

The Long-Term Outcomes of Induction Chemoradiotherapy Followed by Surgery for Locally Advanced Non-Small Cell Lung Cancer

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Key Words

Non-small cell lung cancer · Locally advanced non-small cell lung cancer · Induction chemotherapy · Surgical resection · Prognosis

Abstract

Background: Although the concept of induction therapy followed by surgical resection for locally advanced non-small cell lung cancer (LA-NSCLC) has found general acceptance, the appropriate indications and the strategy for this treatment are still controversial. **Methods:** From 2000 through 2008, 36 patients received concurrent chemoradiotherapy followed by surgery. We retrospectively reviewed these cases, analyzed the outcomes and examined the prognosis. **Results:** The median radiation dose given was 60 Gy. Chemotherapy included a platinum agent in all cases; cisplatin-based chemotherapy was administered to 9 cases, and a carboplatin-based chemotherapy regimen was administered to 27. A complete resection was performed in 94% of the patients. Seventeen (47.2%) patients exhibited a complete pathological response, and downstaging was induced in 26 (72%) cases. The morbidity and 30-day mortality rates were 11.1 and 0%, respectively. The 5-year overall survival rate in the patients with complete resection (n = 33) was 83.3%. **Conclusions:** Induction chemoradiotherapy followed by surgery for LA-NSCLC provided a favorable prognosis for selected patients. A complete pathological response was found in about half of cases. This strategy is feasible and was associated with low morbidity and high resectability rates, suggesting that it contributed to improving the treatment results.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, and approximately one third of patients with lung cancer are diagnosed to have locally advanced disease [1]. Locally advanced non-small cell lung cancer (LA-NSCLC) has a significantly worse prognosis in comparison to less advanced disease [2]. However, appropriate indications pertaining to surgical treatment in this subgroup of patients are still lacking and are controversial [3, 4]. The theoretical advantages of preoperative induction therapy lie in a potential increase in the resectability rate, better compliance and a lower rate of distant relapse owing to eradication of micrometastases, both of which may contribute to achieving long-term survival for these patients. Although the concept of induction therapy followed by surgical resection has found general acceptance, it is still controversial in clinical practice from the perspectives of the timing of surgery and the precise procedure [5–7]. Therefore, information about the long-term outcomes and the most appropriate strategy for this subgroup is urgently needed. The aim of this study was to retrospectively identify the outcomes of induction chemoradiotherapy followed by surgery in patients with LA-NSCLC.

Patients and Methods

Patients

All patients gave their written informed consent for treatment, with the observational research and privacy policy fully explained. The pretreatment evaluation included a medical history, physical examination, complete blood cell count and serum chemistry data, including serum electrolyte, liver enzyme, bilirubin, creatinine and coagulation values. Patients were eligible for this study if they had histologically or cytologically documented stage III LA-NSCLC that was deemed resectable. Our eligibility requirements included being <75 years old, having an Eastern Cooperative Oncology Group performance status of 0–1, no previous chemotherapy or radiotherapy, and adequate pretreatment hematological function, renal function (a normal serum creatinine concentration), hepatic function and pulmonary function. We calculated the predicted residual pulmonary function using the following formula: predicted residual pulmonary function = pulmonary function × (1 – resected pulmonary segments/number of pulmonary segments on the actual state).

Surgery was indicated for patients with a forced expiratory volume in 1 s of >600 ml/m² [8]. Patients were excluded if they had contralateral hilar lymph node metastasis, a serious preexisting disease or a radiation field that exceeded half of one lung. Tumor staging was performed based on chest radiography, a computed tomography (CT) scan of the chest and upper abdomen and a bronchoscopy. Patients underwent a preoperative cardiovascular risk assessment, including ECG and ultrasound cardiography. The patients' records, including their clinical data, preoperative examination results, histopathological findings and the TNM stages were reviewed.

The preoperative assessments included chest roentgenography and CT of the chest, upper abdomen and the brain. Positron emission tomography (PET) scans were used in the assessment of the clinical staging. Magnetic resonance imaging (MRI) of the brain was routinely employed. Mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration was not routinely performed for the evaluation of N2 disease. Most of the cases were suspected to have invasive and extranodal expansion based on the CT and PET findings.

Treatment Plan

All patients received preoperative therapy including chemotherapy and concurrent definite radiotherapy. Patients were given docetaxel (DTX) at 30 mg/m² and carboplatin (CBDCA) at an area under the curve of 3 every 2 weeks for 6 courses [9], or they received cisplatin (CDDP) at 80 mg/m² and DTX at 60 mg/m² on day 1 [1], or CDDP at 80 mg/m² on day 1 and etoposide (VP16) at 100 mg/m² on days 1–3 [10] of a 21-day treatment cycle for 3 planned cycles.

