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INVITED COMMENTARY

A number of retrospective reports have suggested that lymphovascular invasion (LVI) represents a high-risk pathologic feature in patients with resected non-small cell lung cancer (NSCLC), and negatively affects their survival after surgical resection. Mollberg and associates [1] conducted a systematic review and metaanalysis of 20 published studies that reported the comparative survival with and without LVI among patients with resected stage I NSCLC to investigate the association of LVI with the recurrence-free survival (RFS) and overall survival (OS). In total, 8,032 patients were examined for LVI and survival data, and 23.4% of the cases of completely resected stage I NSCLC were proven to exhibit LVI (range, 4.9% to 48.6%). Importantly, the meta-analysis demonstrated that, after adjusting for potential confounders, LVI was significantly associated with a worse RFS (hazard ratio 2.52, 95% confidence interval: 1.73 to 3.65) and OS (hazard ratio 1.81, 95% confidence interval: 1.53 to 2.14). Such data can potentially identify patients at an increased risk of recurrence, and the descriptor might also warrant consideration of inclusion in future revisions of the TNM of lung cancer after a more detailed assessment of even larger patient cohorts. In addition, the researchers suggested that resected stage I NSCLC patients harboring LVI might benefit from adjuvant chemotherapy.

Although this study metaanalytically revealed the significance of LVI in patients with resected NSCLC, the definition of LVI was not clearly described in this article. Mollberg and colleagues [1] examined retrospective studies that evaluated the presence of lymphatic or blood vessel invasion, or both, as a single covariate, whereas the studies that used blood vessel invasion or lymphatic vessel invasion as two different covariates were excluded. However, can these two factors be regarded as one factor, namely, LVI? As the researchers discuss in the Comment section, it is true that differentiating blood vessel invasion from lymphatic vessel invasion is difficult, but the clinical

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significance of these two factors might be different, as some studies suggested. Accordingly, in addition to the prospective study proposed by Mollberg and associates [1], a future prospective study is warranted to discriminate between lymphatic and blood vessel invasion, as well as to investigate their significance in patients with resected NSCLC. The subjects might be completely resected NSCLC patients in pathologic stage IA who were not recommended to receive any adjuvant treatment as a result of a phase III trial. Furthermore, the methodologies, such as an immunohistochemical analysis, should be developed to differentiate blood vessel invasion from LVI.

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ORIGINAL ARTICLE

A feasibility trial of postoperative adjuvant chemotherapy with S-1, an oral fluoropyrimidine, for elderly patients with non-small cell lung cancer: a report of the Lung Oncology Group in Kyushu (LOGIK) protocol 0901

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Abstract
Background The present study was designed to determine whether adjuvant chemotherapy with S-1 after surgical resection is feasible in elderly patients with non-small cell lung cancer (NSCLC), using a multi-institutional trial.
Methods From July 2009 to July 2011, 25 patients received the following regimen: 2 weeks of administration and 1 week of withdrawal of S-1 at 50–100 mg/body per day in an outpatient setting. The primary endpoint of this trial was the completion rate of eight cycles.
Results The completion rate of eight cycles was 70.8 % [95 % confidence interval (CI) 52.7–89.0 %]. The perfect completion rate of eight cycles on schedule with full doses without delays was 50 % (95 % CI 30.0–70.0 %). The reasons for incomplete cycles were: patient refusal in four cases, anorexia in two cases and thrombocytopenia in one case. As a consequence of delays and/or dose reductions, the relative dose intensity of S-1 was 76.3 %.
Conclusions Adjuvant chemotherapy with S-1 at a reduced dose and schedule was therefore found to be a feasible treatment for elderly Japanese patients who had undergone surgical resection for NSCLC (UMIN Clinical Trials Registry number UMIN000002383).

Keywords Non-small cell lung cancer · Elderly Japanese patients · Adjuvant chemotherapy · S-1 and multi-institutional trial

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Introduction

In a randomized phase III trial, adjuvant chemotherapy with uracil-tegafur (UFT) was reported to reduce the risk of relapse and death from lung cancer following surgical resection in Japanese patients with stage I adenocarcinoma [1]. S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan) is an orally active combination of tegafur [a prodrug of 5-fluorouracil (5-FU)], gimeracil (an inhibitor of dihydropyrimidine dehydrogenase, which degrades fluorouracil) and oteracil (which inhibits the phosphorylation of fluorouracil in the gastrointestinal tract, thereby reducing the gastrointestinal toxic effects of fluorouracil) in a molar ratio of 1:0.4:1 [2]. S-1 was developed to improve the tumor-selective cytotoxicity of 5-FU while reducing gastrointestinal toxicity through the addition of these modulators. In fact, S-1 was found to be useful as adjuvant chemotherapy after curative surgery in Japanese patients with locally advanced gastric cancer in a randomized phase III trial [3]. We have previously reported the results of a feasibility trial (LOGIK 0601) of postoperative chemotherapy with S-1 for non-small cell lung cancer (NSCLC) [4]. In that trial, the adjuvant chemotherapy consisted of eight cycles (2 weeks of administration and 1 week of withdrawal) of S-1 at 80–120 mg/body per day in an outpatient setting. The completion rate was 78.6 % in patients younger than 70 years of age and 42.9 % in those aged 70 or older. The rate of patients with mild renal impairment (60 ml/min $\leq$ creatinine clearance $<$ 80 ml/min) tended to be higher among the elderly patients than among the younger patients, and S-1 administration was discontinued due to subjective symptoms, such as anorexia, during the early courses.

On the basis of this background, we conducted a feasibility trial of a reduced dose of S-1 for elderly patients with NSCLC in order to improve compliance.

Patients and methods

Patients

From July 2009 to July 2011, 25 patients who had undergone surgical resection for NSCLC were registered into a multi-institutional trial of a reduced dose of S-1. All patients were required to have undergone complete resection of all gross disease, to be 70 years of age or older, have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 and have no uncontrolled cardiac or hepatic disease. All patients had an adequate bone marrow function (3000/mm^3 $\leq$ total leukocyte count $\leq$ 12,000/mm^3, 2000/mm^3 $\leq$ absolute neutrophil count (ANC) $\leq$ 8000/mm^3, platelet count $\geq$100,000/mm^3 and hemoglobin level $\geq$9.0 g/dL), an adequate renal function (defined as serum creatinine level $\leq$ the upper normal limit for the laboratory) and an adequate hepatic function (defined as total bilirubin level $<$1.5 mg/dL and serum aspartate transaminase (AST) and/or alanine aminotransferase (ALT) levels less than twice the upper normal limit for the laboratory). No patients had severe cardiac disease or arrhythmia on electrocardiogram, and the room air oxygen partial pressure was $\geq$60 mmHg for all patients. For each patient, the pathological stage of the disease was based on the TNM classification of the Union Internationale Contre Cancer (UICC) [5]. The histological analysis of the tumor was based on the WHO classification for cell types [6]. The toxicity criteria were based on the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The clinico-pathological characteristics of the patients, excluding one patient who never underwent chemotherapy due to patient refusal, are shown in Table 1. This study was performed in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines. Written informed consent was obtained from all patients before study entry. Trial

Table 1 Clinico-pathological characteristics of the patients

Parameter	No.	%
Age (years), median (range)	76 (71–85)	
Gender		
Male	16	64
Female	9	36
Performance status (ECOG)		
0	17	68
1	8	32
Operative procedure		
Lobectomy	20	80
Pneumonectomy	4	16
Bilobectomy	1	4
Histological type		
Adenocarcinoma	17	68
Squamous cell	5	20
Large cell carcinoma	2	8
Adeno-squamous	1	4
Pathological stage		
IB	10	40
IIA	6	24
IIB	3	12
IIIA	5	20
IIIB	1	4

document approval was obtained from the institutional review board of each participating institution.

Treatment schedule

Treatment was initiated within 4 to 8 weeks after surgery. The patients received two oral doses of S-1 for 2 weeks followed by 1 week of no chemotherapy. The actual dose of S-1 was selected for each patient as follows: body surface area (BSA) <1.25 m^2, 25 mg twice a day; 1.25 m^2 $\leq$ BSA $<$ 1.5 m^2, 40 mg twice a day; and BSA >1.5 m^2, 50 mg twice a day. If the total leukocyte count and ANC were $\geq 3000/mm^3$ and $\geq 1500/mm^3$, respectively, and if the other eligibility criteria were satisfied, the patient could receive the next cycle. Treatment was allowed to be delayed for up to 3 weeks from day 1 of the current cycle to allow patients sufficient time to recover from drug-related toxicity. The blood counts and chemistries were examined at least once per week. The patients were not to receive prophylactic granulocyte colony stimulating factor (G-CSF) during any cycle. The use of G-CSF was allowed only for patients with ANC $<500/mm^3$, neutropenic fever or documented infections while neutropenic.

