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The Efficacy Of Concurrent Chemoradiation For Locally Advanced Non-Small Cell Lung Cancer Prospectively Treated At Cho Ray Hospital, Vietnam From 3/2009 To 3/2012

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List of Abbreviations

2D RT	2 Dimensional Radiotherapy
3D CRT	3 Dimensional Conformal Radiotherapy
AAH	Atypical alveolar hyperplasia
ADC	Adenocarcinoma
AUC	Area under the curve
AJCC	American Joint Committee on Cancer
BAC	Bronchioalveolar carcinoma
CR	Complete response
CT	Chemotherapy
CTV	Clinical Target Volume
CT scan	Computed tomography scan
CTC	Common Toxicity Criteria
D max	Maximal dose
DSA	Digitally Subtraction Angiography
DVH	Dose Volume Histogram
GTV	Gross Tumor Volume
Gy	Gray
ICRU	International Committee on Radiological Units and Measurements
KPS	Karnofsky Performance Status
LD	Longest diameter
LNL	Lower normal limit
Lt.	Left
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
No.	Number
ns	not significant
OAR	Organ at risk
OS	Overall survival

PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
P-value	Probability value
PTV	Planning Target Volume
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
Rt.	Right
RTOG	Radiation Therapy Oncology Group
SCC	Squamous cell carcinoma
SGOT	Serum glutamic oxalo-acetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TNM	T- tumor, N- nodes, M- metastasis
UICC	Union for International Cancer Control
UNL	Upper normal limit
V20	% Volume of an OAR receiving more than 20Gy
vs.	Versus
WHO	World Health Organization

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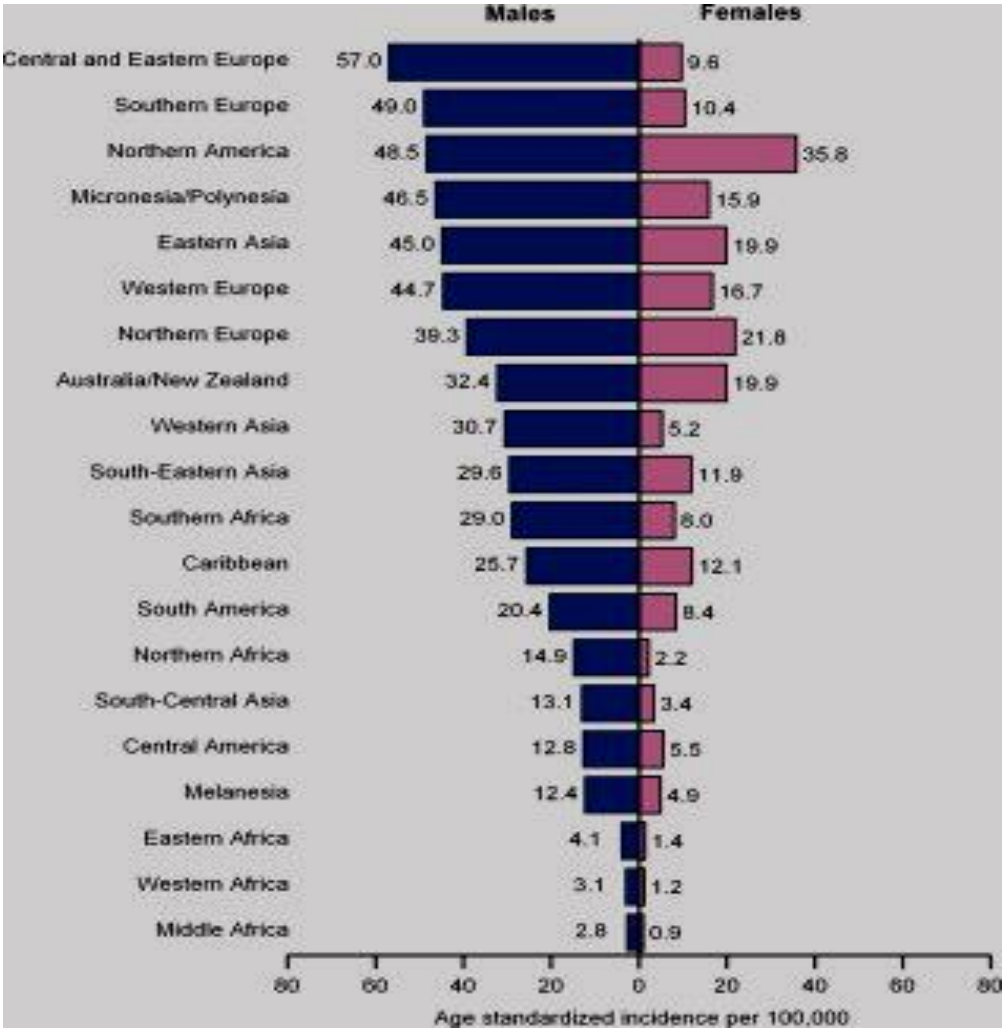
1. INTRODUCTION AND PURPOSE OF THE STUDY

1.1. Epidemiology of lung cancer

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide. Lung cancer accounted for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of the deaths globally in 2008 (Jemal et al. 2008). In the United States, it was estimated that there were 215,020 new lung cancer cases diagnosed and 161,840 deaths (American Cancer Society 2004). In Europe, lung cancer accounted for 12% of approximately 3.2 million new cancer cases, and 19.7% (334,800) of cancer-related deaths in the year of 2006 (Ferlay et al. 2007).

Figure 1.1. Age-standardized lung cancer incidence rates (Ferlay et al. 2010)



Lung cancer is rapidly emerging as a major cause of mortality in the Middle East, Africa, and Asia as well. In Japan, 71,228 annual cancer-related deaths were attributed to lung cancer. During 2005, approximately 500,000 lung cancers were diagnosed in China (Yang et al. 2005) and death rates attributable to this disease were expected to increase substantially over the next several decades (Zhang et al. 2003).

In Vietnam, lung cancer was the second most common cancer with 20,659 new cases and 17,583 deaths annually (Jemal et al. 2008).

1.2. Smoking and lung cancer

Smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females (Ezzati et al. 2003). In the United States, approximately 80% of lung cancer deaths in men and women are due to tobacco abuse. Since 1965, the prevalence of smoking in the United States has declined significantly (Giovino et al. 2002). Jemal et al. observed that smoking prevalence and lung cancer death rates in the United States correlate inversely with state tobacco control efforts (Jemal et al. 2004).

In the European Union, prevalence of smoking varies among different populations but dose coincide with low socioeconomic status, particularly in women. Women started smoking several decades later than males. Thus, lung cancer rates in females are increasing in many countries except the United States, Canada, the United Kingdom, and Australia, where they are plateau (Bray et al. 2010).

Despite their lower prevalence of smoking (less than 4% adult smokers), Chinese females have higher lung cancer rates (21.3 cases per 100,000 females) than those in certain European countries such as Germany (16.4 cases per 100,000) and Italy (11.4 cases per 100,000), with an adult smoking prevalence of about 20%. The relatively high burden of lung cancer in women is thought to reflect indoor air pollution from unventilated coal-fueled stoves and from cooking fumes in China (Lam et al. 2004).

In men, lung cancer death rates are decreasing in most Western countries, including many European countries, North America, and Australia, where the tobacco epidemic peaked by the middle of the last century. However, lung cancer rates are increasing in countries such as China and several other countries in Asia and Africa. In these countries, the epidemic of smoking has been established more recently and smoking prevalence continues to either increase or show signs of stability (Youlden et al. 2008).

The risk of lung cancer is related to duration as well as intensity of smoking. In general, the evolving patterns of lung cancer appear attributable at least in part to filters, tar content, and other variations in tobacco blends implemented to produce a more palatable nicotine delivery system. A hospital-based case control study carried out in the National Cancer Institute in Hanoi, investigating the role of tobacco and cancers, found that 'water pipe' smoking, a traditional and very popular type of smoking in the past and during the Vietnam war, is also strongly related to lung and superior aero-digestive tract cancer (Pham HA et al. 1999).

Peto et al. reported a 16-fold increase in cumulative lung cancer risk in persistent smokers; this risk is doubled for individuals who initiate smoking before age 15 (Peto et al. 2000).

Tobacco abuse has global economic, social, and medical ramifications. Overall, the trends in lung cancer incidence and mortality reflect tobacco consumption in various countries. Presently, China is the largest producer and consumer of tobacco products. Nearly 70% of males and 5% of females age 15 years and older are smokers. A total of 320 million Chinese smokers constitute approximately one third of all smokers worldwide. In China, the average daily consumption of cigarettes rose from one in 1950 to ten in 1990, a rate that was similar to that seen in the United States between 1910 and 1950. In addition, the prevalence of passive smoking in China exceeds 50%. Much of this exposure occurs in the home among women and children. As a result of current tobacco exposure, the incidence of lung cancer in China will increase dramatically during the next several decades, with predicted death rates attributable to tobacco approaching 3 million by the year of 2050. Similar trends will be occurring in other Asian countries, such as Vietnam and Taiwan (Zhang et al. 2003).

As a country with a very high level of tobacco production and consumption, the cultivated surface for tobacco plants in Vietnam was about 24,000 hectares and tobacco production represented about 2 billion packs of cigarettes. These were mainly sold in the domestic market and the estimated annual level of consumption was about 600 cigarettes per capita (Hoang et al. 1995).

The results of a survey in 1995 showed that 73.4% of males and 3.9% of females are smokers. The onset of smoking was at a young age: 70% of smokers began before the age of 25 years (Pham XD et al. 1995).

Levy et al. projected that a tenfold increase in cigarette tax would decrease smoking by 30% during the next three decades in Taiwan (Levy et al. 2005). Similar projections have been published regarding the potential impact of cigarette taxation on smoking prevalence in Vietnam.

Other known risk factors for lung cancer include exposure to several occupational and environmental carcinogens such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons (Ginsberg et al. 2004).

1.3. Pathology of lung cancer (Appendix A).

1.3.1. Adenocarcinoma

Adenocarcinomas were most common histological type of lung cancer. They are often located in the periphery of the lung and in the smaller airways. The precursor lesion for pulmonary adenocarcinoma is considered to be atypical alveolar hyperplasia (AAH). AAH frequently measures less than 5 mm in diameter, and is composed of atypical type II pneumocytes proliferating on an alveolar wall that is either normal in thickness or altered by inactive fibrous scarring. There is a histological spectrum between AAH and small non-mucinous bronchioloalveolar carcinoma. These neoplasms are difficult to differentiate by cytological, histological, and genetic techniques. Lesions 5mm in diameter or less are usually made up of relatively small cells with limited nuclear atypia in comparison to larger lesions, which exhibit progressively more abnormal cells. The frequency and rate of progression from AAH to cancer is considered to be quite low, in the range of 1% to 5% over a period of years (Nakanishi et al. 1990).

1.3.2. Bronchioloalveolar carcinoma

Bronchioloalveolar carcinoma (BAC) is found in mucinous and non-mucinous variants. The mucinous type is characterized by the growth of malignant mucus containing goblet cells on the surface of alveolar walls. As such, it is often characterized by pools of mucous, and be associated with the so-called colloid variant of adenocarcinoma in which mucous is predominant over tumor cells. Mucinous BAC has a tendency to be multifocal and fatal. Non-mucinous BAC is composed of type II pneumocytes or Clara cells exhibiting nuclear anaplasia and pleomorphism greater than AAH, but less than other types of adenocarcinoma. The malignant cells spread over the alveolar walls in a monolayer, which

presents a barrier to gas exchange in the affected alveolar sac, leading to right to left intrapulmonary shunt (Lynch et al. 2004).

1.3.3. Large cell carcinoma

Large cell carcinomas are composed of large cells without cytoplasmic differentiation, and account for approximately 15% of all lung cancers. With more extensive sampling and electron microscopy, many undifferentiated large cell carcinomas can be classified more appropriately as poorly differentiated adenocarcinoma or, rarely, squamous cell carcinoma. The prognosis of large cell undifferentiated carcinoma is similar to that of adenocarcinoma and, in most clinical trials; the two histological types are grouped together. Large cell carcinoma show a partial neuroendocrine phenotype recognized from carcinoid histology, immunostaining for chromogranin A or synaptophysin, or the ultrastructural demonstration of dense core granules. When accompanied by necrosis, high mitotic rate, and tumor necrosis, these carcinomas are associated with a poor prognosis (Chan et al. 1995, Moro et al. 1994).

1.3.4. Squamous cell carcinoma

Squamous cell carcinoma classically arises in proximal segmental bronchi via progression through stages of dysplasia. In its earliest form (carcinoma in situ), malignant squamous cells spread over the bronchial surface, often involving submucosal glands, without invasion through the basement membrane. Because there is exfoliation of the malignant cells from the bronchial surface, squamous cell carcinoma can be detected by cytological examination at its earliest stage. Occasionally this is before it is evident on chest x-ray, because of its origin in the electron-dense bronchi, which render them radiographically occult. With further growth, squamous cell carcinoma invades the basement membrane and extends into the parenchyma and bronchial lumen, producing obstruction with resultant atelectasis or pneumonia. Histologically, squamous cell carcinoma is composed of sheets of epithelial cells with individual cell keratinization, intercellular bridges, or pearl formation. Squamous cell carcinoma tends to be slow-growing, and it is estimated that the progression of in situ carcinoma to a clinically apparent tumor takes three to four years (Carter et al. 1985).

1.3.5. Adeno-squamous carcinoma

Adeno-squamous carcinomas have histological areas differentiated into both squamous cell carcinoma and adenocarcinoma. They are predominantly found in the periphery of the lung

and have clinical behavior more like that of adenocarcinoma. However, studies suggest that they are a cytogenetically distinct entity (Takamori et al. 1991)

1.3.6. Pleomorphic carcinomas

This grouping of tumors includes carcinomas with giant and usually multinucleated cells, those carcinomas with a spindle cell, pseudo-sarcomatous configuration, and those with both carcinoma and sarcoma morphology, including the rare pulmonary blastoma. All are aggressive malignancies and usually found at a high stage, but survival is stage-dependent (Ginsberg et al. 1992)

1.3.7. Carcinomas of salivary gland type

These carcinomas include muco-epidermoid carcinomas (low and high grade), recognized by their characteristic intermediate or transitional cells, adenoid-cystic carcinoma, which shares the aggressiveness of its salivary gland counterpart, and the low-grade, acinic cell carcinoma. All are predominantly found in large bronchi and thought to arise from submucosal gland epithelium (Yousem et al. 1987).

1.4. Clinical manifestations

The signs and symptoms of patients who suffer from lung cancer depend on the histology of the tumor and the extent of loco-regional invasion, as well as the location, size, and number of distant metastases. Many patients present with an asymptomatic lesion discovered incidentally on chest radiography or CT scan.

Tumors arising in the larger airways cause persistent cough, wheezing or hemoptysis. If pleural surfaces are involved either by the primary tumor or associated infection, pleuritic pain develops with or without a pleural effusion. The loss of lung function was associated with dyspnea, the severity of which depends on the amount of lung involved and the patient's underlying pulmonary reserve. Tumors invading the chest wall typically produce either stabbing or burning radicular pain with or without pleural effusion.

Tumors arising within the superior sulcus are associated with a Pancoast syndrome due to invasion of the lower brachial plexus (T1 and C8 nerve roots), stellate ganglion, and chest wall or vertebral bodies. Invasion or encasement of structures within the mediastinum result in superior vena cava syndrome, recurrent or phrenic nerve palsy, esophageal dysphagia, trachea-esophageal fistula, or pericardial effusion.

Nearly all patients with advanced non-small cell lung cancer exhibit symptoms referable to their disease on initial presentation. Fatigue and decreased activity are reported by more than 80% of individuals, and most patients also experience cough, dyspnea, anorexia, and weight loss. The presenting complaints of patients with metastatic disease are largely determined by the specific sites involved, such as bone, brain, liver, and adrenal glands. In addition, patients could exhibit a variety of paraneoplastic syndromes such as hypertrophic pulmonary osteoarthropathy, clubbing of the digits, etc. (Ginsberg et al. 2004).

1.5. Treatment of locally advanced non–small cell lung cancer

Non-small cell lung cancer (NSCLC) includes adenocarcinoma and its bronchioloalveolar subset, squamous cell carcinoma, and large cell carcinoma, in decreasing order frequency of occurrence. Non-small cell lung cancer (NSCLC) accounts for at least 80% of all lung tumors. About 35% of these patients present with locally advanced non-metastatic disease (Jemal et al. 2004).

Stage III non–small cell lung cancer is defined as loco-regionally advanced disease, based upon mediastinal lymph node involvement or extension into extra-pulmonary structures, without evidence of distant metastases. The International Staging System subdivides stage III NSCLC into stages IIIA and IIIB. Stage IIIA is based upon the presence of ipsilateral mediastinal lymph node (N2) involvement or a T3 lesion with positive hilar nodes (N1). Stage IIIB disease is characterized by supraclavicular or contralateral mediastinal lymph node involvement (N3) or a T4 primary tumor (Greene et al. 2002).

Patients with stage IIIA disease are stratified clinically into those with bulky and non-bulky disease, based upon the presence of lymph nodes > 20mm in short-axis diameter, as measured by CT, or groupings of multiple smaller lymph nodes. These distinctions between non-bulky and bulky IIIA and IIIB disease are important for prognostic purposes, rather than for determining the therapeutic approach (Appendix B).

Despite therapeutic advances over the past two decades, these patients' prognosis remains poor, with a 5-year survival rate of only 10 –15%. Until the late 1980s, radiotherapy was the only treatment option. The Radiation Therapy Oncology Group (RTOG) had shown that local disease control was improved by increasing the total dose to 60Gy delivered in 30 fractions over 6 weeks (Perez et al. 1982, Perez et al. 1986).

1.5.1. Induction chemotherapy and radiation

The 1990s saw the emergence of both sequential and concurrent combinations of chemotherapy and radiotherapy. A number of randomized phase III trials, and several meta-analyses, showed that chemo-radiotherapy was superior to radiotherapy alone in terms of overall survival (Le Chevalier et al. 1992, Auperin et al. 2006).

LeChevalier et al. randomly assigned 353 patients to receive either induction chemotherapy with lomustine, vindesine, cyclophosphamide, and cisplatin followed by 65Gy of radiotherapy or radiotherapy alone, with 3-year survival rates of 12% versus 4%, respectively ($P<0.02$). This trial also monitored the pattern of relapse (local versus systemic) and found that the reduced failure and improved survival rate in chemotherapy-treated patients was a result of improved distant disease control (Le Chevalier et al. 2000).

The Cancer and Leukemia Group B (CALGB) conducted a seminal study (CALGB 8433) in which patients with inoperable stage IIIA or IIIB disease were randomly assigned to receive two cycles of cisplatin and vinblastine over 5 weeks followed by radiation therapy to 60Gy versus radiation therapy to 60Gy without chemotherapy. The response rate was 56% for patients receiving chemotherapy and radiation compared with 43% for patients receiving radiation therapy alone; median survival time were 14 months versus 10 months, respectively ($p=0.0066$). More importantly, there was a 17% survival rate at 5 years in the combined-modality therapy arm versus a 7% rate in the radiation therapy alone arm, with few patients experiencing relapse after 2 to 3 years of follow-up (Dillman et al. 1996).

Not all trials testing induction chemotherapy in stage III NSCLC have been positive (Morton et al. 1991). However, it has been pointed out that those trials used less aggressive chemotherapy and entered smaller cohorts of patients. The survival advantage with induction chemotherapy has been confirmed by a meta-analysis of these trials (Marino et al. 1995).

1.5.2. Concurrent chemotherapy and radiation

Concurrent therapy seemed to give better results than sequential therapy, but this needed to be demonstrated. In a phase III trial from the West Japan Lung Cancer Group, 320 patients were randomly assigned to receive thoracic radiation (56Gy, split-course) either after or concurrent with cisplatin ($80mg/m^2$), vindesine ($3mg/m^2$), and mitomycin ($8mg/m^2$) chemotherapy. Patients receiving concurrent therapy had a median survival time of 16.6 months compared with 13.3 months for the sequentially treated patients ($p=0.03$). The 5-

year survival rate was also superior for the concurrently treated patients (15.8%) compared with patients receiving sequential therapy (8.9%). This was the first randomized phase III trial to show a statistically significant improvement in overall survival after concurrent chemo-radiotherapy, with no increase in esophageal toxicity (Furuse et al. 1999).

