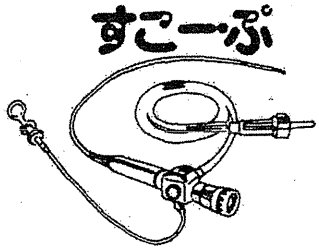
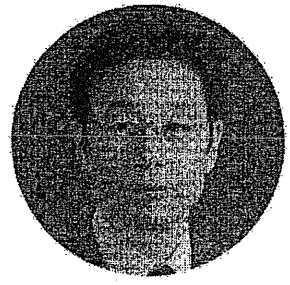


気道ステント雑感



大阪市立総合医療センター呼吸器外科　多田弘人

当院開設当時の呼吸器外科部長，飯岡壮吾先生がステント治療をはじめて18年になります．開設早々に飯岡部長がマルセイユで硬性気管支鏡の取り扱いを習得してこられ，当院のステント挿入手技が向上するとともに近隣からの紹介が激増しました．

その当時にメタリックステントが新規市販品として手に入るようになり，本学会の大きなテーマの1つとしても取り上げられてきました．しかし最近は，硬性気管支鏡やステントの新規開発はありません．この10年間くらいは当初の情熱が冷めたのか，少なくとも関西地区ではステントを多用している施設は増加していないようです．どうして増加しないのでしょうか？

2012年の4月からステント治療の点数が約9万円と以前より2万円近く上がりますが，それでも治療コストには見合わないと思います．第一に，ステントは特定医療材料として1つまでが約5万円償還されるので，高いステントを使うと1つでも赤字ですし安いステントを使っても3つも使えば全くの赤字です．第二に，この手技はリスクが高いために，安全に行おうとすると多人数の関与が必要になります．気道という生命維持に不可欠な部分の治療であるため，最悪のことを考えるとpercutaneous cardiopulmonary support (PCPS)の準備が必要と考える先生方も多いでしょう．実際低酸素血症を覚悟で治療する場面もしばしばあり，術中死亡の危険性を常にはらんでいます．そういった人的資源を常に準備する必要があり，そのハードルは結構高いものと思われます．第三の原因は，対象症例がかなり癌の末期に近い方になるために，ステント挿入がうまくいったとしても，医療側が達成感を持つのが難しいことです．最後に，対象症例がそれほど多くはないことが挙げられると思われます．滅多にないので技術習得が困難であることが，普及を妨げています．

以上のようなバックグラウンドに加え，もっと大きな障害があります．硬性気管支鏡を行うには全身麻酔を必要とし，手術場を使用することが望ましいことです．現在の日本では，手術場と麻酔医というリソースをそう簡単に生み出すことはできませんので，やりたい施設であっても硬性気管支鏡を用いたステント治療を行うのはなかなか困難です．

当院での硬性気管支鏡を使った気道処置は，この2年間で約100例に上ります．複

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数回施行症例もあるため新規症例はその7割くらいですが，当院の症例数は増加傾向にあります．これは，周辺施設で硬性鏡を行う施設が減少していることに起因していると思っています．自分たちでやらないで，ステントの適応を理解しないまま救急車で搬送しようとされる先生も増えてきているようにも思われます．今後は，ステント治療の適応についてもう一度確認する必要があるようにも考えます．

こういった事態に対応するためには，ステント挿入・硬性気管支鏡の保険点数のより一層の増加を要求する必要があると思います．関係各位の努力を期待するものです．

Original Article

A Phase 3 Study of Induction Treatment With Concurrent Chemoradiotherapy Versus Chemotherapy Before Surgery in Patients With Pathologically Confirmed N2 Stage IIIA Nonsmall Cell Lung Cancer (WJTOG9903)

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BACKGROUND: This study sought to ascertain whether induction-concurrent radiotherapy added to chemotherapy could improve the survival of patients undergoing surgery for stage IIIA N2 nonsmall cell lung cancer (NSCLC). **METHODS:** Patients with pathologically proven N2 disease were randomized to receive either induction chemotherapy (docetaxel 60 mg/m^2 and carboplatin AUC [area under the receiver operating characteristic curve] = 5 for 2 cycles) plus concurrent radiation therapy (40 Gy) followed by surgery (CRS arm) or induction chemotherapy followed by surgery (CS arm). They subsequently underwent pulmonary resection when possible. **RESULTS:** Sixty patients were randomly assigned between December 2000 and August 2005. The study was prematurely terminated in January 2006 because of slow accrual. The most common toxicity was grade 3 or 4 leukopenia in 92.9% of patients in the CRS arm and 46.4% in the CS arm. Induction therapy was generally well tolerated, and there were no treatment-related deaths in either arm. Downstaging in the CS arm and CRS arm was 21% and 40%, respectively. The progression-free survival (PFS) and overall survival (OS) in the CS arm were 9.7 months and 29.9 months (PFS, hazard ratio [HR] = 0.68, P = .187), and those in the CRS arm were 12.4 months and 39.6 months (OS, HR = 0.77, P = .397), respectively. The PFS with and without downstaging was 55.0 and 9.4 months, respectively (HR = 3.39, P = .001). The OS with and without downstaging was 63.3 and 29.5 months, respectively (HR = 2.62, P = .021). **CONCLUSIONS:** The addition of radiotherapy to induction chemotherapy conferred better local control without significant adverse events. Tumor downstaging is important for prolonging the OS in patients with stage IIIA (N2) NSCLC. *Cancer* 2012;118:6126-35. © *2012 American Cancer Society.*

KEYWORDS: induction therapy before surgery, phase 3 study, carboplatin, docetaxel, stage IIIA nonsmall cell lung cancer.

Lung cancer is the leading cause of cancer death in most industrialized countries. Nonsmall cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers. One-third of patients with NSCLC are found to have locally advanced tumors (stage IIIA or IIIB) at the time of initial diagnosis. Pulmonary resection remains the only accepted mode of therapy and hope for potential cure in patients with early stage I or II NSCLC. However, patients with stage IIIA, N2 disease are at substantial risk of recurrence and death even after complete surgical resection. The resectability of patients with stage III locally advanced lung cancer is only 14% to 20%, and the corresponding 5-year survival rate ranges from

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13% to 36%.[1,2] When pathologic involvement of the mediastinal lymph nodes is documented prior to surgical resection, a high rate of both local and distant failure with resection alone has provided the rationale for a combined modality approach consisting of induction chemotherapy or chemoradiotherapy before surgery. Induction therapy has several theoretical advantages,[3] such as increasing the sensitivity of tumors in early-stage disease, decreasing the tumor volume to enable better local control in subsequent surgery, faster eradication of clinically undetected micrometastatic disease, and better patient tolerance and compliance compared with postsurgery treatments.

With regard to preoperative chemotherapy for stage IIIA lesions with mediastinal lymph node metastasis, 5 randomized clinical trials of induction chemotherapy prior to surgery have been conducted.[4-8] Two of these studies involved small cohorts (n = 60) that included mainly stage IIIA, N2 disease, and showed a significant survival advantage associated with induction chemotherapy compared with surgery alone.[5,6] None of the other trials reported any beneficial outcome for bimodality therapy compared with surgery alone.[4,7,8]

Induction treatment using combined concurrent chemoradiotherapy prior to surgery resulted in NSCLC cure rates of 30% to 40% at 5 years and appeared to improve survival over treatment with surgery alone.[9-11] We conducted a phase 2 trial of induction chemoradiotherapy before surgery in 22 patients with stage IIIA NSCLC who have pathologically proven mediastinal lymph node metastasis.[12] The chemotherapy regimen used was cisplatin and etoposide, and the radiation dosage was 40 Gy. The response rate was 64% and the 5-year survival rate was 41%. Subsequently, we conducted a phase 2 study of induction chemoradiotherapy before surgery in 40 early stage NSCLC (stage IB, II).[13] Carboplatin (AUC = 5), and docetaxel (60 mg/m^2) were administered once every 3 weeks for 2 cycles concurrent with 40 Gy radiation. In patients with no evidence of disease progression, thoracotomy was performed 3 to 5 weeks later. All the patients completed induction chemoradiotherapy, and 39 patients underwent thoracotomy and were completely resected. There were no treatment-related deaths, and estimated 5-year survival was 69.9%. Induction concurrent chemotherapy (carboplatin plus docetaxel) with 40 Gy of thoracic radiotherapy was considered to be feasible and tolerable. Based on the findings of these 2 previous phase 2 trials, we planned a phase 3 study in which patients with pathologically documented stage IIIA (N2) NSCLC were randomized to either an induction chemotherapy followed by surgery (CS) arm, or an induction-concurrent chemoradiotherapy followed by surgery (CRS) arm. The primary endpoint of this trial was the overall survival rate at 5 years.