Radiation treatment planning for all patients was based on CT scans. Radiation therapy was administered with 2.0-Gy daily fractions by a linear accelerator generating 10-MV photons. The initial radiotherapy target volume was the primary tumor, and ipsilateral hilar and mediastinal lymph nodes by anteroposterior parallel-opposed fields with a 1- to 1.5-cm margin around the primary tumor and involved nodes up to 60 Gy, targeted in 6 weeks without interruption. A shrinking field technique was used. Mediastinal lymph nodes were irradiated at up to 40 Gy for prophylaxis with tissue homogeneity corrections. These doses were calculated at the central axis without the use of lung correction. The paraesophageal nodes were included if the lesion was in the lower lobe. The contralateral hilum was excluded [11].

Routine re-evaluation was carried out according to the New Guidelines for Evaluation of the Treatment Response of Solid Tumors [12]. In principle, the period between the end of the radiation treatment and surgery was at least 8 weeks. Before surgery, a second risk analysis was performed, and the decision regarding surgical intervention was made jointly by a committee including the attending radiation oncologist, thoracic surgeon, medical oncologist and pulmonologist. For example, a case with radiation pneumonitis was excluded. Following re-evaluation, surgery was attempted for patients in whom R0 resection was deemed possible.

All surgeries were performed via open thoracotomy, and systematic mediastinal lymph node dissection (en bloc removal of the mediastinal fatty tissue containing the lymphatics) was performed as well. Extended resection was defined as a procedure that included combined resection of the surrounding structures and a complex lobectomy with reconstruction of the bronchus [13]. A resection was considered to be complete if, after review of the surgery and pathology reports, both surgical margins and the highest mediastinal lymph node were found to be free of tumor cells. The bronchial stump was, in principle, covered with pericardial fat tissue or an intercostal muscle pedicle. The pathological effect of induction therapy was classified according to the *General Rule for Clinical and Pathological Record of Lung Cancer*, sixth edition [14] as a pathologically complete response (complete cancer cell death; Ef3), a major response (fewer than one third of cancer cells were viable; Ef2) or a minor response (more than one third of cancer cells were viable; Ef1). The patients with complete resection did not receive any additional treatment.

All resected specimens were subjected to a pathological examination according to the 7th edition of the TNM classification as described by the IASLC. Follow-up information was obtained from all the patients through office visits or by telephone interviews. The patients were basically evaluated every 3 months by a physical examination, chest roentgenography, an analysis of the blood chemistry variables and measurements of the tumor marker levels. As a general rule, chest and abdominal CT scans, brain MRI and a bone scintiscan were obtained every 6 months for the first 2 years after surgery and annually thereafter for 5 years or more. Additional examinations were performed if any symptoms or signs of recurrence were detected. Survival was calculated from the date of surgery until death or the date of the last follow-up.

Statistical Analysis

The Kaplan-Meier method was used to estimate the probability of survival, and survival differences were analyzed using the log-rank test. Differences were considered to be statistically significant for p values <0.05. The data were analyzed using the StatView software package (Abacus Concepts, Inc., Berkeley, Calif., USA).

Results

Patient Characteristics

From 2000 through 2008, 1,121 consecutive patients with lung cancer underwent pulmonary resection at our institution. Of those, 44 LA-NSCLC patients who underwent induction chemoradiotherapy followed by surgery were included in this study. A salvage operation was performed for 8 patients. Therefore, a total of 36 patients (3.2%) were evaluable, and their characteristics are shown in [table 1](#). The patient sample consisted of 32 males and 4 females, with a mean age of 57.6 years (range, 29–74 years). The tumors included 19 adenocarcinomas, 15 squamous cell carcinomas (SQ), 1 adenosquamous carcinoma and 1 large-cell neuroendocrine carcinoma. Eight patients were in stage IIB, 16 in stage IIIA and 12 in stage IIIB.

Clinical Response and Survival

Twenty-seven patients received CBDCA plus DTX, 8 received CDDP plus DTX and 1 patient received CDDP plus VP16. The cumulative median radiation dose to the primary tumor was 60 Gy (range, 50–60 Gy). The median number of courses of induction chemotherapy was 3. The clinical response to the induction therapy was complete response in 1 patient, partial response in 32 and stable disease in 3 patients.

