CHAPTER II

LITERATURE REVIEWS

1. Lung cancer

1.1 Epidemiology and incidence

Nowadays lung cancer is the most common malignancy worldwide, especially in men. It accounts for an estimated of 960,000 new cases and 850,000 deaths each year among men, and 390,000 new cases and 330,000 deaths among women (2). In addition, it was also the leading cause of cancer deaths above the other types of cancer. In 2008, the International Agency for Research on Cancer (IARC) revealed that lung cancer patients were the most common cause of cancer death (1.31 million) followed by stomach cancer (780,000) and liver cancer (699,000) (2).

In Thailand, the actual data during 1989-2000 indicated that trends of the numbers of all cancer sites from 1990 to 2008 has increased every year even though the incidence rate was stable (51). At the end of the 21st century approximately 103,000 new cancer cases of all sites are projected, and that liver cancer will still be the leading type in both genders followed by lung cancer (51). Lung cancer ranked the second cause of death above the other types of cancer for many years until the latest update of data in 2007 (52). The incidence rate of lung cancer is highest in the northern region at Lampang followed by Chiang Mai, and Udonthani province, respectively (6, 7). For Maharaj Nakorn Chiang Mai hospital, the numbers of lung cancer is growing every year. Over the period of 2003-2005, the number of new lung cancer patients were 622, 684, and 730 respectively (53). Although, the latest data

over the period of 2006-2008 was shown that the number of patients who have visited out-patients department clinics had declined to 3,465, 3,285, and 1,816 times, respectively (54). However, these patient groups have remained the major problem above the other types of cancer, especially in men.

In addition, lung cancer patients are more common among men than women, especially those who are older than 70 years. Only 5-10 % of lung cancer cases are diagnosed under 50 years of age (38). Deesomchok et al. (4) at Maharaj Nakorn Chiang Mai surveyed 619 cancer patients, they found that the gender ratio of male: female was 1.79: 1 with the majority of age in the range of 61-70 years old of both genders, and the mean age of 60.1 years. Generally, 85 % of all lung cancer cases were in the advanced stage (8, 9). Similarly the study by Deesomchok et al. found that 82.4 % of patients were at present in the advanced stage (4). Collectively, lung cancer is an awful type of cancer, very difficult to cure and poor in prognosis. Therefore, presently it is the major public health problem in many parts around the world including in Thailand specifically in the northern region.

1.2 Causes

The lung cancer causes are composed of many factors. First, smoking which is the preliminary cause above the other factors at about 80-90 % of all cases (38, 55, 56). The risk is among heavy smokers which is estimated to be 10-25 times compared with nonsmokers (55). Moreover, it risks are depending on many factors such as, number of cigarettes smoked per day, duration of smoking, age at which smoking began, inhalation patterns, and tar content of cigarettes (55). Second, environmental tobacco smoke (ETS)/ or passive secondhand or passive smoking, which can be detected approximately 1.6 % of all lung cancer cases (57). Third, diet and food

supplements, although at the present there is still insufficient data to support on the effect of dietary factors on lung cancer risks. However the early evidence recommended that some of nutrients such as, processed meat (eg, sausage, pressed duck, and cured pork), deep fried cooking, and chili have been associated with an increased lung cancer risk. Conversely, some of the nutrients may prevent carcinogenesis, such as vitamin A or beta-carotene, vitamin C, vitamin E, and selenium (55, 56). Fourth, air pollution, whether from the motor vehicles and diesel engine exhausts, power plants, and industrial or residential emissions releasing of polycyclic aromatic hydrocarbon compounds which may increase the risk of lung cancer more, especially in the urban areas (38, 56). Fifth, occupational exposure, estimated that over half of the occupational cases are caused by asbestos (1). In addition, the other most common agents including radon, diesel engine exhaust, and silica while these agents account for approximately 3-17 % of lung cancer (58). Sixth, exercise and physical activity, many studies concluded that moderate to high levels of leisure-time physical activities are associated with a 13 % to 30 % reduction in lung cancer risk (56). Seventh, alcohol consumption, also found that people who have consumed at least 30 g/d of alcohol are at greater risk than among those who abstained from alcohol (56). Finally, genetic factors, many of the studies demonstrated that who have a family cluster having a history of lung cancer, the incidence of lung cancer was higher than who don't have a history of lung cancer (1). Overall, it indicated that the cause of lung cancer was composed of many factors. However, the preliminary and commonest cause still being given importance is mainly on smoking.

