

## Induction Concurrent Chemoradiotherapy Using Paclitaxel and Carboplatin Combination Followed by Surgery in Locoregionally Advanced Non-Small Cell Lung Cancer – Asian Experience

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### Abstract

**Introduction:** It has been established that combined chemoradiotherapy treatment benefits selected patients with stage III Non Small Cell Lung Cancer (NSCLC). However, locoregional recurrence still poses a problem. The addition of surgery as the third modality may provide a possible solution. We report our experience of using the triple-modality approach in this group of patients. **Materials and Methods:** This is a retrospective review of 33 patients with stage III NSCLC treated between 1997 and 2005. Patients have good performance status and no significant weight loss. There were 26 males (79 %) with median age of 63 years (range, 43 to 74) and median follow-up of 49 months. Seventy-six percent had Stage IIIA disease. Chemotherapy consisted of paclitaxel at 175 mg/m<sup>2</sup> over 3 hours followed by carboplatin at AUC of 5 over 1 hour. Thoracic radiotherapy was given concurrently with the second and third cycles of chemotherapy. All patients received 50 Gray in 25 fractions over 5 weeks. **Results:** The main toxicities were grade 3/4 neutropenia (30%), grade 3 infection (15 %) and grade 3 oesophagitis (9%). Twenty-five patients (76%) underwent surgery. Of the 8 who did not undergo surgery, 1 was deemed medically unfit after induction chemoradiotherapy and 4 had progressive disease; 3 declined surgery. Nineteen patients (58 %) had lobectomy and 6 had pneumonectomy. The median overall survival was 29.9 months and 12 patients are still in remission. **Conclusion:** The use of the triple-modality approach is feasible, with an acceptable tolerability and resectability rate in this group of patients.

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**Key words:** Chemoradiotherapy, Neoadjuvant treatment, Surgery

### Introduction

Lung cancer is the leading cause of cancer mortality in Singapore.<sup>1</sup> The age standardised incidence rate is 45 per 100,000/year. Non-small cell lung cancer (NSCLC) comprises about 80% of all lung cancers and usually presents in the advanced stages (65% to 80%). Managing locally advanced Stage IIIA and IIIB NSCLC is often fraught with difficulties. The poor prognosis associated with this group of patients is partly due to the inoperability and the high loco-regional and distant failures despite radiation and chemotherapy. In the past, radiotherapy

alone was the traditional mode of treatment with a dismal 5-year survival rate of 3% to 5%. Combined modality treatment with chemotherapy and radiotherapy has been shown to produce superior results compared to radiotherapy alone. In an update of the landmark CALGB 8433 study, Dillman et al<sup>2</sup> showed a significant survival benefit for the chemo-radiotherapy group over the radiotherapy alone group which has been sustained for more than 7 years of follow-up (13% compared with 6% 7-year survival rate). However loco-regional failure continues to remain the main problem with at least 45% of patients still relapsing

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locally.<sup>2</sup> The introduction of surgery as a third modality after adequate down staging with chemoradiotherapy may address this problem. Various phase II trials that investigate the role of using tri-modality treatment involving chemotherapy, radiotherapy and surgery for this group of patients have shown encouraging survival results of 13 to 37% 5 year survival with the local failure rate still ranging from 11% to 36%.<sup>3-9</sup> An Intergroup Phase III trial which randomised patients with Stage IIIA disease to receive either induction chemoradiation prior to surgical resection to concurrent chemoradiation alone has recently demonstrated a better survival of 27.2% and 20.3% at 5 years in the surgical and non-surgical arms respectively, but this result was not statistically significant.<sup>10</sup> We report our experience of using tri-modality treatment in this group of patients.