MATERIALS AND METHODS

Eligibility

The present study was undertaken at multiple academic and community hospitals in Japan. The 6th edition of the TNM staging system was used to stage the lung cancers using a computed tomography (CT) scan of the chest and upper abdomen; bone scan; and CT or magnetic resonance imaging (MRI) scan of the brain. Inclusion criteria were stage IIIA (pN2) disease: T1, T2, or T3 primary NSCLC with pathological proof of N2 disease (from biopsy samples of the ipsilateral mediastinal nodes that were visible on a CT scan). The size of the metastatic mediastinal lymph node was more than 1 cm along the short axis. Patients were assessed together by a thoracic surgeon, a radiation oncologist, and a medical oncologist or pulmonologist to establish whether N2 disease was present to the extent that concurrent chemotherapy and radiotherapy were indicated instead of definitive resection. It was also necessary to determine whether each lesion was potentially resectable. Additional inclusion criteria were measurable disease as defined by the World Health Organization (WHO), an Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate hematologic, hepatic, cardiac, renal (serum creatinine $\leq$ 1.5 mg and creatinine clearance $\geq$ 40 mL/hour), and pulmonary functions (including partial pressure of arterial oxygen [PaO_2] $\geq$ 70 Torr, forced expiratory volume in 1 second [$FEV_{1.0}$] $\geq$ 1.5 L). The exclusion criteria were prior malignancy other than nonmelanoma skin cancer or adequately treated stage I in situ cervical cancer, uncontrolled angina pectoris, a history of congestive heart failure or myocardial infarction within 3 months, pulmonary fibrosis detectable by CT scan, chronic obstructive pulmonary disease ($FEV_{1.0} \leq 65\%$), and greater than 10% weight loss within the previous 6 months.

All patients provided written informed consent after study approval by the institutional review board of each participating center.

Study Design and Treatment

In the current phase 3 multicenter trial, patients were randomly assigned on a 1:1 basis to an induction CS arm or an induction CRS arm (Fig. 1). The patients were then

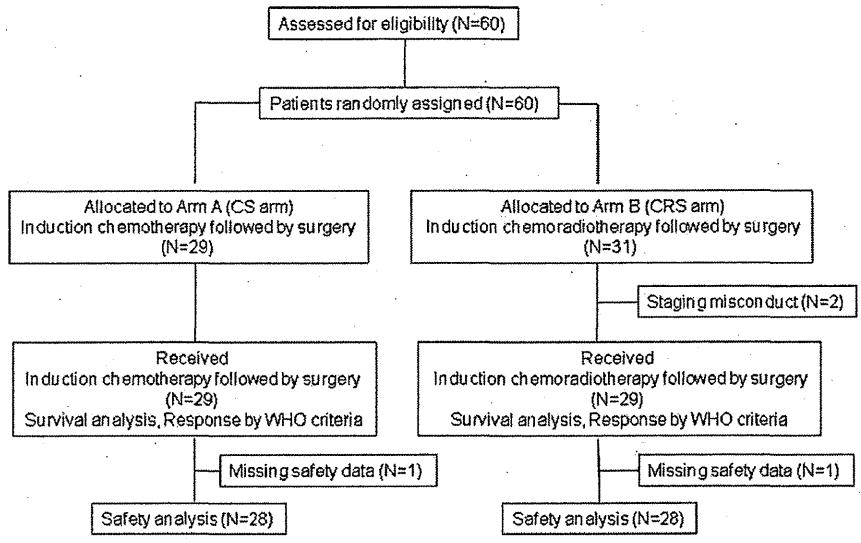

Figure 1. CONSORT diagram is shown for this study. CRS indicates concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; WHO, World Health Organization.

stratified by sex, institution, and number of mediastinal lymph nodes. The induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m^2 on days 1, 22, intravenous infusions). Thoracic radiotherapy (40 Gy in 20 fractions of 2 Gy over 4 weeks) was also administered from day 1 in the CRS arm (Fig. 2)

All patients were treated with a linear accelerator photon beam of 6 MV or more. At the commencement of this multi-institutional study, a 3-dimensional (3D) treatment planning system using CT was not available at some of the participating institutions. Hence, 2-dimensional (2D) treatment planning techniques were allowed. Radiation doses were specified at the center of the target volume, and doses were calculated assuming tissue homogeneity without correction for lung tissues. The primary tumor and involved nodal disease received 40 Gy in 2 Gy fractions over 4 weeks via the anterior and posterior opposing portals. Radiation fields included the primary tumor with a margin of at least 1.0 cm, and the ipsilateral hilum and mediastinal nodal areas with a margin of 0.5 to 1.0 cm from the paratracheal lymph nodes (#2) to 4.5 cm below the tracheal bifurcation including subcarinal lymph nodes (#7). The contralateral hilum was not included. The supraclavicular areas were not treated routinely, but the ipsilateral supraclavicular area was treated when the primary tumor was located in the upper lobe.

The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose-reduction guidelines were specified in the protocol for both treatment arms. Patients in the CRS arm who could not be treated surgically within 6 weeks after induction therapy received further radiotherapy of up to 66 Gy in 33 fractions in total. In this boost radiotherapy procedure, the spinal cord was excluded from the radiation fields.

Patients were scheduled for a chest CT scan 4 to 6 weeks after completion of the last chemotherapy cycle and were followed up every 2 months for at least 5 years. During this time, the patients received CT scans of the chest and upper abdomen, CT or MRI scans of the brain, and bone scans every 6 months.

Statistical Methods

Analyses were performed by intention to treat, using only eligible patients. The primary endpoint was the survival rate at 5 years. Overall survival (OS) was defined as the time from randomization to death from any cause.

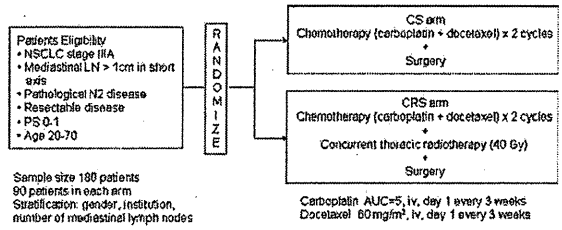

Figure 2. The study schema is shown. AUC, area under the receiver operating characteristic curve; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; iv, intravenous; LN, lymph node; NSCLC, nonsmall cell lung cancer; PS, performance status.

Secondary endpoints were the response rate and the toxicity of induction therapy, resectability rate, downstaging rate, death from any cause, operative morbidity, progression-free survival (defined as the time from randomization to disease progression), and patterns of failure. We calculated the sample size assuming a 2-sided log-rank test with a type I error rate of 0.05 and 80% statistical power, and a follow-up of 5 years.

The target sample size was 180 patients to detect a 20% absolute improvement in the CRS arm,[12] assuming 20% 5-year OS in the CS arm. Kaplan-Meier methods were used to estimate the median OS and PFS. The HRs and the 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model, and the OS and PFS were analyzed using the log-rank test.

RESULTS

Patient Characteristics

Between December 2000 and August 2005, 60 patients were randomly assigned and 58 patients were treated. The 2 untreated patients (both in the CRS arm) did not satisfy the eligibility criteria and were excluded from the subsequent analyses. Because of the slow patient accrual, this study was terminated at 60 enrollments in accordance with a Data Safety and Monitoring Committee recommendation made in December 2005. Patient characteristics were well-balanced in terms of age, sex, histology, smoking history, and TNM stage. The chemotherapy cycles of induction therapy did not differ between the CS arm (mean 2 ± 0 standard deviation) and the CRS arm (mean 1.9 ± 0.3 standard deviation). Regarding the number of patients possessing multistation mediastinal lymph node metastases, there was no difference between the 2 arms ($P = .297$; Table 1).

