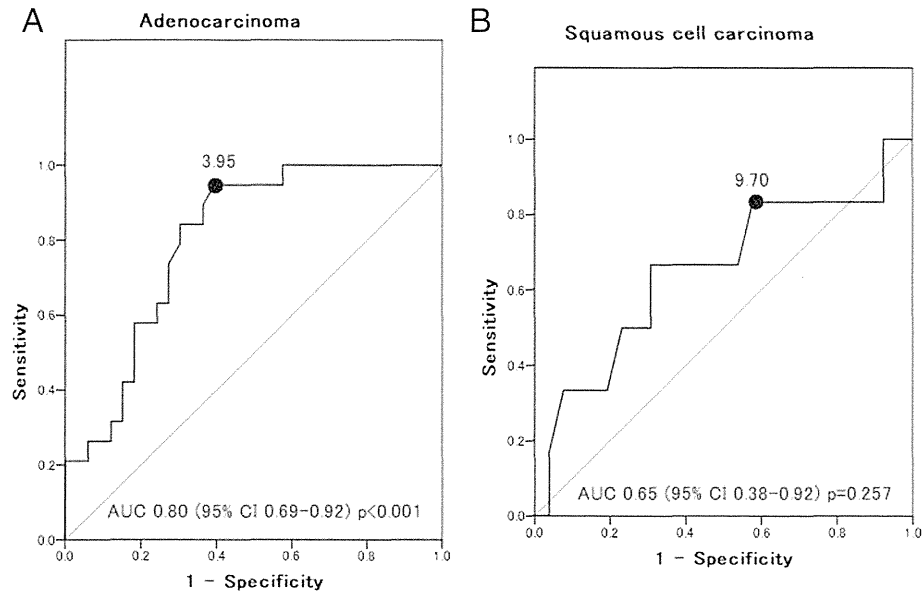

Figure 1 Receiver-operating characteristics (ROC) curve for predicting recurrence. (A) Adenocarcinoma: AUC 0.80 (95% CI: 0.69 to 0.92), P <0.001. **(B)** Squamous cell carcinoma: AUC 0.65 (95% CI: 0.38 to 0.92), *P* =0.257. AUC, area under the curve; CI, confidence interval.

sensitivity and specificity. The prognostic evaluation was performed by considering the disease-free survival (DFS) period. DFS was defined as the time until lung cancer recurrence, second cancer occurrence, or non-lung-cancer-related death. The DFS was analyzed using the Kaplan-Meier method. Differences in DFS were assessed using the log-rank test. To assess the potential independent effects on the DFS, we performed multivariate analyses using the Cox proportional hazards model. A *P* value of <0.05 was considered as statistically significant.

Results

Clinical characteristics

The characteristics of the patients are summarized in Table 1. A total of 52 patients had invasive ADC, and 32 had SQC. The patients ranged in age from 46 to 83 years (mean: 69.0 years). There were 56 men and 28 women. The median value of the SUVmax of all the tumors was 7.4 ± 4.7 (range: 0 to 18.1). The patient age, sex, and mean SUVmax differed significantly between the histological subtypes.

Relationship between the maximal standardized uptake value and clinicopathological findings

Among the ADC patients, a statistically significant correlation was observed between the SUVmax and the degree of tumor differentiation (*P* =0.008), pleural invasion (*P* =0.001), vascular invasion (*P* =0.001), and nodal status (*P* =0.007). In contrast, among the SQC patients, no statistically significant

Table 3 Comparison of SUVmax between ADC and SQC

Factor	ADC: SUVmax Low	High	*P* value	SQC: SUVmax Low	High	*P* value
Pleural invasion			0.027			0.064
No	19	19		17	9	
Yes	2	12		1	5	
Vascular invasion			0.042			0.735
No	17	16		9	6	
Yes	4	15		9	8	
Nodal status			0.016			0.365
N0	21	23		16	10	
N1 + 2	0	8		2	4	
Cox-2 expression			0.001			0.473
Negative	13	5		12	7	
Positive	8	26		6	7	
Ki-67 expression			0.011			0.087
Negative	15	11		11	4	
Positive	6	20		7	10	
VEGF expression			0.003			0.999
Negative	12	5		9	7	
Positive	9	26		9	7	

ADC: adenocarcinoma, Low/High = SUVmax 3.95. SQC: squamous cell carcinoma, Low/High = SUVmax 9.70. Cox-2, cyclooxygenase-2; SUVmax, maximal standardized uptake value; VEGF, vascular endothelial growth factor.

associations were observed between the SUVmax and any of the clinicopathological factors (Table 2).

