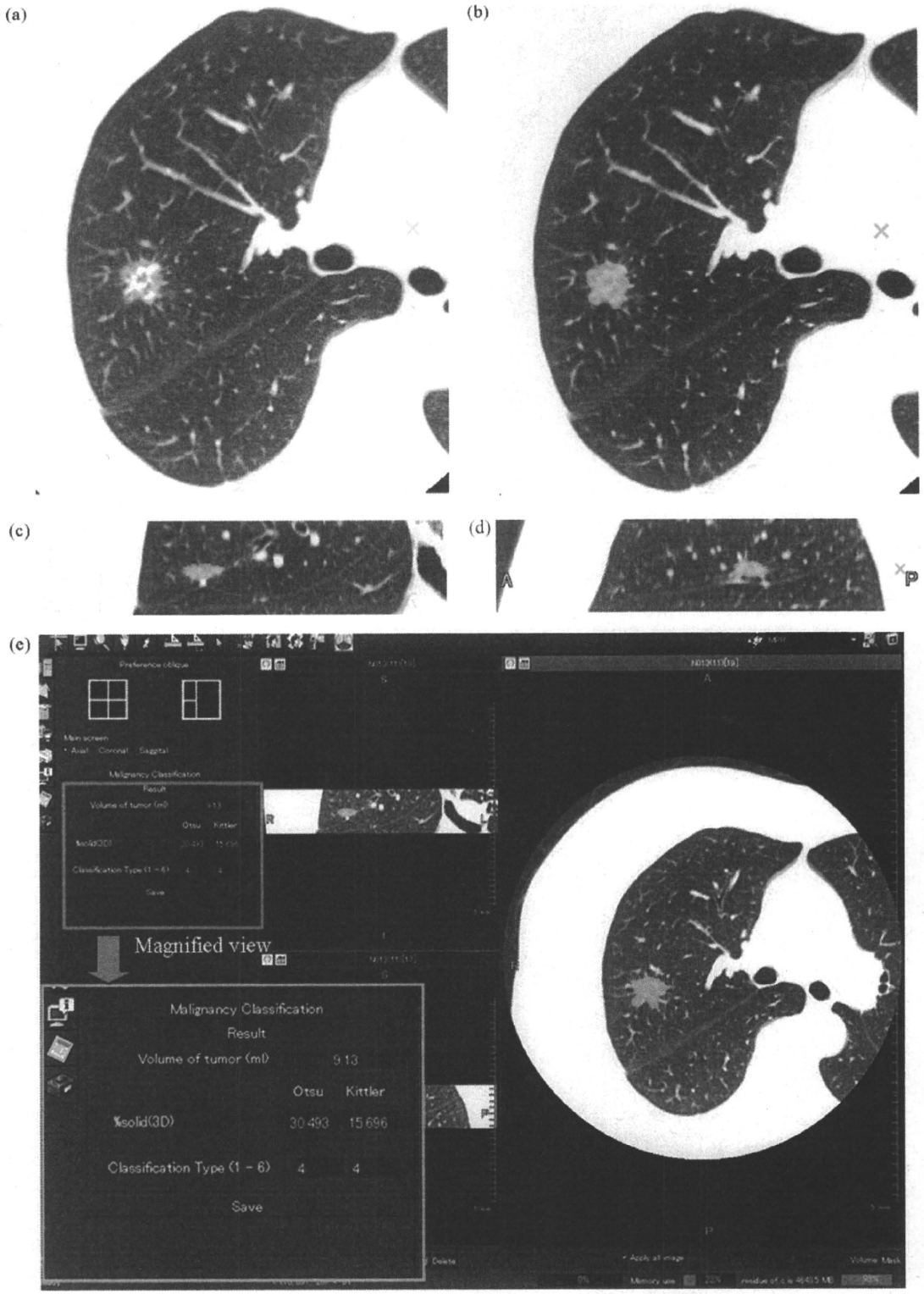


**Fig. 3.** A case of type 4 tumor in a 68-year-old woman. Axial CT image (a) shows a tumor with an area that consisted of GGO and solid parts. The green areas ((b) axial CT image, (c) coronal CT image, and (d) sagittal CT image) show an extracted tumor. Overall view of our software is shown by (e). Green frame is a magnified view of red frame. Our software indicates a tumor volume of 9.13 ml: 3D%solid using Method-1 is 30.493% and using Method-2 (Kittler's method) is 15.696%. Our software classified this tumor as type 4 (mixed type with an area that consisted of GGO and solid parts that have air-bronchogram or that show a punctate distribution).

