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QUALITY OF LIFE ASSESSMENT IN METASTATIC (STAGE IV) LUNG CANCER PATIENTS

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DEDICATION

To my precious sister...

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ABSTRACT

Kivrak B. Quality of Life Assessment in Metastatic (Stage IV) Lung Cancer Patients. Yeditepe University Institute of Health Sciences Clinical Pharmacy Master Thesis. Istanbul, 2009.

Purpose: The aims of the present study are to investigate the possible changes in QOL between the baseline (pre-treatment), after the first, second and third chemotherapy treatments with newly diagnosed patients with metastatic SCLC (small cell lung cancer) and NSCLC (non-small cell lung cancer) receiving platinum-based chemotherapy, to determine which effects factors such as age and smoking habit have on quality of life, and to observe the correlation between quality of life and performance status scales (ECOG, KPS).

Materials and Methods: The study was conducted at the outpatient and inpatient Oncology Clinics of the Lutfi Kirdar Teaching and Research Hospital in Istanbul, Turkey Seventeen patients with advanced small-cell lung cancer and with stage IV non-small cell lung cancer were considered. Patients filled the EORTC core questionnaire QLQ- C30 (version 3.0) and the lung cancer module QLQ-LC13 at four different times (pre-treatment and post-treatment) during the treatment and follow-up. Demographic, clinical data and performance status of the patients were also recorded.

Results: From the baseline to the third chemotherapy, there was a significant increase in treatment-related side effects including sore mouth ($p < 0.05$, $F= 1.085$), dysphagia ($p < 0.05$, $F= 6.559$), peripheral neuropathy ($p < 0.05$, $F= 7.040$), and alopecia ($p < 0.05$, $F= 0.9904$). At the same time, there was a significant decrease in GHS ($p< 0.005$, $F= 1.520$) and Functional Scales including physical functioning ($p< 0.05$, $F= 3.336$), role functioning ($p< 0,05$, $F= 1.016$), emotional functioning($p< 0.05$, $F= 3.173$), cognitive functions ($p< 0.005$, $F= 4.152$), and social functioning ($p<0.05$, $F=6.14$). There was also an increase in symptom scales including nausea and vomiting ($p< 0.05$, $F= 1.301$), dyspnea ($p < 0.023$, $F= 1.931$), insomnia ($p < 0.05$, $F= 1.523$), and appetite loss ($p < 0.003$, $F= 1.668$). The mean age of the patients was 59 and there was not a correlation between age and quality of life ($p> 0.05$). There was not a significant correlation between duration of smoking and QOL scores ($p> 0.05$). The mean ECOG performance was 2.05 ± 0.15 and KPS was 60.00 ± 4.11. There was a strong significant negative correlation ($r= -0.71$, $p< 0.05$) between ECOG performance and all domains of the EORTC QLQ-C30. There was a strong significant positive correlation ($r= 0.74$, $p< 0.05$) between KPS and all domains of the EORTC QLQ-C30.

Conclusion: This study confirmes that performance status scales (ECOG, KPS) are strong prognostic factors in patients with advance lung cancer. It appears from our data that advanced NSCLC and SCLC PS=2 patients probably do not benefit from platinum-

based chemotherapy. The assessments of QOL should also be routine for all patients with advanced NSCLC and SCLC. This information may be useful in developing treatment programs that minimize chemotherapy side effects while maximizing the well being of patients. The formation of a oncology care team consisting of physicians, clinical pharmacists and nurses is very important in order to provide good pharmaceutical care to the lung cancer patients. These problems might be managed with the contribution of a clinical pharmacist. Further studies could focus on defining the role and benefits of the clinical pharmacist within the Oncology team.

Key Words: Quality of Life, ECOG, KPS, Metastatic non-small cell lung cancer, Advanced small-cell lung cancer, Clinical Pharmacist

ÖZET

Kivrak B. Metastatik (Evre IV) Akciger Kanserli Hastalarda Yasam Kalitesi Degerlendirilmesi. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Klinik Eczacılık Mastır Tezi. İstanbul, 2009.

Amaç: Yeni tani konmus, platinyum-bazli kemoterapi tedavisi goren metastatik akciger kanserli hastalarin yasam kalitelerinin tedavi oncesi, birinci, ikinci ve ucuncu kemoterapi suresince degerlendirilmesi, yas ve sigara kullanim aliskanliklarinin yasam kalitesine etkisi ve yasam kalitesi ile performans skalalarin (ECOG, KPS) arasindaki iliskinin incelenmesi bu calismanin esas amacidir.

Materyal ve Metot: Bu calisma Istanbul Kartal Egitim ve Arastirma Hastanesi Onkoloji Klinik ve Polikliniklerinde yurutulmustur. Yaygin evre kucuk hucreli akciger kanseri ve metastatik (Evre IV) kucuk hucre disi akciger kanserli 17 hasta calismaya dahil edildi. Hastalar EORTC QLQ-C30 anketi ve anketin akciger kanseri QLQ-LC13 modulunu, tedavi oncesi, birinci, ikinci ve ucuncu kemoterapi suresince cevaplandirdi. Demografik, klinik datalar ve performans statuleri kaydedildi.

Bulgular: Tedavi oncesinde ucuncu kemoterapi sonrasina suresince hastalarda tedaviye bagli yan etkilerde: agizda agri ($p < 0.05$, $F= 1.085$), disfaji ($p < 0.05$, $F= 7.040$), periferal noropati ($p < 0.05$, $F= 7.040$) ve alopesi ($p < 0.05$, $F= 0.9904$) sonuclarinda anlamli degisiklikler gozlenmistir. Ayni zamanda hastalarin genel saglik durumlarinda ve fiziksel fonksiyonlari ($p< 0.005$, $F= 1.520$), rol fonksiyonlari ($p< 0,05$, $F= 1.016$), duygusal fonksiyonlari ($p< 0.05$, $F= 3.173$), kognitif fonksiyonlari ($p< 0.005$, $F= 4.152$) ve sosyal fonksiyonlarini ($p<0.05$, $F=6.14$) iceren fiziksel fonksiyonlarinda anlamli degisiklikler saptanmistir. Bulanti-kusma ($p< 0.05$, $F= 1.301$), dispne ($p < 0.023$, $F= 1.931$), insomnia ($p < 0.05$, $F= 1.523$) ve istah kaybi ($p < 0.003$, $F= 1.668$) semptomlarinda artis gozlenmistir. Hastalarin ortalama yasi 59' idi ve yasam kalitesi ile yas arasinda anlamli bir iliski yoktu ($p> 0.05$). Sigara kullanim suresi ile yasam kalitesi arasinda anlamli bir iliski yoktu ($p> 0.05$). Hastalarin ortalama ECOG performans skoru 2.05 ± 0.15 , KPS 60.00 ± 4.11 olarak hesaplandi. ECOG parformance skoru ile EORTC QLQ-C30 anketinin butun bolumleri arasinda anlamli negatif ($r= -0.71$, $p< 0.05$) bir korelasyon gozledi. KPS ile EORTC QLQ-C30 anketinin butun bolumleri arasinda ise anlamli pozitif bir korelasyon oldugu saptandi ($r= 0.74$, $p< 0.05$)

Sonuc: Bu calisma performans durum skalalarinin (ECOG, KPS) metastatik akciger kanserli hastalarda guclu bir prognostik faktor oldugunu onaylamaktadir. Calismamiz ile performans skalasi ECOG= 2 olan yaygin evre kucuk hucreli akciger kanseri ve metastatik (Evre IV) kucuk hucre disi akciger kanserli hastalarinin platinyum bazli tedaviden fayda gormediklerini gostermistir. Bu grup hastalarda yasam kalitesi olcumu rutin olarak yapilarak elde edilen veriler, yan etkileri dusuren, yasam kalitesini yukselten

yeni tedavi planlarinin gelistirlmesinde kullanilabilir. Onkoloji hastalarına iyi bir farmasötik bakım verilebilmesi açısından doktorların, klinik eczacıların ve de hemşirelerin bir yoğun bakım ekibi oluşturması çok önemlidir Bu yan etkiler bir klinik eczacı katkısıyla kontrol altına alınabilir. Gelecek araştırmalarda onkoloji ekibinde bir klinik eczacının rolünü ve faydasını belirleyici çalışmalar yapılabilir.

Anahtar Kelimler: Yasam Kalitesi, ECOG, KPS, Metastatik kucuk hucre-disi akciger kanseri, Yaygin kucuk hucreli akciger kanseri, Klinik Eczaci

CONTENTS

SYMBOLS AND ABBREVIATIONS

CAV	Cyclophosphamide, Adriamycin and Vincristine
CT	Computed Tomography
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer Module
ETS	Environmental Tobaco Smoke
FACT-L	Functional Assessment of Cancer Therapy-Lung
FDG- PET	2- [18F] fluoro-2-deoxy-D-glucose Position Emission Tomography
GHS	Global Health Status
KPS	Karnofsky Performance Scale
LCSS	Lung Cancer Symptom Scale
MRI	Magnetic Resonance Imaging
NSCLC	Non- Small Cell Lung Cancer
PS	Performance Status
QOL	Quality of Life
SCC	Squamos Cell Carcinoma
SCLC	Small Cell Lung Cancer
SVC	Superior Vena Cava Syndrome
TBNA	Transbronchial Percutaneous Fine-Needle Aspiration Biopsy
TPNA	Transthoracic Percutaneous Fine-Needle Aspiration Biopsy

VAS	Visual Analog Scale
VATS	Video Assisted Thoracoscopy
YHS	Age Standardized Rate

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1. INTRODUCTION

Lung cancer is one of the leading causes of cancer death globally. It carries a

greater mortality rate than colorectal, breast, and prostate cancers collectively. In the year 2000 alone, lung cancer was responsible for 692,000 male and 156,000 female deaths [1]. Approximately 85% of patients with lung cancer are diagnosed at an advanced stage that is not amenable to surgical intervention. As a result, these patients require chemotherapy and/or radiotherapy. In spite of several advancements in chemotherapeutic regimens and the addition of many newer drugs, the 5-year survival rate has improved only marginally from 5% in the 1950s to approximately 14% by 1996. The overall 1-year survival rate is less than 20% [2].

Lung cancer continues to claim thousands of lives every year globally. Several newer therapies so far have failed to significantly prolong survival or offer curative benefit. In view of the high morbidity and short survival, assessment of QOL needs to be included as an end point in evaluation and treatment of lung cancer. Quality of life measurements also help in predicting survival, evaluating efficacy of various treatment regimens, and comparing one regimen with another.

Moreover, lung cancer is not just associated with a high mortality rate but a high morbidity rate as well, with a significant proportion of patients severely incapacitated by disease-related symptoms such as chest pain, cough, hemoptysis, and dyspnea [3]. In such a grim scenario, the evaluation and improvement of quality of life (QOL), as well as alleviation of symptom distress, assumes great importance in the overall management of these patients.

