Table 4. Univariate Analyses Using Logistic Regression Model

Variable	No. of Patents	Relative Risk	95% Confidence Interval	*p* Value
Maximum tumor diameter	118	1.063	1.005–1.124	.03
Margin distance	118	0.840	0.772–0.915	< 0.0001
Location				
Difficult to resect region	29	1.000		
Easily resectable region	89	0.149	0.058–0.038	< 0.0001
Stapler				
Complete	85	1.000		
Partial	18	2.542	0.900–7.175	0.078
Not used	15	16.52	3.465–78.77	0.0004
Thoracotomy				
Open	72	1.000		
Video-assisted thoracic surgery	46	0.466	0.211–1.028	0.058

Further Analysis Using Maximum Tumor Diameter and Margin Distance

We conducted a further analysis using the two independent factors in order to identify the threshold distance. The ratio of margin distance to maximum tumor diameter in the negative group was 0.9 ± 0.6 (mean ± standard deviation) as compared with 0.3 ± 0.3 in the positive group ($p < 0.0001$). In every positive case, the sum of margin distance divided by maximum tumor diameter was less than 1 (Fig 2). Furthermore, there was no malignant surgical margin found among the seven lesions that had a margin distance greater than 2 cm, which is generally believed to be a safe margin distance [17].

Comment

One of the most serious problems of a limited resection in cases of NSCLC is a high rate of surgical margin relapse [1–7], whereas the Lung Cancer Study Group has suggested a diminished survival rate among patients who undergo resection less than a lobectomy. Therefore, an appropriate technique must be applied to avoid such relapse. Postoperative radiation therapy can reduce the risk of local recurrence [9] and its role after wedge resection, which is currently being investigated in a prospective study [18]. Brachytherapy has also been attempted during operations [19] with preliminary results revealing no instances of significant radiation pneumonitis or local recurrence. Although these treatments may reduce the risk of margin relapse, an adequate margin distance remains the strongest defense.

Table 5. Multivariable Analyses Using Logistic Regression Model

Variable	Relative Risk	95% Confidence Interval	*p* Value
Maximum diameter	1.096	1.602–1.130	0.006
Margin distance	0.853	0.798–0.908	0.003
Location			
Difficult to resect region	1.000		
Easily resectable region	0.820	0.187–1.320	0.754
Stapler			
Complete	1.000		
Partial	2.153	0.601–7.717	0.239
Not used	7.972	1.257–50.54	0.027

There is no clear information regarding what constitutes an adequate margin distance when a wedge resection is performed. Allen and Parirolero [20] recommended a margin of 1 cm in cases with a malignant nodule, whereas it is commented that a margin of 1.5 cm in a deflated lung and 2 cm in an inflated one are generally acceptable in a textbook of thoracic surgery [17]. However, scant data have been reported regarding the size of margins obtained. As described in our previous study [14], a margin relapse can occur even if a wedge-resected NSCLC has a margin of more than 1 cm, or 1.5 cm in a deflated lung, as well as malignant negative histology findings. Furthermore, it has been found that margin relapse occurs only in cases of a cytologically malignant positive margin [12–15]. In addition, another disadvantage of wedge resection is blindness in relation to the segmental and interlobar lymph nodes.

Attaining a malignant negative surgical margin is very important to prevent margin relapse, and Lewis and colleagues reported [16] that both size and location of the tumor are directly related to the margin obtained. In the present study, a univariate analysis revealed a high number of lesions that were difficult to resect and a shorter margin distance in the positive group. In addition, maximum tumor diameter and type of stapling used had an influence on the malignant status of the surgical margin. Although the performance of a thoracotomy was not statistically significant, the average distance from the margin to the tumor in thoracotomy cases was smaller than that in video-assisted thoracic surgery cases. This was likely because of the selection bias in both thoracotomy and video-assisted thoracic surgery cases, as well as technical limitations. When a multivariate analysis was carried out, both margin distance and maximum tumor diameter were independent variables. Therefore, it is important to obtain as great a margin distance from the

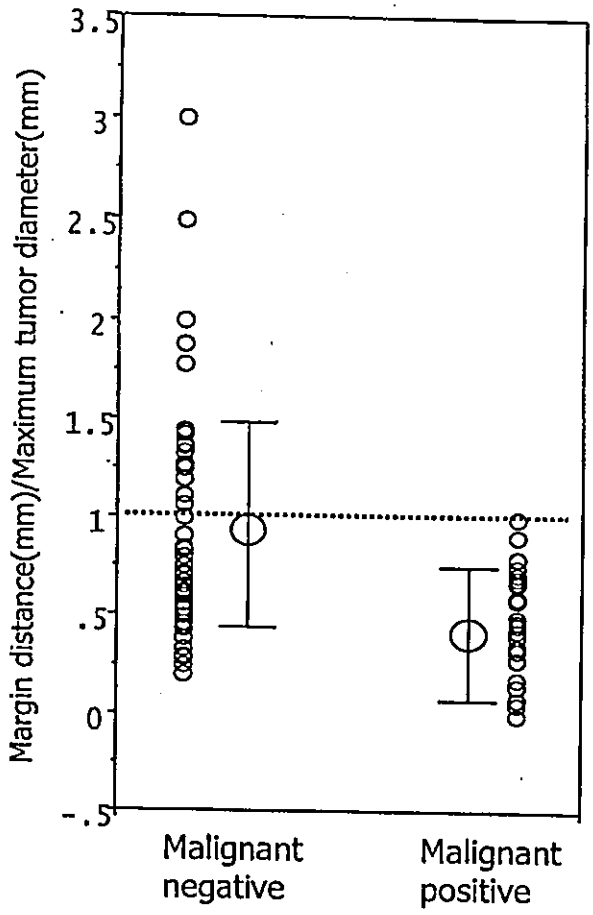

Fig 2. Margin distance from tumor compared with the maximum tumor diameter according to malignant status at surgical margin of excised tumor. The margin distance from the tumor as compared with the maximum tumor diameter was 0.9 ± 0.6 cm (mean ± standard deviation) in the negative group and 0.3 ± 0.3 cm (mean ± standard deviation) in the positive group ($p < 0.0001$). In every positive case, the sum of the margin distance from the tumor divided by the maximum tumor diameter was less than 1.

surgical margin to the tumor as possible regardless of tumor size.

The margin distance from the tumor can also restricted by anatomical issues. For example, removal of a tumor with a 1.0 or 1.5 cm margin that is located in a difficult region to resect may be complicated, as the margin distance obtained is relative to tumor size. If the removed tumor is 0.5 cm in size, then a 1.5 cm margin may be sufficient, whereas the same size margin with a tumor 3 cm in size would likely be insufficient. Therefore, analysis using the two independent variables to determine the ratio of the distance from the surgical margin to the tumor diameter is mandated.

The rate of malignant negative margin occurrence was 100% when a tumor was resected with a greater margin distance from the surgical margin to the tumor than the maximum tumor diameter. That is, the distance threshold of the malignant-safe margin was equal to the maximum tumor diameter. The run-across method can reveal the malignant status of a surgical margin [12, 14]; therefore, using this technique during surgery is strongly recommended. However, a margin distance of greater than maximum tumor diameter in a deflated lung may be a good measurement to insure a malignant-safe margin, if the run-across method cannot be utilized.

There were some limitations to this study. The number of high-risk patients was 41 (39%), whereas 77 (61%) had a normal lung. There may have been patho-anatomical differences between these two groups of patients, but an insufficient margin distance was permitted because a complete lobectomy for NSCLC was utilized in cases of nondiagnosed pulmonary nodules. Thus, the distance threshold for a malignant negative surgical margin was able to be determined.

In conclusion, a multicenter, prospective study revealed that when an NSCLC tumor was excised, malignant positive margins were not found when the margin distance was greater than the maximum tumor diameter. This amount of distance is warranted to prevent margin relapse in cases of NSCLC excision.

We appreciate the cooperation of Satoru Yamamoto, MD, of the Division of Clinical Pathology at National Kinki-Chuo Hospital for Chest Diseases; cytopathologist, Taikichi Hashimoto at Toneyama National Hospital for cytologic diagnosis of the harvested materials; and the cooperation of the members of Thoracic Surgery Study Group of Osaka University: Masahito Ikeda, MD, at Otemae Hospital; Kiyohiko Fijiwara, MD, and Masayoshi Inoue, MD, at Habikino Hospital; Shin-Ichi Takeda, MD, Yoshitomo Okumura, MD, and Teruaki Asada at National Toneyama Hospital; and Hirohisa Hirabayashi, MD, at Osaka University Graduate School of Medicine.