Dose adjustments and withdrawal

Treatment was suspended in patients with grade 1 renal impairment, grade 2 liver dysfunction or grade 3 hematological or non-hematological toxicities until a sufficient recovery from drug-related toxicity was achieved. The treatment was thereafter resumed at a reduced dose, as shown in Fig. 1. Patients who were not able to receive drugs for 6 weeks from day 1 of the previous cycle or who had grade 2 or greater renal impairment, grade 3 or greater liver dysfunction, or grade 4 or greater hematological or non-hematological toxicities were withdrawn from the study. Patients with prior dose reductions who experienced toxicities that would cause a second dose reduction were withdrawn from the study.

Endpoints and sample size consideration

The primary endpoint of this study was the completion rate of eight cycles of adjuvant chemotherapy with S-1. The secondary endpoints were toxicity, dose intensity and delay duration and rate. The sample size was determined using the standard two-stage phase II design of the South West Oncology Group (SWOG) [7]. We set a completion rate of 80 % as the expected rate and 50 % as the acceptable lowest rate with a power of 0.9 at a one-sided significance level of 0.05. This required the recruitment of 21 eligible patients. Assuming that some irrelevant cases would be recruited, we planned to enroll 25 patients in the study. The accrual period and period of follow-up after accrual closure were 30 and 6 months, respectively.

Statistical analysis

The difference in means was tested using the Wilcoxon rank sum test. A p value <0.05 was considered to be statistically significant. All statistical tests were two-sided, with the exception of the one-sided exact binomial test of the observed completion rate against the null hypothesis of the acceptable lowest rate. The confidence interval of each proportion was calculated using the exact method assuming binomial distribution. All data were analyzed using the Stata ver 9.2 software program (Stata Coop., TX, USA).

Results

Treatment and toxicity

The trial profile is shown in Fig. 2. A total of 25 patients were enrolled in the study. However, one patient withdrew consent before administration of S-1. The completion rate of eight cycles and the perfect completion rate of eight cycles on schedule with full doses without delays were 70.8 % [95 % confidence interval (CI) 52.7–89.0 %] and

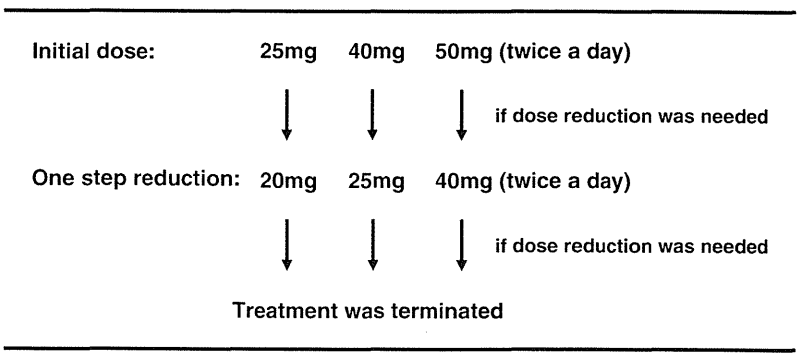

Fig. 1 Schematic drawing of the dose modifications made in this study

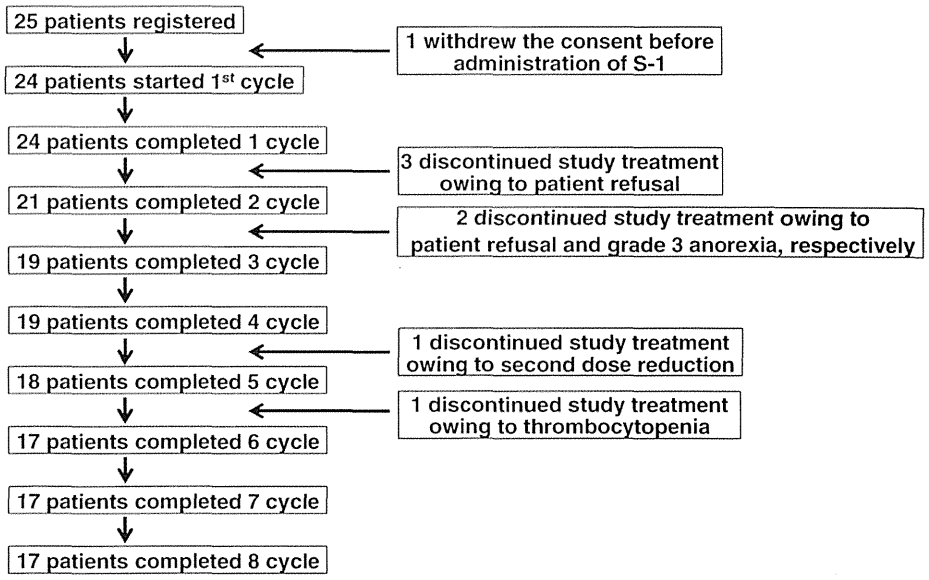

Fig. 2 Trial profile

Table 2 Hematological and non-hematological toxicities

	Grade			Grade 3/4 (%)
	2	3	4	
WBC	1	0	0	0
ANC	1	0	0	0
Hb	2	0	0	0
Plt	1	0	0	0
Febrile neutropenia	0	0	0	0
AST	0	0	0	0
ALT	0	0	0	0
Hyperbilirubinemia	3	0	0	0
Hypocalcemia	0	0	0	0
Hypokalemia	0	0	0	0
Hypernatremia	0	0	0	0
Hyponatremia	0	0	0	0
Fatigue	1	0	0	0
Alopecia	0	0	0	0
Anorexia	3	1	0	1 (4)
Diarrhea	1	0	0	0
Nausea/vomiting	2	0	0	0
Dermatitis	3	0	0	0
Skin hyperpigmentation	1	0	0	0
Oral mucositis	0	0	0	0

WBC white blood cell, *ANC* absolute neutrophil count, *Hb* hemoglobin, *Plt* platelets, *AST* aspartate transaminase, *ALT* alanine aminotransferase

50 % (95 % CI 30.0–70.0 %), respectively. The completion rate of eight cycles of chemotherapy was significantly higher than the acceptable lowest rate of 50 % ($p < 0.001$).

Regarding dose reductions of S-1, one patient received a one-level reduction in cycle 3. As a consequence of delay and/or dose reductions, the relative dose intensity (the actual delivered dose divided by the planned dose) of S-1 was 76.3 %. Among the five octogenarian patients who were included in this study, two patients completed eight cycles. Table 2 shows the hematological and non-hematological adverse events of grade 2 or worse in thirty-one patients who received at least one cycle. This regimen was associated with a manageable level of toxicity. No toxicity deaths occurred. Severe non-hematological toxicity was uncommon.

Discussion

This feasibility trial is the first report to examine postoperative adjuvant chemotherapy with S-1 in elderly Japanese patients with NSCLC. The completion rate of eight cycles and the perfect completion rate of eight cycles on schedule with full doses without delays were 70.8 and 50 %, respectively.

Standard regimens for adjuvant chemotherapy in postoperative patients with stage II–IIIA NSCLC currently use intravenous administration of a cisplatin doublet. However, oral adjuvant chemotherapy with UFT, which improved survival among Japanese patients with stage I adenocarcinoma, allows completion of the regimen with only mild adverse events [1]. Such oral drugs enable patients to undergo treatment on an outpatient basis, and are suitable for maintaining patient quality of life. S-1 was found to be useful as an adjuvant chemotherapy after curative surgery in Japanese patients with locally advanced gastric cancer in