QOL studies in this area are very important, especially where few medical differences can be expected in the effectiveness of the treatments. There is a debate around the treatment of lung cancer as to which treatment modality should be administered and until what point in the evolution of the disease. This controversy is more intense in advance disease.

Numerous tools are being used in lung cancer patients to assess QOL. These include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC- QLQ-C30) and its lung cancer module (EORTC-QLQ-LC13) EORTC has a study group on Quality of Life. One of the tasks that this study group has addressed has been the development of questionnaires that assess QOL in international clinical trials. In this sense, the QOL group decided to create a combined assessment system that includes a core questionnaire, which could evaluate issues common to different cancer sites and treatments, and various modules complementing the core questionnaire [4,5]. These modules include specific aspects of treatments or disease sites including breast, neck, head and others [6]. Besides, EORTC group developed the third version of this instrument. The first module was the lung cancer module QLQ-LC13 [7]. This module was developed to assess the specific symptoms of lung cancer and its treatments that were not covered at all, or insufficiently, in the core questionnaire. It has previously been shown that EORTC-QLQ-C30 appears to yield a more reliable and comprehensive instrument of QOL in this patient cohort that could be achieved by the other tools [4].

The aims of the present study are to investigate the possible changes in QOL between the baseline (pre-treatment), after the first, second and third chemotherapy treatments with newly diagnosed patients with metastatic SCLC and NSCLC receiving platinum-based chemotherapy, to determine which effects factors such as age and smoking habit have on quality of life, and to observe the correlation between quality of life and performance status scales (ECOG, KPS) and also to throw light on and make suggestions regarding the future possible role of a clinical pharmacist in Oncology clinics.

2. THEORITICAL PART

2.1. LUNG CANCER

2.1.1. Epidemiology

Cancer is shown to cause 22.8% of all deaths, second only to heart disease. (Table 1) [8] At the end of the 20th century, lung cancer had become one of the leading causes of cancer death in both men and woman in the world [9]. Among cancer deaths, lung cancer is known to be the most common cause of death in both sexes and it is responsible for the 12.8% of all cancer cases and 17.8% of the all cancer deaths [10]. In US, 5 year relative survival rate for lung cancer for the period of 1996 to 2003 was 16%, reflecting a steady but slow improvement from 13% from 1975 to 1977 (Table 2) [11].

Table 1 : US Mortality Rates, 2005 [8]

Rank	Cause of Death	No. of Deaths	% of all deaths
1	Heart Diseases	652,091	26.6
2	Cancer	559,312	22.8
3	Cerebrovascular diseases	143,579	5.9
4	Chronic lower respiratory diseases	130,933	5.3
5	Accidents (unintentional)	117,809	4.8
6	Diabetes mellitus	75,119	3.1
7	Alzheimer disease	71,599	2.9
8	Influenza & pneumonia	63,001	2.6
9	Nephritis	43,901	1.8
10	Septicemia	34,136	1.4

Table 2: Five-year Relative Survival (%)* Rates, US, 1975-2003) [11].

Type of Cancer	1975- 1977	1984- 1986	1996- 2003

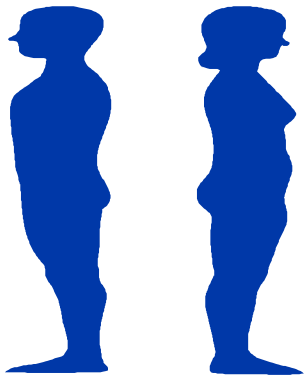
All types	50	54	66
Breast (female)	75	79	89
Colon	51	59	65
Leukemia	35	42	50
Lung and Bronchus	13	13	16
Melanoma	82	87	92
Non-Hodgkin Lymphoma	48	53	64
Ovary	37	40	45
Pancreas	2	3	5
Prostate	69	76	99
Rectum	49	57	66
Urinary Bladder	74	78	81

In the United States alone, it is estimated that there will be 215,000 new cases of lung cancer in 2008 and that lung cancer would account for 31% of cancer deaths in men and 26% of cancer deaths in woman, a total of 161,840 deaths (Table 3) [12].

Table 3 : 2008 Estimated US Cancer Deaths [12]

Lung & bronchus	**31%**
Prostate	10%
Colon & rectum	8%
Pancreas	6%
Liver & intrahepatic bile duct	4%
Leukemia	4%
Esophagus	4%
Urinary bladder	3%
Non-Hodgkin lymph	3%
Kidney & renal pelvis	3%
All other sites	24%

Men 294,12 **Women 271,530**



Lung & bronchus	**26 %**
Breast	15 %
Colon & rectum	9%
Pancreas	6 %
Ovary	6 %
Non-Hodgkin lymp.	3%
Leukemia	3%
Uterine corpus	3%
Liver & intrahepatic bile duct	2%
Brain	2%
All other sites	25%

In our country, according to Ministry of

Health data, 1994 general cancer incidance was 33.1/ 100.000 and among cancer deaths, lung cancer is responsible for 17.6% of all cancer cases (Table 4,5) [13] . This figure is the 12.8% of the all new cancer cases and increases by 3% yearly. [14]. According to a retrospective study between 1999 and 2003 in Turkey, the total male/female ratio was 12.1 /1. Most commonly diagnosed histological types were epidermoid carcinoma in male (p=0,01) and adenocarcinoma in female (p<0,01) [15]

Table 4: Cancers most frequently seen in Turkey, male [13]

Location	**Rough rate (per hundred thousand)**	**YSH* (World)**	**Number of cases**
Trachea, bronchus, **lung**	3.2	47.7	12862
Stomach	9.6	12.2	3320
Urinary bladder	8.6	11	2952
Colon and Rectum	7.4	9.1	2545
Larynx	6.4	8	2206
Prostate	6.1	8	2099

* YSH: per hundred thousand, age standardized rate, world standart population

Table 5: Cancers most frequently seen in Turkey, female [13]

Location	**Rough rate (per hundred thousand)**	**YSH* (World)**	**Number of cases**
Breast	19,9	22	6729
Colon and Rectum	7,6	8,5	2571
Stomach	5,7	6,4	1915
Ovary	4,8	5,4	1628
Trachea, bronchus, **lung**	4,6	5,3	1572
Leukemia	4,4	4,7	1505

2.1.2. Etiology

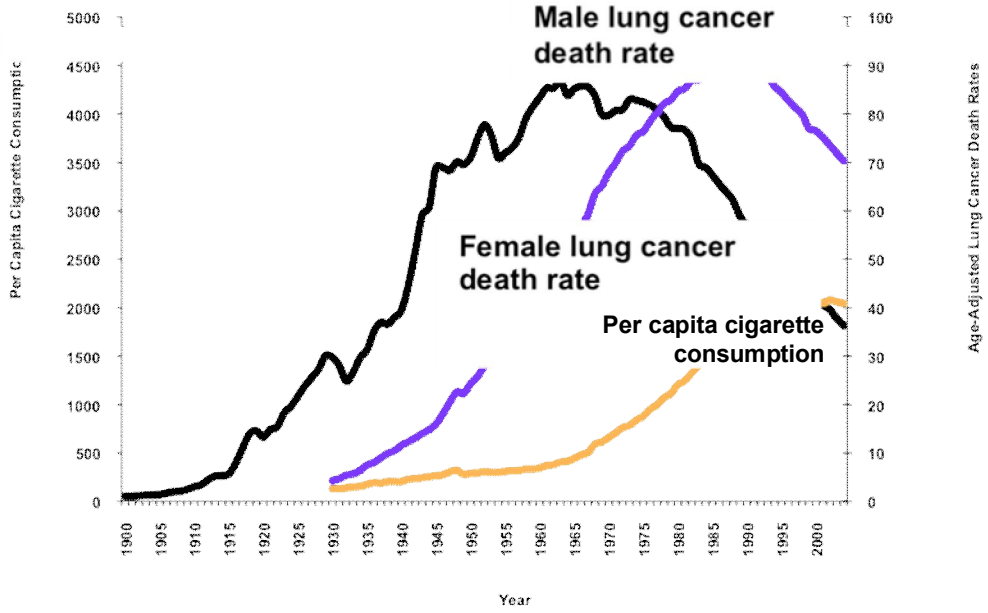
2.1.2.1.Smoking

By 1950, case-control epidemiologic studies showed that cigarettes were strongly associated with the risk of lung cancer [16,17]. Although the causes of lung cancer are almost exclusively environmental, it is likely that there is substantial individual variation in the susceptibility to respiratory carcinogens. The risk of the disease can be conceptualized as reflecting the joint consequences of the interrelationship between exposure to etiologic (or protective) agents and the individual susceptibility to these agents (Table 6) [18, 19]

The leading cause of lung cancer, accounting for approximately 90% of lung cancer cases in the United States and other countries [20]. Compared to never-smokers, smokers have about a 20- fold increase in lung cancer risk at present.

Passive smokers inhale a complex mixture of smoke that is now widely referred to as *environmental tobaco smoke* (ETS). The National research Council reviewed the epidemiologic evidence that conclude that nonsmoking spouses who were married to cigarette smokers were about 30% more likely to develope lung cancer than nonsmoking spouses who were married to nonsmokers [21].

Table 6: Tobacco Use in the US, 1900-2004 [18]



2.1.2.2. Diet

Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant nutrients may protect against oxidative DNA damage and thereby protect against cancer [22].

2.1.2.3. Occupational Exposures

Among cancers that are associated with occupational exposures, lung cancer is the most common [23].

2.1.2.4.Asbestos

Asbestos, a well- estabilished occupational carcinogen, refers to several forms of fibrous, naturally occuruig silica minerals [24]. The epidemiologic evidence dates to the 1950's, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer [25].

2.1.2.5. Radiation

Epidemiologic studies of populations that have been exposed to high doses of radiation show that lung cancer is one of the cancers associated with exposure to ionizing radiation.

2.1.2.6. High- LET Radiation (Radon)

Radon is an inert gas that is produced naturally from radium series of uranium that can cause damage to the DNA of cells of the respiratory epitelium.

2.1.2.7. Low- LET Radiation (X- Rays and Gamma Rays)

Epidemiologic data relating low-LET radiation to lung cancer stem from the following three principal populations: the atomic bomb survivors in Japan [26]; patients with disease such as ankylosing spondylitis [27] or tuberculosis [28], who received multiple radiation treatments; and occupational groups in professions who are exposed to radiation [29].

Arsenic, nickel, chromium, polycyclic aromatic hydrocarbons are the other carconogenic agents.

2.1.2. 8. Genetic

Epidemiologic studies showing that a family history of lung cancer predicts increased risk further support a genetic basis for lung cancer susceptibility. In a large study in Louisiana segregation analysis suggested that lung cancer inheritance was consistent with a mendelian co-dominant autosomal gene determining the early onset of disease [30].