Surgery and Pathological Response

The median time from the end of the induction therapy until surgery was 94 days (range, 46–199 days). The operation was performed during a mean of 323 min (range, 190–530 min), and the mean blood loss was 407 ml (range, 107–1,098 ml). Only 1 case needed a blood transfusion. The surgical procedures included a lobectomy in 31 patients, bilobectomy in 2 patients, partial resection in 1 patient and a right-sided pneumonectomy in 2 patients. Eight cases and 1 case underwent a lung resection combined with a chest wall resection and azygos vein resection, respectively. Thirty-four patients had a complete tumor resection with microscopically negative margins. The reasons for the incomplete resections (n = 2) were as follows: residual cancer cells in the parietal pleura in 1 case and in the mediastinal lymph node in 1 case. Thus, a complete resection was performed in 94% of the patients.

Pathological Findings

With regard to the pathological effect of induction therapy, there were 17 (47.2%) patients who exhibited an Ef3 response, 12 who exhibited an Ef2 response and 7 who exhibited an Ef1 response. One case with complete response and 16 cases with partial response (50% of the 32 partial response cases) also showed an Ef3 response based on the imaging evaluations ([table 2](#)). With regard to the stage, downstaging was induced in 26 (72%) patients overall. Downstaging was obtained in 50% of the IIB patients, in 88% of the IIIA and in 67% of the IIIB patients ([table 3](#)).

Surgical Morbidity and Mortality

The morbidity and 30-day mortality rates were 11.1 and 0%, respectively. The morbidity included atelectasis, chylothorax, prolonged air leakage and empyema in 1 case each (table 4). One patient suddenly died from hemoptysis after right upper sleeve lobectomy 34 days after the procedure. Therefore, the 90-day mortality rate was 2.8%.

Prognosis and Recurrence

The median follow-up period was 2,246 days. The majority of the sites of tumor recurrence were hematogenous metastases. In total, 9, 2 and 2 cases had hematogenous, locoregional and both types of recurrences, respectively. Eighteen patients were alive and free of cancer at the last follow-up, while 11 and 2 patients had died of cancer or another cause (acute myocardial infarction and pneumonia in 1 case each), and 5 patients were alive with cancer.

The global 5-year overall survival (OS) rate was 77.8% in the present series (fig. 1a); the 5-year OS rates in the patients with complete resection (n = 33) and in those with stage III cancer were 83.3% (fig. 1b) and 79.9% (fig. 1c), respectively; the 5-year OS rate in both the non-SQ and SQ patients was 77.8% (fig. 2a); the 5-year OS rates in the patients with Ef1–2 and Ef3 response were 72.7 and 81.9%, respectively (p = 0.55) (fig. 2b), and the 5-year OS rates in the patients with and without downstaging were 83.9 and 53.6%, respectively (p = 0.39) (fig. 2c).

Discussion

This study included one expected and one novel finding. First, the non-SQ histology, Ef3 response and downstaging had a tendency to be associated with a favorable prognosis. These phenomena were expected. For example, adenocarcinoma histology has previously been reported to be associated with a more favorable prognosis [15]. Thus, the chemoradiotherapy response would be expected to differ between SQs and adenocarcinomas. Additionally, the data regarding the pathological response were consistent with previous results [16, 17]. The results of several clinical trials have indicated that a pathological response was the most important predictor of long-term survival [7, 18, 19]. Moreover, the favorable trend for cases with downstaging in this study is also consistent with the findings of previous studies [7, 20, 21].

Second, the treatment-related death in only 1 case and the overall favorable prognosis were somewhat unexpected. Our overall morbidity and mortality rates were exceptional. Previous studies have reported that the rate of postoperative morbidity ranged from 40 to 60%, and the mortality rates ranged from 4 to 20% [13, 22, 23]. The reported incidences of postoperative morbidity and mortality after induction therapy have varied in different studies, probably due to the sample size, eligibility criteria, the regimens used for preoperative treatment and the experience of the medical staff [24, 25]. There was a low frequency of morbidity and no 30-day postoperative mortality in our series. These excellent results might be due to selection bias given the retrospective nature of our analysis. Our eligibility requirements included patients at a relatively young age and with a good performance status and adequate organ function. The prolonged survival seen in this study might also partly be explained by these factors.

However, we think that these findings might have been due to a long period between the completion of radiation and surgery. This time lapse was about double that in other reports [26–28]. This might have reduced the preoperative risk and been useful for patient selection.

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In fact, we performed restaging after induction therapy to allow for the selection of the patients who had previously been considered to be unlikely to benefit from surgery [29].

