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# Surgical Resection Following Induction Chemoradiotherapy for Locally Advanced Lung Cancer

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**Fourteen patients with primary bronchogenic carcinoma, including 6 stage IIIA patients and 7 IIIB disease patients, underwent a pulmonary resection following cisplatin-based chemotherapy concurrent with 40 Gy of irradiation. The operations included 10 lobectomies, a bilobectomy, 2 pneumonectomies and a sleeve lobectomy. Dissection of the branches of the pulmonary artery was difficult, and an angioplastic procedure was employed in 2 patients. The average operating time was 306 minutes, and average blood loss was 338g. All patients were managed routinely, without any special measures. No major postoperative complication occurred, and patients were discharged from 11 to 35 days following surgery. Operative mortality rate was 0%. The median survival time was 36 months, and the 2-year survival rate was 68%.**

**There is usually a tremendous amount of fibrosis in the mediastinum and hilum following induction therapy, and therefore, dissection of the adhesion is difficult. However, with meticulous dissection, it is possible to perform a successful operation without fatal complications.**

**Key Words:** lung cancer, resection, induction chemoradiotherapy

## Introduction

The .prognosis of primary bronchogenic carcinoma remains poor despite recent advances in operation techniques, chemotherapy and radiotherapy. Surgery can provide a cure for approximately 70% of the patients with stage I lung cancer. However, long-term survival rates following resection for stages IIIA and IIIB disease is unsatisfactory.

In an effort to improve upon the poor results given by conventional therapy, induction chemotherapy and concurrent chemoradiotherapy followed by surgical resection have been becoming more promising treatments for locally advanced lung cancer. These multimodality therapies may contribute to an improved outlook on treatment of this deadly illness, however, surgeons must be aware of the higher risk of injuring vital organs in the thorax compared to conventional pulmonary resection.

This retrospective study summarizes the results of surgical resection following concurrent chemoradiotherapy for treatment of lung cancer, and discusses the intra- and post-operative morbidity and mortality.

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## Materials and Methods

### *Patient Population*

During a period from July 1992 to January 1998, 14 patients with primary bronchogenic carcinoma consecutively underwent thoracotomy after concurrent chemoradiotherapy at the Ehime Prefectural Central Hospital. The age of the patients at the time of operation ranged from 48 to 70 years, with the average being 59. There were 13 men and one woman in the group. Four tumors were on the right, and 10 on the left. A histological diagnosis of squamous cell carcinoma was made in 7 patients, of adenocarcinoma in 4 and of large cell carcinoma in 2. In one patient, postoperative pathologic examination revealed no viable cells as a result of the induction therapy. Before beginning the induction therapy, 6 patients were judged to have had stage IIIA tumors and 7 to have had stage IIIB disease (Table 1).

### *Combined Treatment Modality*

The chemotherapy regimen consisted of cisplatin (20

**Table 1.** Data of patients undergoing resection of lung with primary bronchogenic carcinoma after concurrent chemoradiotherapy

| Case | Age | Sex | Primary Site* | Histology** | TNM Staging Before Induction | Pathologic TNM After Surgery |
|---|---|---|---|---|---|---|
| 1 | 65 | M | LU | Sq | T4N2M0 | T4N2M0 |
| 2 | 49 | M | LU | Ad | T4N0M0 | T1N0M0 |
| 3 | 59 | M | RM | Sq | T2N2M0 | T2N2M0 |
| 4 | 68 | F | LU | La | T4N2M0 | T0N1M0 |
| 5 | 62 | M | LU | Ad | T4N2M0 | T4N0M0 |
| 6 | 66 | M | LU | Sq | T4N2M0 | T0N0M0 |
| 7 | 59 | M | LL | Sq | T1N1M0 | T1N0M0 |
| 8 | 48 | M | RU | Ad | T3N1M0 | T3N0M0 |
| 9 | 49 | M | LL | Ad | T4N1M0 | T3N0M0 |
| 10 | 63 | M | LU | La | T3N2M0 | T1N2M0 |
| 11 | 70 | M | LU | Sq | T2N2M0 | T3N0M0 |
| 12 | 48 | M | LU | ? *** | T4N0M0 | TxN0M0 |
| 13 | 53 | M | RU | Sq | T2N2M0 | T3N1M0 |
| 14 | 68 | M | RU | Sq | T3N2M0 | T1N0M0 |

* LU=left upper lobe; RM=right middle lobe; LL=left lower lobe; RU=right upper lobe.
** Sq=squamous cell carcinoma; Ad=adenocarcinoma; La=large cell carcinoma.
*** No viable tumor cell was seen.

mg/m$^2$ on days 1 through 5) and etoposide (40 mg/m$^2$ on days 1 through 5) infusion, given every third week. In 3 patients, ifosfamide, vindesine or 5-fluorouracil was given as an option to etoposide. Total doses ranged from 250 to 450 mg for cisplatin, and from 500 to 700 mg for etoposide, administered over 5 weeks. A Corticosteroid (125 mg of methylprednisolone or 60 mg of prednisolone) was given from the start of chemotherapy with the dose tapering off from 15 to 112 days.