Relationship between the maximal standardized uptake value and immunohistochemical findings

Among the ADC patients, the Cox-2-positive, Ki-67-positive, and VEGF-positive cases showed a significantly higher SUVmax than the cases that were negative for these markers. On the other hand, among the SQC patients, the Cox-2-positive and Ki-67-positive cases showed a significantly higher SUVmax than the cases that were negative for these markers (Table 2). Using a multiple stepwise regression analysis, Cox-2 expression (P =0.007) and Ki-67 expression (P =0.028) remained as significant factors that were independently related to the SUVmax in the ADC patients, but only Ki-67 expression (P =0.037) remained significant in the SQC patients.

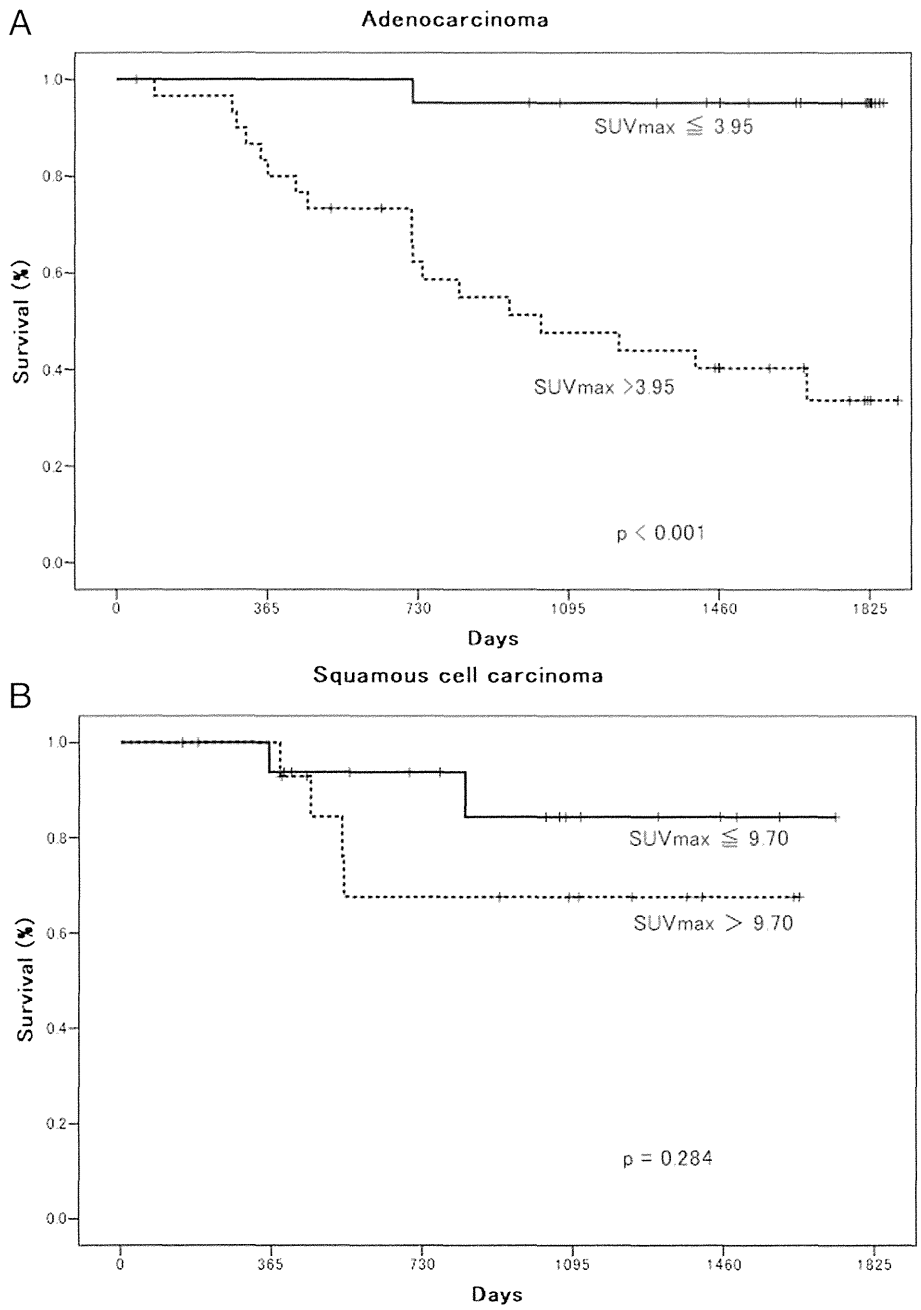

Figure 2 Kaplan-Meier disease-free survival curve according to the maximal standardized uptake value (SUVmax). (A) Adenocarcinoma: log-rank P <0.001. **(B)** Squamous cell carcinoma: log-rank P =0.284.