A clinical study in Turkey observed 1500 cases of lung cancer diagnosed between the years 1995-2000 and investigated family tendency of lung cancer in a control group including partners of 600 patients with family histories of cancer. In

40% of 1500 patients with lung cancer, there was a positive family history of lung cancer with regard to malignity [31]

Many carcinogenic compounds in tobacco smoke (e.g, polycyclic aromatic hydrocarbons) undergo metabolic activation by phase I enzymes of the cytochrome p450 system to form reactive intermediates that bind to DNA and cause genetic injury. Two of these enzymes have been investigated with regard to lung cancer risk (CYP1A1 and CYP2D6) [32].

Glutathione S-transferase is a phase II enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. There are at least four genetically distinct classes of the glutathione S-transferases as follows: μ, α, π, and θ. The results of several studies have shown that individuals with high activity of the glutathione S-transferase μ-polymorphism have lower risk of lung cancer [33].

2.1.2.9. Presence of Acquired Lung Disease

Increased susceptibility to lung cancer may result from previously incurred lung damage. Such acquired lung diseases assume the following two major forms:

(1) those that obstruct airflow, such as chronic obstructive pulmonary disease
(2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.

It is mentioned that patients with tuberculosis are 8 times more at risk of developing cancer than those without. Ten to fifteen years pass between the development of tuberculosis and the onset of cancer in these patients. According to a study in Turkey between the years of 1990 and 1995, 15 of 1012 (1.48%) lung cancer patients had a history of tuberculosis [34].

2.1.3. Pathology

The term lung cancer comprises all malignant neoplasms arising from the bronchial, bronchiolar, or alveolar epithelium. Lung cancers are commonly divided into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These tumors are grouped due to similarities in their prognosis and management (Table 7, 8) [35].

Table 7: Lung Cancer Histological Classification

A-Non- small cell lung cancer (NSCLC) (% 70-75)
1. Squamos cell carcinoma (%25-30)
2. Adenocarcinoma (% 30-35)
3. Large cell carcinoma (%10-15)
B- Small cell lung cancer (SCLC) (% 20-25)
C- Combined types (% 5-10)

Table 8: 2004 World Health Organization Classification of Malignant Epithelial Tumors

Squamous cell carcinoma
Variants: papillary, clear cell, small cell, basaloid
Small cell carcinoma
Variants: combined small cell lung carcinoma
Adenocarcinoma
Variants: acinar, papillary, bronchioloalveolar, solid adenocarcinoma with mucin, adenocarcinoma with mixed subtypes, fetal, mucinous, signet ring, clear cell

Large cell carcinoma

Variants: large cell neuroendocrine carcinoma, basaloid, lymphoepithelioma-like, clear cell, rhabdoid phenotype

Adenosquamous carcinoma

Sarcomatoid carcinoma

Variants: pleomorphic, spindle cell, giant cell, carcinosarcoma, pulmonary blastoma

Carcinoid tumors

Variants: typical, atypical

Carcinomas of the salivary gland type

Variants: mucoepidermoid, adenoid cystic, epithelial–myothelial

2.1.3.1. Non- Small Cell Carcinoma

2.1.3.1.1. Squamos Cell Carcinoma(SCC)

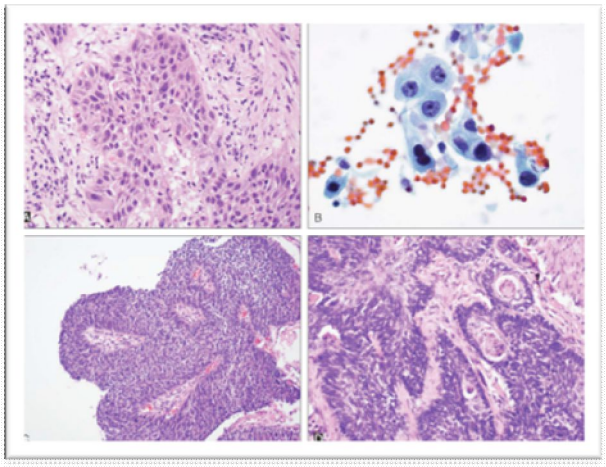


Figure 1: Pathology of small cell carcinoma

Squamous cell carcinoma (Figure 1), which tends to occur centrally and is highly associated with smoking history, is defined as a malignancy showing squamous differentiation. As such, the tumor cells classically contain intercellular bridges and form keratin,

although these features may be difficult to identify in poorly differentiated tumors. SCC varies from small endobronchial obstructive tumors to large cavitated masses that can replace an entire lung. The masses are gray-white or yellowish, often with

a dry flaky appearance that reflects the keratinization. Necrosis and hemorrhage are common; cavitation is seen in one-third of cases [36].

2.1.3.1.2. Adenocarcinoma

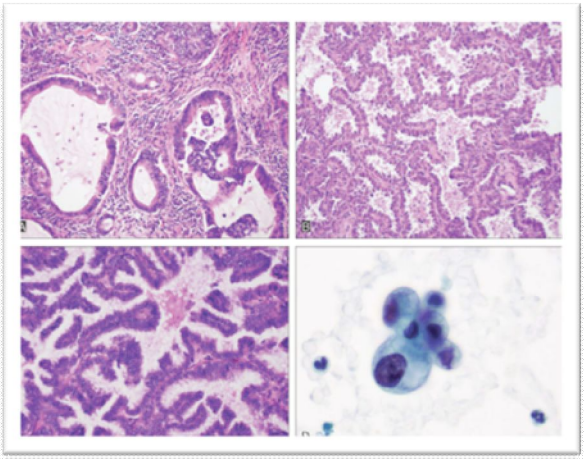


Figure 2: Pathology of adenocarcinoma

Adenocarcinomas (Figure 2) occur predominantly in smokers, although nonsmokers are more likely to develop adenocarcinoma than other lung cancer types. Adenocarcinomas tend to occur more peripherally, but can occur almost anywhere, can be multifocal or fill an entire lobe. Radio graphically they are associated with solid opacities, ground-glass opacities, or mixed patterns, generally correlating with the amount of in situ and invasive components of the tumor. Solid adenocarcinomas may be virtually indistinguishable [37].

2.1.3.1.3. Broncho alveolar Carcinoma

Bronchoalveolar carcinoma (BAC), also called alveolar cell carcinoma or bronchoalveolar tumor, is a subset of pulmonary adenocarcinoma in which cylindrical tumor cells grow upon the walls of preexisting alveoli. BAC is classified as mucinous, nonmucinous (most common), or mixed [38].

2.1.3.1.4. Large Cell Carcinoma

Large cell carcinoma, also called large cell anaplastic carcinoma and large cell undifferentiated carcinoma, is defined as a malignant epithelial tumor with large nuclei, prominent nucleoli, and usually well-defined cell borders without the characteristic features of SCC, small cell, or adenocarcinoma. (Figure 3) [39].

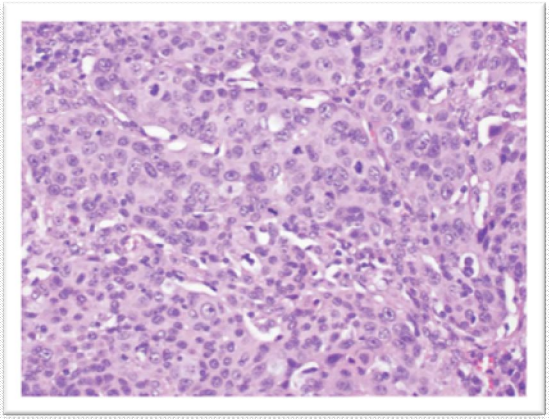


Figure 3: Pathology of large cell carcinoma

2.1.3.2. Small Cell Lung Cancer

Small cell carcinoma is a poorly differentiated neuroendocrine tumor that tends to occur centrally and is highly associated with smoking. Incidence rates of small cell carcinoma are higher among men than women but a higher percentage of lung cancers are of small cell origin among women than men [40]. Small cell carcinoma consists of smaller but obviously malignant cells with little cytoplasm, characteristic finely granular ("salt and pepper") chromatin without prominent nucleoli, and greater than 10 mitoses per 2 mm^2 (Figure 4). The cells are defined as "small," meaning fewer than 21 mm in diameter [41].

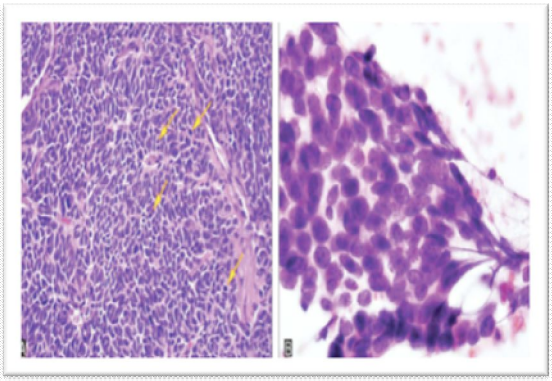


Figure 4: Pathology of small cell lung cancer

2.1.4. Clinical Presentation

Only 5-10 % of lung cancer patients are asymptomatic at the time of diagnosis [42]. Symptoms, signs, and laboratory test abnormalities relating to lung cancer can be classified as those caused directly by the primary lesion, those related to intra-thoracic spread or to distant metastasis, and those related to paraneoplastic syndromes.

Cough, dyspnea, and chest discomfort are the most common presenting symptoms in lung cancer (Table 9) [43].

Table 9: Lung Cancer Common Symptoms and Signs

Symptoms and Signs	Range of Frequency (%)
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–35
Bone pain	6–25
Clubbing	0–20
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing and stridor	0–2

Cough may be due to airway obstruction, post obstructive pneumonia, excessive mucus production, parenchymal metastases, or pleural effusion and can

lead to significant functional debility and impairment of quality of life. Many patients have a chronic ‘‘smokers cough’’ leading them to ignore the gradual change brought on by a developing lung tumor [44].

Hemoptysis due to a friable endobronchial tumor frequently results in the production of blood-streaked sputum [45].

Dyspnea occurs in most patients with lung cancer during the course of their disease due to a wide variety of causes, including direct impingement of the airway, underlying chronic lung disease, radiation- or chemotherapy-induced pneumonitis, infection, pleural effusion, or pulmonary embolism [46].

Superior vena cava (SVC) syndrome is characterized by cough, dyspnea, and facial, neck, and upper extremity edema and venous distention. It is usually due to obstruction of the SVC by massive right para-tracheal lymphadenopathy or by direct extension of a primary right upper lobe tumor into the mediastinum [47].

The commonest sites of hematogenous metastases are contralateral lung, brain, liver, bone, adrenal gland, and extrathoracic lymph nodes. However, lung cancer can spread to any site in the body, including skin, soft tissues, pancreas, bowel, ovary, and thyroid.

Lung cancer is the most common cause of brain metastases. The symptoms of brain metastases vary depending on the location of the lesion and the degree of associated edema or hemorrhage and include headache, nausea, vomiting, focal weakness, seizures, confusion, ataxia, and visual disturbances. Leptomeningeal carcinomatosis may present as headache and cranial nerve palsies without structural abnormalities on brain imaging (Table 10) [48].