External radiation therapy to the primary tumor and adjacent mediastinum, a dose of 40 Gy (2 courses of 20 Gy in 10 fractions), was given concurrently with chemotherapy over a period of 6 to 7 weeks in 13 patients. One 48-year-old man underwent 70 Gy of radiation in 56 fractions on days 1 through 38.

Two to 34 days, with an average 10 days, following the end of irradiation regimen, patients were evaluated for clinical response and resectability of their tumors by means of fiberoptic bronchoscopy, computed tomography (CT) or magnetic resonance imaging (MRI) of the chest.

Twenty-four to 76 days, with an average 40 days, following the completion of induction treatment, a thoracotomy was carried out. The patients underwent a lobectomy, bilobectomy or pneumonectomy with hilar and mediastinal lymph node dissection. All operations were performed under general anesthesia in combination with epidural anesthesia, and with one-lung ventilation by means of a double lumen endotracheal tube. In general, dissection of pleural adhesions, mobilization of the lung, and exposure and dissection of the branches of a pulmonary artery was not easy. Not infrequently, it took an hour or more to identify and divide a branch of the pulmonary artery. A cord tape tourniquet for proximal control of the main pulmonary artery was placed for ready use, as a contingency, should the pulmonary artery become injured. The bronchial stump was closed with 3-0 nylon interrupted sutures according to Sweet's method. The closed stump was not covered with pleura or a fat pad. In one case of a right upper sleeve lobectomy, the anastomosis was carried out with 4-0 monofilament polyglyconate sutures and wrapped with a pedicled anterior mediastinal fat pad.

Three patients underwent either a combined wedge resection of another lobe, a resection of partial pleura adjacent to the tumor, or a resection of the adventitia of the thoracic aorta. Two patients underwent a left upper lobectomy with partial resection of the left main pulmonary artery. A right upper sleeve lobectomy was carried out on one patient.

All patients except one who underwent a left pneumonectomy was extubated immediately following completion of the operation. Postoperative management at the intensive care unit (ICU) was discontinued the next day in all patients. In the postoperative period, corticosteroid was not administered to any patient. All patients were managed routinely, and no special measures were undertaken. Only one patients underwent post-operative adjuvant chemotherapy or radiotherapy.

Histological typing and TNM staging were classified and the effect of the induction therapy (Ef) was graded according to the General Rule for Clinical and Pathological Record of Lung Cancer[1].

## Result

Thirteen of the fourteen patients underwent radical resection with histologically negative resection margins. One patient who underwent a right upper sleeve lobectomy had a microscopically positive margin on the proximal end of the bronchial sleeve and was treated with postoperative radiotherapy (30 Gy in 10 fractions) combined with chemotherapy (10 mg of cisplatin for 10 days). The operating time ranged from 210 to 440 minutes, with an average of 306 minutes. The amount of bleeding during the operations ranged from 115 to 668 g, with an average of 338 g, and 3 patients received transfusion of 1 to 3 units of packed red blood cells.

Trouble with performing a resection of the lung were encountered in 12 of the 14 cases, and included difficulty in dissecting dense pleural adhesion in 5, difficulty in dissecting the pulmonary artery in 9, an undissectable

interlobar lymph node in 1 and perforation of the bronchus in 1 patient (Table 2).

Pleural adhesion was awkward, and combined resection of the parietal pleura was carried out in 3 cases. A part of the adventitia of the descending aorta was resected in one patient.

**Table 2.** Intraoperative Difficulties

| Situation | No. of Cases |
|---|---|
| Difficulty in dissecting adherent pleura | 5 |
| (Combined resection of parietal pleura) | (3) |
| Difficulty in dissecting pulmonary artery | 9 |
| (Pulmonary arterioplasty) | (2) |
| Undissectable interlobar lymph node | 1 |
| Perforation of proximal bronchus | 1 |

In 2 of the 9 patients, perivascular fibrosis caused difficulty in dividing the branches of the pulmonary artery, so techniques of arterioplasty were employed. A portion of the side wall of the left pulmonary artery was excised and the defect in the artery was oversewn using 5-0 polypropylene suture. In the remaining 7 cases, meticulous dissection of the vascular sheath resulted in the successful dividing of the branches of the pulmonary artery.