Prognostic value of maximal standardized uptake value and immunohistochemical findings

We used an ROC curve analysis to evaluate whether the SUVmax could predict recurrence (Figure 1). The ROC curves identified an optimal SUVmax cutoff value of 3.95 for predicting recurrence in patients with ADC (area under the curve (AUC) =0.80, P <0.001), but not for patients with SQC (AUC =0.65, P =0.257). We divided the patient population based on a SUVmax cutoff value of 3.95 for the ADC patients and 9.70 for the SQC patients. Among ADC patients, a high SUVmax was significantly correlated with pleural invasion (P =0.027), vascular invasion (P =0.042), nodal status (P =0.016), Cox-2 expression (P =0.001), Ki-67 expression (P =0.011), and VEGF expression (P =0.003) (Table 3). On the other hand, among the SQC patients, a high SUVmax was not significantly correlated with these factors.

The DFS of ADC patients with a high SUVmax was significantly poorer than that of patients with a low SUVmax (P <0.001, log-rank test; Figure 2A). In contrast, the DFS of SQC patients with a high SUVmax was not significantly poorer than that of patients with a low SUVmax (P =0.284, log-rank test; Figure 2B). A univariate analysis of DFS was performed using the variables of pathological stage, SUVmax, Cox-2 expression, Ki-67 expression, and VEGF expression. Among the ADC patients, all the variables were associated with DFS; among the SQC patients, however, only Cox-2 expression was associated with DFS (Table 4). In a multivariate analysis, pathological stage and SUVmax were independent prognostic factors for DFS among the ADC patients, but only Cox-2 expression was an independent prognostic factor for DFS among the SQC patients (Table 4).

Table 4 Results of the univariate and multivariate cox regression analysis of disease-free survival

	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
A) Adenocarcinoma						
Pathological stage	1.26	1.14-1.10	0.001	1.15	1.02-1.30	0.019
SUVmax	19.42	2.58-146.0	0.001	9.19	1.10-76.54	0.040
Cox-2 expression	4.08	1.18-14.04	0.026	1.57	0.40-6.22	0.521
Ki-67 expression	4.44	1.59-12.38	0.004	1.77	0.54-5.77	0.342
VEGF expression	5.52	1.27-23.94	0.023	1.67	0.36-7.78	0.515
B) Squamous cell carcinoma						
Pathological stage	1.16	0.99-1.36	0.073	1.09	0.88-1.36	0.432
SUVmax	2.46	0.45-13.43	0.300	1.14	0.14-9.40	0.906
Cox-2 expression	9.46	1.10-81.40	0.041	7.36	1.04-72.05	0.048
Ki-67 expression	1.68	0.31-9.20	0.548	1.32	0.23-7.54	0.753
VEGF expression	0.52	0.10-2.84	0.450	0.62	0.89-4.31	0.627

Pathological stage: I versus II + III. CI, confidence interval; Cox-2, cyclooxygenase-2; HR, hazard ratio; SUVmax, maximal standardized uptake value; VEGF, vascular endothelial growth factor.

Discussion

In this study, we investigated the correlations among the expressions of tumor angiogenic biomarkers, the SUVmax on FDG-PET, and the prognosis according to histological subtypes. As a result, some clear differences in the prognostic value of SUVmax and Cox-2 expression were observed between ADC and SQC. Until now, most publications discussing the correlation between the SUVmax and clinicopathological or prognostic factors have not investigated tumors according to histological subtype. Recently, Tsutani *et al.* reported that the SUVmax of the primary tumor was a powerful prognostic determinant for patients with ADC, but not for those with SQC [17]. The present study provides the evidence showing correlations among the expressions of biomarkers, the SUVmax, and prognosis according to histological subtype. The important findings of this present study were as follows: (i) the SUVmax was correlated with clinicopathological and biological factors in patients with ADC, but not in those with SQC; ii) the SUVmax was a powerful prognostic factor in patients with ADC, but not in those with SQC; (iii) Cox-2 expression was a powerful prognostic factor in patients with SQC, but not in those with ADC. These findings suggest that the SUVmax had no significant value when considering therapeutic strategies for patients with SQC.