References

1. Kodama K, Doi O, Higashiyama M, Yokouchi H. Intentional limited resection for selected patients with T1N0M0 non-small-cell lung cancer. J Thorac Cardiovasc Surg 1997;114: 347–53.
2. Yoshikawa K, Tsubota N, Kodama K, Ayabe H, Taki T, Mori T. Prospective study of extended segmentectomy for small lung tumors: the final report. Ann Thorac Surg 2002;73: 1055–8.
3. Yamato Y, Tsuchida M, Watanabe T, et al. Early results of a prospective study of limited resection for bronchioloalveolar adenocarcinoma of the lung. Ann Thorac Surg 2001;71:971–4.
4. Watanabe S, Watanabe T, Arai K, Kasai T, Haratake J, Urayama H. Results of wedge resection for focal bronchioloalveolar carcinoma showing pure ground-glass attenuation on computed tomography. Ann Thorac Surg 2002;73: 1071–5.
5. Miller JI, Hatcher CR Jr. Limited resection of bronchogenic carcinoma in the patient with marked impairment of pulmonary function. Ann Thorac Surg 1987;44:340–3.
6. Yano T, Yokoyama H, Yoshino I, Takamok K, Asoh H, Hata K, et al. Results of a limited resection for compromised or poor-risk patients with clinical stage I non-small cell carcinoma of the lung. J Am Coll Surg 1995;181:33–7.
7. Crabbe MM, Patrissi GA, Fontenelle LJ. Minimal resection for bronchogenic carcinoma: should it be standard therapy? Chest 1989;95:968–71.
8. Shennib HAF, Landreaneau RJ, Mulder DS, Mark M. Video-

assisted thoracoscopic wedge resection of T1 lung cancer in high risk patients. Ann Surg 1993;218:555–60.
9. Martini N, Bains MS, Burt ME, et al. Incidence of local recurrence and second primary tumors in resected stage I lung cancer. J Thorac Cardiovasc Surg 1995;109:120–9.
10. Lung Cancer Study Group prepared by Ginsberg RJ, Robinstein LV. Randomized trial of lobectomy versus limited resection for T1N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615–23.
11. Landreneau RJ, Sugrebaker JS, Mack MJ, et al. Wedge resection versus lovectomy for stage I (T1 N0 M0) non-small cell lung cancer. J Thorac Cardiovasc Surg 1997;113:691–700.
12. Sawabata N, Mori T, Iuchi K, Maeda H, Ohta M, Kuwahara O. Cytologic examination of surgical margin of excised malignant pulmonary tumor: methods and early results. J Thorac Cardiovasc Surg 1999;117:618–9.
13. Higashiyana M, Kodama K, Yokouchi H, Takami K, Nakayama T, Horii T. A novel test of the surgical margin in patients with lung cancer undergoing limited surgery: lavage cytology technique. J Thorac Cardiovasc Surg 2000;120:412–3.
14. Sawabata N, Matsumura A, Ohta M, et al. Cytologically malignant-positive margin of wedge resected c-stage I non-small cell lung cancer. Ann Thorac Surg 2002;74:1953–7.
15. Higashiyana M, Kodama K, Takami K, Higashi N, Nahayanma T, Yokouchi H. Intraoperative lavage cytologic analysis of surgical margins in patients undergoing limited surgery of lung cancer. J Thorac Cardiovasc Surg 2003;125:101–7.
16. Lewis RJ, Caccavale RJ, Sisler GE, Mackenzie JW. Video-assisted thoracic surgical resection of malignant lung tumors. J Thorac Cardiovasc Surg 1992;104:1679–87.
17. Fell SC, Kirby TJ. Limited pulmonary resection. Thoracic surgery, 2nd ed. New York: Churchill Livingstone. 2002;36:1002–4.
18. Krasna MJ, Reed CE, Nugent WC, et al. Lung cancer staging and treatment in multidisciplinary trials: cancer and leukemia group B cooperative group approach. Ann Thorac Surg 1999;68:201–7.
19. D'Ammato TA, Galloway M, Szydlowski G, Chen A, Landreneau RJ. Intraoperative brachytherapy following thoracoscopic wedge resection for stage I lung cancer. Chest 1998;114:1112–5.
20. Allen MS, Parirolero PC. Inadequacy, mortality, and thoracoscopy. Ann Thorac Surg 1995;59:6.

Notice From the American Board of Thoracic Surgery

The 2004 Part I (written) examination will be held at the Sofitel O'Hare Hotel, Rosemont, Chicago, IL, on November 21, 2004. The closing date for registration is August 1, 2004. Those wishing to be considered for examination must request an application because it is not automatically sent.

To be admissible to the Part II (oral) examination, a candidate must have successfully completed the Part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the Board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201; telephone: (847) 475-1520; fax: (847) 475-6240; e-mail: info@abts.org.

原著

同側肺内転移を伴った原発性非小細胞肺癌手術例の予後因子と再発形式に関する検討

福原謙二郎*, 中川 勝裕, 塩野 裕之, 門田 嘉久
出口 寛, 安光 勉

要 旨

同側肺内転移を伴った肺癌切除例（以下pm（+）例）の予後推定に役立てるべく，当科での89例（pm1：65，pm2：24）につき，種々の臨床因子をretrospectiveに検討した．pm1，2例の3，5年生存率は各々28.9%，14.2%と26.6%，21.3%で両群間に有意差を認めなかった．pm（+）例を生存期間3年以上群（n＝22）と未満群（n＝67）にわけ比較したところ，CEA値，p-n因子について両群間に有意差を認めた．多変量解析でもp-n因子（p＝0.020），CEA値（p＝0.049）が独立予後因子であった．pm（+）例のうち，CEA値正常かつp-n 0例（n＝20）の5生率は50.7%で，IB期，IIA期手術例（同：53.3%，47.1%）と同程度で，IIIB期手術例（同：9.4%）より有意に予後良好であった．また，89例中61例で術後再発し，うち53例は遠隔転移で，そのうち肺内転移が56.6%（同側：対側＝13.3：86.7）と最多であった．以上より，pm（+）肺癌においては，CEA値，p-n因子が有意な独立予後因子で，肺内転移の存在のみでIIIB期以上とするのには問題があると考えられた．

索引用語：pm（+）肺癌，予後因子，再発形式
lung cancer with intrapulmonary metastasis, prognostic factor, patterns of recurrence

はじめに

取り扱い規約上IIIB期以上に分類される，肺内転移を伴った肺癌症例（以下pm（+）肺癌）の中には比較的予後良好な症例も散見される．今回，我々はpm（+）肺癌切除例の予後推定に役立てるべく種々の臨床因子を検討したので報告する．

対象と方法

対象は，1998年12月までの当科における非小細胞肺癌切除例1544例中，病理組織学的に同側肺内転移を認めた89例で，pm1が65例，pm2が24例であった．生存率は全死因を死亡としてKaplan-Meier法で算出し，有意差検定にはlog-rank testを用いた．諸因子間の独立性検定にはχ^2検定を用い，予後因子の多変量解析にはCoxの比例ハザードモデル(ステップワイズ法)を用いた．有意水準はいずれもp＜0.05とした．

当院における，同一組織型における多発肺癌の診断基準は，異なった肺区域に存在し，且つ各々の病巣でcarcinoma *in situ* からの発生が認められるものとしている．また，①細胞亜型，細胞形態の点で各病巣とも異なる，②中心部瘢痕の形成，胸膜陥凹の有無の程度，③各病巣が非進行癌で，相互のリンパ経路にない場合は各々の病巣を独立したものとする，といった点を考慮し，この基準にあわない同一組織型肺癌を肺内転移と診断した．

CEAの測定はRIA法を用い，5ng/ml以上を異常とした．

なお，本検討はretrospectiveな検討であり，pm2例は全例同側単発例で，かつ結果的に術前CTまたは術中触診にて腫瘤の存在を同定し得た症例のみが対象となっている．また，pm2症例に対しては，基本的には

大阪府立呼吸器・アレルギー医療センター
（大阪府立羽曳野病院 外科）
*現りんくう総合医療センター・市立泉佐野病院 外科
原稿受付 2003年4月18日
原稿採択 2003年7月18日

機能温存のために葉切除＋部分切除を施行したが，二葉切除，全摘となった症例もあった．

結　果

pm（+）肺癌手術例において，pm1，2の別に予後をみた（Fig. 1）．pm1，pm2症例の3生率，5生率はそれぞれ28.9%，14.2%と26.6%，21.3%で両群間に有意差は認められなかった．

pm1，2の別では予後に差がなかったので，pm（+）肺癌手術例を生存期間で3年以上群と3年未満群にわけ，種々の因子を比較した（Table 1）．CEA値（平均値）は3年以上群が1.78ng/mlと3年未満群の26.64ng/mlに比し有意に低値で，病理病期n因子は3年以上群で有意にn0の割合が高かった．年齢，性，臨床病期N因子，組織型，リンパ管侵襲陽性率，静脈侵襲陽性率，腫瘍最大径，pm1，2の別，術後補助療法の有無，術式の各因子については二群間に有意差を認めなかった．多変量解析でも，CEA値，病理病期n因子が独立的予後因子であった（Table 2）．そこで，pm（+）肺癌切除例のうち，p-n0かつCEA値正常症例（pm1：16例，pm2：4例）の予後をみると，かかる症例の5生率は50.7%で，IB期，IIA期手術例の5生率53.3%，47.1%と同程度であった．また，pm(+)肺癌を除くIIIB期手術例（5生率：9.4%）より有意に予後良好であった（Fig. 2）．

次に，pm（+）肺癌における術式別生存曲線をみた（Fig. 3）．葉切除（葉切除＋部分切除または二葉切除）症例と全摘症例との間で，予後に有意差を認めなかった．

pm（+）肺癌における術式別のpmの内訳と再発形式をみた（Table 3）．pm2ゆえに葉切除＋部分切除または二葉切除を施行した症例は12例，全摘を施行した症例は12例であった．術後再発は89例中61例で認められ，うち53例は遠隔転移であった．いずれの術式にお

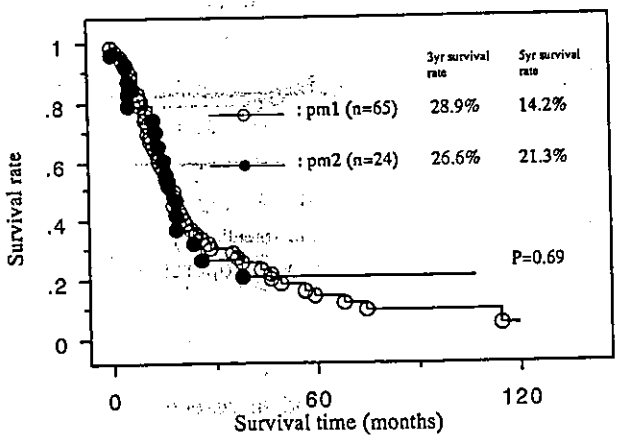

Fig. 1 Survival rates of patients with intrapulmonary metastases (pm).

