Original Article

Treatment Outcomes of Combined Chemoradiation in Locally Advanced, Unresectable Non-Small Cell Lung Cancer: A Single Institution Study

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Objective: To report the outcomes of chemoradiation treatment in locally advanced non-small cell lung cancer [NSCLC] patients and determine the factors affecting survival.

Materials and Methods: The medical records of 1,325 NSCLC patients treated with radiotherapy in our division between 2008 and 2013 were reviewed. The patient characteristics, the management characteristics, and outcome data were recorded and analyzed. Univariate and multivariate analysis were performed to identify the prognostic factor for overall survival [OS].

Results: One hundred three patients were included in the analysis. With a median follow-up time of 13.27 months, these patients had a median OS time of 21.4 months (95% CI 17.6 to 25.2) and median progression-free survival [PFS] time of 11.67 months (95% CI 9.69 to 13.65). The 2-year OS and PFS rate were 34.0% and 21.4%, respectively. For the patients treated by concurrent and sequential chemoradiation, the 2-year OS rates were 31.0% and 37.8% (p = 0.349) and the 2-year PFS rates were 24% and 20.6% (p = 0.690), respectively. The multivariate analysis revealed that age (hazard ratio [HR] 1.68, 95% CI 1.06 to 1.69) and stage (HR 2.13, 95% CI 1.43 to 3.39) were significant prognostic factors for OS.

Conclusion: The treatment of locally advanced NSCLC in the authors' hospital is feasible and the outcomes are comparable to others. The concurrent and sequential chemoradiation did not show any statistically significant difference in survival rate. The factors that associated with poor prognosis are age (older than 60 years) and stage (IIIB).

Keywords: Chemoradiation, Non-small cell lung cancer, Outcome, Prognostic factor

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According to the International Agency for Research on Cancer [IARC], there were 14.1 million new worldwide cancer cases in 2012, of which 1.8 million (13%) were lung cancer. Moreover, lung cancer was also the leading cause of cancer death in men and the second leading cause in women, with an estimated 1.6 million (19.4%) deaths in 2012[1]. Generally, lung cancer can be divided roughly into two groups by histopathology as small cell lung cancer [SCLC] 15% and non-small cell lung cancer [NSCLC] 85%. Thirty percent of NSCLC patients were diagnosed as a locally advanced, unresectable stage. For many decades, thoracic radiation [TRT] alone proved to be a mainstay of treatment for this group but unfortunately, the treatment outcomes remained disappointing with the median survival times of 9 to 13 months and two-year survival rates of 15% to 20%[2-4]. Attempts to improve treatment outcomes for these patients such as using altered fractionated radiation, induction chemotherapy then concurrent chemoradiation, concurrent chemoradiation, and sequential chemoradiation were established. At the Division of Radiation Oncology, Faculty of Medicine, Chiang Mai University, Thailand, the authors treated locally advanced, unresectable NSCLC patients by combined chemotherapy and TRT for two decades. The treatment included both concurrent and sequential chemoradiation. The present retrospective review aimed to report the results of treating NSCLC in Northern Thailand.

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Material and Methods

Upon approval by the local Ethics Committee, the present study retrospectively reviewed data of

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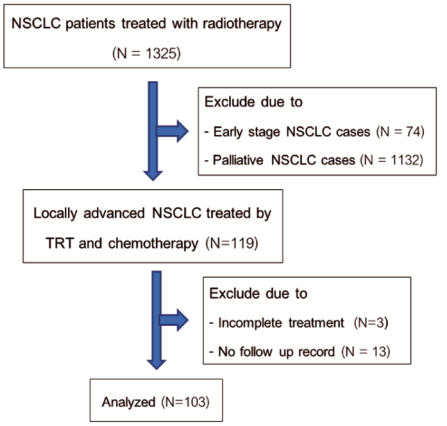

Figure 1. CONSORT diagram for patient inclusion and exclusion.

the patients diagnosed and treated for unresectable locally advanced NSCLC in the Division of Radiation Oncology, Faculty of Medicine, Chiang Mai University, Thailand between January 1, 2008 and December 31, 2013 (IRB No. RAD-2557-02757). Cases were identified by searching the electronic medical records and supplementing information with the hospital medical records.

Eligible patients had a histological diagnosis of NSCLC, unresectable locally advanced stage, age of 18 years or older, no evidence of distant metastases, and had received complete treatment by chemotherapy and TRT. The patients who did not have pathological confirmation for NSCLC, did not complete a metastatic work up (abdominal and brain imaging, bone scan), or did not have follow-up records for at least one month after treatment were excluded.

