厚生労働科学研究費補助金

がん臨床研究事業

「末梢小型非小細胞肺がんに対する縮小手術の有用性を検証する」に関する研究

平成23年度　総括研究報告書

研究代表者　鈴木　健司

平成24（2012）年　3月

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（3年計画2年目）

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末梢小型非小細胞肺がんに対する縮小手術の有用性を検証する研究

研究代表者　鈴木　健司　順天堂大学医学部呼吸器外科教授

研究要旨
50 年以上標準とされてきた肺癌に対する肺葉切除に換えて、小型肺癌に対しては縮小手術が標準治療となり得るか否かを検証する。CT 発見の小型肺癌に対して縮小切除を適切に適応することができれば、患者の負担が劇的に減り、試験の結果によっては世界で初めて肺癌に対する縮小切除の道が開ける。本研究では縮小切除の臨床試験を二本立てとして計画し、JCOG 肺がん外科グループ 32 施設と WJOG の 53 施設のグループ共同研究であり、現在、症例集積中である。

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A. 研究目的

肺癌に対する標準的外科治療が肺葉切除であるとされたのは実に 50 年前である。胸部 CT をはじめとする様々な診断機器が発達するにつれて小型の肺癌が多く見つかるようになり、これまでいくつかの縮小切除の妥当性を問う研究がなされてきたが、そのほとんどはエビデンスのレベルとしては低い報告であった。本研究はこのような状況を鑑み、小型肺癌に対する標準的な外科治療として縮小切除が妥当であるかどうかを多施設共同前向き試験として、大規模に検証するものである。縮小手術の有用性を科学的に証明することができれば、肺癌外科治療における患者負担を大きく軽減することにつながる。

B. 研究方法

【研究形式】
本研究は二つの臨床試験からなる。
いずれも多施設共同前向き試験であり、JCOG（日本臨床腫瘍研究グループ：肺がん外科グループ32施設）とWJOG（NPO法人西日本がん研究機構：53施設）のグループ間共同研究（inter group study）として行う。研究代表者は試験全

体の進捗状況を把握し、研究分担者からの症例集積を奨励する。

試験	試験形態	必要症例数	登録期間	追跡期間	Primary endpoint
JCOG 0802	第三相試験（非劣性）	1100例	3年	5年	全生存期間
JCOG 0804	第二相試験	330例	6年	10年	無再発生存期間

【対象症例】

１）胸部単純写真と造影胸部CT(conventional)のいずれかもしくは両方で肺癌が疑われる（術前組織学的診断、細胞学的診断の有無は問わない）。２）胸部CTにて主病巣の最大径2cm以下かつ臨床病期N0と診断。３）JCOG0802では胸部薄切CT上での画像的浸潤癌（充実性成分の径＞腫瘍径の25%）、JCOG0804では画像的非浸潤癌（充実性成分の径≦腫瘍径の25%）。４）病巣の中心部が肺野末梢（肺野外套3分の１）に存在。５）薄切CT画像にて主病巣径の少なくとも1方向の計測が可能。６）20歳以上80歳未満である。７）肺葉切除可能であると判断される。８）試験参加について充分な説明後、患者本人の自由意志により文書で同意が得られている。

【症例登録とランダム割付】

両試験とも、JCOG参加施設からの登録はJCOGデータセンターでの、WJOG参加施設からの登録はWJOGデータセンターでの、中央登録方式をとる。

JCOG0802でのランダム割付では、JCOGとWJOGは別々に登録を行うため必然的に「グループ」が層別因子となるが、さらにそれぞれの登録において、動的調整因子として①施設、②性別、③組織型（腺癌か非腺癌か）、④年齢（70歳以上、未満）、⑤薄切CTによる画像イメージがsolidかnon-solid、を用いる。

【治療内容】

JCOG0802：割付に従い、以下の治療を実施する。

症例登録-ランダム割付→ A群：肺葉切除

→ B群：縮小切除（区域切除）

JCOG0804は単群の試験であり、楔状切除が可能な症例には楔状切除、そうでない症例では区域切除を行う。

【解析方法】

JCOG0802では予定症例数の半数の登録時点と症例集積終了後に計２回の中間解析を行い、登録終了５年後に最終解析を行う。中間解析と最終解析はJCOGとWJOGを代表してJCOGデータセンターが解析を行う。

