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研究」に関する研究

平成22年度　総括研究報告書

研究代表者　鈴木　健司

平成23（2011）年　3月

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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（intergroup 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
JCOG0802	第三相試験（非劣性）	1100例	3年	5年	全生存期間
JCOG0804	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。

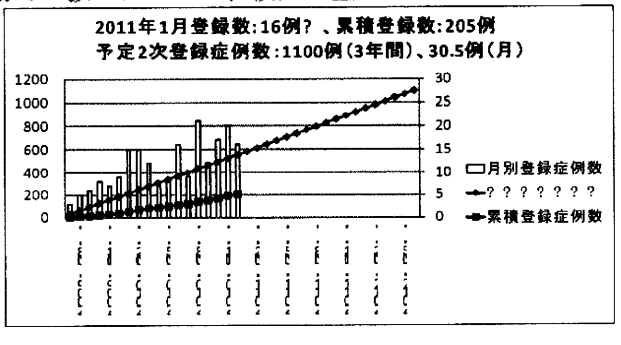
JCOG0804：閾値5年無再発生存割合を95%、期待5年無再発生存割合を98%、α片側0.05、検出力を90%以上とし、二項分布に基づく正確（exact）な信頼区間を求めるとした時の必要適格例数は311例となる。不可避的に発生するであろう術中に判明する不適格例等を5%程度見込み、予定登録数を330例とした。

（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

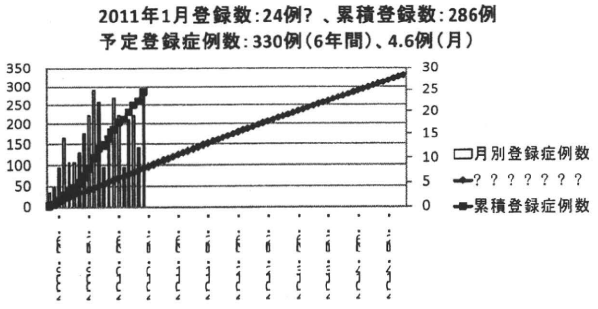
JCOG0802は必要症例数1100例の第三相試験であり、症例の登録は3年を見込んでいる。これはJCOG肺癌外科グループに参加している施設で行われる2cm以下の肺癌切除例数が1000件以上であり、第三相試験という、患者同意の取りにくい試験であることを見込んでも3年で十分と予測したものである。実際に試験開始してみると図に示すように予定症例集積を大きく下回る結果となった。この理由の主なものは腫瘍の位置などの手術手技上の問題の他に、重複癌の症例が予想を遙かに上回る状況であったことが挙げられる。既往に5年以内の胃癌があれば、たとえば、本試験には登録することが出来ない。当然のことながら肺癌の予後を検証する研究が他の癌の既往に左右されては話にならない。しかし一方でこのような重複癌症例が数多く含まれる対象であることを考慮すると、将来本研究の結果を日常診療に当てはめる際には、重複癌症例をも含めた検証が必要となるのも事実である。今後はこのような重複癌症例の臨床試験場での扱いについて、検証を重ねる必要がある。



JCOG0802は平成23年1月の時点で205例が登録

されている。これまでに重大な治療関連死などもなく、順調に症例は集積されているといえる。

一方 JCOG0804 は 284 例が平成 23 年 1 月時点で登録されており、予定登録症例数の 330 例の 86%に既に達している。これは前述の 0802 に比べて重複癌が少ないことを示しており、興味深い。本来 0804 は 6 年で集積、10 年フォロー、つまり 16 年後の結果ということであるが、このペースであれば、かなり早くに結果が発表されることになろう。



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る。JCOG0802 では予定参加施設 34 施設のうち 31 施設で、JCOG0804 では 34 施設のうち 33 施設での IRB 承認が得られており、全施設からの IRB 承認が得られれば登録ペースは今より改善すると見込まれる。

平成 23 年度は今後ますますの症例を登録していく予定である。

F. 健康危険情報

なし

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

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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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Prognostic Evaluation of Nodal Staging Based on the New IASLC Lymph Node Map for Lung Cancer

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Key words
- lung cancer
- lymph node
- staging

Abstract

Background: The purpose of this study was to evaluate the new lymph node map proposed by the International Association for the Study of Lung Cancer (IASLC) from the point of prognosis, and to identify the significant prognostic factors in each pathological N stage.

