# SURVIVAL OF PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER AT UBON RATCHATHANI CANCER CENTER, THAILAND

Kitiporn Srisam-ang[1], Amornrath Podhipak[2], Kulaya Narksawat[2], Pongsatorn Supaattagorn[1] and Mathuros Tipayamongkholgul[2]

[1]Ubon Ratchathani Cancer Center, Ubon Ratchathani; [2]Department of Epidemiology, Faculty of Public Health, Mahidol University, Bangkok, Thailand

Abstract. This survival analysis was conducted at Ubon Ratchathani Cancer Center to determine the prognostic factors for survival of patients with stage IIIA, stage IIIB, and stage IV non-small-cell lung cancer (NSCLC) patients treated at the center between 1997-2001. The study sample included 210 patients with non-small-cell lung cancer. Diagnosis and staging were defined employing the TNM system. The majority of lung cancer patients were smokers (66.7%), lived in Ubon Ratchathani Province (40.0%), male (77.6%), and agriculturalists (74.8%). Seventy-seven percent of patients died within five years, 19.5% were lost to follow-up and 2.9% were still alive in 2003. The estimated median survival time was 6.3 months (95% CI 5.4-7.3); the median survival times for stages IIIA, IIIB, and IV were 16.3, 7.0, and 4.5 months, respectively. The overall 1-, 2- and 3-year survival rates of NSCLC were 28.9, 7.9, and 3.3, respectively. The differences in survival of patients in the various stages of the disease were statistically significant ($p<0.0001$), adjusted for age and sex. Treatment with combination methods and at an early stage in the disease were associated with significant prolongation of survival. For stage IIIA, the estimated median survival times by treatment with chemotherapy was 7.0 months, radiotherapy was 16.0 months, surgery and others 16.3 months, and chemotherapy plus radiotherapy was 19.5 months. However, only chemotherapy versus surgery and others was significantly different ($p=0.0307$). The median survival times for stage IIIB patients treated with chemotherapy, radiotherapy, surgery and others, chemotherapy and radiotherapy, and supportive treatment were 7.0, 7.0, 9.0, 14.7, and 3.0 months, respectively. The differences between surgery and others versus supportive treatment, chemotherapy and radiotherapy versus supportive treatment were significantly different ($p=0.0392$, $p=0.0433$, respectively). For stage IV, the median survival times for patients treated with chemotherapy, radiotherapy, chemotherapy and radiotherapy, and supportive treatment were 5.0, 4.3, 6.5, and 1.0 months, respectively. The differences between chemotherapy, radiotherapy, chemotherapy and radiotherapy versus supportive treatment, all were significantly different ($p=0.0020$, $p<0.0001$, $p<0.0001$, respectively). The 2-year survival rates for stages IIIA, IIIB, and IV were 16.0, 4.1, and 2.2%, respectively. The results of the study show that stage IIIA has the longest survival time. They also show that appropriate treatment is a significant factor in improving the survival of lung cancer patients.

## INTRODUCTION

While cancer is a global problem, there is remarkable variation in the types of cancer that predominate in different parts of the world, and especially between developed and developing countries. Cancer of the lung is the most common cancer in the world. In 1990, an estimated 1,037,000 new cases were diagnosed worldwide, accounting for 12.8% of all new cancers. Mortality attributable to lung cancer was estimated to be 920,000 deaths, 17.8% of all cancer deaths (Srivatanakul, 1999).

At the beginning of the 20th century, lung cancer was a rare malignancy. It is now occurring in epidemic proportions worldwide. It is the most common cause of death from malignancy in the US. The incidence and mortality rates of these tumors are excessive and, although declining modestly in men, continue to increase in women (Green *et al*, 1993). The estimated number of lung cancer cases in the US in 1998 was

Correspondence: Kulaya Narksawat, Department of Epidemiology, Faculty of Public Health, Mahidol University, 420/1 Rajvithi Road, Bangkok 10400, Thailand.
E-mail: phkns@mahidol.ac.th

171,500 (91,400 men and 80,100 women), whereas the estimated number of deaths was 160,100 (93,100 men and 67,000 women). Lung cancers were estimated to account for 14% of cancer incidence (15% in men and 13% in women) and 28% of cancer mortality (32% in men and 25% in women) in 1998. (Brownson *et al*, 1998). In 1999, approximately 172,000 new cases of lung cancer were diagnosed and 158,000 deaths reported (Figlin *et al*, 2001). Rates of lung cancer have generally increased throughout the world, with sharp increases for woman in many western countries. Lung cancer kills both men and women in the US, more than any other type of cancer, causing an estimated 154,900 deaths in 2002 (Herbst *et al*, 2002). Rates of lung cancer are highest in North America and Europe, and lowest in Africa, Asia and South America. Eastern Europe, at present, has the highest national rates of lung cancer.

Many factors are responsible for the increase in cancer. Cancer is a disease that often takes many years to develop. In many parts of the world, people are living longer. The increase in cancer incidence thus partially reflect changes in the population structure. Changing life styles, in particular tobacco smoking, alcohol drinking and diet, also have a crucial part to play.