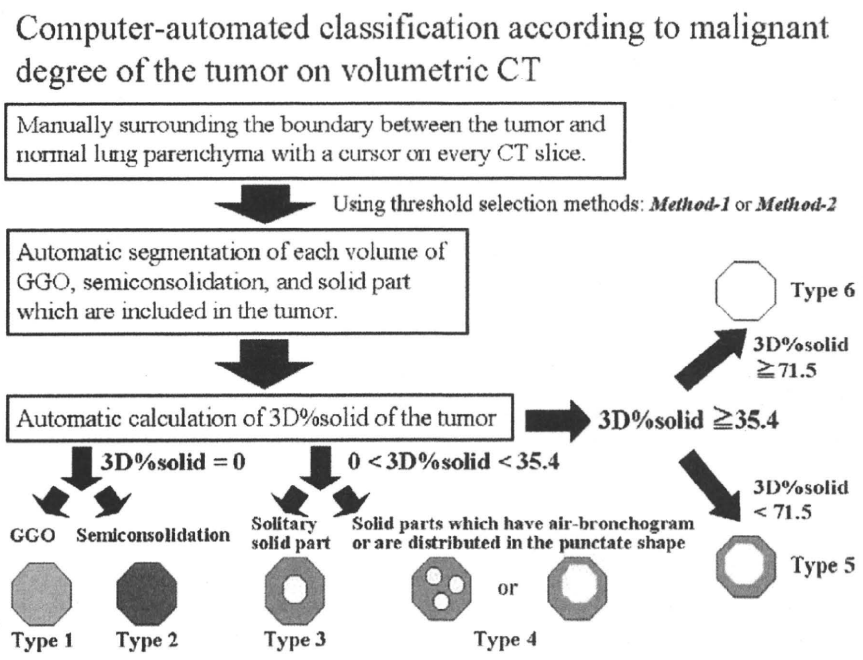


**Fig. 4.** Flow chart of computer-automated classification according to malignant degree of the tumor on volumetric CT.

This radiologist obtained the following information from the thin-slice CT images: the maximum dimension of tumor using a pulmonary window level setting (level, 600 HU; width, 1600 HU), the largest dimension of the perpendicular axis using a pulmonary window level setting, the maximum dimension of tumor using a mediastinal window level setting (level, 40 HU; width, 400 HU), and the largest dimension of the perpendicular axis using a mediastinal window level setting.

Highlighting of the boundary between the tumor and normal lung parenchyma using our software was conducted by two independent chest radiologists (4 and 8 years of experience). After discussion, the data from one experienced chest radiologist (the same radiologist who measured 2D%solid on CT) were used for analysis.

We evaluated three matters (vascular, lymphatic and pleural invasion) as pathological prognostic factors and examined the correlation of these three prognostic factors with the four explanatory variables: the visual classification of the subgroup; the classification using Method-1; the classification using Method-2 and manually measured 2D%solid.

### 2.5. Statistical analysis

Statistical analysis was performed using commercially available software (MedCalc Version 8.0.0.1, Frank Schoonjans, Mariakerke, Belgium). Inter-observer agreements of highlighted boundaries between tumors and normal lung parenchyma were assessed by Bland and Altman's method [15]. Agreements between visual and computer-automated classification were evaluated using the weighted $\kappa$ statistic and classified as poor ($\kappa = 0.00–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), good ($\kappa = 0.61–0.80$), or excellent ($\kappa = 0.81–1.00$). Univariate and multivariate analyses were performed by logistic regression analysis. Forward and backward stepwise procedures were used to determine the combination of factors that were essential in predicting prognosis. A $p$ value $< 0.05$ was considered to indicate significant difference.

## 3. Results

### 3.1. Inter-observer agreements

Inter-observer agreement between the two observers that manually highlighted the boundary between the tumor and normal lung parenchyma (mean bias ± 1.96 standard deviations) was −2.2 ± 9.5 mm (Fig. 5).

### 3.2. Agreements between visual classification and computer-automated classification

The visual classification by radiologists was as follows: type 1 (11/46 cases, 24%), type 2 (2/46, 4%), type 3 (4/46, 9%), type 4 (9/46, 20%), type 5 (13/46, 28%) and type 6 (7/46, 15%). The agreement between visual and computer-automated classification are shown in Table 3. Overall concordance between visual classification and classification using Method-1 was 32 (70%) of 46 tumors (weighted kappa = 0.799). Overall concordance between visual classification and the classification using Method-2 was 29 (63%) of 46 tumors (weighted kappa = 0.758).