Curran et al. report the results of the RTOG 94-10 study, which compared three schedules: sequential treatment with cisplatin–vinblastine induction chemotherapy followed by radiotherapy at a total dose of 63Gy (arm 1); a concurrent schedule in which two cycles of cisplatin–vinblastine were administered during the same radiotherapy schedule as in arm 1 (arm 2); and another concurrent schedule combining cisplatin–etoposide chemotherapy with bi-fractionated radiotherapy at a total dose of 69.6Gy (arm 3). Arm 2 was first compared with the sequential schedule, which served as the reference treatment, and then arm 3 was compared with the better of the other two arms. The median survival time was superior for patients receiving concurrent daily radiation (17.0 months) compared with patients receiving sequential therapy (14.6 months); this result was statistically significant (p=0.038). The overall 4-year survival rate was also better for patients on the concurrent arm compared with the sequential arm (21% versus 12%, respectively) (Curran et al. 2011).

A similar experience has been reported by Fournel et al in the Groupe Lyon-Saint-Etienne d'Oncologie Thoracique – Groupe Français de Pneumo - Cancérologie study NPC 95-01. In this phase III trial, 212 patients received thoracic radiation (66Gy) and were randomly assigned to either the sequential arm with induction chemotherapy consisting of cisplatin (120mg/m^2) and vinorelbine (30mg/m^2 weekly) or to concurrent therapy consisting of cisplatin (20mg/m^2) and etoposide (50mg/m^2) for two cycles along with thoracic radiation. All patients received consolidation chemotherapy that consisted of cisplatin (80mg/m^2) and vinorelbine (30mg/m^2 weekly) for eight cycles. Median survival time of 14.5 months was observed for the sequentially treated patients compared with 16.3 months for the concurrent arm. It is important to note that this result did not achieve statistical significance (p=0.24). The 2- and 4-year survival rates in the sequential arm were 26.5% and 14.2%, respectively, and in the concurrent arm were 39.3% and 20.7%, respectively, (Fournel et al. 2005). However, the benefit persisted at 5 years, in which the improvement in overall survival observed with the concurrent schedule was stable at 5 years (18.5% versus 8.5%) and at 7 years (15% versus 5.8%) (Fournel et al. 2008).

In an additional European trial reported by Zatloukal et al, 102 patients were randomly assigned to four cycles of cisplatin (80mg/m^2) and vinorelbine (25mg/m^2) chemotherapy with radiation (60Gy) starting on either the second cycle (concurrent arm) or after the completion of the chemotherapy (sequential arm). The median survival time was significantly longer for patients receiving concurrent therapy (16.6 months) compared with patients receiving sequential therapy (12.9 months) (Zatloukal et al. 2004).

1.5.3. Induction/ consolidation chemotherapy in addition to concurrent chemo-radiotherapy

Although it is clear that concurrent chemo-radiotherapy is superior to sequential chemotherapy followed by radiation or radiation alone in patients with good performance status and no significant weight loss, several important questions remain controversial and unanswered. It is not certain whether patients benefit from additional chemotherapy administered at systemically active doses (in the induction or consolidation phase) in addition to concurrent chemo-radiotherapy (Auperin et al. 2010, Blackstock et al. 2007).

A phase III study (CALGB 39801) randomly assigned 366 patients with locally advanced NSCLC to two cycles of induction chemotherapy with paclitaxel (200mg/m^2) and carboplatin administered every 3 weeks followed by weekly paclitaxel (50mg/m^2) and carboplatin (AUC=2) with thoracic radiation or the same regimen without induction chemotherapy. The median survival time was a mere 12 months (95% CI, 10 to 16 months) without the induction regimen and only 14 months (95% CI, 11 to 16 months) with the induction therapy (Vokes et al. 2007).

These results are not that different from those observed in the seminal CALGB study conducted two decades ago that compared radiation alone (9.6 months) with sequential chemotherapy followed by radiation (13.7 months) (Dillman et al. 1990). Unlike the previous CALGB studies, weight loss of more than 5% was not a specific exclusion criterion in this study. In the subset of patients with weight loss of more than 5% (n=87), induction therapy followed by concurrent chemo-radiotherapy resulted in a better overall 3-year survival rate than concurrent chemo-radiotherapy alone (23% versus 10%, respectively).

In Southwest Oncology Group (SWOG) study 9504, 83 patients with stage IIIB disease were treated with cisplatin-etoposide, and concurrent radiotherapy followed by three cycles of docetaxel; this regimen resulted in an impressive median survival time of 26 months and

a 3-year survival rate of 37% (Gandara et al. 2003). These results compared favorably with their previous study (SWOG 9019) in the same population when patients were treated with cisplatin-etoposide, and concurrent radiation followed by two additional cycles of cisplatin and etoposide. In this study, the median survival time was 15 months, and the 3-year survival rate was 17% (Albain et al. 2002). Although the SWOG 9504 results are encouraging after a series of disappointing results, the unprecedented results raised questions regarding patient selection given the known heterogeneity of the locally advanced NSCLC subset.

Several other randomized phase II and III trials have compared induction chemotherapy followed by concurrent chemo-radiotherapy versus concurrent chemo-radiotherapy followed by consolidation chemotherapy. Neither strategy proved superior to chemo-radiotherapy alone. However, several lines of evidence support early chemo-radiotherapy (Akerley et al. 2005, Belani et al. 2005, Vokes et al. 2007, Hanna et al. 2008).

The Hoosier Oncology Group (HOG) conducted a phase III study involving 203 patients with locally advanced NSCLC who received cisplatin, etoposide, and thoracic radiation; patients without disease progression were then randomly assigned to observation or three cycles of docetaxel administered every 3 weeks. Of 203 patients enrolled, 147 (72%) were randomly assigned to consolidation docetaxel (n=73) or observation (n=74). The addition of docetaxel did not improve progression-free survival or overall survival in this study. Consolidation docetaxel resulted in increased rates of infections, pneumonitis, and treatment-related death when compared with observation alone. The overall survival time for the entire study population was 21 months (95% CI, 17.1 to 25.3 months), and the 3-year survival rate was 28%, which is better than any multi-institutional randomized study reported so far in this population (Hanna et al. 2008).

Two recent Japanese trials (Yamamoto et al. 2010, Segawa et al. 2010) showed no superiority of chemotherapy regimens including third-generation drugs compared with older protocols. Concurrent chemo-radiotherapy gave median overall survival time often exceeding 20 months and 2-year survival rates of between 40% and 60%. Surprisingly, these favorable results were obtained with the same chemotherapy regimen as that used in the trial published by Furuse et al (Furuse et al. 1999).

Currently, technological advances in thoracic radiotherapy, including four-dimensional dosimetry and intensity-modulated radiation therapy, may contribute to improvement of

results (Liao et al. 2010). Indeed, conformal radiotherapy reduces toxicity for healthy bystander tissues and, in some patients, allows the dose to be increased, up to 74Gy (Bradley et al. 2010).

1.6. Purpose of the study

Vietnam is located on the eastern Indochina Peninsula. It covers a total area of approximately 331,210 km^2, making it almost the size of Germany (357,021 km^2). The census in 2009 recorded population of Vietnam as standing at approximately 85.8 million, ranking 13^{th} in globally. According to the National Registry of Cancer, Vietnam had 150,000 new cases of cancer each year (Pham et al. 2002). The leading cancers in this country were lung, liver, stomach, colorectum and nasopharynx in males and breast, cervix, stomach, liver, colon–rectum and lung in females. The data of cancer statistics in Vietnam are shown in Table 1.1 (Ferlay et al. 2010).

Table 1.1. Cancer statistics of Vietnam (Ferlay et al. 2010)

Types of cancer	Morbidity (n, %)	Mortality (n, %)
Liver	23,251 (20.8)	21,748 (26.5)
Lung	20,659 (18.5)	17,583 (21.4)
Stomach	15,068 (13.5)	11,327 (13.8)
Colorectal	7,367 (6.6)	4,131 (5)
Breast	6,830 (6.1)	2,423 (3)
Cervix	5,174 (4.6)	2,472 (3)
Hematology	4,355 (3.9)	3,594 (4.4)
Nasopharynx	3,537 (3.2)	2,688 (3.3)
Central nervous system	3,220 (2.9)	2,646 (3.2)
Others	22,120 (19.8)	13,394 (16.3)

There was a shortage in cancer hospitals in this country, especially radiotherapy (RT) facilities and these facilities were located in the major cities such as Hanoi and Ho Chi Minh City. The available RT equipment in Vietnam were included 10 Brachytherapy units, 7 Simulators, 14 Co-60 Teletherapy units, 8 Linear Accelerators, 3 Gamma-Knifes and 1 Cyber-Knife. This is well below from the IAEA recommendation of at least one machine per million populations (Le TA 2008).

Cho Ray hospital was a government teaching hospital that belongs to Ministry of Health. It was located in Ho Chi Minh City and was also the top referral hospital for more than 30 provincial hospitals in South Vietnam. Cho Ray had more than 40 clinical wards, surgical departments for almost every kind of cancer. It had comprehensive diagnostic imaging (Ultrasound, CT scan, MRI, and DSA) and nuclear medicine (SPECT, PET – CT) facilities. The Department of Oncology, which was established in 2002, had 6 radiation oncologists, 4 medical oncologists, 6 medical physicists, 16 radiation therapists and 7 nurses. This department was well-equipped with two Linear Accelerators, one Simulator, two Treatment Planning Systems (DSS and Leibinger). The available radiotherapy techniques included 2D radiotherapy, 3D-CRT and radiosurgery.

In Vietnam, many lung cancer patients came to hospital in very advanced stages, therefore, their survival were quite poor. As stated previously, the optimal treatment for locally advanced NSCLC continued to involve, but combined-modality therapy has led to improve survival rates versus treatment with radiation alone or sequential chemo-radiotherapy, and was the standard of care. However, due to the shortage in radiotherapy equipment, many stage III NSCLC patients in this country were being treated with palliative intent by chemotherapy alone or supportive care only. This was the main reason why we would like to set up a study to treat the patients with stage III NSCLC by concomitant chemo-radiotherapy with the following objectives:

1- **Primary objective**:

- Determine the efficacy of combining radiotherapy and chemotherapy concurrently in treatment of the patient with stage III NSCLC by analyzing the median survival time in the study population.

2- **Secondary objectives**:

- Determine the efficacy of combining radiotherapy and chemotherapy concurrently in treatment of the patient with stage III NSCLC by analyzing the progression-free survival, the overall survival and the response rate.
- Assess the safety and tolerability of patients receiving concomitant chemo-radiotherapy.

2. PATIENTS AND METHODS

2.1. Patients

Non-small cell lung cancer (NSCLC) includes adenocarcinoma and its bronchioloalveolar subset, squamous cell carcinoma, and large cell carcinoma, in decreasing order frequency of occurrence. Stage III non-small cell lung cancer is defined as loco-regionally advanced disease, based upon mediastinal lymph node involvement or extension into extra-pulmonary structures, without evidence of distant metastases (Greene et al. 2002).

All patients who presented to the Department of Oncology, Cho Ray hospital, Ho Chi Minh City, Vietnam with lung cancer over a three year period from March 1st, 2009 to March 1st, 2012 were recorded in a prospective database. Patients with stage III NSCLC who satisfied the following inclusion criteria were accrued into this prospective study. The study cohort was selected from all patients with locally advanced NSCLC who presented to the Department of Oncology during this period. The study protocol was approved by the Institutional Review Board of Cho Ray hospital.

2.1.1. Inclusion criteria

Patient must satisfy all the following entry criteria before participating in the study:

1. Age greater than 18 years
2. Histologically proven non-small cell lung cancer (NSCLC) including squamous cell carcinoma, adenocarcinoma, bronchioloalveolar carcinoma, large cell carcinoma.
3. Untreated locally advanced stage IIIA or stage IIIB: no prior systemic chemotherapy, thoracic radiotherapy or complete surgical resection.
4. Karnofsky Performance Status ≥ 80% (Appendix D)
5. Patients without weight loss > 10% within the previous 3 months before diagnosis
6. Adequate bone marrow, hepatic and renal functions:

– Granulocyte count > 2.0 x 10^9/l
– Platelet count > 100 x 10^9/l
– Hemoglobin > 10 g/dl
– Total Bilirubin < 1.5 x ULN
– Transaminases < 2.5 x ULN

– Creatinine < 1.5 x ULN

– Forced expiratory volume in 1 second (FEV1) > 800mL

7. Patients were required to have at least one measurable lesion according to RECIST criteria (Appendix E)

8. Patients were able to comply with the treatment protocol and follow-up.

9. Signed written consent form.

2.1.2. Exclusion criteria

Patient should not enter the study if any of the following applied:

1. NSCLC stage I, II and IV.

2. NSCLC stage IIIB with malignant pleural effusion.

3. Concomitant/ uncontrolled medical disorder (cardiac failure or myocardial infarction within the previous three months; uncontrolled hypertension or arrhythmia)

4. Weight loss > 10% within the previous three months

5. Pre-existing malignant pleural effusion

6. Ascites or pericardial effusion

7. Active secondary malignancy except appropriately treated carcinoma in situ of the cervix or skin basal cell cancer.

8. Known hypersensitivity to the study drugs or to drugs with similar chemical structures

9. Women if pregnant or breast-feeding or with positive pregnancy test at inclusion

2.2. Diagnosis

Two weeks before study entry, the patients who satisfied all selection criteria and not committed to exclusion criteria were undertaken a complete medical history and a physical examination, together with preliminary investigations. These included: weight, performance status, white blood counts/ granulocytes, hemoglobin, platelet count, SGOT, SGPT, total bilirubin, albumin, glucose and creatinine. Pulmonary function tests and an ECG were also performed on patients before study entry. Radiographic assessments, including CT scans and bone scans, were obtained to document tumor staging for eligibility. CT scans were used consistently for all evaluations and tumor measurements during the entire study period.

2.3. Treatment

2.3.1. Rationale of treatment

Combined chemo-radiation therapy was currently considered a standard of care for patients with stage IIIA or IIIB NSCLC who were not candidates for surgical resection. Concomitant chemo-radiotherapy offered an alternative strategy for combined therapy because it could provide both local and distant control simultaneously. Various agents have been used either sequentially or concurrently in many trials of combined chemo-radiotherapy for NSCLC. Clinically, however, no chemotherapy combination has proven superiority in a combined-modality setting (Vokes et al. 2005).

The analysis of many prospectively randomized trials in stage III NSCLC revealed a significant increase in treatment–related toxicities within concurrent chemo-radiation protocols, especially with second generation chemotherapy (Curran et al. 2011, Furuse et al. 1999, Fournel et al. 2005).

The benefit of the introduction of third-generation has begun to be assessed in terms of less treatment-related adverse events (Belani et al. 1997, Choy et al. 2000, Vokes et al. 2002). The ECOG study that compared four commonly used regimens (cisplatin/paclitaxel, cisplatin/docetaxel, cisplatin/gemcitabine and carboplatin/paclitaxel) for front-line therapy of advanced NSCLC demonstrated similar efficacy including response rate, median survival and 1-year survival for all four regimens. Therefore, carboplatin/paclitaxel was chosen as the reference regimen for other ECOG trials based on its favorable therapeutic index (Schiller et al. 2002). The results of a Southwest Oncology Group study also demonstrated a favorable tolerability profile for the carboplatin/paclitaxel regimen compared with cisplatin/vinorelbine (Kelly et al. 2001).

Radiosensitizer properties of paclitaxel have been shown both in vitro and in animal models (Mote et al. 1996, Leonard et al. 1996). Efforts to improve the tolerability profile of this regimen have focused on administration of lower doses of paclitaxel (175 to 200mg/m^2) or by administering paclitaxel on a weekly schedule (Kosmidis et al. 2000). Weekly schedules were preferred as a compromise between possible radiosensitization and feasibility. In Vietnam, the regimen of carboplatin and paclitaxel was still the most commonly used regimen for the treatment of advanced NSCLC. Therefore, this combination at reduced dose was chosen to combine concurrently with radiotherapy for locally advanced non-small cell lung cancer at Cho Ray.

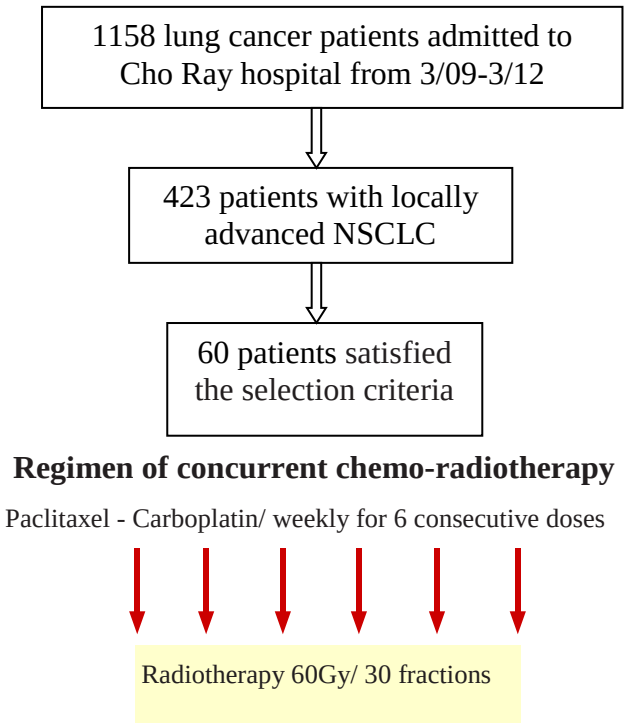
2.3.2. Chemotherapy administration

Following entry into the study, patients were planned to receive weekly paclitaxel with carboplatin for six consecutive weeks. The paclitaxel was administered at 45mg/m^2 intravenously (in one hour) and the carboplatin being given at a formula time versus concentration curve (AUC) of two intravenously (in 30 minutes) following administration of paclitaxel.

Surface area was calculated using actual patient's height and weight. The dose of carboplatin was calculated at 25 plus creatinine clearance x the desired AUC, according to the Calvert formula. In which, creatinine clearance was determined as 140 – patient age x weight in kilograms ÷ by 72 x serum creatinine x (0.85 for female patients) (Calvert et al. 1995).

Thirty minutes before paclitaxel, patients received intravenous premedication consisting of Dexamethasone 8 mg, Promethazine 50mg, and Ranitidine 50mg or other drugs of the same classes in comparable doses. Patients could receive anti-emetics, if required, but no cytotoxic, hormone, or immunotherapy and no regular supportive treatment with granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor.

Figure 2.1. Schema of patient selection for the study



Chemotherapy dose modifications

1. Platelet count of 50,000 to 74,999/mm^3 or granulocyte count of 1,000 to 1,499/mm^3 on the day of planned treatment, 50% of carboplatin and paclitaxel were administered.
2. Platelet count of less than 50,000/mm^3 and for a granulocyte count of less than 1,000/mm^3, chemotherapy was withheld.
3. For esophagitis, mucositis, stomatitis and dermatitis of grade 3, during radiotherapy, paclitaxel was delayed one week and carboplatin was continued. Paclitaxel was resumed once toxicity had resolved to grade 2.
4. For grade 4 toxicities, all protocol therapy was held and resumed at a 50% dose following resolution of toxicity to grade 2.

2.3.3. Radiation therapy

Radiotherapy was administered concurrently with 6 cycles of chemotherapy, starting on day 1 of the first cycle of chemotherapy. A total dose of 60Gy was administered at five fractions per week for 6 consecutive weeks at fractionation of 2Gy.

2.3.2.1. Radiotherapy planning and delivery

Data acquisition for radiotherapy was performed on a Siemens Somatom® Sensation 4 CT scanner (Siemens AG) fitted with a flat tabletop and laser localization. Patients were immobilized in the supine position and arms resting over the head to allow for lateral fields. Immobilization device for patient's body included a lungboard (Medtec). CT scan images (after injection of contrast medium) were acquired in the treatment position before planning and simulation. CT acquisition covered the whole treated volume, including tumor, nodes, spinal cord, lungs and heart, i.e. usually from larynx to L2. The slices were contiguous and 5mm in thickness.

Radiotherapy planning was performed on DSS® (Decision Support System) Multidata computerized 3-D treatment planning system (Multidata System International Corporation). Blocks were designed according to computer dosimetry, i.e. taking into account the physical penumbra around the PTV. A Siemens Symview® treatment simulator (Siemens AG) was used for verification simulation. Simulation films were also taken to further assess setup and field arrangements. Radiotherapy was delivered on a Siemens Primus® linear accelerator (Siemens AG) with 6MV photon energies. Treatments

usually consisted of three to four fields at 3-4 gantry angles. Portal images of treated beams with blocks were taken on the first day of treatment to verify setup and plan.