Table 1. Patient Demographics

Characteristic	CS	CRS	*P*
Registered patients	29	31	
Median age (range), y	57.0 (36-70)	58.0 (34-69)	.947
Sex (M/F)	19/10	21/10	.855
Histology (adenocarcinoma/ squamous carcinoma/other)	16/8/5	23/5/3	.422
Smoker/nonsmoker	22/7	23/8	.881
T 1/2/3	11/14/4	11/18/2	.577
N 0/1/2/3	0/0/29/0	0/0/30/1	.329
Lymph node station (single/multiple)	15/14	11/20	.297
M 0/1	29/0	30/1	1.000
Staging misconduct	0	2	
Survival analysis	29	29	
Missing safety data	1	1	
Safety data analysis	28	28	

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.

The 25 patients (89%) in the CS arm and 20 patients (71%) in the CRS arm completed 2 cycles of chemotherapy at full dose. There was no difference in dose intensity of docetaxel and carboplatin between the 2 arms. Docetaxel dose intensity in each arm was as follows: 1.00 ± 0.00 (CS arm, first course), 0.99 ± 0.04 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.94 ± 0.08 (CRS arm, second course). Carboplatin dose intensity in each arm was as follows: 0.97 ± 0.16 (CS arm, first course), 0.95 ± 0.12 (CS arm, second course), 1.00 ± 0.00 (CRS arm, first course), 0.88 ± 0.14 (CRS arm, second course).

In the CRS arm, 28 of 29 patients received 40 Gy of radiation dose as scheduled and the remaining 1 patient received only 34 Gy because of neutropenic fever. A total of 77% of patients underwent 3D treatment planning radiation using computed tomography.

Treatment Efficacy

The tumor response for the induction therapy was 7 PRs, 19 NCs, 2 PDs in the CS arm, and 7 PRs, 19 NCs, 2 PDs in the CRS arm. Overall response rate was 25% in both arms. The number of patients who underwent surgery was 25 of 29 (86.2%) in the CS arm and 26 of 29 (89.7%) in the CRS arm. The reasons for patients not undergoing surgery were PD in 2 patients, no recovery of PS after chemotherapy in 1 patient, and patient refusal in 1 patient in the CS arm, and PD in 2 patients and no recovery from adverse events in 1 patient in the CRS arm. Postprotocol treatment of patients not undergoing surgery was radiotherapy in 2 patients, chemoradiotherapy in 1 patient, and best supportive therapy in 1 patient in the CS arm,

Table 2. Toxicity, From National Cancer Institute Common Toxicity Criteria, Version 2.0

Adverse Event	Chemotherapy + Surgery (n = 28)		Chemoradiotherapy + Surgery (n = 28)		*P*
	Grade 1 + 2	Grade 3 + 4	Grade 1 + 2	Grade 3 + 4	
Nausea	19 (67.9%)	0	21 (75.0%)	3 (10.7%)	.554
Vomiting	2 (7.1%)	0	7 (25.0%)	1 (3.6%)	.036
Fever	5 (17.9%)	0	14 (50.0%)	0	.011
Dyspnea	0	0	1 (3.6%)	0	.313
Infection	2 (7.1%)	2 (7.1%)	4 (14.3%)	1 (3.6%)	.716
Peripheral neuropathy	2 (7.1%)	0	1 (3.6%)	0	.553
Allergic reaction	1 (3.6%)	0	5 (17.9%)	0	.084
Dysphagia	0	0	9 (32.1%)	0	
Leukopenia	12 (42.9%)	13 (46.4%)	2 (7.1%)	26 (92.9%)	.075
Neutropenia	6 (21.4%)	21 (75.0%)	3 (10.7%)	25 (89.3%)	.313
Anemia	25 (89.3%)	0	24 (85.7%)	2 (7.1%)	.639
Thrombocytopenia	12 (42.9%)	0	19 (67.9%)	2 (7.1%)	.014
Increased transaminase	8 (28.6%)	0	12 (42.9%)	1 (3.6%)	.168
Increased creatinine	2 (7.1%)	0	7 (25.0%)	0	.069

and single-agent chemotherapy in 3 patients in the CRS arm. The downstaging rate was 20.8% (5 of 24, missing data 1 patient) in the CS arm and 40.0% (10 of 25, missing data 1 patient) in the CRS arm ($P = .215$). After downstaging, pTNM of patients in the CS arm was pT1N0M0, pT2N0M0, pT3N0M0, pT1N1M0, and pT2N1M0 in 1 patient each. On the contrary, pTNM of patients in CRS arm was T0N0M0 in 3 patients (pathologic complete response), T1N0M0 in 2 patients, T2N0M0 in 4 patients, and T2N1M0 in 1 patient. The surgical procedures used and the number of patients treated were as follows: lobectomy in 20, bilobectomy in 3, wedge resection plus segmentectomy in 1, and pneumonectomy in 1 (the CS arm); lobectomy in 23, bilobectomy in 1, and exploratory thoracotomy in 2 (the CRS arm).

Toxicity

Table 2 summarizes the toxicity characteristics among the treated patients. The most common toxicity was a grade 3 or 4 leukopenia in 26 patients (92.9%) in the CRS arm and 13 patients (46.4%) in the CS arm ($P = .075$). Grade 3 or 4 neutropenia was reported in 25 (89.3%) and 21 (75.0%) patients in the CS arm ($P = .313$). Grade 3 or 4 thrombocytopenia was reported in 2 patients (7.1%) in the CRS arm but was not observed in any patient in the CS arm. Among the nonhematological toxicities, grade 1 or 2 vomiting was reported in 7 (25.0%) cases in the CRS arm and in 2 (7.1%) in the CS arm ($P = .036$). Grade 1 or 2 fever was reported in 15 patients (50.0%) in the CRS arm and 5 (17.9%) in the CS arm ($P = .011$). Grade 1 or 2 dysphagia due to radiation was reported in 9 patients (32.1%) in the CRS arm. Other toxicities during induction therapy did not differ between the arms. No treatment-related deaths were reported throughout the trial in either arm.

Survival and First Relapse Site

Median follow-up times for surviving patients in the CS and CRS arms were 60.7 months (range 1.8 to 86.5 months) and 60.8 months (range 44.5 to 87.5 months), respectively. Progression-free survival (PFS) did not improve in the CRS arm versus the CS arm (median, 12.4 months vs 9.7 months; HR = 0.68 [95% CI = 0.38-1.21], $P = .187$; Fig. 3A). Overall survival (OS) also did not improve in the CRS arm versus the CS arm (median, 39.6 months vs 29.9 months; HR = 0.77 [95% CI = 0.42-1.41], $P = .397$; Fig. 3B). The 3-year survival rates in the CRS and CS arms were 51.7% and 39.3%, and the 3-year PFS rates were 34.5% and 17.9%, respectively. The median OS of patients with and without downstaging in the CRS arm was 72.1 months and 31.2 months, respectively (HR = 4.16 [95% CI = 1.16-14.93], $P = .018$). In the CS arm, these values were 32.6 months and 29.0 months, respectively (HR = 1.47 [95% CI = 0.424-5.09], $P = .542$). Exploratory analyses of all patients from both arms according to mediastinal downstaging showed that patients without downstaging (n = 35) had a median PFS of 9.4 months and a 3-year PFS rate of 14.3% (Fig. 4A). However, patients with downstaging (n = 15) had a significantly longer median PFS of 55.0 months and a 3-year PFS rate of 60.0% (HR = 3.39 [95% CI = 1.54-7.48], $P = .001$). In terms of the OS, patients without downstaging had a median OS of 29.5 months, with a 3-year survival rate of 40.0% (Fig. 4B). In contrast,

