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

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Abstract

Background

Adenosquamous carcinoma (ASC) is a rare malignant tumor with a squamous cell carcinoma (SCC) and adenocarcinoma (AC) component. It behaves more aggressively than other histologic subtypes of lung cancer. We studied the clinicopathological features and computed tomography (CT) findings of ASC and assessed the effect of tumor location and the extent of the AC component in ASC on the clinical and radiological 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 they 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), subjective symptoms (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 group. 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 as well as 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.

Introduction

Adenosquamous carcinoma (ASC) is a rare biphasic malignant tumor with squamous cell carcinoma (SCC) and adenocarcinoma (AC) components that are detected in 0.4–4% 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 gender, and an advanced tumor stage. Autopsy and/or surgically resection data showed that it is difficult to make a definite diagnosis of ASC in the initial stages.

Computed tomography (CT) scanning could be useful especially 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 1 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]. Considering 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 clinicopathological 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 clinical and radiological characteristics of ASC.

Materials 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 were diagnosed with ASC, and the most recent World Health Organization (WHO) 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 2 observers (YW and KT). When reviewing the histology slides, we paid particular attention to key histology 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 as well as 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 1 of the following 5 predominant patterns: lepidic, acinar, papillary, micropapillary, or solid predominant [11].

Review of CT Images

CT images were examined by 2 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 as well as the position of the tumor in the lobe (central versus 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 sub-segmental 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 using SPSS Statistics 21 (IBM Corporation, Somers, NY). The Student *t*-test and χ^2 test were used. Overall survival curves were calculated using the log-rank test. Univariate survival analysis was 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 amongst men (n = 33, 64%) than women (n = 19, 36%) ($P = 0.07$). The median age of patients at the time of diagnosis was 67 years (range, 37–84 years). Thirty-five (67%) of the 52 patients who presented without pulmonary symptoms had abnormal findings on chest radiographs that were obtained during periodic examination. Symptoms in the remaining 18 (35%) patients included hemosputum (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 history of smoking rate 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 3 cases, the histological diagnosis made at the primary hospital differed from the diagnosis made at our hospital. Two patients were diagnosed with

SCC at the primary hospital, but after biopsy at our hospital, they were diagnosed with NSCLC or AC, while the third patient was diagnosed with 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 histological 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). Amongst 12 cases 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.

Histological 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 (TTF-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, 4 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 2 cases (4%). In addition, emphysema was seen in 18 (35%), interstitial pneumonia in 7 (13%), and inflammatory changes surrounding the tumor in 18 (35%) cases.

We found significant correlations between inflammatory changes surrounding the tumor and pathological obstructive pneumonia ($P < 0.001$). There were no other significant correlations between CT and pathology 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). Overall survival curve and recurrent-free survival curves are shown in Fig 3. The median, 5-year overall survival, and 5-year recurrent-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 Table1.

Comparison of Clinicopathological Features and CT Findings between the Central and Peripheral Location

ASC was subdivided into a central (n = 9) or peripheral (n = 43) group based on the location of the

tumor. The following characteristics were significantly more common in the central group: larger tumor size ($P < 0.001$); subjective symptoms ($P = 0.01$), especially hemosputum ($P = 0.02$); and an 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 30/52 cases that had a preoperative diagnosis.

Histological 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 of patients with centrally located ASC was worse than those with peripherally located ASC ($P = 0.007$, Table1). However, multivariate analysis found no statistical significant differences between the groups.

Comparison of Clinicopathological and CT Findings with Predominant Histological Component

ASC was subdivided into an AC- (n = 24) or SCC- (n = 28) predominant group. Subjective symptoms including hemosputum, tended to be seen more often in the SCC-predominant group ($P = 0.11$). There were no correlations between gender or a history of smoking and SCC predominance. Predominant components influenced the preoperative diagnosis. A preoperative diagnosis of AC was more prevalent amongst AC-predominant ASC cases ($P = 0.01$) and a preoperative diagnosis of SCC was more prevalent amongst SCC-predominant ASC cases ($P = 0.05$, Table 5). However, there were no significant differences in predominant histological 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 ($P = 0.03$). Amongst the 6 peripheral GGO groups in AC-predominant ASC, pathological findings showed a lepidic growth pattern of AC in 5 (83%) cases. However, ill-defined

patterns were more frequently seen in the SCC-predominant group (P = 0.11). There were no other significant differences between the SCC- 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 clinicopathological 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. Similar to previous reports, in our study, ASC tended to occur in men and those with a history of smoking [10,12-14]. Previous studies reported high rates of smoking amongst 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. A larger tumor size, subjective symptoms including hemosputum, and a more advanced disease stage (stages III or IV) were more commonly seen amongst centrally located ASC as compared to 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 histological predominance of AC or SCC. In addition, histological 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 reported that centrally located ASC has a larger SCC component than peripherally located ASC [6,16], and this might be because centrally located ASCs follow a growth pattern of bronchial 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. Subjective symptoms, including hemosputum, were significantly more prevalent in the SCC versus the AC predominant group ($P = 0.11$). In addition, subjective symptoms, including hemosputum, 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].