Figure 2.2. Data acquisition with Siemens Somatom® Sensation 4 CT scanner

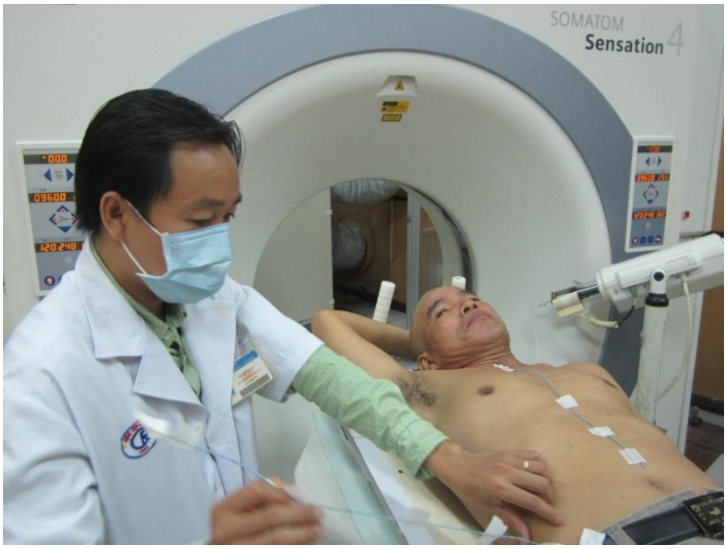
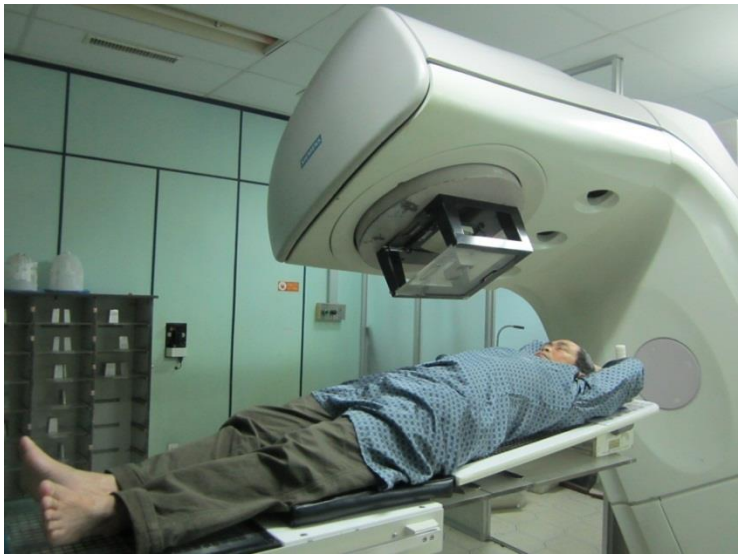


Figure 2.3. Radiotherapy on Siemens Primus® linear accelerator



2.3.2.2. Definitions of target volumes

Gross Tumor Volume (GTV)

GTV was the gross demonstrable extent and location of the malignant growth (primary tumor and involved lymph nodes). The determination of the GTV was based on clinical, endoscopic and CT scan. The extension of the primary tumor was determined using the CT

lung windows. Lymph nodes were defined as involved if larger than 15mm, if they showed central hypodensity or if multiple lymph nodes larger than 10mm were seen in the same compartment. Lymph nodes were defined using CT mediastinal soft tissue windows.

Clinical target volume (CTV)

CTV involved adding a margin for suspected micro extension around the primary GTV. Standard margin of 5mm was set around the GTV primary involved lymph nodes.

Planning Target Volume (PTV)

PTV was designed to treat the primary tumor and macroscopically involved lymph node compartments. The PTV adds margins to the GTV and considers both oncological subclinical extension and geometrical (setup and motion uncertainty) factors. A lateral margin of 10mm and a 15mm margin in the cranio-caudal direction (as breathing mobility is higher in z direction) are added to the GTV.

Dose was specified according to ICRU 50. Dose was calculated at the ICRU reference point preferentially at the intersection of the treatment beams in the isocenter plane. The surface of the PTV was covered by the 95% isodose. The maximum dose was located in the target volume and should not exceed 110% isodose. Normalization could use the median dose in the PTV. Single doses of 2Gy/fraction were given each day, five days a week to total dose of 60Gy. All fields were treated daily. Breaks were avoided if possible.

2.3.2.3. Critical organs

Critical organs were defined as the lungs and spinal cord. The doses delivered to these organs was calculated and displayed on dose-volume histograms. The recommended radiotherapy planning dose constraints were defined as:

- Lung: The volume of lung receiving greater than 20Gy (V20) should be kept less than 35% of the total volume of both lungs minus the PTV: V20 < 35% lung volume.
- Spinal cord: The maximum dose to the spinal cord should be less than 45Gy. Dmax < 45Gy.

2.3.2.4. Irradiation techniques

A CT-based 3-D treatment technique was designed to treat an individually shaped target volume and minimize dose to critical organs at risk (spinal cord, lung). An isocentric technique using multiple fields and shaped beams with satellite blocks was recommended. Sparing of the contralateral lung was considered paramount. Ideally, the total lung volume

(excluding the PTV) that received more than 20Gy should be less than 35% (dose volume histogram analysis). The dose to the spinal cord should not exceed 45Gy at a single dose of 2Gy. Anterior-posterior/ posterior-anterior fields with spinal cord shielding were not recommended as it resulted often in reduced doses to the target volume. Documentation of the treatment techniques at the simulator and representative port verification at the treatment machine at first day of radiotherapy were mandatory.

2.3.2.5. Modifications of radiotherapy

1. Hematological toxicities: in case of febrile neutropenia associated or not with platelets < 10.000/mm^3, the radiotherapy should be delayed until the patient has recovered with apyrexia.
2. Esophagitis grade 3: chemotherapy should be delayed for one week. Radiotherapy should be continued, if possible. If the patients had not recovered after two weeks, the patient would be withdrawn from the study. Treatment should be discontinued in case of grade 4 esophagitis.

2.4. Methods

All patients who presented to the Department of Oncology with lung cancer from March 1st, 2009 to March 1st, 2012 were recorded in a prospective database. The patients had pathological diagnosis by endoscopic biopsy, lymph nodes biopsy or post-surgery. All patients underwent staging with clinical examination, bronchial endoscopy, abdomen ultrasound, CT scan of the brain, chest and abdomen with or without contrast, and bone scan.

2.4.1. Data survey and documentation

Patients were informed on their diagnosis, prognosis and treatment alternatives. Clinical details were recorded prospectively and included name, gender, age, personal and family histories, social habits like smoking, histology, clinical presentation, performance status, weight loss in previous three months, details of treatment regimen, toxicities and outcome of treatment.

2.4.2. Evaluation of responses

All eligible patients were considered as assessable for responses and toxicities. Cell blood count, transaminases, blood urea nitrogen (BUN), serum creatinine were repeated once a

week during the treatment period. In order to record response rates, patients underwent a repeated CT scan at 8-12 weeks following the ending of treatment. The results of this scan were compared with baseline CT scan and responses were evaluated in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.0) (Appendix E).

For the follow up after the treatment, repeated CT scans were obtained every three months in the first year and every six months in the following years or when recurrences were suspected. All survival time were defined as the time from start of treatment to progression or last follow-up (progression-free survival) or death of any cause (overall survival).

2.4.3. Endpoints of study

The primary endpoint was the median survival time analyzed in the study population.

The secondary endpoints were:

- Progression-free survival,
- Overall survival,
- Response rates,

A multivariate analysis using a Cox proportional hazard model for time to progression and time to death/ last follow-up was performed taking into account the following prognostic factors:

- Stages (IIIA/ IIIB),
- Histological subtypes (Adenocarcinoma/ Squamous cell carcinoma/ Bronchioloalveolar carcinoma),
- Age groups (under 60 years old/ from 60 – 69 years old/ over 69 years old),
- Pretreated weight loss status (under 5% or from 5-10% of their normal weights).
- Performance status score at baseline (KPS 100/ KPS 90/ KPS 80).

2.4.4. Toxicity assessment

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) classification version 2.0 was used to classify all adverse events and toxicities (Appendix C). All observed toxicities were recorded after each cycle. Hematologic parameters were observed weekly. Blood chemistry parameters and clinical examination results were also obtained before every cycle of chemotherapy and after the end of therapy.

Hematological parameters were consisted of white blood count, granulocytes, platelets and hemoglobin. Biochemical parameters included serum glutamic oxaloacetic transaminase

(SGOT), serum glutamic pyruvic transaminase (SGPT), and serum creatinine. In addition, non-hematological toxicities such as nausea/ vomiting, alopecia, dermatitis, fatigue/ anorexia, weight loss, infection, odynophagia/ dysphagia and cough/ dyspnea should be assessed by clinical exam.

Maximum NCI-CTC grades or severity were reported by cycle and by patient. In order to examine the evolution of biochemical toxicities, worst NCI-CTC grade would be analyzed in relation to the grade presented at baseline.

2.5. Statistics

This trial was a single institution, prospective, single-arm study. The statistical analysis was performed using STATA 11.0 software package (Statacorp®). Continuous data was summarized with the following parameters: frequency, median (if $n \geq 3$), range and mean and standard deviation of the mean if relevant. Categorical data was presented in contingency tables with frequencies and percentages of each modalities (including missing data modality). To describe time dependent parameters, Kaplan-Meier curves and life tables by subgroups were provided. Log-rank test were performed to compare the subgroups for progression-free survival and overall survival. $P< 0.05$ was considered statistically significant. Multivariate analyses were performed to take into account the prognostic factors. A Cox proportional hazard model would be applied to the data.

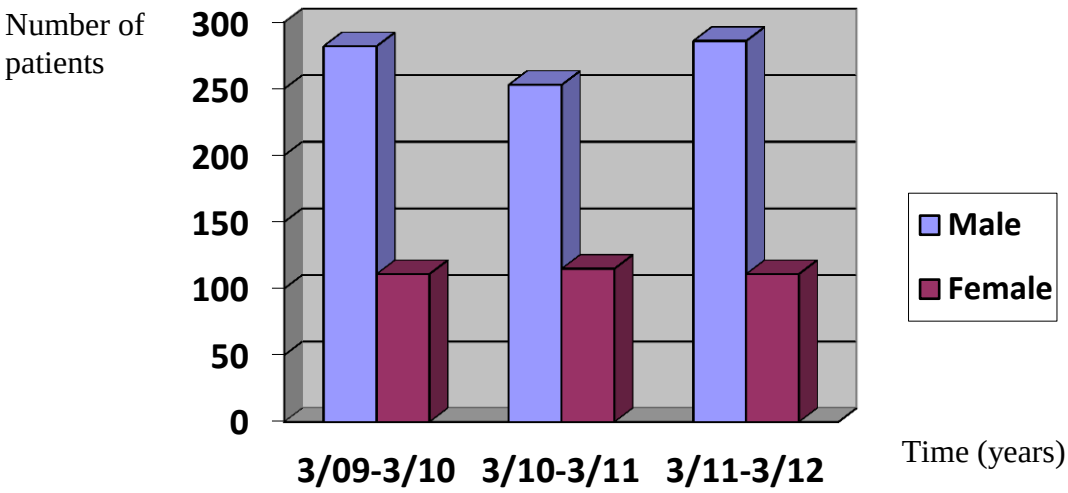
3. RESULTS

3.1. Characteristics of lung cancer patients at Cho Ray hospital

All patients who presented to the Department of Oncology, Cho Ray hospital, Ho Chi Minh city, Vietnam with lung cancer from March 1st, 2009 to March 1st, 2012 were recorded in a prospective database. The patients had previous pathological diagnosis by endoscopic biopsy, lymph nodes biopsy or post-surgery. All patients were recorded their ages, genders, races, primary referral hospitals, clinical symptoms at presentation, subtypes of histology, stage of disease and treatment options.

There were 1,158 patients diagnosed with lung cancer and treated at Department of Oncology, Cho Ray hospital. The number of male patients decreased slightly in the year of 2010 but the number of female patients were almost unchanged in three consecutive years (Figure 3.1).

Figure 3.1. Amount of lung cancer patients in three years



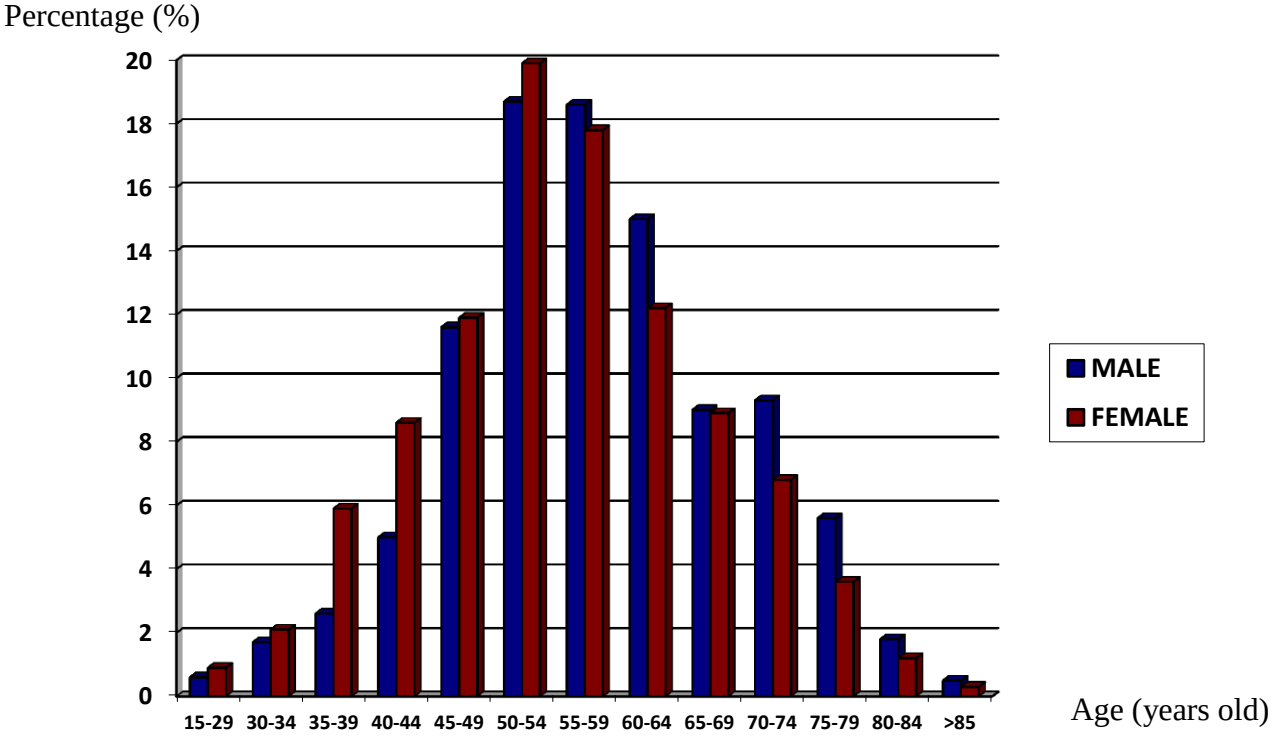
3.1.1. Patient demographics

Age and gender:

All patients were Vietnamese, including 821 men (70.9%) and 337 women (29.1%). Thus, the ratio of male to female patients was approximately 7: 3. As shown in Figure 3.2, the age distributions of male and female patients were quite similar, although women in general were slightly younger than men at the time of diagnosis.

In men, 9.9% of lung cancer cases were diagnosed among people aged 0 to 44 years, 30.3% in the 45 to 54 age group, 33.6% in the 55 to 64 age group, and 26.2% among those aged 65 years and over. In females, 17.5% of lung cancer cases were diagnosed among people aged 0 to 44 years, 31.8% in the 45 to 54 age group, 30% in the 55 to 64 age group, and 20.8% among those aged 65 years and over. The median age was 56 years old (with the range from 20 to 87 years of age). The median ages at the time of diagnosis in male and female were 57 (range from 26 to 87) and 55 (range from 20 to 86), respectively.

Figure 3.2. Age distribution of patients at the time of diagnosis



Geographic referral patterns

Cho Ray hospital is located at Ho Chi Minh city. It is also the main referral hospital for the South of Vietnam, that has a population of 40 million. Patients admitted to Cho Ray with lung cancers came from almost all provinces in the South Vietnam. Many patients lived at Ho Chi Minh city (29.1%) and in nearby regions such as Dong Nai Province (5.7%), Long An Province (4.4%), Binh Duong Province (4%) and Tien Giang Province (3.5%). A small percentage of patients (ranging from 1.3% to 3.6%) came from the Provinces of Bac Lieu, Kien Giang, Daklak, Khanh Hoa and Phu Yen which are 400-700 km from Ho Chi Minh city (Figure 3.3).

Figure 3.3. Geographic referral patterns (Map of South of Vietnam)

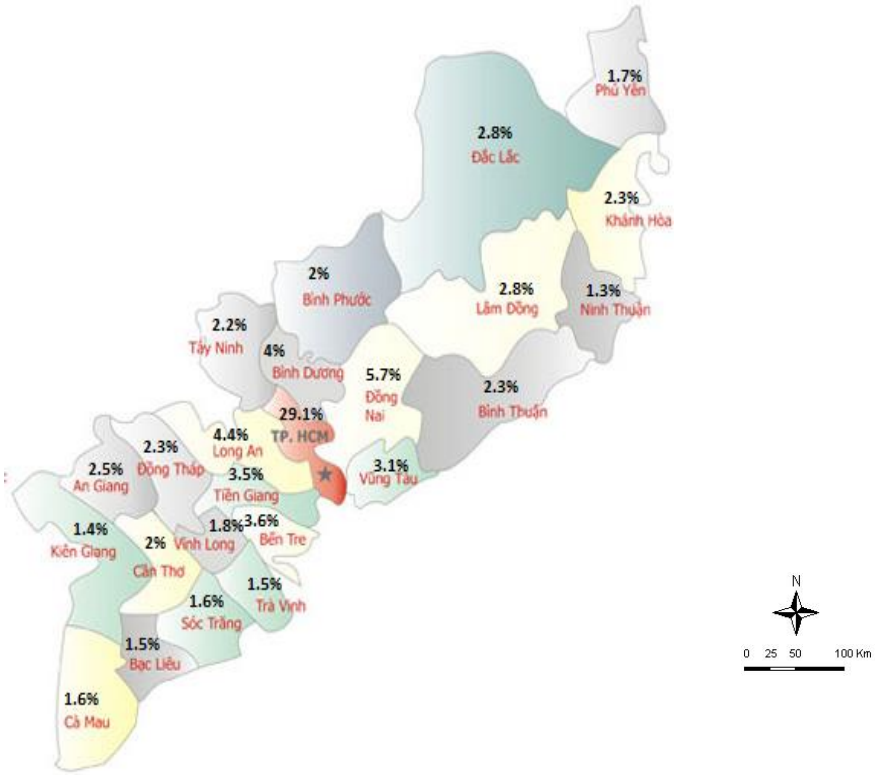


Table 3.1. Patient baseline characteristics

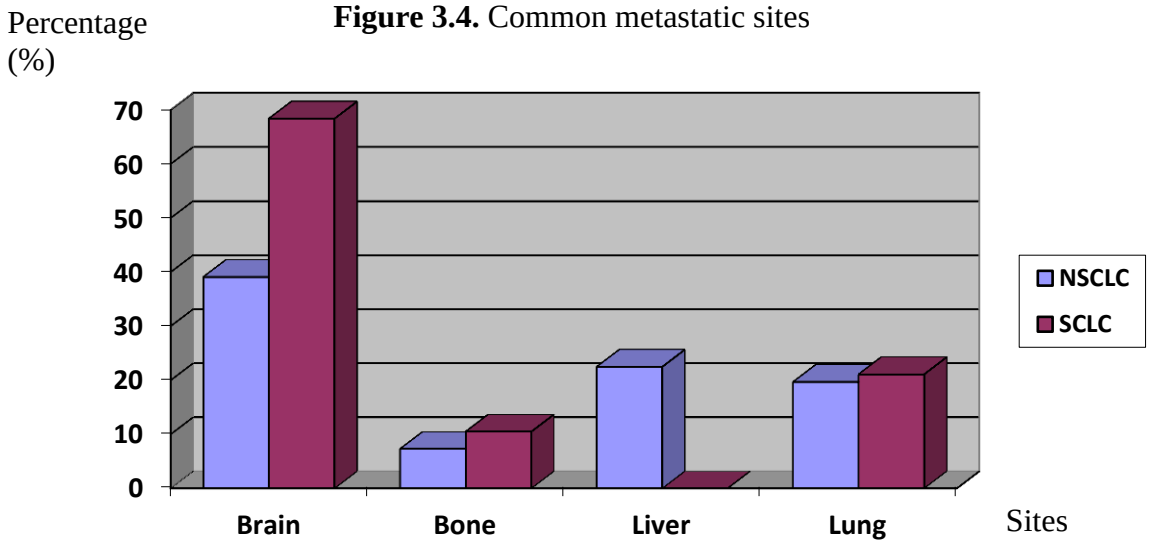
Characteristics	Number of patients	Percentage (%)
Amount of patients	1,158	100
Gender		
Male/ Female	821/ 337	70.9/ 29.1
Histology		
Adenocarcinoma	745	64.3
Squamous cell carcinoma	131	11.3
Small cell carcinoma	57	4.9
Large cell carcinoma	9	0.8
Others	216	18.7
TNM staging		
Stage I	26	2.2
Stage II	101	8.7
Stage III	449	38.8
Stage IV	582	50.3

3.1.2. Pathological and staging characteristics

The patients, suspected of having lung cancer, were initially seen in the Department of Chest Surgery or Department of Respiratory Medicine for definitive histological diagnosis. They were then referred to the Department of Oncology for further consultation and treatment. Therefore, all patients in this series were confirmed lung cancer by histology or cytology.

