Is limited resection appropriate for radiologically "solid" tumors in small lung cancers?

Is Limited Resection Appropriate for Radiologically "Solid" Tumor in Small-Sized Lung Cancer?

Aritoshi Hattori MD, Kenji Suzuki MD, Takeshi Matsunaga, MD, Mariko Fukui MD, Yoshitaka Kitamura MD, Yoshikazu Miyasaka MD, Yukio Tsushima MD, Kazuya Takamochi MD, Shiaki Oh MD.

Division of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan

Key words: segmentectomy, prognosis, lymph node metastasis

Address: Kenji Suzuki, MD, Professor and Chairman, Division of General Thoracic Surgery, Juntendo University School of Medicine, 1-3, Hongo 3-chome, Bunkyo-ku, Tokyo, 113-8431, Japan, Phone: +81-3-3813-3111, Fax: +81-3-5800-0281, E-mail: kjsuzuki@juntendo.ac.jp

Running title: Lung cancer and limited surgery

Words: 2316 words

Abstract

Background.

Small-sized lung cancers showing a wide area of ground-grass opacity (GGO) on thin-section computed tomography (CT) are considered to be a good candidate for limited surgical resection, because of its minimally invasive nature. On the other hand, the validity of limited resection for radiologically "solid" tumors is still controversial in small-sized non-small cell lung carcinoma.

Methods.

Between 2008 and 2010, 680 consecutive patients underwent pulmonary resection for lung cancer. The findings obtained by preoperative computed tomography were reviewed for all 680 patients and categorized as pure GGO, mixed GGO, or pure solid. All patients were evaluated by positron emission tomography (PET) and the maximum standardized uptake value (SUVmax) was recorded. Several clinicopathological features were investigated to identify predictors of hilar or mediastinal lymph node metastasis using uni- or multivariate analyses.

Results.

Two hundred twenty-seven of the patients with clinical stage IA lung cancer showed a solid or mixed GGO appearance on thin-section CT scan. Among them, nodal involvement was found pathologically in 42 (26%) patients with pure solid tumors, but in only 4 (6%) patients with mixed GGO tumors ($p=0.0002$). Among the 131 T1a patients, 94 (71.8%) had solid tumor, and nodal involvement was observed in 15 (16.0%). Among the 94 pure solid T1a tumors, the CEA level and SUVmax were significant predictors of lymph node involvement by tumor based on a multivariate analysis. The frequency of lymph node metastasis was approximately 27% for patients with pure "solid" lung cancer and high SUVmax, even for T1a tumor.

Conclusions.

Lymph node metastasis is frequently observed for pure "solid" lung cancer, especially for tumors that show a high SUVmax. If limited surgery is indicated for solid lung cancer, a thorough intraoperative evaluation of lymph nodes is needed to prevent locoregional failure.

Introduction

The introduction of computed tomography (CT) for the screening of lung cancer has made it possible to detect small-sized lung nodules [1]. Limited surgical resection has gradually become a standard treatment for small-sized lung cancers, and pulmonary segmentectomy accounts for approximately 8.4% of all pulmonary resections in Japan according to a study by The Japanese Association for Thoracic Surgery [2]. Several authors have reported that lung cancers which show a wide area of ground-grass opacity (GGO) have a good prognosis and in most cases their pathologic features are minimally invasive [3-7]. Thus, these tumors are considered to be candidates for limited surgical resection.

On the other hand, there is still some controversy regarding the use of limited surgical resection for “solid” tumors because of the high frequency of lymph node involvement. A surgical consensus has not yet been reached regarding small-sized solid tumors, since such tumors have a potentially invasive pathological nature. To identify patients in whom limited surgical resection would be suitable, preoperative diagnosis of the biological invasiveness of a lung cancer, through the classification of these “solid” tumors into several subgroups, may be warranted. In the current retrospective study, we sought to determine the validity of limited surgical resection for small-sized solid tumors.

Patients and Methods

This protocol was approved by the ethics committee at our institute. All patients provided the written informed consent before trial enrollment.

Between January 2008 and December 2010, 680 consecutive patients underwent pulmonary resection for lung cancer. For all 680 patients, the findings of preoperative computed tomography were reviewed by the authors (A.H., T.M., and K.S.). A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. The size of the tumors was determined preoperatively based on the findings of thin-section CT scan. In addition, all tumors were subsequently evaluated to estimate the extent of GGO with thin-section CT scan with 2 mm collimation. The lung was photographed with a window level of -500 to -700 H and a window depth of 1000-2000 H as a “lung window”. The solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of a slight, homogeneous