JCOG0804では中間解析は行わない。

【予定症例数】

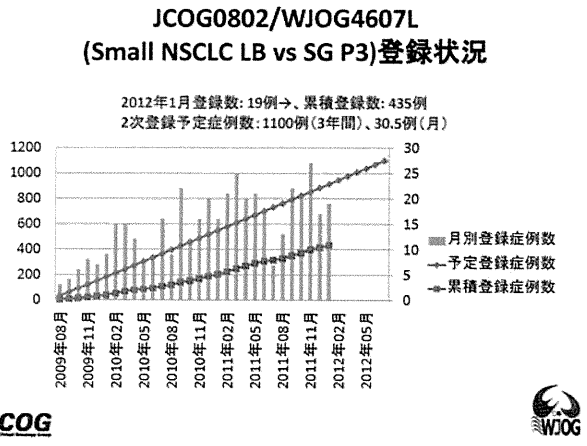
JCOG0802：各群515例。標準治療である肺葉切除の5年生存率を過去のデータから90%と見込み、縮小切除のそれが肺葉切除より劣らないことを証明するため非劣性の許容域を5%と設定した。α=0.05（片側）、β=0.20とし、登録期間3年、観察期間を登録終了後5年とした場合、１群515例が必要となる。若干の不適格症例や追跡不能例を見込んで全体で1100例と設定した。

JCOG0804：閾値5年無再発生存割合を95%、期待5年無再発生存割合を98%、α片側0.05、検出力を90%以上とし、二項分布に基づく正確（exact）な信頼区間を求めるとした時の必要適格例数は311例となる。不可避的に発生するであろう術中に判明する不適格例等を5%程度見込み、予定登録数を330例とした。

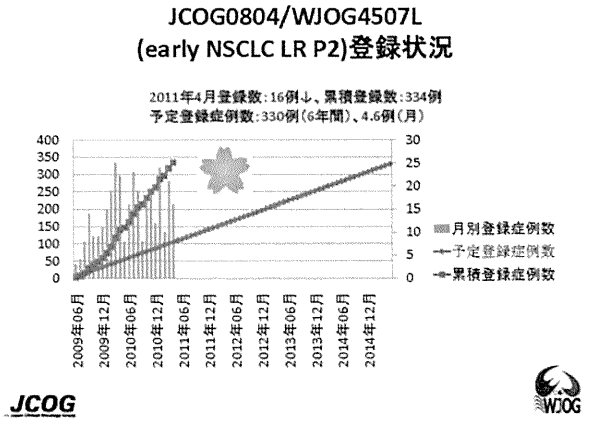
（倫理面の配慮）

「臨床研究に関する論理指針」およびヘルシンキ宣言を遵守し、実施にあたっては２つの共同研究グループ（JCOG・WJOG）のプロトコール審査委員会および参加施設の倫理審査委員会（IRB）の承認を必須としている。各施設 IRB での審査・承認後、研究目的と内容について説明文書を用いて充分説明の上、自由意志による同意を文書で得る。

C. 研究結果



JCOG0802は2012年2月の時点で435例が登録されている（2月1日現在）。JCOG0802では年齢の上限を 85 歳とするなど改訂をし、症例集積のペースは向上する見込みであり、引き続き登録の推進を図っていく予定である。



JCOG0804 は 2011 年 4 月 26 日をもって登録終了となった。今後予後をフォローし、最終解析を 2021 年に行う予定である。

D. 考察

胸部 CT 検診の普及に伴って肺野小型肺癌の発見が増加しており、QOL 等の面から至適術式の検討は急務である。本研究により縮小手術の有用性が検証されれば、小型肺癌に対する縮小手術の国際的な標準化、治療成績の向上と均てん化を目指した治療体系の確立が期待される。本研究の結果、縮小切除の有用性が検証されれば、臨床病期 IA 期の肺野小型非小細胞肺癌患者に対して、エビデンスに基づいて、肺葉切除より優れた低侵襲標準治療が確立され、術後肺機能の温存を含む患者 QOL の向上が期待される。0804 の研究成果の先には外科切除以外の局所療法によって肺癌が治癒可能であるという可能性が世界で初めて示されることになる。逆に縮小切除の有用性が検証されなくても、十分なエビデンスがないまま広く行われようとしている縮小切除ではなく、末梢小型病変であっても当該病期では肺葉切除が確固たる標準治療として確立され、患者がより安心して治療を受けることができるようになることが期待される。この試験結果は、ポジティブであってもネガティブであっても診療ガイドラインや関連領域の教科書を書き換えることになる。一方、縮小手術の有用性が証明されれば、さらに次のステップとして、定位放射線治療などの非観血的治療との比較試験が行われると予想される。

E. 結論

JCOG 肺がん外科グループ 32 施設に加えて、WJOG 53 施設とのグループ間共同研究（intergroup study）では、2cm 以下の肺癌患者は登録予定全施設で年間約 1700 名ある。同意取得割合を 20-30%とすると、年間約 400 名の患者登録が見込まれ、両試験とも登録期間は約 3 年を要すると見込んでいたが、0804 については、2011 年 4 月の時点で症例集積は終了した。

0802 については、年齢の上限を 85 歳とするなどプロトコールの改訂を行い症例集積のペースの向上を図る。

F. 健康危険情報

JCOG0802 健康危険情報

肺癌に対する手術中に生じた有害事象(高カリウム血症)

