

Induction Chemoradiation Therapy with Cisplatin plus Irinotecan Followed by Surgical Resection for Superior Sulcus Tumor

Katsuhiko Shimizu,¹ Masao Nakata,¹ Ai Maeda,¹ Takuro Yukawa,¹ Yuji Hirami,¹
Kazuo Tanemoto,¹ and Mikio Oka²

Purpose: In this study, we retrospectively evaluate the safety and efficacy of induction chemoradiation using cisplatin plus irinotecan followed by surgical resection for superior sulcus tumor (SST).

Methods: We reviewed the records of four patients with solitary, previously untreated T3-4, N0-1 superior sulcus nonsmall cell lung cancers. Patients received two cycles of chemotherapy, cisplatin and irinotecan, every 4 weeks. Radiotherapy directed at the tumor was administered with a split schedule at the total dose of 40 Gy in 20 fractions. Thoracotomy was performed 4 weeks after completion of the chemoradiation.

Results: The toxicities of chemoradiation were mainly hematologic and were well-tolerated. Complete resection could be performed in all cases, and there was no postoperative mortality. At present, all the patients remain alive, and one has a local recurrence.

Conclusion: This trimodality approach is a safe and effective approach for the local control of SST. Further studies are necessary to confirm the results. (*Ann Thorac Cardiovasc Surg* 2010; 16: 326–330)

Key words: superior sulcus tumor, induction chemoradiation, cisplatin, irinotecan

Introduction

In 1932, Pancoast reported the characteristic clinical features of superior sulcus tumor (SST) as severe pain around the shoulder and arm, atrophy of the muscles of the hand, and Horner's syndrome.¹⁾ Treatment of nonsmall cell lung cancer (NSCLC) in the superior sulcus is associated with

difficulties related to the anatomical location of the tumors, namely, their potential to involve adjacent vital structures, including the brachial plexus, subclavian vessels, and spine.

With increasing experience in combined modality therapy during the past 15 years, induction chemoradiotherapy followed by resection was reported as an effective treatment strategy for locally advanced NSCLC,²⁾ and small studies have suggested that this approach might also be appropriate for SST.³⁾ Recent results of a large prospective multi-institutional trial of the Southwest Oncology Group (Intergroup 0160) also suggested that an intensive multimodality approach based on induction chemoradiotherapy and surgery should be recommended as the modern standard of care for Pancoast tumors.^{4,5)} However, the optimal protocol for chemotherapy in this setting is still undefined. Cisplatin/etoposide therapy has been commonly used in induction chemoradiation for

From ¹Division of Thoracic and Cardiovascular Surgery, Department of Surgery; and ²Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Okayama, Japan

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Address reprint requests to Katsuhiko Shimizu: Division of Thoracic and Cardiovascular Surgery, Department of Surgery, Kawasaki Medical School, 577, Matsushima, Kurashiki, Okayama 701-0192, Japan.
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Table 1. Patient characteristics

Case	Age/Gender	Side/main location	size (mm)	c-TNM	c-stage	Histology	Leading symptom
1	50M	Right/SS	53	T4N0M0	3B	SQ	Pain
2	55F	Right/AA	53	T3N0M0	2B	AD	Pain
3	59M	Right/SS	57	T4N0M0	3B	AD	Horner's syndrome
4	54M	Right/SS	63	T4N0M0	3B	AD	Pain

SQ, squamous cell carcinoma; AD, adenocarcinoma; AA, anterior apical; SS, superior sulcus.

locally advanced NSCLC. A recent study reported that cisplatin/irinotecan plus radiotherapy may be one of the most effective strategies for locally advanced NSCLC.⁶⁾

In this study, we retrospectively evaluated the safety and efficacy of induction chemoradiation therapy with cisplatin plus irinotecan followed by surgical resection for SST.

Patients and Methods

We reviewed the records of four patients who underwent induction chemoradiation with cisplatin plus irinotecan and surgery for SST from 2005 to 2007 at our institution. All four had solitary, previously untreated T3 or T4, N0-1 superior sulcus NSCLC. Prestudy staging included CT scans of the chest and upper abdomen, MRI of the brain, and a bone scintigram. Positron emission tomography (PET) was performed in one patient.