Radiographic imaging showed that the frequency of peripheral GGO was higher in the AC group than in the SCC predominant group ($P = 0.03$). Among 6 peripheral GGO groups, 5 (83%) cases had a lepidic growth pattern, which is 1 of the histological features of AC. This finding suggests that peripheral GGO, as seen on CT, could be 1 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 resections 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 3 of our cases, the histologic diagnosis made at the primary hospital differed from the histologic diagnosis made at our hospital, and in 1 of these cases, there was a difference between the histologic and cytologic diagnoses. Similar discrepancies between biopsy 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 as well as 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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Table 1. Independent Impacts of Valuables on Patient Overall Survival Estimated by Univariate and Multivariate Analysis

	Univariate	Multivariate		
Variables	*p* Value	HR	95% CI	*p* Value
Gender				
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 the 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. Non-lepidic	0.02	0.239	0.020-2.810	0.255

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

Table 2. Patients characteristics according to location between peripheral and central

	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 > 5cm	6	4	0.06
Operative side			
Right side	23	5	0.60
Lobar location			
Upper	25	7	0.24
Subjective symptom	12	7	0.01
Hemosputum	4	4	0.02
Cough	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. Pathological Characteristics between Peripheral and Central Location

	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

	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.

Table 5. Preoperative diagnosed cases between AC>SCC and AC ≦SCC

	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.

Figure legends

Fig 1.

Fig 1. Adenocarcinoma component with lepidic predominant and squamous cell component are completely separated from one another (H&E X10).

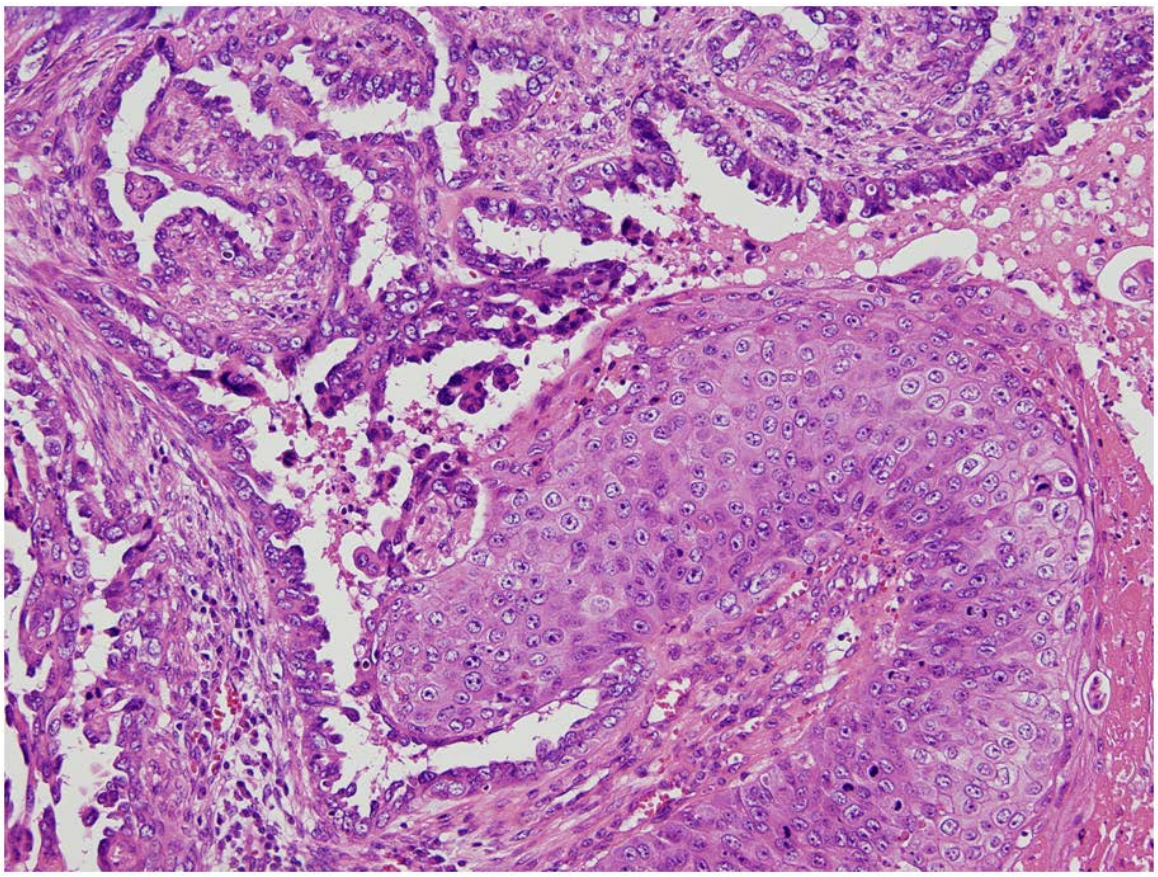

Fig 2.