Although lung cancer can metastasize to any bone, the axial skeleton and

proximal long bones are most commonly involved. Pain due to bone metastases is present in up to 25% of patients at initial diagnosis. Radiation can relieve pain in 60–70% of patients with symptomatic bone metastases. Zoledronic acid, bisphosphonate, can significantly decrease the incidence of skeletal-related adverse events in lung cancer patients with bone metastases [49].

Constitutional symptoms, such as depression, fatigue, anxiety, insomnia, anorexia, and cachexia, cause significant debility in patients with lung cancer. Depression and psychological distress are very common, but are infrequently recognized and treated [50].

Paraneoplastic syndromes are effects of cancer that occur systemically or at sites distant from tumor and, as such, are not related to direct anatomic involvement by tumor. They are usually caused by either an aberrant autoimmune response to tumor antigens or an ectopic cytokine or hormone production by tumor cells. Although many of the symptoms of NSCLC and SCLC are attributable to mass effect and direct impingement upon vital organs, less commonly individuals with lung cancer present with symptoms related to hypercalcemia [51], hyponatremia [52], Cushing's syndrome [53], Lambert-Eaton syndrome, and other neurologic disorders.

Table 10: Lung cancer symptoms according to tumor invasion [48]

Primary tumor	Intrathoracic spread	Extrathoracic spread
Cough	Chest wall invasion	Bone pain
Dyspnea	Oesophageal symptoms	Confusion, personality change
Chest discomfort	Horner syndrome	Elevated alkaline phosphate level
Haemoptysis	Pleural effusion	Focal neurological defects
	Laryngeal nerve paralysis	Headache
	Superior vena cava syndrome	Nausea, vomiting

2.1.5. Diagnosis

2.1.5.1. Non-Invasive procedures

Sputum cytology; remains a simple test with a positive predictive value that can approach100%, but it has a sensitivity rate of only 10% to15% [54,55,56]. The highest yield occurs in patients with large centrally located tumors.

Chest Radiography; posterior-anterior and lateral chest radiographs remain the simplest method for identifying patients with lung cancer. A standard chest radiograph can detect a lesion a small as 3 mm in diameter; however, unsuspected nodules generally are not seen until more than 5 mm in diameter. Associated atelectasis, postobstructive pneumonitis, abscess, bronchiolitis, pleural reaction, rib erosion, pleural effusion, or bulky mediastinal lymphadenopathy may be identified on radiographs, raising suspicions of a primary lung malignancy. Plain chest radiography has a low predictive value in the determination of mediastinal nodal metastases; the sensitivity is approximately 60% [57].

Computed Tomography; As a single comprehensive study, CT remains the most effective noninvasive technique for evaluating suspected or known lung cancer and the mediastinum, which may contain associated metastatic disease. Unfortunately, the accuracy of CT scanning in identifying metastatic disease in mediastinal lymph nodes is highly variable, with sensitivity ranging from 51% to 95% [58]

Magnetic Resonance Imaging (MRI); MRI is not used for the routine evaluation of patients with lung cancer; however, it does have specific advantages over CT. Because of the heightened ability of MRI to discern neurologic and vascular structures, tumors that reside in close proximity to neurovascular structures may be more accurately assessed. MRI is most useful in evaluating

patients with superior sulcus tumors.

Position Emission Tomography Scanning; Over the last several years, PET scanning with 2- [18F] fluoro-2-deoxy-D-glucose (FDG-PET) has been increasingly used in the diagnosis and staging of lung cancer. This test identifies areas of increased glucose metabolism, which is a common trait in pulmonary tumors.

A recent analysis of over 55 original works evaluating the diagnostic and staging effectiveness of FDG-PET was performed. PET scanning was found to be very sensitive (96%), less specific (78%), and to have equal negative and positive predictive ability (90%) at discriminating between malignant and benign pulmonary lesions. Inversely, FDG-PET staging of the mediastinum was very specific (96%) but less sensitive (83%), and its negative predictive value was very high (96%) [59].

Laboratory markers; several tumor markers (Carcino-embryonic antigen; neuron specific enolase) have been evaluated in the workup of lung cancer. However, common sense is that they are not useful in finding the diagnosis but are of some importance in follow-up and prognosis [60,61]

2.1.5.2. Invasive procedures

Bronchoscopy; essential and standard technique for the evaluation of patients with pulmonary neoplasms; it remains he most important procedure for determining the endobronchial extent of disease. For lesions that are visible by endoscopy, an accurate histological diagnosis can be achieved in over 90% of cases [62].

Fine-Needle Aspiration Biopsy; Transthoracic percutaneous fine-needle aspiration biopsy (TPNA) and Transbronchial percutaneous fine-needle aspiration

biopsy (TBNA) for diagnosis and staging of bronchogenic carcinoma has evolved in the United States since the 1970s. In the diagnosis of lung cancer by fine-needle aspiration, results showed the following: 89% sensitivity of procedure, 99% sensitivity of diagnosis, 96% specificity, 99% positive predictive value,70% negative predictive value, 91% efficiency, 0.8% false-positive interpretation, and 8% false negative rate.

Transthoracic Percutaneous Fine-Needle Aspiration Biopsy; TPNA has significantly heightened the ability to diagnose intrathoracic pathologic processes. With fluoroscopic or CT guidance, tissue samples can be obtained from poorly accessible sites in the lung, mediastinum, abdomen, and retroperitoneum. The procedure is performed under local anesthesia using a 22 gauge Chiba needle attached to a stopcock and syringe. TPNA has been shown to be over 90% effective in establishing a final diagnosis [63].

Transbronchial Fine-Needle Aspiration Biopsy; It has been used most commonly to sample endobronchial and peripheral lesions and significantly improves the diagnostic yield when coupled with standard diagnostic measures (washings, brushings, and biopsies) [64]. Sensitivity rates were 85.5% and 52.7% for the 19 and 22 gauge needles, respectively [65]

Mediastinoscopy; In 1954, Harken and colleagues introduced the use of the Jackson laryngoscope to explore the mediastinum through a supraclavicular incision. Currently, it is the best method for invasive evaluation of the middle mediastinum to include the peritracheal and subcarinal lymph nodes. In a very complete study by Inculet and colleagues of over 350 patients studied prospectively by mediastinoscopy and compared with patients evaluated by CT scan, mediastinoscopy was found to have a sensitivity rate of 67%, which is comparable with that of CT [66]

Mediastinotomy; Anterior mediastinotomy permits direct visual access of the anterior mediastinum through the second, third, or fourth anterior inter space, with or without removal of a short portion of the adjacent cartilage [67]. For right-sided lesions, the procedure provides access to the proximal pulmonary artery and superior vena cava. The procedure is used on the left side to evaluate disease in the sub-aortic and lateral aortic regions.

Thoracoscopy; Thoracoscopy permits visualization of the entire visceral, parietal, and mediastinal pleural surfaces. Excision or incision biopsies for establishing N and M status can be performed safely under direct vision. With the introduction of video technology and the refinement of endoscopic stapling devices, video-assisted thoracoscopy (VATS) has enabled a broader range of applications, including resectional techniques

2.1.6. Staging

SCLC is classified simply as either limited disease (disease confined to one hemothorax including the mediastinal, contralateral hilar, and ipsalateral scalene, or supravicular lymph nodes) or extensive disease (disease extending beyond the confines of limited disease) [68]

NSCLC is treated according to stage, and the results of treatment are stage dependent. The TNM system is used for staging based on the evaluation of three factors: tumor (T), lymph nodes (N), and metastases (M). T, N and M elements are further sub-classified as stage I to IV. (Table 11) (69)

Table 11: TNM Staging of Lung Cancer [69]

PRIMARY TUMOR (T)		**TNM STAGING**	
TO	No evidence of primary tumor	IA	T1N0M0
Tis	Carcinoma in situ	IB	T2N0M0
T1	Tumor <3 cm and not involving the mainstem bronchus	IIA	T1N1M0
T2	Tumor is: >3 cm, involving mainstem bronchus >2 cm from the carina, invading visceral pleura, or associated with lobar atelectasis or obstructive pneumonitis	IIIB	T2N1M0 T3N0M0
T3	Direct invasion of chest wall, diaphragm, mediastinal pleura, pericardium, mainstem bronchus <2 cm from carina, or associated with atelectasis or obstructive pneumonitis of entire lung	IIIA	T3N1M0
T4	Direct invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebrae, carina, or associated with malignant effusion or satellite nodules in the same lobe		T1N2M0 T2N2M0
REGIONAL LYMPH NODES (N)			T3N2M0
NO	No regional nodal metastasis	IIIB	T4N0M0
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, or intrapulmonary nodes involved by direct primary tumor extension		T4N1M0 T4N2M0
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes		T1N3M0
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes		T2N3M0 T3N3M0
DISTANT METASTASIS (M)			T4N3M0
MO	No distant metastasis	IV	Any T Any N Ml
Ml	Distant metastasis present or metastatic nodules in non-primary tumor lobe(s)		

2.1.7. Treatment

A cornerstone of treatment of patients with extensive stage SCLC is multiagent chemotherapy. The first highly effective regimen to be established as a standard for small cell lung cancer patients was cyclophosphamide, adriamycin and vincristine (CAV). Multiple effective chemotherapy regimens now exist for the treatment of SCLC. Patients who present with extensive disease (incliding vrain metastases), cranial radiation and high- dose dexamethasone should be given [70].

In limited stage disease, combined modality therapy with chemotherapy and radiation therapy to the chest is superior to either treatment used alone [71].

Surgical resection is the treatment of choice for patients with stage IA disease. Patients with satisfactory pulmonary reserve should undergo a lobectomy. If pulmonary function is limited or there are other co-morbidities, a segmental or wedge resection can be done to preserve postoperative pulmonary function. Older studies suggest that the local recurrance rate for segmental or wedge resection is 10% to 20% higher than that for lobectomy. For patients with stage one non small cell lung cancer who are medically inoperable, two prospective studies have reported five-year rates of 10%and 27% for primary thoracic radiation, consisting of 6000 cGy. Although the tumors are larger in stage IB than in stage IA and may involve the visceral pleura, surgery is notheless the mainstay of treatment [72].

Stage I patients are very important target for smoking cessation and chemoprevention efforts, since second primary tumors or complications of smoking are a major cause of morbidity and mortality in this group. The long-term survival rate for this group of patients is in the 60% to 70% range [73].

Surgery is the treatment of choice for patients with stage IIa NSCLC. These

patients may have a limited (N1) lymph node involvement at the time of surgery. For patients with hilar or intrapulmonary lymph node involvement at surgery, the appropriate postoperative adjuvant therapy continues to be controversial [74].

Tumors involving the chest wall or the superior sulcus (T3 N0) often require a combination of radiation chemotherapy in conjunction with aggressive surgery. Larger, but resectable, tumors involving the hilar lymph nodes (T2 N1) often require a complete pneumonectomy or, alternatively, a complex bronchial resection and anastomosis (sleeve resection) to save a portion of life [75].