a randomized phase III study, namely the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) [3]. In that trial, patients assigned to the S-1 group received two oral doses of 40 mg of S-1 per square meter of body surface area per day for 4 weeks followed by 2 weeks of no chemotherapy during the first year after surgery. Tsukuda et al. [8] reported a randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in patients with advanced head and neck cancer. In that study, patients were randomly assigned to receive either oral S-1 for 2 weeks followed by a 1-week rest in repeating cycles for 6 months or S-1 for 4 weeks followed by a 2-week rest in repeating cycles for 6 months. They reported that the schedule of 2 weeks of administration followed by 1 week of rest was more feasible for the 6-month oral administration protocol of S-1. Therefore, we conducted a feasibility trial (LOGIK 0601) of postoperative chemotherapy with S-1 in patients with NSCLC [4]. The adjuvant chemotherapy consisted of eight cycles (2 weeks of administration and 1 week of withdrawal) of S-1 at 80–120 mg/body per day in an outpatient setting. The completion rate was 42.9 % in patients 70 years of age or older and 78.6 % in patients younger than 70. The rate of patients with a mild renal impairment (60 ml/min $\leq$ creatinine clearance $<$ 80 ml/min) tended to be higher among the elderly patients than among the younger patients. Gimeracil, also called 5-chloro-2, 4-dihydroxypyridine (CDHP), is a component of S-1 and is an inhibitor of dihydropyrimidine dehydrogenase that degrades fluorouracil. It is worth mentioning that CDHP is known to predominantly undergo urinary excretion through glomerular filtration [9]. Renal function often decreases with advancing age [10]. Fujita et al. [11] compared the areas under the concentration–time curves (AUCs) of 5-FU and CDHP and the oral clearance rate of tegafur between patients 75 years of age or older and patients younger than 75 to assess the effects of aging on the pharmacokinetics of the components of S-1. The median AUC of CDHP was significantly higher in the patients 75 years of age or older than in the patients younger than 75 ($p = 0.004$). The median oral clearance rate of tegafur in the patients 75 years of age or older was significantly lower than that in the patients younger than 75 ($p = 0.011$). The increase in the CDHP concentration was caused by a decrease of glomerular filtration in the elderly patients. The authors reported that no significant differences in the AUCs of active 5-FU between the patients 75 years of age or older and the patients younger than 75 were found ($p = 0.598$). The opposing effects of aging on the oral clearance rate of tegafur and the AUC of CDHP may offset each other, thus resulting in unchanged systemic exposure to 5-FU. A higher blood concentration of 5-FU might be achieved in elderly patients if the oral clearance rate of tegafur was equal to that observed in younger patients. S-1 administration should be reduced in elderly patients with NSCLC in the adjuvant setting.

Lung cancer is predominantly a disease of the elderly, and although the incidence of lung cancer has decreased recently in younger adults, it has increased in patients aged 70 years or older. More than 50 % of lung cancer diagnoses are made in patients older than 65 years of age, and 30–40 % of diagnoses are made in patients older than 70 [12, 13]. Reports of the feasibility of surgery in elderly patients (>70 years of age) with early-stage tumors show that operative procedures can be performed safely with overall survival results that are similar to those seen in younger patients [14–16]. Perioperative mortality of 3 % and morbidity of 10 % were seen in one series examining patients aged 70 years or older [15], and no mortalities were reported in another series examining 40 patients older than 80 years. However, in the latter series, non-lethal postoperative complications approached 20 % [16]. The careful selection of elderly patients for lung cancer surgery is necessary; however, age alone does not appear to be a contraindication to surgery.

The minimum dose of S-1 was 80 mg daily in the ACTS-GC trial. Another adjuvant chemotherapy trial in patients with locally advanced colorectal cancer (ACTS-CC) employed the same dose during four cycles [17]. The proportions of patients older than 70 years of age in the former and latter studies were 26 and 37 %, respectively. There are no descriptions of dose intensity specific to elderly patients, although there is a description of the dose reduction used in all patients. The rate of chemotherapy compliance among patients older than 70 years of age is not known. Whether dose reduction allows sufficient power to prevent recurrence of lung cancer remains unclear. A retrospective analysis of chemotherapy compliance among elderly patients in JBR.10 was reported [18]. The mean dose intensities of vinorelbine and cisplatin were 13.2 and 18.0 mg/m^2/week in the young patients and 9.9 and 14.1 mg/m^2/week in the elderly patients, respectively. The elderly patients received significantly fewer doses of both drugs. However, adjuvant chemotherapy significantly prolonged overall survival in the elderly patients (hazard ratio 0.61, 95 % CI 0.38–0.98, $p = 0.04$). In an analysis of the ACTS-GC trial, when the protocol completion cases were divided into two groups according to compliance with S-1 administration, the 5-year survival curves for patients with $\geq$90 % compliance and patients with 70 to $\leq$90 % compliance overlapped (in-house experimental data; Taiho Pharmaceutical). We therefore believe that the dose reduction used in our study provides sufficient adjuvant chemotherapy for treating lung cancer with S-1, as observed in gastric cancer. Conducting further studies and providing a long-term follow-up is therefore necessary to clarify the remaining issues.

Exploratory subgroup analyses of elderly groups in JBR.10 showed that in patients up to 75 years of age, the overall survival was similar to that of younger patients, although this was not the case in patients older than 75 years [18]. However, in that study, the disease-specific survival rate was similar for all age groups, including patients older than 75 years. A possible explanation for this lies in the observation that the patients older than 75 years had proportionately more deaths that were unrelated to lung cancer or its treatment compared with the other subgroups. Among the five octogenarian patients who were included in our trial, only two completed eight cycles (40 %) and two refused to continue the protocol treatment after the first cycle. Both the elderly patients and their physicians may have been less willing to tolerate even modest degrees of toxicity, particularly at a time when the benefits of adjuvant chemotherapy were unproven. Adjuvant chemotherapy should not be withheld from elderly patients purely on the basis of age. However, determining the optimal treatment for patients older than 75 years, especially for patients of super-advanced age such as octogenarians, still requires further study.

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Conflict of interest All authors declare no conflict of interest.

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Clinicopathologic Features and Computed Tomographic Findings of 52 Surgically Resected Adenosquamous Carcinomas of the Lung

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Background. Adenosquamous carcinoma (ASC) is a rare malignant tumor with a squamous cell carcinoma (SCC) and an adenocarcinoma (AC) component. It behaves more aggressively than other histologic subtypes of lung cancer. We studied the clinicopathologic features and computed tomographic (CT) findings of ASC and assessed the effect of tumor location and the extent of the AC component in ASC on the clinical and radiologic characteristics of ASC.

Methods. A diagnosis of ASC was made in 53 (1.1%) of 4,923 patients who underwent resection for primary lung cancer. Fifty-two of these patients underwent preoperative high-resolution CT imaging and were enrolled in our study.

Results. ASC was peripherally located in 43 patients and centrally located in 9. Tumor size larger than 5 cm ($p = 0.012$) and CT findings of inflammatory changes surrounding the tumor ($p = 0.040$) were independent prognostic factors. Larger tumor size ($p < 0.001$), chief complaints ($p = 0.01$), advanced tumor stage ($p = 0.03$), obstructive pneumonia ($p < 0.01$), and CT findings of inflammatory changes surrounding the tumor ($p = 0.005$) were associated with central location. Twenty-four cases were predominantly AC, and 28 were predominantly SCC. Peripheral ground-glass opacity (GGO) on CT was more often seen in the AC-predominant groups ($p = 0.03$).

Conclusions. ASC patients presented with centrally located obstructive pneumonia typical of SCC and with peripheral GGO typical of lepidic AC. Tumor size that exceeded 5 cm and CT findings of inflammatory changes surrounding the tumor were strong predictors of poor prognosis.

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Adenosquamous carcinoma (ASC) is a rare biphasic malignant tumor with squamous cell carcinoma (SCC) and adenocarcinoma (AC) components that are detected in 0.4% to 4% of patients with lung cancer [1]. Previous studies reported that clinical features of ASC are commonly found in men, in patients with peripheral ASC, and in those who have a history of smoking. The prognosis of pulmonary ASC was found to be worse than that of AC or SCC, and prognostic factors include lymph node metastases, male sex, and advanced tumor stage. Autopsy and/or surgically resection data have shown that it is difficult to make a definite diagnosis of ASC in the initial stages.

Computed tomography (CT) scanning could be especially useful in the diagnosis of AC because ground-glass opacity (GGO) is a common finding in pulmonary AC with a lepidic growth pattern. Despite this, only one study reported on a series of detailed CT radiographic characteristics of pulmonary ASC. These characteristics included a peripherally located mass with lobulation and intratumoral necrosis within the tumor [2]. However, these characteristics are not specific to pulmonary ASC and are also seen in pleomorphic carcinoma, large cell neuroendocrine carcinoma, and carcinoid tumor of the lung [3–5]. In consideration of the location of the tumor in the lungs, ASC was described as being less peripheral than AC and less central than SCC [6].

In the present study, we analyzed the clinicopathologic features and CT findings of pulmonary ASC to identify specific characteristics of ASC that could aid in the diagnosis and prognostic predictions of this cancer. In addition, we assessed the impact of tumor location and the extent of the AC component in ASC on the clinical and radiologic characteristics of ASC.

Material and Methods

Case Selection

The institutional review board of the National Cancer Center Hospital, Tokyo, Japan, approved the study (2010-0077). Between 1998 and 2011, 4,923 patients underwent surgical resection for primary lung carcinoma at this institute and received diagnoses of ASC, and the

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most recent World Health Organization classification was confirmed in 53 (1.1%) cases [1]. In 52 of these cases, high-resolution CT scans were conducted before surgical resection, and the results were available. Staging was based on the criteria of the 7th edition of the tumor, node, metastasis classification for lung cancer [7].