情報源:肺野末梢小型肺癌に対する肺葉切除と縮小手術との第三相試験：JCOG0802 における JCOG 効果･安全性評価委員会に対する有害事象報告（DSMC-ADR1151）

評価：グレード B(試験の継続およびプロトコールの内容については問題ないと判断されている。緊急の対応を要するものではない。)

G. 研究発表

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H.　知的財産権の出願・登録状況

１．特許取得

なし

２．実用新案登録

なし

３．その他

なし

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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末梢小型非小細胞肺がんに対する縮小手術の有用性を検証する研究

研究成果の刊行物・別刷

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A Prospective Radiological Study of Thin-Section Computed Tomography to Predict Pathological Noninvasiveness in Peripheral Clinical IA Lung Cancer (Japan Clinical Oncology Group 0201)

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Purpose: Pathological noninvasiveness needs to be precisely predicted in preoperative radiological examinations of patients with early lung cancer for the application of limited surgery.

Patients and Methods: Patients with clinical T1N0M0 peripheral lung cancer were recruited. Radiological findings of the main tumor were evaluated as to ground-glass opacity with thin-section computed tomography. The primary end point was specificity, i.e., the proportion of patients with radiologically diagnosed invasive lung cancer to patients with pathologically diagnosed invasive lung cancer. The precision-based planned sample size was 450. We expected that the lower limit of the 95% confidence interval (CI) for specificity should be satisfied in ≥97% of patients.

Results: We enrolled 811 patients from 31 institutions between December 2002 and May 2004. The primary end point was evaluated in 545 patients. The specificity and sensitivity for the diagnosis of pathologically diagnosed invasive cancer were 96.4% (161/167, 95% CI: 92.3–98.7%) and 30.4% (115/378, 95% CI: 25.8–35.3%), respectively, i.e., a negative result. Nevertheless, the specificity for lung adenocarcinoma ≤2.0 cm with ≤0.25 consolidation to the maximum tumor diameter was 98.7% (95% CI: 93.2–100.0%), and this criterion could be used to radiologically define early adenocarcinoma of the lung.

Conclusions: Although our predetermined criterion for specificity was not statistically confirmed, radiological diagnosis of noninvasive lung cancer with a thin-section computed tomography scan corresponded well with pathological invasiveness. Radiological noninvasive peripheral lung adenocarcinoma could be defined as an adenocarcinoma ≤2.0 cm with ≤0.25 consolidation.

Key Words: Ground-glass opacity, Bronchioloalveolar carcinoma, Thin-section, Computed tomography, Limited resection.

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Lung cancer is the leading cause of cancer death worldwide.[1] Occult lymph node metastasis in hilum and mediastinum are found in approximately 15 to 20% in the literature[2,3]; however, a conventional preoperative workup cannot detect these metastases. Thus, a major lung resection with lymphadenectomy is recommended even for small-sized lung cancer.

There are two indications for the use of limited surgical resection. Some authors insist that only the size of the main tumor is an indication for limited surgical resection.[4–6] This strategy is supported by segmentectomy as the limited surgery and an intraoperative evaluation of the hilar lymph node. If there is lymph node involvement, then the surgery is converted from segmentectomy to major lung resection. Thus, diagnosis from intraoperative frozen sections of several lymph nodes is mandatory for this strategy, and a wide wedge resection, another limited surgical resection technique, is not suitable because it is impossible to evaluate the status of the hilar nodes using this approach. Conversely, a wide wedge resection can be used as a limited surgical resection for peripheral lung cancer.[7–9] This strategy should be adopted on the supposition that the lung cancer has not metastasized to the nodes. As the intraoperative nodal status cannot be estimated using a wide wedge resection, a preoperative evaluation of the primary tumor is vital. Preoperative predictors for the lack of metastasis to the lymph node are necessary for this strategy. The findings from thin-section computed tomogra-

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phy (CT) are reported to be the best predictors for the invasiveness and nodal status of lung cancers.[10–17] It has been proposed that lung cancer with a consolidation less than 50% of the maximum tumor diameter could be one of the most promising definitions to predict "early" lung cancer; however, this definition was derived from retrospective studies, and it should be confirmed in a prospective study.

Therefore, we performed a multiinstitutional prospective study for the radiological diagnosis of early lung cancer (Japan Clinical Oncology Group [JCOG] 0201) to assess these retrospective findings. If the validity of the criteria to radiologically diagnose "early" lung cancer is confirmed by this study, then a limited surgical resection could be used instead of a major lung resection.

PATIENTS AND METHODS

Patient Eligibility Criteria

The eligibility criteria were as follows: (1) a suspected or diagnosed lung cancer based on the findings from a plain x-ray and/or CT scan; (2) clinical stage IA, i.e., T1N0M0, by thoracic enhanced CT; (3) the center of the tumor was located peripherally, i.e., the outer half of the lung field on CT; (4) measurable at least in one dimension in thin section CT; (5) age range from 20 to 75 years, (6) no prior thoracotomy; (7) feasible for pulmonary lobectomy; and (8) obtained written informed consent.