Once identified, re-staging according to the American Joint Committee on Cancer [AJCC] staging system seventh edition[5] for all patients was performed. The patient/tumor epidemiological characteristics, management and outcome data were recorded. Overall survival [OS] was defined as the time from the date of diagnosis to the date of death due to any cause or recent follow-up. Progression-free survival [PFS] was defined as the time from the date of diagnosis to the date of the first event (local or distant progression or death from any cause).

The descriptive analysis along with Kaplan-Meier method to plot the survival curves for the OS rate, PFS rate was used. The comparison of the survival curve between different stages and treatments was determined by the log-rank test. Univariate and multivariate parameter analysis of the potential prognostic significance for OS used Cox proportional hazards models with *p*-value smaller than 0.20 for univariate analysis. The hazard ratio [HR] and 95% confidence interval [CI] were computed as well. Throughout, a *p*-value smaller than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS statistical software version 20 (Chicago, Illinois, USA).

Results

The medical records of 1,325 NSCLC patients treated with radiotherapy in the authors' division between 2008 and 2013 were reviewed, of which 103 patients were included in the analysis (Figure 1). There were 72 males and 31 females with a mean age of 61.6 years (range 38.9 to 83.2 years). The patients' baseline characteristics, disease, and treatments are shown in Table 1.

All of the patients received chemotherapy and

Table 1. Patients' characteristics

Characteristics	Number (%) total = 103 cases
Age (years)	
Mean (range)	60.6 (38.9 to 83.2)
<60	46 (44.7)
≥60	57 (55.3)
Sex	
Male	72 (69.9)
Female	31 (30.1)
Performance status	
ECOG 0	57 (55.3)
ECOG 1	46 (44.7)
TNM staging (AJCC 7th edition)	
T staging	
• T1	17 (16.5)
• T2	23 (22.3)
• T3	33 (32.1)
• T4	30 (29.1)
N staging	
• N0	6 (5.8)
• N1	4 (3.9)
• N2	49 (47.6)
• N3	44 (42.7)
Staging grouping (AJCC 7th edition)	
IIIA	45 (43.7)
IIIB	58 (56.3)
Pathology	
Squamous cell carcinoma [SCCA]	47 (45.6)
Adenocarcinoma	45 (43.7)
Others	11 (10.7)
Treatment	
Concurrent chemoradiation [CCRT]	58 (56.3)
Sequential chemoradiation [SEQ]	45 (43.7)

ECOG = Eastern Cooperative Oncology Group; AJCC = American Joint Committee on Cancer

radiation therapy with a median radiation dose of 60 Gy (range 60 to 74). Ninety-two patients (89.3%) received radiotherapy by two-dimensional radiation therapy and the remainder received three-dimensional conformal radiation therapy [3D-CRT]. Despite the variation of chemotherapy regimen across medical oncologists, 102 patients (99%) received a platinum-based doublet regimen.

Overall survival and progression-free survival

According to the census date (August 31, 2015), 21 patients are still alive, of which 15 patients also have disease control for both loco-regional and distant sites. With a median follow-up time of 13.27 months (range 1 to 80.5 months), these patients had a median OS time of 19.36 months (95% CI 15.2 to 23.5) and the 2-year OS rate of 34.0%. Because five patients were followed up by the physicians in other hospitals, eight patients are hill tribe people and four patients live in the border area of Thailand and Myanmar and never showed up for follow-up, we cannot have the full data regarding the treatment result and disease control. Therefore, the PFS time was analyzed from the data of 84 patients and the median PFS time was 11.67 months (95% CI 9.69 to 13.65 months) with the 2-year PFS rate 21.4%. The failure pattern included locoregional recurrence in 35 patients (41.6%), distant recurrence in 20 patients (23.8%) and both locoregional and distant recurrence in six patients (0.07%).

When characterized by staging, the 2-year OS rate of the patients in stage IIIA was 51.1% and stage IIIB was 20.7%, which showed statistically significant differences (p = 0.004). In addition, for the PFS rate, stage IIIA patients showed significant higher 2-year PFS rate than stage IIIB patients (40% versus 8.2%, p = 0.003) (Figure 2). To compare treatment results between concurrent chemoradiation [CCRT] and sequential chemoradiation [SEQ], the 2-year OS rates were 31.0% and 37.8% (p = 0.349) and the 2-year PFS rates were 24% and 20.6% (p = 0.690) for the patients treated by CCRT and SEQ respectively (Figure 3).