Pathologic Studies

All sections were stained with hematoxylin and eosin (Fig 1). The histopathology specimens were independently examined by two observers (YW and KT). When reviewing the histology slides, we paid particular attention to key histologic features, such as the presence of keratinization or absence of the alveolar filling growth pattern, so as to differentiate between high-grade mucoepidermoid carcinoma and squamous metaplasia in AC and to distinguish between glandular differentiation in SCC and in ASC. Furthermore, immunohistochemical analyses, which could identify AC and SCC components, were performed in cases that were difficult to classify during the histology review [8]. We also examined the relationship between the intratumoral distribution area of the AC and SCC components, including the border of each component.

The following features of the tumors were observed: proportions of the AC and SCC components, necrosis, and lymphatic, vascular, and pleural invasion. We subdivided ASCs according to the extent of the AC component. When the AC component was less than 60%, the ASC was considered SCC predominant, and when the AC component was equal to or more than 60%, the ASC was considered AC predominant [9, 10]. Furthermore we used the International Association for the Study of Lung Cancer classifications of lung adenocarcinoma to further subdivide AC components into one of the following five predominant patterns: lepidic, acinar, papillary, micropapillary, or solid predominant [11].

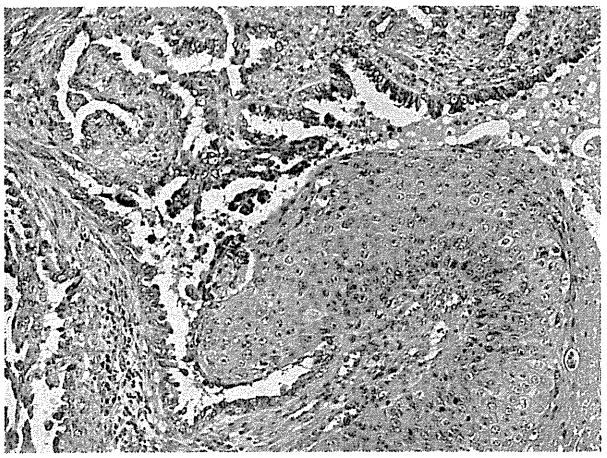

Fig 1. Adenocarcinoma component with lepidic predominant and squamous cell component are completely separated from one another. (Hematoxylin and eosin; ×10.)

Review of CT Images

The CT images were examined by two observers (YW and MK), who noted the location, size, shape of the margin, and internal characteristics of the tumors. A description of the location of the tumor included identification of the affected lung lobe and the position of the tumor in the lobe (central vs peripheral). In this study, all information regarding the location of tumors was based on the CT findings. Central tumors were defined as those involving proximal to segmental bronchus. Peripheral tumors were defined as those surrounded by lung parenchyma or positioned distal to subsegmental bronchi. CT images were evaluated for the presence of tumor–lung interface features, including marginal definition, lobulation, pleural indentation, spiculation, and peripheral GGO. To determine the internal characteristics of tumors, air bronchogram, calcification, cavity, and enhancement patterns were evaluated. The enhancement patterns of nodules were examined on contrast-enhanced CT and noted as either heterogeneous or homogeneous. We also evaluated the characteristics of the environment surrounding the tumor such as presence of emphysema or interstitial fibrosis and inflammatory changes surrounding the tumor (Fig 2), including obstructive and aspiration pneumonia.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics 21 (IBM Corporation, Somers, NY). Student's t test and χ^2 test were used. Overall survival curves were calculated by use of the log-rank test. Univariate survival analysis was

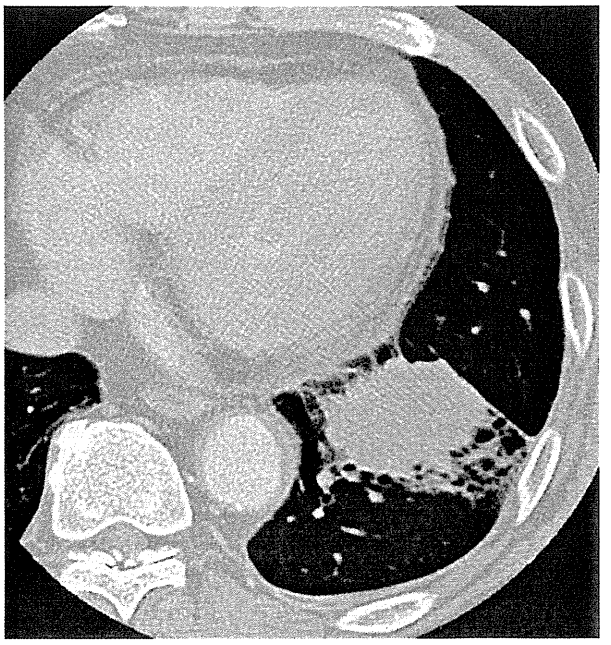

Fig 2. High-resolution computed tomographic image showing inflammatory changes surrounding the tumor in centrally located adenosquamous carcinoma.

performed with the log-rank test and Cox's proportional hazard regression. In the multivariate Cox model, variables with $p < 0.10$ from Wald's test for univariate models were included. Statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

ASC was more prevalent among men (n = 33, 64%) than among women (n = 19, 36%) ($p = 0.07$). The median age of the patients at the time of diagnosis was 67 years (range, 37 to 84 years). Thirty-five (67%) of the 52 patients who presented without pulmonary symptoms had abnormal findings on chest roentgenograms that were obtained during periodic examination. Symptoms in the remaining 18 (35%) patients included hemoptysis (n = 8), cough (n = 7), back or shoulder pain (n = 3), and clubbed fingers (n = 1). Smoking was marginally correlated with ASC (75%, $p = 0.06$). The rate of smoking was lower in female patients with ASC than in male patients (42.1% vs 93.9%).

Preoperative histologic and/or cytologic diagnosis at our hospital yielded the following: 12 patients (40%) with AC, 12 patients (40%) with SCC, 4 patients (13.3%) with non-small cell lung carcinoma (NSCLC), and 2 patients (6.7%) with ASC. Of note, in three cases, the histologic diagnosis made at the primary hospital differed from the diagnosis made at our hospital. Two patients received diagnoses of SCC at the primary hospital, but after biopsy at our hospital, they received diagnoses of NSCLC or AC. The third patient received a diagnosis of AC at the primary hospital, but biopsy performed at our hospital confirmed a diagnosis of SCC.

To elucidate the discordance between clinical features and preoperative histologic diagnosis, we assessed whether patients diagnosed with SCC were female, had a history of smoking, had a CT finding of peripheral GGO, or had a high serum level of carcinoembryonic antigen (CEA). Among 12 patients with a preoperative diagnosis of SCC, only 1 (8.3%, $p = 0.62$) had a CT finding of peripheral GGO, 7 (58.3%, $p = 0.55$) had high serum CEA (>5) values, and 3 did not have a history of smoking (25.0%, $p = 0.69$).

Lymph node metastasis was found in 19 (37%) of the 52 tumors (N1 and N2 in 12 [23%] and 7 [13%] patients, respectively). Stage I, II, III, and IV tumors were found in 26 (69%), 13 (25%), 11 (21%), and 2 (4%) patients, respectively.

Histologic Findings

The AC component of tumors varied between 10% and 90% (mean, 50.3%). Vascular invasion was observed in 47 (90%), lymphatic permeation in 36 (69%), pleural invasion in 33 (63%), tumor necrosis in 25 (48%), and obstructive pneumonia in 18 (35%) cases. With regard to the relationship between intratumoral distribution of each AC and SCC component, 20 (38%) patients had a clear abuttal between the AC and SCC components. All 20 cases showed centrally located SCC components with peripherally located AC components, and there were no cases of centrally located AC components with peripherally located SCC components. In another 32 (62%) cases, the AC and SCC areas were mixed, rather than completely separated from one another. Of the 52 cases, 46 (88%) were positive for thyroid transcription factor-1 in the AC component.

With regard to the predominant component of AC, the most prevalent was the acinar component, predominant in 18 cases (35%); followed by lepidic predominant in 11 cases (21%); papillary predominant in 9 cases (17%); solid predominant in 8 cases (15%); and micropapillary predominant in 6 cases (12%). Lepidic predominant tumors tended to be located in the peripheral part of the tumor nodule ($p < 0.001$).