The exclusion criteria included (1) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ and (2) interstitial pneumonitis, lung fibrosis, or severe pulmonary emphysema.

All patients underwent a preoperative CT scan, and hilar or mediastinal nodes less than 1.0 cm in the shortest diameter were regarded as clinical N0. Disease stages were determined based on the tumor node metastasis classification of the International Union Against Cancer, 6th edition.[18] The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center. The JCOG Data Center conducted the central registration, data management, central monitoring, and statistical analysis.

Radiological Evaluation of the Primary Tumor

A contrast-enhanced CT scan was performed to evaluate the entire lung for preoperative staging. In addition, the main tumor was evaluated preoperatively to estimate the extent of ground-glass opacity (GGO) with thin-section helical CT scan with 1 to 3 mm collimation. Images were reconstructed with a field of view of 15 to 20 cm. The lung was photographed with a window level of −500 to −700 H and a window width of 1000 to 2000 H as a lung window setting, and with a window level of 30 to 60 H and a window width of 350 to 600 H as a mediastinal window setting. The evaluated factors on the lung window were the maximum diameters of the tumor and consolidation; the presence of a pleural tail; air bronchogram; the homogeneity of consolidation; and the sharpness of the tumor margin. The maximum tumor diameter was also evaluated from the mediastinal window. The consolidation 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, homogenous increase in density that did not obscure the underlying vascular markings.

Surgical Intervention

A preoperative needle biopsy or cytology was not required. When the diagnosis of lung adenocarcinoma was preoperatively made, a lobectomy and lymph node dissection were recommended; otherwise, an intraoperative frozen section diagnosis was performed, and if the tumor had histology other than adenocarcinoma, the protocol treatment was terminated, and the patients were excluded from the analysis. If the tumor was intraoperatively diagnosed as an adenocarcinoma, major lung resection and lymph node dissection were recommended. For some adenocarcinomas with large GGO areas, such as "pure GGO," a limited surgical resection was allowed, but this population was excluded from the primary end point analysis.

Pathological Diagnosis

The resected specimen was sectioned at intervals of 5 to 10 mm throughout the whole lung. The main tumor was sectioned into 2 to 4 mm slices, and the following pathological factors were evaluated by means of hematoxylin and eosin staining, and elastic fiber staining: histological typing; grade of differentiation; Noguchi's classification[19]; the maximum diameter of the main tumor and central fibrosis; pleural involvement; vascular invasion; lymphatic invasion; and intrapulmonary metastasis. Histological typing was determined according to the classification system of the World Health Organization.[20]

Study Design

Surgical resection was performed after the radiological evaluation of the peripherally located adenocarcinoma. The mode of surgery was basically a pulmonary lobectomy and lymph node dissection, and the postoperative pathological diagnosis was compared with the preoperative radiological diagnosis of early lung cancer. If the postoperative pathological diagnosis of "noninvasive adenocarcinoma" of the lung was predicted by the preoperative radiological diagnosis, a limited surgical resection or other nonsurgical local therapy was indicated.

Definition of Radiological Noninvasive and Invasive Lung Cancer

On the basis of retrospective findings,[10–15] radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter (consolidation/tumor ratio, C/T ratio) less than 0.5, indicating a tumor with a wide GGO area (Figure 1). Additionally, we adopted other criteria for radiological noninvasive lung cancer. One was the tumor shadow disappearance rate (TDR),[17] and the other was the visual estimation (VE) of the consolidation component.[11] TDR was evaluated from the maximum tumor diameter on the lung and mediastinum windows. TDR was calculated using the following formula: TDR = tumor size on mediastinal window/tumor

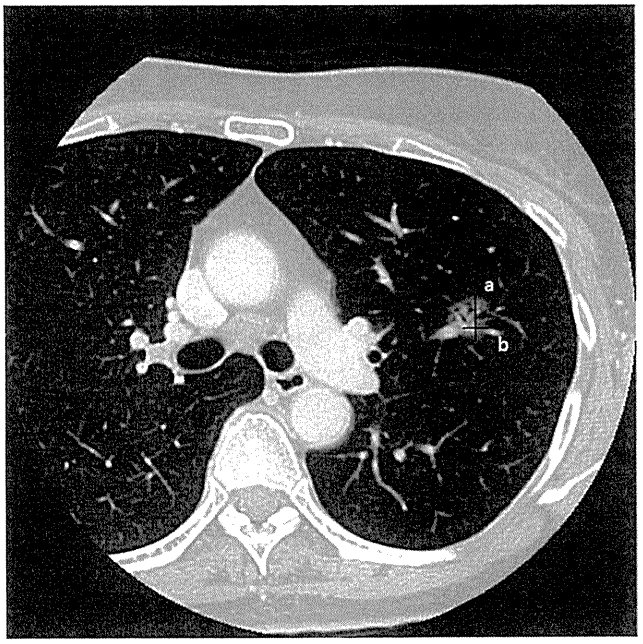

FIGURE 1. Example of radiological noninvasive lung cancer. The maximum diameter of consolidation (*B*) is less than the half of the maximum tumor diameter (*A*), which means tumor with wide area of ground glass opacity.