Table 2 Multivariate prognostic factor analysis.

Variables	Hazard ratio (95% C.I.)	P-value
Serum CEA :normal vs high	1.772 (1.001-3.140)	0.0499
p-n factor :n0 vs n1,2	2.182 (1.130-4.215)	0.0201

Table 1 Distribution of clinical features according to postoperative survival years.

	≧3years (n=22)	<3years (n=67)	P-value
Age (mean)	46-77(63.9)	37-79 (61.0)	0.556
Gender (M:F)	17:5	49:18	0.945
Serum CEA (ng/ml)	1.78±0.46	26.64±16.65	0.002
c-N factor (N0:N1+N2)	15:7	35:32	0.288
Histology (Ad:Sq:La)	17:5:0	45:17:5	0.392
p-n factor (n0:n1+n2)	12:10	15:52	0.007
Positive rate of invasion of lymphatic vessel	87.5%	84.5%	0.999
Positive rate of vascular invasion	68.2%	82.8%	0.228
Size(mm) (mean)	11-74 (38.1)	17-130 (45.6)	0.243
pm1:pm2	17:5	48:19	0.784
Adj.therapy (done:none)	13:9	43:24	0.800
operative method (lob.:bilob.:pn.)	12:4:6	40:7:20	0.633

Ad: adeno ca.; Sq: squamous ca.; La: large cell ca.; pm: intrapulmonary metastasis (1: same lobe with primary; 2: different lobe from primary); Adj.: adjuvant; lob.: lobectomy(+ partial resection); bilob.: bilobectomy; pn.: pneumonectomy

いても，遠隔転移の約6割が肺内転移であった．術式別に，術後遠隔転移としての肺内転移の発生側をみると(Table 4)，片肺全摘術後は無論全例が対側であるが，同側残存肺再発が起こりうる葉切除術後も21例中17例（81.0%）で両側を含めた対側肺内転移を認めた．

考　察

1997年UICCにより肺癌病期分類が改訂され，原発巣と同一葉内の肺内転移（pm1）は一律にT4に，同側，対側を問わず他肺葉にあるとき（pm2）はM1に分類されることとなった[1]．これにより，肺内転移を伴う症例の病期はすべて，一般的に手術による治癒が困難とみなされるIII B期以上に分類されることになるが，実際その切除症例の中に予後良好な症例が少なからず存在することが知られている[2,3]．今回我々はpm(+)肺癌切除例の予後推定に役立てるべく種々の臨床因子を検討した．

まず，今回のような肺内転移症例を検討するにあたっては，多発癌との鑑別が問題になる．実際，本検討例の中にも多発癌が混入し，そのために転移癌の予後が良くなっている可能性もある．多発癌と転移癌の鑑別の精度を上げるために，従来の病理形態学的鑑別法に加え，遺伝子学的手法[4]や免疫組織化学的手法[5]の導入の試みが報告されているが，術前に結果が明らかとなるわけでなく，p53 mutation[4]等も癌細胞に必ず認められるものではないため，その意義を確定し，臨

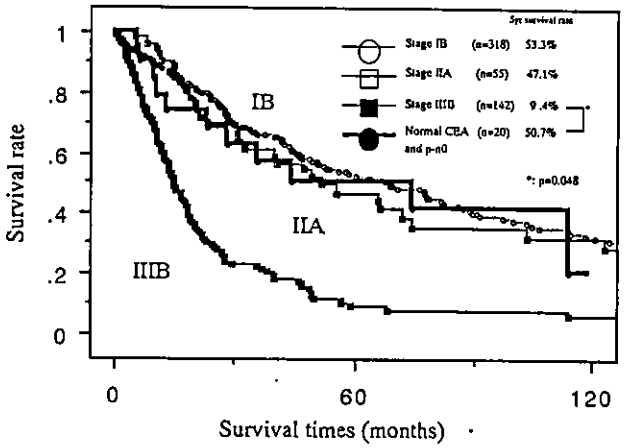

Fig. 2 Survival rates of pm patients with normal CEA and p-n0. (A comparison with p-stage I B, II A and III B patients)

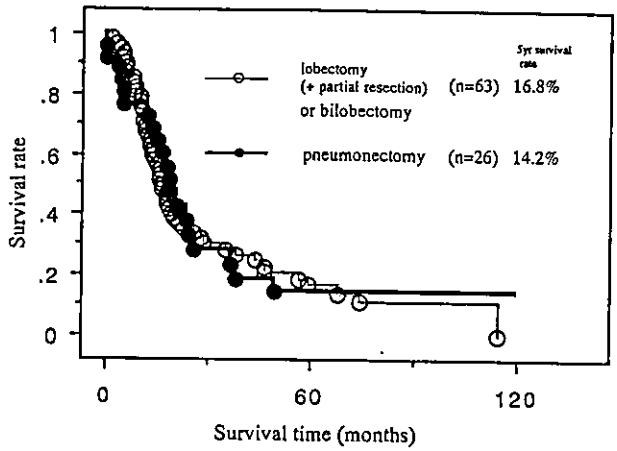

Fig. 3 Survival rates by type of operative method in patients with pm.

Table 3 Location of pm and patterns of recurrence by type of operative method in resected lung cancer patients with pm.

Operation	Location of pm		Recurrence (+)		
	pm1	pm2	(n=)	Local	Distant (overlapping)
Lobectomy(+ partial resection) or bilobectomy (n=63)	51	12	43 (68.3%)	6	37; pm 21, bone 11, brain 6, lymph node 4, liver.1, kidney 1
Pneumonectomy (n=26)	14	12	18 (69.2%)	2	16; pm 9, brain 4, bone 3, liver 1, lymph node 1
Total (n=89)	65	24	61 (68.5%)	8	53

Table 4 Sites of newly recognized pm by type of operative method in resected lung cancer patients with pm.

Operation	Newly recognized pm after operation	
	(n=) (%)	Sites Ipsi. : Contra. : Bi.
Lobectomy(+ partial resection) or bilobectomy (n=63)	(21/63) (33.3%)	4:9:8
Pneumonectomy (n=26)	(9/26) (34.6%)	0:9:0
Total (n=89)	30	4:18:8

Ipsi.: ipsilateral, Contra.: contralateral, Bi.: bilateral.

床応用するためにはさらなる検討が必要と考えられる．pmか多発かの正確な診断が困難である現時点においては，十分な議論の上，多発肺癌を定義し，残りをpmとするのが実際的であると考えた．

今回の検討では，pm1例とpm2例の予後に有意差を認めなかった．これまでの諸家の検討では，我々と同様に両群間に差がなかったとする報告[6-8]と，pm2例の予後の方が不良であったとする報告[9,10]がある．この差がどのようにして生じたのかは明らかでないが，完全に否定しえない多発癌症例の混入や，各検討での限られた症例数も一因と考えられた．また，同じpm2の中でも，同側と対側では病的意義が異なる可能性もある[10]．

また，今回の検討により，術前CEA値とp-n因子の両因子が単変量，多変量の両解析にてpm（+）肺癌手術例の有意な予後因子であることが明らかとなった．n因子についてはこれまでもpm（+）肺癌において，重要な予後因子であると報告されてきた[2,3]．一方，CEA値については，臨床病期I期症例においては予後因子となることが報告されている[11,12]が，pm（+）肺癌のような進行癌ではこれまで詳細な検討がなされていなかった．本検討において，IIIB，IV期に分類されるp-n0，CEA値正常のpm（+）肺癌手術例の5生率はIB，IIA期手術例と同程度であったことからも，今後はp-n因子や，術前CEA値を考慮に入れたstagingを検討する余地もあると考えられた．ただし，本検討はretrospectiveな検討であり，pm 2例は全例同側単発例で，かつ結果的に術前CTまたは術中触診にて腫瘤の存在を同定し得た症例のみが対象となっているため，手術適応の決定には，対側例や多発例を含めた検討を要すると考えられた．

pm（+）肺癌においては術式別予後に有意差はなく，術後再発の大部分が遠隔転移であり，その約半数が肺内転移であった．手術中に残存肺を入念に触診し，腫瘤のないことを確認しているが，触知できないpmが存在した可能性は否定できない．また，pm 2症例に対しては，基本的には機能温存のために葉切除＋部分切除を施行したが，二葉切除，全摘となった症例もあった．同側残存肺再発が起こりうる葉切除術後でも，その大部分が両側を含めた対側肺内転移であったことから，肺内転移の存在ゆえの片肺全摘は再発予防には有効ではなく，術後補助療法を行うため，またPSの維持のため可及的に避けた方がよいと思われた．

結　語

1．pm（+）肺癌において，CEA値と病理病期n因子が有意な独立予後因子で，肺内転移の存在のみでIIIB期以上とするのには問題があると考えられた．2．pm（+）肺癌においては術式別予後に有意差はなく，その再発形式の大部分が同側残存肺内転移以外の遠隔転移であったことから，全身に対する有効な補助療法の確立が望まれる．