CT Findings of the Tumor

Tumors tended to be positioned in the intermediate or peripheral part of the affected lobe (83%, $p = 0.05$). With regard to pleural indentation, four cases were not evaluated because of chest wall invasion. Tumor–lung interface characteristics were as follows: ill-defined interface in 38 patients (72%), pleural indentation in 32 (62%), lobulation in 23 (44%), spiculation in 19 (37%), and peripheral GGO in 7 (13%). With regard to internal characteristics, air bronchogram was seen in 14 (27%), cavity formation in 10 (19%), homogeneous enhanced pattern in 7 (13%), and calcification in two cases (4%). In addition, emphysema was seen in 18 (35%), interstitial pneumonia in seven (13%), and inflammatory changes surrounding the tumor in 18 (35%) cases.

We found significant correlations between inflammatory changes surrounding the tumor and pathologic obstructive pneumonia ($p < 0.001$). There were no other significant correlations between CT and pathologic findings.

Follow-Up and Clinical Outcome

Five cases were excluded from our analysis of follow-up and clinical outcome because they did not have adequate follow-up time periods. Among 47 patients, 21 (45%) were alive, and the average follow-up time was 46 months. Nineteen (90%) of the 21 surviving patients had no recurrence, and 2 (9.5%) had disease progression as indicated by the presence of metastatic lesion(s). The overall survival curve and recurrence-free survival curves are shown in Figure 3. The median, 5-year overall survival, and 5-year recurrence-free survival rate were 66 months, 54.3%, and 41.2%. Multivariate analysis revealed the following to be independent prognostic factors: a larger tumor (>5 cm, $p = 0.012$) and CT findings of inflammatory changes surrounding the tumor ($p = 0.040$) (Table 1). Figure 4 shows the Kaplan-Meier overall survival curves with the prognostic variables listed in Table 1.

Comparison of Clinicopathologic Features and CT Findings Between the Central and Peripheral Location

Cases of ASC were subdivided into central (n = 9) and peripheral (n = 43) groups based on the location of the tumor. The following characteristics were significantly

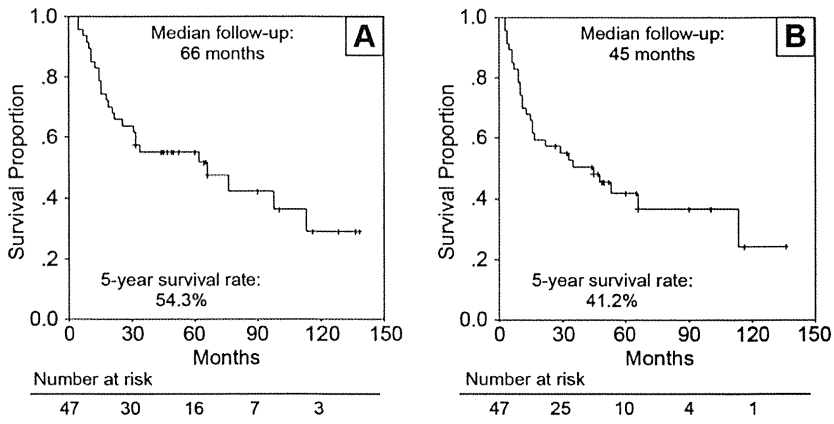

Fig 3. (A) Overall survival curves for adenosquamous carcinoma cases. (B) Recurrence-free survival curves for adenosquamous carcinoma cases.

more common in the central group: larger tumor size ($p < 0.001$); chief complaints ($p = 0.01$), especially hemoptysis ($p = 0.02$); and advanced tumor stage ($p = 0.03$) (Table 2). There were no significant differences between the groups with regard to age, sex, smoking history, operative site, or lymph node metastasis. There were no correlations between preoperative diagnosis and tumor location in the 30 of 52 cases that had a preoperative diagnosis.

Histologic findings showed that the central group had a higher frequency of obstructive pneumonia ($p < 0.01$), but vascular invasion, pleural invasion, necrosis, lepidic, and solid predominant components of AC did not differ significantly between the groups (Table 3).

CT showed that the central group had a higher frequency of inflammatory changes surrounding the tumor ($p = 0.005$), but the tumor–lung interface and internal characteristics did not differ significantly between the groups (Table 4). Univariate analysis showed that the prognosis in patients with centrally located ASC was worse than in those with peripherally located ASC ($p = 0.007$) (Table 1). However, multivariate analysis found no statistically significant differences between the groups.

Table 1. Independent Impacts of Variables on Patient: Overall Survival Estimated by Univariate and Multivariate Analysis

		Multivariate		
Variable	Univariate *p* Value	HR	95% CI	*p* Value
Sex				
Male vs female	0.01	0.761	0.193–3.004	0.697
Smoking				
Former/current vs never	0.005	5.664	0.761–42.143	0.090
Tumor size (cm)				
>5 vs. ≤5	<0.001	4.697	1.409–15.661	0.012
CEA (ng/mL)				
>5 vs. ≤5	<0.001	1.217	0.320–4.623	0.774
Lymph node metastasis				
Positive vs negative	0.04	2.071	0.496–8.650	0.318
Tumor stage				
III or IV vs I or II	<0.001	2.896	0.632–13.283	0.171
Tumor location				
Peripheral vs central	0.007	0.766	0.269–2.182	0.618
CT findings of inflammatory changes surrounding tumor				
Positive vs negative	<0.001	3.198	1.055–9.692	0.040
Pleural invasion				
Positive vs negative	0.009	0.866	0.239–3.130	0.826
Predominant type of adenocarcinoma				
Lepidic vs nonlepidic	0.02	0.239	0.020–2.810	0.255

CEA = carcinoembryonic antigen; CI = confidence interval; CT = computed tomography; HR = hazard ratio.

Comparison of Clinicopathologic and CT Findings With Predominant Histologic Component

Cases of ASC were subdivided into AC-predominant (n = 24) and SCC-predominant (n = 28) groups. Subjective symptoms, including hemoptysis, tended to be seen more often in the SCC-predominant group ($p = 0.11$). There were no correlations between sex or a history of smoking and SCC predominance. Predominant components influenced the preoperative diagnosis. A preoperative diagnosis of AC was more prevalent among AC-predominant ASC cases ($p = 0.01$) and a preoperative diagnosis of SCC was more prevalent among SCC-predominant ASC cases ($p = 0.05$) (Table 5). However, there were no significant differences in predominant histologic component and histologic findings of pleural invasion, lymphatic permeation, vascular invasion, necrosis, obstructive pneumonia, and a lepidic or solid predominant pattern in AC component.

Regarding the CT findings, evidence of peripheral GGO was noted more often in the AC-predominant group ($p = 0.03$). Among the six peripheral GGO groups in AC-predominant ASC, pathologic findings showed a lepidic growth pattern of AC in five (83%) cases. However, ill-defined patterns were more frequently seen

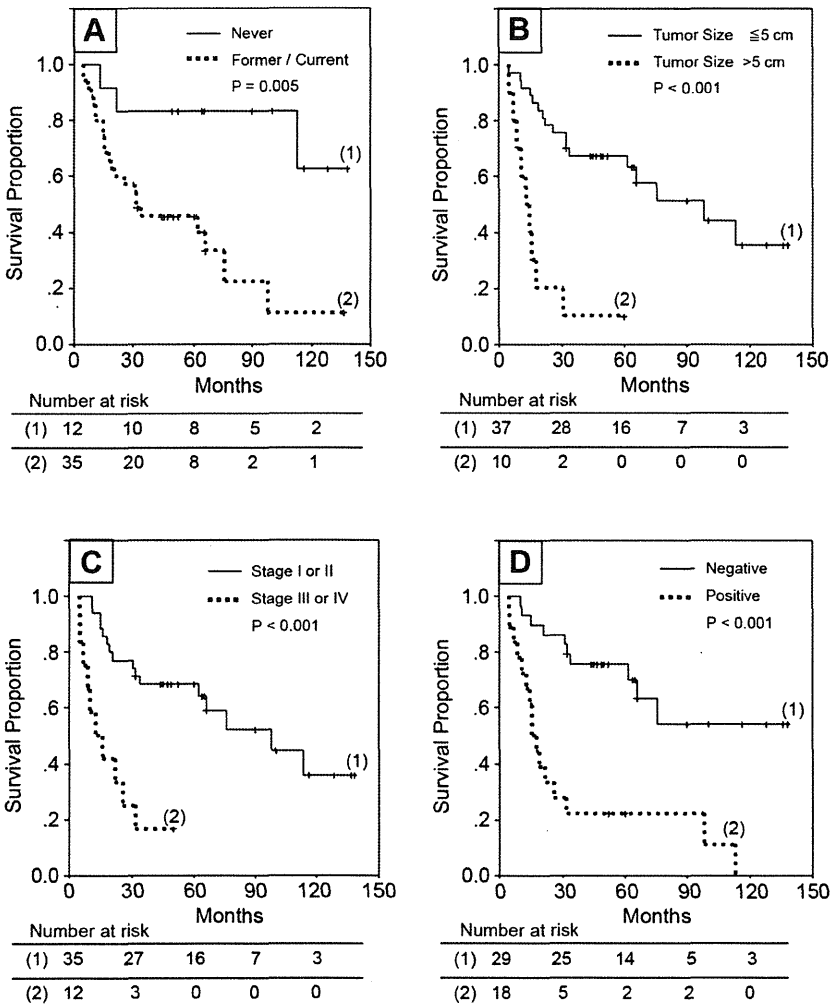

Fig 4. Overall survival (OS) analysis. (A) OS curves for patients with never smoker and former or current smoker status ($p = 0.05$). (B) OS curves for patients with tumor size >5 cm and ≦ 5cm ($p < 0.001$). (C) OS curves for patients with stage I or II and III or IV ($p < 0.001$). (D) OS curves for patients with positive and negative CT findings of inflammatory changes surrounding the tumor ($p < 0.001$).