By world standards, the incidence of lung cancer in females of northern Thailand is rather high. In Asia, the incidence in women in Chiang Mai is second only to that in Tianjin, China. In Thailand, the estimated age-standardized incidence rate (ASR) of lung cancer is 26.5 per 100,000 in men and 11.1 per 100,000 in women. For men, the ASR is highest in Lampang (54.6 per 100,000) followed by Chiang Mai (ASR=34.2), Bangkok (ASR=23.6), Khon Kaen (ASR=16.8) and Songkhla (ASR=14.2). For women, the ASR of lung cancer is highest in Chiang Mai (ASR=29.1), followed by Lampang (ASR=26.5), Bangkok (ASR=6.4), Khon Kaen (ASR=6.4) and Songkhla (ASR=4.6). The ratio of males to females with lung cancer varies between 1.2:1 in Chiang Mai to 2.8:1 in Bangkok and Songkhla. The most common histological type is adenocarcinoma, particularly in women, although squamous cell carcinoma is slightly more frequent in men in Lampang and Songkhla. Squamous cell cancer is more common in Thai smokers, while amongst non-smokers (mainly women) adenocarcinoma was more common. In the northeastern region of Thailand, the data for lung cancer were collected by Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. They reported that by incidence rate, lung cancer is second in men and seventh in women. (Srivatanakul, 1999).

In 1995, The National Cancer Institute established the Ubon Ratchathani Cancer Center, to which the northeastern region of Thailand has easy access. The cancer statistics show that lung cancer is a major cause of morbidity. The incidence rates of lung cancer at the Ubon Ratchathani Cancer Center are that it ranks first in males and seventh in females. The treatment of lung cancer there has never evaluated, as well as the prognostic factors influencing the survival of NSCLC patients. In this study, existing information regarding lung cancer patients was reviewed and analyzed for survival time and its prognostic factors.

Variables included in the study were: demograghic factors (age, sex, marital status, education, and past history of smoking), histological factors (histological type, and histological grading), pathological factors (tumor site and stage), and treatment methods (chemotherapy, radiotherapy, surgery and chemotherapy, surgery and radiotherapy, surgery and chemotherapy and radiotherapy, chemotherapy and radiotherapy, and supportive treatment).

The survival time is the time from the date of first treatment up to the date of death (due to cancer). Death due to other causes were not considered. The tracing of patient status was performed via the cancer registry, civil registration, telephone calls, postcards and home visits up to June 2003. The interview was performed using a structured questionnaire. Informed consent was signed by the patients, if alive. If the patients were dead or lost to follow-up, data was abstracted from the medical record only, and in such cases informed consent was signed by the physicians who treated the patients, with the permission of the institute's director. The research proposal was approved by the Mahidol University ethics committee and the committee of the cancer center.

The treatment methods under investigation were divided into two main groups: 1) single treatments which NSCLC patients received (either chemotherapy or radiotherapy), and 2) combined treatments which NSCLC patients received, which were classified into 4 types (chemotherapy plus radiotherapy, surgery plus chemotherapy, surgery plus radiotherapy, surgery plus chemotherapy and radiotherapy and supportive treatment. Supportive treatment was the symptomatic treatment of patients who refused or did not get any therapy. Advanced NSCLC was defined as stages IIIA, IIIB, and IV, which were diagnosed by physicians and recorded on the patient's chart or on a hospital record using the TNM system.

## RESULTS

From 1997 to 2001, a total of 210 patients with NSCLC at the Ubon Ratchathani Cancer Center had documents on either histopathological types or histopathological grades or both. Thirty-six had missing values for histopathological grades. From tracing via mail, telephone calls, and home visits up to June 2003, it was found that 6 were still alive and 35 were lost to follow-up. The majority of the patients were between 60-74 years old at diagnosis (43.3%), whereas the rest (37.1%) were between 45-59 years, 14.3% less than 45 years and 5.2% were 75 years and over. The mean age at diagnosis was 57.6 years (SD 11.2). There were 163 males and 47 females. The majority of them was diagnosed in 2001 (28.1%). Eighty-nine percent were married, 5.7% were separated, 3.8% and 1.0% were single and widowed, respectively. The most common occupation was agriculturist (74.8%). Seventy-nine percent had an elementary education, 13.8% had a secondary education and 3.8, 1.9, and 1.0% had bachelor or higher, vocational education and no education, respectively. Ninty-nine percent of them were Thai and Bhuddist. The highest percentage of patients lived in Ubon Ratchathani Province (40.0%). There were 140 smokers (66.7%) and 70 non-smokers (33.3 %). More than half of the NSCLC patients (67.6%) had no underlying disease. The histological types were as follows: 75 squamous cell carcinomas, 107 adenocarcinomas, 25 large cell carcinomas, and 3 adenosquamous carcinomas. The histological grading was as follows; 13 were well differentiated, 57 moderately differentiated, 65 poorly differentiated, 39 undifferentiated, and 36 unknown. Twenty-six cases were in stage IIIA, 84 cases in stage IIIB, and 100 cases in stage IV. The most common site for the primary lesion was the right upper lobe in 31%. One hundred and sixteen NSCLC patients (55.2%) were treated with a single treatment, either by chemotherapy (19.1%) or radiotherapy (36.2%). Seventy-three patients (34.8%) were treated with combination treatment, such as surgery plus chemotherapy (2.4%), surgery plus radiotherapy (7.6%), surgery plus chemotherapy plus radiotherapy (2.8%) or chemotherapy plus radiotherapy (21.9%). Twenty-one patients (10.0%) were treated with supportive treatment only. Fifty-two percent had no metastasis, the rest had metastasis to the bone (22.8%) or brain (15.2%). The final outcomes were dead (77.6%), alive (2.9%) and lost to follow-up (19.5%) (Table 1).