文　献

1) UICC: TNM classification of malignant tumors. 5th ed. Wiley-Liss, New York, 1997.
2) 佐藤雅美，斉藤泰紀，薄田勝男，他：肺癌切除例におけるpm症例の検討―特に多発癌の可能性の観点から―．肺癌 **30**: 913-919, 1990.
3) Shimizu N, Ando A, Date H, et al: Prognosis of undetected intrapulmonary metastases in resected lung cancer. Cancer **71**: 3868-3872, 1993.
4) Matsuzoe D, Hideshima T, Ohshima K, et al: Discrimination of double primary lung cancer from intrapulmonary metastasis by p53 gene mutation. Br J Cancer **79**: 1549-1552, 1999.
5) 細田　裕，和泉宏幸，新　謙一，他：同時性多発非小細胞肺癌症例の臨床病理学的検討．肺癌 **42**: 93-97, 2002.
6) Koike T, Terashima M, Takizawa T, et al: Results of surgery for primary lung cancer based on the new international staging system. Jpn J Thorac Cardiovasc Surg **47**: 313-317, 1999.
7) Okada M, Tsubota N, Yoshimura M, et al: Evaluation of TMN classification for lung carcinoma with ipsilateral intrapulmonary metastasis. Ann Thorac Surg **68**: 326-

331, 1999.
8) Okumura T, Asamura H, Suzuki K, et al: Intrapulmonary metastasis of non-small cell lung cancer: A prognostic assessment. J Thorac Cardiovasc Surg **122**: 24-28, 2001.
9) 赤荻栄一，三井清文，鬼塚正孝，他：同側肺内転移を持つ肺癌切除例の検討．肺癌 **34**: 483-488, 1994.
10) 藤澤武彦，山口　豊，齋藤幸雄，他：肺非小細胞癌切除例における肺内転移と予後に関する検討．肺癌 **35**: 247-252, 1995.
11) Suzuki K, Nagai K, Yoshida J, et al: Prognostic factors in clinical stage I non-small cell lung cancer. Ann Thorac Surg **67**: 927-932, 1999.
12) Sawabata N, Ohta M, Takeda S, et al: Serum carcinoembryonic antigen level in surgically resected clinical stage I patients with non-small cell lung cancer. Ann Thorac Surg **74**: 174-179, 2002.

Prognostic factors and failure patterns in resected non-small cell lung cancer cases with ipsilateral intrapulmonary metastasis (pm(+) lung cancer)

Kenjiro Fukuhara , Katsuhiro Nakagawa, Hiroyuki Shiono, Yoshihisa Kadota*
Kan Ideguchi, Tsutomu Yasumitsu

Osaka Prefectural Medical Center for Respiratory and Allergic Disaeses, Osaka, Japan
(Department of Surgery, Osaka Prefectural Habikino Hospital, Osaka, Japan)
*Department of Sugery, Rinku General Medical Center, Izumisano Municipal Hospital, Osaka, Japan

A retrospective study was performed to evaluate patterns of recurrence and prognosis in resected non-small cell lung cancer cases with ipsilateral intrapulmonary metastasis (pm (+) lung cancer (n=89: pm1 (metastasized in the same lobe with primary): 65, pm2 (metastasized in the different lobe from primary): 24). The 3-year and 5-year survival rates of patients with pm1 and pm2 were 28.9%, 14.2% and 26.6%, 21.3%, respectively (N. S.).

When we divide pm (+) lung cancer patients into two groups (group ①: patients who survived more than 3 years (n= 22): group ②: patients who survived less than 3 years (n= 67)), significant differences were recognized between the groups in CEA value (p= 0.002) and p-n factor (p=0.007). Multivariate analyses also showed that both factors were significant prognostic factors. The 5-year survival rate of pm (+) lung cancer patients with normal CEA level and p-n0 disease was 50.7%, which was nearly equal to stage I B (53.3%) and II A (47.1%) patients and significantly higher than III B (9.4%) patients.

No significant difference in survival rates according to operative method was observed in pm (+) lung cancer patients. Postoperative distant metastases were detected in 53 of 89 (59.6%) pm (+) lung cancer patients, and 56.6% of these were intrapulmonary metastases (only 13.3% of which were ipsilateral).

These results suggest that pneumonectomy is not useful to prevent recurrence in pm (+) lung cancer patients and the staging system should be revised to consider CEA level and p-n factor because of good prognosis in pm (+) lung cancer patients with normal CEA level and p-n0 disease.

原著

喫煙係数からみた肺癌手術予後

福原謙二郎*，中川 勝裕，阪口 全宏，岩崎 輝夫，安光 勉

要 旨

肺癌術後の予後因子としての喫煙の影響を明らかにするために，病理病期Ⅰ期肺癌切除例579例を対象として，以下の検討を加えた．生存期間を目的因子とし，年齢，性，ⅠA，B期の別，術前と術後の循環器呼吸器系合併症の有無，喫煙係数（Brinkman Index：以下B．I．），組織型の7項目を共変量としてCoxの比例ハザードモデルによる単変量，多変量解析を行った．単変量解析では，7項目全てが有意な共変量であった．多変量解析（ステップワイズ法）では，年齢，A，B期の別，術前合併症の有無，喫煙係数の4項目が有意な独立予後因子で，喫煙係数はHazard ratio 2.007で，年齢に次いで予後への影響が大きかった．多喫煙群（B.I. ≧400）の予後は，少喫煙群（B.I. ＜400）に比し有意に不良であったが，他病死を打ち切りとすると，二群間に差は認めなくなった．他病死の内訳は肺炎，呼吸不全等の呼吸器系疾患44例，続発癌33例，心筋梗塞，脳卒中等の循環器系疾患24例，その他21例であった．

以上より，Ⅰ期肺癌切除例においては，年齢，病理病期，術前循環器呼吸器系合併症の有無，喫煙係数の4項目が有意な独立予後因子で，喫煙係数は年齢に次いで影響が大きかった．この対象群では予後の差は他病死によるものと考えられた．

索引用語：喫煙係数，肺癌手術患者，予後
Brinkman Index, resected lung cancer patients, prognosis

はじめに

喫煙は肺癌発生の重要な因子と考えられているが，肺癌術後の予後因子としての喫煙の意義は明らかにされてはいない．喫煙は肺癌の発生だけでなく手術予後にも悪影響を及ぼす可能性がある．すでに発生した肺癌においては，病期やn因子などの癌の進行度そのものが予後因子として圧倒的な力を持っている．そのため喫煙の手術予後への影響を検討するためには，早期症例を対象として行うのが望ましいと考えた．今回われわれは，対象を病理病期Ⅰ期症例のみに絞って，循環器系，呼吸器系合併症や，それに関連する死因等も考慮し，喫煙の予後因子としての意義をより詳細に検討したので報告する．

大阪府立呼吸器・アレルギー医療センター
（大阪府立羽曳野病院 外科）
*現りんくう総合医療センター・市立泉佐野病院 外科
原稿受付 2003年6月17日
原稿採択 2003年8月6日

対象と方法

1976年9月から1998年12月までの当科における原発性肺癌切除例1544例中，病理病期Ⅰ期症例579例を対象とした．

予後の解析において，生存曲線は全死因を死亡または他病死を打ち切りとしてKaplan-Meier法で作成し，有意差検定はLog-rank testで行った．死亡時に肺癌の再発を認めなかった症例を他病死とした．また，諸因子間の独立性検定にはχ^2検定を用い，予後因子に関しては，年齢，性，病理病期ⅠA，Bの別，術前および術後循環器系，呼吸器系合併症（以下，合併症）の有無，喫煙係数（一日当たりの喫煙本数×喫煙継続年数），組織型（腺癌と腺癌以外）の7項目を共変量としたCoxの比例ハザードモデルによる単変量および多変量解析（ステップワイズ法）を行った．年齢と喫煙係数については，それぞれ60と400を区分点として，その前後でのカテゴリカルな変数として扱った．有意水準

はいずれもp<0.05とした．なお本検討においては，肺気腫，閉塞性肺炎，高血圧，心房細動，脳梗塞後等で投薬を必要としている場合や術前肺機能検査で障害を認めた症例を術前合併症あり，術後に肺炎，無気肺，不整脈，虚血性心疾患の増悪等を来し治療を要した症例を術後合併症ありと定義した．

結　果

病理病期Ⅰ期肺癌切除例579例を，喫煙係数が400以上の多喫煙群(n=420)と400未満の少喫煙群(n=159)にわけ，年齢，性，病理病期ⅠA，Bの別，術前および術後合併症の有無，組織型の6種類の背景因子を検討した（Table 1）．多喫煙群に，年齢60歳以上，男性，術前後合併症あり，腺癌以外の組織型が有意に多かった．次に，年齢，性，病理病期ⅠA，Bの別，術前後合併症の有無，喫煙係数，組織型の7項目を共変量とした単変量解析をおこなったところ，上記の7項目のいずれもが有意な予後因子であった（Table 2）．各因子の相関性を考慮して，多変量解析（ステップワイズ法）で検討したところ，年齢，喫煙係数，病理病期ⅠA，Bの別，術前合併症の有無の4項目が有意な独立予後因子で，喫煙係数は年齢に次いで予後への影響が大きな因子である事が判明した（Table 3）．

生存曲線では多喫煙者の予後は，少喫煙者に比し有意に不良であった(Fig. 1)．しかし，他病死122例を打ち切りとして検討すると，二群間の予後に有意差は認められなかった（Fig. 2）．このことから，予後の差は他病死によるものと考えた．そこで，他病死を打ち切

Table 1 Clinical features according to Brinkman Index (B. I.).