in the SCC-predominant group ($p = 0.11$). There were no other significant differences between the SCC-predominant and AC-predominant groups. Overall survival was not correlated with the predominant histologic component ($p = 0.89$).

Comment

In the present study, we investigated the clinicopathologic and radiographic features of patients with pulmonary ASC. As far as we could establish, this is the largest study to have examined the CT findings of lung ASC thus far. Similarly to previous reports, in our study, ASC tended to occur in men and those with a history of smoking [10, 12–14]. Previous studies have reported high rates of smoking among those with ASC (76.3% to 90.0%) [9, 12, 14], but in our study, the smoking rate among female patients with ASC was lower (42.1%) than that among men (93.9%). Nevertheless, this rate was higher than the smoking rate of 22.9% found among female lung cancer patients enrolled in a large cohort study in Japan [15]. Taken together, these results indicate that ASC is intimately linked to a history of smoking.

To ascertain the clinical impact of the position of the tumor in pulmonary ASC, we compared the characteristics of centrally and peripherally located ASC. Larger tumor size, subjective symptoms including hemoptysis, and a more advanced disease stage (stage III or stage IV) were more commonly seen among centrally located ASC than among peripherally located ASC. Tumor location (peripheral or central) was not an independent prognostic factor in this study. CT imaging showed that centrally located ASC tended to have inflammatory changes surrounding the tumor ($p < 0.005$), and this finding was not influenced by the histologic predominance of AC or SCC. In addition, histologic analysis confirmed that the frequency of obstructive pneumonia was higher in patients with centrally located tumors than in those with peripherally located tumors ($p < 0.01$). Previous studies have reported that centrally located ASC has a larger SCC component than peripherally located ASC [6, 16], and this might be because centrally

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Table 2. Patient Characteristics According to Location Between Peripheral and Central

Variable	Peripheral (n = 43)	Central (n = 9)	*p* Value
Age (y)			
Median	69	66	0.42
Range	37–84	52–79	
Age >70	18	3	0.47
Gender			
Male	26	7	0.28
Female	17	2	
Smoking history			
Former or current smoker	32	7	0.60
Never smoker	11	2	
Tumor size (cm)			
Median	3.4	5.5	<0.001
Range	1–7	3.2–9	
Tumor size >5 cm	6	4	0.06
Operative side			
Right side	23	5	0.60
Lobar location			
Upper	25	7	0.24
Chief complaint	12	7	0.01
Hemoptysis Cough	4	4	0.02
	4	3	0.09
CEA (ng/mL)			
Median	6.3	8.4	0.47
Range	1–44.6	1–35	
Tumor stage			
I or II	35	4	0.03
III or IV	8	5	
Lymph node metastasis			
N0	29	4	0.18
≥N1	14	5	
Postoperative recurrence	16	7	0.06

CEA = carcinoembryonic antigen.

Table 3. Pathologic Characteristics Between Peripheral and Central Locations

Variable	Peripheral (n = 43)	Central (n = 9)	*p* Value
Vascular invasion	38	9	0.37
Pleural invasion	27	6	0.57
Lymphatic permeation	28	8	0.16
Necrosis	19	6	0.20
Obstructive pneumonia	11	7	<0.01
Predominant component (AC>SCC)	20	4	0.60
Lepidic predominant of AC	10	1	0.38
Solid predominant of AC	10	3	0.40

AC = adenocarcinoma; SCC = squamous cell carcinoma.

Table 4. CT Characteristics According to Location Between Peripheral and Central

Variable	Peripheral (n = 43)	Central (n = 9)	*p* Value
Tumor–lung interface features			
Ill-defined	32	6	0.46
Lobulation	20	3	0.37
Pleural indentation	27	5	0.64
Spiculation	17	2	0.28
Peripheral GGO	6	1	0.65
Internal characteristics			
Air bronchogram	11	3	0.46
Calcification	2	0	0.03
Cavity	9	1	0.44
Homogeneous	6	1	0.60
Other findings			
Inflammatory changes surrounding the tumor	11	7	0.005
Emphysema	12	4	0.63
Interstitial pneumonia	6	1	0.43

CT = computed tomography; GGO = ground-glass opacity.

located ASCs follow a growth pattern of bronchialz obstruction or compression-like SCC.

To ascertain whether a predominant epithelial component affected clinical features, ASC cases were subdivided according to AC or SCC predominance, and differences between the groups were assessed. Chief complaints, including hemoptysis, were significantly more prevalent in the SCC-predominant group than in the AC-predominant group ($p = 0.11$). In addition, chief complaints, including hemoptysis, were significantly more common among patients in the central group. Because SCC is more often located centrally, a SCC predominant component in ASC may result in presenting symptoms that resemble the symptoms of SCC. The predominant components of ASC influenced the preoperative diagnosis as shown in Table 5. Preoperative diagnosis might depend on the predominant epithelial component, and ASC might be treated according to the diagnosis that coincides with the predominant component, AC or SCC, especially in non-resectable cases. Similar to previous reports, we did not find statistically significant differences between the proportion of the AC component and prognosis [10, 17].

Table 5. Preoperative Diagnosed Cases Between AC>SCC and AC≦SCC

Variable	AC>SCC (n = 24)	AC≦SCC (n = 28)	*p* Value
Preoperative diagnosis	14 (58%)	16 (57%)	
Adenocarcinoma	9	3	0.01
Squamous cell carcinoma	3	9	0.05
Non-small cell carcinoma	2	2	0.65
Adenosquamous carcinoma	0	2	0.28

AC = adenocarcinoma; SCC = squamous cell carcinoma.

Radiographic imaging showed that the frequency of peripheral GGO was higher in the AC-predominant group than in the SCC-predominant group ($p = 0.03$). Among six peripheral GGO groups, five (83%) cases had a lepidic growth pattern, which is one of the histologic features of AC. This finding suggests that peripheral GGO, as seen on CT, could be one of the predictive markers of AC-predominant ASC, especially in cases where a diagnosis of SCC with peripheral GGO is based on a biopsy specimen. In the present study, only 6.7% of cases had an accurate preoperative diagnosis of ASC (preoperative diagnosis was based on histologic and/or cytologic findings.). Analysis of ASC on autopsy and/or surgical resection confirms that an accurate initial diagnosis of ASC is difficult to make [12, 13, 18, 19], and only 5% of cases were correctly diagnosed with ASC preoperatively [18]. Interestingly, in three of our cases, the histologic diagnosis made at the primary hospital differed from the histologic diagnosis made at our hospital, and in one of these cases, there was a difference between the histologic and cytologic diagnoses. Similar discrepancies between biopsy specimens and cytology samples have been reported previously [13, 19], and these discrepancies were one of the key signs for suspected ASC.

With regard to the prognostic factors obtained from CT imaging, we found that inflammatory changes surrounding the tumor served as an independent prognostic factor ($p = 0.040$). Thus far, there have been no reports of a correlation between CT findings and ASC prognosis. In the present study, CT findings of inflammatory changes surrounding the tumor were correlated with obstructive pneumonia ($p < 0.001$) and a tumor with a diameter of more than 5 cm, which was one of the prognostic factors in this study ($p < 0.001$). In stage IB NSCLC, obstructive pneumonia and a tumor size of more than 3 cm were also found to be prognostic factors [20]. The definition of inflammatory change surrounding the tumor includes T2 factors such as obstructive pneumonia and peripheral atelectasis. These T2 factors may thus affect prognosis. T2 factors were not confounding factors in this study when inflammatory changes surrounding the tumor were considered. Therefore, CT findings of inflammatory changes surrounding the tumor could be a prognostic factor in ASC.