Methods: We reviewed 647 consecutive patients with surgically resected non-small cell lung cancers. Survival was analyzed according to N stage and three prognostic subgroups: N1a (single N1 zone), N1b (multiple N1 zones) or N2a (single N2 zone), and N2b (multiple N2 zones). The following prognostic factors were evaluated for each N stage: location of involved zones, number of involved lymph nodes, stations and zones, and the presence of skip metastases.

Results: (1) The survival curves showed a stepwise deterioration as the N stage increased. (2) No significant difference was observed in survival between the different locations of involved zones in each N stage. (3) In N2 patients, the presence of skip metastases was a significant prognostic factor in multivariate analysis.

Conclusions: The proposed IASLC map is valid for prognostic stratification. The prognostic impact of the presence of skip metastases on N2 disease should therefore be taken into consideration when carrying out the forthcoming revision of the TNM staging system.

Introduction

An appropriate staging system is indispensable, not only for predicting prognosis but also for planning the treatment strategy for lung cancer patients. The current tumor node metastasis (TNM) staging system for lung cancer was last revised in 1997 [1], with only a minor revision in 2002 [2]. The International Staging Committee (ISC) of the International Association for the Study of Lung Cancer (IASLC) has proposed a new TNM staging system for the next revision (7th edition) published in 2009 [3]. Although the T and M descriptors were newly defined based on differences in survival, the N descriptor remained unchanged [3].

The 7th edition of the TNM Classification for Lung Cancer [3] was established based on 67 725 cases of non-small cell lung cancer (NSCLC) treated by all modalities of care between 1990 and 2000. Of these patients, a total of 38 265 patients had information on their clinical N status, and 28 371 patients who underwent surgical treatment had information on their pathological N status. The pathological N staging data was collected mainly from Japan (n = 1721, 60%), with the remaining data taken from Europe (n = 701, 24%), North America (n = 380, 13.2%), and Australia and Taiwan (n = 74, 2.6%) [4]. Since Naruke et al. proposed the first lymph node map in 1967 [5,6], the Naruke map has been used to describe the anatomic locations of intrathoracic lymph nodes in Japan. However, the Mountain-Dresler modification of the American Thoracic Society (MD-ATS) map [7] has been widely used in North America and Europe. To achieve uniformity and promote future analyses of a planned prospective international database, the IASLC proposed a new lymph node map which reconciles the differences between the currently used maps [8].

One of the most important issues concerning the current N staging system is that the N stage is defined based only on the anatomical extent of the involved lymph nodes. It is not surprising that a higher N stage disease tends to show a worse prognosis than the earlier N stage disease considering the lymphatic stream. However, numerous researchers have reported that both N1 and N2

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disease represented heterogeneous groups in terms of survival. Therefore, it is important to identify the significant prognostic factors in each pathological N stage which deserve being included in a forthcoming revision of the TNM staging system.

The purpose of this study was to evaluate a proposed IASLC lymph node map from the point of prognosis and to identify significant prognostic factors in each pathological N stage.

Material and Methods

We reviewed 647 consecutive patients who underwent major lung resection (at least lobectomy) for NSCLC between September 1999 and December 2007 in our department. Conventional ipsilateral mediastinal lymph node dissection (SND: systematic nodal dissection or sampling) was performed in 528 patients. Extended radical lymph node dissection (ERD: cervical and bilateral mediastinal lymph node dissection) through a median sternotomy [9, 10] was performed in 119 patients. Induction chemotherapy and/or radiotherapy were not routinely performed if complete resection was possible based on the radiological findings. In this series, no patient received induction therapy.