1.3 Symptoms

Generally, the nature of lung cancer symptoms can be divided into three major stages which are composed of, asymptomatic stage, asymptomatic stage but can detect the disease, and symptomatic stage (59). A presentation of symptom stage, can be subdivided into four groups as follows: local symptoms, regional/ intrathoracic spread symptoms, metastatic symptoms, and paraneoplastic syndrome (1, 59, 60). Each of the symptom groups is composed of many symptoms that will be shown as follows:

Local symptoms are composed of coughing which is the most common of symptoms followed by hemoptysis, chest pain, dyspnea, wheezing sound, and pneumonia. Intrathoracic spread symptoms are composed of hoarseness from laryngeal nerve being compressed, phrenic nerve paralysis, dysphagia, stridor sound, superior vena cava syndrome, pleural effusion, Horner's syndrome, Pancoast's syndrome, and lymphangitic spread. Metastatic symptoms, the common sites of spread are to the brain followed by bones and the other areas throughout the body to liver, adrenal gland, and lymph node. The clinical manifestation depends on the extent of specific organ dysfunction. Paraneoplastic syndrome, accounts for approximately 10-20 % of all cancers. The more common syndromes associated with lung cancer are shown as follows: cachexia, endocrinologic syndromes, neurologic syndromes, musculoskeletal syndromes, mucocutaneous manifestations, and hematologic syndromes and vascular manifestation (1, 59, 60).

Moreover, lung cancer symptoms normally vary and are frequently mixed. Also, these depend on many factors including stages of disease, period of time after diagnosis, and treatment types. The study of McCorkle and Benoliel (61) showed that

distress symptoms in newly diagnosed lung cancer patients are more common than the other samples of patients, which agrees with the study of Degner and Sloan (62) who showed that patients with lung cancer had the highest level of distress symptoms other than cancer patients in ambulatory care. At the same time, the other most common symptoms in both studies were fatigue, pain, loss of appetite, coughing, and insomnia (61, 62). Furthermore, in cases of advanced stage patients with uncontrolled symptoms of lung cancer have reported that pain, dyspnea and anorexia are the most common symptoms other than above symptoms (63). Especially, pain which is usually induces other symptoms such as distress and depression. The review study of Potter and Higginson (64) found that the overall weighted mean prevalence of pain experienced by patients was 47 % (range 6-100 %), at out-patients clinics was 27 % (range 8-85 %), in palliative care patients was 76 %, and 73 % of the pain caused by itself. Moreover, the symptoms change following treatment. Kaasa et al. (65) study in advanced NSCLC compared the symptoms during chemotherapy and radiation therapy treatment, the results were found that in the group who received chemotherapy the common symptoms were nausea, vomiting, and hair loss, whereas in the group who received radiation therapy the common symptoms were dysphagia and sore throats. At Maharaj Nakorn Chiang Mai Hospital, Deesomchok et al. (4) the results were examined in 619 lung cancer patients and the results showed that coughs, weight loss, dyspnea, chest pain, and hemoptysis are the most common of symptoms.

Therefore, from the many review studies, it was pointed out that lung cancer symptoms vary, have a multiple of symptoms, are different at various points of the illness trajectory, and among various treatments there are more aggressive symptoms in advanced stage of disease.

1.4 Types

Lung cancer is divided broadly into two main categories; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Small cell lung cancer grow rapidly and metastasis widely, accounts approximately 20-25 % of all types of lung cancer (1). Furthermore, according to the International Association for the Study of Lung cancer (IASLC), SCLC can be divided into 3 subgroups, pure small cell, mixed (small cell and large cell), and combined (small cell and squamous cell or adenocarcinoma) (1). NSCLC approximately accounts for 85 % of all cases (1) and divide into three major groups by the World Health Organization definition (WHO) e.g. squamous cell cancers (epidermoid carcinoma, spindle cell variant), adenocarcinomas (acinar adenocarcinoma, papillary adenocarcinoma, bronchioloalveolar carcinoma, solid carcinoma with mucus formation), and large cell (undifferentiated) carcinomas (large cell/undifferentiated, giant cell, clear cell). In addition, the other types that are excluded from the three major groups above are such as adenosquamous carcinoma, bronchial gland carcinoma (adenoid cystic carcinoma, mucoepidermoid tumor), and carcinoid tumor (typical, atypical) (1). Among these types, adenocarcinoma is the most common type, approximately 30-35 % followed by squamous cell carcinoma, small cell, and large cell carcinoma, respectively (1). At Maharaj Nakorn ChiangMai hospital, Deesomchok et al. (4) showed that adenocarcinoma (42.6 %) is the most common followed by squamous cell carcinoma (33 %), small cell carcinoma (12.4 %) and large cell carcinoma (2.9 %), respectively. Others that are unclassified in cell type account for about 9.1 %.

1.5 Stages

Generally the categorization of NSCLC is staged according to the TNM classification (1). The T factor is used to describe the extent of the primary tumor, the N factor is the extent of regional lymph node involvement, and the M factor is the presence of distant metastases. The subgroups of each of the stages are shown as follows;

Stage grouping – TNM subsets

Stage	TNM subset	Stage	TNM subset
0	Carcinoma in situ		T2N2M0, T3N2M0
1A	T1N0M0	3B	T4N0M0, T4N1M0
1B	T2N0M0		T4N2M0, T1N3M0
2A	T1N1M0		T2N3M0, T3N3M0
2B	T2N1M0		T4N3M0
	T3N0M0	4	Any T Any N M1
3A	T3N1M0, T1N2M0		

The SCLC group was usually staged according to a simple two-stage system developed by the Veteran's Administration Lung Cancer Study Group. Also, from an expert panel of the International Association for the Study of Lung Cancer that reviewed the staging of SCLC had recommended no change in this two-stage system (38). More of the details are shown as follows:

1. Limited disease (LD): the tumor is confined to one hemithorax and its regional lymph nodes, including the ipsilateral mediastinal, ipsilateral supraclavicular,

and contralateral hilar nodes. In addition, LD may be defined simply as a localized tumor that may easily be encompassed within an acceptable radiotherapy portal. Tumors that present with ipsilateral pleura effusions, left laryngeal nerve involvement, or superior vena cava obstruction are still considered limited.