Stage III lung cancer comprises a wide spectrum of disease presentations. Some patients who have a peripheral tumor and no mediastinal adenopathy on chest computed tomography scan are nevertheless found to have a low volume of mediastinal lymph node involvement with no extracapsular spread. The long term survival rate for this group of patients following complete resection ranges from 18 % to 30% with surgery alone in single institution series. The use of preoperative (neoadjuvant) chemotherapy with or without current radiation therapy can produce long term survival in some patients with stage IIIA disease. Combined- modility therapy utilizing neoadjuvant chemotherapy, radiation therapy, and surgery appears to be a worthwhile strategy in some patients with adequate performance status in stage IIIA NSCLC [76].

Owing the invasion of the mediastinum, hearth, or other structures, T4 NSCLC is unresectable. He outcome for most patients with stage IIIB NSCLC is similar to that of patients with stage IV disease [77].

Stage IV non-small cell lung cancer (NSCLC) denotes the presence of metastatic disease and is largely incurable using present-day therapies. For more patients under age 75 years with good performance status, the best first approach is double-agent chemotherapy utilizing carboplatin plus a second agent, usually

paclitaxel, gemcitabine, or docetaksel. Benefits are usually within the the first six or eight weeks.In contrast, single agent can be given weekly or twice monthly with less toxicity [78] (Table 12).

Patients who have an ECOG performance status of 0 or 1 seem to benefit more than patients with performance status 2 from the combination of a platinum agent, either cisplatin or carboplatin, and a second agent [79].

Table 12: Stage IV NSCLC Common Treatment [78]

Regimen	Dose	Common Side Effects
Docetaxel	75 mg / m^2	nausea and vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy
Cisplatin	75 mg / m^2	
Cisplatin	100 mg/ m2 iv	nausea and vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, hydration
Gemcitabine	1,000 mg/ m2 iv	
Paclitaxel	225 mg m2 iv	neutropenia, myelopsuppresion, hyperensitivity, sensory neuropathy, nausea and vomiting
Carboplatin	AUC 6 iv	
Cisplatin	60-100 mg /m2 iv	cytotoxicity, nausea and vomiting, peripheral neuropathy
Etopozide	0-120 mg/ m2 iv	

2.2. QUALITY OF LIFE

2.2.1. Definition of Quality of Life

The assessment of a patient of cancer broadly includes two sets of endpoints cancer outcomes and patient outcomes. Cancer outcomes measure the response of a patient to treatment, duration of response, symptom free period, and early recognition of relapse. Patient outcomes, on the other hand, assess the survival benefit attained after treatment as measured by the increase in life span, and the QOL before and after therapy.

Unfortunately, physicians tend to concentrate on the cancer-related outcomes only. Consequently, assessment of QOL remains a neglected area.

Quality of life is a broad, subjective, and multidimensional concept that includes:

- Physical health and symptoms.
- Functional status and activities of daily living
- Mental well being and social health, including social role functioning [80]

Quality of life can also be simply defined as the effect of an illness and its therapy upon a patient's physical, psychological, and social well being as perceived by the patient himself [81]. However, being a highly subjective variable, there can be no universal consensus over this definition. The intra- and inter-observer variation can be large, and more importantly, may even vary at different points of time. Since it is impossible to define any universally agreed standard for comparison, the subject and observer usually have different perceptions of the same outcome.

Furthermore, significant subjective variability may exist within the same patient regarding his problems. For example, he may endure pain for a short while without

compromising his daily activities, but over an extended period, this pain may dominate his life and cause significant impairment of various activities [80].

Over the past few years, increasing attention is being paid to the evaluation of QOL in various diseases, including lung cancer. Numerous instruments have been developed, mainly in the form of questionnaires, which were subsequently validated in different settings and translated in several languages. However, other techniques, such as personal or telephone interviews, may also be used for this purpose.

Measuring QOL is especially useful in phase-III trials since it allows the investigator to make, in most cases, definite conclusions regarding the efficacy of a particular therapeutic regimen. Quality of life assessments should be given due priority whenever it is expected that the survival differences between the treatment groups is going to be small (a frequent occurrence), or when the difference in at least one factor predicting QOL is expected to be large. The effect of two different therapeutic modalities on QOL and overall survival helps select the better modality. In fact, a particular treatment may be preferred if it improves the QOL even if the survival is not superior to the other.

On the other hand, a treatment may be unsatisfactory and may be rejected if the QOL remains similar or worsens compared to another modality, without offering any survival advantage. However, two situations present a difficulty: one, if the treatment improves QOL but worsens survival, and, when QOL deteriorates but survival improves. In these situations, the choice of treatment is usually made jointly by the physician and the patient after detailed consideration of all relevant aspects[82].

2.2.2. Attributes of an ideal quality of life instrument

Any QOL questionnaire should possess the following attributes [83]:

- Reproducibility: ability to yield the same results repeatedly under the same conditions.
- Validity: accuracy with which it measures what it is supposed to measure.
- Responsiveness: ability to detect clinically significant changes over time.
- Interpretability: ability to provide results that can make sense

2.2.3. Quality of life and Lung Cancer

Quality of life is closely linked to symptom burden and severity in lung cancer. Loss of physical functioning, psychological events such as depression, and reduced overall QOL is associated with uncontrolled symptoms [84, 85]. In addition, depression has also been found to be an independent prognostic factor for lung cancer irrespective of stage [86].

Over the last decade, over 50 instruments have been developed and used to measure QOL in lung cancer. Quality of life instruments are mainly classified in the following categories: generic or disease-specific. Generic instruments are further sub classified into Health profiles and Utility measurements (Table 13) [80].

Health profiles are single instruments primarily used to measure each important facet of QOL. They have the advantage of being valid and reproducible over a wide variety of diseases, as well as being able to demonstrate change with treatment. However, they are not disease-specific and hence, may miss important aspects of QOL of the disease under evaluation. They are also lengthy and time-consuming compared to the recent site-specific questionnaires available.

Utility measurements, on the other hand, measure an individual's perception of a single symptom, e.g. dyspnea or chest pain. The commonest in use is the Visual analog scale (VAS). Visual analog scale eliminates the restrictions imposed by fixed responses (better/worse, or yes/no), and allows a flexible response in a continuum, thereby allowing finer descriptions and assessments of any subjective state. Visual analog scale has been extensively used in QOL studies, mostly to quantify dyspnea, and has been found to be a reliable and reproducible tool [87, 88].

Disease-specific questionnaires are those that incorporate questions relevant to a particular disease. The commonly used specific QOL instruments for lung cancer are the Functional Assessment of Cancer Therapy-Lung (FACT-L), Lung Cancer Symptom Scale (LCSS), and the EORTC-QLQ-LC 13.

Table 13: Classification of QOL instruments [80]

Generic		**Disease specific**
Health profiles	**Utility measurements**	
Nottingham	Visual analog scale (VAS)	
Health profile (38)		Functional living index-cancer (22)
Short form-36		EORTC QOL-30 (30)
Health survey		Daily dairy card (22)
Sickness impact profile (136)		Functional assessment of cancer therapy – lung (41)
		Lung cancer symptom scale (15)
		EORTC QOL LC-13

2.2.4. European organization for the treatment and research of cancer quality of life questionnaire (EORTC QLQ-C30) and EORTC QLQ LC 13

In order to overcome the shortcomings of the QOL instruments existing at the time, the EORTC initiated a large-scale multinational program in 1986 to try and develop a comprehensive questionnaire that covers all areas of QOL assessment. This program included 305 patients across 13 countries. The outcome was a 30-item questionnaire, which included five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, nausea, and vomiting), and one global health and QOL scales. This instrument was tested in the USA, Australia, Europe, and Japan and demonstrated a high reliability and validity across the continents [89].

The EORTC QLQ-LC 13 questionnaire was developed in 1994 as a lung cancer specific supplementary to the EORTC QLQ-C30. This is a 13-item instrument that assesses lung cancer related symptoms [cough and haemoptysis (one item each), dyspnea (three items)], treatment related side-effects [sore mouth or tongue, dysphagia, hair loss, tingling hands, and feet (one item each)], pain (three items), and pain medication (one item). All items are rated on a 4-point Likert scale and 7-point numerical analog scale with a reporting time frame of 1 week. Extensive field studies demonstrated significant changes in symptom and treatment toxicity subscale scores over time, with symptoms improving and treatment related side effects increasing during chemotherapy [90].

Thus, it was found to be a clinically valid and useful tool to assess disease and treatment-specific symptoms in lung cancer patients. The EORTC-QLQ C30 and EORTC-QLQ LC-13 are often used together in order to obtain a comprehensive evaluation of QOL in lung cancer. Over the last decade, it has been translated into 17 other languages and is now the most widely used QOL questionnaire in cancer patients.

2.2.5. Performance status and quality of life

Performance status has been frequently used as a proxy of QOL since the 1970s. It is an important prognostic factor and predictor of survival of lung cancer patients [86]. There is good correlation between PS and global QOL, including psychological, physical, and symptomatic well-being. Performance status also correlates well with the number and severity of symptoms. The most well established markers of PS are the Karnofsky Performance Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG). Karnofsky Performance Scale is a simple and widely used numerical instrument for rapidly quantifying the PS of an individual based on his level of independence [91]. This scale rates the PS of a patient in multiples of 10, from 0 (worst) to 100 (best) depending on the ability to perform his activities. Various studies have demonstrated a direct relationship between KPS and the perceived QOL in patients with cancer, including lung cancer [86]. In a study of 57 disease free survivors of lung cancer, KPS was found to be the best predictor of QOL [92]. However, another study that evaluated 139 patients of lung cancer receiving palliative treatment, KPS was found to be only weakly associated with the QOL as measured by EORTC QLQ C30 [93].

Similar results have been observed in studies that used the ECOG Scale. This scale is a five-grade observer rating of patients' physical ability ranging from 0 (normal) to 4 (disabled) [94]. Buccheri and Ferrigno performed a validation study using ECOG and KPS on a large sample of 471 patients and concluded that both instruments are valid, however, the ECOG was found to be slightly superior [95]. Aaronson et al. used the ECOG and EORTC QLQ-C30 to evaluate QOL in 354 patients with lung cancer undergoing chemotherapy or radiotherapy [86]. They found a strong correlation between the PS (assessed by ECOG scale) and physical, role, cognitive functioning, and overall QOL (assessed by EORTC QLQ-C30). These results suggest that measurement of PS by either KPS or ECOG may serve as a useful and simple surrogate marker of QOL.

3. MATERIALS & METHODS

3.1. Setting and Sample

The study was conducted at the outpatient and inpatient Oncology Clinics of the Lutfi Kirdar Teaching and Research Hospital in Istanbul, Turkey. The hospital is a 750-bed facility located in the Anatolian part of Istanbul. Because of its location, it usually serves people who come from neighboring cities such as Bursa, Adapazari and Izmit.