Preoperatively, the mediastinal and hilar lymph node status was defined as positive if the chest computed tomography showed that the shorter axis of any node was larger than 1 cm. Mediastinoscopy, positron emission tomography, and endobronchial ultrasound were not performed routinely in this series. However, scalene node biopsy was performed in patients with suspicion of N3 (supraclavicular) involvement at the time of physical examination. When N3 involvement was confirmed pathologically, the patients did not undergo surgery. The number of patients classified by clinical N status was 512 N0, 47 N1, 85 N2, and 3 N3 (contralateral), respectively.

Histological tumor type was determined according to the World Health Organization classification [11]. All dissected lymph nodes were pathologically examined and classified according to the anatomical location on the Naruke map [6]. Involved node levels were reclassified according to a new IASLC lymph node map [8]. In brief, lymph nodes at stations 1 to 4 were grouped together into the upper zone, stations 5 and 6 into the aortopulmonary zone, station 7 into the subcarinal zone, stations 8 and 9 into the hilar zone, and stations 12 to 14 into the peripheral zone. Station 10 on the Naruke map indicates the lymph nodes around the main bronchus. It was impossible to retrospectively differentiate station 10 lymph nodes located in the subcarinal area from those located adjacent to the upper border of the main bronchus because they were not described separately. Therefore, some patients with subcarinal station 10 involvement on the Naruke map might be understaged as N1, which corresponds to station 7 (N2) on the new IASLC lymph node map. For N3 disease, we compared the patients with supraclavicular zone involvement and those with either contralateral hilar or mediastinal zone involvement.

The survival time was defined from the date of surgery to the date of death by any cause or the last follow-up date. The median follow-up period for surviving patients was 45 months (range 0–133 months). The survival curves were estimated by the Kaplan-Meier method and the difference in survival was tested by the log-rank test. Multivariate analyses were performed using the Cox proportional hazards model. The following variables were analyzed for each pathological N stage: the location of involved zones, number of involved lymph nodes, stations and zones, and the presence of skip metastases. In N2 patients, "skip metastasis" was defined as any N2 node metastasis without N1 node involvement. In N3 patients, "skip metastasis" was defined as any N3 node metastasis without either N1 or N2 node involvement. The ISC of the IASLC suggested that nodal disease involvement could be subdivided into three distinct prognostic groups: N1a (single N1 zone), N1b (multiple N1 zones) or N2a (single N2 zone), and N2b (multiple N2 zones) [4]. Survival was also analyzed according to the proposed three prognostic subgroups. A p value of less than 0.05 was considered significant.

Table 1 Patient characteristics.

Characteristic	No. (%)
Gender	
▸ male/female	432 (67%)/215 (33%)
Extent of lung resection	
▸ lobectomy	601 (93%)
▸ bilobectomy	25 (4%)
▸ pneumonectomy	21 (3%)
Mode of lymph node dissection	
▸ sampling	34 (5%)
▸ SND	494 (76%)
▸ ERD	119 (18%)
Tumor side	
▸ left/right	256 (40%)/391 (60%)
Histology	
▸ adenocarcinoma	455 (70%)
▸ squamous cell carcinoma	143 (22%)
▸ large cell carcinoma	22 (3%)
▸ adenosquamous carcinoma	8 (1%)
▸ others	19 (3%)
Pathological stage	
▸ IA	223 (34%)
▸ IB	143 (22%)
▸ IIA	26 (4%)
▸ IIB	75 (12%)
▸ IIIA	100 (15%)
▸ IIIB	66 (10%)
▸ IV	14 (2%)
Pathological N status	
▸ N0	427 (66%)
▸ N1	91 (14%)
▸ N2	101 (16%)
▸ N3	28 (4%)

SND = systematic nodal dissection or sampling; ERD = cervical and/or bilateral mediastinal lymph node dissection

Results

There were 432 males and 215 females, ranging in age from 23 to 86 years with a median age of 65 years. The histological classification was adenocarcinoma in 455 patients, squamous cell carcinoma in 143, large cell carcinoma in 22, adenosquamous carcinoma in 8, and others in 19, respectively. The number of patients classified by pathological N status was 427 N0, 91 N1, 101 N2, and 28 N3, respectively. Patient characteristics are summarized in ○ **Table 1**.