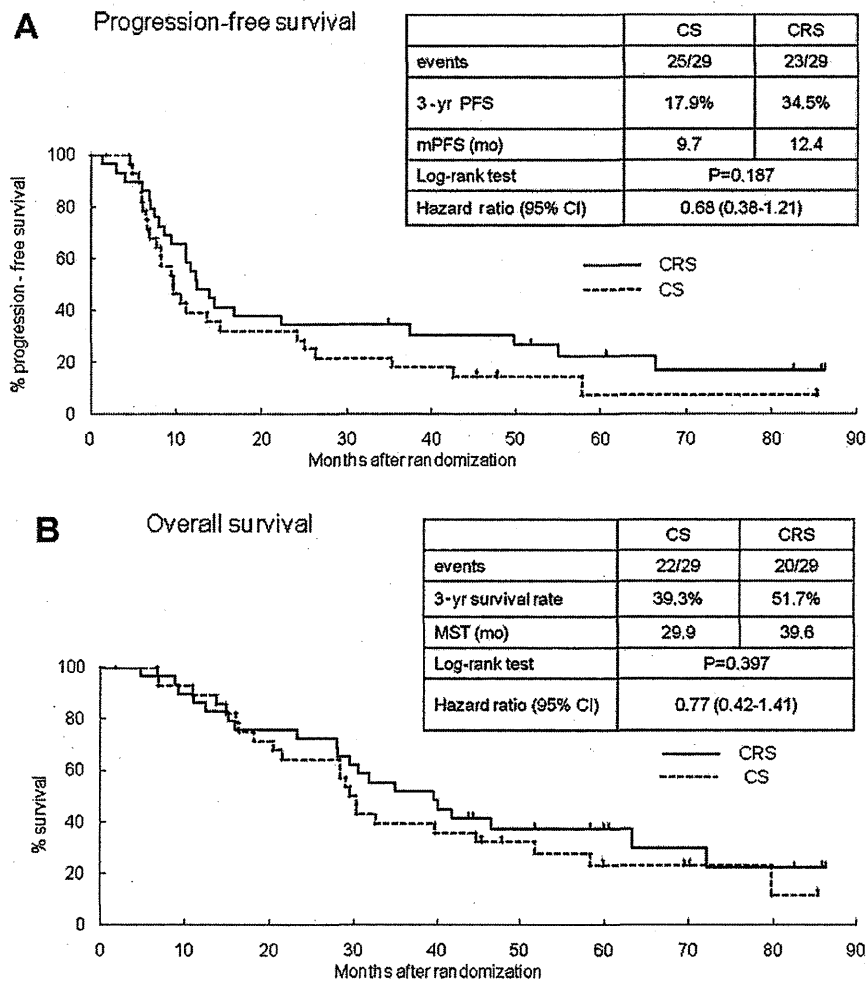

Figure 3. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival analyses. CI, confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

patients with downstaging had a significantly longer OS of 63.3 months, with a 3-year survival rate of 66.7% (HR = 2.62 [95% CI = 1.12-6.09], $P = .021$).

Relapse was noted in 25 patients out of 28 in the CS arm (missing data 1) and in 24 out of 29 in the CRS arm. Local lymph node relapse in the CS arm and CRS arm occurred in 7 and 5 patients, respectively. Distant relapse occurred in 13 and 15 patients in the CS and CRS arms, respectively. Local and distant relapses occurred in 5 and 4 patients in the CS and CRS arms, respectively (Table 3). It is noteworthy that the brain and lung are the most frequent sites of distant metastasis (21 patients). One notable difference in the relapse pattern was the recurrence in the radiation field of the hilar and mediastinal lymph nodes. This was 41% (12 of 29 patients) in the CS arm, significantly higher than the 17% (5 of 29 patients) found in the CRS arm ($P = .0435$, chi-square test).

DISCUSSION

Our present study focuses on stage IIIA disease with pathologically proven mediastinal lymph node metastasis by investigating whether CRS would confer a better 5-year survival than CS. The observed trend was of a better OS and PFS in the CRS arm than in the CS arm. The median OS in the CRS and CS arms was 39.6 months

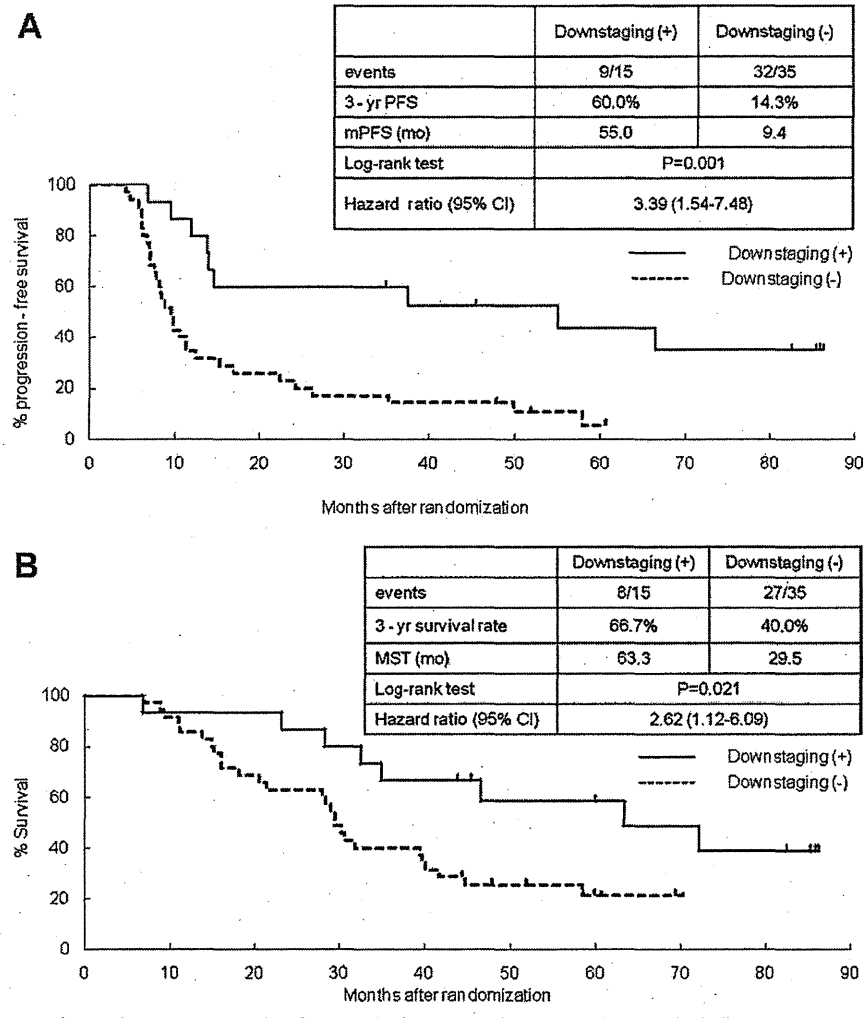

Figure 4. Curves are shown for (A) progression-free survival (PFS) and (B) overall survival of all resected patients according to downstaging. CI indicates confidence interval; CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery; MST, median survival time.

and 29.9 months, respectively. The median PFS in the CRS and CS arms was 12.4 months and 9.7 months, respectively. These differences are not statistically significant due to the small sample size. However, the median OS in the CRS arm in our study is clearly favorable compared with previous reports (13-32 months) in which patients with stage IIIA and IIIB disease were treated with preoperative chemoradiotherapy.[9-12] In particular, Albain et al recently reported a phase 3 study of concurrent chemoradiotherapy with or without surgical resection for stage IIIA, N2 NSCLC.[14] The median OS with and without surgery was 23.6 months and 22.2 months, respectively ($P = .24$) and the median PFS was better in patients with surgery (12.8 months vs 10.5 months, $P = .017$). In further exploratory analysis, the median OS was improved in the surgical group when a lobectomy was performed compared with a matched nonsurgical group (33.6 months vs 21.7 months, $P = .002$). However, the OS for patients in the pneumonectomy subgroup of the surgical cohort was not significantly poorer than that of the matched cohort in the nonsurgical group (18.9 months vs 29.4 months). A randomized study conducted by the German investigators directly compared CS with CRS in patients with stage IIIA-IIIB NSCLC.[15] The interventional-concurrent group

Table 3. First Relapse Site

Relapse Site	CS (n = 25)	CRS (n = 24)
Local	7	5
Hilar/mediastinal lymph node[a]	7	3
Supraclavicular lymph node	1	3
Distant	13	15
Lung	5	11
Bone	3	4
Liver	2	3
Brain	9	9
Para-aortic lymph node	0	2
Others	0	4
Local + distant	5	4
Hilar/mediastinal lymph node[a]	5	2
Supraclavicular lymph node	2	3
Lung	3	2
Bone	1	0
Pericardium	2	0
Brain	1	2
Others	2	0

Abbreviations: CRS, concurrent chemoradiotherapy followed by surgery; CS, chemotherapy followed by surgery.
[a] Recurrence in the radiation field.

was to receive 3 cycles of cisplatin and etoposide, followed by twice-daily radiation (total 45 Gy) with concurrent weekly carboplatin and vindesine, and then surgical resection. The control chemotherapy group was to receive 3 cycles of cisplatin and etoposide followed by surgery and then further radiotherapy. Of 524 eligible patients, 142 of 264 (54%) in the interventional group and 154 of 260 (59%) in the control group underwent surgery; 98 of 264 (37%) and 84 of 260 (32%) underwent complete resection. There was no significant difference according to the treatment group for PFS (intervention group: median 9.5 months vs control group: 10.0 months) or for OS (median 15.7 months vs 17.6 months). This may be due to the fact that they enrolled a substantial proportion of patients with a high disease burden (15% with T4N2 and 22% with T4N3).