Induction therapy regimen

Based on a Japanese phase II study,⁶⁾ chemotherapy consisted of two cycles of cisplatin 60 mg/m² on day 1 and irinotecan 50 mg/m² on days 1, 8, and 15. The thoracic radiation was administered once daily in a split schedule. Five days a week with 2 Gy a day from day 2 of each chemotherapy cycle, with a total of 20 Gy provided in each of the first and second cycles. The total radiation dose was 40 Gy. The radiation target, defined by CT, included the primary tumor and the ipsilateral supraclavicular region, but not the mediastinum or hilum. The toxicities of the induction chemotherapy were recorded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

Evaluation after induction therapy and guidelines for surgical resection

Two weeks after completion of induction therapy, the patients were reassessed by physical examination and CT scans of the chest, upper abdomen, and brain. Response determinations were required at this point in the study.

Thoracotomies were undertaken in patients without distant metastases or local progression. Complete response (CR) was defined as complete radiological disappearance of all measurable or assessable disease. Partial response (PR) was defined as a 30% or greater decrease relative to the baseline of the sum of the perpendicular diameter of all measurable lesions. Progression was defined as a 20% or greater increase in the sum of the perpendicular diameter of all measurable lesions. Stable disease (SD) was defined by lesions that did not meet the criteria for CR, PR, or progression.

Thoracotomy was performed 4 weeks after completion of the induction chemoradiation. A lobectomy was required for the primary tumor resection. Areas of direct tumor extension into the chest wall or spine were resected en bloc along with the involved lung lobe. Complete mediastinal lymphadenectomy was performed.

Results

Patient characteristics

The patient characteristics are outlined in Table 1. The median age of the patients was 54.5 years (range, 50 to 59). The primary tumors were usually large, with a median tumor size of 57 mm (range, 53 to 63). In three patients, the SST invaded the chest wall and spine. In one, the tumor was mainly located in the lung apex associated with Pancoast syndrome.

Induction therapy

There were no treatment-related deaths. One patient received only one cycle of chemotherapy because of the development of grade 4 neutropenia, whereas both cycles of chemotherapy could be completed in the remaining three patients. The induction therapy was well tolerated. Leukopenia, neutropenia, and anemia were the most common grade 3 or more severe toxicities. After the induction therapy, no patients showed CR, but one (25%) showed PR and three (75%) SD (Table 2).

Table 2. Chemoradiotherapy

Case	Cycle	Radiation dose (Gy)	Adverse events (Grade 3 or 4)	Response	Reduction ratio
1	2	40	None	SD	15%
2	1	36	Neutropenia	SD	15%
3	2	40	Neutropenia	SD	0%
4	2	40	None	PR	50%

SD, stable disease; PR, partial response.

Table 3. Surgery

Case	Surgery (resected costae/vertebral body)	p-TNM	p-stage	Ef (months)	Complication	Recurrence	Survival
1	RUL (2,3,4) (Th3)	T4N0M0	3B	2	None	None	50
2	RUL (1,2)	T3N0M0	2B	1	None	None	46
3	RUL (2,3) (Th2)	T4N0M0	3B	1	None	Local	34
4	RUL (2,3,4) (Th2)	T3N0M0	2B	2	Af	None	18

Ef, effect of induction therapy.

1: minor response (more than two-thirds of the cancer cells viable)

2: major response (fewer than one-third of the cancer cells viable)

Af, atrial fibrillation.

Surgery

Lobectomy and chest wall resection were undertaken in all cases. More complex procedures, such as vertebral body partial resection, were undertaken also in three patients. Complete resection could be performed in all cases, and there was no postoperative mortality.

Histological findings

The final pathological responses are shown in Table 3. The pathological effects of induction therapy were evaluated according to *General Rules for Clinical and Pathological Records of Lung Cancer*, 6th edition. A major response (fewer than one-third of the viable cancer cells) was achieved in two patients. A minor response (more than two-thirds of the viable cancer cells) was observed in two patients.

A review of postinduction therapy CT scan reports and pathology reports showed that three of the four patients had a large residual mass on the CTs, but at operation, only a few scattered foci of tumors within mostly residual fibrosis were observed.

Survival and relapse information

As of March 31, 2009, after a median observation period of 36 months (range, 18 to 50), all patients remained alive. One (case 3) had a local recurrence in the vertebral body at 12 months after surgery and received chemotherapy.