## Materials and Methods

### Eligibility

All patients had histologically confirmed non-small cell lung cancer obtained via bronchoscopy, transthoracic needle or open biopsy. They all had locally advanced disease (Stage IIIA/ IIIB) which was deemed to be potentially resectable, good performance status of ECOG 2 or less, no significant weight loss (<5%) and had adequate cardiac, renal, haematological, hepatic and bone marrow functions. Patients who had malignant pleural effusions were excluded. All patients had the following staging investigations which included computed tomography (CT) scans of the chest, abdomen and brain and bone scan performed to exclude any systemic involvement. Mediastinoscopic examination was done at the discretion of the thoracic surgeons. This retrospective analysis was approved by the Investigational Review Board of the institution and informed consent was waived because of the retrospective data collection.

### Chemotherapy Schedule

All the patients underwent induction chemo-radiotherapy before being reassessed for surgical resection. Each cycle of chemotherapy consisted of paclitaxel at a dose of 175 mg/m<sup>2</sup> over 3 hours intravenous infusion. This was followed by carboplatin dosed to a target area under the concentration-time curve of 5 (AUC = 5 mg mL/min) as determined by the Calvert formula given over 1 hour.<sup>11</sup> The chemotherapy was given on Day 1 and Day 22 during thoracic irradiation. Because of the logistical problem of commencing radiotherapy immediately upon final treatment decisions, some patients had to wait about 3 weeks before radiation could commence. Hence this group of patients may have received one cycle of chemotherapy alone before the onset of concurrent chemoradiotherapy and the carboplatin was dosed to AUC of 6 mg ml/min.

### Radiotherapy

All patients were treated using the conformal radiotherapy technique. A treatment planning CT was done for the delineation of target volumes and a 2- or 3-field arrangement was used. The clinical target volume (CTV) was defined as the volume of tissues around the gross target volume (GTV) plus a margin for microscopic involvement and electively encompassed the ipsilateral hilar lymph nodes, superior mediastinal, subcarinal lymph nodes and the inferior mediastinal lymph nodes (for lower lobe tumours). Contralateral mediastinal and hilar lymph nodes were not irradiated electively. The planning target volume (PTV) encompassed the CTV with a margin of 1.5 to 2 cm. All patients were treated with external beam radiation on a linear accelerator with 6-10 megavoltage energy. A total dose of 50 Gy in 25 daily fractions over 5 weeks was prescribed to the 100% isodose surface.

### Surgery

Surgery was carried out within 6 weeks of completion of chemoradiotherapy. Patients who achieved complete or partial response or stable disease (assessed by CT evaluation) were referred to the cardiothoracic surgeon for reassessment of resectability. The extent of pulmonary resection was left to the discretion of the surgeon. Mediastinal lymph node dissection was performed on all patients.

### Evaluation of Response

Clinical response to the induction therapy was determined based on CT scan evaluation 1 month after the completion of induction chemoradiotherapy treatment. The response was assessed using standard WHO criteria: complete response (CR) was defined as the disappearance of all measurable and evaluable lesions for at least 4 weeks; partial response (PR) was a 50% reduction in the sum of the perpendicular diameters of all measurable lesions lasting for at least 4 weeks; stable disease (SD) was defined as a less than 25% increase in the size of all lesions without the appearance of new lesions; progressive disease (PD) was defined as more than a 25% increase in the size of all lesions or the appearance of new lesions.

### Evaluation of Toxicities

Patients were seen prior to each cycle of chemotherapy and weekly during the chemoradiotherapy treatment. Toxicities were graded according to the National Cancer Institute (NCI) Common Toxicity Criteria Version 2. Acute radiation-induced toxicities were graded based on Radiation Therapy Oncology Group (RTOG) criteria. After completion of treatment, patients were followed up at 3-monthly intervals for the first 2 years and 6-monthly from the third to fifth year and then yearly thereafter.

## Statistics

The time-to-tumour progression and overall survival probabilities were estimated using the Kaplan-Meier method. Time-to-tumour progression was computed from the time of starting chemotherapy to the first documented disease progression. Subjects who were free of disease at last follow-up or who died but without cancer were considered censored cases. Death data was obtained from the Singapore Death Registry. The survival time was calculated from the time of diagnosis to the time of death or the date of last contact for surviving patients. All statistical analyses were generated using SPSS for Windows Version 11.5 and performed on an intention-to-treat basis.