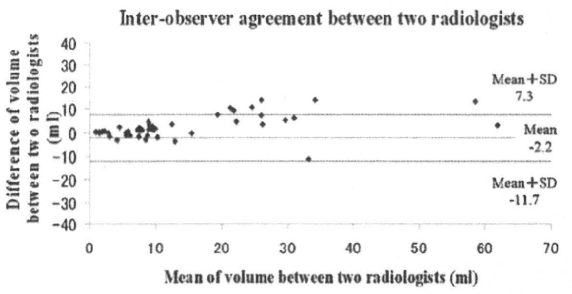


**Fig. 5.** Bland–Altman plot of inter-observer agreement between two radiologists.

**Table 3**
The agreement between visual and computer-automated classification (Method-1 or Method-2).

| | Visual classification | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | Type 1 | Type 2 | Type 3 | Type 4 | Type 5 | Type 6 | |
| Method-1 (Otsu's method) | | | | | | | |
| Type 1 | 9 | 1 | 0 | 0 | 0 | 0 | 10 |
| Type 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Type 3 | 0 | 1 | 2 | 2 | 1 | 0 | 6 |
| Type 4 | 1 | 0 | 1 | 5 | 0 | 0 | 7 |
| Type 5 | 0 | 0 | 1 | 2 | 11 | 2 | 16 |
| Type 6 | 0 | 0 | 0 | 0 | 1 | 5 | 6 |
| Total | 11 | 2 | 4 | 9 | 13 | 7 | 46 |
| Weighted kappa value | | | | 0.799 | | | |
| Method-2 (Kittler's method) | | | | | | | |
| Type 1 | 10 | 2 | 1 | 0 | 0 | 0 | 13 |
| Type 2 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| Type 3 | 1 | 0 | 0 | 3 | 2 | 0 | 6 |
| Type 4 | 0 | 0 | 3 | 5 | 1 | 0 | 9 |
| Type 5 | 0 | 0 | 0 | 0 | 10 | 3 | 13 |
| Type 6 | 0 | 0 | 0 | 0 | 0 | 4 | 4 |
| Total | 11 | 2 | 4 | 9 | 13 | 7 | 46 |
| Weighted kappa value | | | | 0.758 | | | |

### 3.3. Manually measured 2D%solid on the maximum cross-section of CT

Manually measured 2D%solid (mean ± standard deviation) according to the visual classification is shown in Table 4. In the case of solid parts that have air-bronchogram or that show a punctate distribution (type 4), the radiologist made all possible efforts to measure the 2D%solid of tumors.

### 3.4. Pathologic characteristic according to classification of tumors

Pathologic characteristics in small pulmonary adenocarcinomas according to visual and computer-automated classification are summarized in Table 5. In both localized BAC ($n = 16$) and adenocarcinoma without BAC component ($n = 1$), there were no differences in distribution of pathologic characteristics among visual classification, classification using Method-1, and classification using Method-2. In adenocarcinoma with BAC component ($n = 29$), there were differences in distribution of pathologic characteristics among these three types of classifications. Univariate and multivariate logistic regression analyses are summarized in Tables 6.1 and 6.2. Univariate logistic regression analyses showed that classification using Method-1 and manually measured 2D%solid were both significantly useful in estimating all three pathological prognostic factors: lymphatic invasion ($p = 0.01$, 0.0007), vascular invasion ($p = 0.017$, 0.003) and pleural invasion ($p = 0.03$, 0.046). Multivariate logistic regression analyses also demonstrated that classification using Method-1 and manually measured 2D%solid were both significantly useful in estimating lymphatic invasion ($p = 0.0027$, 0.0007), vascular invasion ($p = 0.012$, 0.003) and pleural invasion ($p = 0.025$, 0.021).

**Table 4**
Manually measured two-dimensional % solid (2D%solid) according to visual classification.

| Visual classification | 2D%solid (mean ± SD) |
|---|---|
| Type 1 ($n = 11$) | 0 ± 0 |
| Type 2 ($n = 2$) | 0 ± 0 |
| Type 3 ($n = 4$) | 0.182 ± 0.149 |
| Type 4 ($n = 9$) | 0.055 ± 0.072 |
| Type 5 ($n = 13$) | 0.444 ± 0.191 |
| Type 6 ($n = 7$) | 0.948 ± 0.135 |
| Total ($n = 46$) | 0.297 ± 0.354 |

## 4. Discussion

The present study demonstrates that our custom-developed software is useful for predicting lymphatic invasion, vascular invasion and pleural invasion in small peripheral adenocarcinomas. Even though pulmonary nodules show various CT patterns (GGO, semiconsolidation, part-solid, and pure solid) and have solid parts with a punctate distribution, predicting the pathological prognostic factors of them on CT images is feasible using our custom-developed software.