Discussion

The success of combined-modality therapy for locally advanced NSCLC during the 1980s and 1990s led directly to the development of treatment for SST. It was considered that induction chemoradiation followed by resection might be a logical strategy for SST, which presents a formidable challenge with respect to local control. However, the optimal protocol for chemotherapy is still undefined for SST. Cisplatin-based therapy has commonly been used for induction chemoradiation. According to the literature, the major protocols used for induction therapy are MVP (mitomycin/vinblastine/cisplatin),^{3,7)} carboplatin and paclitaxel,⁸⁾ cisplatin and etoposide^{4,9)} (Table 4).

On the other hand, two phase III studies comparing cisplatin plus irinotecan with cisplatin plus vindesine for advanced NSCLC have been conducted in Japan, and cisplatin plus irinotecan therapy was found to be one of the significant independent factors determining a favorable outcome.¹⁰⁾ Based on these data, cisplatin plus irinotecan was selected for the reference arm in the trials conducted in Japan. Preclinical and clinical studies demonstrated the radiosensitizing activity of irinotecan.¹¹⁾ Therefore it was considered that cisplatin/irinotecan plus radiation therapy might be among the most effective treatment strategies for locally advanced NSCLC. Although a previ-

Table 4. Chemoradiation plus surgery for superior sulcus tumor: review of the literature (from 1990)

First author (publication)	Patients' numbers	CT regimen	RT dose (Gy)	Complete resection (%)	Recurrence (%)		
					local	distant	both
Martinez (1994)	18	MVP/MCP	46	76	9.0	NR	NR
Attar (1998)	11	TJ	60	82	NR	NR	NR
Rusch (2007)	116	EP	45	76	8.6	32.8	6
Marra (2007)	31	EP	45	94	3.2	22.6	3.2
Kunitoh (2008)	75	MVP	45	68	13.3	33.3	12

MVP, mitomycin, vindesine, cisplatin; MCP, mitomycin, cisplatin, followed by carboplatin; TJ, paclitaxel, carboplatin; EP, etoposide, cisplatin; NR, not reported.

ous Japanese dose-finding trial of cisplatin/irinotecan with concurrent radiotherapy (60 Gy) could not be completed because of unacceptable toxicity,¹²⁾ Oka et al. reported from a phase I trial that split-course radiotherapy with a rest period between two chemotherapy cycles demonstrated tolerability and yielded a good response rate.¹³⁾ Fukuda et al. reported the results of a phase II trial and concluded that this regimen seemed to be effective for local control and survival.⁶⁾ Therefore we used this regimen for the treatment of SST.

In this study, complete resection could be performed in all cases, and a major response was achieved in half of the patients. This therapeutic approach was very likely to be equally effective for the local control of SST and for that of advanced NSCLC. Moreover, it is worthy of note that none of our cases developed distant metastasis, which, according to the literature, is the most frequent relapse pattern in patients with SST. Its frequency has been variously reported to be 41%,⁵⁾ 35%,⁷⁾ and 26%,⁹⁾ and the brain appears to be the most frequent site of metastasis. Chen et al. described that irinotecan and carboplatin therapy are an effective treatment strategy for patients with brain metastasis associated with small cell lung cancer.¹⁴⁾ Chou et al. described that irinotecan-based chemotherapy is an effective treatment approach for brain metastasis associated with various cancers.¹⁵⁾ Based on these data, irinotecan-based chemotherapy seems to be advantageous for suppressing the development of distant metastasis, especially to the brain.

The results of this feasibility trial suggest that an intensive multimodality approach based on combined chemoradiotherapy and surgery is well tolerated. Inasmuch as a large randomized trial for patients with SST is difficult because of the relatively infrequent occurrence of this disease, the present clinical evidence from several studies, including this small one, suggests that induction chemoradiotherapy and surgery may be recommended as

the modern standard of treatment for SST. Future trials should investigate the role of new combinations of chemotherapeutic agents, both as a treatment agent for occult metastasis and as radiation sensitizers to improve the local control rate of the disease.

In conclusion, induction chemoradiation using cisplatin plus irinotecan and surgery for SST is a safe and effective approach to the treatment of local control and survival in patients with SST. More extensive trials, however, are necessary to confirm the results.

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