## Results

### Patient Characteristics (Table 1)

A total of 33 patients were treated between 1997 and 2005. Table 1 shows the characteristics of the patients and the treatments received. There were 26 (79%) males and the median age was 63 years (range, 43 to 74). Nineteen patients had mediastinoscopic assessment done. Most of the patients were diagnosed with Stage IIIA (n = 25, 76%) and 8 with Stage IIIB. The majority had T2 (42%) and/or N2 (88%) disease and adenocarcinoma was the most common histological subtype (42%).

The median number of cycles of chemotherapy given was 3. The majority of the patients (n = 28, 85%) received the prescribed radiation dose of 50 Gy. Thoracic radiation for 1 patient was terminated prematurely when she developed metastatic disease to the brain.

Twenty-nine (88%) patients achieved at least a stable clinical response after the induction chemoradiotherapy but only 25 (76%) patients underwent surgery. For those who did not have surgery, 1 was deemed medically unfit, 3 refused surgery and 4 had progression of disease. The majority had a lobectomy (58%). Of the 6 patients who had pneumonectomy, 2 had right-sided pneumonectomy. Five out of 8 patients with Stage IIIB disease (62.5%) were able to achieve successful resection of the tumour after induction chemoradiation.

### Tumour Response (Table 2)

Among the 25 patients who underwent triple modality treatment, 6 patients (24%) were found to have complete pathological response at the time of surgical resection. Majority of the patients, however, still had residual disease either at the original tumour or at the nodal sites.

### Treatment Toxicities (Table 3)

The commonest toxicity was grade 3 or 4 neutropenia reported in 10 (30%) patients. Five (15%) patients had grade 3 infection, 3 (9%) had grade 3 or 4 anaemia and 3

Table 1. Demographics and Clinical Characteristics of All Patients

Characteristics	No. of patients	%
Age (y)		
Median	63	
Range	43-74	
Gender		
Male	26	79
Female	7	21
Stage		
IIIA	25	74
IIIB	8	24
T- Stage		
T1	2	6
T2	14	42
T3	10	30
T4	7	21
N- Stage		
N1	3	9
N2	29	88
N3	1	3
Histology		
Adenocarcinoma	14	42
Squamous	10	30
Large cell	2	6
Poorly differentiated	4	12
NOS	3	9
Number of cycles of chemotherapy		
1	2	6
2	11	33
3	14	42
4	6	18
Radiation dose received		
50 Gy	28	85
>50 Gy	4	12
<50 Gy	1	3
Surgery performed		
No	8	24
Yes	25	76
Types of surgery		
Lobectomy	19	58
Pneumonectomy	6	18

(9%) had grade 3 esophagitis. There were no toxic deaths from chemoradiotherapy. However, there was 1 perioperative mortality from severe surgical emphysema in a patient who had a left lobectomy performed.

### Survival Analysis

At the time of analysis, 12 patients (36%) were still alive

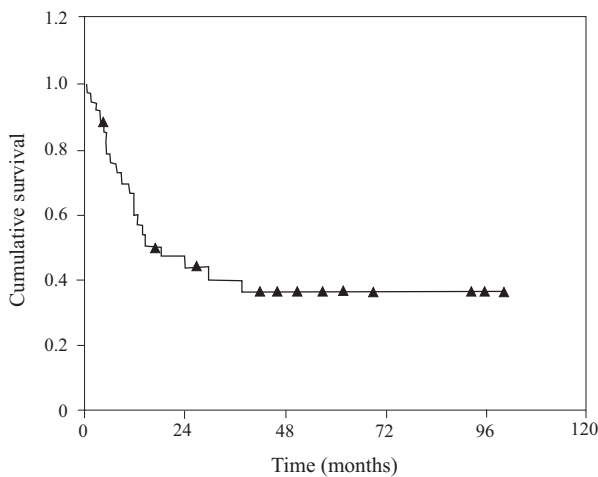


Fig. 1. Kaplan-Meier estimate of the time-to-progression survival curve of 33 patients with ▲ representing a censored observation.