### Overall survival time

The overall 1-, 2-, and 3-year survival rates for non-small-cell lung cancer patients were 28.87, 7.49 and 3.28%, respectively. The median survival time was 6.33 months (95% CI, 5.37-7.29), giving a death rate of 7.80 per 100 person-months. The overall survival curve is shown in Fig 1.

The age at diagnosis was re-categorized as <60 and >60 years. The 2-year survival rate was

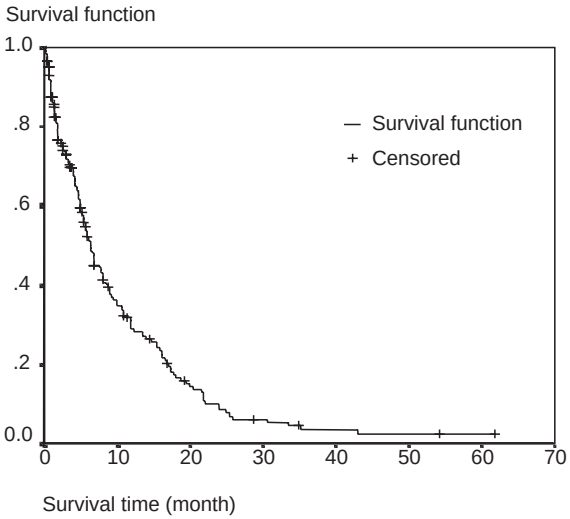


Fig 1–The overall survival curve of NSCLC patients.

Table 1
General characteristics of NSCLC patients.

| Characteristic | | Number | Percent |
|---|---|---|---|
| Age at diagnosis (years) | >45 | 30 | 14.3 |
| (Mean 57.63, SD=11.17) | 45-59 | 78 | 37.1 |
| | 60-74 | 91 | 43.3 |
| | ≥75 | 11 | 5.2 |
| Sex | Male | 163 | 77.6 |
| | Female | 47 | 22.4 |
| Year of diagnosis | 1997 | 21 | 10.0 |
| | 1998 | 33 | 15.7 |
| | 1999 | 51 | 24.3 |
| | 2000 | 46 | 21.9 |
| | 2001 | 59 | 28.1 |
| Marital status | Married | 188 | 89.5 |
| | Separated | 12 | 5.7 |
| | Single | 8 | 3.8 |
| | Widowed | 2 | 1.0 |
| Occupation | Agriculturist | 157 | 74.8 |
| | Govt official | 26 | 12.4 |
| | Merchant | 11 | 5.2 |
| | Employee | 10 | 4.8 |
| | Other | 6 | 2.9 |
| Education | No education | 2 | 1.0 |
| | Elementary | 167 | 79.5 |
| | Secondary education | 29 | 13.8 |
| | Vocational education | 4 | 1.9 |
| | Bachelor or higher | 8 | 3.8 |
| Smoking status | Non-smoker | 70 | 33.3 |
| | Smoker | 140 | 66.7 |
| Underlying disease | No underlying disease | 142 | 67.6 |
| | Tuberculosis | 16 | 7.6 |
| | Diabetes melitus | 4 | 1.9 |
| | Heart disease | 2 | 1.0 |
| | Hypertension | 2 | 1.0 |
| | Other[a] | 26 | 12.4 |
| Histological type | Adenocarcinoma | 107 | 51.0 |
| | Squamous cell carcinoma | 75 | 35.7 |
| | Large cell carcinoma | 25 | 11.9 |
| | Adenosquamous carcinoma | 3 | 1.4 |
| Histological grade | Well differentiated | | |
| | Moderately differentiated | 13 | 6.2 |
| | Poorly differentiated | 57 | 27.1 |
| | Undifferentiated | 65 | 31.0 |
| Stage | IIIA | 26 | 12.4 |
| | IIIB | 84 | 40.0 |
| | IV | 100 | 47.6 |
| Position of tumor | Right upper lobe | 65 | 31.0 |
| | Left upper lobe | 40 | 19.0 |
| | Right middle lobe | 37 | 17.6 |
| | Left lower lobe | 19 | 9.0 |

Table 1
General characteristics of NSCLC patients (continued).

| Characteristic | | Number | Percent |
|---|---|---|---|
| | Right lower lobe | 18 | 8.6 |
| | Left middle lobe | 14 | 6.7 |
| | Mixed | 17 | 8.1 |
| Treatment Method | | | |
| Single | Chemotherapy | 40 | 19.1 |
| | Radiotherapy | 76 | 36.2 |
| Combination | Surgery + Chemotherapy | 5 | 2.4 |
| | Surgery + Radiotherapy | 16 | 7.6 |
| | Surgery + Chemo + Radiotherapy | 6 | 2.8 |
| | Chemo + Radiotherapy | 46 | 21.9 |
| | Supportive treatment | 21 | 10.0 |
| Metastasis organs[b] | No metastasis | 110 | 52.4 |
| | Bone | 48 | 22.9 |
| | Brain | 32 | 15.2 |
| | Liver | 10 | 4.3 |
| | Opposite lung | 8 | 3.8 |
| | Skin | 7 | 3.3 |
| | Adrenal grand | 2 | 1.0 |
| | Eye | 1 | 0.5 |
| Last status | Dead | 163 | 77.6 |
| | Alive | 6 | 2.9 |
| | Lost to follow up | 41 | 19.5 |

[a]Other = Peptic ulcer, thyroid disease, asthma, renal failure, or allergy.
[b]more than one site was possible.