As shown in Table 3.1, adenocarcinomas were the most common subtype of pathology with 745 patients (64.3%). Squamous cell carcinomas were less common with 131 patients (11.3%). Small cell lung cancer (SCLC) was infrequently with percentage of 4.9%. Large cell carcinomas represented only 0.8% of the group. The remainder (216 patients - 18.7%) was not specified. This group included mainly cases where the sample was inadequate for classification, but allowed the diagnosis of a malignant tumor.

Figure 3.4. Common metastatic sites

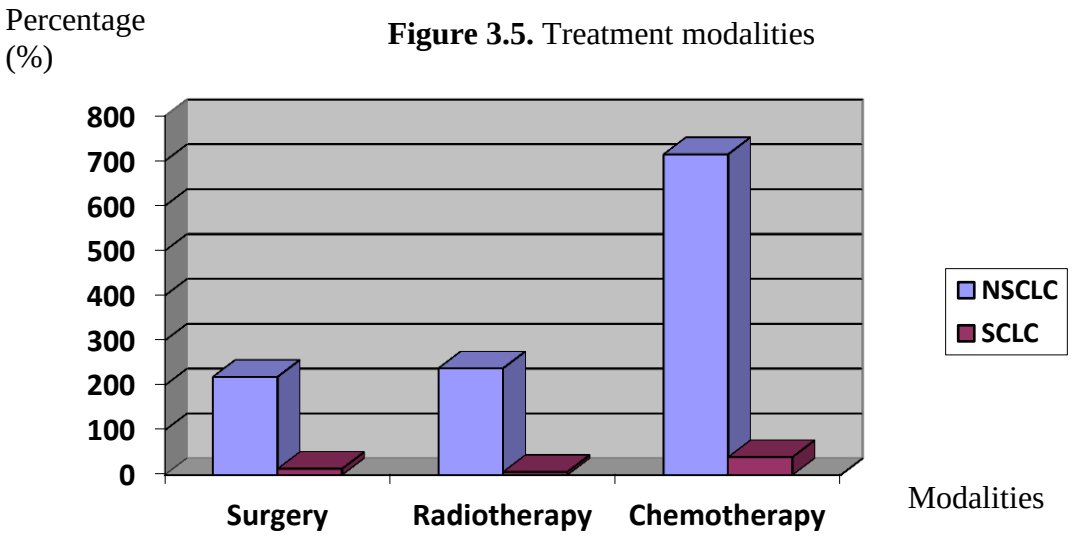


All patients underwent staging with clinical examination, bronchial endoscopy, chest CT scan with or without contrast and abdomen ultrasound. CT scan of brain and/or bone scan were done when clinical symptoms were suspected. The majority of non-small cell lung cancer (986 cases, 89.5%) were diagnosed when their disease were at locally advanced (38.4%) or metastatic (51.1%) stages. Only 115 patients (10.5%) were diagnosed at earlier stages, which were potentially curable with surgery, including 24 patients (2.2%) at stage I and 91 patients (8.3%) at stage II. In patients with small cell lung cancer (SCLC), only twelve patients (21%) admitted to hospital with limited stages and forty-five patients

(79%) were diagnosed at extensive poor prognostic disease. As shown in Figure 3.4, forty per cent (233 patients) had neurologic symptoms as first clinical presentation to Cho Ray. Consequently, the brain was the most common site of metastases in both non-small cell lung cancers (39.1%) and small cell lung cancers (68.4%). Other common sites of metastases in patients with non-small cell lung cancers were liver (22.5%), lung and pleura (19.7%) and bones of multiple sites (7.3%). Other common sites of metastases in patients with small cell lung cancers were lung and pleural metastases (21.1%), bone (10.5%). There was no case of liver metastasis was recorded.

3.1.3. Treatment modalities

Figure 3.5. Treatment modalities



As shown in Figure 3.5, 219 patients of non-small cell lung cancer (19.9%) had surgery of any kind, ranging from tumor biopsy via thoracotomy, lobectomy to pneumonectomy. 238 patients (21.6%) were irradiated alone or combined with surgery or chemotherapy. The intent of radiotherapy in this group included curative intent to high total dose of 50 – 60Gy. Radiotherapy with palliative intent was delivered to control local symptoms due to bronchial obstruction, hemoptysis, SVC obstruction and chest invasion and/or metastatic disease resulting in brain edema, bony pain and spinal cord compression. 715 patients (64.9%) received chemotherapy alone or in combined setting such as concurrent chemo-radiotherapy or as post-operative adjuvant treatment. In patients with small cell lung cancer, chemotherapy was main treatment option in 40 patients (70.2%). Only 14 patients (24.6%) were underwent resection surgery and 7 patients (12.3%) were irradiated with curative intent.

3.2. Characteristics of patients with stage III non-small cell lung cancer

The study cohort was selected from all patients with locally advanced NSCLC who presented to the Department of Oncology, Cho Ray hospital, Ho Chi Minh city, Vietnam. Among 423 patients diagnosed of locally advanced NSCLC, there were only 60 patients (14.2%) that satisfied the inclusion criteria and not committed to exclusion criteria to join the study. Following selection, all patients received weekly paclitaxel at 45 mg/m^2 intravenously (one hour) with carboplatin administered at a formula time versus concentration curve (AUC) of two intravenously (30 minutes) following administration of paclitaxel. Concurrent radiotherapy to 60Gy was administered at five fractions per week for six consecutive weeks at 2Gy/fraction. According to the treatment plan, radiotherapy was administered concurrently with six cycles of chemotherapy, starting on day 1 of the first cycle of chemotherapy.

3.2.1. Patient demographics

Table 3.2. Age, gender and subtypes of pathology

Subtypes of pathology	Males		Females		Total	
	No. of patients	Mean age (years old)	No. of patients	Mean age (years old)	No. of patients	Mean age (years old)
SCCs	6	62.8	0	0	6	62.8
ADCs	30	57.6	15	54.8	45	56.7
BACs	6	61.7	3	59	9	60.8
Total	42	58.9	18	55.5	60	58

Out of sixty patients, there were a total of 42 men (70%) and 18 women (30%). The ratio of male/female patients was 2.33/1. The mean age of patients was 58 years old with the range from 40 to 79 years old. 60% of patients were younger than 60 and 15% aged greater than 69 years old. In general, female patients were younger than male patients. Mean age of male and female patients was 58.9 years old (ranging from 40 – 79) and 55.5 years old (ranging from 43 – 78) in respectively.

Forty-five patients (75%) were classified as adenocarcinoma (ADC), nine patients (15%) as bronchioloalveolar carcinoma (BAC) and the remainder (10%) as squamous cell carcinoma (SCC). Male patients occupied 100% in SCC group and two thirds in patients with ADCs and BACs. The female patients occupied one third in ADCs and BACs and no

female patient was seen in group of SCCs. The patients with ADCs were the youngest (with mean age of 56.7 years old) and the SCCs were the oldest (with mean age of 62.8 years old). Patients with BACs had mean age of 60.8 years old. Male patients with SCCs were oldest (62.8 years old) while female patients with ADCs were youngest (54.8 years old).

Smoking history: Among sixty patients, there were only twenty-two (36.7%) of non-smokers. 94.4% of women didn't smoke in the past history while 88% of men were former or current smokers. The mean pack-years among all smokers were 29.8 (ranging from 1 to 120 pack-years). All male patients with squamous cell carcinoma were smokers. The percentage of male smokers in adenocarcinoma and bronchioloalveolar carcinoma was 86.7% and 83.3%, respectively. There was only one female smoker with histological diagnosis of adenocarcinoma.

3.2.2. Clinical manifestations

Table 3.3. Symptoms of patients at admission

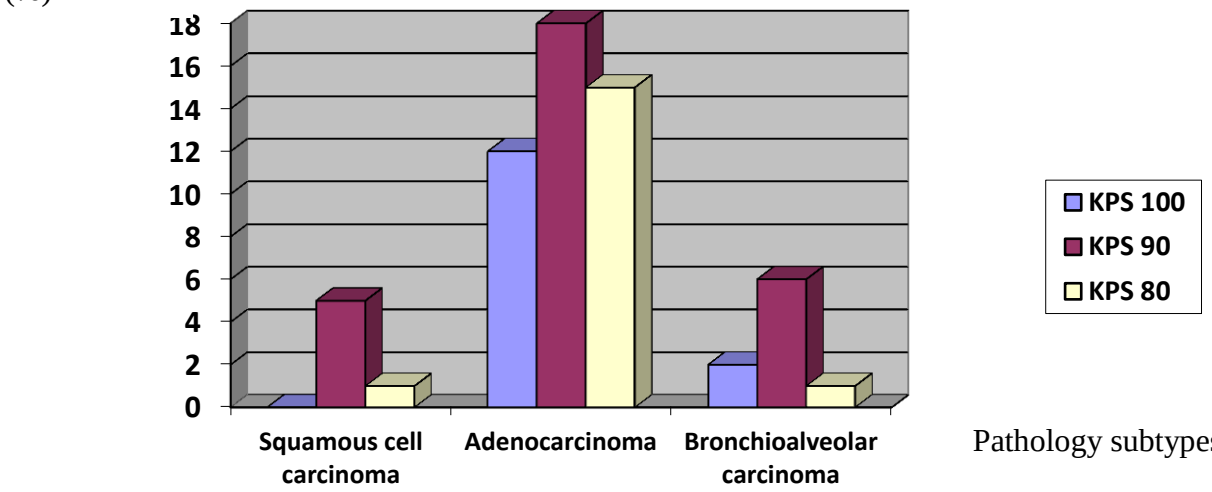
Symptoms	**SCC** n=6 (100%)	**ADC** n=45 (100%)	**BAC** n=9 (100%)	**Total** n=60 (100%)
Cough	6 (100)	26 (65)	8 (88.9)	40 (72.7)
Hemoptysis	3 (50)	11 (27.5)	1 (11.1)	15 (27.3)
Chest pain	5 (83.3)	25 (64.1)	6 (66.7)	36 (66.7)
Dyspnea	1 (16.7)	12 (30.8)	1 (11.1)	14 (25.9)
Fatigue	0 (0)	5 (12.5)	1 (11.1)	6 (11.1)
Hoarseness	1 (20)	2 (5)	2 (22.2)	5 (9.3)
Dysphagia	0 (0)	3 (7.5)	0 (0)	3 (5.6)

Cough (72.7%) and chest pain (66.7%) were two most common symptoms in patients of NSCLC. Squamous cell carcinoma patients usually presented with obstructive and local invasive symptoms such as cough (100%), chest pain (83.3%) and hemoptysis (50%). Patients with adenocarcinomas not only presented with local symptoms such as cough (65%) and chest pain (64.1%) but also complained of systemic symptoms such as dyspnea (30.8%) and fatigue (12.5%). Bronchioloalveolar carcinoma patients had similar presentations as patients with adenocarcinomas in both local and systemic symptoms.

Hoarseness due to invasion to recurrent laryngeal nerve in left main bronchus occurred in 5 patients (9.3%) in all three types of non-small cell lung cancer.

Performance status of patients at the time of diagnosis

Figure 3.6. Performance status of patients at the time of diagnosis



Karnofsky performance status scale (KPS) was utilized to evaluate the general status of all patients at the time of admission. 71.6% of patients presented with KPS scores from 90 to 100. There were eight men and six women with a KPS score of 100. Twenty-nine patients (48.3%) with a KPS score of 90 (including twenty-one men and eight women). Seventeen patients (28.3%) had KPS score of 80 (including thirteen men and four women).

In general, female patients had a better performance status than male patients. The ratio of KPS scores of 100/90/80 in male patients were 0.6/1.6/1 and in female patients were 1.5/2/1 in respectively. As shown in Figure 3.8, no patient with SCC had KPS score of 100, five patients had KPS score of 90 (83.3%) and one patient had KPS score of 80 (16.7%). In patients with ADCs, 66.7% had KPS score ranging from 90-100, including 12 patients with KPS 100 (26.7%) and 18 patients with KPS score of 90 (40%). 33.3% had KPS score of 80. In patients with BACs, eight patients (88.9%) had KPS score ranging from 90-100, including two patients (22.2%) with KPS score of 100 and six patients (66.7%) with KPS score of 90. Only one patient (11.1%) had KPS score of 80.

Weight loss status at the time of diagnosis

Table 3.4. Weight loss status at the time of diagnosis

Weight loss status	**Gender**	**SCC** n=6 (100%)	**ADC** n=45 (100%)	**BAC** n=9 (100%)	**Total** n=60 (100%)
Weight loss <5%	Male	4 (66.6)	17 (37.8)	3 (33.3)	24 (40)
	Female	0 (0)	13 (28.9)	3 (33.3)	16 (26.7)
	Total	4 (66.7)	30 (66.7)	6 (66.7)	40 (66.7)
Weight loss 5-10%	Male	2 (33.3)	13 (28.9)	3 (33.3)	18 (30)
	Female	0 (0)	2 (4.4)	0 (0)	2 (3.3)
	Total	2 (33.3)	15 (33.3)	3 (33.3)	20 (33.3)

Forty patients (66.7%), including 24 male patients and 16 female patients, had no weight loss or weight loss under 5% of their normal weight in previous 3 months. Twenty patients (33.3%), including 18 male and 2 female patients, lost weight ranging from 5 to 10% of their normal weight at the time of diagnosis (Table 3.4). 57.1% of male patients had their weight loss under 5% while in female patients, this rate was 88.9%. In all three groups of pathology, one third of patients lost weight ranging from 5 to 10% and remaining two thirds of patients had no weight loss or loss under 5% of their normal weight.

3.2.3. Staging characteristics

3.2.3.1. Primary tumors (T)

There were 36 lung cancer patients (60%) who had a right-sided tumor. Twenty-four patients (40%) had tumors on the left side. Thus, the ratio of right-sided to left-sided tumors was 1.5/1. Twenty-six patients (43.4%) had tumors in upper lobes of the lung. Fifteen patients (25%) had tumors in lower lobes. Seventeen patients (28.3%) had tumors in main bronchi. Only two patients had tumors in middle lobes (Table 3.5).

Table 3.5. Sites of primary tumors

Tumor (T) sites	SCC n=6 (100%)	ADC n=45 (100%)	BAC n=9 (100%)	Total n=60 (100%)
Rt. main bronchus	1 (16.7)	7 (15.5)	2 (22.2)	10 (16.7)
Lt. main bronchus	1 (16.7)	6 (13.3)	0 (0)	7 (11.7)
Rt. upper lobe	2 (33.3)	11 (24.4)	3 (33.3)	16 (26.7)
Lt. upper lobe	0 (0)	7 (15.5)	3 (33.3)	10 (16.7)
Middle lobe	0 (0)	2 (4.4)	0 (0)	2 (3.3)
Rt. lower lobe	1 (16.7)	6 (13.3)	1 (11.1)	8 (13.3)
Lt. lower lobe	1 (16.7)	6 (13.3)	0 (0)	7 (11.7)

In ADCs patients, the ratio of right to left side tumors was 1.37/1. 39.9% of primary tumors (18 patients) were in upper lobes. 28.8% of primary tumors (13 patients) were in main bronchi. 26.6% of primary tumors (12 patients) were in lower lobes. Two patients (4.4%) had primary tumors in the middle lobes of the lung.

In groups of SCCs, primary tumors originated equally in both sides of main bronchi (2 patients), upper lobes (2 patients) and lower lobes (2 patients). Ratio of right to left sided tumors was 2/1. In groups of BACs, 66.6% of primary tumors (6 patients) were in upper lobes. Two patients (22.2%) had tumors in right main bronchi. One patient (11.1%) had tumor in right lower lobe. Ratio of right to left sided tumors was 1.5/1.

Table 3.6. Mean size of primary tumors

Types of pathology	Male		Female		Total	
	No. of patients	Mean T sizes (mm)	No. of patients	Mean T sizes (mm)	No. of patients	Mean T sizes (mm)
SCC	6	55.3	0	0	6	55.3
ADC	30	51.3	15	41	45	48.1
BAC	6	51.7	3	36.7	9	46.7
Total	42	51.9	18	40.2	60	48.6

As shown in Table 3.6, the average size of primary tumors was 48.6 mm. The mean size of tumors in male patients was 51.9 mm, being larger than tumors in female patients who had a mean of 40.2 mm. The mean size of tumors in groups of SCCs, ADCs and BACs were

55.3 mm, 48.1 mm and 48.6 mm, respectively. Male patients with SCCs had the largest tumor size (55.3 mm). Meanwhile, female patients with BACs had the smallest mean size of primary tumor (36.7 mm).

3.2.3.2. Regional lymph nodes (N)

Table 3.7. Sites of involved regional lymph nodes

Regional lymph nodes (N)	**SCC** n=6 (100%)	**ADC** n=45 (100%)	**BAC** n=9 (100%)	**Total number** (% of Ns)
Upper paratracheal	0 (0)	5 (8.9)	0 (0)	5 (6.7)
Lower paratracheal	1 (12.5)	7 (12.5)	0 (0)	8 (10.7)
Sub-aortic	2 (25)	5 (8.9)	1 (9.1)	8 (10.7)
Para-aortic	3 (37.5)	24 (42.8)	8 (72.7)	35 (46.7)
Sub-carinal	1 (12.5)	8 (14.2)	1 (9.1)	10 (13.3)
Hilar	1 (12.5)	4 (7.1)	1 (9.1)	6 (8)
Scalene	0 (0)	1 (1.7)	0 (0)	1 (1.3)
Supraclavicular	0 (0)	2 (3.4)	0 (0)	2 (2.6)
Total number (% of Ns)	8 (100)	56 (100)	11 (100)	75 (100)

Involved regional lymph nodes were defined by chest CT scan with contrast. There were total of 75 lymph nodes which were recorded in 60 patients. Middle mediastinal lymph nodes were more commonly seen such as para-aortic (46.7%) and sub-aortic (10.7%) regions. Superior mediastinal lymph nodes which consisted of upper paratracheal and lower paratracheal nodes were seen in 17.4% of all cases. Inferior mediastinal (sub-carinal nodes) and hilar lymph nodes occupied 13.3% and 8%, respectively. Scalene and supraclavicular lymph nodes were rarely seen (3.9%) and found in ADC tumors only.

Table 3.8. Mean size of regional lymph nodes

Types of pathology	**Male**		**Female**		**Total**	
	No. of patients	Mean N size (mm)	No. of patients	Mean N size (mm)	No. of patients	Mean N size (mm)
SCC	6	32	0	0	6	32
ADC	30	26.5	15	32.7	45	28.3
BAC	6	17.5	3	26.7	9	20.6
Total	42	25.9	18	31.6	60	27.5

In general, mean size of involved lymph nodes in patients of SCCs (32 mm) was larger than in patients of ADCs (28.3 mm) and BACs (20.6 mm).The mean size of lymph nodes in male patients was 25.9 mm, being smaller than lymph nodes in female patients whom had a mean of 31.6mm. Male patients with SCCs had the largest node size (32mm) while, male patients with BACs had the smallest (17.5 mm).