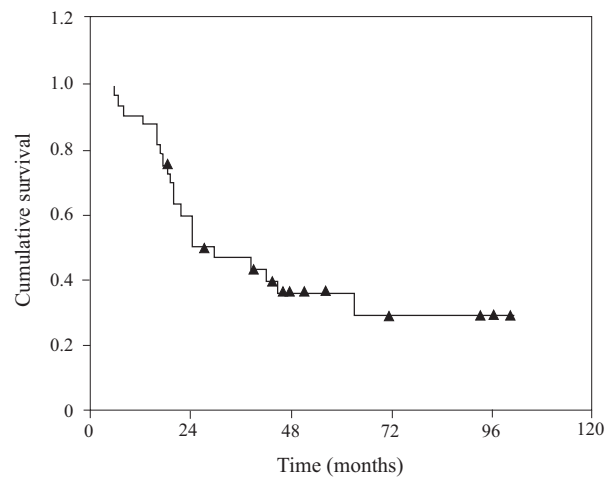


Fig. 2. Kaplan-Meier estimate of the overall survival curve of 33 patients with ▲ representing a censored observation.

Table 2. Response to Treatment

Response	No. of patients	%
Clinical response		
Complete	1	3
Partial	22	67
Stable	6	18
Progressive disease	4	12
Pathological response		
Complete	6	18
Partial	19	58

Table 3. Treatment Toxicities

Toxicity	No. of patients			%
	Grade 3	Grade 4	Total	
Neutropenia *	5	6	11	30
Anaemia	1	2	3	9
Thrombocytopenia	0	1	1	3
Infection	5	0	5	15
Oesophagitis	3	0	3	9

\* One patient had grade 3 toxicity in cycle 2 and grade 4 in cycle 3.

with a median follow-up time of 49 months (18.2-100.6 months). The median follow-up for all the 33 patients was 24.3 months (5.8-100.6 months). One patient was lost to follow-up after surgery. Eighteen (55%) died due to disease progression, 1 (3%) from perioperative complications, 1 (3%) from ischemic heart disease and 1 (3%) had committed suicide.

Disease progression was observed in 20 patients (61%) among the whole cohort; 12 patients were still in remission. The median time-to-tumour progression was 18.2 months (95% CI, 3.0 to 33.5 months). The estimated 5-year time-to-tumour progression was 36% for all patients (Figure 1) with the 5-year time-to-tumour progression for Stage IIIA and IIIB of 37% and 33% respectively.

The median overall survival was 29.9 months (95% CI, 11.4 to 48.4 months) with a 5-year overall survival rate of 36% (Fig. 2). There was no difference in survival outcome between patients with stage IIIA and stage IIIB disease with a median survival of 24.3 and 29.9 months respectively ( $P = 0.617$ ). However, the small number of stage IIIB

patients precluded any firm conclusions from this observation.

*Relapse Status (Table 4)*

Among the 33 patients, 11 had loco-regional relapse as the first site of relapse; 5 with systemic relapse and the remaining 4 had both local and systemic failures. For those who had surgical resection, 7 patients failed locoregionally; 4 had systemic relapses and 2 failed both locally and distally (not shown in table).

**Discussion**

The outcome of patients with Stage III locally advanced non-small cell lung cancer is generally poor. Less than 10% of these patients survive 5 years if treated with primary surgery alone.<sup>12,13</sup> This is due to the extent of the disease that precludes complete resection and the high rates of local and/or distant relapses. Primary radiotherapy used to be the sole modality resorted to in patients deemed to be poor surgical candidates. However, results have been dismal with a median survival of 7 to 10 months and a 2 year survival of 7-15%.<sup>2,12,14,15</sup> This has set the stage for a

Table 4. Relapse Status

	No. of patients	%
Relapse status		
No	12	36
Yes	20	61
Unknown	1	3
Sites of relapse		
Locoregional	11	33
Systemic	5	15
Locoregional and systemic	4	12

plethora of trials involving various combinations of modalities, i.e. chemotherapy, radiation and surgery.