11.7% for the age group <60 years and 4.4% for ≥60 years. The median survival times for age <60 and >60 years were 6.5 and 6.0 months, respectively. The median survival time was 6.2 months for males and 8.1 months for females. The 2-year survival rate was 7.9% for males and 9.3% for females.

Comparison of the overall survival curves for patients who were non-smokers and smokers, adjusted for age and sex, showed no significant different (p=0.4011). The 2-year survival rate was 12.8% among the non-smokers and 5.7% among the smokers. The median survival time for patients who were non-smokers and smokers were 6.5 and 6.1 months, respectively. The median survival time was 5.8 months for patients with a tumor site in the upper lobe, and 7.0 months, 8.1 months, and 4.8 months for patients with tumor sites in the middle lobe, lower lobe, and mixed group, respectively. The 2-year survival rates for patients with tumor sites in the upper lobe, middle lobe, lower lobe and mixed were 9.2, 8.8, 8.0, and 0.0%, respectively. After adjusting for age and sex, there was no significant difference between the survival rates of patients with different sites of disease (p=0.2636). The median survival time was 16.3 months in stage IIIA patients, 7.0 months in stage IIIB and 4.5 months in stage IV. The 2-year survival rates for patients with stage IIIA, IIIB and IV disease were 20.0, 6.9, and 3.7%, respectively. The difference in the hazard ratio between the stages was not statistically significant (p<0.0001). The median survival time was 6.2 months for the patients with squamous cell carcinoma, 7.0 months for patients with adenocarcinoma, 5.6 months for patients with large cell carcinoma and 4.3 months for patients with adenosquamous carcinoma. The 2-year survival rates of patients with squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous carcinoma were 4.1, 11.4, 8.2,

and 0.0%, respectively. The difference in the hazard ratio between the groups of histological type was not statistically significant (p = 0.9755). The median survival times of the patients with well differentiated, moderately differentiated, poorly differentiated and undifferentiated disease were 2.4 months, 6.5 months, 5.7 months and 4.8 months, respectively. The 2-year survival rate was 0.0% for the patients with well differentiated, 8.8% for moderately differentiated, 4.4% for poorly differentiated, and 10.3% for undifferentiated disease. The difference in the hazard ratio between the groups by histological grading was not statistically significant (p=0.4324). The median survival time for patients with single treatment was 5.8 months, 10.8 months for combination treatment and 1.9 months for supportive treatment. The 2-year survival rates for the patients with single, combination and supportive treatments were 4.2, 14.8, and 0.0%,

Table 2
Relationship between demographic characteristic, prognostic factors and treatment methods of NSCLC patients, adjusted for age and sex.

| Prognostic factors | HR[a] | 95%CI of HR | p-value[b] |
|---|---|---|---|
| Education | | | 0.9003 |
| Elementary or lower education | 1.00 | | |
| Secondary or higher education | 0.97 | 0.65 - 1.45 | |
| Occupation | | | 0.2976 |
| Agriculture | 1.00 | | |
| Other[c] | 0.83 | 0.57 - 1.18 | |
| Smoking | | | 0.4011 |
| Non-smoker | 1.00 | | |
| Smoker | 1.21 | 0.77 - 1.90 | |
| Tumor site | | | 0.2636 |
| Upper lobe | 0.65 | 0.35 - 1.21 | |
| Middle lobe | 0.55 | 0.28 - 1.06 | |
| Lower lobe | 0.53 | 0.27 - 1.07 | |
| Mixed | 1.00 | | |
| Staging | | | <0.0001 |
| IIIA | 1.00 | | |
| IIIB | 2.02 | 1.23 - 3.31 | |
| IV | 3.18 | 1.96 -5.17 | |
| Histologic type | | | 0.9755 |
| Squamous cell carcinoma | 1.00 | | |
| Adenocarcinoma | 0.97 | 0.68 - 1.37 | |
| Large cell carcinoma | 1.04 | 0.61 - 1.78 | |
| Adenosquamous carcinoma | 1.21 | 0.37 - 4.01 | |
| Histopathologic grade | | | 0.4324 |
| Well differentiated | 1.00 | | |
| Moderately differentiated | 0.62 | 0.38 - 1.17 | |
| Poorly differentiated | 0.80 | 0.43 - 1.50 | |
| Undifferentiated | 0.73 | 0.37 - 1.41 | |
| Treatment method | | | <0.0001 |
| Single treatment | 0.30 | 0.18 - 0.48 | |
| Combination treatment | 0.20 | 0.12 - 0.33 | |
| Supportive treatment | 1.00 | | |

HR[a] = Hazard Ratio, adjusted for age, sex and clinical extent of disease; [b]Chi-square test; Other[c]= Government official, employee, housewife, merchant, monk.