The overall survival rate at 3 years and 5 years was 76% and 69%, respectively. The survival curves according to the pathological N status are shown in ○ **Fig. 1**. The overall 5-year survival rate/median survival time was 84%/not reached in N0 patients, 52%/62

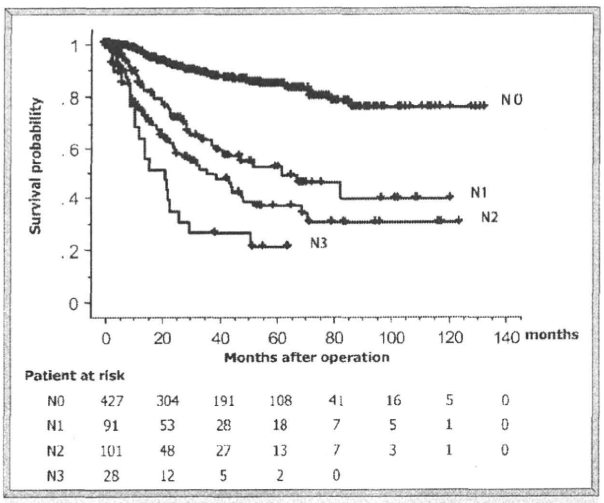

Fig. 1 Survival curves for patient subgroups as stratified by the N descriptors. The *p* value for the ordered log-rank test is less than 0.0001.

Table 2 Univariate analyses for prognostic factors in pathological N1 patients.

Variables	No.	MST (months)	*p* value
Number of involved N1 lymph nodes			
▸ single/multiple	54/37	82/40	0.2
Number of involved N1 stations			
▸ single/multiple	58/33	82/48	0.4
Number of involved N1 zones			
▸ single/multiple	70/21	82/48	0.5

MST = median survival time

Table 3 Univariate analyses for prognostic factors in pathological N2 patients.

Variables	No.	MST (months)	*p* value
Number of involved N2 lymph nodes			
▸ single/multiple	19/82	NR/31	0.1
Number of involved N2 stations			
▸ single/multiple	53/48	72/31	0.02
Number of involved N2 zones			
▸ single/multiple	69/32	44/34	0.5
Presence of skip metastases			
▸ yes/no	30/71	NR/26	0.004

MST = median survival time; NR = not reached

months (95% confidence interval [95% CI], 31–94 months) in N1, 36%/36 months (95% CI, 20–52 months) in N2, and 20%/22 months (95% CI, 10–34 months) in N3, respectively. The *p* value for the ordered log-rank test was less than 0.0001.

The median survival time was not reached in patients with single hilar zone involvement (n = 27), and was 84 months in those with single peripheral zone involvement (n = 43), respectively. There was no significant difference in survival between patients with single N1 zone disease ($p = 0.8$). The median survival time was 72 months in patients with single upper mediastinal zone involvement (n = 43), 17 months in those with single aortopulmonary zone involvement (n = 9), 26 months in those with single subcarinal zone involvement (n = 12), and 50 months in those with single lower mediastinal zone involvement (N = 5), respectively. No significant differences in survival were identified among patients with single N2 zone disease ($p = 0.4$). The median survival time was 23 months in N3 patients with single contralateral hilar/mediastinal zone involvement (n = 16) and 12 months in those with single supraclavicular zone involvement (n = 10), respectively. There was no significant difference in survival between patients with single N3 zone disease ($p = 0.1$). Therefore, no significant differences were observed in survival between locations of involved zones in each pathological N stage.

In N1 disease, patients with single N1 lymph node involvement, single N1 station involvement, and single N1 zone involvement tended to have a better prognosis than those with multiple N1 involvement. However, their differences were not statistically significant (**Table 2**). In N2 disease, the number of involved stations and the presence of skip metastases were significant prognostic factors in univariate analysis (**Table 3** and **Fig. 2 A–D**). Multivariate analysis showed that the presence of skip metastases alone was significant ($p = 0.005$). In almost all of the N3 patients, lymph nodes were involved in multiple lymph nodes (n = 27), stations (n = 27), and zones (n = 26). There was no patient with skip metastases in the group with N3 disease. The group of N3 disease patients was a homogeneous population with regard to the pattern of lymph node metastases.