Clinical feature	B.I.< 400 (n= 159)	B.I.≧ 400 (n= 420)	p-value
Age (<60 : ≧60)	55 : 104	105 : 315	0.029
Gender (male : female)	28 : 131	382 : 38	< 0.0001
p-stage (IA : IB)	85 : 74	190 : 230	0.09
Preoperative complication (no : yes)	103 : 56	214 : 206	0.004
Postoperative complication (no : yes)	122 : 37	247 : 173	< 0.0001
Histology (others : adeno ca.)	28 : 131	272 : 148	< 0.0001

Table 2 Prognostic factors according to Cox's proportional hazards model (univariate analysis).

Factor	Hazard ratio	95% C.I.	p-value
Age (<60 v.s. ≧60)	2.624	1.908-3.610	p<0.0001
Gender (male v.s. female)	0.616	0.460-0.825	p=0.001
p-stage (IA v.s. IB)	1.494	1.173-1.902	p=0.001
Preoperative complication (no v.s. yes)	1.596	1.257-2.026	p=0.0001
Postoperative complication (no v.s. yes)	1.652	1.299-2.102	p<0.0001
Brinkman Index (<400 v.s. ≧400)	2.007	1.461-2.756	p<0.0001
Histology (others v.s. adeno ca.)	0.756	0.593-0.963	p=0.023

Table 3 Prognostic factors according to Cox's proportional hazards model (multivariate analysis).

Factor	β	Standard error	p-value
Age	0.853	0.165	p<0.0001
Preoperative complication	0.358	0.123	p=0.0036
Brinkman Index	0.597	0.163	p=0.0002
p-stage	0.290	0.124	p=0.0195

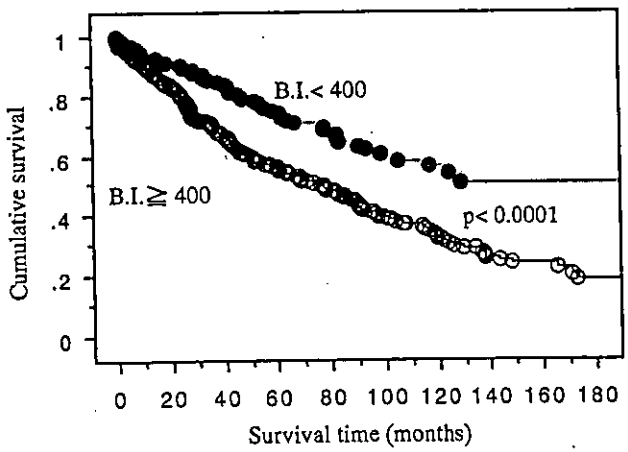

Fig. 1 Overall survival curves by Brinkman Index in patients with p-stage I lung cancer.

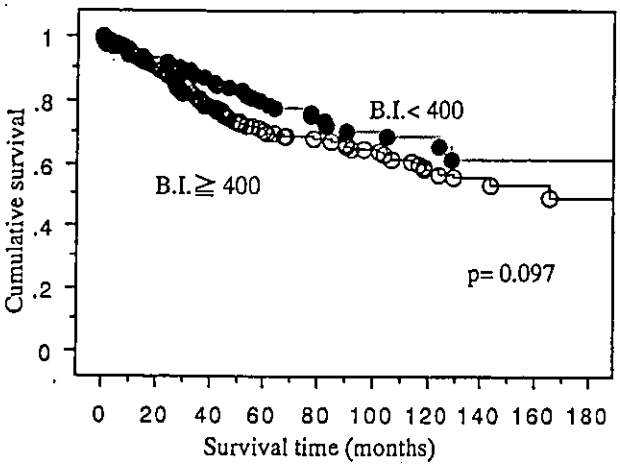

Fig. 2 Disease-specific survival curves by Brinkman Index in patients with p-stage I lung cancer.

りとした多変量解析（ステップワイズ法）を行ったところ，年齢，病理病期ⅠA，Bの別の2項目が有意な独立予後因子であった（Table 4）．

他病死の内訳は，肺炎や呼吸不全などの呼吸器疾患が44例，胃癌や肝癌などの続発癌が33例，心筋梗塞や脳卒中等の循環器疾患が24例，その他は老衰，事故死や不明例が21例であった（Table 5）．

考　　察

喫煙は肺癌発生の重要な因子と考えられているが，肺癌切除術後の予後因子としての喫煙の意義は明らかではない．喫煙は肺癌の発生だけでなく，手術予後にも悪影響を及ぼす可能性があるが，すでに発生した肺癌においては，病期やn因子といった癌の進行度そのものが予後因子として圧倒的な力を持っており[1]，喫煙の手術予後への影響を検討するためには，早期症例を対象として行うのが望ましいと考えた．今回，我々は，対象を病理病期Ⅰ期症例のみに絞って，喫煙がその発生に悪影響をもたらしうる循環器系，呼吸器系合併症[2]やそれに関連する死因等も考慮し，喫煙の予後因子としての意義をより詳細に検討した．

これまでの喫煙と肺癌手術予後に関する報告は，全病期を対象としたものが多い[1,3-5]．Sobueらは，単変量解析の結果より，腺癌手術例において喫煙が予後因子となると報告している[3]．一方，多変量解析を加えた他の報告ではいずれも喫煙が独立予後因子とはならないと結論している[1,4,5]．これは，上述の如く，すでに発生した肺癌においては，病期やn因子といった癌

Table 4 Disease-specific prognostic factors according to Cox's proportional hazards model (multivariate analysis).

Factor	β	Standard error	p-value
Age	0.591	0.204	p=0.0037
p-stage	0.679	0.174	p<0.0001

Table 5 Causes of deaths unrelated to lung cancer.

Cause of death	Case number
Pulmonary disease	44
Second primary cancers	33
Cardiac and cerebrovascular disease	24
Others and unknown	21

の進行度そのものが予後因子として圧倒的な力を持っているためと考えられた．Ⅰ期肺癌術後予後と喫煙に関する報告では，自験例と同様に独立予後因子となるとする報告[6]と，独立予後因子とはならず，静脈侵襲[7]やerbB-2発現，p53発現等[8]の生物学的悪性度の指標が独立予後因子となるとする報告がある．本検討は喫煙および喫煙の影響を受けやすい循環器系，呼吸器系合併症の予後への寄与をみることを主眼において共変量を選択したので，喫煙が有意の予後因子と判断されたと考える．

本検討において，全死亡を非打ち切りとした場合，年齢，病理病期，術前循環器，呼吸器系合併症の有無，喫煙係数の4項目が有意な独立予後因子であったが，他病死を打ち切りとした検討では病理病期と年齢のみが有意な独立予後因子であった．以上より，Ⅰ期肺癌手術例において，喫煙は有意な独立予後因子であるものの，多喫煙群の死因として他病死が多く，その予後には他病死が大きく影響していることが判明した．

喫煙による全身および気道局所の免疫力の低下[9-11]やp53遺伝子の変異[12]が報告されているが，喫煙のみが肺癌の生物学的な悪性度を左右しているとは考えが

たく，喫煙が肺癌術後の予後因子として働く機序は不明である．しかし，本検討において，他病死例の死因として喫煙に関連の深い呼吸器，循環器系合併症や第二癌が多かったこと，また喫煙習慣がコントロール可能な因子であることから，今回の結果は重喫煙しないことの重要性をより明確にできたと考えられた．

結　語

I期肺癌切除例においては，年齢，病理病期，術前循環器，呼吸器系合併症の有無，喫煙係数の4項目が有意な独立予後因子で，喫煙係数は年齢に次いで予後への影響が大きかったが，予後の差は他病死によるものと考えられた．

文　献

1) Myrdal G, Lambe M, Gustafsson G, et al: Survival in primary lung cancer potentially cured by operation: Influence of tumor stage and clinical characteristics. Ann Thorac Surg **75**: 356-363, 2003.
2) Kearney DJ, Lee TH, Reilly JJ, et al: Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. Chest **105**: 753-759, 1994.
3) Sobue T, Suzuki T, Fujimoto I, et al: Prognostic factors for surgically treated lung adenocarcinoma patients, with special reference to smoking habit. Jpn. J. cancer res. **82**: 33-39, 1991.
4) Sioris T, Husgafvel-Pursiainen K, Karjalainen A, et al: Survival in operable non-small-cell lung cancer: role of p53 mutations, tobacco smoking and asbestos exposure. Int J Cancer **86**: 590-594, 2000.
5) Suzuki K, Nagai K, Yoshida J, et al: Prognostic factors in clinical stage I non-small cell lung cancer. Ann Thorac Surg **67**: 927-932, 1999.
6) Fujisawa T, Iizasa T, Saitoh Y, et al: Smoking before surgery predicts poor long-term survival in patients with stage I non-small cell lung carcinomas. J Clin Oncol **17**: 2086-2091, 1999.
7) Suzuki K, Nagai K, Yoshida J, et al: Conventional clinicopathologic prognostic factors in surgically resected nonsmall cell lung carcinoma. A comparison of prognostic factors for each pathologic TNM stage based on multivariate analyses. Cancer **86**: 1976-1984, 1999.
8) Harpole DH, Jr., Herndon JE, II, Wolfe WG, et al: A prognostic model of recurrence and death in stage I non-small cell lung cancer utilizing presentation, histopathology, and oncoprotein expression. Cancer Res **55**: 51-56, 1995.
9) Thomas RW, Holt RG, Keast D: Development of alterations in the primary immune response of mice by exposure to fresh cigarette smoke. Int Arch Allergy **46**: 481-486, 1974.
10) Daniele RP, Dauber JH, Altose MD, et al: Lymphocytes studies in asymptomatic cigarette smokers. Am Rev Respir Dis **116**: 997-1005, 1977.
11) Chalmer J, Holt PG, Keast D, et al: Cell-mediated immune responses to transplanted tumors in mice chronically exposed to cigarette smoke. J Natl Cancer Inst **55**: 1129-1134, 1975.
12) Esposito V, Baldi A, Luca A, et al: Prognostic value of p53 in non-small cell lung cancer: relationship with proliferating cell nuclear antigen and cigarette smoking. Hum Pathol **28**: 233-237, 1997.