Systemic chemotherapy is another neoadjuvant treatment modality that has been administered before surgery. The postsurgery OS in these cases was found to range from 20 to 28.7 months, and the 3-year survival rate ranged from 17% to 45%.[4-8] More recently, van Meerbeeck et al conducted a phase 3 trial that investigated the role of surgery versus radiotherapy after induction chemotherapy in 579 patients with pathologically documented stage IIIA, N2, NSCLC.[16] Patients received 3 cycles of platinum-based chemotherapy, and nonprogressors were then randomized for surgery (n = 164) or thoracic radiotherapy (n = 165). The median and 5-year OS values for patients assigned to the resection group versus the radiotherapy group were 16.4 versus 17.5 months and 15.7% versus 14%, respectively (HR = 1.06 [95% CI = 0.84-1.35]). However, the median OS was poorer than in our present study (39.6 months in the CRS arm) or in the study by Albain et al (23.6 months in chemoradiotherapy in the surgery arm).

The response rate from induction chemoradiotherapy in our study was relatively low (25%) and is poorer than the 59% to 74% reported for other concurrent chemoradiotherapy studies.[9-12] The most likely reason is that the period between induction therapy and surgery in our patients was short and shrinkage could not be confirmed in many cases, which resulted in a low response rate and a high stable disease rate (67.9%). Another possible reason is that in the present study we used a suboptimal preoperative radiation dose schedule (40 Gy in 20 fractions over 4 weeks). A better response rate is typically achieved following a higher radiation dose (45 Gy)[14] or hyperfractionated accelerated irradiation.[9-11,15,17,18] An exploratory analysis showed that the OS of our patients with downstaging (72.1 months) was significantly better than that of patients without downstaging (31.2 months) in the CRS arm ($P = .008$), although this survival benefit in patients with downstaging was not demonstrated in the CS arm ($P = .542$). Although the in-field recurrence was significantly higher in the CS arm compared with the CRS arm, this did not translate to better PFS or OS in the CRS arm because there was no significant difference of distant and distant + local recurrence between the 2 arms (CS vs CRS, 18/28; 64% vs 19/29; 65%). The number of patients having multistation lymph node disease in the CS arm was relatively high (14 of 29, 52%) compared with the CRS arm (11 of 31, 35%). This tendency might have led to low downstaging rate in the CS arm because irradiation has potent local control effect. The high downstaging rate and the absence of treatment-related death in our CRS arm translated into a longer median OS (39.6 months) and higher 3-year survival rate (51.7%). Choi et al[9] conducted a phase 2 study of an induction treatment involving twice-daily radiation and concurrent chemotherapy in 42 patients with stage IIIA NSCLC, and reported that the 5-year survival rate in patients with pathological complete response (79%) was significantly higher ($P = .04$) than that in patients with pN1 (42%) or pN2

(15%). In addition, Betticher et al[19] conducted a multicenter phase 2 trial of the efficacy of neoadjuvant docetaxel-cisplatin in 90 patients with NSCLC who had locally advanced N2 disease. Using multivariate analyses, they demonstrated that mediastinal clearance (downstaging rate: 60%, $P = .0003$,) and complete resection ($P = .0006$) were strong prognostic factors. These data indicate that, in patients with stage IIIA NSCLC, downstaging in mediastinal lymph nodes significantly improves the survival outcome. Small sample size and low downstaging rate appear to be reasons why the same tendency was not observed in our patients in the CS arm. Downstaging may be related to a chemotherapy regimen and chemotherapy cycles delivered, because cisplatin is generally more effective than carboplatin in inducing tumor shrinkage, and tumor response is most efficacious at 3 cycles of chemotherapy.[20]

Induction chemotherapy or chemoradiotherapy in our present trial was well tolerated by patients in both arms, with excellent treatment compliance. No grade 3/4 fever was found in either arm, despite the high incidence of grade 3/4 neutropenia (75% in the CS arm, 89.3% in the CRS arm), nor was any grade 3/4 radiation esophagitis observed in the CRS arm. Conversely, grade 3/4 esophagitis has been recorded in 8% to 53% of patients where radiation was delivered in a hyperfractionated accelerated fashion.[9-11,17,18] More importantly, no treatment-related deaths were observed in either arm in our trial during the induction and postoperative periods. Lobectomies may be safely performed following induction therapy, whereas pneumonectomy, especially on the right, may carry an unacceptable rate of perioperative mortality.[14,15] The appropriate selection of patients to undergo resection following induction therapy is thus critical.

Our study was prematurely terminated because of poor accrual rate. We assume several reasons for poor accrual. The first reason was stage migration that upgraded former stage IIIA disease to stage IV disease due to more frequent usage of brain MRI and positron emission tomography in staging. Hence, the number of stage IIIA N2 patients is not as large as a decade ago. The second reason was the difference of definition of resectability between thoracic surgeons and pulmonary physicians (or medical oncologists). The third reason was the preference of surgeons and/or medical oncologists to treat their patients with more effective chemoradiotherapy in terms of local control. The final reason was the reluctance of some thoracic surgeons to carry out preoperative chemoradiotherapy due to the possibilities of postsurgical complications. This theme of induction therapy before surgery is extremely vital, and therefore we will have to overcome poor accrual in future randomized phase 3 trials. To accomplish the trial, it is very important to perform diagnostic procedures such as mediasitinoscopy, thoracoscopy, or bronchofiberscopic transbronchial biopsy. We also need to establish less toxic chemotherapy regimens such as carboplatin plus paclitaxel or platinum compounds plus pemetrexed, adopt less toxic radiation modality, make consensus on operability among surgeons and medical oncologists, and recruit more participating institutions.

Conclusions

The addition of radiotherapy to the induction chemotherapy regimen for stage IIIA (N2) NSCLC appears to confer better local control without adding significant adverse events. The favorable local control in this CRS arm did not translate to a significant survival difference. We consider this was due to the small sample size. Tumor downstaging after induction therapy is an important factor for improving patient survival.

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The authors made no disclosure.

REFERENCES

1. Mountain CF. Revisions in the international system for staging lung cancer. *Chest.* 1997;111:1710-1717.
2. Goya T,Asamura H,Yoshimura H, et al; Japanese Joint Committee of Lung Cancer Registry. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. *Lung Cancer.* 2005;50:227-234.
3. Shepherd FA. Induction chemotherapy for locally advanced non-small cell lung cancer. *Ann Thorac Surg.* 1993;55: 1585-1592.
4. Pass HI,Pogrebniak HW,Steinberg SM,Mulshine J,Minna J. Randomized trial of neoadjuvant therapy for lung cancer: interim analysis. *Ann Thorac Surg.* 1992;53:992-998.
5. Rosell R,Gómez-Codina J,Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med.* 1994;330:153-158.
6. Roth JA,Fossella F,Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst.* 1994;86:673-680.
7. Depierre A,Milleron B,Moro-Sibilot D, et al; French Thoracic Cooperative Group. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol.* 2002;20:247-253.