The prognosis of pulmonary adenocarcinoma with a larger area of GGO on thin-section CT images is much better than that of pulmonary adenocarcinoma of solid type on CT regardless of its maximal tumor dimension [4,16–21]. The extent of GGO is one of the most important prognostic factors. In fact, there were differences in distribution of pathologic characteristics among visual classification, classification using Method-1, and classification using Method-2 in adenocarcinomas with BAC component which is commonly detected on CT as GGO (Table 5). Many reports have demonstrated that manually measured 2D%solid on thin-section CT images was useful for predicting the prognostic outcome of small pulmonary adenocarcinomas [4,14,17–19,22–26]. However, the reproducibility of manual measurements is poor in evaluating small nodules [27,28]. Furthermore, malignant nodules do not always grow symmetrically, and tumors are often a heterogeneous mixture of GGO and solid parts. GGO can only be evaluated visually on CT images because there is no quantitative definition of GGO. Therefore, it is difficult to accurately measure the area of GGO and solid parts that have air-bronchogram or that show a punctate distribution, and considerable disagreement among radiologists on the diagnosis can arise.

Recent advances in diagnostic modalities have enabled the detection of increasingly smaller pulmonary adenocarcinomas with or without GGO in elderly patients. A suitable surgical approach that achieves the most benefit for these patients must be considered, and limited surgical resection has the benefit of preserving the postoperative quality of life without impairment of respiratory function [29]. Some reports [30,31] have suggested that

**Table 5**
Pathologic characteristics in small pulmonary adenocarcinomas according to visual and computer-automated classification.

| Histopathologic diagnosis | Visual classification | Numbers of invasive tumors | | | Classification using Method-1 (Otsu) | Numbers of invasive tumors | | | Classification using Method-2 (Kittler) | Numbers of invasive tumors | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LI | VI | PI | | LI | VI | PI | | LI | VI | PI |
| Localized BAC $n=16$ | Type 1 ($n=9$) | 0 | 1 | 0 | Type 1 ($n=8$) | 0 | 1 | 0 | Type 1 ($n=11$) | 0 | 1 | 0 |
| | Type 2 ($n=2$) | 0 | 0 | 0 | Type 2 ($n=1$) | 0 | 0 | 0 | Type 2 ($n=1$) | 0 | 0 | 0 |
| | Type 3 ($n=1$) | 0 | 0 | 0 | Type 3 ($n=3$) | 0 | 0 | 0 | Type 3 ($n=2$) | 0 | 0 | 0 |
| | Type 4 ($n=3$) | 0 | 0 | 0 | Type 4 ($n=3$) | 0 | 0 | 0 | Type 4 ($n=1$) | 0 | 0 | 0 |
| | Type 5 ($n=1$) | 0 | 0 | 0 | Type 5 ($n=1$) | 0 | 0 | 0 | Type 5 ($n=1$) | 0 | 0 | 0 |
| | Type 6 ($n=0$) | 0 | 0 | 0 | Type 6 ($n=0$) | 0 | 0 | 0 | Type 6 ($n=0$) | 0 | 0 | 0 |
| Adenocarcinoma with BAC component $n=29$ | Type 1 ($n=2$) | 0 | 0 | 0 | Type 1 ($n=2$) | 0 | 0 | 0 | Type 1 ($n=2$) | 0 | 0 | 0 |
| | Type 2 ($n=0$) | 0 | 0 | 0 | Type 2 ($n=0$) | 0 | 0 | 0 | Type 2 ($n=0$) | 0 | 0 | 0 |
| | Type 3 ($n=3$) | 1 | 1 | 1 | Type 3 ($n=3$) | 1 | 0 | 0 | Type 3 ($n=4$) | 2 | 2 | 0 |
| | Type 4 ($n=6$) | 3 | 2 | 0 | Type 4 ($n=4$) | 1 | 1 | 0 | Type 4 ($n=8$) | 3 | 2 | 1 |
| | Type 5 ($n=11$) | 6 | 4 | 1 | Type 5 ($n=14$) | 9 | 6 | 1 | Type 5 ($n=11$) | 8 | 5 | 2 |
| | Type 6 ($n=7$) | 7 | 5 | 2 | Type 6 ($n=6$) | 6 | 5 | 3 | Type 6 ($n=4$) | 4 | 3 | 1 |
| Adenocarcinoma without BAC component $n=1$ | Type 1 ($n=0$) | 0 | 0 | 0 | Type 1 ($n=0$) | 0 | 0 | 0 | Type 1 ($n=0$) | 0 | 0 | 0 |
| | Type 2 ($n=0$) | 0 | 0 | 0 | Type 2 ($n=0$) | 0 | 0 | 0 | Type 2 ($n=0$) | 0 | 0 | 0 |
| | Type 3 ($n=0$) | 0 | 0 | 0 | Type 3 ($n=0$) | 0 | 0 | 0 | Type 3 ($n=0$) | 0 | 0 | 0 |
| | Type 4 ($n=0$) | 0 | 0 | 0 | Type 4 ($n=0$) | 0 | 0 | 0 | Type 4 ($n=0$) | 0 | 0 | 0 |
| | Type 5 ($n=1$) | 1 | 0 | 0 | Type 5 ($n=1$) | 1 | 0 | 0 | Type 5 ($n=1$) | 1 | 0 | 0 |
| | Type 6 ($n=0$) | 0 | 0 | 0 | Type 6 ($n=0$) | 0 | 0 | 0 | Type 6 ($n=0$) | 0 | 0 | 0 |
| Total $n=46$ | Type 1 ($n=11$) | 0 | 1 | 0 | Type 1 ($n=10$) | 0 | 1 | 0 | Type 1 ($n=13$) | 0 | 1 | 0 |
| | Type 2 ($n=2$) | 0 | 0 | 0 | Type 2 ($n=1$) | 0 | 0 | 0 | Type 2 ($n=1$) | 0 | 0 | 0 |
| | Type 3 ($n=4$) | 1 | 1 | 1 | Type 3 ($n=6$) | 1 | 0 | 0 | Type 3 ($n=6$) | 2 | 2 | 0 |
| | Type 4 ($n=9$) | 3 | 2 | 0 | Type 4 ($n=7$) | 1 | 1 | 0 | Type 4 ($n=9$) | 3 | 2 | 1 |
| | Type 5 ($n=13$) | 7 | 4 | 1 | Type 5 ($n=16$) | 10 | 6 | 1 | Type 5 ($n=13$) | 9 | 5 | 2 |
| | Type 6 ($n=7$) | 7 | 5 | 2 | Type 6 ($n=6$) | 6 | 5 | 3 | Type 6 ($n=4$) | 4 | 3 | 1 |