Induction Concurrent Chemoradiation Therapy for Invading Apical Non-Small Cell Lung Cancer

Objective: Although non-small cell lung cancer (NSCLC) involving the superior sulcus has been generally treated with radiation therapy (RT) followed by surgery, local recurrence is still a big problem to be solved. We investigated a role of induction therapy, especially induction concurrent chemoradiation therapy (CRT), on the surgical results of this type of NSCLC. *Method:* We retrospectively reviewed 30 patients with NSCLC invading the apex of the chest wall who underwent surgery from 1987 to 1996. Ten patients (57±8 years) received surgery alone, 9 (55±13 years) received RT (42±7 Gy) followed by surgery and 11 (51±9 years) received cisplatin based chemotherapy and RT (47±5 Gy) as an induction therapy. *Results:* Two and 4-year survival rates were 30% and 20% in patients with surgery alone, 22% and 11% in patients with induction RT, and 73% and 53% in patients with induction CRT, respectively. The survival was significantly better in patients with induction CRT than those with induction RT or surgery alone. Univariate analysis demonstrated that curability (yes versus no: p=0.027) and induction therapy (surgery alone and RT versus CRT: p=0.0173) were significant prognostic factors. Multivariate analysis revealed that only induction therapy (p=0.0238) was a significant prognostic factor. *Conclusions:* Induction CRT seems to improve the survival in patients with NSCLC invading the apex of the chest wall compared with induction RT or surgery alone.
(Jpn J Thorac Cardiovasc Surg 2004; 52: 120–126)

Key words: lung cancer surgery, chemotherapy, radiation therapy, pancoast tumor

Shinichiro Miyoshi, MD,[1,2] Keiji Iuchi, MD,[3] Kenji Nakamura, MD,[4] Katsuhiro Nakagawa, MD,[5] Hajime Maeda, MD,[6] Kiyoshi Ohno, MD,[7] Kazuya Nakahara, MD,[8] Noboru Nakano, MD,[9] Meinoshin Okumura, MD,[3] and Mitsunori Ohta, MD.[1]

Non-small cell lung cancer (NSCLC) involving the superior sulcus has been generally treated with radiation therapy (RT) followed by surgery since two representative reports by Shaw et al.[1] and Paulson.[2] Surgery is thought to be important because RT alone does not sterilize the local tumor area.[3] Recently, concurrent chemoradiation therapy (CRT) has been applied for stage IIIA or IIIB NSCLC as induction therapy,[4,5] which has produced better locoreginal control and surgical results than that consisting of chemotherapy (ChT) or RT alone. More recently, CRT has been used for the treatment of NSCLC involving the superior sulcus before surgery and reported that CRT appears to offer improved survival compared with induction RT alone.[6-9] We have also applied CRT to NSCLC patients involving the apex of the chest wall[10] resulting in an excellent locoreginal control.

In this study, we reviewed the surgical results of this type of NSCLC operated at Osaka University Hospital and the affiliated hospitals. This study allows us to compare three treatment modalities consisting of surgery alone, surgery+RT, and surgery+CRT in those patients.

Subjects and Methods

A retrospective study of 30 patients with NSCLC

From the [1]Division of Thoracic Surgery, Department of Surgery (E1), Osaka University Graduate School of Medicine, Osaka, the [2]Department of Cardiothoracic Surgery, Dokkyo University School of Medicine, Tochigi, the [3]Department of Surgery, National Kinki Central Hospital for Chest Diseases, Osaka, the [4]Department of Surgery, National Kure Medical Center, Hiroshima, the [5]Department of Surgery, Osaka Prefectural Habikino Hospital, the [6]Department of Surgery, National Toneyama Hospital, the [7]Department of Surgery, Osaka Koseinenkin Hospital, the [8]Department of Surgery, Otemae Hospital, Osaka, and the [9]Department of Surgery, National Ehime Hospital, Ehime, Japan.
Received for publication June 10, 2003.
Accepted for publication October 2, 2003.
Address for reprints: Shinichiro Miyoshi, MD, Department of Cardiothoracic Surgery, Dokkyo University School of Medicine, 880 Kitakobayashi, Mibu, Tochigi 321-0293, Japan.

Table I. *Patient characteristics*

		NIT *n=10*	*RT* *n=9*	*CRT* *n=11*
Gender	male	10	9	10
	female	0	0	1
Age (yr)		57±8	55±13	51±9
HS		2	4	4
Histology	Ad	6	5	5
	Sq	0	1	2
	La	3	1	2
	AdSq	1	2	0
	unknown	0	0	2
follow up interval (yr)		5.6±0.9	5.3±1.0	3.8±0.6

NIT, No induction therapy; *RT*, radiation therapy; *CRT*, chemoradiation therapy; *HS*, Horner's syndrome; *yr*, years; *Ad*, adenocarcinoma; *Sq*, squamous cell carcinoma; *La*, large cell carcinoma; *AdSq*, adenosquamous carcinoma.

involving the apex of the chest wall, who underwent surgery at Osaka University Hospital and its affiliated hospitals between 1987 and 1996, was performed. Invading apical lung cancer was defined as a primary NSCLC, which involves the superior sulcus or anterior apical region cranially beyond the first rib. The diagnosis was made based on the clinical presentation of pain around the shoulder and upper extremity, and by chest roentgenography, computed tomography (CT) and/or magnetic resonance imaging (MRI). Distant metastasis was also detected by brain CT or MRI, abdominal CT and bone scintigrapy. Pathological diagnosis was formed by transbronchial biopsy using a flexible fiberopic bonchoscope or CT-guided needle biopsy.

Patient characteristics are shown in Table I according to the three preoperative treatment regimens such as no induction therapy (NIT), RT, and CRT. Ten patients belonged to NIT, 9 to RT, and 11 to CRT. All patients but one were male. A mean age was 57±8 years in NIT, 55±13 years in RT and 51±9 years in CRT. Horner's syndrome was observed in 2 of NIT, 4 of RT, and 4 of CRT, respectively. Adenocarcinoma and large cell carcinoma occupied more than two thirds of all and squamous cell carcinoma only 3 (10%). Histological diagnosis was not obtained in 2 patients. Follow up interval was 5.6±0.9 years in NIT, 5.3±1.0 years in RT, and 3.8±0.6 years in CRT. Patient characteristics were not different among the three groups.

Preoperative and postoperative adjuvant therapies employed were shown in Table II. Six of the NIT group received 40 to 60 Gy of the RT postoperatively, 2 of the 6 received 2 courses of cisplatin (C)+mitomycin (M)+vindesine (V), concurrently. One patient of the NIT group received two courses of CV postoperatively.

Table II. *Preoperative and postoperative adjuvant therapies*

		NIT *n=10*	*RT* *n=9*	*CRT* *n=11*
Induction therapy				
ChT	CMV	–	–	5
	CV	–	–	3
	CBDCA+Ep	–	–	3
RT (Gy)				
	mean	–	42±7	47±5
	range	–	30–52.5	40–56
Postoperative therapy				
	NT	3	1	7
	ChT	1	6	1
	RT	4	2	1
	CRT	2	0	2

NIT, No induction therapy; *RT*, radiation therapy; *CRT*, chemoradiation therapy; *ChT*, chemotherapy; *NT*, no therapy; *C*, cisplatin; *M*, mitomycin; *V*, vindesine; *CBDCA*, carboplatin; *Ep*, etoposide.

Nine patients in RT group received 30 to 52.5 Gy preoperatively to the primary tumor and mediastinum or the primary tumor alone, and 6 (60%) of them received 2 courses of postoperative ChT including CMV or CV. Eleven patients in the CRT group received 40 to 56 Gy and 2 courses of CMV, CV, or carboplatin+etoposide, concurrently. Seven (64%) of the CRT group did not receive postoperative adjuvant therapy.