3.2.3.3. TNM stage

Table 3.9. TNM stage

Stage	**IIIA**			**IIIB**				
	T2N2	**T3N1**	**T3N2**	**T3N3**	**T4N0**	**T4N1**	**T4N2**	**T4N3**
N (%)	6 (10)	3 (5)	25 (41.7)	3 (5)	4 (6.7)	4 (6.7)	12 (20)	3 (5)
Total		34 (56.7)				26 (43.3)		

In staging of primary tumors (T stages), there were six patients (10%) of T2, thirty-one patients (51.7%) of T3, and twenty-three patients (38.3%) of T4. In staging of involved lymph nodes (N stages), there were four patients (6.7%) of N0, seven patients (11.7%) of N1, forty-three patients (71.7%) of N2 and six patients (10%) of N3. Therefore, thirty four patients (56.7%) were classified as stage IIIA and 26 patients (43.3%) as stage IIIB. In stage IIIA, most patients (73.5%) were classified as T3N2M0. In stage IIIB, patients classified as T4N2M0 predominated with 46.2%.

Table 3.10. Stages of disease, pathology and gender of patients

Stages	**Gender**	**SCC** n=6 (100%)	**ADC** n=45 (100%)	**BAC** n=9 (100%)	**Total** n=60 (100%)
IIIA (n= 34)	Male	4 (66.7)	15 (33.3)	5 (55.5)	24 (40)
	Female	0 (0)	8 (17.8)	2 (22.2)	10 (16.7)
IIIB (n=26)	Male	2 (33.3)	15 (33.3)	1 (11.1)	18 (30)
	Female	0 (0)	7 (15.5)	1 (11.1)	8 (13.3)

Proportion of stage IIIA patients were 57.1% and 55.6%, respectively, in male and female patients. In three subgroups of pathology, there were more patients with stage IIIA in SCCs (66.7%) and BACs (77.8%) than in patients with ADCs (51.1%).

3.2.4. Treatment characteristics

3.2.4.1. Radiotherapy

Table 3.11. Characteristics of radiotherapy

Types of pathology	Mean V20 of lung (%)	Mean field length (cm)	Mean spinal cord dose (Gy)	Mean interruption time (days)
SCC (n=6)	33.3	14.1	37.2	3.8
ADC (n=45)	27.9	13.9	40.4	4.3
BAC (n=9)	25.1	13.5	40.4	3.2
Total (n=60)	28	13.9	40.1	4.1

Total dose of radiotherapy: Fifty-six patients (93.3%) received 60Gy as protocol, two patients (3.3%) received 50Gy, one patient (1.7%) received 56Gy and one patient (1.7%) received 54Gy. All these four patients were ADCs. The reasons for not completing radiotherapy were treatment-related complication (one patient) and patient refusal (three patients).

Planning target volume and field length: The median volume of planning target volumes (PTV) of all patients was 540.5 cm^3 (ranging from 191.5 cm^3 to 1197.3 cm^3). The mean of field length in patients with SCCs, ADCs and BACs were 14.1 cm, 13.9 cm and 13.5 cm, respectively.

Organ of interests: Lung and spinal cord were two most important critical organs. All the plans of radiotherapy were checked with V20 of the lung and maximal dose to spinal cord. Mean percentage of the total volume of both lungs minus the PTV receiving greater than 20Gy (V20) of all patients was 28% (ranging from 15 – 42%). Mean V20 of SCCs was highest with 33.3%. Mean V20 in ADCs and BACs were 27.9% and 25.1%, respectively. Mean of spinal cord doses of all patients was 40.1Gy (ranging from 18 – 44Gy). Mean spinal cord dose in SCCs was lowest with 37.2Gy. Mean spinal cord dose in ADCs and BACs patients were higher with the same dose of 40.4Gy.

Treatment time and interruptions: The mean duration of radiotherapy in all patients was 6.4 weeks (ranging from 5.1 to 8.3 weeks). Thirty-six patients (60%) had treatment interruptions during course of radiotherapy. Among these, twenty one patients had one treatment interruption. Eleven patients had 2. Three patients had 3 and one patient had 4 treatment interruptions. The average duration of radiotherapy interruption was 4.1 days

(range from 1 to 11 days). The mean interruption duration in patients with SCCs, ADCs and BACs were 3.8, 4.3 and 3.2 days, respectively. Reasons for treatment interruptions were mostly due to machine break-downs and on public holidays. Only one patient had an interruption due to grade 4 side effects – i.e. radiation esophagitis.

3.2.4.2. Chemotherapy

Table 3.12. Characteristics of chemotherapy

Chemotherapy characteristics	**SCC** n=6 (100%)	**ADC** n=45 (100%)	**BAC** n=9 (100%)	**Total** n=60 (100%)
5 cycles completed	0	4 (8.9)	1 (11.1)	5 (8.3)
6 cycles completed	6 (100)	41 (91.1)	8 (88.9)	55 (91.7)
Delayed treatment	3 (50)	16 (35.5)	4 (44.4)	23 (38.3)
Dose reduction	1 (16.7)	7 (15.6)	3 (33.3)	11 (18.3)

Cycles completed: Fifty-five patients (91.7%) completed six cycles of chemotherapy as protocol including six patients (100%) of SCCs, forty-one patients (91.1%) of ADCs and eight patients (88.9%) of BACs. Five patients (8.3%) stopped chemotherapy at fifth cycle of which four patients had ADCs and one patient had BAC. The reasons for not completing chemotherapy were treatment-related complications (including four patients with esophagitis and one with neutropenia).

Treatment delay: Twenty-three patients (38.3%) had delayed doses during the chemotherapy cycles that extended over a period of six weeks. The rate of delayed doses in patients with SCCs, ADCs and BACs was 50%, 35.5% and 44.4% in respectively. The reasons for delayed chemotherapy were treatment-related complications (fourteen patients with grade 3 or 4 esophagitis, two patients with grade 3 dermatitis and one patient with grade 3 neutropenia). The remainder (6 patients) delayed one to several days due to their personal reasons.

Dose reduction: A dose reduction of chemotherapy was required in 11 patients (18.3%). The reasons for reducing dose of chemotherapy were drug-related hematologic side effects (eight patients with grade 2 or 3 neutropenia and two patients with grade 2 thrombocytopenia) and radiotherapy-related complication (one patient with grade 4 esophagitis). The rate of dose reduction of chemotherapy in patients with SCCs, ADCs and BACs were 16.7%, 15.6% and 33.3%, respectively.

3.2.5. Safety and tolerability

Hematological, liver and renal function toxicities

Table 3.13. Hematological, liver and renal function toxicities

Toxicities	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	23 (38.3)	27 (45)	8 (13.3)	2 (3.3)	0 (0)
Leukopenia	21 (35)	19 (31.7)	13 (21.6)	6 (10)	1 (1.7)
Neutropenia	37 (61.7)	14 (23.3)	7 (11.7)	1 (1.7)	1 (1.7)
Thrombocytopenia	55 (91.7)	3 (5)	2 (3.3)	0 (0)	0 (0)
SGOT/SGPT	37 (61.7)	18 (30)	5 (8.3)	0 (0)	0 (0)
Serum creatinine	48 (80.0)	12 (20)	0 (0)	0 (0)	0 (0)

According to classification of NCI-CTC version 2.0, common maximal hematological toxicities consisted of leukopenia (65%), anemia (61.7%) and neutropenia (38.3%). Thrombocytopenia (8.3%) was rarely seen with three patients in grade 1 and two patients in grade 2. In addition, hepatic dysfunction (SGOT/SGPT increase) occurred not very frequently with 30% in grade 1 and 8.3% in grade 2. Serum creatinine increase was mild and not common with twelve patients (20%) in grade 1 toxicities. As shown in Table 3.13, grade 3 or 4 toxicities were presented only in two patients (3.3%) with anemia, seven patients (11.7%) with leucopenia and two patients (3.3%) with neutropenia. No patient had severe toxicities of thrombocytonia, liver or renal function.

Non-hematological toxicities

Table 3.14. Non-hematological toxicities

Toxicities	Grade 0 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea/ Vomiting	37 (61.7)	6 (10)	16 (26.7)	1 (1.7)	0 (0)
Fatigue/ Anorexia	12 (20)	12 (20)	22 (36.7)	13 (21.7)	1 (1.7)
Alopecia	35 (58.3)	11 (18.3)	14 (23.3)	0 (0)	0 (0)
Dermatitis	31 (51.7)	7 (11.7)	20 (33.3)	2 (3.3)	0 (0)
Weight loss	36 (60)	20 (33.3)	4 (6.7)	0 (0)	0 (0)
Cough/ Dyspnea	33 (55)	9 (15)	16 (26.7)	2 (3.3)	2 (3.3)
Esophagitis	20 (33.3)	3 (5)	23 (38.3)	13 (21.7)	1 (1.7)

Non-hematological side effects were usually related to radiation therapy. They included fatigue or anorexia (80%), esophagitis (66.7%), dermatitis (48.3%), alopecia (41.7%), weight loss (40%) and nausea or vomiting (28.3%) during the treatment time. As severe adverse events, fourteen patients (23.3%) presented with grade 3 or 4 of dysphagia or odynophagia due to radiation esophagitis. These patients required intravenous nutrition. One patient had grade 4 of dysphagia which progressed to fibrosis and required esophageal dilatation. Severe nausea or vomiting was uncommon with one patient (1.7%) in grade 3. Radiation dermatitis was seen in just two cases (3.3%) with severe grade.

As acute and/or sub-acute complication, cough and/or dyspnea symptoms occurred in 27 patients (45%) during the treatment and some patients kept suffered persistently after treatment. Of these, four patients (6.6%) had grade 3 or 4 of cough or dyspnea (with two patients in each grade). After treatment, there were four patients (6.7%) who presented with severe dyspnea (two patients), neutropenia infection (one patient) or severe cachexia (one patient) and passed away within the first three months. These should be due to irreversible treatment-related complications or disease progression.

3.2.6. Responses to treatment

Table 3.15. Response rates

Subtypes of pathology	Complete responses	Partial responses	Stable diseases	Progressive diseases
SCC	0	3	1	1
(n=5/100%)	(0%)	(60%)	(20%)	(20%)
ADC	2	22	11	7
(n=42/100%)	(4.8%)	(52.4%)	(26.2%)	(16.7%)
BAC	1	4	3	1
(n=9/100%)	(11.1%)	(44.4%)	(33.3%)	(11.1%)
Total	3	29	15	9
(n=56/100%)	(5.4%)	(51.8%)	(26.8%)	(16%)

There were four patients (6.7%) died at other hospitals or at home before coming back to us for assessment. The reasons were due to severe adverse events or disease progression. According to criteria of RECIST (Appendix E), overall response rate of all assessable patients was 57.2%. There were 5.4% patients with complete responses and 51.8% with partial responses. 26.8% had stable diseases and the rest had progressive disease.

In patients with SCCs, no patient had complete response and three patients (60%) had partial response. In patients with ADCs, 24 patients (57.2%) gained overall responses, including two patients (4.8%) with complete responses and twenty-two patients (52.4%) with partial responses. In patients with BACs, five patients (55.5%) gained objective responses, including one patient (11.1%) with complete response and four patients (44.4%) with partial response.

3.2.7. Survival time

Figure 3.7. Progression-free survival curve by Kaplan-Meier method

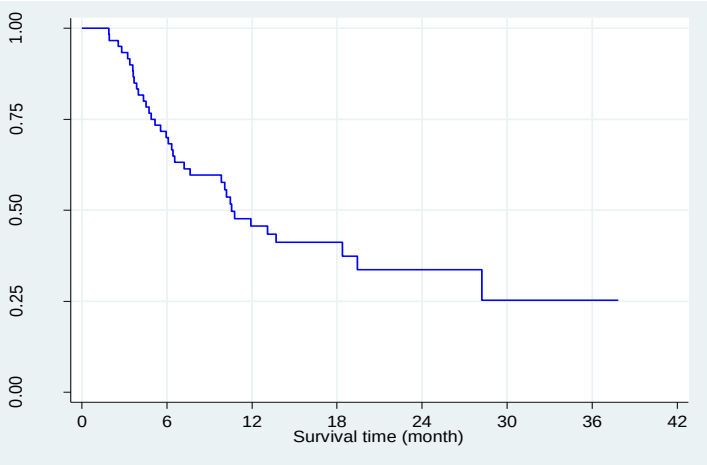
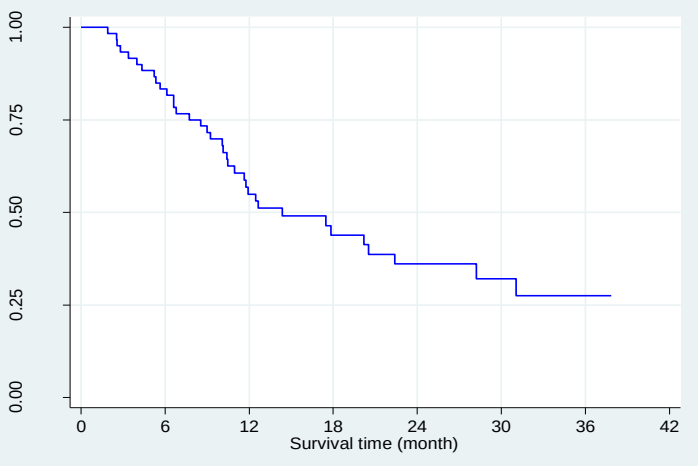


Figure 3.8. Overall survival time curve by Kaplan-Meier method



The last day of follow up was set on December 1st, 2012. That means, the last patient who was recruited to the study had at least six months of follow-up. With the median 12.7 months of follow up, 36.7% of patients were still alive, two patients missing of follow-up and 60% of patients have deceased. Of these, 11.1% (4 patients) died within the first three months due to irreversible treatment-related complications, 22.2% (8 patients) had early local progression and/or metastases in the first six months. In addition, 11.1% (4 patients) died of non-related lung cancer causes, including two cerebrovascular strokes, one myocardial infarction and one hepatocellular carcinoma.

Overall survival (OS) is defined as a time from the first day of radiotherapy till the death of any cause. Progression-free survival (PFS) is defined as a time from the first day of radiotherapy till disease progression, death or last known follow-up. In this study, the median of progression-free survival and overall survival were 10.6 months and 14.4 months in respectively (both ranging from 1.9 months to 37.8 months). Overall survival rates at 12 and 24 months were 54% and 37% in respectively.

3.2.7.1. Survival time according to gender of patients

Table 3.16. Survival time of male and female patients

Gender	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
Males	42	10.5	0.8	12.6	0.6
Females	18	13.7		17.5	

Figure 3.9. Progression-free survival curves of male and female patients

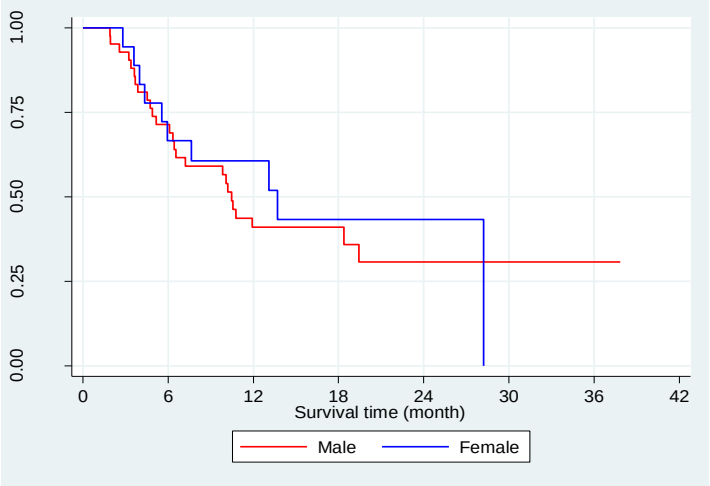
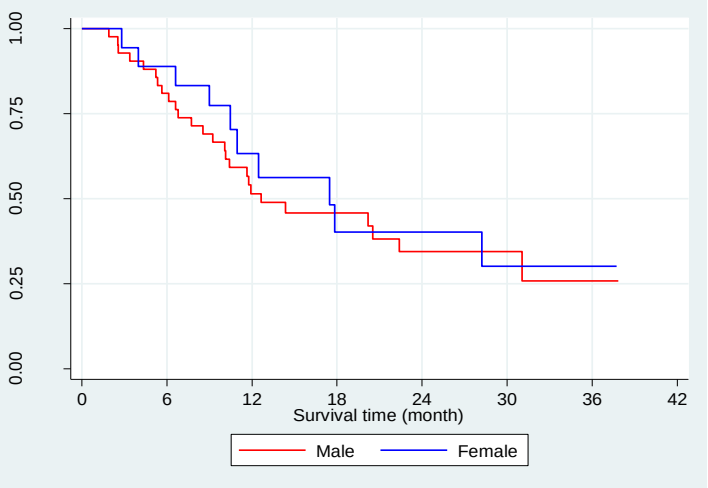


Figure 3.10. Overall survival curves of male and female patients



Both progression-free survival and overall survival time in female patients were more favorable than male patients. Median survival time to progression in male and female patients was 10.5 months and 13.7 months in respectively, leading to a hazard ratio of 0.9 (95% CI, 0.43 – 1.89) but not significantly different (p = 0.8, log-rank test). The median of overall survival time in male and female patients were 12.6 months and 17.5 months in respectively, leading to a hazard ratio of 0.8 (95% CI, 0.4 – 1.7) and not statistically significant (p = 0.6, log-rank test).

3.2.7.2. Survival time according to age group of patients

Table 3.17. Survival time of patients <60, 60–69 and >69 years of age

Age of patients	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
< 60 years old	36	13.1		17.5	
60-69 years old	15	10.6	0.42	22.4	0.28
> 69 years old	9	4.5		6.6	

Figure 3.11. Progression-free survival curves of patients <60, 60–69 and >69 years old

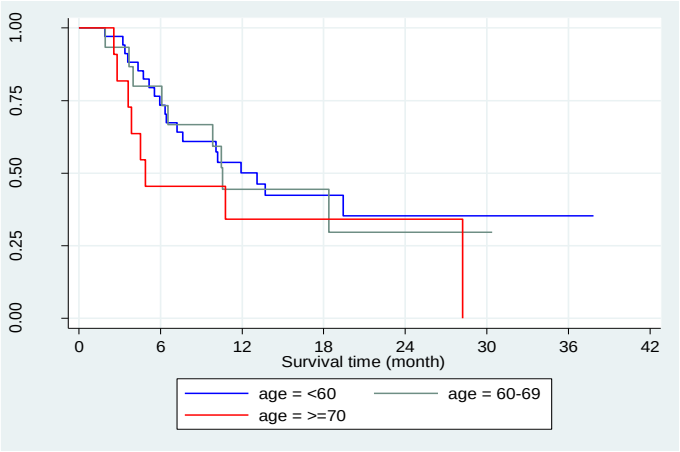
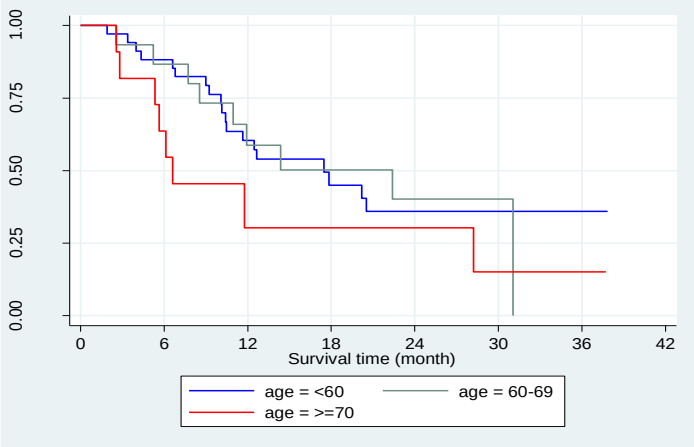


Figure 3.12. Overall survival curves of patients <60, 60–69 and > 69 years old



We divided all patients into three age subgroups: under 60, 60 to 69 and older than 69 years old. The median of progression-free survival and overall survival time was greatest in patients with age from 60-69 years old (10.6 and 22.4 months, respectively). In contrast, the patients older than 69 years old had poorest survival with median time to progression of 4.5 months and median overall survival time of 6.6 months. However, the differences in both PFS and OS time among three groups were not statistically significant ($p > 0.05$, log-rank test). When compared age group under 60 and 60-69 years old, the median time to progression was not dissimilar with the hazard ratio of 1 (95% CI, 0.5 – 2.3) ($p = 0.9$, log-rank test).