TABLE 1. Relationship Between Radiological and Pathological Features

	Pathological Diagnosis	
Radiological Diagnosis	**Noninvasive**	**Invasive**
Noninvasive[a]	A	C—undertreated
Invasive	B—overtreated	D

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.5 (see text).
Specificity = D/(C + D), sensitivity = A/(A + B), positive predictive value = A/(A + C), and negative predictive value =D/(B + D).

size on lung window. For VE, the consolidation component was defined as the proportion of the area of consolidation to that of the tumor visually estimated without measuring the diameter; a value less than 0.5 was diagnosed as noninvasive cancer. We compared the sensitivity and specificity of these three methods of radiological evaluation.

Definition of Pathological Noninvasive and Invasive Lung Cancer

The provisional pathological definition of noninvasive lung cancer was defined as a lung adenocarcinoma without nodal involvement, vascular invasion, or lymphatic invasion.

End Point and Planned Sample Size

The primary end point was the specificity based on the radiological diagnosis using the C/T ratio. The relationship between the radiological and pathological diagnoses is presented in Table 1. If limited surgical resection was performed on a patient with radiological noninvasive but pathological invasive cancer, the treatment was considered as "undertreatment" (group C, Table 1). Conversely, if major surgical resection was performed on a patient with radiological invasive but pathological noninvasive cancer, the treatment was defined as "overtreatment" (group B), and a limited surgical resection may be indicated. Patients with radiological and pathological noninvasive lung cancer belonged to group A; group D included patients with radiological and pathological invasive lung cancer. Considering that local recurrence of lung cancer results in a dismal prognosis, undertreatment should be avoided at any cost. Therefore, the number of patients belonging to "C" of Table 1 should be minimized, and the primary end point of specificity was defined as the proportion of patients with radiologically diagnosed invasive lung cancer in patients with pathologically diagnosed invasive lung cancer, i.e., D/(C + D). Conversely, patients with radiological invasive but pathological noninvasive lung cancer, who belong to category "B," may undergo overtreatment. The number of patients in the "B" category should be minimized, and sensitivity was selected as a secondary end point. Sensitivity was defined as the proportion of patients with radiologically diagnosed noninvasive cancer in patients with pathologically diagnosed noninvasive cancer, i.e., A/(A + B).

The primary end point was evaluated for the patients who were resected with a lobectomy and lymph node dissection, diagnosed with adenocarcinoma, and who were regarded as eligible in the radiological central review. We expected that the lower limit for the 95% confidence interval (CI) of specificity was satisfied in ≥97% of patients for an estimated sample size of 400 pathological invasive cancer cases. Assuming the sensitivity is 50% and the 95% CI range is ≤15%, the estimated sample size for pathological noninvasive cancer was 50 cases. The precision-based planned sample size was 450, i.e., ≥400 cases for pathological invasive cancers and ≥50 cases for pathological noninvasive cancers.

Central Review of Radiological Evaluation

To ensure the final diagnosis, radiological findings based on thin-section CT were reviewed by six reviewers. This radiological central review was indicated for patients who were preoperatively or intraoperatively diagnosed with adenocarcinoma. CT findings were evaluated coincidentally by the six reviewers, and the final results were decided in consensus.

Exploratory Analysis

We conducted additional exploratory analyses for patients with an adenocarcinoma ≤2.0 cm in size and evaluated the specificity and sensitivity. We also evaluated two other cutoff values for the C/T ratio on lung window, 0.25 and 0.75, to identify the optimal cutoff value to predict pathologically noninvasive adenocarcinoma of the lung.

RESULTS

Patients' Characteristics

Between December 2002 and May 2004, we enrolled 811 patients from 31 institutions. We expected that the number of pathological noninvasive and invasive cancers was 50 and 400, respectively; however, we recruited patients with

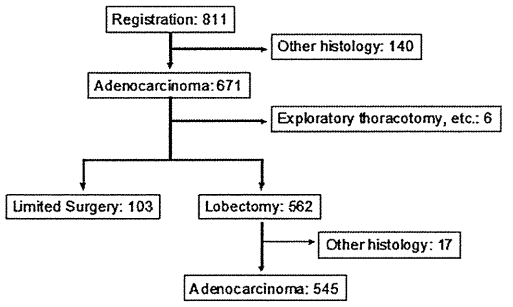

FIGURE 2. Scheme for study population. Finally, 545 patients with adenocarcinoma were the population for the primary analysis.