Univariate and multivariate analysis

In univariate analyses, the factors that showed potential poor prognostic factors for the OS were older age (more than 60 years), higher stage (stage IIIB), and treated by CCRT scheme (Table 2). Performing multivariate analyses, only age (HR 1.68, 95% CI 1.06 to 1.69) and stage (HR 2.13, 95% CI 1.43 to 3.39) remained significant prognostic factors for OS (Table 2).

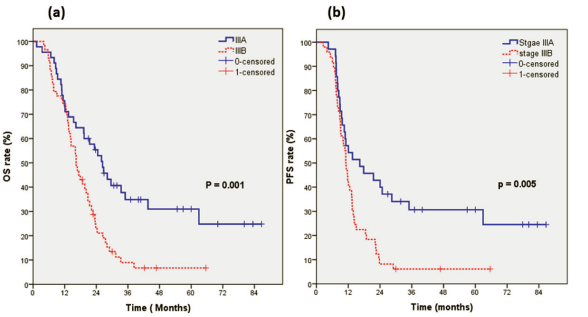

Figure 2. Survival rate (a) and progression-free survival rate (b) according to stage.

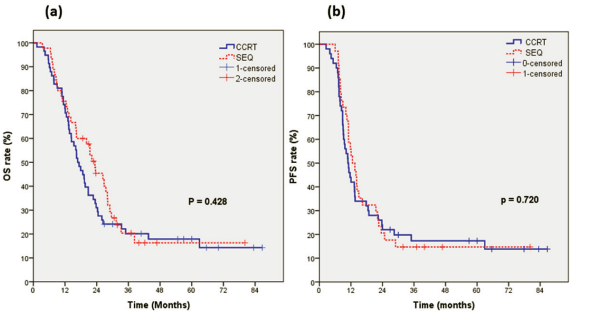

Figure 3. Survival rate (a) and progression-free survival rate (b) according to treatment scheme, CCRT = concurrent chemoradiation; SEQ = sequential chemoradiation.

Discussion

Since the 1990s, adding chemotherapy to TRT has been increasingly used to treat locally advanced NSCLC. With diversity of the randomized data about the benefit of combination treatment[6-13], subsequent meta-analysis[14,15] confirmed a better result of treatment with the addition of chemotherapy to TRT. Therefore, the standard treatment for locally advanced NSCLC has been changed to a combination of TRT and chemotherapy. An international collaborative meta-analysis[14] collected individual patient data from 9,387 patients included in 52 randomized clinical trials aimed to prove the role of chemotherapy in the treatment of NSCLC. The meta-analysis showed a 13% reduction in the risk of death with a HR of 0.87 and absolute benefit of 4% at 2 years when adding cisplatin-based chemotherapy to radiation. Another meta-analysis from 14 articles with 2,589 patients was reported by Pritchard and Anthony[15]. They compared the risk of death of patients who were treated with radiotherapy to those that were treated with the combination of chemotherapy and TRT. The relative risks of death at 1, 2, and 3 years were 0.88 (95% CI 0.80 to 0.9), 0.87 (95% CI 0.81 to 0.94), and 0.83 (95% CI 0.77 to

Table 2. Univariate and multivariate analysis of prognostic survival factors

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI for HR	*p*-value	HR	95% CI for HR	*p*-value
Sex						
Male	1.00					
Female	0.72	0.43 to 1.20	0.212			
Age (years)						
≤60	1.00			1.00		
>60	1.70	1.06 to 2.71	0.028	1.68	1.06 to 1.69	0.029*
Performance status						
ECOG 0	1.00					
ECOG 1	1.10	0.69 to 1.76	0.698			
Pathology						
SCCA	1.00		0.480			
Adenocarcinoma	0.67	0.32 to 1.40	0.289			
Others	0.64	0.31 to 1.33	0.235			
Stage						
IIIA	1.00			1.00		
IIIB	2.15	1.32 to 3.51	0.002	2.13	1.43 to 3.39	0.001*
Treatment						
CCRT	1.00			1.00		
SEQ	0.65	0.41 to 1.04	0.070	0.68	0.43 to 1.07	0.093

HR = hazard ratio; ECOG = Eastern Cooperative Oncology Group

* Statistically significant (*p*-value <0.05)

0.90), respectively and lead to a mean increase in life expectancy of about two months.