8. Nagai K,Tsuchiya R,Mori T, et al; Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group. A randomized trial comparing induction chemotherapy followed by surgery with surgery alone for patients with stage IIIA N2 non-small cell lung cancer (JCOG 9209). *J Thorac Cardiovasc Surg.* 2003;125:254-260.
9. Choi NC,Carey RW,Daly W, et al. Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small-cell lung cancer. *J Clin Oncol.* 1997;15:712-722.
10. Eberhardt W,Wilke H,Stamatis G, et al. Preoperative chemotherapy followed by concurrent chemoradiation therapy based on hyperfractionated accelerated radiotherapy and definitive surgery in locally advanced non-small-cell lung cancer: mature results of a phase II trial. *J Clin Oncol.* 1998;16:622-634.
11. Thomas M,Rübe C,Semik M, et al. Impact of preoperative bimodality induction including twice-daily radiation on tumor regression and survival in stage III non-small-cell lung cancer. *J Clin Oncol.* 1999;17:1185-1193.
12. Katakami N,Nishimura T,Takakura S, et al. Phase II study of combined modality therapy for non-small cell lung cancer patients with pathologically confirmed stage III, N2 disease [in Japanese] (abstract). *Haigan.* 1999;39:536.
13. Katakami N,Naya R,Nishimura T, et al. Long term results of induction carboplatin (CBDCA) and docetaxel (DOC) with concurrent radiation in early-stage non-small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol.* 2005;23(16 suppl): (abstract 7237).
14. Albain KS,Swann RS,Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009;374:379-386.
15. Thomas M,Rübe C,Hoffknecht P, et al; German Lung Cancer Cooperative Group. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* 2008;9:636-648.
16. van Meerbeeck JP,Kramer GW,Van Schil PE, et al; European Organisation for Research and Treatment of Cancer-Lung Cancer Group. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst.* 2007;99:442-450.
17. Friedel G,Budach W,Dippon J, et al. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: a single-center study. *J Clin Oncol.* 2010;28:942-948.
18. Hehr T,Friedel G,Steger V, et al. Neoadjuvant chemoradiation with paclitaxel/carboplatin for selected stage III non-small-cell lung cancer: long-term results of a trimodality phase II protocol. *Int J Radiat Oncol Biol Phys.* 2010;76:1376-1381.
19. Betticher DC,Hsu Schmitz SF,Totsch M, et al. Mediastinal lymph node clearance after docetaxel-cisplatin neoadjuvant chemotherapy is prognostic of survival in patients with stage IIIA pN2 non-small-cell lung cancer: a multicenter phase II trial. *J Clin Oncol.* 2003;21:1752-1759.
20. Hotta K,Matsuo K,Ueoka H,Kiura K,Tabata M,Tanimoto M. Meta-analysis of randomized clinical trials comparing Cisplatin to Carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2004;22:3852-3859.

EGFR Gene Mutations

Is it Prognostic or Predictive in Surgically Resected Lung Cancer?

Tetsuya Mitsudomi, MD, and Hirohito Tada, MD†*

The role of mutation of the *EGFR* gene as a predictive factor for epidermal growth factor tyrosine kinase inhibitor (EGFR-TKI) therapy in the treatment of metastatic non–small-cell lung cancer (NSCLC) was established by the IPASS trial,[1] which compared gefitinib with platinum doublet chemotherapy in clinically selected patients with a higher chance of *EGFR* mutation. In that trial, the hazard ratio (HR) of progression-free survival for gefitinib was 0.48 in patients with *EGFR* mutation, whereas it was 2.85 for patients without *EGFR* mutation.[1] The superiority of EGFR-TKI over chemotherapy, in terms of progression-free survival, was confirmed in five subsequent phase III trials in patients selected on the basis of *EGFR* gene mutation.[2–6] However, the role of *EGFR* mutation as a predictive or prognostic factor remains unclear in patients with earlier-stage disease, who undergo surgical resection.

In 2008, Marks et al.[7] reported a more favorable prognosis for NSCLC patients with *EGFR* mutation, compared with those without mutation, as assessed using univariate analysis. After this report, we published the similar observation that *EGFR* mutation was prognostic in univariate analysis; however, its prognostic value was lost when the analysis was adjusted for sex, smoking status, tumor grade, and stage.[8] Patients who received EGFR-TKI were excluded from both studies to avoid the predictive impact of *EGFR* mutation. As *EGFR* mutations are associated with female sex, nonsmoking status, or Asian ethnicity, all of which are known to be better prognostic factors, it may be difficult to determine the real effect of *EGFR* mutation itself, even by using multivariate analysis.

In this issue of *Journal of Thoracic Oncology*, D'Angelo et al.[9] updated the study by Marks et al.[7] by reporting that NSCLC patients with *EGFR* mutation had a lower risk of death compared with those without *EGFR* mutation (HR = 0.51, $p < 0.001$), using the largest NSCLC cohort ever described ($n = 1118$). However, because the predictive role of *EGFR* mutation has now been established in metastatic lung cancer, it was neither possible nor practical to exclude the 72 patients who received EGFR-TKI from the 222 patients with *EGFR* mutation. Therefore, it is still not very clear whether tumors with an *EGFR* mutation themselves behave dormantly in patients.

It would be more important to determine the predictive value of *EGFR* mutations for EGFR-TKI in a postoperative adjuvant setting. In the BR.19 trial, patients with completely resected stage IB–IIIA NSCLC were randomized to receive adjuvant gefitinib or placebo treatments.[10] Subsequently, the protocol was amended to allow adjuvant platinum doublet therapy before TKI. However, the enrollment in BR.19 was stopped when 503 patients were enrolled and all patients were taken off the medication study because the interim analysis of the S0023 trial demonstrated that the administration of maintenance gefitinib after chemoradiotherapy with consolidation docetaxel in locally advanced NSCLC was worse than the placebo.[11] The results of the BR.19 trial, with at least 4 years of follow-up, were presented at the 2010 annual meeting of the American Society of Clinical Oncology.[10]

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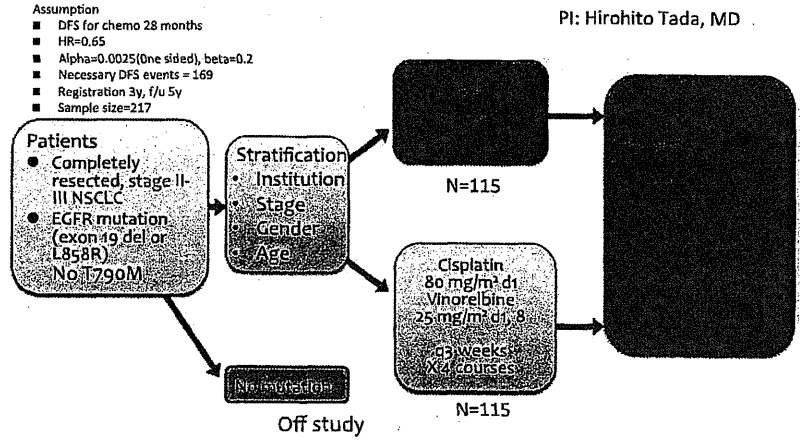

FIGURE 1. Schema of ongoing randomized phase III trial of adjuvant gefitinib versus cisplatin and vinorelbine in completely resected (stages II–IIIA) NSCLC patients with mutated *EGFR* (WJOG6410L, IMPACT study). NSCLC, non-small-cell lung cancer.

In the overall population, there was no significant difference in overall survival between the two arms ($p = 0.83$). However, it was very difficult to understand why patients who received adjuvant gefitinib seemed to have a higher risk of death (HR = 1.58, $p = 0.16$) even in a subset of patients with *EGFR* mutation ($n = 76$).[10] Considering that the study was prematurely terminated, and lacked drug exposure as well as statistical power, the question regarding the role of adjuvant gefitinib remains unanswered, even after that trial.

D'Angelo et al.[9] in this issue of *Journal of Thoracic Oncology* also compared outcomes in patients harboring *EGFR* mutation, who received adjuvant EGFR-TKI ($n = 82$) with those in patients who did not ($n = 202$), which is also the update of the previous publication.[12] They found that adjuvant EGFR-TKI was associated with a lower risk of recurrence (HR = 0.43, $p = 0.001$); however, this was not translated into a statistically significant difference in OS (HR = 0.50, $p = 0.076$). Because this was not a randomized trial, patient distribution was not well balanced; younger patients with higher stages receiving neoadjuvant/adjuvant cytotoxic chemotherapy were more common in the EGFR-TKI group.[9] Despite these flaws, the results of this study are certainly encouraging.