The number of patients following the classification according to the proposed N subgroups was 70 N1a, 21 N1b, 69 N2a, and 32 N2b, respectively. The median survival time was 82 months (95% CI, 37–128 months) in N1a patients, 44 months (95% CI, 22–65 months) in N1b or N2a (48 months [95% CI, 32–63 months] in N1b and 44 months [95% CI, 1–87 months] in N2a), and 34 months (95% CI, 26–41 months) in N2b, respectively. The survival curves according to the proposed three prognostic subgroups are shown in **Fig. 3**. The *p* value for the ordered log-rank test was less than 0.0001.

Discussion

In the revision of the current TNM staging classification for lung cancer, the T and M descriptors were subclassified based on differences in survival. In contrast, there was no change in the N descriptors [12]. For over three decades, the N descriptors have remained unchanged. In this study, the survival curves also showed stepwise deterioration as the N stage increased. However, numerous researchers have reported that both N1 and N2 disease patients were heterogeneous populations [13–15]. The number of involved lymph nodes [16], stations [16–18], and the presence of skip metastases [19–21] have been described as prognostic factors. Using these prognostic factors, it may be possible to stratify patients in each N stage into several homogeneous subgroups. Therefore, we evaluated whether these factors have a prognostic impact in each pathological N stage.

We could not identify any prognostic factors in N1 patients. The sample size may have been too small to reveal statistically significant differences. In N2 patients, the number of involved stations and the presence of skip metastases were significant prognostic factors in univariate analysis. Only the presence of skip metastases was significant in multivariate analysis. The existence of lym-

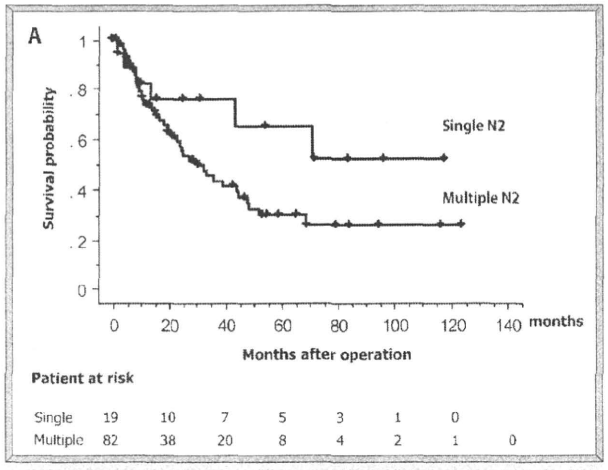

Fig. 2A Survival curves for N2 patient subgroups stratified according to the number of involved lymph nodes ($p = 0.1$).

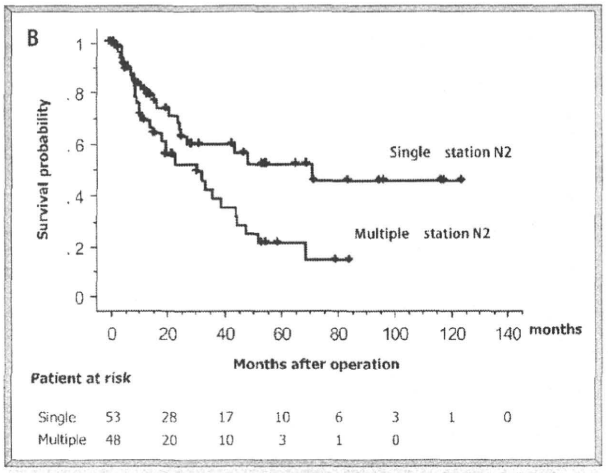

Fig. 2B Survival curves for N2 patient subgroups stratified according to the number of involved lymph node stations ($p = 0.02$).