Table 3
Relationship between stages and treatment methods in NSCLC patients by multivariated analysis and Cox's proportional hazard model, adjusted for age and sex.

| Stage | Treatment methods | 2-year survival | HR | 95 % CI of HR | p-value |
|---|---|---|---|---|---|
| IIIA | | 16.03 | | | 0.1611 |
| | 1. Chemotherapy | | 1.00 | | |
| | 2. Radiotherapy | | 0.50 | 0.12-2.09 | |
| | 3. Surgery + other | | 0.21 | 0.05-0.87 | |
| | 4. Chemo + Radiotherapy | | 0.20 | 0.04-1.04 | |
| IIIB | | 4.07 | | | 0.269 |
| | 1. Chemotherapy | | 0.41 | 0.13-1.29 | |
| | 2. Radiotherapy | | 0.34 | 0.11-1.10 | |
| | 3. Surgery + other | | 0.27 | 0.08-0.94 | |
| | 4. Chemo + Radiotherapy | | 0.28 | 0.08-0.96 | |
| | 5. Supportive | | 1.00 | | |
| IV | | 2.17 | | | <0.0001 |
| | 1. Chemotherapy | | 0.18 | 0.06-0.53 | |
| | 2. Radiotherapy | | 0.14 | 0.06-0.31 | |
| | 3. Chemo + Radiotherapy | | 0.11 | 0.05-0.27 | |
| | 4. Supportive treatment | | 1.00 | | |

Other: radiotherapy or chemotherapy or both

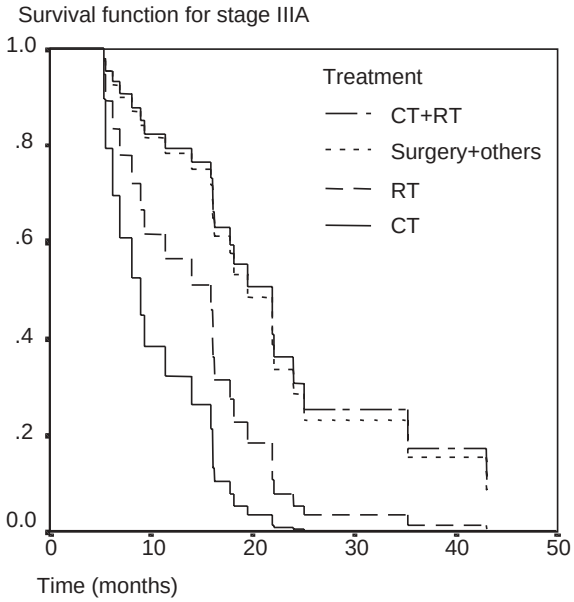


Fig 2–Survival curves of NSCLC patients stage IIIA and treatment methods, adjusted for age and sex.

respectively. The differencse in the risk of death between the groups by treatment method were statistically significant (p<0.0001).

According to previous statistical analysis, the stages of disease and treatment methods were associated with the survival time of the NSCLC patients. Naturally, the NSCLC patients received different treatments in each stage of their disease. To find out the effect of the treatment methods on survival time, analysis of the data was stratified based on the stage of the disease (Table 3).

### Stage IIIA

After adjusting for age and sex, the NSCLC patients treated with radiotherapy, surgery and others, chemotherapy plus radiotherapy had a lower risk of death than with chemotherapy alone, 0.50 times (95%CI=0.12-2.09), 0.21 times (95%CI=0.05-0.87), and 0.20 times (95%CI= 0.04-1.04), respectively. The risk of death was not significantly different between the stages of the disease (p=0.1611), but when chemotherapy versus surgery and others was compared, there was a statistically significant difference (p=0.0307) (Table 3 and Fig 2).

### Stage IIIB

After adjusting for age and sex, the NSCLC patients treated with chemotherapy, radio-

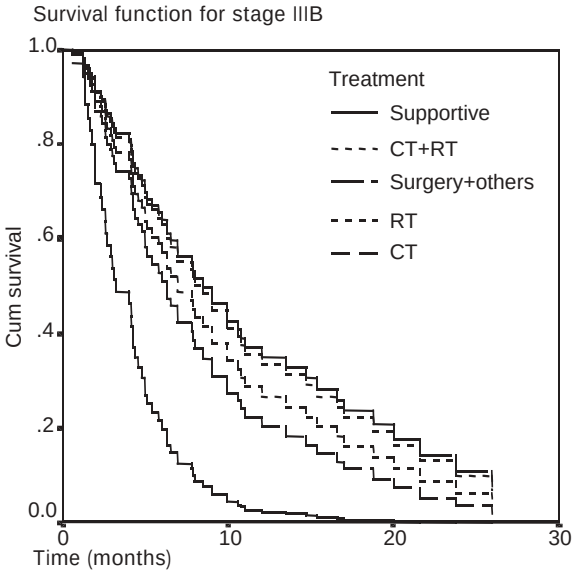


Fig 3–Survival curves for NSCLC patients stage IIIB and treatment methods, adjusted for age and sex.