In conclusion, ASC has the characteristics of both epithelial components; for instance, ASC presents with centrally located obstructive pneumonia akin to SCC and with peripheral GGO similar to AC in AC-predominant ASC cases. An accurate preoperative diagnosis of ASC is very difficult. In our study, a tumor size larger than 5 cm and CT findings of inflammatory changes surrounding the tumor strongly predicted a poor prognosis.

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CASE REPORT

Three-dimensional multidetector computed tomography may aid preoperative planning of the transmanubrial osteomuscular-sparing approach to completely resect superior sulcus tumor

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Abstract The anterior transcervical-thoracic approach clearly exposes the subclavian vessels and brachial plexus. We believe that this approach is optimal when a superior sulcus tumor (SST) invades the anterior part of the thoracic inlet. However, this approach is not yet widely applied because anatomical relationships in this procedure are difficult to visualize. Three-dimensional tomography can considerably improve preoperative planning, enhance the surgeon's skill and simplify the approach to complex surgical procedures. We applied preoperative 3-dimensional multidetector computed tomography to a case where an SST had invaded the anterior part of the thoracic inlet including the clavicle, sternoclavicular joint, first rib, subclavian vessels and brachial plexus. After the patient underwent induction chemotherapy, we performed the transmanubrial osteomuscular-sparing approach and added a third anterolateral thoracotomy with a hemi-clamshell incision and completely resected the tumor.

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Keywords 3-Dimensional computed tomography · Anterior transcervical-thoracic approach · Superior sulcus tumor · Surgical techniques · Transmanubrial osteomuscular-sparing approach

Abbreviations

3-D	Three dimensional
CT	Computed tomography
DICOM	Digital imaging and communication in medicine
MD	Multidetector
SST	Superior sulcus tumor
VATS	Video-assisted thoracoscopic surgery

Introduction

The anterior transcervical-thoracic approach applied by Dartevelle and colleagues [1] clearly exposes the subclavian vessels. Furthermore, Grunenwald's [2, 3] improvement preserves the clavicle and sternoclavicular joint. In this procedure, referred to as the "transmanubrial osteomuscular-sparing approach", part of the manubrium and the first costal cartilage are sectioned and moved away with the clavicle. We believe that this approach is optimal when a superior sulcus tumor (SST) has invaded the anterior part of the thoracic inlet. However, this approach is not yet widely applied. One of the reasons may be the difficulty in understanding the concept of this method. Another problem pointed out by several authors is the occasional need for additional thoracotomies for lobectomies with lymph node dissection.

New technologies can considerably improve preoperative planning, enhance the surgeon's skill and simplify the

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approach to complex surgical procedures. Recently, surgical simulation based on preoperative 3-dimensional multidetector computed tomography (3-D MDCT) scans has been developed in the field of thoracic surgery as well as head and neck surgery, neurosurgery, and orthopedic surgery [4, 5]. We applied preoperative 3-D MDCT to a surgical case where an SST had invaded the anterior part of the thoracic inlet, including the clavicle, sternoclavicular joint, first rib, subclavian vessels and brachial plexus. We first applied induction chemoradiotherapy and then completely resected the tumor using the transmanubrial osteomuscular-sparing approach plus a third anterolateral thoracotomy with a hemi-clamshell incision.

Case

A 71-year-old man was referred to our hospital for a detailed examination after he complained of bloody sputum and paralysis of his right upper arm in the medial antebrachial cutaneous nerve area. A chest CT scan revealed a large mass measuring 5 cm in diameter in the apex of the right lung. The CT images indicated that the mass had invaded the first rib, and possibly the subclavian vessels and brachial plexus (Fig. 1a, b). Non-small cell carcinoma was diagnosed on the basis of the results of a transbronchial lung biopsy. After the patient underwent a detailed examination that included a brain MRI and PET-CT scanning, he was treated with preoperative induction chemoradiotherapy, which is the standard treatment for SSTs (clinical T4N0M stage IIIB). The tumor shrank in size following 2 cycles of q3wks, cisplatin (80 mg/m^2) D1 plus vinorelbine (20 mg/m^2) D1, 8 with 40 Gy of irradiation (Fig. 1c). Thereafter, we performed a right upper lobectomy and combined resection the first rib and brachial plexus (C8 and Th1).

One of the major goals of this operation was to preserve the mobility of the right arm, the patient being an actor. He stated that he did not want the surgery if the mobility of his right arm was affected. With this in mind, we used a 3-D MDCT viewer that runs on QuickTime software to simulate the surgery and to understand the anatomical relationship between the SST and the thoracic inlet, including the clavicle, sternoclavicular joint, first rib, subclavian

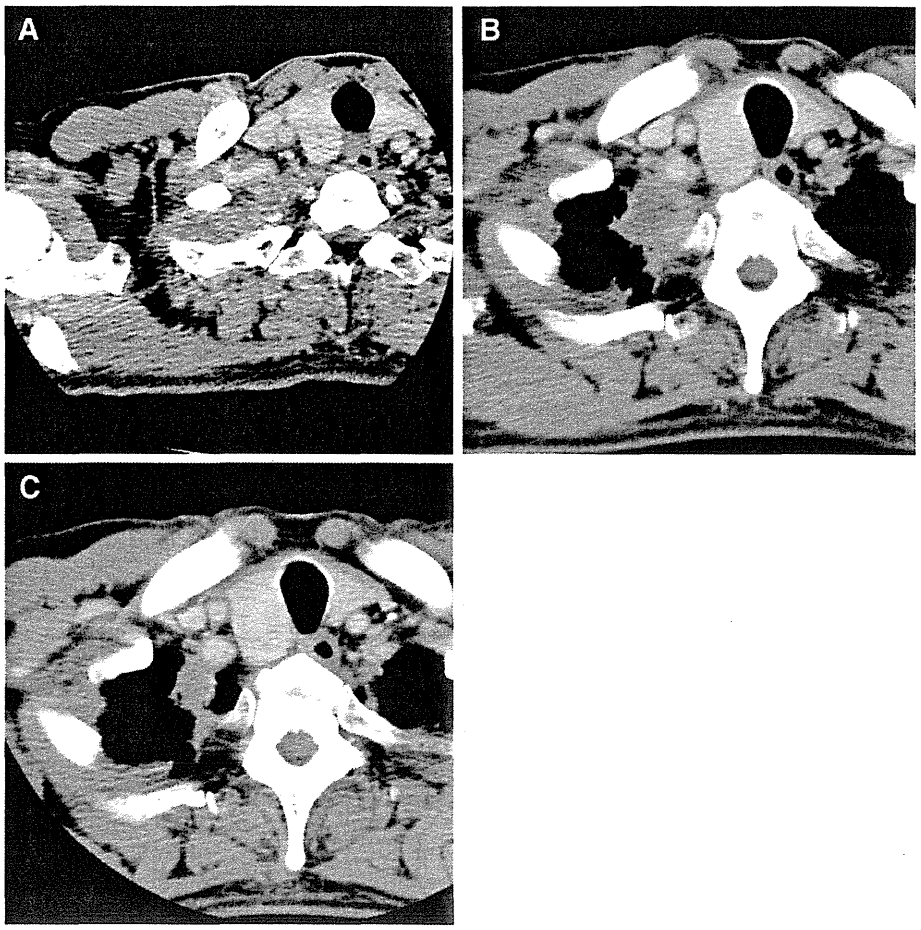

Fig. 1 Chest CT images revealed a superior sulcus tumor invading the anterior part of the thoracic inlet before (**a**, **b**) and after (**c**) chemoradiotherapy. This tumor potentially invaded subclavian vessels and brachial plexus (**a**)