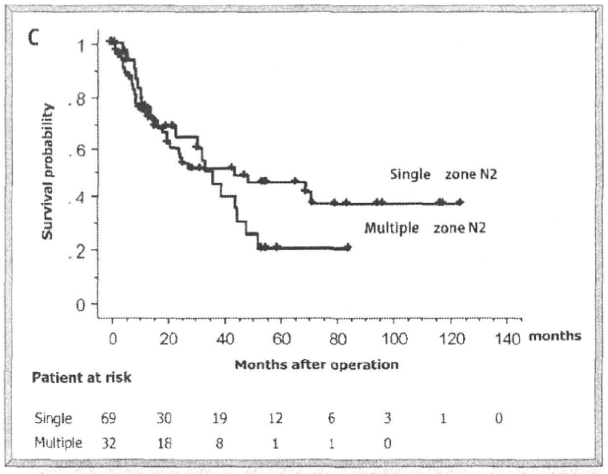

Fig. 2C Survival curves for N2 patient subgroups stratified according to the number of involved lymph node zones ($p = 0.4$).

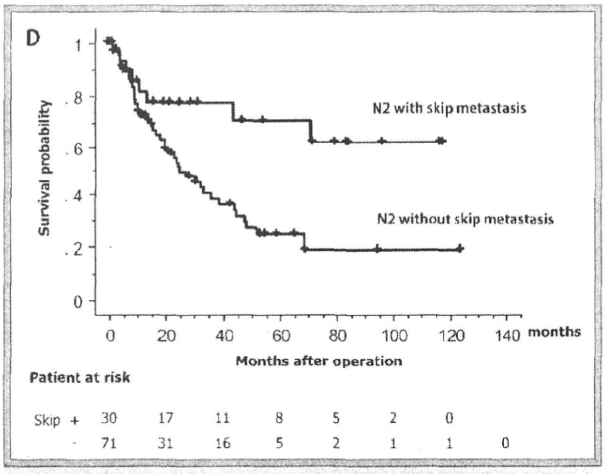

Fig. 2D Survival curves for N2 patient subgroups stratified according to the presence or absence of skip metastasis ($p = 0.004$).

phatic channels going directly to the mediastinum was suggested to be a possible mechanism for skip metastasis [22]. If this is true, N2 disease with skip metastasis may be equal to N1 disease in terms of the extent of lymph node metastases. In the present study, the survival curve of N2 patients with skip metastasis was similar to that of N1 patients. The ISC of the IASLC evaluated patient survival based on the presence or absence of skip metastases, but no meaningful difference was identified [4]. The presence of skip metastases can be found after SND; however, we were unable to accurately identify skip metastases after sampling. The prognostic impact of skip metastases should be validated prospectively in a larger number of patients who have undergone SND. In the present series, 119 (18%) of 647 patients underwent ERD, which is an extension of the dissected area to the bilateral and/or cervical mediastinum through a median sternotomy. Although there seems to be little survival benefit of ERD for pathologic N3 patients, at least ERD would result in accurate lymph node staging by reducing the possibility of stage migration. Because there is little prognostic data on patients with surgically resected N3 disease [9,10], we believe that this study is valuable to clarify the nature of N3 disease. In the present study, almost all N3 patients had lymph node involvement in multiple lymph nodes, stations and zones, and no N3 patients had skip metastases. We concluded that N3 disease patients were a population with a homogeneously poor prognosis with regard to the extent and pattern of lymph node metastasis, even if completely dissected.

We validated the new IASLC map from the point of postoperative prognosis. Because survival differences between different zones were not statistically significant within each pathological N stage, the proposed IASLC map was valid for prognostic stratification. The ISC of the IASLC identified three different prognostic groups according to the number of involved zones: single N1 zone (N1a) with a 5-year survival rate of 48%; multiple N1 zones (N1b) or