Although complete resection is known to play a central role as a curative treatment for LA-NSCLC after induction chemotherapy [30, 31], our survival data were still much better than those in past reports. Careful patient selection is important for multimodality approaches, and the identification of patient subgroups who are likely to have an advantageous outcome after preoperative chemoradiation, and a narrowing of inclusion criteria to further increase the proportion of patients who go on to have surgery with complete resection should be the aim [21]. Of note, a complete pathological response was found in about half of our cases. Our pathological response rate was relatively high. Sakai et al. [9] reported that the overall response rate was 91%, based on an analysis of 32 patients with stage III unresectable NSCLC. In fact, 27 among the 36 cases in our series were treated with DTX and CBDCA. The use of a radiation sensitizer, which both of these drugs are, might have led to the higher pathological response rate [32, 33]. For this reason, the decisions regarding treatment should be made in a multidisciplinary setting that includes a thoracic surgeon, a medical oncologist and a radiation oncologist to determine the most appropriate treatment strategy [34].

There are several limitations that must be taken into account when considering the present findings. These include the retrospective nature of the study and the fact that it was carried out at a single institution. There were imbalances in the patients' characteristics that cannot be excluded due to the small number of patients and the selection bias for the patients. Furthermore, this study included T3N0 cases (so-called Pancoast tumors). Nevertheless, the current results highlight an important issue, because the long-term outcome of induction chemoradiotherapy followed by surgery for LA-NSCLC was favorable. A complete pathological response was found in about half of our cases. This strategy is feasible, and was associated with low morbidity and high resectability rates, suggesting that it contributed to improving the treatment results.

Disclosure Statement

There are no conflicts of interest or financial interests for any of the authors in association with this study.

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Table 1. Patient characteristics

Gender	
Male	32
Female	4
Mean age (range), years	57.6 (29–74)
Histology	
AD	19
SQ	15
ADSQ	1
LCNEC	1
Clinical stage	
IIB	8
IIIA	16
IIIB	12
Regimen of chemotherapy	
CBDCA/DTX	27
CDDP/DTX	8
CDDP/VP16	1
Pulmonary resection	
Lobectomy	31
Bilobectomy	2
Pneumonectomy	2
Partial resection	1
Curability	
Complete resection	34
Incomplete resection	2
Response	
CR	1
PR	32
SD	3
Pathological responsiveness	
Ef1	7
Ef2	12
Ef3	17

Values represent numbers of patients unless stated otherwise. AD = Adenocarcinoma; ADSQ = adenosquamous carcinoma; LCNEC = large-cell neuroendocrine carcinoma; CR = complete response; PR = partial response; SD = stable disease.

Table 2. Clinical and pathological responses

	Pathological responses			
	Ef1 (n = 7)	Ef2 (n = 12)	Ef3 (n = 17)	total (n = 36)
Clinical responses				
CR	0	0	1	1
PR	6	10	16	32
SD	1	2	0	3

CR = Complete response; PR = partial response; SD = stable disease.

Table 3. Relationship between the clinical diagnosis and pathological downstaging

Clinical stage	Pathological stage	n	Downstaging, %
IIB (n = 8)	0	3	50
	I	1	
	IIB	3	
IIIA (n = 16)	0	9	88
	I	5	
	IIIA	2	
IIIB (n = 12)	0	5	67
	I	3	
	IIIB	4	

Table 4. Outcome after surgery

Morbidity	4 (11.1%)
Atelectasis	1
Chylothorax	1
Prolonged air leak	1
Empyema	1
90-day mortality	1 (2.8%)
Hemoptysis	1