more pathological noninvasive and less invasive cancer than expected. Thus, we increased the total sample size to recruit more than 400 patients with pathological invasive cancer. Nevertheless, the primary end point proved to be lower than expected before sufficient numbers of pathological invasive cancer cases were recruited. Therefore, the accrual of patients was terminated before the planned period. We recruited 357 men and 454 women (age range, 27–75 years; median, 61 years). Among them, 671 (82.7%) patients were diagnosed with lung adenocarcinoma at the time of the surgical resection. The other cases included benign pathology or other type of cancers, such as pulmonary metastasis of colorectal cancer. Of the 671 patients with lung adenocarcinoma, 562 (83.8%) underwent major lung resection, 103 (15.3%) underwent limited resection, five (0.75%) underwent exploratory thoracotomy, and one underwent another procedure. Among the 562 patients, 17 (3.0%) patients were ineligible based on their postoperative pathological findings (Figure 2). Thus, the remaining 545 patients satisfied the inclusion criteria (described in the Patients and Methods section) and were taken into the primary analysis (Table 2).

Evaluation of the Primary End Point and Comparison among the Three Methods of Radiological Evaluation

The primary end point was evaluated among the 545 patients who met the inclusion criteria (Table 3). The specificity and sensitivity of the diagnosis for pathologically invasive cancer based on the C/T ratio from the lung window was 96.4% (161/167, 95% CI: 92.3–98.7%) and 30.4% (115/378, 95% CI: 25.8–35.3%), respectively. As a result, the lower 95% CI limit for specificity did not exceed the prespecified threshold of 97%. The specificity and sensitivity for the diagnosis of pathologically invasive cancer based on the TDR from the mediastinal window was 89.8% (150/167, 95% CI: 84.2–94.0%) and 44.4% (168/378, 95% CI: 39.4–49.6%), respectively. The most favorable specificity was obtained by the evaluation of the C/T ratio, and the lowest specificity was observed by the TDR method.

Radiological-Pathological Association in Lung Adenocarcinoma ≤2.0 cm in Size

Additional exploratory analysis was performed for lung adenocarcinoma ≤2.0 cm in size in the maximum tumor dimension to examine the appropriate tumor size for diagnosis of radiological early lung cancer. The specificity and sensitivity for the diagnosis of pathological invasive cancer based on the C/T ratio from the lung window was 97.5% (95% CI: 91.2–99.7%) and 31.0% (65/210, 95% CI: 24.8–37.7%), respectively. The point estimate of specificity was

TABLE 2. Characteristics of 545 Eligible Patients for the Investigation of the Primary Endpoint

Characteristics	Number of Patients
Clinical factors	
Gender	
Men	233
Women	312
Age range (median)	35–75 (62)
Maximum tumor dimension	
≤1.0cm	30
>1.0–2.0	270
>2.0–3.0	243
>3.0	2
Radiological factors	
Cons/Tumor ratio[a]	
Non-invasive (≤ 0.5)	137
The others (> 0.5)	381
TDR[b]	
Non-invasive (≤ 0.5)	234
The others (> 0.5)	311
Visual estimation of consolidation[c]	
Non-invasive (≤ 0.5)	200
The others (> 0.5)	345
Surgical factors	
Type of surgery	
Pneumonectomy	1
Lobectomy	544
Pathological factors	
Final histological diagnosis[d]	
Adenocarcinoma	529
Squamous cell carcinoma	7
Large cell carcinoma	4
Others	5
Lymph node metastasis	
Positive	47
Negative	498
Vascular invasion[e]	
Positive	100
Negative	443
Lymphatic invasion[f]	
Positive	113
Negative	428

[a] There were 27 cases of which tumors could not be evaluated the size of consolidation on lung window because of their unclear margin.
[b] TDR was calculated with the following formula: TDR = tumor size on mediastinal window/tumor size on lung window.
[c] The size of consolidation component was evaluated with visual estimation.
[d] Patients with adenocarcinoma which was diagnosed at the time of surgery were eligible and there were 16 patients with different final pathological diagnosis.
[e] There were one missing data and one unknown findings.
[f] There were one missing data and three unknown findings.
Cons, consolidation, TDR: tumor disappearance ratio.

TABLE 3. Relationship Between Radiological and Pathological Features in the 545 Eligible Cases

	Pathological Diagnosis[b]	
Radiology (Cutoff: 0.5)[a]	**Noninvasive**	**Invasive**
Consolidation/tumor ratio on lung window		
Noninvasive[a]	115	6
Invasive	263	161
Sensitivity		30.4% (95% CI: 25.8–35.3)
Specificity		96.4% (95% CI: 92.3–98.7)
TDR		
Noninvasive[a]	168	17
Invasive	210	150
Sensitivity		44.4% (95% CI: 39.4–49.6)
Specificity		89.8% (95% CI: 84.2–94.0)
Visual estimation of consolidation		
Noninvasive[a]	140	11
Invasive	238	156
Sensitivity		37.0% (95% CI: 32.2–42.1)
Specificity		93.4% (95% CI: 88.5–96.7)

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.5, indicating a tumor with a wide GGO area (see text).