2. Extensive disease (ED): in case of pericardial involvement and bilateral pulmonary parenchymal involvement were considered in this stage. Also because of the radiotherapy portal required to encompass, this bulk of diseases would be too large and would be associated with a significant risk of unacceptable toxicity.

In addition, the incidence among both major groups of lung cancer patients found that approximately one third of patients with NSCLC presented with stage 4 disease, and nearly half (44 %) presented with stage 3 tumors. For SCLC, 40 % presented in limited stage and 60 % presented in extensive stage (1).

1.6 Treatment

The treatment strategies in NSCLC vary and are strongly dependent on the stage of disease ranging from surgery to palliative chemotherapy. At the early stage, the primary option of treatment which is commonly considered is surgical resection (66). However, the number of patients that are appropriate for surgery is limited, 20-25 % abroad (67) whilst in Thailand only approximately 12.8 % of patients are suitable for surgery (67). For advanced stage, the treatment options vary from single option, such as radiotherapy, chemotherapy, hormone therapy, and supportive care (commonly in stage IV) until combined therapy is radiochemotherapy. In addition, the physicians may consider radiotherapy or chemotherapy followed by surgery. The other options maybe to initiate surgery followed by radiation or chemotherapy.

Nevertheless, these treatment options depend on the stage of patients, co-morbidity and readiness of each patient (68).

SCLC, treatment is generally aggressive and the option commonly used is based on chemotherapy (1). The oncologist may generally consider combination chemotherapy because of its higher response rate and survival rate than single agent chemotherapy. In addition, the other treatment options may be chosen, such as surgery, thoracic radiation or prophylaxis cranial irradiation, nevertheless it depends on the primary stage of disease (60). However, the present study will be specific only in patients with advanced stage, so the treatment option that will be chosen is mainly chemotherapy.

2. Chemotherapy and new agent targeted therapy

Chemotherapy is commonly used in patients with cancer particularly in the advanced stage of all cancer types. Also as lung cancer is frequently diagnosed in advanced stage, therefore the first choice of treatment for these patients is chemotherapy (13). Nowadays, there are many types of chemotherapy lines such as, first chemotherapy line which defines as the first drug group that is commonly considered to the patients, this may also be called standard therapy such as, double agent platinum-based therapy or nonplatinum-based doublets are an acceptable alternative (e.g., cisplatin, carboplatin, gemcitabine, vinorelbine, paclitaxel) (68, 69). Second or third chemotherapy line is defined as the next drug group that is given if the disease has not responded or reoccurred during or after the first chemotherapy is less well-defined (e.g., docetaxel, pemetrexed, erlotinib, gefitinib) (68, 69). However, at present there are new agents of therapy line called targeted therapy (e.g,

bevacizumab or cetuximab). Many studies showed it has less toxicity than chemotherapy and also can increase overall survival and response rates. In addition, previous studies showed that whether the addition of a targeted therapy to the initial chemotherapy or continuation of the targeted agent after completion of the chemotherapy have yielded superior overall survival rates in comparison to chemotherapy only, however the appropriately time to combined these drugs is still controversial. In addition, the concerns about acute and potential cumulative toxicities as well as economic costs have raised questions about these drugs (68, 69). Therefore, the mainstay of therapy in the present with advanced lung cancer patients is still chemotherapy.

For Maharaj Nakorn Chiang Mai hospital, the chemotherapy regimens that are commonly used can be divided into two major groups followed by type of lung cancer (NSCLC & SCLC). However, the type of drugs that are administered in both cancer groups were in the same group (platinum-based regimen), so the side effects of chemotherapy follow the same patterns, and generally administered for four to six courses at three to four weeks apart (70). In addition, the principle for considering these drugs depends on many factors such as type of cancer, cost-effectiveness, quality of life and the readiness of each of the patients (70).

In NSCLC, a combination of chemotherapy drugs is the most common such as a paclitaxel regimen with carboplatin administered for four courses every three weeks, and a gemcitabine regimen with carboplatin administered for only two courses followed by six sessions of radiation therapy. Whereas, the single agent chemotherapy which is commonly used is vinorelbine administered for four courses every three weeks, and taxotere administered for four to six courses every three weeks

(70). While in the SCLC, the first line of drugs which is commonly used at the present is four to six courses of etoposide and cisplatine both at the limited stage and extensive stage. In addition, in the limited stage, patients may receive two courses followed by one session of radiation therapy concluded by chemotherapy for four courses again, whereas the extensive stage was usually administered for four to six courses every three weeks (70).