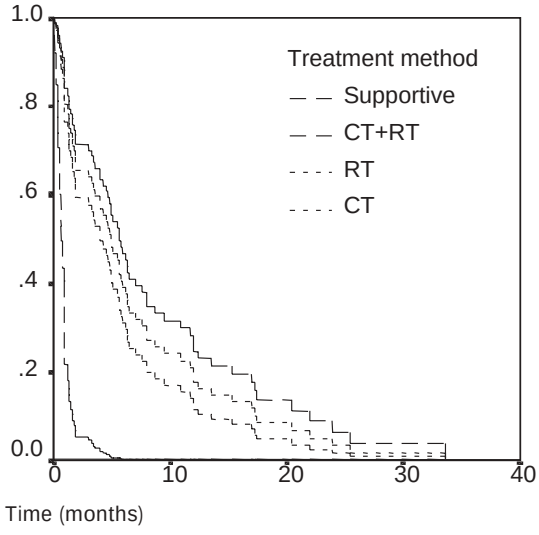


Fig 4–Survival curves for NSCLC patients stage IV and treatment methods, adjusted for age and sex.

therapy, surgery and others, chemotherapy plus radiotherapy had a lower risk of death than supportive treatment, 0.41 times (95% CI= 0.13-1.29), 0.34 times (95%CI=0.11-1.10), 0.27 times (95%CI=0.08-0.94), and 0.28 times (95%CI= 0.08-0.96), respectively. The risk of death was not significantly different between the types of treatment (p=0.269), but when surgery and others versus supportive treatment was compared, there was a statistically significant difference (p=0.0392); chemotherapy plus radiotherapy versus supportive treatment were also significantly different (p=0.0433) (Table 3 and Fig 3).

### Stage IV

After adjusting for age and sex, the NSCLC patients treated with chemotherapy, radiotherapy, chemotherapy and radiotherapy had a lower risk of death than with supportive treatment, 0.17 times (95%CI=0.06-0.53), 0.14 times (95%CI=0.06-0.31), and 0.11 times (95%CI= 0.05-0.27), respectively. The risk of death was statistically different between treatments (p<0.0001). When comparing chemotherapy versus supportive, radiotherapy versus supportive, chemotherapy and radiotherapy versus supportive treatment, they were all significantly different (p=0.002, p<0.0001, p<0.0001, respectively) (Table 3 and Fig 4).

## DISCUSSION

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer deaths in both men and women (Socinski *et al*, 2001). NSCLC accounts for approximately 80% of all lung carcinoma. At least three-fourths of patients with NSCLC are unresectable at presentation because the disease has had metastases or is locally advanced (Riantawan *et al*, 1999a). Survival among those beyond the surgical stage is uniformly short. This study tried to identify prognostic factors for survival of NSCLC patients in advanced stages in northeastern Thailand during 1997-2001.

There are several reasons for the attempt to identify prognostic factors of survival in NSCLC patients. Knowledge of these factors allows us to design better clinical studies and to make comparisions unbrased by age and sex. Taking these variables into account is particularly important for the treatment of advanced non-small-cell lung cancer. The variability of survival duration due to individual characteristics can mask a true but mild theropeutic effect. We can also attempt to predict the prognosis for individual patients by modeling survival distribu-

tion as a function of these variables in the patient. These classifications can be useful in choosing a treatment for an individual patient.

In comparing demographic factors, treatment methods, histological factors and pathological factors in terms of survival, it is often necessary to adjust for patient-related factors that can potentially affect the survival time of the patient. In our study, the influence of age and sex was statistically controlled.

Staging

The survival outcomes in stages IIIA, IIIB, and IV were very poor, particularly in stage IV, giving a 2-year survival of only 3.7% followed by patients in stage IIIB with a 2-year survival of 6.9%. The survival outcome of patients in stage IIIA was highest at a 2-year survival of 20.0%. The sharp drop in survival within the first two years in stage IV reflects the aggressive nature of the disease, both in terms of distant metastases and local invasiveness. However, the staging of some patients is incorrect upon first presentation. Hence, the determination of metastatic involvement upon diagnosis is essential for the evaluation of outcomes in all studies. These modifications have probably led to changes in the assessment of survival as reported by Feinstein *et al* (1985).

Treatment

Our results confirmed the effects of treatment for patients with NSCLC in stages IIIA, IIIB, and IV, treated by single, combination, or supportive treatment. The effects of combination treatment methods have been reported by many investigators (Eagan *et al*, 1987; Albain *et al*, 1995; Edelman *et al*, 1996; Martin *et al*, 2002). Combination treatment was found to be a significant independent prognostic factor for survival ($p<0.0001$). Despite evidence for the benefits of chemotherapy in patients with NSCLC (Hickish *et al*, 1998; Cullen *et al*, 1999; Shepherd *et al*, 2000; Phunmanee *et al* 2001), only 19.0% of this subgroup of patients in our study received it. This represents a major difference in practice compared with other studies, where chemotherapy is the standard treatment (Rapp *et al*, 1988, Hickish *et al*, 1998; Cullen *et al*, 1999). This may reflect the poor provision of chemotherapy facilities at this study center.