The actuarial survival rates were calculated with the method of Kaplan and Meier. The statistical difference of survival was examined with the log rank test. The relative importance of various prognostic factors

Table III. *Surgical technique for resection of invading apical lung cancer*

	NIT n=10	*RT* n=9	*CRT* n=11
Thoracotomy approach			
anterior	1	4	5
posterolateral	9	4	6
anterior+posterolateral	0	1	0
Lung resection			
upper lobectomy	8	8	10 (sleeve 1)
upper and middle bilobectomy	0	1	0
pneumonectomy	0	0	1
partial resection or segmentectomy	2	0	0
LN dissection			
ND0, 1	0	2	1
ND2a	9	5	4
ND3	1	2	6
Associated resected organs			
ribs (1–5)	10	8	11
vertebral body or transverse process	1	3	3
brachial nerves	0	3	1
subclavian artery and/or vein	0	4	1
Curability			
curative	8	5	11
non-curative	2	4	0

NIT, No induction therapy; *RT*, radiation therapy; *CRT*, chemoradiation therapy; *LN*, lymph node; *ND1*, hilar lymph node dissection; *ND2a*, mediastinal lymph node dissection; *ND3*, neck lymph node dissection.

for postoperative survival as identified by multivariate analysis was analyzed with Cox's proportional hazards model with the forward stepwise method. Association between categorical variables was examined by the χ^2 test. Continuous variables were compared with the Student's Newman Keul's multiple comparison test. Statistical analyses were performed with the commercially available personal computer programs SPSS (SPSS, Inc., Chicago, Ill, USA) or Statview J (SAS Institute Inc., cary, NC, USA). A p value of less than 0.05 was considered significant.

Results

Surgical technique. All patients with induction therapy underwent surgery about one month after the induction therapy. Surgical technique for resection of invading apical lung cancer is shown in Table III. Anterior thoracotomy recommended by Masaoka et al.[11] was employed in 10 patients, posterolateral thoracotomy by Shaw et al.[1] in 19 and both in one. Upper lobe lobectomy and dissection of the mediastinal lymphnodes or more including supraclavicular lymph nodes were standard procedures. Chest wall including the first rib or more ribs was resected in 29 patients, vertebral body and/or transverse process in 7, brachial nerves in 4, subclavian artery and/or vein in 5. A curative operation was performed 8 in NIT, 5 in RT and 11 in CRT, respectively.

Pathological TNM classification.[12] Postoperative pathological TNM classification of the patients is shown in Table IV. Five patients in CRT who had a pathological complete response were categorized as stage 0. Pretreatment clinical TNM classifications of those had been T3N0M0 in 2, T3N2M0 in 1, and T4N0M0 in 2. Thirteen patients were in stage IIB, 4 in stage IIIA, 6 in stage IIIB, and 2 in stage IV.

Postoperative complications. Postoperative complications were summarized in Table V. Twelve patients had 18 postoperative complications, which were arrythmia in 4, pneumonia in 4, respiratory failure in 3, and others in 7. One patient in RT group died of respiratory failure. The morbidity rate was 12/30 (40%) and mortality rate was 1/30 (3.3%). There was no difference in the postoperative morbidity rate among the three groups.

Table IV. *Pathological TNM classification*

	NIT n=10	*RT n=9*	*CRT n=11*
stage 0			
T0N0M0	0	0	5
stage IIB			
T3N0M0	6	4	3
stage IIIA			
T3N2M0	2	1	1
stage IIIB			
T3N3M0	1	0	1
T4N0M0	0	2	0
T4N1M0	0	0	1
T4N2M0	1	0	0
stage IV			
T3N0M1	0	2	0

NIT, No induction therapy; *RT,* radiation therapy; *CRT,* chemoradiation therapy.

Table V. *Postoperative complications*

	NIT n=10	*RT n=9 (1)*	*CRT n=11*
patients	2	4	6
complications	4	6	8
arrythmia	1	0	3
pneumonia	1	2	1
respiratory failure	0	3 (1)	0
others	2	1	4

( ): Hospital death.
NIT, No induction therapy; *RT,* radiation therapy; *CRT,* chemoradiation therapy.

Table VI. *Postoperative recurrence*

	NIT n=10	*RT n=9 (2)*	*CRT n=11*
recurrence*			
yes	8	8 (1)	3
no	2	1 (1)	8
recurrent sites**			
local	6	5	2
distant	6	8 (1)	2

( ) : A case with distant metastasis, *p=0.002, **p=0.056.
NIT, No induction therapy; *RT,* radiation therapy; *CRT,* chemoradiation therapy.

Postoperative recurrence and survival. Postoperative recurrence was depicted in Table VI. Total recurrence including local and distant sites was observed in 8 of the NIT group, 8 of the RT group, and 3 of the CRT group. The recurrence rate was significantly lower in the CRT group than the NIT or the RT group (p=0.002) and the local recurrence rate tended to be lower in the CRT group compared with the NIT or the RT group (p=0.056).

The survival curves of the three groups were shown in Figure 1. Two and 4-year survival rates were 30% and 20% in the NIT group, 22% and 11% in the RT group, and 73% and 53% in the CRT group, respectively. The survival rate of the CRT group was significantly better than that of the NIT or the RT group (p=0.048).

Prognostic factors. Univariate and multivariate analyses were performed to investigate prognostic factors. The results are shown in Table VII. Although operative curability and induction therapy were significant prognostic factors by univariate analysis, only induction therapy was a significant prognostic factor by multivariate analysis.

Discussion

RT followed by radical surgical resection is currently a standard approach for NSCLC involving the superior sulcus, which has resulted in about a 30% survival at 5 years.[2,7] Those patients receiving a complete resection achieved a further better prognosis.[13] These findings suggest that locoreginal control is the most important strategy for the treatment of this type of tumor.

However, preoperative RT is not good enough to sterilize the tumor area.[3] About 40 to 50% of thoracotomy patients with Pancoast tumor have resulted in an incomplete resection.[13-15] The rate of pathological complete response, where no viable cancer cells were found in the resected specimens, is also low about 7 to 24%.[3,14,16] Some surgeons have prompted the use of preoperative and postoperative radiotherapy[14] or intraoperative brachytherapy[13] to achieve better locoreginal control.

We also employed induction RT for the first two cases. After surgery, local recurrence occurred in one patient and distant metastasis in the other. Then, CRT was applied to the subsequent 4 cases, all of which demonstrated a pathological complete response in the surgical specimens.[10] Thus, for the purpose of investigating the effect of CRT, we reviewed patients with NSCLC invading the apex of the chest wall who underwent surgery at Osaka University Hospital and the affiliated hospitals from 1987 to 1996. During this

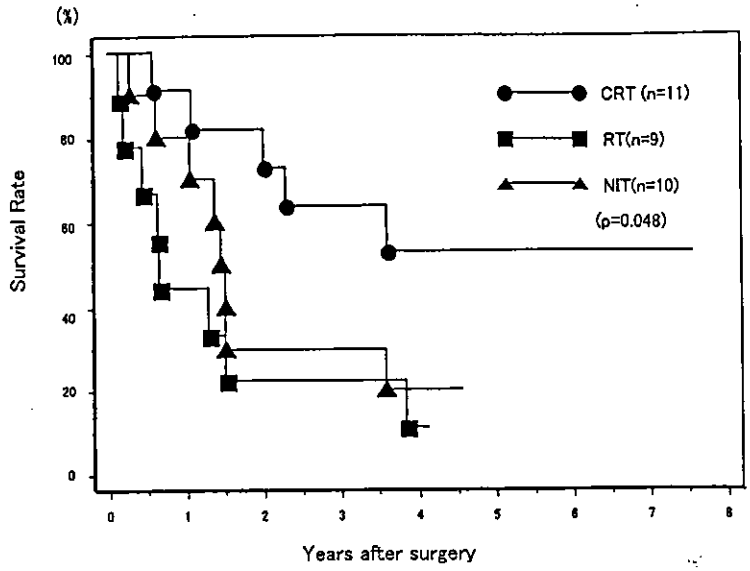

Fig. 1. Survival curves in patients with concurrent chemoradiation therapy (CRT), radiation therapy (RT), and without induction therapy (NIT). The survival rate of the CRT group is significantly better than that of the NIT or the RT group (p=0.048).

Table VII. *Prognostic factors*

univariate analysis	age, HS, N factor, T factor, LN dissection	
	pathological stage	NS
	curability (yes vs. no)	p=0.027
	induction therapy (NIT+RT vs. CRT)	p=0.017
multivariate analysis	induction therapy (NIT+RT vs. CRT)	p=0.0238
		relative risk=0.3092
		95% confidence interval=0.1117–0.8554

NIT, No induction therapy; *RT*, radiation therapy; *CRT*, chemoradiation therapy; *HS*, Horner's syndrome; *LN*, lymph node; *vs.*, versus; *NS*, not significant.

period, three preoperative treatment modalities such as NIT, RT and CRT were employed. Although the three different treatment groups were fairly evenly matched, the NIT group seemed to have a less invasive disease because of less associated resection organs and high complete resection rate (Table III). The finding that there was no difference in survival between the NIT group and the RT group may suggest that RT is effective as an induction treatment. However, compared with the CRT group, there was a significant difference in survival.

Four previously published reports [6-9] have also suggested that CRT is the optimal induction therapy for patients with the superior sulcus tumor. The summary of the four reports and our series is shown in Table VIII. Regimens of the chemotherapy were cisplatin or carboplatin based and the dose of radiation was 45 to 60 Gy. The complete resection rate was extremely high from 76.4 to 100%. The pathological complete response rate was 33.7 to 70.5% and if minimal microscopic residual disease was included, the response rate was further high. Local recurrence rate was 0 to 23%. As a result, 2-year and 4-year survival rates have been extremely improved to 73 to 93%, and to 53 to 84%, respectively. In our series, if two patients, who died of esophageal cancer and lung tuberculosis postoperatively, are censored, the 4-year survival rate of the CRT group was 78.7%. These reports suggest that CRT may improve the likelihood of pathologic complete response, local control, and overall survival.