2.1 Response of chemotherapy treatment

Generally, the responses of chemotherapy can be categorized into four major groups as follows: first complete response (CR) is defined as complete disappearance of all known lesions. Second, partial response (PR) is defined as at least 50% decrease in total tumor size and no appearance of new lesions or progression of any lesion. Third, stable disease (SD) is defined as neither PR nor PD criteria met. The last, progressive disease (PD) is defined as a 25% or more increase in the size of one or more measurable lesions and no CR, PR and SD documented before increased disease or new lesions. All of these guidelines follow WHO principles (71).

2.2 Benefit of chemotherapy

Nowadays, chemotherapy is still being developed, although in the past few years it seems stable in its effects (12). However, many studies showed that chemotherapy is of benefit in cases of ameliorated symptoms, increased survival rate and improved quality of life, although the amplitude level of benefits remains disappointing (14, 16, 17). Especially in advanced stages in lung cancer patients who have received chemotherapy compared with palliative care, the results showed clearly that those patients in the group receiving chemotherapy have higher survival rates and

better quality of life than patients who are only receiving palliative cancer treatments (13, 15, 17)

2.3 Side effects of chemotherapy

Although chemotherapy gives many benefits, it also has many adverse effects or toxicities that depended on many factors, such as administration schedule, drug regimen and dosage, as well as concomitant illness. Many previous studies pointed out that many toxicities or side effects were produced from chemotherapy, and causes change from the micro level of molecular, pathophysiological to the macro level of physical and psychological aspect. For instance, it destroys bone marrow which impairs the production of red blood cells resulting in anemia and a decrease in the oxygen transport capacity of the blood. It is also related to fatigue symptoms, thrombocytopenia, decrease in platelets, white blood cells and results to increase the risk of infections (25, 27, 28). In addition, it also causes many physical problems, such as nausea and vomiting, diarrhea, fatigue, constipation, insomnia, sore mouth, pain, appetite loss, alopecia, dry and rash skin, body composition changes, ataxia, peripheral neuropathy and psychological problems (i.e. anxiety, depression, and sleep disturbances) (22-24, 26, 29).

2.4 Common chemotherapy regimens and adverse effects (27, 35-40, 72)

Table 1 Common chemotherapy regimens in lung cancer and adverse effects

Abbreviation: N & V= Neusea and vomiting, ARDS=Acute respiratory distress syndrome

Chemotherapy regimens	**Side effect and other**	**Pulmonary toxic and related effect**	**Cadiovascular**
Carboplatin	N & V, myelosuppression, thrombocytopenia, anemia, alopecia, hepatotoxicity neutropenia	-	-
Paclitaxel	N & V, Myelosuppression, mucositis, alopecia, appetite loss, change in taste, thinned or brittle hair, pain in the joints of the arms or legs, peripheral neuropathy	Acute pneumonitis, ARDS, hypersensitivity reaction,dyspnea	Cadiotoxicity, ECG abnormalities, arrhythmias, ventricular tachycardia, heart block, hypotension
Vinorelbine	N & V, myelosuppression, alopecia, nuetropenia, constipation and paraesthesias, neuropathy	-	-
Cisplatin	N & V, myelosuppression, hearing loss, anemia, alopecia, nephrotoxicity, electrolyte disturbance, diarrhea, tinnitus neurotoxicity, anorexia, constipation, hypocalcemia,	-	Cadiotoxicity, Acute myocardial infarction, vascular damage, alteration in platelet aggregation and hypomagnesemia

Table 1 (Continued)

Chemotherapy regimens	Side effect and other	Pulmonary toxic and related effect	Cadiovascular
Gemcitabine	N & V, myelosuppression, fatigue, diarrhea, anemia, thrombocytopenia, mouth sore, shortness of breath, sleep disturbance, alopecia, neutropenia	Acute pneumonitis, ARDS, dyspnea hypersensitivity reaction	-
Etoposide	N & V, myelosuppression, alopecia, mucositis, diarrhea, neuropathy	Acute pneumonitis, progressively pulmonary fibrosis, hypersensitivity reaction, wheezing, dyspnea	Cadiotoxicity
Docetaxel	Myelosuppression, alopecia, nuetropenia, thrombocytopenia anemia, fatigue, edema, erythematous maculopapular rash, pleural effusion, asthenia, skin reaction, diarrhea	Acute pneumonitis, pleural disease, hypersensitivity reaction	-
Cyclophospham ide/ Ifosfamide	N & V, myelosuppression, neutropenia, bladder toxicity, renal toxicity, gonadal atrophy, hematuria	Acute pneumonitis, progressive pulmonary fibrosis, pleural disease	Cadiotoxicity