An enlarged lymph node suggesting metastasis was fixed onto the side wall of the left pulmonary artery in a 70-year-old patient, who underwent a pneumonectomy. In one patient perforation of the intermediate trunk of the right bronchus occurred while dissecting the bronchus with adhesion of the interlobar lymph node, but the site of the injury was distal to the ultimate line of transection of the bronchus, so that a successful bilobectomy was carried out without a bronchoplastic procedure.

Post-surgical pathological examination revealed that the effects of induction chemoradiotherapy on the tumors were classified as Ef.c (no viable cancer cell) in 4 patients, Ef.2 (viable cancer cells seen in less than one-third of the tumor) in 6 patients, and Ef.1 (viable cancer cells seen in one-third or more of the tumor) in 4 patients.

Post-operative course was uneventful in 10 of the 14 patients. There was no operative death, and the hospital mortality rate was 0%. Three patients had an alveolar air leak requiring chest tube drainage for 8 days or longer. Major complications such as atelectasis, pneumonia, respiratory failure, bronchopleural fistula, hemothorax and empyema did not occur in any patient. Hospitalization after the surgery ranged from 11 to 35 days, with an average of 20 days (Table 3).

**Table 3.** Post-operative Course

| Event | No. of Patients |
|---|---|
| Duration of chest tube drainage | |
| 3- 5 days | 7 |
| 9-11 days | 3 |
| 21-22 days | 2 |
| Hospital stay following Surgery | |
| 11-14 days | 4 |
| 15-21 days | 6 |
| 22-35 days | 4 |
| Post-operative complications | |
| Prolonged air leak | 3 |
| Pleural effusion | 1 |

Estimates of survival for the 14 patients, with follow-up of 5 months to 6 years, showed a median survival time of 36 months, and the 2-year survival rate for these patients was 68% (Fig. 1). Six patients died of cancer 5 to 36 months after the surgery, and there were documented disease recurrences in 5 patients, including brain metastasis in 2, pulmonary metastasis in 1, relapse in the bronchial stump in 1 and carcinomatous pleuropericarditis in 1 patient. Two patients who survived for 37 and 45 months died of perforation of a gastric ulcer and infarction of the brain stem, respectively (Table 4).

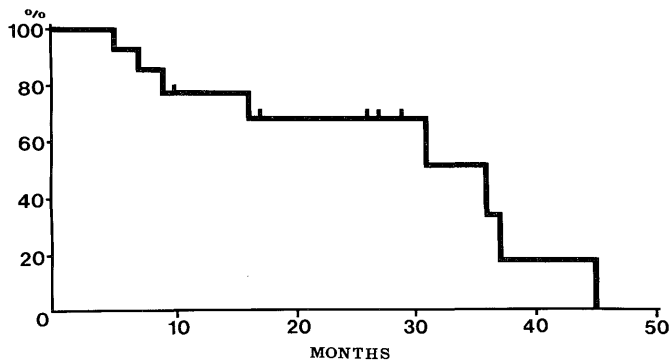


**Fig. 1** Overall probability of survival (death from any cause) of 14 patients undergoing pulmonary resection following induction chemoradiotherapy for primary bronchogenic carcinoma. Zero time on abscissa represents the date of pulmonary resection.

## Discussion

The prognosis of primary lung cancer is unsatisfactory, although surgery may provide a long-term cure for selected patients. Long-term chance of survival following the resection of stage III lung cancer is disappointing, and the treatment of advanced disease remains

**Table 4.** Response and Outcome of Pulmonary Resection Following Induction Chemoradiotherapy

| Patient | Age | Surgery | Effect of Induction Therapy | Follow-up |
|---|---|---|---|---|
| 1 | 65 | Lobectomy | Ef. 2 | 5 mo., died |
| 2 | 49 | Lobectomy | Ef. 2 | 37 mo., died |
| 3 | 59 | Bilobectomy | Ef. 1 | 16 mo., died |
| 4 | 68 | Lobectomy | Ef. 2 | 36 mo., died |
| 5 | 62 | Lobectomy | Ef. C | 9 mo., died |
| 6 | 66 | Lobectomy | Ef. C | 31 mo., died |
| 7 | 59 | Lobectomy | Ef. C | 45 mo., died |
| 8 | 48 | Lobectomy | Ef. 2 | 7 mo., died |
| 9 | 49 | Pneumonectomy | Ef. 2 | 29 mo., alive |
| 10 | 63 | Lobectomy | Ef. 2 | 27 mo., alive |
| 11 | 70 | Pneumonectomy | Ef. 1 | 26 mo., alive |
| 12 | 48 | Lobectomy | Ef. C | 17 mo., alive |
| 13 | 53 | Sleeve lobectomy | Ef. 1 | 10 mo., alive |
| 14 | 68 | Lobectomy | Ef. 1 | 5 mo., alive |

controversial[2,3,4]. Preoperative chemoradiotherapy in patients with lung cancer is a theoretically attractive concept, in which the tumor size can be reduced, facilitating a complete resection and treatment of micrometastases, but these theoretical advantages have yet to be proven to yield clinical benefit or improve chance of survival.