Selection criteria required for patients were:

- Diagnosed with metastatic [stage IV] lung cancer
- Within 2 weeks of diagnosis
- Have not yet received treatment
- No mortality until after the third chemotherapy

All participants were Turkish-speaking, conscious, and fully informed of their cancer diagnosis.

After obtaining verbal consent, patients filled in QOL questionnaires at four different points:

- At the baseline (prior to the first course of chemotherapy)
- The first day of the second chemotherapy
- The first day of the third chemotherapy
- The first day of the fourth chemotherapy

Patients were not able to complete the questionnaire by themselves while they were receiving chemotherapy. The researcher asked each question one at a

time. Patient's gender, age, performance status (ECOG, Karnofsky), and smoking rate were also recorded. Structured interviews, each of which lasted 30 to 90 minutes, were conducted from the questionnaire. Interviews were conducted in outpatient clinics or by telephone.

Seventeen patients fulfilled these criteria and were asked to participate in this study. Four patients declined participation. Five patients who gave their informed consent did not want to answer the questions before the first, second, third, or fourth chemotherapy treatment. Two patients died during the course of the study.

3.2. Instruments

The questionnaires completed by patients were the EORTC core questionnaire QLQ- C30 (version 3.0) and the lung cancer module QLQ-LC13. The questionnaire is cancer specific, multidimensional, can be used in different cultures, and is translated to several languages, including Turkish [85].

This questionnaire is composed of 30 questions organized into five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global health status (GHS)/ QOL scale, and a number of single items assessing additional symptoms (dyspnea, sleep disturbance, constipation, and diarrhea). For the assessment of respiratory symptoms, the EORTC lung cancer module (QLQ- LC13) was used. This supplemental questionnaire contains 13 questions concerning symptoms frequently present in lung cancer patients (8). For the majority of the functioning scales and symptom scales, a 4-point response scale is used, except for the physical and role functioning scales, where dichotomous response choices are employed, and for global health status/ QOL, where a 7-point scale is used. All

scores are linearly converted to a 0 to 100 scale. For the functional and global health status/QOL scales, higher scores represent a lesser degree of symptoms. For the symptom scales, higher scores represent a greater degree of symptoms. The reliability and validity of these questionnaires have been confirmed in international studies [7, 85].

The Karnofsky Performance Scale (KPS) and The Eastern Cooperative Oncology Group (ECOG) performance scales were used to assess the performance status (PS) of the patients. KPS is a simple and widely used numerical instrument for rapidly quantifying PS of an individual based on his level of independence. This scale rates the PS of a patient in multiples of 10, from 0 (worst) to 100 (best), depending on their ability to perform the activities (Table 14) [96].

Similar results have been observed in studies that used the ECOG scale. This scale has a five-grade observer rating of patients' physical ability ranging from 0 (normal) to 4 (disabled) (Table 15).

Table 14: Karnofsky performance scale

Grade	Description
100%	No symptoms.
90%	Able to carry on normal activity; minor signs or symptoms of disease.
80%	Able to carry on normal activity with effort; some signs or symptoms of disease.
70%	Cares for self, unable to carry on normal activity or do active work.
60%	Requires occasional assistance but is able to care for most of own needs.
50%	Requires considerable assistance and frequent medical care.
40%	Disabled; requires special care and assistance.
30%	Severely disabled; hospitalization indicated, although death not imminent.
20%	Very ill; hospitalization necessary; active supportive treatment required.
10%	Moribund, fatal processes progressing rapidly.
0 %	Patient expired.

Table 15: Eastern Cooperative Oncology Group (ECOG) performance status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory (can walk) and able to carry out work of a light or sedentary (sitting) nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

3.3. Statistic Analysis

Scores of EORTC- QLQ-C30 scales were linearly transformed as suggested in the EORTC- QLQ- C30 manual [97]. All the variables are expressed as mean ± standard deviation. Statistical analysis was carried out using Prism® (version 5 for Mac OS X 2009). QOL differences between the baseline, first, second and third chemotherapy were analyzed using repeated-measures one-way analysis of variance (ANOVA). Pair-wise, *post hoc* comparison was performed between the groups at the baseline, first, second, and third chemotherapy applying Tukey test. P-values less than 0.005 (95 % confidence intervals) were regarded as statistically significant.

Correlation coefficients between global health status and age/smoking habit/ECOG/KPS were calculated by using Pearson correlation analysis. A value of $p<0.05$ in a two-tailed distribution was considered statistically significant.

4. RESULTS

4.1. Demographics

The baseline characteristics of the patients included in the study are summarized in Table 16.

A total of 17 patients completed the EORTC QLQ-C30 questionnaire (Table 2) and LC13 (Table 3) module. ECOG and KPS (Table 4) were evaluated from the baseline (post-diagnosis, pre-treatment), and after the first, second and third chemotherapy.

There were some significant quality of life differences between the baseline and the fourth chemotherapy ($p<0.05$).

Table 16: Demographic and Clinical Characteristics of the Patients

Variables	N= 17 (%)	Mean
Age, yr		59.29 ± 1.73
Gender, No		
Male	14 (82.35)	
Femaie	3 (17.64)	
Histology		
Small cell	3 (17.64)	
Non-small cell	14 (82.35)	
Adenocarcinoma	11 (64.70)	
Others	3 (17.64)	
Metastatic area		
Hemotorax	9 (52.94)	
Bone	3 (17.64)	
Brain	1 (5,88)	
Liver	1 (5.88)	
Other	3 (17.64)	
Biopsy area		
Bronchoscopy	14 (82.35)	
Bronchoscopy+Transthorasic tru-cut biopsy	3 (17.64)	
Treatment		
paclitaxel+ carboplatin	6 (35.29)	
cisplatin+ etoposide	8 (47.05)	
cisplatin+ gemcitabine	2 (11.76)	
docetaxel+ cisplatin	1 (5.88)	
Smoking		
20 pack/ years	10 (58.82)	
25 pack/ years	3 (17.64)	
50 pack/ years	4 (23.52)	

Table 17: QLQ scores according to QLQ-C30 at the four assessments

EORTC QLQ-C30 (n=17)				
Areas	**Baseline**	**1st Chemotherapy**	**2nd Chemotherapy**	**3rd Chemotherapy**
Global Health Status/ QLQ	35.78 ± 3	35.29 ± 4	27.45 ± 3	23.04 ± 1
Functional scales*				
Physical functioning	53.73 ± 4	49.02 ± 3	43.14 ± 3	38.04 ± 3
Role functioning	52.94 ± 6	41.18 ± 3	38.24 ± 4	35.29 ± 3
Emotional functioning	62.25 ± 6	57.35 ± 4	50.00 ± 6	40.69 ± 6
Cognitive functions	64.71 ± 8	61.76 ± 7	45.10 ± 4	35.29 ± 5
Social functioning	44.12 ± 5	43.14 ± 3	32.35 ± 3	23.53 ± 4
Symptom scales**				
Fatigue	56.21 ± 4	55.56 ± 3	60.13 ± 3	66.67 ± 3
Nausea and vomiting	17.65 ± 6	33.33 ± 4	43.14 ± 6	47.06 ± 4
Pain	54.90 ± 6	55.88 ± 4	60.78 ± 5	68.63 ± 4
Dyspnea	56.86 ± 4	45.10 ± 4	54.90 ± 3	62.75 ± 5
Insomnia	49.02 ± 7	62.75 ± 9	78.43 ± 3	78.43 ± 3
Appetite loss	49.02 ± 8	58.82 ± 8	76.47 ± 6	88.24 ± 4
Constipation	41.18 ± 6	35.29 ± 5	39.22 ± 3	41.18 ± 4
Diarrhea	19.61 ± 5	21.57 ± 4	23.53 ± 5	27.45 ± 6
Financial difficulties	27.45 ± 6	31.37 ± 6	37.25 ± 3	39.22 ± 4

*Functional scales, score range from 0 to 100, with a higher score representing a higher level of functioning.

**Symptoms/ side effects, the scores range from 0 to 100, with higher scores denoting a higher level of symptoms and side effects.

Table 18: QLQ scores according to LC13 at the four assessments

QLQ-LC13 Areas	Baseline	1st Chemotherapy	2nd Chemotherapy	3rd Chemotherapy
Symptom scales*				
Cough	58.82 ± 5	49.02 ± 4	58.82 ± 4	60.78 ± 4
Haemoptysis	37.25 ± 7	29.41 ± 8	50.98 ± 5	50.98 ± 6
Dyspnea	52.94 ± 3	54.25 ± 3	58.17 ± 2	65.36 ± 2
Pain in chest	41.18 ± 8	39.22 ± 5	54.90 ± 6	62.75 ± 5
Pain in arm or shoulder	52.94 ± 4	43.14 ± 4	50.98 ± 4	52.94 ± 4
Pain in other parts	29.41 ± 8	35.29 ± 8	33.33 ± 9	29.41 ± 8
Sore mouth	11.76 ± 4	37.25 ± 8	49.02 ± 6	56.86 ± 5
Dysphagia	29.41 ± 7	43.14 ± 6	56.86 ± 4	62.75 ± 4
Peripheral neuropathy	43.14 ± 6	62.75 ± 4	62.75 ± 2	76.47 ± 3
Alopecia	0	49.02 ± 5	78.43 ± 3	86.27 ± 4

*The scores range from 0 to 100, with higher scores representing a higher level of symptoms and side effects

Table 19: ECOG and KFS performance scale at the four assessments.

PERFORMANCE SCALE	Baseline	1st Chemotherapy	2nd Chemotherapy	3rd Chemotherapy
ECOG*	2.05 ± 0.1	2.23 ± 0.1	2.52 ± 0.1	2.58 ± 0.1
KARNOFSKY**	60 ± 4	55.88 ± 3	50 ± 3	45.29 ± 2

* ECOG, score range from 0 to 4, with a lower score representing a higher level of performance.

** KFS, score range from 0 to 100, with a higher score representing a higher level of performance.

4.2 EORTC QLQ-C30

4.2.1. Global Health Status / QLQ

With respect to Global Health Status, there was a continuous downward trend from the baseline to the third chemotherapy. The decreases between the baseline and third chemotherapies ($p < 0.005$) and the second and third chemotherapies ($p < 0.005$) were significant ($F = 1.520$).