The survival of patients with advanced NSCLC in various reports is uniformly short (Cellerino *et al*, 1991; Dev *et al*, 1996, Riantawan *et al*, 1999b). The median survival of patients with supportive treatment in this study was 1.4 months (6 weeks). This is similar to a previous study, reported by Riantawan *et al* (1999b) which found that NSCLC patients receiving supportive care in stage IIIB had a median survival of 13 weeks. For stage IV, the median survival was 8 weeks. For pooled data in stage IIIB and stage IV, the median survival was 11 weeks.

In summary, survival probability reduced sharply after diagnosis. The overall 1, 2-, and 3-year survival rates were poor (28.9, 7.5, and 3.3%, respectively) with a median survival of 6.3 months (95%CI, 5.4-7.3), which is comparable to other reports (Rapp *et al*, 1988, Riantawan *et al*, 1999a). The differences in survival between stages IIIA, IIIB, and IV is not surprising, as there is a good correlation between prognosis and the stage. Factors predicting better survival in this study were patients with stage IIIA and the combination treatment method. These results should be interpreted with the knowledge that they have been adjusted for potentially important confounding factors (age and sex). In addition, other variables have been suggested by several researchers that influence NSCLC survival, such as performance status (Vansteenkiste *et al*, 1997; Shepherd *et al*, 2000), T stage (Vansteenkiste *et al*, 1997; Bouchardy *et al*, 1999), weight loss (Paesmans *et al*, 1995, Vansteenkiste *et al*, 1997), quality of life (Shepherd *et al* 2000; Ratanatharathorn *et al*, 2000), and white blood cell and CEA levels (Paesmans *et al*, 1995, Shepherd *et al*, 2000). In this study, these variables were not included in the analysis because of the absence of this information in the medical records. Coexisting medical disorders and other clinical parameters, such as general condition, cardiovascular and pulmonary function, are not available from the registry files.

Stages of disease and treatment methods were associated with survival time in NSCLC patients. In fact, NSCLC patients in the same stage may receive different treatments. Thus, to find out the effect of treatment methods on survival time, the analysis was stratified based on stages of disease.

NSCLC patients after receiving treatment, stratified by stage

Stage IIIA. By clinical stage, patients with stage IIIA designated a centrally located primary tumor near the carina (T3), limited extrapulmonary extension of the primary tumor (T3), and/or an ipsilateral mediastinal lymph node metastasis (N2). When surgery was contraindication for treatment of the patients with stage IIIA, chemotherapy and radiotherapy were mainly used. In this study, patients who received chemotherapy alone, radiotherapy alone, demonstrated median survival times of 7 months and 16 months, respectively. Patients who received surgery and chemotherapy or radiotherapy or both demonstrated a median survival time of 16.3 months; patients who received chemotherapy and radio therapy had a median survival time of 19.5 months.

The result of Cox's regression analysis also confirmed the difference in median survival times for the four treatments: chemotherapy alone, radiotherapy alone, chemotherapy plus radiotherapy, and surgery plus chemotherapy or radiotherapy or both. The result of this study shows that there was no statistically significant difference between the treatment methods in this stage. But the risk of death in the patients after they received combination of surgery and chemotherapy or radiotherapy or both was about 0.21 times the risk of death in patients who received chemotherapy alone, with statistically significant difference, after controlling for age and sex. Our experience is in agreement with others studies, such as Roth *et al* (1994), which randomly assigned 60 patients with stage IIIA disease to directly undergo surgery or to receive preoperative chemotherapy before surgery. The gain in overall survival for the preoperative chemotherapy arm was significant, $p<0.008$. Induction chemoradiotherapy (CT/RT) for stage IIIA NSCLC has been proved to be very effective in downstaging tumors and seemingly improving survival in a group of patients with a very high chance of both local and distance relapse. (Albain *et al*, 1995; Choi *et al*, 1997). It would seem that combined modality therapy would be most useful when tumor downstaging would facilitate a complete resection in the absence of N2 disease, a known marker for distant metastases (Wright *et al*, 2002). Ahn *et al* (2001) applied tri-modality treatment consisting of preoperative concurrent chemoradiotherapy followed by surgical resection for 31 NSCLC with stage IIIA and mediastinal lymph node metastases. The median survival period for all 31 patients and the 22 patients who underwent surgical resection was 19 months in each case. The survival and disease-free survival rates at 2 years in all the patients were 37.2% and 35.5%, respectively, while those of the 22 patients who underwent surgical resection were 43.2% and 25.6%, respectively. These results are similar to the present study. The effect of surgical and chemotherapy or radiotherapy or both was significantly different in NSCLC patients with stage IIIA disease.

Stage IIIB. The results of this study show that the overall median survival time was 7 months, and the two-year survival rate was 6.9%. By the clinical stage, stage IIIB consists of a direct extension of the primary tumor into the mediastinum, adjacent organs, or structures (T4), malignant pleural effusion (T4), or metastasis to the contralateral mediastinum or supraclavicular and scalene nodes (N3). Treatment for stage IIIB is mainly be radiotherapy, chemotherapy, and supportive treatment.