As mentioned before, the authors' institute has been using combined chemotherapy and TRT to treat NSCLC patients in the northern part of Thailand for more than 20 years. Since the patient population was all Asian, we conducted the present study to report the outcomes of treatment to represent the outcome and prognosis, especially for the Asian population. From the present data, the median OS time was 19.36 months, which was similar to the results from the previous studies that ranged from 12 to 15 months[14,15]. Additionally, the treatment outcomes from the previous reports divided by treatment scheme are listed in Table 2 and our 2-year OS rate along with median survival time from both CCRT and SEQ treatment were comparable to others. Regarding our limitation of follow-up data in 19 patients (18.4%), the PFS results were analyzed by extraction the group of these patients and should be interpreted with caution.

The present retrospective report also demonstrated the practice of our hospital. The treatment decisions were based on physician and patient preference. Focusing on treatment scheme, we treated more patients with CCRT than SEQ (58 versus 45 patients) and found that our 2-year OS rate favored the SEQ group, whereas the 2-year PFS rate favored the CCRT group, which was different from other randomized trials[16-18] and meta-analysis[19] confirming both the OS and PFS benefits of CCRT over SEQ treatment. One of the largest systematic review and individual patient data meta-analysis was performed by The NSCLC Collaborative Group to estimate accurately the effect on survival and acute toxicity[19]. They identified 11 trials, but four trials were excluded because of accrual time and data from one trial was not available, so the meta-analysis included data from six trials that randomly assigned 1,205 patients. The analysis revealed that CCRT had a significant survival benefit compared to sequential treatment with 16% relative reduction in mortality (HR 0.84, 95% CI 0.74 to 0.95, $p = 0.004$). The absolute survival benefit at three and five years were 5.7% and 4.5%, respectively. The concurrent treatment also showed a better PFS (HR 0.90, 95% CI 0.79 to 1.01, $p = 0.07$) with absolute PFS benefit of 2.9% at three years and 2.2% at five years. They believed that decreasing of locoregional failure rate yielded a positive effect on the survival rate as there was no difference in distant failure rates between the two treatment regimens. However, the concurrent treatment is not always the best option for everyone as they commented that the concurrent regimen was generally prescribed in selected good-performance patients.

Afterwards, we established the univariate and multivariate analysis regarding factors that would relate to OS. We found that older age (older than 60 years) and stage (IIIB) were the worst prognostic factors. Likewise giving CCRT treatment was determined as a bad prognostic factor from univariate analysis but not from multivariate analysis. In consequence of the limitation of retrospective data, we believe the higher death rate might be related to patient selection, the oncologists tended to select the patient who had a more aggressive tumor to treat by CCRT. Our data revealed that there were more stage T3 and T4 patients in the CCRT group than the SEQ group (60% versus 46%). Likewise, there were slightly more stage N3 patients in the CCRT group as well (44.8% versus 40%). Evidently, using more delicate radiation technique such as 3D-CRT or intensity modulated radiation therapy [IMRT] gave a better local control and possibly better survival rates than traditional two-dimensional technique[20,21]. The 3D-CRT revealed several significant advantages regarding better tumor and normal tissue delineation, more accurate dose calculation, higher radiation dose to tumor, and lower radiation dose to normal tissue. Since we used the two-dimensional radiation therapy concurrently with chemotherapy to treat most of the patients (87.9%), treatment toxicity might worsen and cause a deteriorating effect on survival. Nevertheless, there were many patients in the CCRT group who received a modified dose of induction therapy for two or three cycles before CCRT that could produce more severe side effects than SEQ and could impact the survival as well.

Conclusion

In summary, the treatment of locally advanced NSCLC in the authors' hospital is feasible and the outcomes are comparable to other studies. The concurrent and sequential chemoradiation did not show statistically significant difference in survival rate but the factors associated with poor prognosis are age (older than 60 years) and stage (IIIB).

What is already known on this topic?

Since the 1990s, the standard treatment for NSCLC has changed because adding chemotherapy to TRT proved to gain a survival benefit over TRT alone, then a question about the best sequencing of treatment approach was explored. Although CCRT showed better OS than SEQ in meta-analysis, it is not always the best option for anyone as they commented that the concurrent regimen is generally prescribed in selected good-performance patients.

What this study adds?

In Thailand, we have been treating these patients by combining chemotherapy and TRT for two decades. The treatment includes both CCRT and SEQ chemoradiation. This study confirmed that the outcomes of locally advanced NSCLC treatment in Thailand are comparable to others and a good patient selection for each treatment regimen is mandatory.

Potential conflicts of interest

The authors declare of no conflict of interest.

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