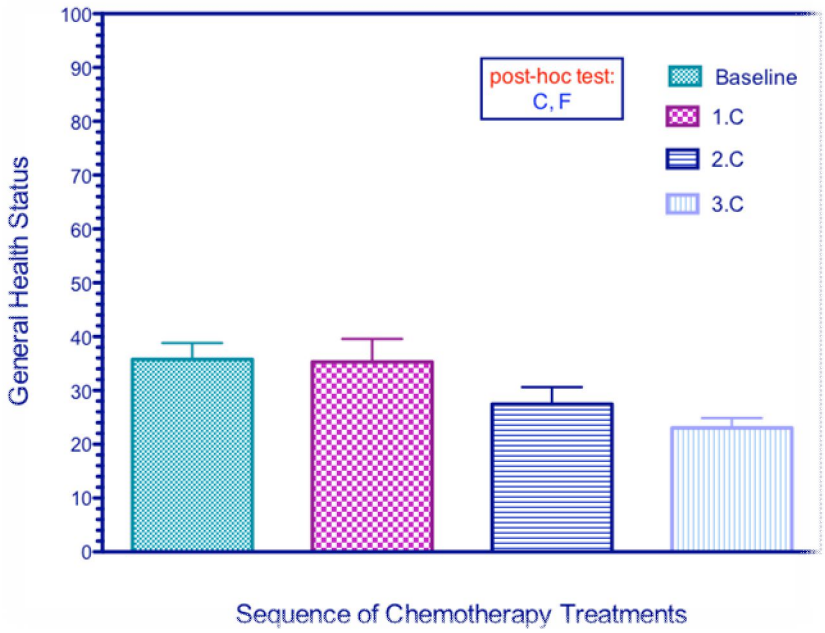


Figure 5: General health status scores at the four assessments

Post-hoc test; A: Baseline vs. 1.chemotherapy, B: Baseline vs. 2.chemotherapy, C:Baseline vs. 3.chemotherapy, D: 1.chemotherapy vs. 2.chemotherapy, E: 1.chemotherapy vs. 3.chemotherapy, F: 2.chemotherapy vs. 3.chemotherapy

4.2.2. Functional Scales

4.2.2.1. Physical Functioning

Regarding Physical Functioning, there was a significant decrease between the baseline and third chemotherapies ($p < 0.05$, $F = 3.336$)

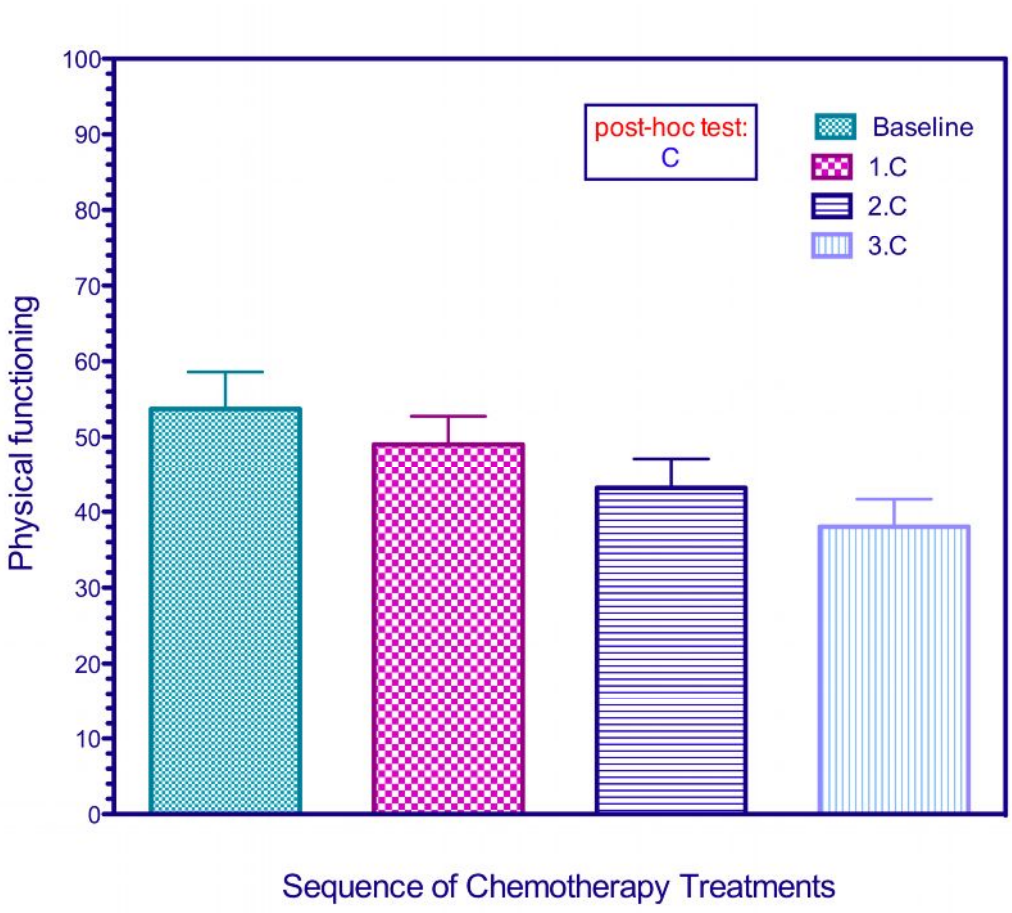


Figure 6: Physical functioning scores at the four assessments

4.2.2.2. Role Functioning

Concerning Role Functioning, there was a significant decrease between the baseline and third chemotherapies ($p < 0,05$, $F = 1.016$). In addition, as can be seen in Table 3, the differences between the three chemotherapies were not significant. ($p > 0.05$).

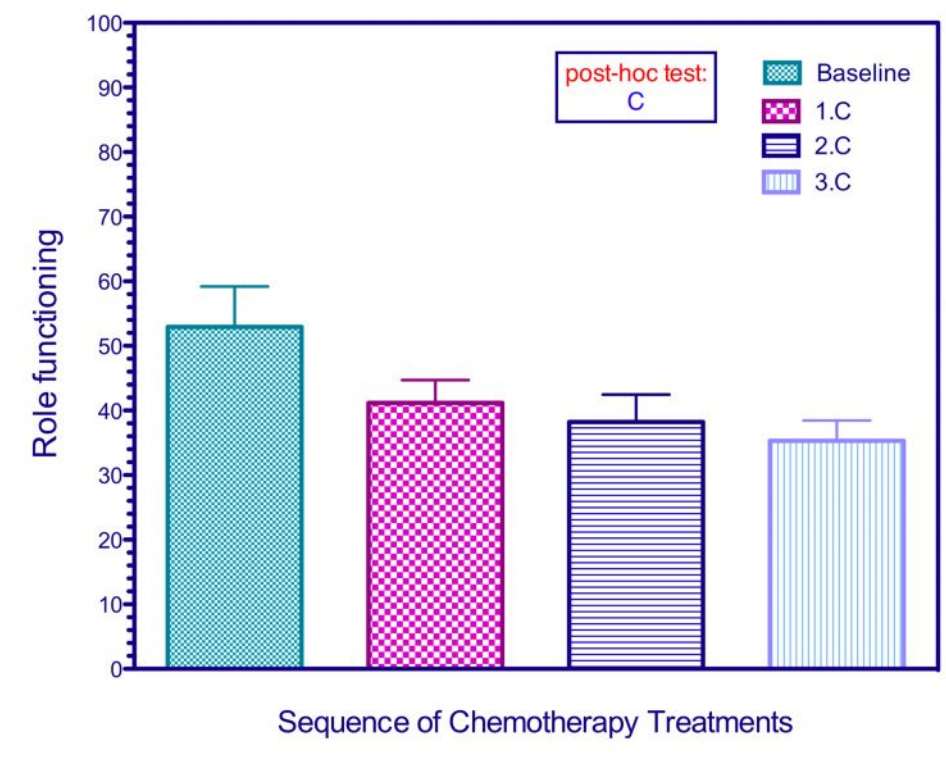


Figure 7: Role functioning scores at the four assessments

4.2.2.3. Emotional functioning

As seen in Figure 8, Emotional Functions became worse following each chemotherapy treatment. There was a significant decrease between the baseline and third chemotherapies ($p < 0.05$, $F = 3.173$).

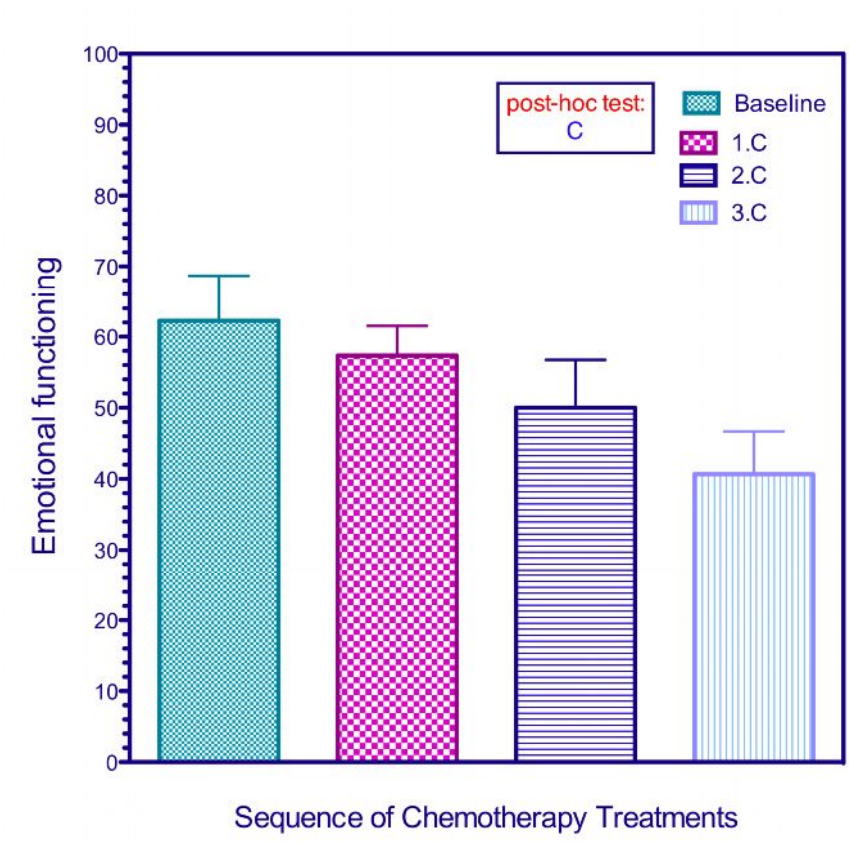


Figure 8: Emotional functioning scores at the four assessments

4.2.2.4. Cognitive Functioning

Regarding Cognitive Functioning, there was a downward trend from the baseline to the third chemotherapy. The decrease between the baseline and

second chemotherapies, the baseline and third chemotherapies, and the first and third chemotherapies ($p < 0.005$, $F = 4.152$) were significant.