Next comes the question of the difference between the patients in this stage who received one of the five different treatment methods. The results of Cox's regression analysis used in comparing hazard risk in the patients shows that the risk of death in the patients who received combination treatments, such as surgery and others, chemotherapy and radiotherapy were about 0.27 times and 0.28 times the risk of patients who received supportive treatment, respectively, with a statistically significant difference, after controlling for age and sex. A combination of chemotherapy and radiotherapy has been shown to improve the outcomes of the patients with locally advanced NSCLC, achieving a median survival of 13-14 months and 5-year survival rates of 13-20% (Schaake-Koning *et al*, 1992; Dillman *et al*, 1996; Saunders *et al*, 1999). The purpose behind using chemotherapy concurrently with radiation therapy is to obtain radiation sensitizing and/or potentiating effect within the radiation volume and early eradica-

tion of micrometastases outside the radiation volume. (Douple and Richmond, 1982; Milstein *et al*, 1996).

Stage IV. The patients with stage IV in this study had a 2-year survival rate of 3.7%; the overall median survival of the group was 4.5 months. The treatment used for patients with stage IV (M1) disease was primary chemotherapy. The goals of therapy were the palliation of symptoms and the prolongation of survival time. However, when a solitary metastatic site occured, both the primary tumor and the solitary matastatic site could be treated with curative intent, either by a surgical or radiotherapeutic approach. The median survival times of the patients who received chemotherapy alone and radiotherapy alone were, 5.0 months and 4.3 months, respectively. The patients who received chemotherapy and radiotherapy or supportive had median survival times of 6.5 months and 1.0 month, respectively. This difference in median survival times was statistically significant.

The result of Cox's regression analysis confirmed the above statement by showing a statistically significant difference in the risk of death. The risk of death in the patients who received chemotherapy alone, radiotherapy alone, and chemotherapy plus radiotherapy were about 0.18 times, 0.14 times, and 0.11 times the risk of death, compared to patients who received supportive treatment after controlling for age and sex.

A recent study of more than 1,200 patients reported by Schiller *et al* (2002), and a study of more than 400 patients by Kelly *et al* (2001), compared several combinations of agents. The results continue to raise questions about the role and efficacy of combination chemotherapy in advanced non-small-cell lung cancer. The median survival ranged from 7.4 to 8.1 months, and the 1-year rate of survival was 31 to 39%.

These two studies confirm that the benefits of combination chemotherapy among the fittest patients with advanced NSCLC are marginal with perhaps a gain in median survival of 2-3 months, similar to the present study with 1.37 months. The median survival time and the rate of survival at 1-year in these two studies was higher than in the present study, because these authors concluded that chemotherapy was best offered only patients with good performance status, but the patients in the present study had poor performance. Shepherd's study (Shepherd *et al*, 2000) of more than 100 patients, reported that chemotherapy was comparable to the best supportive care (BSC). The time to progression was significantly longer in the chemotherapy patients (10.6 weeks versus 6.7 weeks; p=0.001). The median duration of survival for the chemotherapy arm was 7.0 months, and was 4.6 months for the best supportive care group (p=0.047). The 1-year survival rates for chemotherapy and best supportive care were 29% and 19%, respectively. These results are similar to the present study.

Methodologic issue

The most disturbing feature in this report is the low number of patients in same categories and the missing data in the registration files, particularly the histological grading. Therefore, with 36 missing values, multivariate analysis could be performed in only 174 of the 210 patients. This may influence the results presented here. The main reason for the low resectability among our patient population is clearly due to late presentation, as is indicated by the high percentage of patients with stage IIIB and stage IV disease (86.2%). The late presentation appears to be due to delayed referral, or the rendering of diagnostic intervention was unduly delayed. In many instances, the patients themselves presented to the center relatively late, having spent many weeks or months in local health facilities, and not obtaining a final diagnosis. It is apparent that a patient with a malignant pleural effusion, diagnosed at a local health center, naturally has a shorter duration of disease than the one diagnosed at tertiary referral center. Patients presenting to a referral center, therefore, tend to have more advanced disease. The data presented herein arose from a tertiary, referral center. Patients presenting to a referral center are those with more advanced or more problematic disease. Furthermore, it typically takes a number of weeks, or months in some instances, for investigations of negative results at local health facilities prior to the actual referral step. This delay clearly poses a significant impact on the overall stage at final diagnosis.

In the process of follow-up, it may be argued that the method of postal reply may have induced a selection bias towards more responses from those who were alive. As stated, the questionnaires were addressed to the patients and their next-of-kin. This has proved not to be the case in our study. The similar proportion between the alive/death status in the two sources, namely the medical records and the postal reply, refutes this theoretical argument.

The long term emphasis for lung cancer control must remain on primary prevention through tobacco control. If patients have already developed lung cancer and are to have a better chance of survival, a larger proportion of them must receive appropriate treatment. Earlier diagnosis may be achieved by referral guidance and the use of new diagnosis tools. In Ubon Ratchathani Cancer Center, using data collected mainly prospectively, clinical services should be tested against evidence-based standards and awareness of appropriate treatment interventions among clinicians, patients, and carers should be raised. All of these initiatives are capable of incremental improvement in the management of patients with lung cancer. This report represents a baseline from which to measure improvements in the processes of care and outcomes in this northeastern population.

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