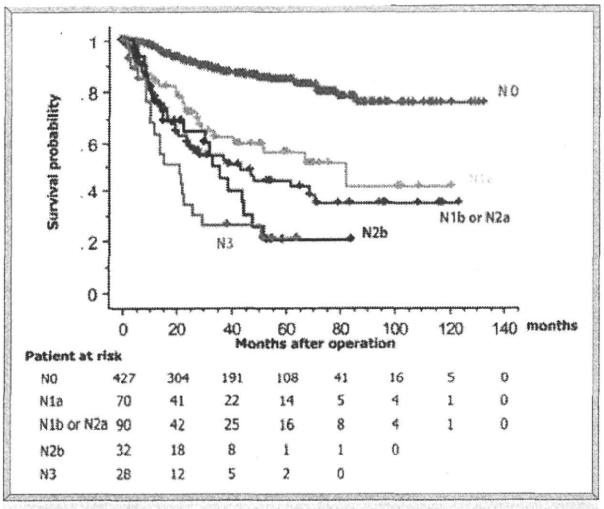

Fig. 3 Survival curves for patient subgroups stratified by N status and the number of involved zones. The *p* value for the ordered log-rank test is less than 0.0001.

single N2 zone (N2a) with 5-year survival rates of 35% and 34%; and multiple N2 zones (N2b) with a 5-year survival rate of 20%. The survival differences between these groups were statistically significant [4]. In the present study, a similar trend for this nodal paradigm was observed. The proposed subdivision of the current N descriptors is worth validating prospectively in larger numbers of patients.

For complete resection of NSCLC, SND or lobe-specific SND is recommended [23]. Technically, both procedures mean en bloc removal of lymph nodes and the surrounding mediastinal fat tissue in each nodal zone [23]. It is almost impossible to classify lymph nodes accurately according to the station numbers after SND or lobe-specific SND. Therefore, labeling lymph nodes according to "nodal zones" is simpler and more useful than according to station numbers in a clinical setting.

There were some limitations associated with the present study. First, this study was a retrospective analysis based on a relatively small number of patients in a single institution. Second, there were some discrepancies in the anatomical definitions between the Naruke map and the new IASLC map. It was impossible to completely translate the nodal stations on the Naruke map into nodal zones on the IASLC map. To overcome these problems, a future prospective validation study for the N staging system according to the new IASLC map in a large number of patients is required.

In conclusion, the proposed IASLC map offers a valid prognostic stratification. The prognostic impact of the presence of skip metastases in N2 disease should therefore be taken into consideration when carrying out the forthcoming revision of the TNM staging system.

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Clinical Trial Note

A Phase III Randomized Trial of Lobectomy Versus Limited Resection for Small-sized Peripheral Non-small Cell Lung Cancer (JCOG0802/WJOG4607L)

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A Phase III study was started in Japan to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral non-small cell lung cancer, excluding radiologically determined non-invasive cancer. This study began in August 2009, and a total of 1100 patients will be accrued from 71 institutions within 3 years. The primary endpoint is overall survival. The secondary endpoints are post-operative respiratory function, relapse-free survival, proportion of local recurrence, adverse events, proportion of patients who complete segmentectomy, duration of hospitalization, duration of chest tube placement, operation time, blood loss and number of autosutures used. This study is one of the first intergroup studies in Japan between the Japan Clinical Oncology Group and the West Japan Oncology Group.

Key words: non-small cell lung carcinoma – thoracic surgery – pneumonectomy – clinical trial – Phase III

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide for both men and women (1). Among patients who underwent surgery for this condition, 36.5% were diagnosed as clinical stage IA (2). Lobectomy with lymph node dissection remains a standard initial therapy even in clinical stage IA non-small cell lung cancer (NSCLC) (3). The Lung Cancer Study Group (LCSG) performed a pivotal study comparing limited resection (segment or wedge) with lobectomy for clinical stage IA NSCLC and found inferior overall survival and three times the local recurrence rate in the limited resection arm (4). However, the LCSG study suffered from issues such as (i) eligibility of tumors with diameter >2 cm; (ii) wedge resection without lymph node dissection performed as limited resection; and (iii) additional eligibility of non-peripheral NSCLC, causing higher local recurrence rates in the limited resection arm. Therefore, we have conducted a Phase III trial to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral NSCLC. Patients with radiologically determined non-invasive lung cancer are excluded, because in these cases, there is a minimal likelihood of having lymph node metastasis and therefore lobectomy with nodal resection is considered to be overly invasive (5).