LI, lymphatic invasion; VI, vascular invasion; PI, pleural invasion.

**Table 6.1**
Univariate logistic regression analyses (forward and backward stepwise procedure).

| Variable | Odds ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|
| Lymphatic invasion | | | |
| Visual classification | 3.99 | 1.6565–9.6293 | 0.002* |
| Classification using the Method-1 (Otsu's method) | 12.36 | 1.7745–86.0956 | 0.01* |
| Classification using the Method-2 (Kittler's method) | 3.7 | 1.6176–8.4713 | 0.002* |
| Manually measured two-dimensional % solid (2D%solid) | 269.91 | 10.5143–6929.15 | 0.0007* |
| Vascular invasion | | | |
| Visual classification | 1.83 | 1.0963–3.0457 | 0.02* |
| Classification using the Method-1 (Otsu's method) | 2.31 | 1.1593–4.5964 | 0.017* |
| Classification using the Method-2 (Kittler's method) | 1.73 | 1.0491–2.8598 | 0.03* |
| Manually measured two-dimensional % solid (2D%solid) | 23.6 | 2.9398–189.5308 | 0.003* |
| Pleural invasion | | | |
| Visual classification | 1.91 | 0.7553–4.8530 | 0.17 |
| Classification using the Method-1 (Otsu's method) | 13.58 | 1.2144–151.9337 | 0.03* |
| Classification using the Method-2 (Kittler's method) | 2.52 | 0.7982–7.9872 | 0.11 |
| Manually measured two-dimensional % solid (2D%solid) | 9.5 | 1.0377–86.9719 | 0.046* |

* Significant difference.

**Table 6.2**
Multivariate logistic regression analyses (forward and backward stepwise procedure).

| Variable | Odds ratio | 95% Confidence Interval | *p* Value |
|---|---|---|---|
| Lymphatic invasion | | | |
| Classification using the Method-1 (Otsu's method) | 2.4 | 1.8249–17.7953 | 0.0027* |
| Manually measured two-dimensional % solid (2D%solid) | 269.9 | 10.5143–17.7953 | 0.0007* |
| Vascular invasion | | | |
| Classification using the Method-1 (Otsu's method) | 2.4 | 1.2176–4.8913 | 0.012* |
| Manually measured two-dimensional % solid (2D%solid) | 23.6 | 2.9398–189.5308 | 0.003* |
| Pleural invasion | | | |
| Classification using the Method-1 (Otsu's method) | 16.3 | 1.3991–189.9486 | 0.025* |
| Manually measured two-dimensional % solid (2D%solid) | 54.6 | 1.08392–1621.0114 | 0.021* |

* Significant difference.

segmental resection for small-sized lung cancer may be acceptable for patients with a tumor 2.0 cm or less in diameter (without nodal involvement), and that a peripherally located lung cancer with no lymph node metastasis might be the optimal indication for a more limited anatomic resection. Consequently, in current clinical settings, where limited surgical resection is desirable, the preoperative diagnosis of the invasiveness of a lung cancer becomes increasingly crucial for deciding the operative procedure. Therefore, in our study, in order to obtain an objective and quantitative assessment tool, we developed software that cannot only calculate 3D%solid of tumors including GGO area, but also automatically classify nodules according to the volumetric rates of the solid parts.