2.5 Effects of chemotherapy on cardiorespiratory fitness

2.5.1 Mechanism of pulmonary function change and previous studies

Many studies supported the effect of chemotherapy to decrease diffusion capacity, although the really pathophysiological mechanisms on lung function changes during chemotherapy is still unclear, however many hypothesizes suggest such possibilities as the alveolar septal thickening with fibrosis, alveolo-capillary membrane alterations, atypical type II pneumocytes and pulmonary endothelial cell injury characteristic after patients were receiving chemotherapy (35). Moreover, the information from the review study by Cutillas et al. (35) stated that chemotherapeutic agents are associated with acute pneumonitis, adult respiratory distress syndrome (ARDS), progressive pulmonary fibrosis, pleural disease, and hypersensitivity reaction that may effect on respiratory symptoms. In addition, many pathologic patterns are observed by biopsy after chemotherapy such as, a variable degree of an inflammation component have been reported, a variety of interstitial pneumonias, usually chronic or nonspecific interstitial pneumonia, also the other factors histological patterns have been noticed including diffuse alveolar damage, bronchiolitis obliterans, organizing pneumonia, obliterative bronchiolitis, hypersensivity pneumonia, alveola duct fibrosis, pulmonary edema, pulmonary hemorrhage, pulmonary hypertension, and pulmonary veno-occlusive disease (35). Finally, these factors affect pulmonary function of the patients followed.

Many previous studies on the effect of chemotherapy on pulmonary function have shown in the same direction to decline of diffusing capacity for various types of cancer (41-46). In addition, the other lung functions such as, FEV_1, FVC, and others generally seemed to increase in patients who responded to chemotherapy and declined

in groups of non-response to chemotherapy. However, the mean values normally did not change. For example the study of Pinson and Klastersky (44) looked into the effects of chemotherapy on lung function change in 44 patients both NSCLC and SCLC after the first three cycles of receiving various combinations of chemotherapy regimens, the results showed statistically non-significant improvements of FEV_1 and VC in responders group and stable values in non-responders group. Maas et al. (43) studied 44 patients with stage III NSCLC treated with three cycles of gemcitabine and cisplatin within one month neoadjuvant chemotherapy on a weekly on days 1, 8, and 15, the result showed significant increase of FEV_1 and FEV_1/VC irrespective of age, presence and severity of COPD, tumor response or number of chemotherapy cycles. The study of Leo et al. (42) in 30 patients with stage IIIa of NSCLC treated by induction chemotherapy with three cycles of cisplatinum and gemcitabine, the result showed significant increase of FEV_1 and FVC. In addition, the latest study of Mohan et al. (16) studied in 44 patients with advanced NSCLC were assessed for pulmonary function at baseline and one month after completion of four cycles of standard chemotherapy regimen consisting of cisplatin and etoposide. The results showed improve lung function in responders group and decline in non-responder group but no significant change in both groups, nevertheless overall there were no changes in pulmonary function.

In summary, from all above reviews in lung cancer patients who received chemotherapy can be divided into two major groups. First, patients who were in locally advanced stage and received induction chemotherapy, the purpose to shrink of the tumor and propose for surgery. The second, patients in advanced stage and cannot be operated on, they received systemic chemotherapy. In both groups, the majority of

studies have always measured the pulmonary function after having at least three cycles of chemotherapy. For the result showed same as the direction by decrease in diffusing capacity after patients received chemotherapy, whereas the others PFTs such as FEV_1, FVC, FEV_1/FVC etc. the results still cannot be resolved. However patients who were responded to the chemotherapy, these outcomes mostly increased, on the contrary, in patients who were non-responded to the chemotherapy, tend to decrease in these variables.

2.5.2 Mechanism of cardiovascular system change and previous studies

Cardiotoxicity is one of the causes of chemotherapeutic regimen's side effects. It is composed of many kinds of drugs such as cyclophosphamide, ifosfamide, fluorouracil especially the anthracycline class that can effect cardiotoxicity both acute, subacute or chronic progressive (73). In addition, among these adverse effects are varied from mild transient blood pressure and/or electrocardiographic changes, and thrombosis to more serious events such as, arrhythmias, myocarditis, pericarditis, myocardial infarction, heart block, ventricular tachycardia and cardiomyopathy, which may end in left ventricular dysfunction or congestive heart failure (36, 37, 73). These symptoms might be happen during or after treatment within days, weeks, months, even years (37). For the mechanisms may cause by cellular damage due to the formation of free oxygen radicals leading to death of cardiac cells, also the induction of immunogenic reactions with the presence of antigen presenting cells in the heart (39).

Moreover, other factors that may affect the cardiovascular system or fitness level of the patients two are common symptoms which are dyspnea and fatigue, it could be directly involved in reducing patients daily activity (32, 34), particularly

fatigue symptoms that can occur in up to 82-96 % of patients receiving chemotherapy (30). By which these symptoms are commonly related to anemia (low level of hemoglobin; < 12.0 g/dl) seen after chemotherapy also affect the neuropathy and muscle disease (32, 50). In addition, a low level of hemoglobin is correlated with poor performance status (48). There is wide recognition that chemotherapy is destructive to bone marrow. Thus, the production of red blood cells is prohibited and leads to poor oxygen levels in blood circulation, these consequences may give patients more fatigue and limit physical function (48-50). In addition, many compensatory mechanisms respond to anemia e.g, increase in pulse rate, cardiac output, peripheral vasodilatation, and blood flow, enhanced oxygen unloading, increased of respiratory rate in an effort to improve blood oxygenation. Therefore, many signs and symptoms can be observed from these results including palpitations, tachycardia, pallor and more exertional dyspnea (48). Moreover, anemia is also related to cerebral hopoxia that can lead to more fatigue levels (48) and also related to decrease of diffusion capacity in lung as well (74). Finally, anemia can affect skeletal muscle, can reduce physical work capacity and exercise tolerance, resulting in breathlessness, tiredness and muscle fatigue (48, 49). These factors are a vicious cycle that will affect both directly and indirectly the cardiovascular system of the patients.