The SUVmax of primary lung nodules has been reported to be helpful in distinguishing between malignant and benign tumors, based on the relatively higher values that are seen for malignant tumors [18]. We speculated that tumors showing a higher SUVmax might be more aggressive and might have a higher proliferation potential. We then examined this hypothesis by studying the correlation between the SUVmax and the expressions of some molecular biomarkers, since the overexpression of these markers is known to accelerate tumor progression in NSCLC patients.

Cox-2 expression is highly correlated with tumor angiogenesis and also regulates other angiogenic factors. Some investigators have demonstrated that Cox-2 is constitutively overexpressed in a variety of epithelial malignancies, such as lung, breast, pancreas, colon, esophagus, and head and neck cancers, and Cox-2 overexpression is usually associated with a poor prognosis [19,20]. To date, some articles have investigated the association between Cox-2 expression and tumor angiogenesis [21]. Recent evidence suggests that Cox-2 plays an important role in tumor-induced angiogenesis through the synthesis of angiogenic prostaglandins, which induce VEGF, and that Cox-2 contributes to neovascularization and may support the vasculature-dependent growth of solid tumors [19].

Our results using resected tissues indicate that the SUVmax of primary tumors might reflect the biological malignant potential, such as tumor angiogenesis. Cancer treatment targeting the control of Cox-2 might become feasible in the future. In 2008, Edelman *et al.* [14] reported that patients with advanced NSCLC tumors with moderate to high Cox-2 expression had a poorer survival outcome than those with a low expression level. Moreover, patients with moderate to high Cox-2 expression had a better tumor response to a Cox-2 inhibitor (celecoxib) in terms of a longer median survival compared with those not receiving celecoxib [14]. On the other hand, in the NVALT-4 study performed in 2011, celecoxib did not improve survival, and Cox-2 expression was not a prognostic biomarker and had no predictive value when celecoxib was added to chemotherapy. However, in a subset analysis, patients with SQC seemed to perform better when treated with celecoxib [22]. Since our results indicate that Cox-2 expression is an independent prognostic factor in SQC, the administration of a Cox-2 inhibitor to patients with SQC seem reasonable.

Immunostaining with the Ki-67 antibody is a widely accepted method for evaluating proliferative activity in a variety of human tumors. Vesselle *et al.* reported the existence of a relationship between the Ki-67 expression index and the degree of FDG uptake in NSCLCs [23]. Also in this study, the expression of Ki-67 was significantly related to the SUVmax in both ADC and SQC. On the other hand, the VEGF family of proteins modulates angiogenesis, which is essential for tumor growth and metastasis. The expression of VEGF has been shown to be associated with tumor angiogenesis, metastasis, and prognosis in several cancers, including NSCLC. To date, two reports have shown a correlation between the expression of VEGF and the SUV on PET-CT [10,16]. Kaira *et al.* demonstrated a significant correlation between VEGF expression and FDG uptake in NSCLCs [10]. However, our results were not similar to the results of previous report.

A feature of this study was the histological classification of the tumors into ADC and SQC. Recently, clear evidence has suggested that the classification of NSCLC into pathologic subtypes is important for the selection of an appropriate systemic therapy, from the viewpoint of both treatment efficacy and the prevention of toxicity. Pemetrexed yields a much better treatment outcome in patients with ADC than in those with SQC [24]. The use of bevacizumab has been shown to be associated with an increased risk of fatal pulmonary hemorrhage in patients with SQC [25]. Epidermal growth factor receptor mutations is more commonly encountered in ADC [26]. Because of the choice of treatment for SQC, further studies are needed. The present study suggests that a Cox-2 inhibitor might be indicated for the treatment of SQC.

Conclusions

In conclusion, some clear differences were observed in the prognostic value of Cox-2 expression and the SUVmax on FDG-PET between patients with ADC and those with SQC. Among patients with SQC, Cox-2 expression was a powerful prognostic factor. In patients with ADC, on the other hand, the SUVmax was a potential biomarker of clinical outcome. These findings indicated that the SUVmax of primary tumors might reflect the biological malignant potential in ADC, but the SUVmax had no significant value for determining the therapeutic strategy in patients with SQC. Further study is needed to investigate other factors that might influence the SUVmax on FDG-PET. The small number of patients was a major limitation of the present study.