3.2.7.3. Survival time according to subtypes of pathology

Table 3.18. Survival time of patients with SCCs, ADCs and BACs

Subtypes of pathology	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
SCCs	6	4.7		10.4	
ADCs	45	10.6	0.38	14.4	0.4
BACs	9	13.7		17.8	

Figure 3.13. Progression-free survival curves of patients with SCCs, ADCs and BACs

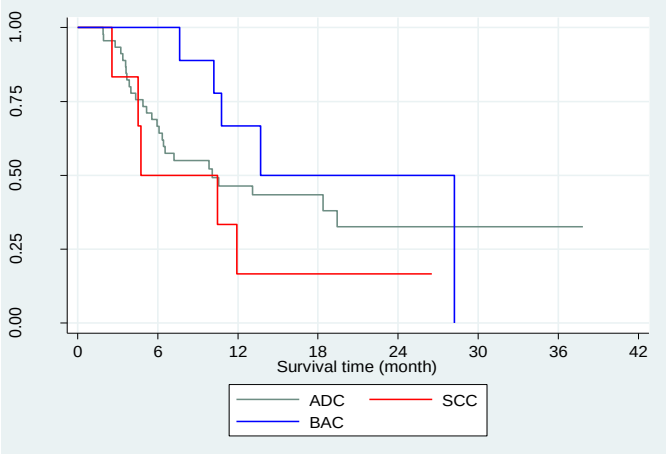
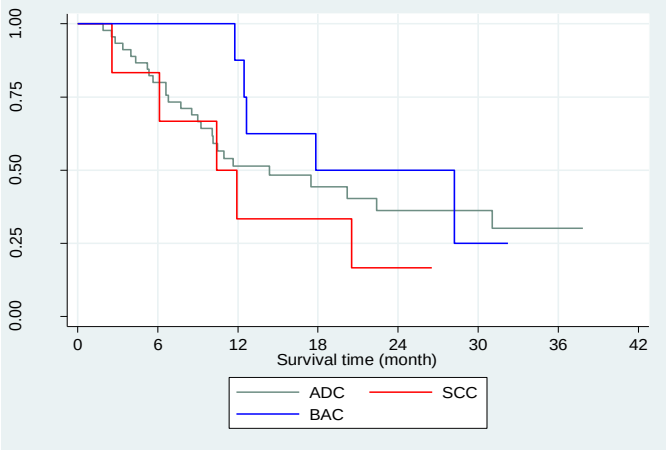


Figure 3.14. Overall survival curves of patients with SCCs, ADCs and BACs



In three subtypes of histology, the median of progression-free survival and overall suvival time was most favorable in patients with BACs (13.7 and 17.8 months, respectively)and

poorer in patients with SCCs (4.7 and 10.4 months, respectively). The median time to progression in patients with SCCs was shorter than patients with ADCs (4.7 versus 10.6 months), leading a hazard ratio of 1.6 (95% CI, 0.6 – 4.1) but the difference was not statistically significant (p=0.4, log-rank test).

The median time to progression in patients with BACs was more favorable than patients with ADCs (13.7 versus 10.6 months), leading a hazard ratio of 0.8 (95% CI, 0.5 - 1.3). The difference wasnot statistically significant (p=0.38, log-rank test). Similarly, overall survival time in patients with BACs was more favorable than patients with ADCs (17.8 versus 14.4 months), leading a hazard ratio of 0.8 (95% CI, 0.5 – 1.3). The difference was not statistically significant (p=0.4, log-rank test).

3.2.7.4. Survival time according to TNM stages

Primary tumor (T) stages

Table 3.19. Survival time of patients with T2, T3 and T4

Tumor stages	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
T2	6	14.8		25.4	
T3	32	10.1	0.09	12.6	0.05
T4	22	6.8		10.5	

Figure 3.15. Progression-free survival curves of patients with T2, T3 and T4

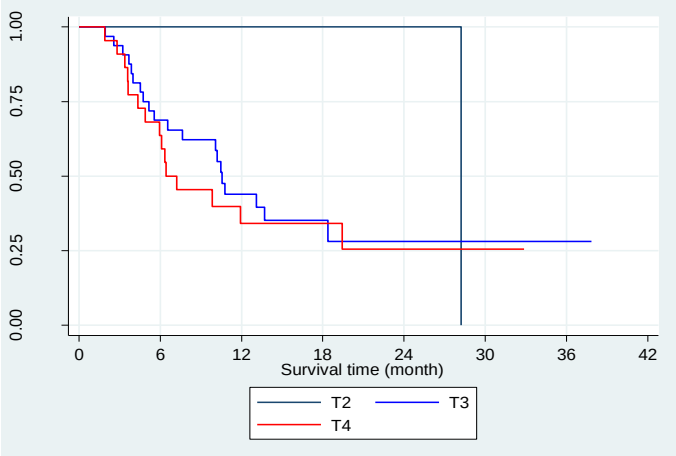
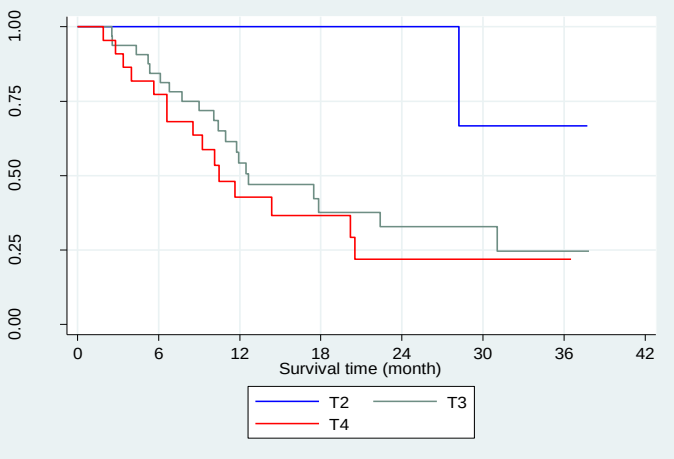


Figure 3.16. Overall survival curves of patients with T2, T3 and T4



There were 6 patients with T2 (i.e. T2N2M0 – stage IIIA) who had most favorable outcome. Their median time to progression and overall survival were 14.8 and 25.4 months, respectively. The median time to progression in patients with T3 tumors was more favorable than patients with T4 (10.1 versus 6.8 months). The differences among three subgroups were not statistically significant (p=0.09, log-rank test). The median survival time in patients with T2, T3 and T4 were 25.4, 12.6 and 10.5 months in respectively. The difference was not statistically significant (p=0.05, log-rank test).

Regional lymph nodes (N)

Table 3.20. Survival time of patients with N0, N1, N2 and N3

Node stages	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
N0	4	11.4		11.4	
N1	7	8.9		11.6	
N2	43	10.2	0.3	17.5	0.5
N3	6	6.6		9	

Figure 3.17. Progression-free survival curves of patients with N0, N1, N2 and N3

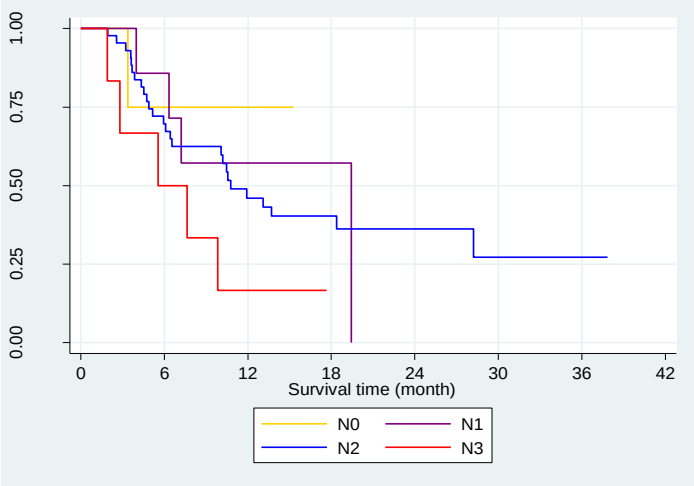
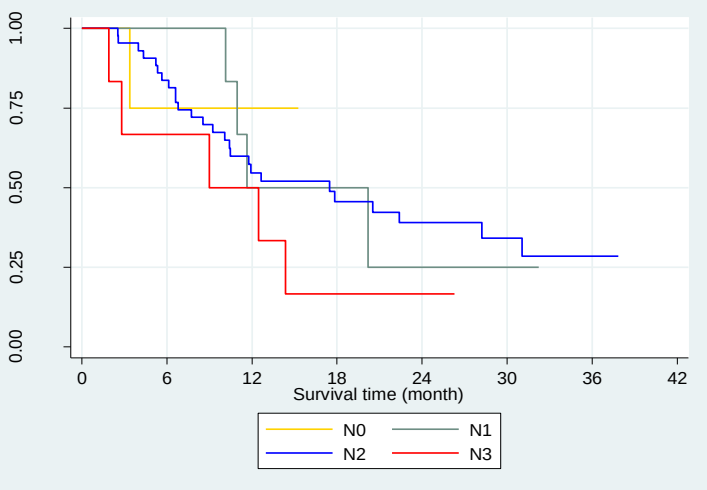


Figure 3.18. Overall survival curves of patients with N0, N1, N2 and N3



The median of progression-free survival time in patients with lymph nodes at stage of N1 was shorter than both two groups of N0 and N2 (8.9 months versus 11.4 and 10.2 months). The median overall survival time in patients with N0, N1 and N2 were 11.4, 11.6 and 17.5 months in respectively. Patients with N3 stage had poorest outcome in terms of median time to progression and overall survival (6.6 and 9 months, respectively). The differences in progression-free and overall survival time among four groups were not statistically significant ($p>0.05$, log-rank test).

Survival time according to stages of diseases

Table 3.21. Survival time of patients with stage IIIA and IIIB

Stages of cancer	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
IIIA	34	13.7	0.11	22.4	0.08
IIIB	26	6.4		10.5	

Figure 3.19. Progression-free survival curves of patients with stage IIIA and IIIB

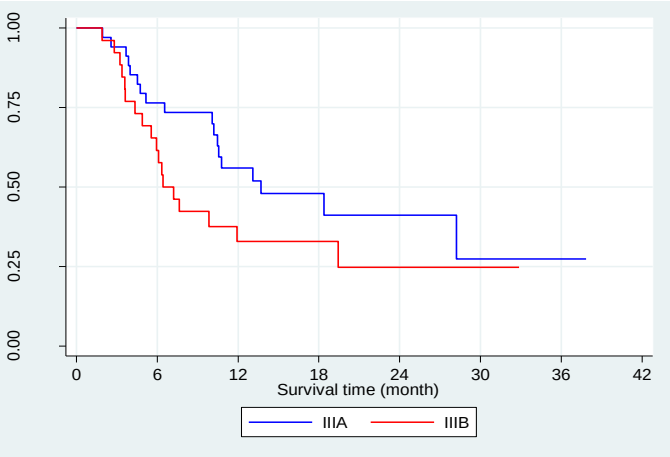
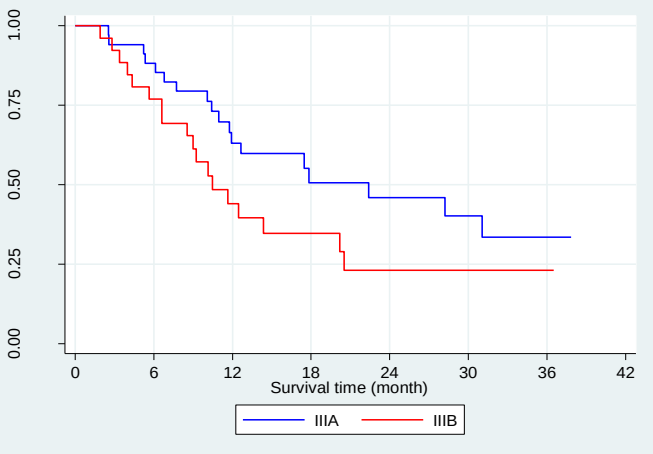


Figure 3.20. Overall survival curves of patients with stage IIIA and IIIB



The median time to progression in patients with NSCLC stage IIIA was more favorable than patients with stage IIIB (13.7 versus 6.4 months), leading a hazard ratio of 1.7 (95% CI, 0.9 – 3.3). The difference wasnot statistically significant (p=0.11, log-rank test). The median of overall survival time in patients with stage IIIA and IIIB were 22.4 months and

10.5 months, respectively. The differences in overall survival time between stage IIIA and stage IIIB patients were not statistically significant (p=0.08, log-rank test) with a hazard ratio of 1.8 (95% CI, 0.94 – 3.54).

3.2.7.5. Survival time according to pretreatment performance status

Table 3.22. Survival time of patients with KPS 100, 90 and 80

Performance status at baseline	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
KPS 100	14	13.4		20.1	
KPS 90	26	10.6	**<0.001**	13.0	**<0.001**
KPS 80	20	5.0		7.7	

Figure 3.21. Progression-free survival curves of patients with KPS 100, 90 and 80

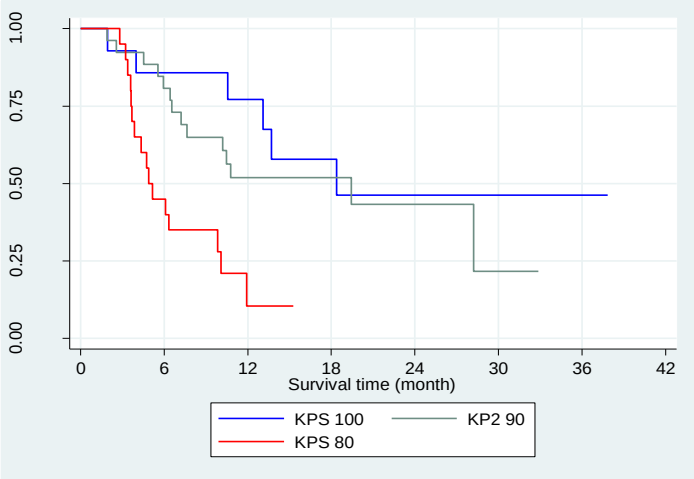
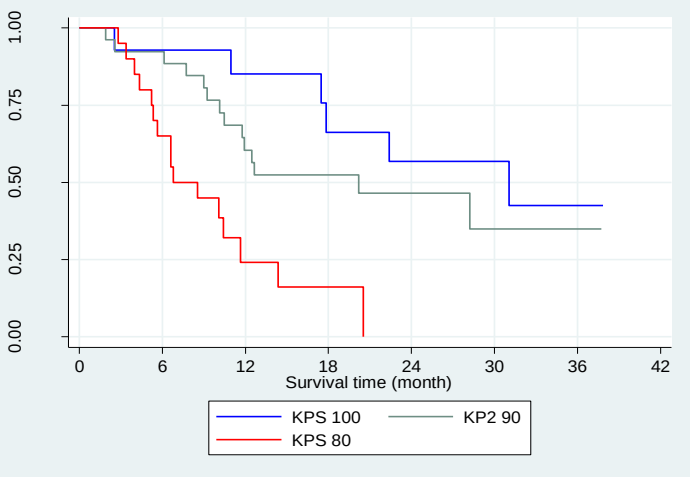


Figure 3.22. Overall survival curves of patients with KPS 100, 90 and 80



The median of progression-free survival time in patients with KPS of 100, 90 and 80 were 13.4 months, 10.6 months and 5.0 months, respectively. The differences in progression-free survival time among three groups were statistically significant (p<0.001, log-rank test). The median of overall survival time in patients with KPS 100 was most favorable with 20.1 months. Patients with KPS 80 had least favorable with the median time at 7.7 months. Patients with KPS 90 had median overall survival time of 13.0 months. Similarly, the differences in overall survival time among three groups were statistically significant (p<0.001, log-rank test).

3.2.7.6. Survival time according to pretreatment weight loss

Table 3.23. Survival time of patients with pretreatment weight loss <5% and 5-10%

Baseline weight loss	No. of patients	Median PFS (months)	P-value	Median OS (months)	P-value
Normal or under 5%	40	13.7	**0.04**	20.5	**0.01**
From 5-10%	20	7.2		10.1	

Figure 3.23. Progression-free survival curves of patients with weight loss < 5% and 5-10%

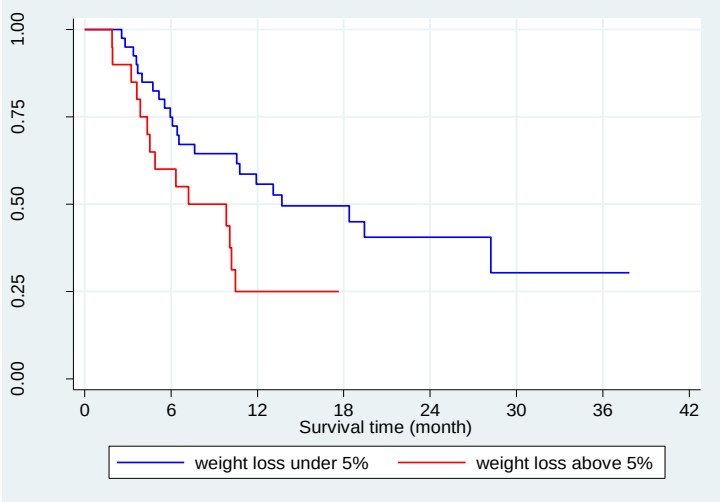
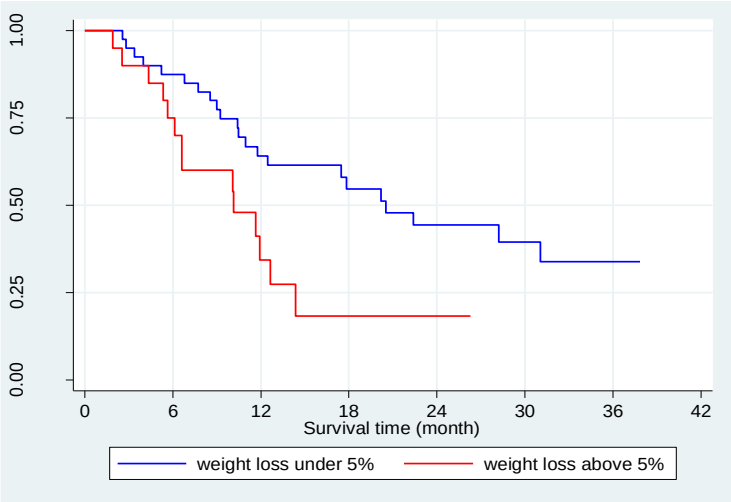


Figure 3.24. Overall survival curves of patients with weight loss <5% and 5-10%



The median of progression-free survival time in patients with weight loss under 5% and from 5 - 10% were 13.7 and 7.2 months, respectively. The differences in progression-free survival time between two groups were statistically significant (p=0.04, log-rank test). The median of overall survival time in patients with weight loss under 5% was 20.5 months. Patients with weight loss from 5 - 10% had less favorable survival time at 10.1 months. The differences in overall survival time between two groups were statistically significant (p=0.01, log-rank test).

3.2.7.7. Prognostic factors to survival time

Table 3.24. Cox proportional hazards regression model for survival

Variables	Progression-free survival		Overall survival	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Female / Male	0.9 (0.43 – 1.89)	0.8	0.8 (0.4 – 1.7)	0.6
Age of patients (years old)				
> 69 / 60 – 69	1.5 (0.6 – 3.9)	0.4	1.4 (0.9 – 2.1)	0.11
> 69 / < 60	1.3 (0.9 – 1.9)	0.2	1.7 (0.6 – 4.6)	0.3
60 – 69 / < 60	1 (0.5 - 2.3)	0.9	1.1 (0.5 – 2.4)	0.9
Subtypes of pathology				
SCC / ADC	1.6 (0.6 – 4.1)	0.4	1.5 (0.6 – 3.8)	0.43
BAC / ADC	0.8 (0.5 - 1.3)	0.38	0.8 (0.5 – 1.3)	0.4
BAC / SCC	0.3 (0.08 -1.2)	0.09	0.3 (0.09 – 1.3)	0.11
Stage of cancer				
IIIB / IIIA	1.7 (0.9 – 3.3)	0.11	1.8 (0.94 – 3.54)	0.08
Performance status at baseline				
KPS 80/ KPS 100	2.2 (1.3 – 3.8)	**0.003**	2.8 (1.5 – 5.0)	**0.001**
KPS 80/ KPS 90	3.1 (1.4 – 6.6)	**0.004**	3.1 (1.5 – 6.7)	**0.003**
KPS 90/ KPS 100	1.46 (0.6 – 3.8)	0.44	1.7 (0.6 – 4.5)	0.3
Weight loss at baseline				
5-10% / < 5%	2.1 (1 – 4.2)	**0.043**	2.4 (1.2 – 4.9)	**0.015**

We analysed the relationship of progression-free and overall survival time to a variety of factors as possible predictive value. They included gender, age of patients, subtypes of histology, stage of cancer, performance status and weight loss of patients at the time of diagnosis. As shown in Table 3.24, the time to progression and overall survival were favorable for female patients, patients with age < 70 years old and stage IIIA, but not statistically significant.