Nevertheless, at present there is still less study on the effects of chemotherapy on exercise capacity, especially in advanced stages of lung cancer patients during chemotherapy treatment. Shin et al. (45) investigated the change of cardiopulmonary exercise tolerance prior to the fourth cycle of chemotherapy in 11 patients with locally advanced NSCLC. The results showed a significant reduction of maximal oxygen

uptake (VO_{2max}). The researcher referred that this result might possible that chemotherapy did not response to the disease. Mohan et al. (16) studied in 44 patients after 4 cycles of chemotherapy in advanced NSCLC, the result showed that increasing in 6MWD (6 minute walk distance) especially in group of good response but not significant however, overall did not change of 6MWD. Whereas, in the study of Kasymjanova et al. with advanced NSCLC (47), they hypothesized that 6MWD decreased after two cycles of chemotherapy and these values may be beneficial for the prognosis in these patients, whereas the results were supported by his hypothesis and suggested that an initial result of 6MWD ≥ 400 meters was useful for prognostic factor for survival in advanced NSCLC patients.

In summary, the overall results found that trend to decline or unchanged exercise capacity after receiving chemotherapy.

3. Effect of chemotherapy on QoL in lung cancer patients

To date, QoL is growing in importance and focused as an end point including evaluation, predicting prognosis or progression of disease and treatment outcomes in patients with cancer (15, 75). At the same time, it seems many studies are increasingly recognizing this outcome. Therefore, this part of the study has reflected the review studies on the effect of chemotherapy to the QoL, and will mainly pay attention to advanced stage of patients with lung cancer.

Many prior studies examined the effect of chemotherapy on QoL after receiving chemotherapy, the majority of these studies showed improvement of global QoL such as Fernandez et al. (19) indicated that 75 % of patients with advanced NSCLC improved QoL after having received first two cycles of high-dose

chemotherapy and had also improved in some of symptoms and declined in others. Bircan et al. (18) investigated the QoL after having received 3 courses of platinum-containing chemotherapy in patients with advanced NSCLC and SCLC as the result showed improved global health status and had decreased many symptoms such as pain, haemoptysis, dyspnea, and coughing; however, alopecia, sore mouth, nausea and vomiting were increased with chemotherapy. Mohan et al. (16) compared patients with advanced NSCLC versus pre and post four cycles of chemotherapy. The findings demonstrated significant improvement in most of the symptoms such as coughing, dyspnea, chest pain, fever, anorexia, weight loss and increase of hemoglobin and albubin levels, also the QoL of patients who responded to chemotherapy showed improvement but not significant; however, overall no improve of QoL. While Paesman (17) examined the review studies in patients with advanced NSCLC, the results showed that most of the trials reported improved QoL after chemotherapy. Like the review studies by Fallowfield and Harper (15) specifically on patients with advanced stage of NSCLC compared between patients receiving various cytotoxic chemotherapy regimens, concluded that changes in health-related quality of life (HRQoL), functional domains appear to be similar between different chemotherapy regimens and generally chemotherapy improved patients' HRQoL. Furthermore, the authors also reported that overall there was improvement of HRQoL in patients who had received chemotherapy as compared with the best supportive care. All of the above mentioned studies concluded that those who experienced an improved of QoL because chemotherapy could alleviate many symptoms even though some symptoms worsened.

In Thailand, Thongprasert et al. (21) compared patients with advanced NSCLC between those receiving best supportive care and best supportive care plus at least two courses of combination chemotherapy on the effect of QoL and clinical outcomes in three different periods, at the entry, third month and post two months after completing chemotherapy. The result showed improvement of QoL in chemotherapy patients only. The latest study of Santisevee (20) compared pre and post one and two months of chemotherapy treatment in patients with advanced NSCLC, the findings pointed out increases of QoL scores, especially in the dimension of emotional well being which is statistically significant whereas the physical and functional well being were not significantly decreased after chemotherapy.