Abbreviations

ADC: adenocarcinoma; DFS: disease-free survival; FDG-PET: fluorodeoxyglucose-positron emission tomography; NSCLC: non-small cell lung cancer; ROC: receiver operating characteristic; SQC: squamous cell carcinoma; SUVmax: maximal standardized uptake value.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Study concept and design: KS, MN. Data acquisition: RO, SS, YN. *Immunohistochemistry*: TY, AM. *Data analysis and interpretation*: KS, AM. Manuscript preparation: KS. Manuscript review: MN. All authors have read and approval the final manuscript.

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References

1. Ung YC, Maziak DE, Vanderveen JA, Smith CA, Gulenchyn K, Lacchetti C, Evans WK: **^{18}Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review.** *J Natl Cancer Inst* 2007, **99**:1753–1767.
2. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, Mortelmans LA, Demedts MG: **Prognostic importance of the standardized uptake value on ^{18}F-fluoro-2-deoxy-glucose–positron emission tomography scan in non–small-cell lung cancer: an analysis of 125 cases.** *J Clin Oncol* 1999, **17**:3201–3206.
3. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Suemasu K, Kobayashi T, Uno K: **Fluorine 18-tagged fluorodeoxyglucose positron emission tomographic scanning to predict lymph node metastasis, invasiveness, or both, in clinical T1 N0 M0 lung adenocarcinoma.** *J Thorac Cardiovasc Surg* 2004, **128**:396–401.
4. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA: **The maximum standardized uptake values on positron emission tomography of a non-small cell lung cancer predict stage, recurrence, and survival.** *J Thorac Cardiovasc Surg* 2005, **30**:151–159.
5. Vesselle H, Freeman JD, Wiens L, Stern J, Nguyen HQ, Hawes SE, Bastian P, Salskov A, Vallieres E, Wood DE: **Fluorodeoxyglucose uptake of primary non-small cell lung cancer at positron emission tomography: new contrary data on prognostic role.** *Clin Cancer Res* 2007, **13**:3255–3263.