However, the differences in progression-free survival time between patients with KPS 100 and KPS 80, between KPS 90 and KPS 80 were statistically significant with hazard ratios of 2.2 (95% CI from 1.3 to 2.8) and 3.1 (95% CI from 1.4 to 6.6), respectively. In terms of overall survival time, these differences were also significant with hazard ratios of 2.8(95% CI from 1.5 to 5.0) and 3.1 (95% CI from 1.5 to 6.7), respectively.

In addition, the differences in the time to progression and overall survival between patients with weight loss <5% and patients with weight loss 5 - 10% were significant with hazard ratios of 2.1 (95% CI from 1 to 4.2) and 2.4 (95% CI from 1.2 to 4.9). Therefore, pretreatment performance status and weight loss were considered as predictive factors for progression-free survival time and overall survival in this study.

3.2.8. Recurrences and metastases

Table 3.25. Patterns of failure to treatment

Failures	**SCCs** n=6 (100%)	**ADCs** n=45 (100%)	**BACs** n=9 (100%)	**Total** n=60 (100%)
Local recurrences	4 (66.7)	14 (31.1)	2 (22.2)	20 (33.3)
Distant metastases	0 (0)	19 (42.2)	4 (44.4)	23 (38.3)

The primary tumor site and/or the chest were the first sites of failure in 20 patients (33.3%), including 6 patients (10%) with both local recurrence and distant metastases. The local recurrence frequency was highest in patients with SCCs (four patients – 66.7%). It was relatively lower in patients with ADCs (fourteen patients – 31.1%) and BACs (two patients – 22.2%). Twenty-three patients (38.3%) had distant metastases. The rate of distant metastases was higher in ADCs (19 patients – 42.2%) and BACs (four patients-44.4%). However, no patient with SCCs presented with distant metastasis.

Among patients with metastases, brain was the most common site with thirteen patients (56.5%). Other frequent sites included bony lesions (nine patients – 39.1%), liver (four patients – 17.4%) and lungs (three patients, one of multiple lesions in both sides and two of contralateral lesions – 13%). There was one patient who developed metastases to brain and then, to abdominal lymph nodes subsequently.

4. DISCUSSION

4.1. Characteristics of lung cancer patients

This was a prospective study which included all patients who presented to the Department of Oncology, Cho Ray hospital, Ho Chi Minh city, Vietnam with lung cancer from March 1st, 2009 to March 1st, 2012. Cho Ray was one of two main hospitals located on Ho Chi Minh city and receives cancer patients for this city and almost all provinces from the South Vietnam. Therefore, the results of this study might reflect some characteristics of lung cancer patients in Vietnam.

4.1.1. Age and gender

During the three years, there were 1,158 patients with lung cancer including 821 males and 337 females admitted to this hospital. The ratio of male to female patients was approximately 7: 3. The median age of all patients was 56 years old (ranging from 20 to 87 years of age). The median ages at the time of diagnosis of male and female population were 57 and 55 years old in respectively.

Age difference between men and women in Cho Ray was consistent with the results of a study in Poland. This community-based cancer registry reported that age at diagnosis was younger for women (60 years old) compared to men (62.2 years old) and more women were under 50 years old to men (23% and 12%) (Radzikowska et al. 2002).

In addition, the age of patients in Vietnam was significantly lower than in many studies in Western countries. Worldwide during 2002, Ezzati reported that 5% of lung cancer cases were diagnosed among people aged 0 to 44 years, 14% in the 45 to 54 age group, 25% in the 55 to 64 age group, and 55% among those aged 65 years and over (Ezzati et al. 2003). While in Cho Ray, these figures were 12.1%, 30.7%, 32.6% and 24.6% in respectively.

In United States, using SEER database from 1975 – 1999, Fu et al. found that median age at the time of diagnosis was 66 years old for both men and women. Women accounted for 35.8% and occupied 40.9% in patients under 50 years old (Fu et al. 2005).

In the province of Oulu (Finland), Makitaro et al. conducted the population-based study with 602 patients and reported the mean age of 67.7 years (Makitaro et al. 2002).

In Tokushima Prefecture - Japan, Kanematsu et al. recruited 2183 lung cancer patients in Tokushima University Hospital and Tokushima Prefectural Central Hospital to review the

epidemiologic and clinical features of lung cancer. Patients older than 75 years old occupied 32% and the mean age was 70 years old (Kanematsu et al. 2010). Higher smoking rate and shorter life expectancy might be one of reasons explained why lung cancer patients in Vietnam were younger than more developed countries.

Table 4.1. Some characteristics of lung cancer patient in Finland, Japan and Vietnam

Characteristics	**Makitaro et al. (1990-1992)**	**Kanematsu et al. (1999-2009)**	**Cho Ray (2009-2011)**
All patients (n, %)	602 (100)	2183 (100)	1158 (100)
Male	510 (85)	1591 (73)	821 (70.9)
Female	92 (15)	592 (27)	337 (29.1)
Mean age	68	70	56
Histological type (n, %)			
Small cell carcinoma	121 (20)	278 (13)	57 (4.9)
Adenocarcinoma	135 (22)	1112 (51)	745 (64.3)
Squamous cell carcinoma	204 (34)	545 (25)	131 (11.3)
Large cell carcinoma	23 (4)	69 (3)	9 (0.8)
Others	33 (6)	179 (8)	216 (18.6)
No histology	86 (14)	0	0
TNM staging (n, %)	519 (86)	2110 (97)	1158 (100)
Stage I	97 (19)	684 (32)	26 (2.2)
Stage II	21 (4)	140 (6)	101 (8.7)
Stage III	185 (36)	608 (28)	449 (38.8)
Stage IV	216 (41)	678 (31)	582 (50.3)

4.1.2. Pathological characteristics

As shown in Table 4.1, adenocarcinomas (64.3%) were the most common histological diagnosis in group of non-small cell lung cancer in our database while small cell lung cancer (SCLC) was not common (4.9%). The geographic distribution of patients with many living far from Ho Chi Minh city and a great proportion of late stage lung cancer patients could explain the small number of SCLC cases in Cho Ray. Many patients might have progressive disease and die before going to hospital.

In Japan, Kanamitsu et al. reported that non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) constituted 87% and 13%, respectively. With regard to NSCLC, the predominant histological type was adenocarcinoma (51%), followed by squamous cell carcinoma (25%), large cell carcinoma (3%) and others (8%) (Kanematsu et al. 2010).

In Finland, squamous cell carcinoma (34%) was also the most common subtype of pathology, consistent to other European trials. Less common subtypes of histology included adenocarcinoma (22%), small cell carcinoma (20%) and large cell carcinoma (4%) (Makitaro et al. 2002).

There was considerable variation in the different histological types of lung cancer between countries. In United States, NSCLC accounted for approximately 80% to 85% of all cases (Jemal et al. 2008). Squamous cell carcinoma accounted for 45% in Europe and approximately 30% of all lung cancer in the United States (Travis et al. 1995).

In Germany, the most frequently histological subtype of lung cancer was non-small cell lung cancer (approximately 75% of lung cancers) and majority of NSCLC were squamous cell carcinomas (Huber et al. 2006).

In contrast, adenocarcinoma tends to be the most common histology subtype in women and this proportion continues to increase over time in Asian countries (Perng et al. 1996, Yoshimi et al. 2003). Adenocarcinoma was the most prevalent form of lung cancer in younger males (under 50 years old) and in women of all ages, in never smokers and in former smokers (Ramalingam et al. 1998).

4.1.3. Staging characteristics

In current study, there were 2.2%, 8.7%, 38.8% and 50.3% of patients who had lung cancer stages of I, II, III and IV in respectively. With regard to non-small cell lung cancer (NSCLC), 89.1% of patients had advanced (III or IV) stages. Common sites for metastases

in patients with lung cancer were brain (39.1%), liver (22.5%) and lung and/or pleura (19.7%). Among patients with small cell lung cancer (SCLC), 79% were diagnosed at extended stages.

Kanematsu et al. reported a comparable percentage of patients with stage III (28%) and IV (31%) of lung cancer. More patients had early stages (I or II) than in Cho Ray series (41% versus 10.9%) (Kanematsu et al. 2010).

As a population-based study, computed tomography (CT) was conducted only in 59% of patients and staging of the cancer were carried out for 86%. Of these, 36% and 41% of patients were diagnosed at stage III and IV, respectively (Makitaro et al. 2002).

In the Surveillance, Epidemiology and End Results (SEER) 2004 registry in United States, 29.7% of new NSCLC cases presented with stage III disease, of which 12.1% were stage IIIA and 17.6% were stage IIIB (Wisnivesky et al. 2005).

4.2. Characteristics of patients with stage III non-small cell lung cancer

There were 60 patients that satisfied the inclusion criteria and not committed to exclusion criteria to join this study. All patients received weekly paclitaxel (dose of 45mg/m^2) and carboplatin (AUC=2) for 6 consecutive weeks. Concurrent radiotherapy to 60Gy was administered at five fractions per week for six consecutive weeks at 2Gy/fraction.

There were several multicenter studies using the similar regimen in literature. From 1995 – 1996, a multi-institutional phase II clinical trial was conducted in United States to evaluate the activity and toxicity of paclitaxel, carboplatin, and concurrent radiation therapy on patients with locally advanced NSCLC (Choy et al. 1998). Then, Belani et al. introduced a randomized phase II study to compare three different weekly schedules of the carboplatin/paclitaxel regimen for patients with advanced NSCLC (Belani et al. 2005).

In Germany, a phase III trial was conducted to compare induction chemotherapy followed by either radiation alone or chemo-radiotherapy (Huber et al. 2006). As a similar trial, Vokes et al. evaluated whether induction chemotherapy before concurrent chemo-radiotherapy would result in improved survival (Vokes et al. 2007). Recently, the West Japan Thoracic Oncology Group conducted a phase III study to compare the second generation regimens at full doses or the third generation regimens at reduced doses in concurrent chemo-radiotherapy setting for stage III NSCLC (Yamamoto et al. 2010).

In the duration of three years, we recruited 60 patients in one institution. With the comparable time, Choy et al. selected only 40 patients from six centers in United States. Other studies with longer recruitment time from 4-6 years had selected a larger number of patients from many sites onto their trials.

Table 4.2. Summary of selected studies with chemoradiation alone or combined with induction/consolidation chemotherapy

References (Phase)	Period	No. of Pts	Induction Therapy	Concurrent Therapy	Consolidative Therapy
Choy et al. (II)	3/1995 – 12/1996	40	NA	66 Gy/ Pac/Carbo	Pac/Carbo
Belani et al. (II)	2/1998 – 6/2001	91	Pac/Carbo	63 Gy	NA
		74	Pac/Carbo	63 Gy/Pac/Carbo	NA
		92	NA	63 Gy/Pac/Carbo	Pac/Carbo
Huber et al. (III)	7/1997 – 5/2002	113	Pac/Carbo	60 Gy	NA
		99	Pac/Carbo	60 Gy/ Pac/Carbo	NA
Vokes et al. (II)	7/1998 – 5/2002	161	NA	66 Gy/ Pac/Carbo	NA
		170	Pac/Carbo	66 Gy/ Pac/Carbo	NA
Yamamoto et al. (III)	9/2001 – 9/2005	146	NA	60 Gy/MVP	MVP
		147		60 Gy/Irino/Carbo	Irino/Carbo
		147		60 Gy/ Pac/Carbo	Pac/Carbo
Cho Ray	3/2009 – 3/2011	60	NA	60 Gy/ Pac/Carbo	NA

Abbreviations: NA, not applicable; Pac, paclitaxel; Carbo, carboplatin; Irino, Irinotecan; MVP: Mitomycin C, Vindesine, Cisplatin.

4.2.1. Patient demography

In general, patients who were selected to most concurrent chemo-radiotherapy trials were younger than patients in general population. A retrospective analysis of all patients enrolled onto Southwest Oncology Group trials between 1993 and 1996 demonstrated that only 25% were 65 years or older (Hutchins et al. 1999). As shown in Table 4.3, mean age of patients in our trial was somewhat younger than patients in other studies.

Table 4.3. Characteristics of patients in concurrent chemoradiation studies with weekly Paclitaxel and Carboplatin

References	**Choy et al.** (1998)	**Belani et al.** (2005)	**Huber et al.** (2006)	**Vokes et al.** (2007)	**Yamamoto et al.** (2010)	**Cho Ray** (2012)
Induction Therapy	NA	NA	Pac/Carbo	NA	NA	NA
Concurrent Therapy (dose in mg/m2)	66Gy Pac(50) Carbo	63Gy Pac(45) Carbo	60Gy Pac(60)	66Gy Pac(50) Carbo	60Gy Pac(40) Carbo	60Gy Pac(45) Carbo
Consolidative Therapy	Pac/Carbo	Pac/Carbo	NA	NA	Pac/Carbo	NA
Mean age (y/o)	60	75% < 70	62.38	63	63	58
Sex (n/%)						
Male	25 (62.5)	62 (67)	86 (86.9)	125 (69)	128 (87.1)	42 (70)
Female	15 (37.5)	30 (33)	13 (13.1)	57 (31)	19 (12.9)	18 (30)
KPS (n/%)						
90-100	19 (47.5)	90 (97.8)	70 (70)	82 (45)	65 (44.2)	43 (71.6)
80	21 (52.5)		20 (20)	94 (52)	81 (55.1)	17 (18.4)
70		2 (2.2)	6 (6)			
No information			3 (3)	5 (3)	1 (0.7)	
Stage (n/%)						
IIIA	12 (30)	35 (38)	10 (10.1)	87 (48)	49 (33.3)	34 (56.7)
IIIB	28 (70)	57 (62)	88 (88.9)	84 (46)	98 (66.7)	26 (43.3)
Not classified			1 (1)	13 (7)		
Histology (n/%)						
ADC	8 (20)	32 (34.8)	19 (19.2)		62 (42.2)	54 (90)
SCC	21 (52.5)	37 (40.2)	62 (62.6)		71 (48.3)	6 (10)
Large cell	9 (22.5)	9 (9.8)	4 (4)			
Mixed		2 (2.2)	3 (3)			
Not classified	2 (5)	12 (13)	11 (11)			

Abbreviations: NA, not applicable; Pac, paclitaxel; Carbo, carboplatin.

Male patients predominated in Cho Ray study with the ratio to women as 2.33/1, greater than in studies of Choy et al. (1.67/1) and Belani et al. (2/1). However, it was relatively lower than in studies of Huber (6.63/1) and Yamamoto (6.75/1).

In most studies, Karnofsky score was utilized to assess the performance status of participants. The majority of patients in this current study had good baseline performance status score of 90 to 100 (71.6%). It was similar to German trial (70%) and favorable than other studies, from 44.2% to 47.5%. Patients with KPS 70 were rarely seen with percentage from 2.2 to 6% in several studies.

About histological characteristics, adenocarcinoma (ADC) and its subtype (bronchioloalveolar carcinoma - BAC) predominated with percentage of 75% and 15%, respectively. There were only 10% squamous cell carcinomas in our study.

In contrast, squamous cell carcinoma (SCC) was more common in Western trials. For example, the frequency of SCC patients in studies of Choy et al., Belani et al., Huber et al., Yamamoto et al. ranged from 40.2% to 62.6%. In addition, large cell carcinoma occupied from 4% to 22.5% in these studies but no case was seen in Cho Ray.

About staging, there were fewer patients with stage IIIB in Cho Ray trial (43.3%) compared with other studies such as Vokes et al. (46%), Belani et al. (62%), Yamamoto et al. (66.7%), Choy et al. (70%) and Huber et al. (88.9%).

4.2.2. Treatment-related adverse events

Hematological toxicities

As shown in Table 4.3, most hematological adverse events in our current data were in grade 0–2. Grade 3 or worse hematological toxicities during concurrent chemo-radiotherapy were infrequently with leukopenia (11.7%), anemia (3.3%) and neutropenia (3.3%). Grade 3 or worse thrombocytonia, liver or renal function adverse events was not recorded.

These figures confirmed the favorable hematological toxicity profile of concurrent chemo-radiation alone with lower dose of weekly paclitaxel (45mg/m^2) in compared to other studies in similar fashion combined with induction or consolidation chemotherapy and greater dose of paclitaxel. With the same dose of paclitaxel as our trial (45mg/m^2), hematological toxicities seemed much more severe in the study of Belani et al. Grade 3 or

worse granulocytopenia was seen in 26% of patients with concurrent chemo-radiotherapy and 12% in chemotherapy consolidation arm (Belani et al 2005).

Vokes et al. also reported more grade 4 toxicities recorded in patients with the arm of induction chemotherapy and concurrent chemo-radiation (40%) compared to patients with the arm of concurrent chemo-radiotherapy only (26%) (Vokes et al. 2007).

Meanwhile, grade 3 or 4 esophagitis in German study occurred only in 12.8% of patients in the chemo-radiotherapy arm and in 6.5% of patients in the alone radiotherapy arm. Low rates of toxicities in this trial might be related to the using of paclitaxel monotherapy combining to radiotherapy (Huber et al. 2006).

Table 4.4. Grade 3-4 toxicities in selected studies of concurrent chemo-radiotherapy

Grade 3-4 toxicities (%)	**Choy et al.** (n=37)	**Belani et al.** (n=92)	**Huber et al.** (n=99)	**Vokes et al.** (n=161)	**Yamamoto et al.** (n=147)	**Cho Ray** (n=60)
Anemia	13.5	10	0	5	6.1	3.3
Leukopenia	51.3	51	2	36	46.9	11.7
Neutropenia	37	26	0	15	23.1	3.3
Thrombocytopenia	7.7	12	0	-	5.4	0
Nausea/Vomiting	8.1	7	3	-	3.4	1.7
Fatigue/Anorexia	-	-	3	20	1.4	23.3
Weight loss	8.1	-	1	-	-	0
Dyspnea/Lung	21.6	16	1	14	2.7	6.6
Esophagitis	45.9	28	12.8	32	7.5	23.4

Non-hematological toxicities

About radiation-related toxicities, dysphagia and cough/ dyspnea were two most common in all studies with concurrent chemo-radiotherapy. Grade 3 or 4 dysphagia or odynophagia due to esophagitis was observed in 23.3% of patients in our trial. This toxicity was usually brief and self-limiting. Despite substantial acute toxicities with concurrent regimen, long-term or late toxicity did not appear to be common. There was only one patients developed late esophageal toxicity and needed dilation of the esophagus. Grade 3 or worse cough/ dyspnea occurred only in 6.7% of patients but there were two patients developed fatal dyspnea after treatment. This could be due to treatment-related pneumonitis or disease progression.

In general, the frequency of esophagitis in current study seemed rather low and tolerable compared with concurrent chemo-radiotherapy combined with induction/consolidation chemotherapy in other trials. In study of CALGB 39801, severe dysphagia and dyspnea were observed in 32% and 14% of patients with concurrent chemo-radiation in respectively (Vokes et al. 2007).

Belani et al. observed that esophagitis was the most common loco-regional toxicity and more pronounced (28%) with the administration of concurrent chemo-radiotherapy (Belani et al. 2005).

The West Japan Thoracic Oncology Group also reported higher rates of severe esophagitis (33.3%) in arm of weekly paclitaxel/carboplatin for 6 weeks plus radiotherapy of 60Gy, followed by two courses of paclitaxel/carboplatin (Yamamoto et al. 2010).