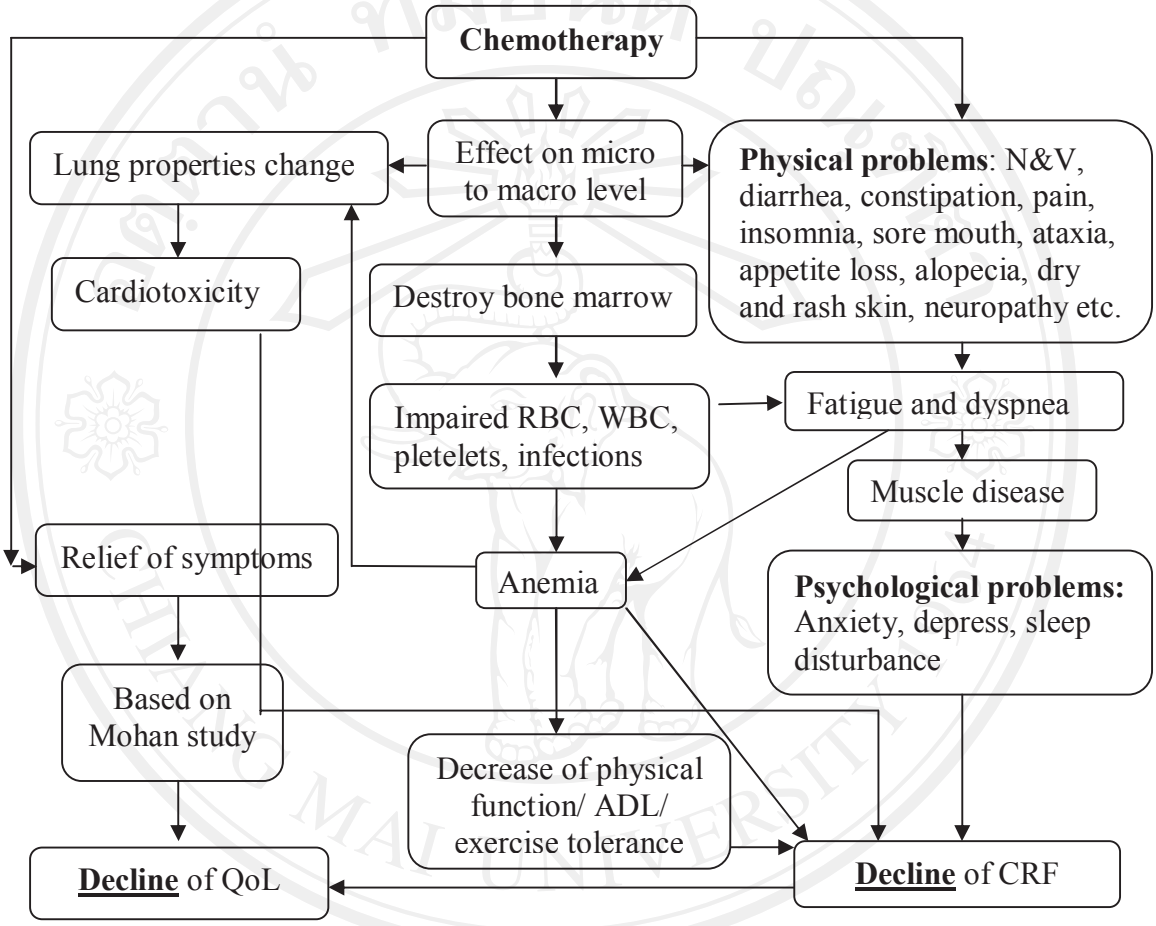
From the reviewed studies, it can be concluded that patients with advanced stage of lung cancer, generally had improved QoL, with chemotherapy when compared with best supportive care alone. However, those previous studies commonly examined patients who had completed a chemotherapy program (at least 3-4 cycles), whereas there are fewer studies looking at the comparison between patients who receive short courses and late courses of chemotherapy on QoL.

Summary and conceptual framework

The evidence from many previous studies have concluded that chemotherapy can directly and indirectly affect cardiorespiratory fitness and quality of life of patients. Chemotherapy has an impact from the micro level to macro level such as changes in lung properties and cardiotoxicity. Chemotherapy deteriorates bone marrow, so it causes impairment of red blood cell production, decrease of platelets and white blood cells and increases the risk of infections. In addition, chemotherapy

has many side effects and brings about both physical and psychological problems such as nausea and vomiting, diarrhea, constipation, appetite loss, sore mouth, pain, neuropathy, muscle disease, anxiety, depression, sleep disturbances etc. Many studies show that fatigue and dyspnea are the most common side effects and also a decline of physical functioning. Therefore, all of these problems are a vicious cycle (see the conceptual framework in figure 1), the conclusion of all of these problems is possibly deterioration of cardiorespiratory fitness of the patient after chemotherapy and in late courses of chemotherapy. In addition, many previous studies show that chemotherapy was able to increase survival rates, alleviate some symptoms and increase QoL. In addition, Mohan et al. stated that even though chemotherapy could alleviate many symptoms after chemotherapy, however it could not be determined that the cardiorespiratory fitness of patients and QoL would be improved as well. Therefore, the present study have two items of the hypothesizes, first, expectations that after patients had received four courses of chemotherapy, the cardiorespiratory fitness should not be greater than after receiving the second course of chemotherapy and before receiving the first course of chemotherapy, respectively. Second, expectations that QoL of patients after receiving four courses of chemotherapy should not be greater than after the second course of chemotherapy and before receiving the first course of chemotherapy, respectively. All of these studies are based on a conceptual framework as show in Figure1 and based on the study of Mohan et al. and Kasymjanova et al. Nevertheless, from the literature reviews, there is no study to compare the effect of chemotherapy on cardiorespiratory fitness and QoL at different courses of chemotherapy, therefore the present study aimed to investigate the effect of

chemotherapy at three time points; before the first course, after the second and the fourth courses of chemotherapy.