Surgery remains virtually the only chance for cure in patients with NSCLC, even in this era of targeted therapy. However, platinum doublet adjuvant chemotherapy, which is the current standard of care, only adds 5% to the 5-year survival rate of surgery alone.[13] It is certainly attractive to presume that postoperative adjuvant EGFR-TKI remarkably improves the outcomes of patients selected according to the presence of *EGFR* mutation. We are now performing a randomized phase III trial comparing adjuvant gefitinib with cisplatin/vinorelbine in patients with *EGFR* mutation (WJTOG6410L) (Fig.1).[14] We assume that the HR for disease-free survival is 0.65, and the sample size is 230. At the end of August 2012, 48 patients had been randomized. Our Chinese colleagues are also running a similar trial (C-TONG1104, NCT01405079). The fact that adjuvant imatinib therapy improves recurrence-free survival compared with placebo treatment (HR = 0.35, $p < 0.0001$) after the resection of primary gastrointestinal stromal tumor with c-kit expression[15] also raises the expectation for adjuvant gefitinib trials for NSCLC.

REFERENCES

1. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
2. Maemondo M, Inoue A, Kobayashi K, et al.; North-East Japan Study Group. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
3. Mitsudomi T, Morita S, Yatabe Y, et al.; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
4. Rosell R, Carcereny E, Gervais R, et al.; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–246.
5. Yang JC-H, Schuler MH, Yamamoto N, et al. LUX-Lung 3: A randomized, open-label, phase III study of afatinib versus pemetrexed and cisplatin as first-line treatment for patients with advanced adenocarcinoma of the lung harboring EGFR-activating mutations. *J Clin Oncol* 2012;30:suppl; abstr LBA7500.
6. Kingery SE, Wu YL, Zhou B, Hoffman RP, Yu CY. Gene CNVs and protein levels of complement C4A and C4B as novel biomarkers for partial disease remissions in new-onset type 1 diabetes patients. *Pediatr Diabetes* 2012;13:408–418.
7. Marks JL, Broderick S, Zhou Q, et al. Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. *J Thorac Oncol* 2008;3:111–116.
8. Kosaka T, Yatabe Y, Onozato R, Kuwano H, Mitsudomi T. Prognostic implication of EGFR, KRAS, and TP53 gene mutations in a large cohort of Japanese patients with surgically treated lung adenocarcinoma. *J Thorac Oncol* 2009;4:22–29.
9. D'Angeloven SP, Janjigianven YY, Ahyeven N, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. *J Thorac Oncol* 2012;7:1815–1822.
10. Goss GD, Arnold A, Shepherd FA, et al. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. *J Clin Oncol* 2010;28:49–55.
11. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008;26:2450–2456.
12. Janjigian YY, Park BJ, Zakowski MF, et al. Impact on disease-free survival of adjuvant erlotinib or gefitinib in patients with resected

lung adenocarcinomas that harbor EGFR mutations. *J Thorac Oncol* 2011;6:569–575.
13. Pignon JP, Tribodet H, Scagliotti GV, et al.; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 2008;26:3552–3559.
14. Tada H, Takeda K, Nakagawa K, et al. Vinorelbine plus cisplatin versus gefitinib in resected non-small cell lung cancer haboring activating EGFR mutation (WJOG6410L). *J Clin Oncol* 2012;30:(suppl; abstr TPS7110).
15. Dematteo RP, Ballman KV, Antonescu CR, et al.; American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009;373:1097–1104.

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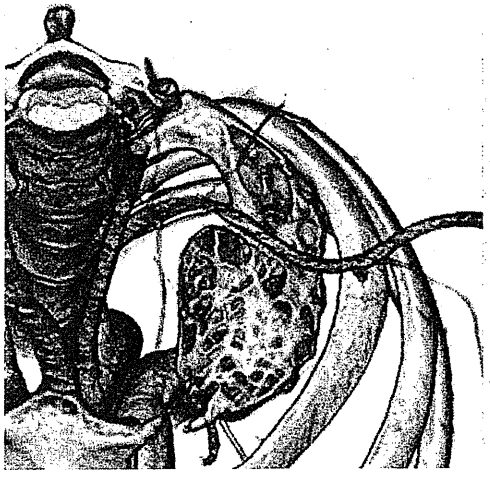

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CASE REPORT

Ectopic bone formation in a subsegmental bronchus

Takuma Tsukioka · Rhoji Yamamoto · Makoto Takahama · Ryu Nakajima · Hirohito Tada

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Abstract A 48-year-old man with fever and dry cough was admitted to our hospital. Imaging examinations revealed a mass lesion with calcification in the right B^3b bronchus and atelectasis in the distal lung area. Subsequently, right S^3 segmentectomy was performed. There was a hard polypoid mass completely obstructing the right B^3b bronchus. Histopathological findings suggested a metaplastic bone formation with mature bone marrow tissue leading to the primary bronchial cartilage. A case of ectopic bone formation in subsegmental bronchus has never been reported thus far. The resident fibroblasts might transform into osteoblasts under appropriate environmental conditions and induce bone formation.

Keywords Bronchial disease · Inflammatory cells · Inflammatory mediators

Introduction

Ectopic bone formation with mature bone marrow tissue in subsegmental bronchus has never been reported. Herein, we report a case of surgically resected ectopic bone formation in the subsegmental bronchus and discuss the cause of the disease.

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Case report

A 48-year-old man with fever and dry cough was admitted to our hospital. He suffered from only dry cough since the previous 2 months. He had no history of any disorder. Chest roentgenogram revealed a decrease in permeability of the right middle lung area (Fig. 1a). A chest computed tomography scan revealed a mass lesion with calcification in the right B^3b bronchus and atelectasis in the lung area distal to the mass lesion (Fig. 1b). Bronchoscopic examination revealed a polyploid lesion obstructing the right B^3b bronchus (Fig. 2a). The lesion was hard and covered by bronchial mucosa, and only normal bronchial mucosal tissue was obtained from transbronchial biopsy.

Preoperative clinical diagnoses were bronchial carcinoid, chondroma and bronchial papilloma. We considered malignant tumor unlikely. However, we considered an operation was indicated for diagnosis and removal of the atelectasis area. Subsequently, right S^3 segmentectomy was performed. There was a hard polyploid mass arising from the entrance of the right B^3b bronchus. The mass lesion completely obstructed the right B^3b bronchus and the peripheral lung area was organized (Fig. 2b). Histopathological findings revealed a metaplastic bone formation containing mature bone marrow tissue leading to the primary bronchial cartilage and organizing pneumonia in the peripheral lung field (Fig. 3).

The postoperative course was good, and he was discharged from the hospital on day 10. Six months after the operation, our patient was asymptomatic.

Discussion

We reported the case of a patient with bone replacement of bronchial cartilage in the right subsegmental bronchus. In

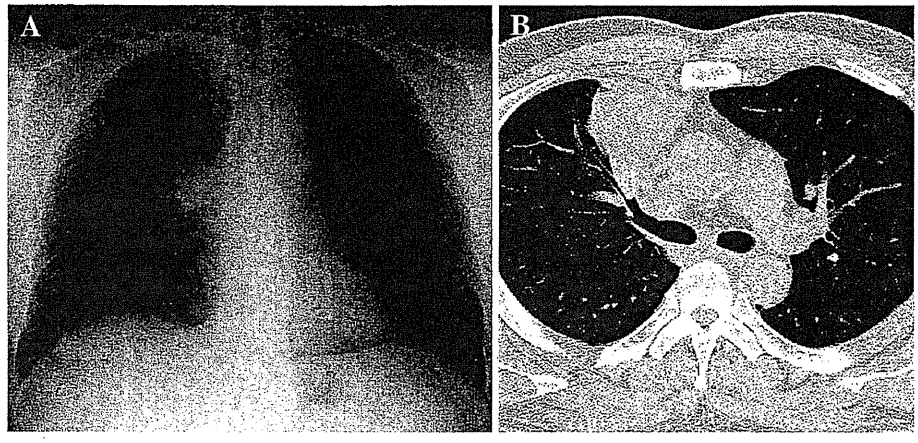

Fig. 1 **a** Chest roentgenogram revealed a decrease in the permeability of the right middle lung area. **b** Chest computed tomography revealed a mass lesion with calcification in the right B^3b bronchus and atelectasis in the lung area distal to the mass lesion