increase in density that did not obscure the underlying vascular markings. In the current study, “solid” tumor was tentatively defined as a tumor in which the ratio of the maximum diameter of consolidation to the maximum tumor diameter (consolidation/tumor ratio, C/T ratio) >0.5. According to the radiological findings on thin-section CT, tumors were divided into three groups: pure GGO, mixed GGO, and pure solid. The “mixed GGO” tumor was defined as a tumor with both a GGO and solid component, and “pure solid” was defined as a tumor with a solid component without GGO. The pure GGO group was excluded from this study. A radiological “solid” tumor was defined as a lung tumor that only showed consolidation on CT. There were 227 patients with clinical stage IA lung cancer with a mixed GGO or “solid” appearance on CT. All patients were evaluated by positron emission tomography (PET) and the maximum standardized uptake value (SUVmax) was recorded. As for the operations, if a tumor is GGO dominant or pure GGO, the patient would be a candidate for limited surgical resection, whereas a major lung dissection with systemic lymph node dissection warrants for a solid tumor belonging to “mixed GGO or pure solid” in our report. Non-anatomic wedge resection was performed for a few patients with the elderly, or cardio-pulmonary high risk.

The medical record of each patient was reviewed with regard to gender, sex, pack-year smoking, clinical T status (c-T1a vs c-T1b), GGO status (mixed GGO vs pure solid), pleural involvement, presence of air bronchogram in the tumor, serum carcinoembryonic antigen level (ng/ml, CEA) and SUVmax on PET. The relationships between these factors and postoperative nodal status were investigated to identify significant predictors in clinical stage IA solid lung cancer. To compare two factors, Fisher’s exact test was used for a statistical analysis. Uni- and multivariate analyses were used to identify the clinical factors that predicted nodal involvement. Multivariate analysis was performed by logistic regression analysis using SPSS Statistics 20 (SPSS Inc.). Forward and backward stepwise procedures were used to determine the combination of factors that were essential for predicting the prognosis. Statistical analysis was considered to be significant when the probability value was less than 0.05.

Results

Among the 227 eligible lung cancers, 158 (69.7%) were pure solid and 69 (30.3%) were mixed

GGO on thin-section CT scan. One hundred twenty-eight of the patients were men and 99 were women. Patients ranged in age from 35 to 89 y, with an average of 66 y. While pathological lymph node involvement was found in 42 (26.6%) patients with pure solid tumors (19 patients in N1 stations and 23 in N2 stations, respectively), it was seen in only 4 (5.8%) of the patients with mixed GGO tumors (3 patients in N1 stations and 1 in N2 stations, respectively) (Table 1). The relationships between GGO status, the mode of surgical resection and the pathological aspects were presented in Table 2. Standard lobectomy was performed for 191 (84.0%) patients (21 patients in N1 stations, 22 in N2 stations, respectively), segmentectomy was performed for 18 (8.0%) patients (2 patients in N1 stations, 1 in N2 stations, respectively), and non-anatomical wedge resection was performed for 18 (8.0%) patients. For clinical-stage IA tumor, multivariate analyses showed that the following factors significantly predicted lymph node metastasis: c-T1b tumors, solid tumor, absence of air bronchogram, abnormal CEA titer, and high SUVmax (Table 3).

With regard to T1a tumors, there were 15 (12.2%) patients with lymph node metastasis. For solid T1a tumors, the frequency of lymph node metastasis was approximately 16%, which is significantly greater than that in the other population (p=0.0370). According to multivariate analyses in patients with c-T1a tumors (n=131), the following factors significantly predicted lymph node metastasis: solid tumor, absence of air bronchogram, abnormal CEA titer, and high SUVmax (Table 4). Moreover, in the subgroup of c-T1a patients with pure solid tumor (n=94), the CEA level and SUVmax significantly predicted postoperative lymph node involvement by multivariate analyses (p=0.0396, 0.0117) (Table 5). Based on these results, 27.3% of c-T1a patients with pure solid tumor showed pathologic lymph node involvement, if patients had both CEA>5 and SUV>5.

Comment

Limited surgical resection has been indicated for a compromised host and/or multiple primary lung cancers. Recently, this indication has been extended to very early lung cancers that are located peripherally and show a GGO appearance on thin-section CT scan [8-13]. While there has been considerable discussion on limited surgical resection for lung cancer with a GGO appearance, there are few studies on limited surgery for lung cancer with a solid appearance on thin-section CT scan, i.e. invasive lung cancer. Invasive lung cancer can be associated with occult lymph node

metastasis, which would result in incomplete resection following limited surgical resection. On the other hand, limited surgery such as segmentectomy is becoming increasingly important as an option for resectable lung cancer with N0 status [14]. Thus, we tried to investigate the feasibility of limited surgical resection for solid, i.e. invasive, lung cancer from the perspective of lymph node metastasis.