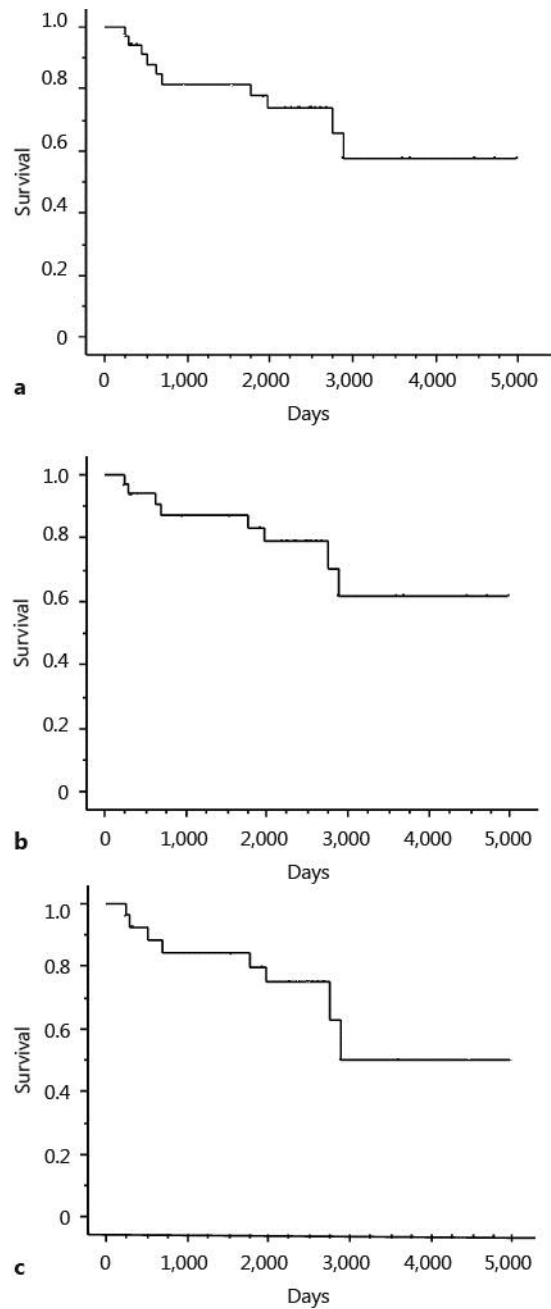


Fig. 1. **a** The results of a Kaplan-Meier analysis of the LA-NSCLC patients who received induction chemoradiotherapy followed by surgery. The 5-year OS rate in the patients was 77.8%. **b** The 5-year OS rate in the patients with complete resection was 83.3%. **c** The 5-year OS rate in the patients with stage III disease was 79.9%.

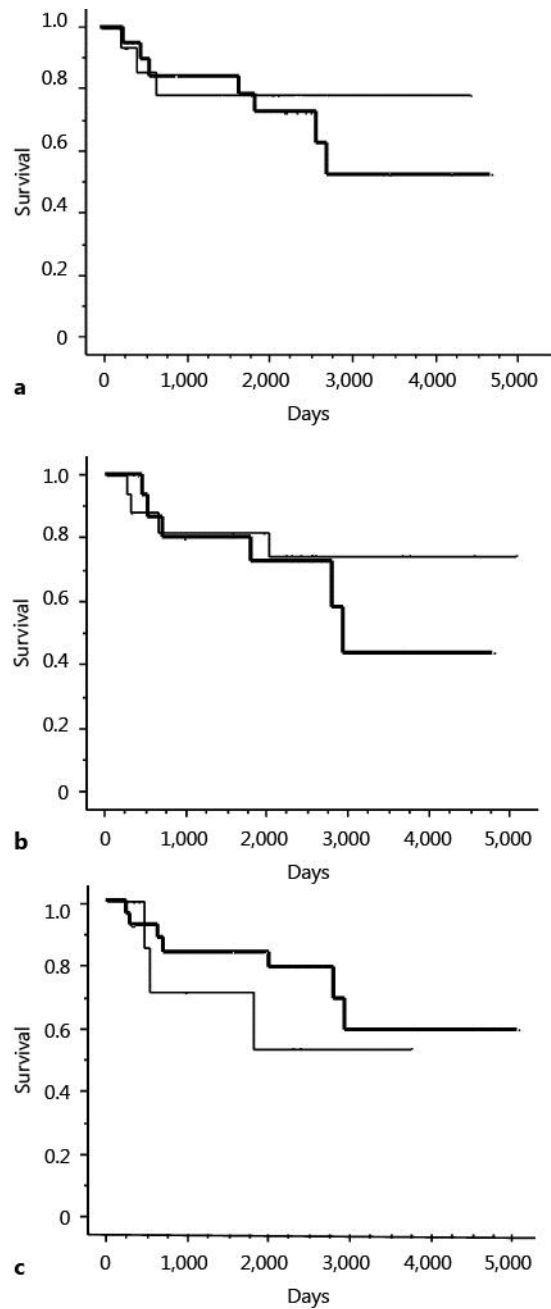


Fig. 2. The results of Kaplan-Meier analyses of the OS of patients stratified by histology, pathological response and downstaging. **a** The 5-year OS rate in both the non-SQ (thin line) and SQ (thick line) patients was 77.8%. **b** The 5-year OS rates in the Ef1–2 (thick line) and Ef3 (thin line) patients were 72.7 and 81.9%, respectively ($p = 0.55$). **c** The 5-year OS rates in the patients with downstaging (thick line) and without downstaging (thin line) were 83.9 and 53.6%, respectively ($p = 0.39$).