Automatic segmentation using the custom-developed software may enable high reproducibility during image assessment regardless of experience. In fact, commercially available software that can segment pulmonary nodules with GGO is already available. A previous study demonstrated that volumetric analysis is a reproducible and promising quantitative method using this commercially available software but that the correlation between the histological classification and the 3D%solid of tumors was no better when obtained using the software than when using manual measurements [32]. Although the automatic segmentation ability of our software can be improved, this software using Method-1 was as useful for predicting lymphatic invasion, vascular invasion and pleural invasion as the prognostic prediction using 2D%solid; in agreement with previous reports.

One of the important purposes of our study is to determine, as objectively as possible, the indication for limited surgical resection for lung adenocarcinomas by using our custom-developed software. Using visual classification, Suzuki et al. [11] demonstrated that types 1–4 were thought to be "minimally invasive" adenocarcinoma and that types 5 and 6 were considered to exhibit a "solid" course with higher possibility of lymph node metastases than types 1–4. If a tumor were classified as being types 1–4, the patient would be a candidate for limited surgical resection; whereas a type 5 or 6 tumor warrants major lung resection with systematic lymph node dissection necessarily. In classification using Method-1, useful for the prognostic prediction in the present study, types 5 and 6 tended to be more invasive than types 1–4 (Table 5): lymphatic invasion (types 1–4 vs. types 5 and 6), 2/24 (8%) vs. 16/22 (72%); vascular invasion, 2/24 (8%) vs. 11/22 (50%); and pleural invasion, 0/24 (0%) vs. 4/22 (18%).

However, six classifications proposed in our study are thought to remain important in order for the surgeon to plan for the management of peripheral lung cancer. In general, the progress of most small nodules that have been difficult to diagnose using CT has occurred over several years; with surgery only being indicated when tumors showed an increase in size on CT images. For instance, type 1 tumors (pure GGO) and type 2 tumors (semiconsolidation) show no solid parts on CT images. Most of the type 1 tumors are BAC, and are often indolent tumors. In contrast, type 2 tumors tend to be adenocarcinoma with pathologically invasive foci and grow in size. Concerning the surgical indications for tumors without solid parts, surgeons usually just monitor type 1 tumors without surgical interventions if the radiologic maximal tumor dimension is unchanged, and do not monitor type 2 tumors [11]. Thus, the clinical strategy depends on the six classifications, and the preoperative use of our custom-developed software will assist in determining a suitable operative method: limited surgical resection for tumors classified as types 1–4 and major lung resection for tumors classified as type 5 or 6.

There were several limitations in the present study. First, the number of patients was small for both the clinical evaluation and examination of the threshold of CT value between GGO and

semiconsolidation and between semiconsolidation and solid part. Subsequent analysis using a greater number of lung tumors is required. Second, in the image analysis, two independent readers were the minimum for this study with the current design. It might have been better for more independent readers to analyze image. Third, solid parts including vessels were calculated in our study, and may have introduced some bias into our results. In order to remove unnecessary vessels, this software will need to be upgraded by using "line filtering" [33], which enhances curvilinear structures, such as vessels and bronchi, in 3D medical images. Forth, although our software enabled automatic classification according to the malignant degree of small peripheral adenocarcinomas by automatically measuring 3D%solid of tumors, the initial highlighting of the boundary between the tumor and normal lung parenchyma was performed manually. The software is currently being upgraded to automate this procedure, which, in turn, may generate more objective results. Finally, our results should have been compared to the volumetric distribution of tumors in pathologic specimens, but postoperative collapse of the lung would have made accurate comparisons difficult.

In conclusion, predicting the pathological prognostic factors of small peripheral adenocarcinomas on three-dimensional CT images is feasible using our custom-developed software for evaluating their degree of malignancy. The application of this software will assist in deciding the future treatment strategies for small-sized adenocarcinoma of the lung following improvements in the filtering and automated segmentation feature.

## Conflict of interest

No authors indicated potential conflicts of interest.

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*Original Article*

# Predictors of Postoperative Survival in Patients with Locally Advanced Non-Small Cell Lung Carcinoma

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**Abstract**

***Purpose.*** A surgical resection for locally advanced non-small cell lung carcinoma (NSCLC) remains controversial. This study analyzed the clinicopathological profile and surgical outcome of patients with locally advanced NSCLC to identify the predictors of survival.

***Methods.*** This study retrospectively analyzed clinical data from 86 patients with pathological T3 or T4 primary NSCLC treated at Chiba University Hospital, and evaluated prognostic factors.