Based on our results, lung cancer with an invasive nature, i.e. preoperative solid appearance on thin-section CT, showed an incidence of lymph node metastasis of more than 20%. Even clinical-T1a patients with radiologically pure solid tumors had an extremely high incidence of pathological lymph node involvement (27.3%), if patients had both CEA>5 and SUV>5. This means that incomplete dissection or sampling of lymph nodes could result in locoregional recurrence. Our results indicate that the breakdown of these solid tumors is warranted to determine the optimal indications for limited surgical resection for small-sized lung cancers. In contrast, for patients at low risk, pulmonary lobectomy instead of limited surgical resection can be performed with a low mortality rate [15]. Thus, in practice, limited surgical resection should be applied with great caution for patients with low risk, especially for tumors that show a pure solid appearance on thin-section CT scan. The final results of the JCOG [14] and CALGB [16] trials should help thoracic surgeons decide whether or not to apply limited surgery for low-risk patients.

This study was limited by a short median follow-up period. Further investigations are warranted.

In conclusion, even in cases of small-sized lung cancer, limited surgical resection is not feasible for pure solid tumor, especially in patients with CEA>5 and SUV>5, due to the high possibility of lymph node involvement. With regard to the efficacy of limited surgical resection for small lung cancers, any final conclusions should be based on the results of phase III trials conducted by JCOG.0802 [14] and CALGB-140503 [16].

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Tables

Table 1 Prognostic Factors and Results of Univariate Analysis for Predictors of Pathologic Nodal Involvement in Clinical-Stage IA Non-Small Cell Lung Cancer

Clinicopathological factors	Number of patients	Number of Patients with Nodal Involvement (%)	P Value*
Total	227	46 (20.3)	
Gender			
Male	128	27 (21.1)	0.7525
Female	99	19 (19.2)	
Age (years)			
More than 70	81	12 (14.8)	0.1677
70 or less	146	34 (23.3)	
Pack-year smoking			
More than 30	78	13 (16.7)	0.3867
30 or less	143	33 (23.1)	
Clinical T status			
c-T1a	131	16 (12.2)	0.0007
c-T1b	96	30 (31.3)	
GGO status			
Pure GGO	68	0	
Mixed GGO	69	4 (5.8)	0.0002
Pure Solid	158	42 (26.6)	
Pleural involvement			
Negative	115	16 (13.9)	0.5101
Positive	112	30 (26.8)	

Air Bronchogram			
Absence	128	39 (30.5)	<0.0001
Presence	99	7 (7.1)	
CEA (ng/ml)			
≦5	178	27 (15.2)	0.0006
5＜	49	19 (38.8)	
SUV max			
≦5	151	17 (11.3)	<0.0001
5＜	76	29 (38.2)	

GGO: ground glass opacity, CEA: carcinoembryonic antigen, SUV: standardized uptake value

* p-value in χ^2 test or Fisher's exact test

Table 2 Relationships between GGO status, Surgical Interventions and Pathological Aspects

	Pure GGO (n=68)	Mixed GGO (n=69)	Pure Solid (n=158)
Operative mode			
Wedge resection	36	3	15
Segmentectomy	22	5	13
Lobectomy	10	61	130
Lymph node dissection			
None	35	3	13
Hilar only	24	11	16
Mediastinal/hilar	9	55	129
Nodal involvement			
N0	68	65	116
N1	0	3	19
N2	0	1	23
Pathology			
Adenocarcinoma (including BAC)	68	68	112
Squamous cell carcinoma	0	1	34
Others	0	0	12

GGO: ground glass opacity, BAC: bronchioloalveolar carcinoma

Table 3 Results of a Multivariate Analysis for Predictors of Nodal Involvement in Clinical Stage IA Non Small Cell Lung Cancer

Variable	Hazard Ratio	95% Confidence Interval	p Value*
Clinical T status	2.967	1.397-6.302	0.0047
GGO status	3.542	1.074-11.683	0.0378
Air Bronchogram	0.189	0.071-0.507	0.0009
CEA	2.781	1.287-6.007	0.0092
SUV	2.553	1.163-5.606	0.0195

GGO: ground glass opacity, CEA: carcinoembryonic antigen, SUV: standardized uptake value

* P-value in logistic regression analysis

Table 4 Results of a Multivariate Analysis for Predictors of Nodal Involvement in Clinical-T1a Non-Small Cell Lung Cancer

Variable	Hazard Ratio	95% Confidence Interval	p Value*
GGO status	8.285	1.020-66.483	0.0478
Air Bronchogram	0.114	0.014-0.950	0.0447
CEA	3.308	1.026-10.664	0.0451
SUV	3.771	1.181-12.038	0.0250

GGO: ground glass opacity, CEA: carcinoembryonic antigen, SUV: standardized uptake value

* P-value in logistic regression analysis

Table 5 Results of a Multivariate Analysis for Predictors of Nodal Involvement in Patients with Clinical-T1a Pure Solid Tumor

Variable	Hazard Ratio	95% Confidence Interval	p Value*
CEA	3.418	1.060-11.018	0.0396
SUV	4.818	1.135-17.662	0.0117

GGO: ground glass opacity, CEA: carcinoembryonic antigen, SUV: standardized uptake value

* P-value in logistic regression analysis