Abbreviation: N & V= Neusea and vomiting, CRF= Cardiorespiratory fitness, RBC= Red blood cell, WBC= White blood cell, ADL=Activity daily living

Figure 1 The conceptual framework of the study (the vicious cycle of chemotherapy)

4. The measurements of the study

4.1 Pulmonary function test

Pulmonary function tests (PFTs) are a group of procedures that measure the function of the lung and have many beneficial uses such as diagnosing a range of

respiratory diseases, measuring how lung disease is progressing, and how serious the lung disease has become. In addition, it can help to assess how a patient is responding to different treatments. The most common of the pulmonary function tests is the spirometry test, which is a physiological test that measures how an individual inhales or exhales a volume of air as a function of time, the outcome may be volume or flow (76). The most important values of spirometry test are composed of many aspects such as forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio, peak expiratory flow rate (PEFR), forced expiratory flow at 25-75 % of FVC ($FEF_{25-75\%}$), predicted value of FEV_1 and predicted value of FVC, etc (76).

Spirometry tests can be undertaken with many differences types of equipment, and the results obtained will depend on technical and as well as personal factors. The examiner should be familiar with relative contraindications such as hemoptysis, pneumothorax, unstable cardiovascular status, including knowing adverse events that may be present during or after the test such as, increased intracranial pressure, syncope, dizziness, oxygen desaturation, and bronchospasm. However, all of the test procedures, the contraindication and precautions should follow the guideline of American Thoracic Society (ATS) (77).

4.2 Six Minute Walk Test (6MWT)

Nowadays, there are many modalities to evaluate the objective examination of functional exercise capacity. The formal test for exercise capacity is cardiopulmonary exercise test/ CPET) (78)which provides a global assessment of the exercise responses and it can also to determine the functional capacity, impairment, the appropriate design of exercise prescription that is specific to each of the person etc. The other tests informal test such as a shuttle-walk test, stair climbing test, twelve

minute walk test and six minute walk test (6MWT). The 6MWT, has been widely used for assessing and evaluating responses to therapeutic intervention for pulmonary and cardiac diseases. It is more reflective of activities of daily living than the other walk tests (79). However, it has some differences from CPET. For example, the CPET can determine peak oxygen uptake and provides total information on exercise test. In contrast, the 6MWT assesses at the submaximal level and usually is used for diagnosing the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation only (80). At the same time, most of the activities in daily living are usually performed at submaximal levels of exertion, so the 6MWT may better reflect functional exercise capabilities than other test. Furthermore, from a qualitative overview of the measurement properties of functional walk test by Solway et al. (79) indicated that 6MWT has good reliability and validity and is a test of choice for the functional walk test in clinical or research avenues.

Although, the 6MWT is a practical, simple test which is easier to administer, better tolerated and better reflects activities of daily living than other walk tests, however it is not easy to perform. The examiner should know the steps of test, command, contraindications and procedure to administer when an adverse event may be happening. And these have shown the contraindication including absolute/ relative contraindication and the reasons for immediately stopping the test, which all of these are essential components that the examiner should know (81).

Absolute contraindication; unstable angina during the previous month and myocardial infarction during the previous month.

Relative contraindication; a resting heart rate of more than 120 beats per min, a systolic blood pressure of more than 180 mmHg, and a diastolic blood pressure of more than 100 mmHg.

Reasons for immediately stopping the test; chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance.

4.3 Quality of life questionnaire in lung cancer

Currently, the QoL questionnaires that are well known and widely used in clinical trials of lung cancer patients are composed of three main types (15, 75), such as the Functional Assessment Cancer Therapy-General (FACT-G) (82), the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaires (EORTC QLQ C30) (83) commonly parallel used with its lung cancer specific module (QLQ-LC13) (84, 85) and Lung Cancer Symptom Scale (LCSS) (86). In addition, all of these questionnaires have demonstrated a good reliability and validity which are appropriate to apply in these patients (82-86). Whereas, the QLQ-C30, is the most commonly used instrument and widely used in countries, such as in the USA, Australia, Japan and many European countries. It has demonstrated a high reliability and validity across the continents (83).

QLQ C30 is already translated into Thai, the first time by Sirisinha et al. (87) and the latest by Silpakit et al. (88), the result showed that Cronbach's α coefficients of the six scales were above 0.7, except for cognitive and social function scales, and test-retest reliability coefficients measured by Pearson's correlation coefficients were high in all of items range from 0.66-0.90. The authors suggest that it has proven to be reliable and valid and appropriate to use in Thai population in all types of cancer. LC-13 was also translated into Thai by Silpakit et al. (88) as well, however validity

or reliability were not determined because the study lacked patients , therefore it needs to be carefully observed, if considered necessary to be used.