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

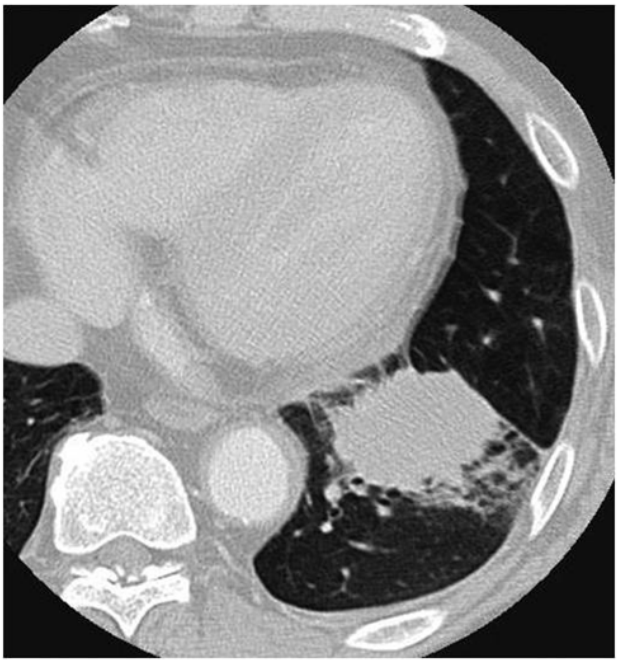

Fig 3.

Fig 3. A, Overall survival curves for adenosquamous carcinoma cases. B, Recurrent-free survival curves for adenosquamous carcinoma cases.

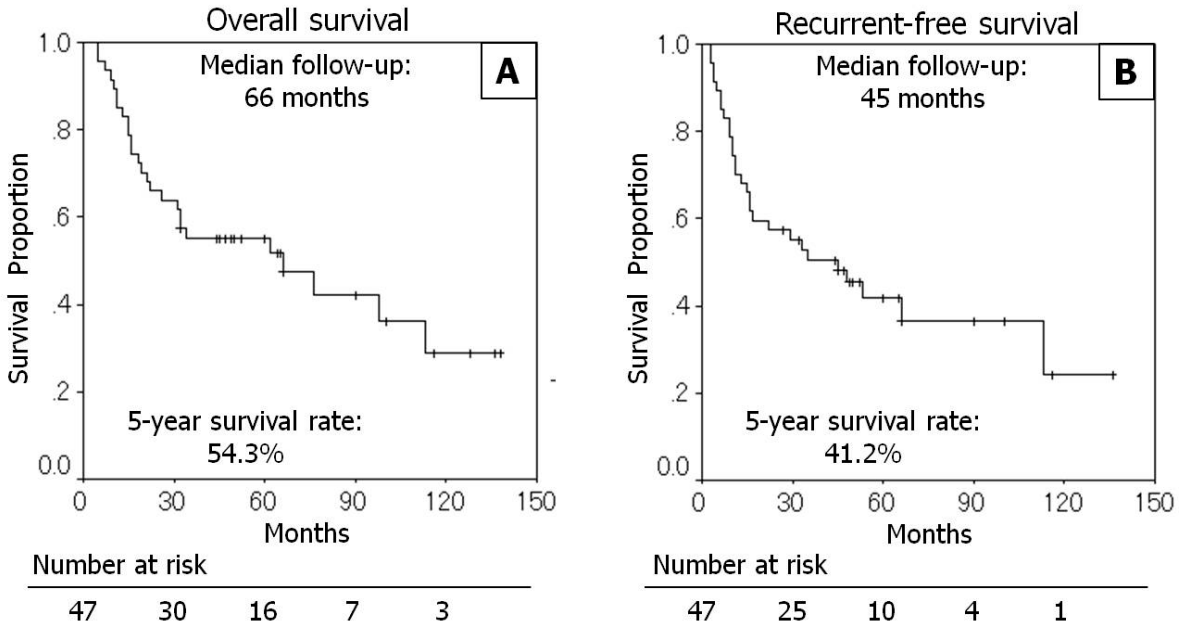

Fig 4.

Fig 4. Overall survival (OS) analysis. A, OS curves for patients with never smoker and former or current smoker (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 for CT findings of inflammatory changes surrounding the tumor (p < 0.001).