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) and the West Japan Oncology Group (WJOG) approved this protocol in January 2009 and

the present study was activated in August 2009. This trial was registered at the UMIN Clinical Trials Registry as UMIN000001272 [http://www.umin.ac.jp/ctr/index.htm].

PROTOCOL DIGEST OF THE JCOG 0802/ WJOG4607L

Objectives

The aim of this study is to evaluate the non-inferiority in overall survival of segmentectomy compared with lobectomy in patients with small-sized (diameter $\leq$2 cm) peripheral NSCLC, excluding radiologically determined non-invasive cancer.

Study Setting

The study was a multi-institutional randomized Phase III study.

Resources

The study was supported in part by Grants-in-Aid for Cancer Research (20S-2, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is overall survival in all eligible patients. Overall survival is defined as days from randomization to death from any cause, and it was censored at the last day when the patient was alive. The secondary endpoints are post-operative respiratory function, relapse-free survival, proportion of local recurrence, adverse events, proportion of patients who successfully undergo segmentectomy, duration of hospitalization, duration of chest tube placement, operation time, blood loss and number of auto-sutures used.

Relapse-free survival is defined as days from randomization to relapse or death from any cause, and it was censored at the latest day when the patient was alive without any evidence of relapse. Local recurrence is defined as tumor recurrence in the ipsilateral thorax, which includes the resection margin of the lung or bronchus, hilar lymph nodes, mediastinal lymph nodes and malignant pleural effusion. As for post-operative respiratory function, the difference between baseline respiratory function and that assessed 6 and 12 months after surgery is evaluated.

Eligibility Criteria

Two-step registration is applied because the imaging eligibility criteria are complicated and histological type of the tumor is to be confirmed intra-operatively in most patients.

Inclusion Criteria for the Primary Registration

For inclusion in the primary registration, patients are required to fulfill all of the following pre-operative criteria.

(i) Contrast-enhanced thoracic computed tomography (CT) fulfills all of the following conditions: (a) single tumor, (b) NSCLC suspected, (c) center of tumor located in the outer third of the lung field, (d) tumor not located at middle lobe, and (e) no lymph node metastasis. (ii) Thin-section CT fulfills both of the following conditions: (a) maximum tumor diameter of $\leq$2 cm and (b) not 'radiologically determined non-invasive cancer' (i.e. the proportion of the maximum diameter of the tumor itself to consolidation is >25%). (iii) Patient age 20–79 years old. (iv) No prior ipsilateral thoracotomy (prior diagnostic thoracoscopy is allowed). (v) No prior chemotherapy or radiation therapy for any malignant diseases. (vi) Expected post-operative FEV1.0 $\geq$ 800 ml and $PaO_2 \geq 65$ torr. (vii) Performance status of 0 or 1. (viii) Sufficient organ function. (ix) Written informed consent.

Exclusion Criteria for the Primary Registration

Patients are excluded from the primary registration pre-operatively if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within the past 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) interstitial pneumonitis, pulmonary fibrosis, or severe pulmonary emphysema; (v) psychosis; (vi) systemic steroidal medication; (vii) uncontrollable diabetes mellitus; (viii) uncontrollable hypertension; (ix) history of severe heart disease, heart failure, myocardial infarction within the past 6 months or attack of angina pectoris within the past 6 months.

Inclusion Criteria for the Secondary Registration

After the confirmation of the inclusion and exclusion criteria for the primary registration, patients are required to fulfill all of the following criteria for inclusion in the secondary registration.

Pre-operative criteria: (i) sufficient organ function and (ii) pre-operative body temperature of $\leq$38°C.

Intra-operative criteria: (i) date of surgery within 28 days of initial registration; (ii) histologically confirmed adenocarcinoma, adenosquamous carcinoma, large cell carcinoma or NSCLC (detailed category unknown); (iii) neither malignant pleural effusion nor pleural dissemination; and (iv) technically possible to perform lobectomy, segmentectomy and nodal dissection.

Randomization

After the confirmation of the inclusion criteria for the secondary registration, registration is made by telephone or fax to the JCOG Data Center or WJOG Data Center. Patients are randomized in each group, JCOG or WJOG, by minimization method balancing the arms with institution, histologic type