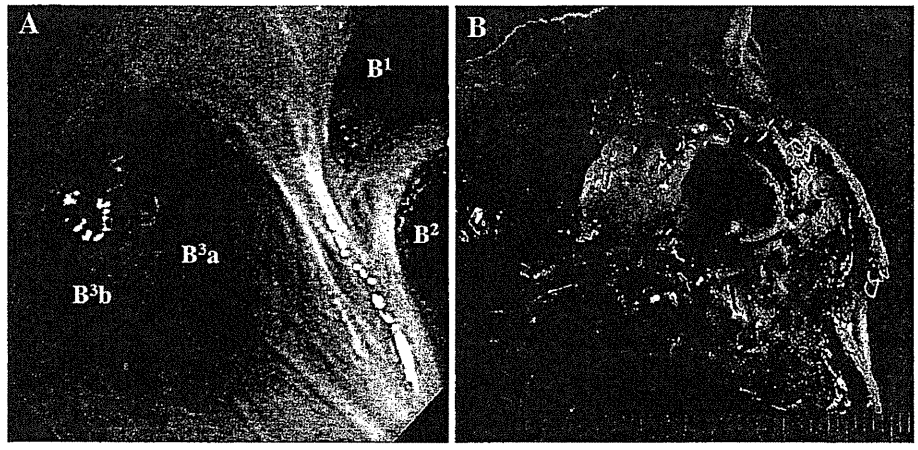

Fig. 2 **a** Bronchoscopic examination revealed a polyploid lesion obstructing the right B^3b bronchus. **b** Examination of the excised specimen revealed a hard elevated lesion leading to the lumen of the right B^3b bronchus

this case, we detected mature bone marrow tissue in the region of metaplastic bone formation. Our case is similar to that of broncholithiasis, and one of the causes of broncholithiasis is ossification of the bronchial cartilage. However, broncholithiasis with bone marrow tissue has never been reported.

Resident fibroblasts are transformed into other mesenchymal cell types, including osteoblasts and chondroblasts. Fibroblasts could transform into osteoblasts under appropriate environmental conditions [1]. Lung cancer or carcinoid tissue sometimes contained ectopic bone formation [2]. Tumor cells are suggested to produce growth factors that transformed resident fibroblasts into osteoblasts and subsequently induced ectopic bone formation [3]. Bronchial cartilage is primarily responsible for maintaining the stability of the airway. Bacterial infection has been implicated in the pathogenesis of metaplastic bone formation of bronchial cartilage [4]. Eum et al. [5] reported that chronic inflammation caused by underlying tuberculosis played a role in the development of metaplastic bone formation of the bronchial cartilage. Other report suggested that poor perfusion of the cartilage might be a cause of metaplastic bone formation of the bronchial cartilage in patients who had undergone lung transplantation [6]. In the wound healing process, macrophages appear at the wound site first, followed by fibroblasts. The infiltrated macrophages generate growth factors, such as fibroblast growth factor, platelet-derived growth factor, and transforming growth factor beta, and stimulate the proliferation of fibroblasts [1]. These growth factors from infiltrated macrophages stimulated the transformation of fibroblasts into osteoblasts and induced ectopic bone formation in the subsegmental bronchus. In present case, various kinds of causes of ectopic bone formation were considered. Our patient suffered from dry cough without fever since the previous 2 months. Bronchial bone formation was induced by some kind of cause, and he might suffer dry cough during the bronchial obstructing process. There might be no symptom of infection during the bone formation process, and fever on admission might be due to the subsequent obstructive pneumonia. We had no identified cause of the bronchial ectopic bone formation in present case. However, we

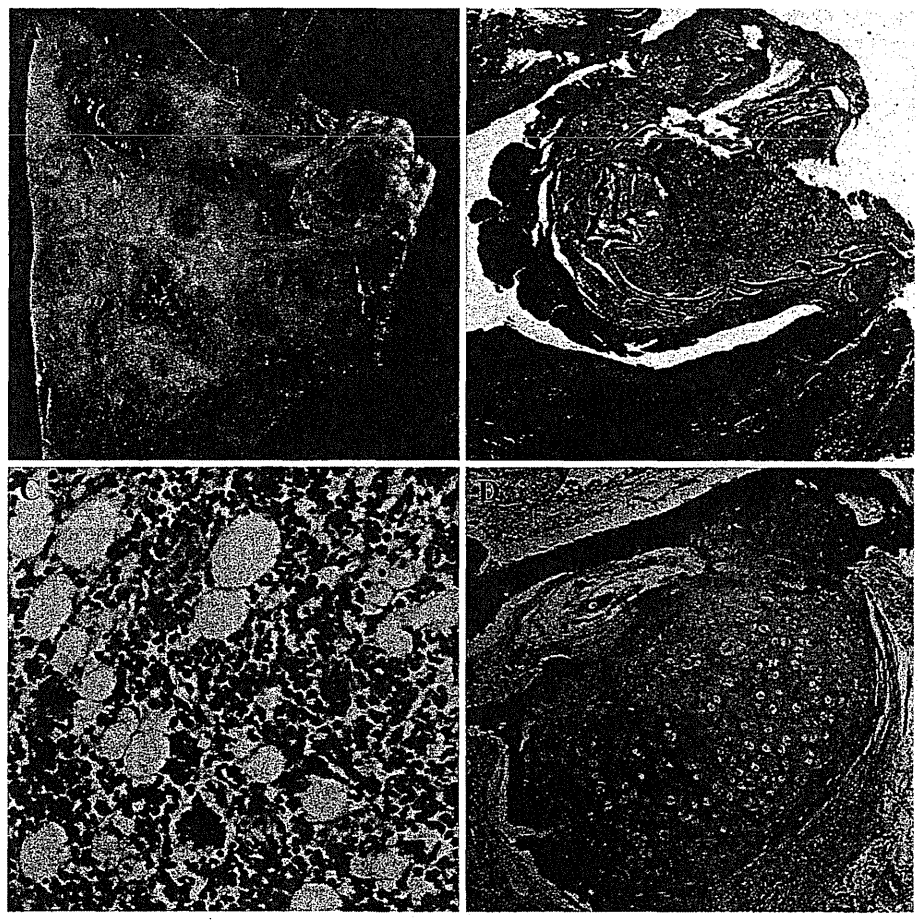

Fig. 3 **a**, **b** Pathological examination revealed ectopic bone formation obstructing the segmental bronchus (**b**: ×20). **c** Mature bone marrow tissue was detected in the ectopic osteogenic lesion (×200). **d** The osteogenic lesion was connected to the original bronchial cartilage (×40)

suggested that non-infectious factors such as ischemia and trauma in the subsegmental bronchus might induce a repair process and lead to ectopic bone formation.

Conclusion

Ectopic bone formation in the subsegmental bronchus is rare. We suggest that resident fibroblasts transform into osteoblasts and induce bone formation during the repair process.

References

1. Bourque WT, Gross M, Hall BK. Expression of four growth factors during fracture repair. Int J Dev Biol. 1993;37:573–9.
2. Chan ED, Morales DV, Welsh CH, McDermott MT, Schwarz MI. Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med. 2002;15(165):1654–69.
3. McLendon RE, Roggli VL, Foster WL Jr, Becsey D. Carcinoma of the lung with osseous stromal metaplasia. Arch Pathol Lab Med. 1985;109:1051–3.
4. Haraguchi M, Shimura S, Shirato K. Morphometric analysis of bronchial cartilage in chronic obstructive pulmonary disease and bronchial asthma. Am J Respir Crit Care Med. 1999;159:1005–13.
5. Eum SY, Kong JH, Jeon BY, Cho SN, Kim J, Via LE, et al. Metaplastic ossification in the cartilage of the bronchus of a patient with chronic multi-drug resistant tuberculosis: a case report. J Med Case Rep. 2010;4:156.
6. Yousem SA, Dauber JH, Griffith BP. Bronchial cartilage alterations in lung transplantation. Chest. 1990;98:1121–4.

Current status of postoperative follow-up for lung cancer in Japan: questionnaire survey by the Setouchi Lung Cancer Study Group—A0901

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