[b] Pathological diagnosis was based on the criteria using nodal status, lymphatic invasion, and vascular invasion.

TDR, tumor disappearance ratio; CI, confidence interval; GGO, ground-glass opacity.

TABLE 4. Radiologic-Pathologic Correlation in Lung Cancer 2.0 cm or Less in Size (Cutoff: 0.25)

	Pathological Diagnosis[b]	
Radiology (Cutoff: 0.25)[a]	**Noninvasive**	**Invasive**
Consolidation/tumor ratio on lung window		
Noninvasive[a]	34	1
Invasive	176	78
Sensitivity	16.2% (95% CI: 11.5–21.9)	
Specificity	98.7% (95% CI: 93.2–100.0)	
TDR		
Noninvasive[a]	58	3
Invasive	152	76
Sensitivity	27.6% (95% CI: 21.7–34.2)	
Specificity	96.2% (95% CI: 89.3–99.2)	
Visual estimation of consolidation		
Noninvasive[a]	26	0
Invasive	184	79
Sensitivity	12.4% (95% CI: 8.3–17.6)	
Specificity	100.0% (95% CI: 95.4–100.0)	

[a] Radiological noninvasive lung cancer was tentatively defined as a tumor with a maximum diameter of consolidation of the maximum tumor diameter <0.25, indicating a tumor with a wide GGO area (see text).

[b] Pathological noninvasive is defined as adenocarcinoma with no nodal involvement, lymphatic invasion, or vascular invasion.

TDR, tumor disappearance ratio; GGO, ground-glass opacity; CI, confidence interval.

higher than observed in the primary analysis, but the lowest limit of the 95% CI for specificity was still lower than 97%.

Evaluation of the Optimal Cutoff Value for the C/T Ratio

Radiologically noninvasive lung cancer was primarily defined in this study as a C/T ratio less than 0.5 on thin-section CT; however, the specificity for this criterion was lower than expected, so we examined two other cutoff values, 0.25 and 0.75, for the C/T ratio in patients with lung adenocarcinoma ≤2.0 cm in size. As a result, the 0.25 cutoff value showed the highest specificity, although its sensitivity was relatively low (Table 4).

DISCUSSION

This is the first multiinstitutional prospective study on the definition of radiological early lung cancer. Several radiological criteria for early lung cancer have been reported, but these reports were based on retrospective and single institute analysis.[10–15] The majority of these reports supported the hypothesis that lung cancer with a consolidation less than 0.5 of the maximum tumor diameter and a wide GGO could be regarded as early lung cancer. If this hypothesis was correct, then a limited surgical resection, instead of lobectomy, should be sufficient to treat this population. Nevertheless, before generalizing the strategy, we had to confirm this hypothesis obtained from retrospective findings on a multiinstitutional basis. On the basis of our results, although the radiological findings of GGO and consolidation were well correlated with the pathologically invasive nature of the tumor, the radiological criteria for early lung cancer using the 50% cutoff value were not valid to predict pathological noninvasiveness. Thus, based on this exploratory analysis, lung carcinoma ≤2.0 cm in size and with a consolidation ≤25% of the maximum tumor diameter was considered to be radiological early lung cancer. We have just started a clinical trial to evaluate the validity of limited resection for lung cancer based on these criteria.

There has not been a general consensus formed on the optimal method to evaluate the extent of GGO. Three methods have been mainly reported: the C/T ratio from the lung window; the TDR from the mediastinal window; and the VE of the extent of GGO from the lung window. Each method has been reported as an optimal method based on a single institute retrospective analysis.[10–15] This study is the first prospective study to compare the three methods. The highest specificity was obtained from the C/T ratio and was the lowest for the TDR method. Conversely, the highest sensitivity was found with the TDR method, and the lowest was for the C/T ratio. Therefore, if the TDR method was used to determine radiological early lung cancer, more invasive cancers would be misdiagnosed as radiologically noninvasive. This situation should be avoided as much as possible because an invasive cancer would be resected using a limited resection that is ill suited for such cancers. Conversely, the C/T ratio provided clinically safe criteria to identify noninvasive cancers. On the basis of the primary analyses, the C/T ratio was the best criterion for the highest specificity. In this trial,

mode of surgery is not controlled for GGO lesions. Such GGO lesions were not included in the primary analysis because of limited surgery which was indicated for these. If these lesions were included for the analysis, sensitivity may increase with a slight decrease of specificity. The point estimate of specificity was much higher for lung cancer ≤2.0 cm in size. When the cutoff value was set as 0.25, the specificity was the highest. In short, a pathological noninvasive cancer can be predicted by a C/T ratio with a cutoff value of 0.25 and a specificity of 98.7% (95% CI: 93.2–100.0%) for lung cancer ≤2.0 cm in size. Thus, we prefer to use the criteria derived from the lung window to select candidates to undergo a limited resection.