***Results.*** Sixty-eight of 86 cases were treated with a complete resection, and 18 were evaluated as an incomplete resection. The 5-year overall survival rate of all cases was 45.7%. Univariate analyses of survival were performed to determine the predictors of overall survival in patients with pathological T3 or T4 NSCLC. Age of 70 years or more, tumor length more than 5 cm, lymph node metastases, incomplete resection, and histology of non-adenocarcinoma were significantly associated with an unfavorable prognosis. Multivariate analyses revealed that older age, incomplete resection, and lymph node metastases were independent predictors of shorter survival.

***Conclusion.*** A complete resection for selected cases is acceptable in the management of T3 or T4 NSCLC.

**Key words** Lung carcinoma · Locally advanced · Lymph node

## Introduction

Lung cancer is the leading cause of cancer death in Japan and worldwide, and despite many improvements in therapy, a diagnosis of lung carcinoma still portends a poor prognosis. Studies of patients with locally advanced non-small cell lung carcinoma (NSCLC) were performed on patients with T3 tumors, especially chest wall invasion, and also demonstrated that patients with T3 tumors have a very poor outcome.[1,2] However, there have so far been few reports that estimate the prognosis of patients with locally advanced NSCLC. There are even fewer reports on the prognosis of patients with T4 tumors. The aim of this study was to retrospectively analyze the clinicopathological features of patients with resectable locally advanced NSCLC in order to identify factors predictive of survival, and to potentially improve the management of this disease.

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## Patients and Methods

From January 1997 to February 2007, 977 patients with primary lung carcinoma underwent surgery at Chiba University Hospital. Among them, 86 patients with T3 or T4 disease were retrospectively reviewed in this study. All patients underwent chest and abdominal computed tomography (CT), brain magnetic resonance imaging (MRI), and bone scintigraphy at the first presentation for evaluation of clinical staging, and were pathologically proven to have T3 or T4 disease postoperatively. Any patients who had malignant pleural effusion, dissemination, or pulmonary metastasis in the same lobe were excluded from this study. Information including demographics, smoking index, tumor size, tumor location, surgical procedure, pathological stage, and surgical outcome was collected from the medical records.

### *Statistical Analysis*

Fisher's exact test was used to compare binomial proportions. The chi-squared test was used to assess differences in sex, tumor site, and surgical methods. The

unpaired *t*-test was used to detect significant differences with respect to patient age, smoking index, and tumor size. The survival time, calculated from the date of surgery until the time of death, was evaluated using the method of Kaplan and Meier.

The prognostic impact of the following clinical variables in these cases was investigated using a Cox proportional hazards multivariate regression model: T factor (T3 versus T4), age (<70 years old versus ≥70 years old), tumor size (≤5 cm versus >5 cm), sex (male versus female), smoking index (0 versus ≥1), operation (lobectomy versus pneumonectomy), symptom (+ versus −), pathological lymph node metastasis (positive versus negative), resection (complete versus incomplete), adjuvant therapy (+ versus −), histology (adenocarcinoma versus others), and site (left versus right). A *P* value of less than 0.05 was considered to be statistically significant.

## Results

The characteristics of patients are summarized in Table 1. Of the 86 cases, 76 were male and 10 were female. The mean age was 65 years (range 41–85). The pathologically defined reasons for a diagnosis of T3 disease were: invasion to the chest wall in 62 cases, of which 7 had a superior sulcus tumor; invasion to pericardium in 7; invasion to diaphragm in 3; invasion to mediastinal pleura in 2; and invasion to the main bronchus in 2 cases. T4 disease was defined by invasion to the left atrium in 6 cases; invasion to the mediastinum in 3; invasion to the superior vena cava in 2; and invasion to the right atrium, thoracic vertebrae, trachea, and aorta in one case each. Surgical mortality was 1.2% in all cases. The 5-year survival rate after surgery of all cases was 45.7%.

Univariate analyses of survival (Table 2) showed that an age of 70 years or more, tumor length more than 5 cm, positive lymph node metastasis, an incomplete resection, and non-adenocarcinoma were all associated with a significantly shorter survival of patients. Multivariate analyses revealed that an incomplete resection, older age, and positive lymph node metastasis were markedly significant independent predictors of shorter survival (Table 3).

## Discussion

Surgical treatment for locally advanced lung carcinoma remains unsatisfactory. Riquet et al. showed that patients with T3 tumors have only 23% to 37% 5-year survival rates following a surgical resection.[1] Martini et al. reported a 5-year survival rate of 30% for patients