Since the advent of cisplatin, the results of chemotherapy for advanced lung cancer have been improving, and employing irradiation in combination with this tumorcidal drug may contribute to survival benefit[5]. Improved survival rates for patients with stage III lung cancer treated with combination chemotherapy and irradiation preoperatively has been reported[6,7,8,9,10,11]. However, physicians should be aware of the risk of perioperative mortality and morbidity in this very aggressive treatment[12]. Actually, a review of the literature revealed that the operative mortality for thoracotomy following induction chemoradiotherapy ranged from 5% to 23%, although no case of death on the operating table has ever been reported[6,7,8,9,10].

Though the amount of fibrosis in the mediastinum and hilum following induction therapy varies, the dissection of the adhesion is difficult. Dissection of the branches of the pulmonary artery is particularly difficult and time-consuming in an operation following irradiation, and therefore surgeons may be reluctant to carry out a pulmonary resection. However, patient and meticulous dissection can make it possible to perform a successful operation and to avoid catastrophically injuring vessels. Bronchoplastic and angioplastic procedures can be carried out even following the chemoradiation therapy[13]. It may be preferred to cover the bronchial stump with a pedicled flap in order to minimize the possibility of disrupting the bronchus which may have a deteriorated healing capacity following irradiation[13,14]. However, in the present series, nobronchopleural fistula occurred in the 13 patients undergoing lobectomies or pneumonectomies without covering the bronchial stump. Careful dissection of the bronchus should be carried out to preserve as much of the bronchial blood supply as possible, and surgeons must not hesitate to employ a covering technique of the bronchial stump or anastomosis whenever they feel uneasy about leaving the suture uncovered.

In the present series, the mean operating time was 306 minutes, which was significantly longer than the average of 239 minutes for the 136 operations without pretreatment undertaken during the same period. However, mean blood loss was 338 g, which did not significantly differ from the mean of 253 g for the conventional operations. The mean duration of hospital stay after surgery was 20 days, which was not significantly different from that without induction therapy in this institution. Only the length of operating time and awkwardness of dissection in a pulmonary resection following induction therapy differed these operations from conventional operations.

In the present series, postoperative complications in 4 patients were nonfatal and healed after 9 to 22 days with chest tube drainage. However, major and potentially fatal complications such as bronchopleural fistula, atelectasis, pneumonia and acute respiratory distress after thoracotomy following induction chemoradiotherapy are not infrequently seen in the literature[6,7,8,9,10]. The explanation for the patients experiencing no major postoperative complications in the present series is unclear. One may account for it by the use of a corticosteroid during the induction therapy, although this was not administered postoperatively. Successful bronchovascular reconstruction after induction chemotherapy postoperatively using low dose steroids has been reported[13].

The median survival time in the present series was 36 months, and the 2-year survival rate was 68%. Five or more patients suffered recurrences, including 3 patients with distant metastases. A locoregional recurrence occurred in one patient whose tumor had no viable cells and whose bronchial margin was negative histologically. Of the 4 patients who had no histologically viable cancer cells in the resected specimen, 2 died of carcinomatous pleuropericarditis and pulmonary metastasis. A review of the literature revealed median survival time of 17 to 36 months[6,8,10] and 2-year survival rates of 40%[8] and 43%[10] following concurrent chemoradiotherapy. The Lung Cancer Study Group reported that of the 18 patients who had disease recurrence after complete resection, none had recurrence only in the chest, and 12 patients (67%) had recurrence only in distant sites[7].

Inconsistent staging is the most difficult problem in the study of treatment of lung cancer. It is not easy to estimate the clinical stage of the disease definitively in spite of the advent of computed tomographic scan and mediastinoscopy. The evaluation of the postoperative stage following induction therapy is even more unreliable because it must be altered by preoperative therapy to various degrees. In the operating field, surgeons are also unable to determine whether or not the fibrotic tissue contains viable cancer cells. Another problem is the delay of eradicating the tumor because of the lengthy pretreatment period. It takes 50 days or more to complete the concurrent chemoradiotherapy program and put the patient on the operating table, and physicians fear the disease advances while consuming the time in induction therapy and in waiting for operation.

The real benefit of induction chemoradiotherapy followed by pulmonary resection has not been universally approved, and the prognosis of advanced lung cancer still remains unsatisfactory even given this aggressive multimodality treatment. Better chemotherapeutic agents and optimal combination of chemotherapy with radiation need to be established. However, despite the risks of operative mortality and morbidity, this discussion of the technical aspects and results of surgery following chemoradiotherapy will encourage surgeons who are involved in or are considering this approach.

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