Treatment adherence

93.3% patients in our study received the full dose of radiotherapy and 91.7% of patients received the planned six cycles of concurrent chemotherapy. The mean treatment time was 6.3 weeks in which 60% of patients had interruptions with average time of 4.1 days due to machine break-down or public holidays. For chemotherapy administration, 38.3% had delayed doses during the chemotherapy cycles and 18.3% had a dose reduction of chemotherapy.

Meanwhile, in the study of Belani et al., there were only 69 - 74% of patients completing all cycles of chemotherapy and 70 - 81% patients received fully the scheduled radiotherapy dose (Belani et al 2005).

4.2.3. Response rates

The overall response rates of 56 assessable patients at Cho Ray hospital were 57.2%, including 3 patients of complete response (5.4%) and 29 patients of partial response (51.8%). These figures were encouraging comparable with results of German trial in which patients in arm of chemo-radiotherapy had overall response rate of 46.4%. This trial also reported significant great number of patients with complete responses (12.1%) in concurrent chemo-radiotherapy arm. However, the number of deceased patients within the first 3 months in this arm was relatively high (8.1%) (Huber et al. 2006).

Choy et al. reported an impressive response rate of 75.7% in assessable 37 patients. Of these, 16.2% had a complete response, 59.5% had a partial response, 10.8% had progressive disease, and 13.5% had stable disease (Choy et al. 1998).

In Japanese study, the objective response rate was 63.3% in patient group of concurrent and consolidation treatment with 3.4% of complete responses and 59.9% of partial responses (Yamamoto et al. 2010).

Table 4.5. Response rates in selected studies of concurrent chemo-radiotherapy

Response rates (%)	**Huber et al.** (n=99)	**Yamamoto et al.** (n=147)	**Choy et al.** (n=37)	**Cho Ray** (n=56)
Complete responses (CR)	12 (12.1)	5 (3.4)	6 (16.2)	3 (5.4)
Partial responses (PR)	34 (34.3)	88 (59.9)	22 (59.5)	29 (51.8)
Stable diseases (SD)	15 (15.2)	32 (21.8)	5 (13.5)	15 (26.8)
Progression diseases (PD)	28 (28.3)	16 (10.9)	4 (10.8)	9 (16)
Died	8 (8.1)	-	-	-
No information	4 (4)	6 (4.1)	-	-
Overall response rates (CR+PR)	46 (46.4)	94 (63.3)	28 (75.7)	32 (57.2)

4.2.4. Survival time

As previously stated, the combined modality regimen was considered as "standard of care" for patients with locally advanced NSCLC. CALGB 8433 was the first major randomized clinical trial to show the significant survival advantage of the combination of sequential chemotherapy and radiotherapy with median survival of 13.7 months (Dillman et al. 1990). Therefore, this median was usually used as the historical control. The results of the present study revealed the median overall survival of 14.4 months, comparing favorably with this reference figure.

As one of the first phase III trial to address the role of induction chemotherapy in the context of concomitant chemo-radiotherapy for stage III NSCLC, Vokes et al. reported that the addition of induction chemotherapy failed to provide a survival benefit over concurrent therapy alone. The median survival time was 12 months in regimen of concomitant chemo-radiotherapy only, not significantly different in comparing with survival of 14 months in induction chemotherapy and combining treatment arm (Vokes et al. 2007).

Comparing three different weekly schedules of the carboplatin/paclitaxel regimen for patients with advanced NSCLC, the best median overall survival (16.3 months) was reported for arm of maintenance therapy after combination treatment (Belani et al. 2005).

As a phase III study, Huber et al. showed a favorable median survival time in patients receiving simultaneous chemo-radiotherapy (18.7 months) comparing to radiotherapy alone (14.1 months) (Huber et al. 2006).

As one of the most recent trial, Yamamoto et al. reported the median survival time in three different of regimens including second generation regimens at full doses or the third generation regimens at reduced doses were 20.5, 19.8, and 22.0 months in respectively (Yamamoto et al. 2010). This survival advantage was definitely related to several factors, including better patient selection (especially the inclusion of positron emission tomography scan and brain magnetic resonance imaging in the initial work-up) and technical improvements in radiotherapy (Blackstock et al. 2007).

Table 4.6. Survival time in selected studies of concurrent chemo-radiotherapy

References	No. of Pts	Regimen of treatment	Median Survival Time (months)	P-value
Choy et al.	40	CCRT – CT cons	20.5	-
Belani et al.	91	IndCT – RT	13.0	Not significant
	74	IndCT- CCRT	12.7	
	92	CCRT – CT cons	16.3	
Huber et al.	113	IndCT – RT	14.1	0.091
	99	IndCT – CCRT	18.7	
Vokes et al.	161	CCRT	12	0.3
	170	IndCT – CCRT	14	
Yamamoto et al.	146	CCRT –CTcons (A)	20.5	0.392 (A vs B) 0.876 (A vs C)
	147	CCRT – CT cons (B)	19.8	
	147	CCRT – CTcons (C)	22	
Cho Ray	60	CCRT	14.4	-

Abbreviations: CCRT, concurrent chemo-radiotherapy; Ind, induction; CT, chemotherapy; cons, consolidation; A - MVP: Mitomycin C, Vindesine, Cisplati; B – Irinotecan, Carboplatin; C – Paclitaxel, Carboplatin.

Prognostic factors

Predefined subgroups of patients were analyzed in this study to determine whether the effect of concomitant chemotherapy varied across subgroups. In terms of survival or progression-free survival, the effect of concomitant chemotherapy appeared greater in patients with female gender, age group from 60-69 years old, earlier stage, good baseline performance status and weight loss under 5%. Among these, pretreatment performance status and weight loss were considered as two significant predictive factors in our trial.

In a meta-analysis included 1764 patients, Auperin et al. suggested the effect of concomitant chemotherapy appeared greater in patients with stage IIIA disease than in those with stage IIIB, both for survival and for event-free survival (Auperin et al. 2006).

4.2.5. Pattern of failures

After median follow-up time of 12.7 months, 38.3% of patients had distant metastases and 33.3% had local recurrences. Local recurrences were more common in squamous cell carcinoma (66.7%). In contrast, there were more distant metastatic cases in adenocarcinoma (42.2%) and bronchioloalveolar carcinoma (44.4%). Brain was the most common site for distant failures (56.5%). Other common metastatic sites included bony lesions (39.1%), liver (17.4%) and lungs (13%).

In study of Choy et al., the primary tumor site failures were seen in 53% of the patients while distant metastasis alone was the first site of failure in 46.6% of the patients. Like our finding, brain was also the most common site for distant metastases (50%) (Choy et al. 1998).

Huber et al. reported that relapse rate was less frequent in the chemo-radiotherapy group compared with the radiotherapy alone group (65.7% versus 85.9%, respectively; $P<0.001$). The authors also realized that there was no difference in the distribution of relapse locations between two arms of treatment (Huber et al. 2006).

5. SUMMARY

This chapter revisits the aims, rationale and approach of the study, and summarizes the principal findings of the research. The next section considers the strengths and limitations of the studies.

5.1. Revisiting the rationale, aims and the approach of the thesis

In Vietnam, non-small cell lung cancer (NSCLC) occupied around 80-85% of lung cancer. Radiotherapy combined with chemotherapy sequentially or concurrently was considered a suitable option for many patients with inoperable stage III NSCLC. However, due to the shortage in radiotherapy equipment in many cancer centers, many patients with this stage were treated with palliative intent such as chemotherapy alone or supportive care only. That is the main reason for setting up a study to treat the patients with stage III NSCLC at Cho Ray hospital by concomitant chemo-radiotherapy. The study aimed to investigate the efficacy of combining radiotherapy and chemotherapy concurrently by analyzing the median survival time, the progression-free survival, the overall survival and the response rate in the study population. It also aimed to assess the safety and tolerability of patients receiving concomitant chemo-radiotherapy.

Patients with stage III non-small lung cancer who satisfied the selection criteria were accrued into this prospective study. The study cohort was selected from all patients with locally advanced non-small cell lung cancer who presented to the Department of Oncology, Cho Ray hospital, Ho Chi Minh city, Vietnam from 1st March 2009 to 1st March 2012.

Following entry into the study, patients were planned to receive weekly paclitaxel with carboplatin concurrent with radiotherapy of 60Gy in 30 fractions for six consecutive weeks. The paclitaxel was administered at 45mg/m^2 intravenously (1 hour) and the carboplatin being given at a formula time versus concentration curve (AUC) of two intravenously (30 minutes) following administration of paclitaxel. Clinical details of all patients were recorded prospectively and included name, gender, age, personal and family histories, social habits like smoking, histology, clinical presentation, performance status, weight loss in previous three months, details of treatment regimen, toxicities and outcome of treatment.

5.2. Summary of the principal findings

The subtypes of histology in this series included adenocarcinoma (75%), bronchioloalveolar carcinoma (15%) and squamous cell carcinoma (10%). There were 70% of males and 30% of females and mean age of patients was 58 years. Smokers occupied 88% of male patients and 5.6% of female patients. Most of patients (71.6%) had KPS score from 90-100. 66.7% of patients had no weight loss or weight loss under 5% of their normal weight in previous three months.

For lung tumor characteristics, the ratio of right to left-sided primary tumors was 1.5/1. The great proportion of tumors (43.4%) located in the upper lobes of the lung, 25% in the lower lobes and 28.3% in the main bronchi. Common sites of lymph nodes involvement in descending order were para-aortic (46.7%), para-tracheal (17.4%), sub-carinal (13.3%) and sub-aortic (10.7%) regions. The frequency of patients with stage IIIA and IIIB were 56.7% and 43.3%, respectively.

For treatment administration, 93.3% received radiotherapy of 60Gy and 91.7% completed 6 cycles of chemotherapy as planned in protocol. The reasons for not completing treatment were treatment-related complication and patient refusal.

Common hematological toxicities in any grade consisted of leukopenia (65%), anemia (61.7%) and neutropenia (38.3%) and thrombocytopenia (8.3%). Grade 3 or 4 hematological toxicities occurred in 3.3% of anemia, 11.7% of leukopenia and 3.3% of neutropenia.

Common non-hematological side-effects included esophagitis (66.7%), fatigue/anorexia (80%), dermatitis (48.3%), alopecia (41.7%), weight loss (40%) and nausea/vomiting (28.3%). Grade 3 or 4 non-hematological toxicities were composed of dysphagia/odynophagia due to esophagitis (23,3%), fatigue/anorexia (23,3%), leukopenia (11.7%) and cough/dyspnea (6.6%).

The objective response rate was 57.2%, including 5.4% of complete responses and 51.8% of partial responses, according to RECIST criteria. With the follow up time of 12.7 months, the median of overall survival and progression-free survival were 14.4 months and 10.8 months in respectively. The median of progression-free and overall survival time trended better in gender of female, age group from 60-69 years old, subtype of bronchioloalveolar carcinomas and patients with stage IIIA. Pretreated performance status and weight loss were two significant prognostic factors.

5.3. Strengths and limitations of the study

One of the strengths of this study was the completeness of the data set. From the perspective of a clinical study to evaluate efficacy of concurrent chemo-radiotherapy alone with regimen of weekly paclitaxel combined carboplatin, the sample size of the current study was relatively small in comparison to other multicenter studies. Consequently, the data should be considered to be explanatory and comparing to similar studies, rather than definitive. A larger sample size should be evaluated to validate our results.

Another limitation of this study was in the patient selection. Due to the required commitment and intense procedures, patients with poor economic conditions and living far from Ho Chi Minh city tended to decline participation.

Besides, approximately 10 - 30% of patients with non-metastatic NSCLC as determined by conventional imaging might be found to have distant metastases with more modern diagnostic tools such as MRI of brain and positron emission tomography (Pfister et al. 2004). This was also our limitation in patient selection in which most were not staged with positron emission tomography scan and brain magnetic resonance imaging. This might explain for several early distant metastasis cases in our report.

6. THESEN

1. From 1/3/2009 to 1/3/2012, 821 men and 337 women were treated due to lung cancers at Department of Oncology, Cho Ray hospital, Ho Chi Minh city, Vietnam. 63.9% of patients were between 45 to 64 years old with median age of 56 years old with a range of 20 – 87 years.
2. 64.3% of the patients had pathology of adenocarcinomas while other subtypes were less infrequently such as squamous cell carcinomas (11.3%), small cell lung cancer (4.9%) and large cell carcinomas (0.8%). In non-small cell lung cancer (NSCLC), 38.4% of the patients were admitted in locally advanced stages and 51.1% in metastatic stages.
3. Among 423 stage III NSCLC patients, there were 60 patients (14.2%), including 42 men and 18 women, received weekly Paclitaxel – Carboplatin combined concurrently with radiotherapy to 60Gy in 6 weeks.
4. In this group, 71.6% of the patients had Karnofsky performance status (KPS) score from 90 to 100 and 66.7% had no weight loss or weight loss under 5% in previous 3 months. Pathological subtypes were composed of 75% of adenocarcinomas (ADC), 15% of bronchiolo-alveolar carcinomas (BAC) and 10% squamous cell carcinomas (SCC). According to 6^{th} edition of IASLC classification, 56.7% of the patients were classified as stage IIIA and 43.3% as stage IIIB.
5. For treatment administration, 93.3% of the patients were irradiated to total dose of 60Gy and 91.7% completed six cycles of chemotherapy as protocol.
6. Common toxicities in any grades were fatigue/anorexia (80%), esophagitis (66.7%), leukopenia (65%), anemia (61.7%) and neutropenia (38.3%). Common grade 3 or 4 toxicities included esophagitis (23.3%), fatigue/anorexia (23.3%), leukopenia (11.7%) and cough/dyspnea (6.6%).
7. Overall responses rate was 57.2%, including 5.4% of complete responses and 51.8% of partial responses. 26.8% of the patients had stable diseases and 16% had progressive disease according to RECIST criteria.

8. With median time of follow up as 12.7 months, 36.7% patients alive, 3.3% patients missing of follow-up and 60% patients deceased. The median of overall survival and progression-free survival were 14.4 months and 10.8 months in respectively.
9. In multivariate analysis, the time to progression and overall survival time trended to be better in gender of female, age of 60-69 years old, bronchioloalveolar carcinoma and stage IIIA, however, pretreatment performance status and weight loss at baseline were two only significant prognostic factors.
10. The strength of this study was the completeness of the data although the sample size was not a huge number in comparison to other multicenter studies. Consequently, the data should be considered to be explanatory and comparing to similar studies, rather than definitive. A larger sample size should be evaluated to validate our results.
11. A limitation of this study was in the patient selection with no patients with poor economic conditions and living far from Ho Chi Minh city coming to participation. An additional limitation of this study was the staging procedure in which most of patients were not staged with positron emission tomography scan and brain magnetic resonance imaging.
12. This study proved that the regimen of weekly paclitaxel – carboplatin chemotherapy combined concurrently with radiotherapy was relatively safe and feasible to do in Vietnam although the careful selection of patients and using of comprehensive staging procedure were necessary.

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8. APPENDICES

Appendix A. WHO Histological Classification Of Lung Cancer (Travis et al. 1999)

EPITHELIAL TUMORS (MALIGNANT)

Squamous cell carcinoma
Variants
Papillary
Clear cell
Small cell
Basaloid
Small cell carcinoma
Variant
Combined small cell carcinoma
Adenocarcinoma
Acinar
Papillary
Bronchioloalveolar carcinoma
Nonmucinous (Clara cell/type II pneumocyte) type
Mucinous (goblet cell) type
Mixed mucinous and nonmucinous (Clara cell/type II pneumocyte and goblet cell) type, or indeterminate cell type
Solid adenocarcinoma with mucin formation
Adenocarcinoma with mixed subtypes
Variants
Well-differentiated fetal adenocarcinoma
Mucinous adenocarcinoma
Mucinous cyst adenocarcinoma
Signet-ring adenocarcinoma
Clear cell adenocarcinoma
Large cell carcinoma
Variants
Large cell neuroendocrine carcinoma
Combined large cell neuroendocrine carcinoma
Basaloid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Large cell carcinoma with rhabdoid phenotype
Adenosquamous carcinoma
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements
Carcinomas with spindle or giant cells
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Others
Carcinoid tumors
Typical carcinoid
Atypical carcinoid
Carcinomas of salivary gland type
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Others
Unclassifiedcarcinoma

Appendix B. International Staging System For Non-Small Cell Lung Cancer (6th Edition)

PRIMARY TUMOR

Tx Primary tumor proven by the presence of malignant cells in thebroncho-pulmonary secretions but not visible on radiographic or endoscopic examination

T0 No primary tumor detected

Tis Carcinoma in situ

T1 Tumor measuring 3 cm or less in its largest dimension surrounded by lung or visceral pleura, or endobronchial tumor, proximal to one lobar bronchus

T2 Tumor measuring more than 3 cm in its greatest dimension or extension to the visceral pleura or atelectasis or obstructive pneumopathy of less than one lung or lobar endobronchial tumor or tumor of one principal bronchus at more than 2 cm from the carina

T3 Tumor of the apex or endobronchial tumor of one principal bronchus at less than 2 cm from the carina but not invading it or atelectasis or tumor in any size with direct extension to the adjacent structures (to the chest wall, to the mediastinal pleura). Extension to the pericardium pariental layer or to the diaphragm or to the mediastinal fat or to phrenic nerve

T3a Atelectasis or obstructive pneumopathy of one entire lung without other criterion for T3

T3b If other criterion/criteria present for a T3

T4 Macroscopic or histological extension to the mediastinum, or heart, or great vessels, or trachea, or oesophagus, or vertebral body or carina, or tumor with a malignant pleural or pericardial effusion, or recurrent involvement, or invasion of the homolateral visceral or parietal pleura which cannot be a result of direct spread of the tumor, or multiple neoplastic nodules in the same lobe of the lung.

T4a All T4 except T4b

T4b Invasion of carina or presence of a malignant pleural effusion

REGIONAL LYMPH NODES

N0 No metastasis to regional lymph node

N1 Metastasis to hilar lymph nodes or to peribronchialhomolateral (interlobar, lobar, segmental) or to both (including direct extension)

N2 Metastasis to the homolateralmediastinal lymph node or subcarinal node

N3 Metastasis to contralateral mediastinal lymph nodes, or to homolateral or contralateral scalene, or sub-clavicular lymph nodes or to contralateral hilar lymph nodes

N3a Metastasis in the controlateral (hilar or mediastinal) lymph nodes

N3b Metastasis in the sub-clavicular fossae or scalene lymph nodes

DISTANT METASTASES

MX Presence of distant metastases cannot be assessed
M0 No distant metastases
M1 Distant metastases present

STAGE GROUPING

Stage	T	N	M
Occult	X	0	0
IA	1	0	0
IB	2	0	0
IIA	1	1	0
IIB	2	1	0
	3	0	0
IIIA	Any except T4	2	0
	3	1	0
IIIB	Any	3	0
	4	Any	0
IV	Any	Any	1
	Several nodules in different lobes		

Appendix C. Classification Of Common Toxicities Criteria (National Cancer Institute Version 2.0)

Toxicity	0	1	2	3	4
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl	8.0 - < 10.0 g/dl	6.5 - < 8.0 g/dl	< 6.5 g/dl
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9/L	≥2.0 - < 3.0 x 10^9/L	≥1.0 - < 2.0 x 10^9/L	< 1.0 x 10^9/L
Neutrophils/ granulocytes (ANC)	WNL	≥1.5 - <2.0 x 10^9/L	≥1.0 - <1.5 x 10^9/L	≥0.5 - <1.0 x 10^9/L	< 0.5 x 10^9/L
Platelets	WNL	< LLN - <75.0 x 10^9/L	≥50.0 - < 75.0 x 10^9/L	≥10.0 - < 50.0 x 10^9/L	< 10.0 x 10^9/L

Toxicity	0	1	2	3	4
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic trans-aminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥ 1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Anorexia	none	loss of appetite	Oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Nausea	None	able to eat	Oral intake significantly decreased	no significant intake, requiring IV fluids	-

Toxicity	0	1	2	3	4
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Infection (documented clinically or microbiologi-cally) with grade 3 or 4 neutropenia	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support

Appendix D. Performance Status Karnofsky Grading

100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active works.
60	Requires occasional assistance but is able to care for most needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalisation is indicated although death not imminent
20	Very sick, hospitalisation necessary, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

Appendix E. Response Evaluation Criteria In Solid Tumors (RECIST)

The evaluation of target lesions will be performed using the sum of the longest diameter (LD) for all of these lesions. The LD will be calculated and reported as the baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease as follows:

Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a **30% decrease** in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a **20% increase** in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

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Training education

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