Combined modality treatment with chemotherapy and radiation has since become the standard approach for managing patients with Stage III locally advanced disease with established results of 8% to 29% 5-year survival rate reported by various randomised trials.<sup>2,14,16,17</sup> As shown in the CALBG study by Dillman et al,<sup>2</sup> improvement in systemic control by combined modality treatment has contributed to a survival advantage. The 5-year survival rate was significantly improved from 6% to 17%. Long-term follow-up analysis revealed a 13% survival rate at 7 years in the chemoradiotherapy arm versus 6% in the radiotherapy alone arm.<sup>2</sup> Unfortunately, most of the patients (80% to 85%) still succumbed to treatment failure within the irradiated field and at distant sites. Similarly, results from the Phase III Intergroup study reaffirmed the superiority of combined chemoradiotherapy compared to standard radiation or other radiotherapy regimens.<sup>10</sup> However, local control remains a main problem.<sup>17</sup> Our centre's experience with induction chemotherapy followed by concurrent chemoradiotherapy in Stage III NSCLC using 2 different platinum-based protocol resulted in a median overall survival of 12-51 months, and a 5-year survival rate of 15%. The locoregional failure rate remains high at 49% to 63%<sup>18,19</sup> which is consistent with the reported rates of 48% to 83% demonstrated in most chemoradiotherapy trials.<sup>20</sup>

A number of phase two trials involving 3 modalities for Stage III NSCLC have evolved with the introduction of surgery after induction chemoradiotherapy, aiming to achieve better outcomes in the local control and survival rates. The results have been promising with 13% to 31% 5-year survival rates.<sup>3-9,17</sup> The locoregional control rate was also better with reported local failure of 11% to 36% among all relapses.<sup>3-6,8-9</sup> Despite the favourable results of these phase two studies, the impact and benefit of an aggressive induction chemoradiotherapy followed by the surgery approach for Stage III NSCLC has yet to be defined. A

recent update of an Intergroup study which randomised patients with Stage IIIA NSCLC to receive either tri-modality treatment or concurrent chemoradiotherapy alone confirms significantly improved progression-free survival but not overall survival when surgery follows chemoradiotherapy in patients with Stage IIIA(pN2) NSCLC, but the trend was better 5-year overall survival with trimodality therapy.<sup>10</sup>

Our report of the use of the tri-modality approach demonstrates the feasibility in use in Asian patients as confirmed by other Asian studies.<sup>21-23</sup> Overall this approach was well-tolerated with acceptable toxicities. There were no deaths related to induction chemoradiation and only 1 reported death was attributed to postoperative complication. Twenty-five patients (75%) were able to undergo resection of the tumour after chemoradiotherapy, producing a rate that was comparable to most studies. We, however, do acknowledge that our study is a small retrospective study with a small sample size collected over a long time frame and not all were staged uniformly.

It also appears that the introduction of surgery after induction chemoradiation plays a potential role in improving locoregional tumour control and survival in locally advanced Stage III NSCLC. Sixty-four per cent (16 of 25) of patients who underwent the tri-modality treatment had local control of their tumours. The survival outcome of our patients is comparable to the studies where the median overall survival varies from 13 to 25 months.<sup>3-9</sup> Our study also demonstrated that patients in Stage IIIB seemed to fare at least as well as those with stage IIIA; 62.5% of those with Stage IIIB disease were able to achieve successful resection and 2 patients continued to remain disease free. However, the numbers are too small for firm conclusions. Nevertheless, it is clear that even patients in this prognostically poor subset can be successfully downstaged with induction chemoradiotherapy for curative resection.

In conclusion, this study demonstrates that trimodality treatment is feasible in Asian patients with Stage III locally advanced NSCLC. Paclitaxel and carboplatin at the given schedule can be delivered safely. The resection rate is high with well-tolerated toxicity and the survival rate is comparable to most phase II multimodality studies. Phase III randomised studies with perhaps a larger sample size to detect a more realistic smaller overall survival benefit are required for a definitive conclusion.

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