When CRT was applied to stage IIIA or IIIB disease as an induction treatment, postoperative complications

Table VIII. *Results of induction chemoradiation therapy for non-small cell lung cancer involving the superior sulcus in literature*

Series		Patients number	RT (Gy)	Complete resection	p-CR	Operative mortality	Survival	
Reference	yr						2yr	4yr
Martinez-Monge[6]	1994	18	46–50	76%	71%	16.6%*		56%
Attar[7]	1998	11	60					72%**
Rusch[8]	2001	83	45	92%	34%	2.4%		70%
Wright[9]	2002	15	51	93%	67%	0%	93%	84%
Present series		11	47	100%	46%	0%	73%	53%

*Including treatment related death, **estimated 5 year survival rate.
yr; Year; *p-CR*, pathological complete response.

became a major problem.[17,18] In our series, however, there was no significant difference in frequency of postoperative complications among the three preoperative treatment modalities and postoperative mortality of the CRT group was 0%. Although Martinez-Monge et al.[6] reported the high rate of treatment-related death (16.6%), a recent large series of Rusch et al.[8] demonstrated the low rate of treatment-related mortality (5%) including 2.4% of operative mortality. In stage IIIA or IIIB disease, one of major operative procedures was pneumonectomy, which was a significant important risk factor for postoperative morbidity and mortality.[17,18] On the contrary, a major procedure for the superior sulcus tumor is upper lobe lobectomy and bronchopleural fistula occurred only in 2.4% in Rusch's series.[8] The low frequency of pneumonectomy employed for the superior sulcus tumor seems to result in the low frequency of fatal postoperative complications after CRT.

There are several limitations in retrospective studies as Wright[9] pointed out. However, the three retrospective studies shown in Table VIII reached the common conclusions, in which induction chemoradiation therapy can produce a high complete resection rate, a high pathologic response rate, and subsequent improved survival in NSCLC invading the superior sulcus. These conclusions were also the same as those of the prospective multi-institutional trial by Southwest Oncology Group.[8] Further studies are needed to obtain the optimal protocol of CRT, which can control not only the locoregional area but also distant metastases.

We appreciate the cooperation of the members of Thoracic Surgery Study Group of Osaka University.

REFERENCES

1. Shaw RR, Paulson DL, Kee JL. Treatment of the superior sulcus tumor by irradiation followed by resection. Ann Surg 1961; 154: 29–40.
2. Paulson DL. Carcinomas in the superior pulmonary sulcus. J Thorac Cardiovasc Surg 1975; 70: 1095–104.
3. Wright CD, Moncure AC, Shepard JA, Wilkins EW Jr, Mathisen DJ, Grillo HC. Superior sulcus lung tumors: Results of combined treatment (irradiation and radical resection). J Thorac Cardiovasc Surg 1987; 94: 69–74.
4. Strauss GM, Herndon JE, Sherman DD, Mathisen DJ, Carey RW, Choi NC, et al. Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small-cell carcinoma of the lung: Report of a cancer and leukemia group B phase II study. J Clin Oncol 1992; 10: 1237–44.
5. Rusch VW, Albain KS, Crowley JJ, Rice TW, Lonchyna V, McKenna R Jr, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy: A Southwest Oncology Group Trial. J Thorac Cardiovasc Surg 1993; 105: 97–106.
6. Martinez-Monge R, Herreros J, Aristu JJ, Aramendia JM, Azinovic I. Combined treatment in superior sulcus tumors. Am J Clin Oncol 1994; 17: 317–22.
7. Attar S, Krasna MJ, Sonett JR, Hankins JR, Slawson RG, Suter CM, et al. Superior sulcus (Pancoast) tumors: Experience with 105 patients. Ann Thorac Surg 1998; 66: 193–8.
8. Rusch VW, Giroux DJ, Kraut MJ, Crowley J, Hazuka M, Johnson D, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Thorac Cardiovasc Surg 2001; 121: 472–83.
9. Wright CD, Menard MT, Wain JC, Donahue DM, Grillo HC, Lynch TJ, et al. Induction chemoradiation compared with induction radiation for lung cancer involving the superior sulcus. Ann Thorac Surg 2002; 73: 1541–4.

10. Miyoshi S, Maebeya S, Suzuma T, Bessyo T, Hirai I, Tanino Y, et al. Induction therapy of invading apical lung cancer. Proceedings of XXX World Congress of The International College of Surgeons, Kyoto, November 25-29, 1996: 995–9.
11. Masaoka A, Ito Y, Yasumitsu T. Anterior approach for tumor of the superior sulcus. J Thorac Cardiovasc Surg 1979; 78: 413–5.
12. Mountain CF. Revisions in the international system for staging lung cancer. Chest 1997; 111: 1710–7.
13. Ginsberg RJ, Martini N, Zaman M, Armstrong JG, Bains MS, Burt ME, et al. Influence of surgical resection and brachytherapy in the management of superior sulcus tumor. Ann Thorac Surg 1994; 57: 1440–5.
14. Shahian DM, Neptune WB, Ellis FH Jr. Pancoast tumors: Improved survival with preoperative and postoperative radiotherapy. Ann Thorac Surg 1987; 43: 32–8.
15. Maggi G, Casadio C, Pischedda F, Giobbe R, Cianci R, Ruffini E, et al. Combined radiosurgical treatment of Pancoast tumor. Ann Thorac Surg 1994; 57: 198–202.
16. Sartori F, Rea F, Calabro F, Mazzucco C, Bortolotti L, Tomio L. Carcinoma of the superior pulmonary sulcus: Results of irradiation and radical resection. J Thorac Cardiovasc Surg 1992; 104: 679–83.
17. Martin J, Ginsberg RJ, Abolhoda A, Bains MS, Downey RJ, Korst RJ, et al. Morbidity and mortality after neoadjuvant therapy for lung cancer: The risk of right pneumonectomy. Ann Thorac Surg 2001; 72: 1149–54.
18. Fowler WC, Langer CJ, Curran WJ, Keller SM. Postoperative complications after combined neoadjuvant treatment of lung cancer. Ann Thorac Surg 1993; 55: 986–9.

原 著

c-N2で縦隔鏡検査陰性であった原発性肺癌手術例の検討

福原謙二郎*，中川 勝裕，安光 勉

要 旨

1976年9月から1998年12月までに，当院において術前胸部CTにてc-N2（縦隔リンパ節の短径≧10mm）と診断され，縦隔鏡検査を施行した原発性肺癌200例中，陰性であった症例は67例であった．うち引き続き根治術を行った59例の既往歴および採取リンパ節の病理組織所見，ならびにc-N2症例の縦隔鏡検査成績をretrospectiveに検討した．縦隔鏡検査の陽，陰性の別と，術前CTでの腫大縦隔リンパ節station数との関連をみると，縦隔鏡陽性例の方が，腫大station数が有意に多かった．59例のp-n因子の内訳はn0：31例，n1：18例，n2：10例で，CTにてc-N2と診断された症例の83.1%（49/59）において，縦隔鏡検査を施行することによりN2の診断を否定できた．n0，n1例のうち，9例で閉塞性肺炎，4例でそれぞれ肺結核，肺非定型抗酸菌症，塵肺，間質性肺炎を合併していた．また，採取リンパ節の病理組織学的検索にて，珪肺性変化を6例，サルコイド反応を3例，結核性変化を1例認めた．その他の26例（53.1%）では，術前にリンパ節腫大を来しうる誘因を有していなかった．n2例のうち，縦隔鏡到達可能域（#1，2，3，4，7浅部）での偽陰性例は2例で，c-N2，縦隔鏡施行例のsensitivityは97.7%，specificityは100%，accuracyは98.4%，negative predictive valueは94.9%，positive predictive valueは100%であった．以上より，c-N2でただちに手術非適応としたり，導入治療を行うことは妥当ではない．非到達域の存在という弱点も有するが，質的診断には縦隔鏡検査が有用である．

索引用語：縦隔鏡，肺癌手術患者，縦隔リンパ節転移診断
mediastinoscopy, resected lung cancer patients, a diagnosis of metastases to mediastinal lymph nodes

はじめに

縦隔鏡検査は縦隔リンパ節転移の有無に関する質的診断が可能で，特に術前治療の対象となりうるc-N2症例においては，その正確な病期決定に有用とされている．そこで今回我々は，術前CT検査にてc-N2と診断され，縦隔鏡検査にて陰性であった症例の既往歴および採取リンパ節の病理組織所見，ならびにc-N2症例の縦隔鏡検査成績をretrospectiveに検討したので報告する．

対象と方法

1976年9月から1998年12月までの，当科における原発性肺癌切除例1544例中，術前胸部CT検査にてc-N2（縦隔リンパ節の短径が10mm以上）と診断され，縦隔鏡検査を施行した症例は200例であった．そのうち，縦隔鏡にてリンパ節転移陰性であった症例は67例であった．うち引き続き開胸術を行った61例から試験開胸例2例を除いた59例を対象とした．因子間の独立性検定にはχ^2検定を用い，有意水準は$p<0.05$とした．

大阪府立呼吸器・アレルギー医療センター
（大阪府立羽曳野病院 外科）
*りんくう総合医療センター・市立泉佐野病院 外科
原稿受付 2003年7月8日
原稿採択 2003年9月8日

結 果

c-N2で縦隔鏡を施行した200例における縦隔鏡検査の陽，陰性の別と，術前CTでの腫大縦隔リンパ節station数との関連をみた．縦隔鏡検査陽性例の方が，術前CTでの腫大縦隔リンパ節station数が有意に多かった（Table 1）．

c-N2，縦隔鏡陰性例59例の最終病理病期n因子の内訳は，n0：31例，n1：18例，n2：10例であった（Table 2）．