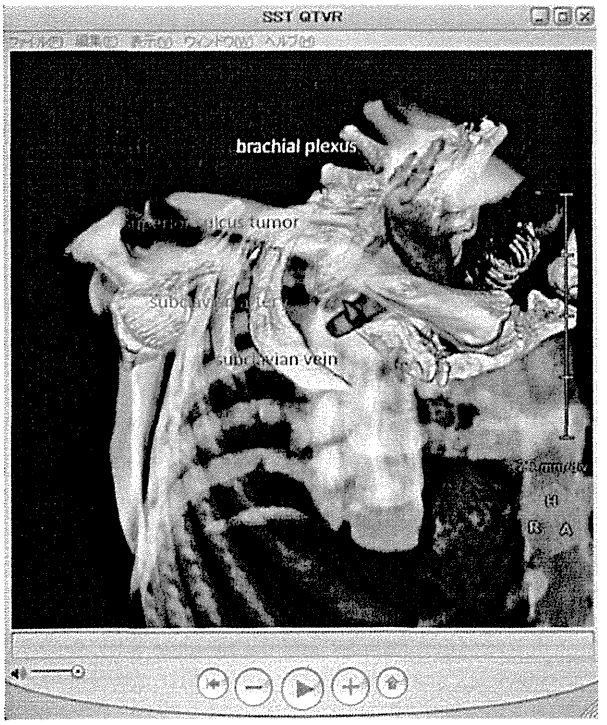

Fig. 2 A preoperative 3-D MDCT reconstruction of the superior sulcus tumor located in the anterior part of the thoracic inlet including the clavicle, sternoclavicular joint, first rib, subclavian vessels and brachial plexus. Made with QuickTime software

vessels and brachial plexus. We planned our surgical approach based on this preoperative simulation (Fig. 2). This 3-D MDCT surgical simulation was performed using a 64-channel multidetector CT (MDCT) (Light Speed VCT, General Electric Company, CT, USA). These digital imaging and communication in medicine (DICOM) data were transferred to a workstation with Synapse Vincent volume-rendering reconstruction software (Fujifilm Corporation, Tokyo, Japan). The DICOM data of MRI were also used to obtain information about the brachial plexus. Both 3D reconstructions of MDCT and MRI were combined and adjusted with costal positions.

On the basis of the results of this surgical simulation, we first applied the transmanubrial osteomuscular-sparing approach to confirm tumor invasion in the upper limit of the C8 segmental branch of the brachial plexus. After confirming that the brachial plexus (C7) was intact intraoperatively (Fig. 3a, b), we carried out a third anterolateral thoracotomy with a hemi-clamshell incision for a right upper lobectomy. Using special 3D viewer that reconstructed both MDCT and MRI, we could understand the anatomical relationship between the SST and the thoracic inlet, including the clavicle, sternoclavicular joint, first rib, subclavian vessels and brachial plexus as a preoperative simulation (Fig. 3c). Finally, we achieved pathological curative resection by performing right upper lobectomy and combined resection of the first rib and brachial plexus (C8 and Th1) with complete mediastinal lymph node dissection. We operated for 7 h with 750 ml of blood loss. His final pathological stage was ypT3N0 (0/18) M0 IIB with Ef. 3: no residual cancer cells.

Discussion

For approximately 40 years, from the 1960s to the 2000s, the treatment strategy for SSTs was induction radiotherapy followed by surgery. This treatment strategy has changed as a result of two Phase II studies that evaluated the use of induction chemoradiotherapy followed by surgery. One was Southwest Oncology Group Trial 9416 (intergroup trial 0160) [6] and the other was Japan Clinical Oncology Group Trial 9806 [7]. The new strategy improved the complete resection rate from about 50 to 70 % and the 5-year survival rate from about 30 to 50 %; as a result, it has become the standard treatment for SST. However, the appropriate surgical technique to completely resect an SST when it invades major anatomical areas is still challenging.

One of the biggest difficulties in achieving complete resection is that when an SST has invaded the thoracic inlet, particularly the anterior transcervical-thoracic area in which the subclavian vessels and brachial plexus are often involved, it is difficult to visualize their anatomical placement. However, the anterior transcervical-thoracic approach developed by Dartevelle and colleagues [1] shows the subclavian vessels clearly. The improvements made by Grunenwald and Spaggiari [2] and Grunenwald et al. [3] to this approach also preserve the clavicle and sternoclavicular joint. During this "transmanubrial osteomuscular-sparing approach", as it is called, part of the manubrium and the first costal cartilage are sectioned and moved away with the clavicle. However, this approach is not still widely used possibly because it is difficult to imagine the anatomical relationships in this procedure or to understand the concept of this approach.

Recently, surgical simulations based on preoperative 3-D CT scans have been developed in the fields of thoracic surgery as well as head and neck surgery, neurosurgery, orthopedic surgery and general surgery. The efficacy of 3-D CT angiography using MDCT for preoperative assessment for thoracic surgery has been described. Accurately depicting individual anatomies of pulmonary vessels and bronchi, and preoperative simulation using 3-D MDCT could play an important role in facilitating a safe and complete VATS lobectomy procedure, as some previous reports suggested [5]. We also previously reported the benefits of a virtual segmentectomy, a novel surgical simulation system based on high-quality 3-D lung modeling,

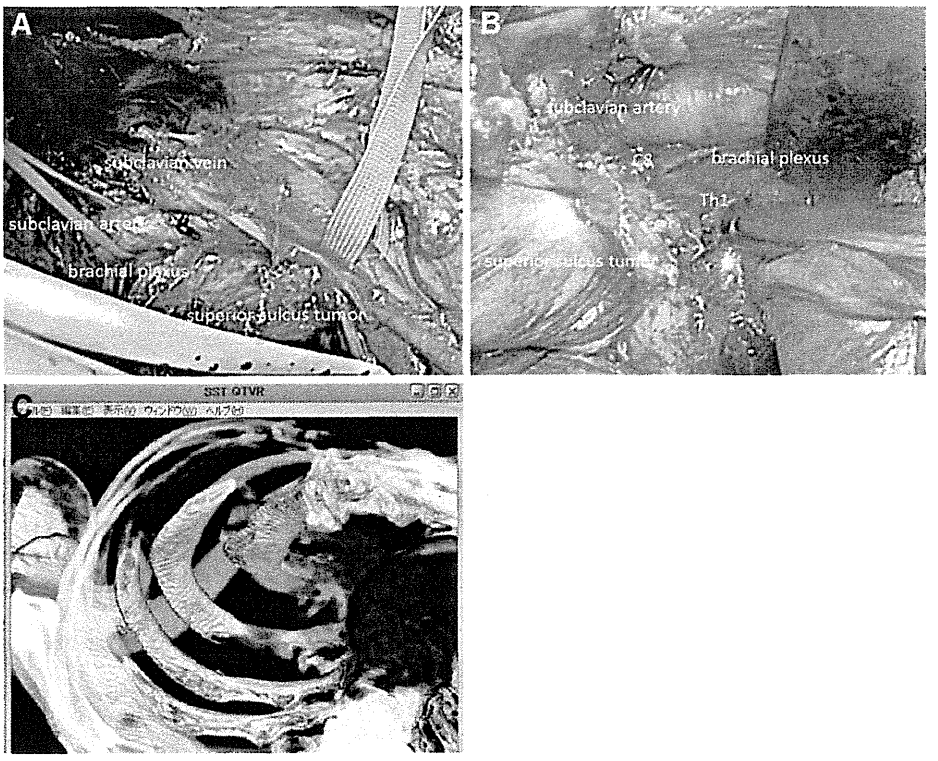

Fig. 3 Operation picture showing the anatomical relationship between the superior sulcus tumor and the subclavian artery, vein and brachial plexus upper limit of C8 of the brachial plexus (**a**, **b**). **c** showed that 3D viewer was able to reconstruct the operation view of **a**, **b**

including vascular and bronchial structures. This new technology can help thoracic surgeons perform appropriate anatomical segmentectomy and curative resection [4].

We performed surgery on our patient with an SST that had invaded the anterior part of the thoracic inlet with the aim of preserving the mobility of his right arm. It was critical to confirm precisely and less invasively whether the tumor had invaded the upper limit of C8 of the brachial plexus. Therefore, we first applied the transmanubrial osteomuscular-sparing approach based on the images we obtained from the 3-D MDCT viewer that showed the anatomical relationship between the SST and the thoracic inlet, including the clavicle, sternoclavicular joint, first rib, and subclavian vessels. Subsequently, we performed a third anterolateral thoracotomy with a hemi-clamshell incision to achieve curative intent resection.

These preoperative simulation and intraoperative navigation using 3-D MDCT appeared to simplify the approach to complex surgical procedures such as the anterior transcervical-thoracic approach including the transmanubrial osteomuscular-sparing approach as well as VATS and segmentectomy. However, as this is apparently the first case report, we have to evaluate further SST cases and other complex surgical procedures. Additionally, we think that there are other examples of new 3-D technology that provide a realistic preoperative simulation and that could help surgeons perform complex operations, such as the thoracic structure model made with a 3-D printer.

Conclusion

We have described the possibility of using 3D-MDCT for preoperative and intraoperative management of complex surgical procedures such as the transmanubrial osteomuscular-sparing approach with an additional third anterolateral thoracotomy with a hemi-clamshell incision to resect an SST following chemoradiotherapy.

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Conflict of interest Two authors (H.S. and N.I.) have given remunerated lectures for Fujifilm. No author received research funding and all had full control of the study design, methods used, outcome parameters, data analysis and production of the written report.

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