**Table 1.** Patients' characteristics

| | T3 | T4 | Total |
|---|---|---|---|
| Age, years (mean) | 66 | 62 | 65 |
| Range | 50–85 | 41–75 | 41–85 |
| Sex | | | |
| Male | 64 | 12 | 76 |
| Female | 8 | 2 | 10 |
| Smoking index (mean) | 926 | 735 | 895 |
| Tumor size, cm (mean) | 4.9 | 5.4 | 5.0 |
| Range | 1.5–10.5 | 2.9–8.0 | 1.5–10.5 |
| Site | | | |
| Right | 43 | 9 | 52 |
| Left | 29 | 5 | 34 |
| Surgery | | | |
| Lobectomy | 64 | 10 | 74 |
| Pneumonectomy | 8 | 4 | 12 |
| Radicality | | | |
| Complete | 59 | 9 | 68 |
| Incomplete | 13 | 5 | 18 |
| Histology | | | |
| Adenocarcinoma | 39 | 5 | 44 |
| Squamous cell carcinoma | 23 | 5 | 28 |
| Large cell carcinoma | 7 | 0 | 7 |
| Others | 3 | 4 | 7 |
| Pathological lymph node metastasis | | | |
| N0 | 43 | 4 | 47 |
| N1 | 12 | 2 | 14 |
| N2 | 16 | 8 | 24 |
| N3 | 1 | 0 | 1 |

**Table 2.** Univariate analyses of survival

| Parameter | Overall survival | | |
|---|---|---|---|
| | *P* value | Hazard ratio | 95% CI |
| pT4[a] | 0.7673 | 1.142 | 0.475–2.747 |
| Age[b] ≥70 years old | 0.0040 | 2.599 | 1.357–4.978 |
| Tumor size[c] >5 cm | 0.0457 | 1.942 | 1.013–3.717 |
| Sex[d] male | 0.5674 | 1.413 | 0.432–4.620 |
| Smoking index[e] 0 | 0.0826 | 2.232 | 0.901–5.526 |
| Operation[f] pneumonectomy | 0.9917 | 1.005 | 0.391–2.584 |
| Symptom[g] + | 0.1356 | 1.695 | 0.847–3.378 |
| pN[h] N+ | 0.0229 | 2.134 | 1.111–4.101 |
| Radicality[i] incomplete resection | 0.0021 | 4.651 | 1.745–12.346 |
| Adjuvant therapy[j] + | 0.1441 | 1.678 | 0.838–3.356 |
| Histology[k] others | 0.0011 | 3.436 | 1.639–7.246 |
| Site[l] left | 0.4036 | 1.329 | 0.682–2.588 |

CI, confidence interval
[a] T factor (pT3 vs pT4)
[b] Age (<70 vs ≥70 years old)
[c] Tumor size (≤5 vs >5 cm)
[d] Sex (male vs female)
[e] Smoking Index (0 vs ≥1)
[f] Operation (lobectomy vs pneumonectomy)
[g] Symptom (+ vs −)
[h] pN: pathological lymph node metastasis, pN (+ vs −)
[i] Radicality (complete vs incomplete)
[j] Adjuvant therapy (+ vs −)
[k] Histology (adenocarcinoma vs others)
[l] Site (right vs left)

**Table 3.** Multivariate analyses for survival

| Parameter | Overall survival | | |
|---|---|---|---|
| | *P* value | Hazard ratio | 95% CI |
| Radicality[a] incomplete resection | 0.0017 | 5.988 | 1.961–18.182 |
| Age[b] ≥70 years old | 0.0019 | 3.377 | 1.564–7.289 |
| pN[c] N+ | 0.0314 | 2.119 | 1.069–4.197 |
| Histology[d] others | 0.2146 | 1.838 | 0.703–4.808 |
| Tumor size[e] >5 cm | 0.1161 | 1.825 | 0.862–3.861 |

CI, confidence interval
[a] Radicality (complete vs incomplete)
[b] Age (<70 vs ≥70 years old)
[c] pN: pathological lymph node metastasis, pN (+ vs −)
[d] Histology (adenocarcinoma vs others)
[e] Tumor size (≤5 cm vs >5 cm)

undergoing complete resection of T3 or T4 tumors with mediastinal invasion, although patients with an incomplete resection or no resection had only a 14% 5-year survival rate.[3]

Although clinical stage IIIB NSCLC including T4 is generally considered to be inoperative, there may be a different biological behavior between tumors with local T4 disease and those with N3.[4] Deperrot et al. reported that surgery for T4 disease requiring cardiopulmonary bypass was associated with severe postoperative complications, though a limited number of patients did have long-term survival.[5] The current study attempted to find identifiers of fit cases for surgery in T3 or T4 NSCLC. This study excluded T4 cases due to malignant effusion or dissemination, since by definition a curative resection cannot be performed. On the other hand, those T4 cases with pulmonary metastasis in the same lobe were also excluded because it has been reported that those cases generally have a better prognosis than other T4 cases.[6] Therefore, the current study may be more representative of "typical" locally advanced T3 or T4 tumors.

A pneumonectomy was performed in 12 of 86 patients (14.0%). The proportion of pneumonectomy in this study was relatively low in comparison to 25% in the