Major lung resection has been recommended as a standard procedure, even for small-sized lung cancer, because lymph node metastasis can be found in approximately 15% of lung cancers ≤2.0 cm size.[2] Nevertheless, our radiological criteria could be used to predict pathological noninvasiveness, and such patients would be candidates to undergo a limited surgical resection. Limited pulmonary resection consists of wide wedge resection or segmentectomy. As for surgical invasiveness, a wedge resection can be performed with a smaller skin incision, reduced blood loss, and a shorter operation time. On the other hand, segmentectomy offers a sufficient surgical margin. To select the optimal limited resection, the key note is the status of lymph node metastasis. A wide wedge resection should be indicated for lung cancer without lymph node involvement.

In conclusion, although our predetermined criterion for specificity was not statistically confirmed, the radiological diagnosis of noninvasive lung cancer using a thin-section CT scan correlated well with pathological invasiveness based on the exploratory investigation. We are planning to perform a study of the efficacy of limited surgical resection for lung cancers selected by the criterion using a cutoff value of 0.25 and a maximum tumor diameter ≤2.0 cm in size. We will use a wide wedge resection as the limited surgical procedure because these cases have a limited potential for nodal involvement or lymphatic/vascular invasion. We are also planning to perform a phase III trial to compare pulmonary lobectomy and segmentectomy for lung cancer ≤2.0 cm in size, excluding patients with radiological noninvasive cancer. If we obtain positive results in these future clinical trials, it will present a good opportunity to change the standard treatment for early-stage lung cancer.

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Postoperative complications and respiratory function following segmentectomy of the lung – comparison of the methods of making an inter-segmental plane☆

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Abstract

Segmentectomy could be one of the standard modes of surgery for the treatment of early lung cancer. However, segmentectomy could be more difficult than lobectomy as to the management of inter-segmental plane. The relationship between methods of dividing an inter-segmental plane and postoperative complication/pulmonary function was investigated in this study. A retrospective study was conducted on 49 patients who underwent segmentectomy of the lung between February 2008 and April 2009 at our institute. Eighteen (36.7%) were male and 31 (63.3%) were female. The inter-segmental plane was divided with only a mechanical stapler in 18 patients, and electrocautery was used in the other 31 patients. There were no significant relationships between clinicopathological features and both procedures, except gender, operative time, and pleurodesis ($P<0.05$). Preserved forced expiratory volume in one second (FEV_1) was not affected by the procedures. Patients who underwent left upper division segmentectomy had significantly more complications. On multivariate analysis, resected segment and intraoperative blood loss were found to be significant predictors for postoperative complications. There were no significant relationships between the methods of making inter-segmental planes and postoperative complications and/or lung functions. Resected segment and intraoperative blood loss were predictors for postoperative complication in segmental resection of the lung.

Keywords: Lung function; Cautery; Dividing device; Stapler

1. Introduction

Pulmonary segmentectomy is one of the options for resectable lung cancer, especially for compromised patients having severe preoperative complications, such as unstable angina, and/or chronic obstructive pulmonary disease (COPD) [1, 2]. Recently, this mode of surgery has been applied for small-sized peripheral lung cancers, as such lung cancers frequently have a minimally-invasive pathological nature [3–9], although phase III trials on the comparison between limited surgery and pulmonary lobectomy have failed to show the superiority of limited resection [10]. We have already started randomized controlled trials for the feasibility of segmentectomy for small-sized lung carcinoma [11]. There is a possibility that in the future, segmentectomy of the lung will be selected as the standard procedure for early lung cancer.

However, controversies still remain as to technical aspects of pulmonary segmentectomy. One of the most difficult points in segmentectomy may be how to make an inter-segmental plane. Some prefer electrocautery for dividing the plane, and others prefer to use a stapler. This preference should be decided based on the following factors: postoperative complication, postoperative pulmonary function, local control for lung cancer and prognosis. However, there have been few reports on these controversies. Thus, we tried to investigate the relationship between the methods for making an inter-segmental plane and postoperative lung function and/or complications.

2. Materials and methods

Between February 2008 and April 2009, lung resection was performed in 378 patients at our institute. Among them segmental resection of the lung was performed in 49 patients and this retrospective study was performed on this population. Segmentectomy was performed for peripherally located lung cancer or suspected lung cancer in the following patients: 1) compromised patients who had severe preoperative complications, such as severe angina pectoris, severe diabetes mellitus with systemic disorder, etc; 2) patients with poor lung function which is defined as postoperative predictive forced expiratory volume in one second (FEV_1) <1000 ml; 3) any patients having minimally-invasive lung cancer 2.0 cm or less in maximum tumor dimension without suspected nodal involvement. Minimally-invasive lung cancer was defined based on the findings of

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