6. Paesmans M, Berghmans T, Dusart M, Garcia C, Hossein-Foucher C, Lafitte JJ, Mascaux C, Meert AP, Roelandts M, Scherpereel A, Terrones Munoz V, Sculier JP: **Primary tumor standardized uptake value measured on fluorodeoxyglucose positron emission tomography is of prognostic value for survival in non-small cell lung cancer.** *J Thorac Oncol* 2010, **5**:612–619.
7. Higashi K, Ueda Y, Sakurai A, Wang XM, Xu L, Murakami M, Seki H, Oguchi M, Taki S, Nambu Y, Tonami H, Katsuda S, Yamamoto I: **Correlation of Glut-1 glucose transporter expression with [^{18}F] FDG uptake in non-small cell lung cancer.** *Eur J Nucl Med* 2000, **27**:1778–1785.
8. Watanabe K, Nomori H, Ohtsuka T, Naruke T, Ebihara A, Orikasa H, Yamazaki K, Uno K, Kobayashi T, Goya T: **[F-18]Fluorodeoxyglucose positron emission tomography can predict pathological tumor stage and proliferative activity determined by Ki-67 in clinical stage IA lung adenocarcinomas.** *Jpn J Clin Oncol* 2006, **36**:403–409.
9. Taylor MD, Smith PW, Brix WK, Wick MR, Theodosakis N, Swenson BR, Kozower BD, Lau CL, Jones DR: **Fluorodeoxyglucose positron emission tomography and tumor marker expression in non-small cell lung cancer.** *J Thorac Cardiovasc Surg* 2009, **137**:43–48.
10. Kaira K, Oriuchi N, Shimizu K, Ishikita T, Higuchi T, Imai H, Yanagitani N, Sunaga N, Hisada T, Ishizuka T, Kanai Y, Endou H, Nakajima T, Endo K, Mori M: **Correlation of angiogenesis with 18F-FMT and 18F-FDG uptake in non-small cell lung cancer.** *Cancer Sci* 2009, **100**:753–758.
11. Shimizu K, Hirami Y, Saisho S, Yukawa T, Maeda A, Yasuda K, Nakata M: **Maximal standardized uptake value on FDG-PET is correlated with cyclooxygenase-2 expression in patients with lung adenocarcinoma.** *Ann Thorac Surg* 2012, **93**:398–403.
12. Menda Y, Bushnell DL, Madsen MT, McLaughlin K, Kahn D, Kernstine KH: **Evaluation of various corrections to the standardized uptake value for diagnosis of pulmonary malignancy.** *Nucl Med Commun* 2001, **22**:1077–1081.
13. Asamura H, Hishida T, Suzuki K, Koike T, Nakamura K, Kusumoto M, Nagai K, Tada H, Mitsudomi T, Tsuboi M, Shibata T, Fukuda H: **Radiographically determined noninvasive adenocarcinoma of the lung: survival outcomes of Japan Clinical Oncology Group 0201.** *J Thorac Cardiovasc Surg* 2013, **146**:24–30.
14. Edelman MJ, Watson D, Wang X, Morrison C, Kratzke RA, Jewell S, Hodgson L, Mauer AM, Gajra A, Masters GA, Bedor M, Vokes EE, Green MJ: **Eicosanoid modulation in advanced lung cancer: cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy–Cancer and Leukemia Group B Trial 30203.** *J Clin Oncol* 2008, **26**:848–855.
15. Martin B, Paesmans M, Mascaux C, Berghmans T, Lothaire P, Meert AP, Lafitte JJ, Sculier JP: **Ki-67 expression and patients survival in lung cancer: systematic review of the literature with meta-analysis.** *Br J Cancer* 2004, **91**:2018–2025.
16. Han H, Silverman JF, Santucci TS, Macherey RS, d'Amato TA, Tung MY, Weyant RJ, Landreneau RJ: **Vascular endothelial growth factor expression in stage I non-small cell lung cancer correlates with neoangiogenesis and a poor prognosis.** *Ann Surg Oncol* 2001, **8**:72–79.
17. Tsutani Y, Miyata Y, Misumi K, Ikeda T, Mimura T, Hihara J, Okada M: **Difference in prognostic significance of maximum standardized uptake value on [18F]-fluoro-2-deoxyglucose positron emission tomography between adenocarcinoma and squamous cell carcinoma of the lung.** *Jpn J Clin Oncol* 2011, **41**:890–896.
18. Bryant AS, Cerfolio RJ: **The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules.** *Ann Thorac Surg* 2006, **82**:1016–1020.
19. Hida T, Yatabe Y, Achiwa H, Muramatsu H, Kozaki K, Nakamura S, Ogawa M, Mitsudomi T, Sugiura T, Takahashi T: **Increased expression of cyclooxygenase 2 occurs frequently in human lung cancers, specifically in adenocarcinomas.** *Cancer Res* 1998, **58**:3761–3764.
20. Ogino S, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, Hazra A, Chan AT, Dehari R, Giovannucci EL, Fuchs CS: **Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer.** *Clin Cancer Res* 2008, **14**:8221–8227.
21. Kim HS, Youm HR, Lee JS, Min KW, Chung JH, Park CS: **Correlation between cyclooxygenase-2 and tumor angiogenesis in non-small cell lung cancer.** *Lung Cancer* 2003, **42**:163–170.
22. Groen HJ, Sietsma H, Vincent A, Hochstenbag MM, van Putten JW, van den Berg A, Dalesio O, Biesma B, Smit HJ, Termeer A, Hiltermann TJ, van den Borne BE, Schramel FM: **Randomized, placebo-controlled phase III study of docetaxel plus carboplatin with celecoxib and cyclooxygenase-2 expression as a biomarker for patients with advanced non–small-cell lung cancer: the NVALT-4 study.** *J Clin Oncol* 2011, **29**:4320–4326.
23. Vesselle H, Salskov A, Turcotte E, Wiens L, Schmidt R, Jordan CD, Vallières E, Wood DE: **Relationship between non-small cell lung cancer FDG uptake at PET, tumor histology, and Ki-67 proliferation index.** *J Thorac Oncol* 2008, **3**:971–978.
24. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS, Mellemgaard A, Park K, Patil S, Rolski J, Goksel T, de Marinis F, Simms L, Sugarman KP, Gandara D: **Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non–small-cell lung cancer.** *J Clin Oncol* 2008, **26**:3543–3551.
25. Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF 3rd, Gaudreault J, Damico LA, Holmgren E, Kabbinavar F: **Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer.** *J Clin Oncol* 2004, **22**:2184–2191.
26. Mitsudomi T, Kosaka T, Endoh H, Horio Y, Hida T, Mori S, Hatooka S, Shinoda M, Takahashi T, Yatabe Y: **Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence.** *J Clin Oncol* 2005, **23**:2513–2520.

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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.

This study was presented at the 65th Annual Scientific Meeting of the Japanese Association for Thoracic Surgery.

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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

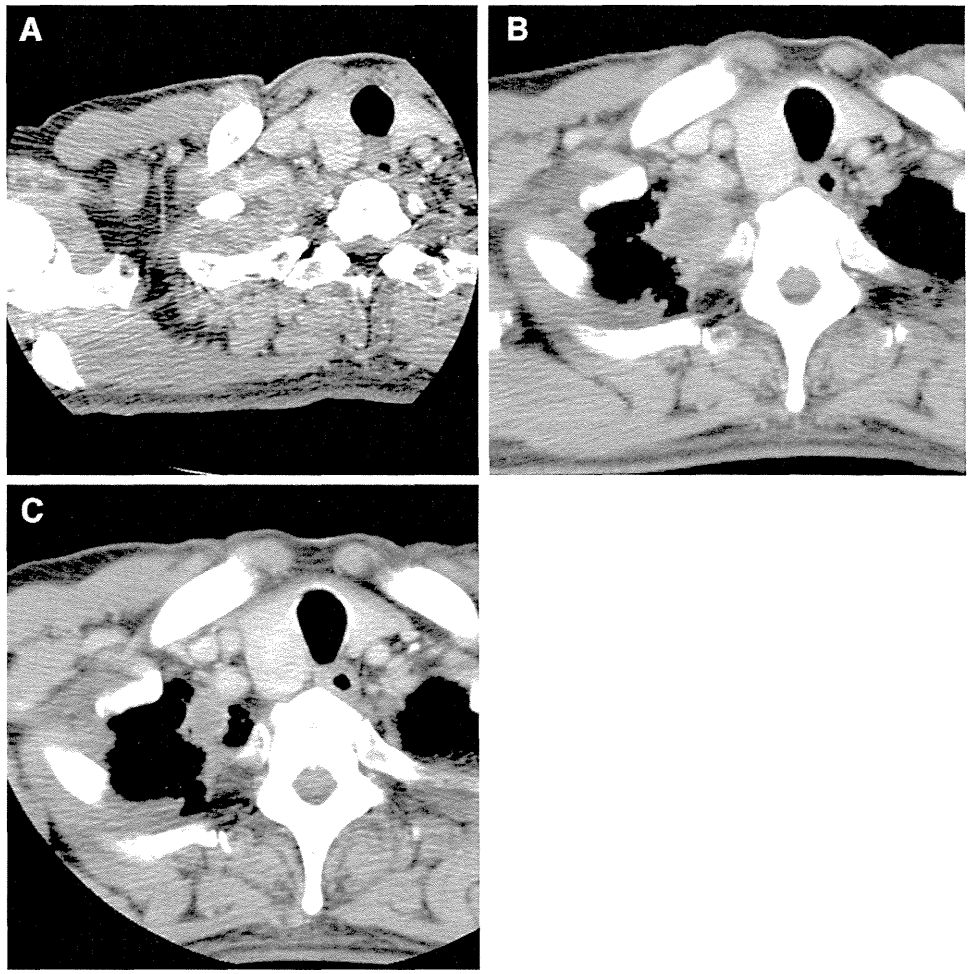

Fig. 1 Chest CT images revealed a superior sulcus tumor invading the anterior part of the thoracic inlet before (**a**, **b**) and after (**c**) chemoradiotherapy. This tumor potentially invaded subclavian vessels and brachial plexus (**a**)

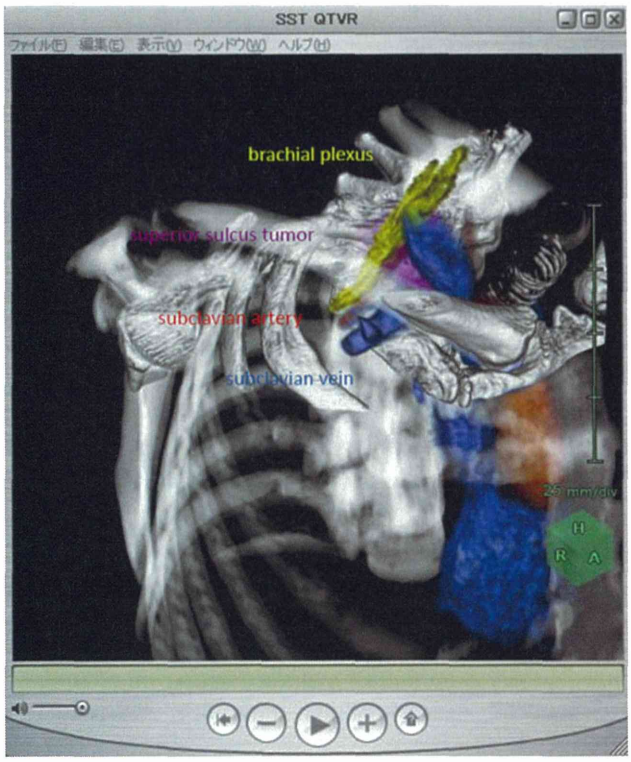

Fig. 2 A preoperative 3-D MDCT reconstruction of the superior sulcus tumor located in the anterior part of the thoracic inlet including the clavicle, sternoclavicular joint, first rib, subclavian vessels and brachial plexus. Made with QuickTime software

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,

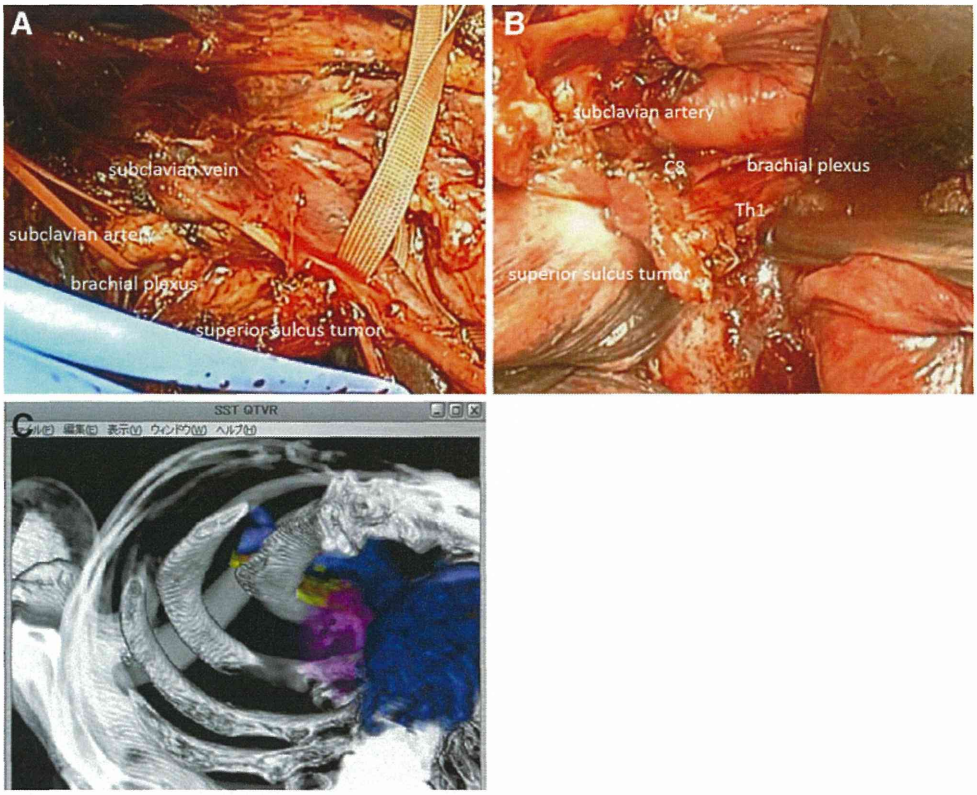

Fig. 3 Operation picture showing the anatomical relationship between the superior sulcus tumor and the subclavian artery, vein and brachial plexus upper limit of C8 of the brachial plexus (**a**, **b**). **c** showed that 3D viewer was able to reconstruct the operation view of **a**, **b**

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.

References

1. Dartevelle PG, Chapelier AR, Macchiarini P, et al. Anterior transcervical-thoracic approach for radical resection of lung tumors invading the thoracic inlet. J Thorac Cardiovasc Surg. 1993;105:1025–34.
2. Grunenwald D, Spaggiari L. Transmanubrial osteomuscular sparing approach for apical chest tumors. Ann Thorac Surg. 1997;63:563–6.
3. Grunenwald D, Spaggiari L, Girard P, et al. Transmanubrial approach to the thoracic inlet. J Thorac Cardiovasc Surg. 1997;113:958–9 (author reply 960–951).
4. Saji H, Inoue T, Kato Y, et al. Virtual segmentectomy based on high-quality three-dimensional lung modelling from computed tomography images. Interact Cardiovasc Thorac Surg. 2013;17:227–32.
5. Ikeda N, Yoshimura A, Hagiwara M, et al. Three dimensional computed tomography lung modeling is useful in simulation and navigation of lung cancer surgery. Ann Thorac Cardiovasc Surg. 2013;19:1–5.
6. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol. 2007;25:313–8.
7. Kunitoh H, Kato H, Tsuboi M, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. J Clin Oncol. 2008;26:644–9.