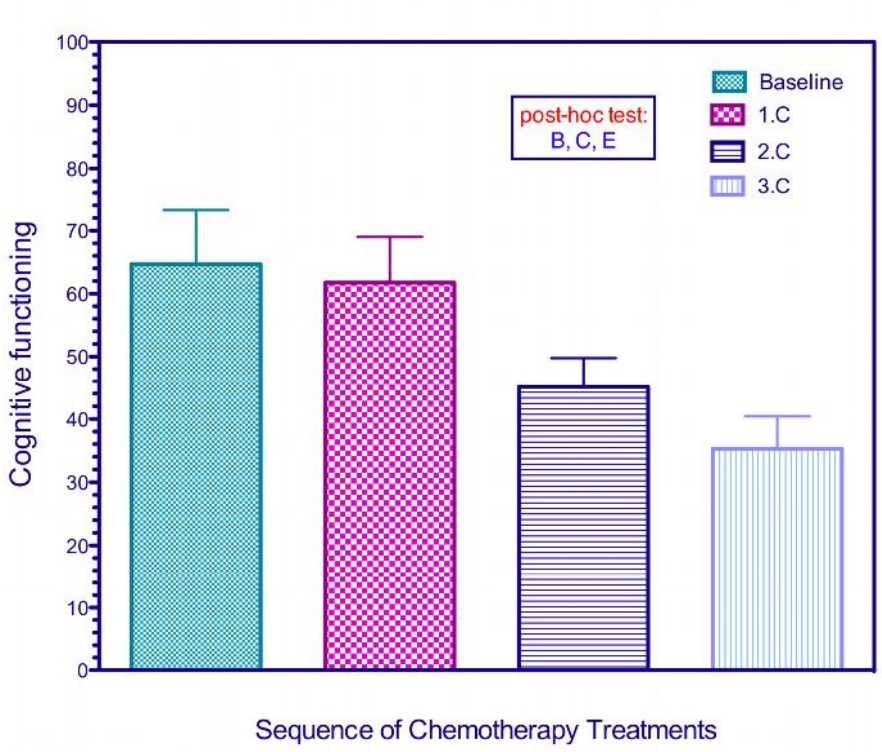


Figure 9: Cognitive functioning scores at the four assessments

4.2.2.5. Social Functioning

Concerning Social Functioning, as seen in Table 25, social functions became worse following each chemotherapy treatment. The decreases between the baseline and third chemotherapies and the first and third chemotherapies ($p<0.05$, $F=6.14$) were significant.

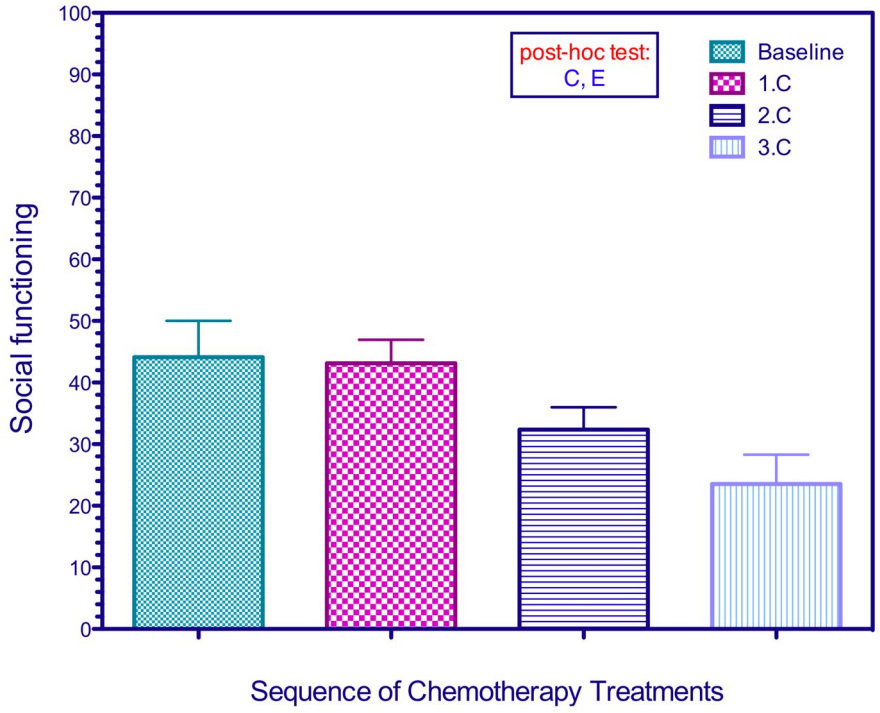


Figure 10: Social functioning scores at the four assessments

4.2.3. Symptom Scales

4.2.3.1. Fatigue

Concerning Fatigue, the baseline mean value was 56.21 ± 4 and there was not a significant difference between the baseline and third chemotherapies ($p>0.05$).

4.2.3.2. Nausea and Vomiting

Concerning Nausea and Vomiting, there was an upward trend from the baseline to the third chemotherapy as well as a significant increase identified between the baseline and second chemotherapies and the baseline and third chemotherapies. ($p < 0.05$, $F = 1.301$).

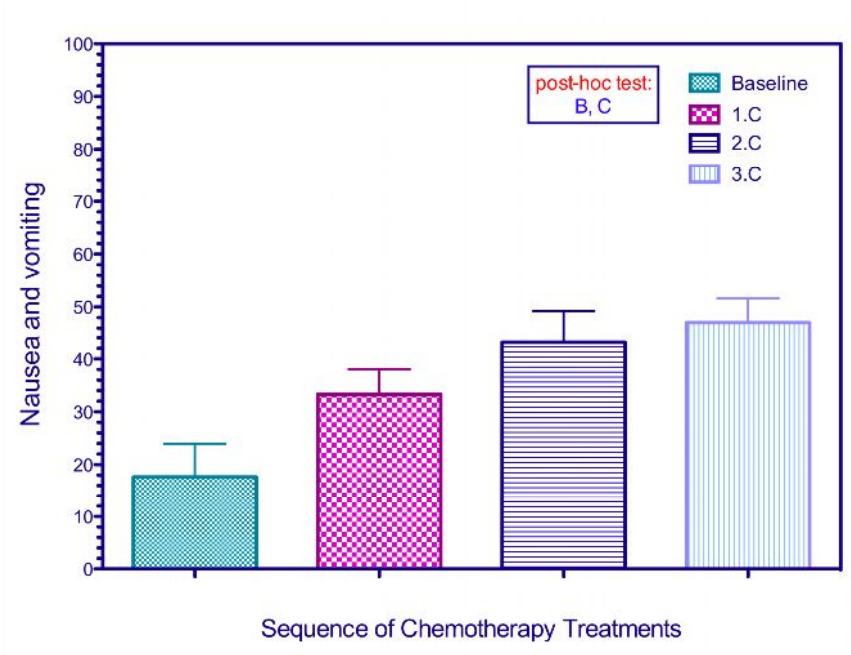


Figure 11: Nausea and vomiting scores at the four assessments

4.2.3.3. Pain

Regarding Pain, there was an increase in pain symptoms from the baseline to the third chemotherapy. The baseline value was 54.90 ± 6. This increase was not significant. ($p > 0.05$)

4.2.3.4. Dyspnea

There was an decrease in Dyspnea symptoms from the baseline to second chemotherapy, but this decrease was not significant. ($p > 0.05$) However, dyspnea symptoms increased from the first chemotherapy to the third. This increase was significant ($p < 0.023$, $F= 1.931$)

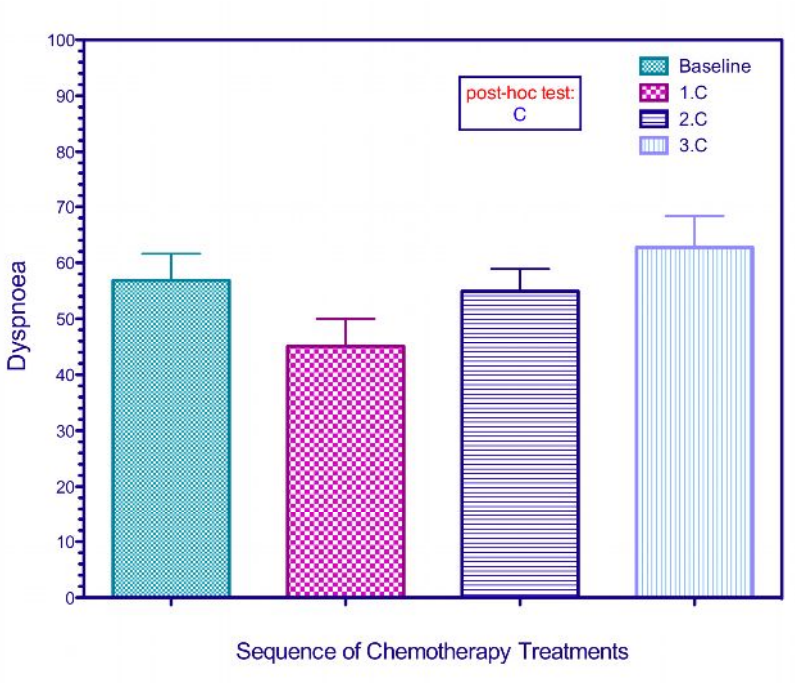


Figure 12: Dyspnea scores at the four assessments

4.2.3.5. Insomnia

Regarding Insomnia, a significant increase was identified between the baseline and second chemotherapies and the baseline and third chemotherapies ($p < 0.05$, $F= 1.523$).

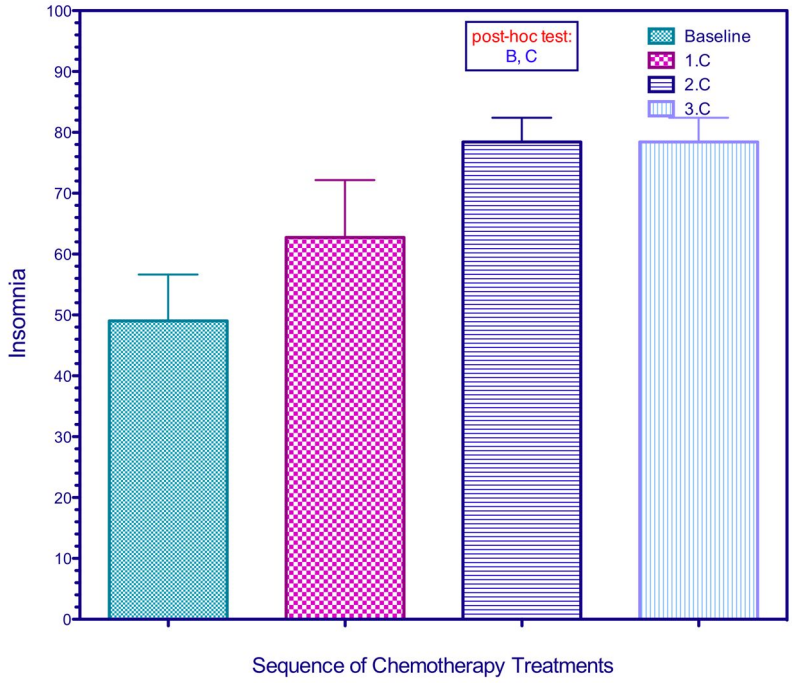


Figure 13: Insomnia scores at the four assessments

4.2.3.6. Appetite Loss

From the baseline to the third chemotherapy, there was an increase in appetite loss. Between the baseline and second chemotherapies, baseline and third chemotherapies, and first and third chemotherapies, there were significant increases ($p < 0.003$, $F = 1.668$).

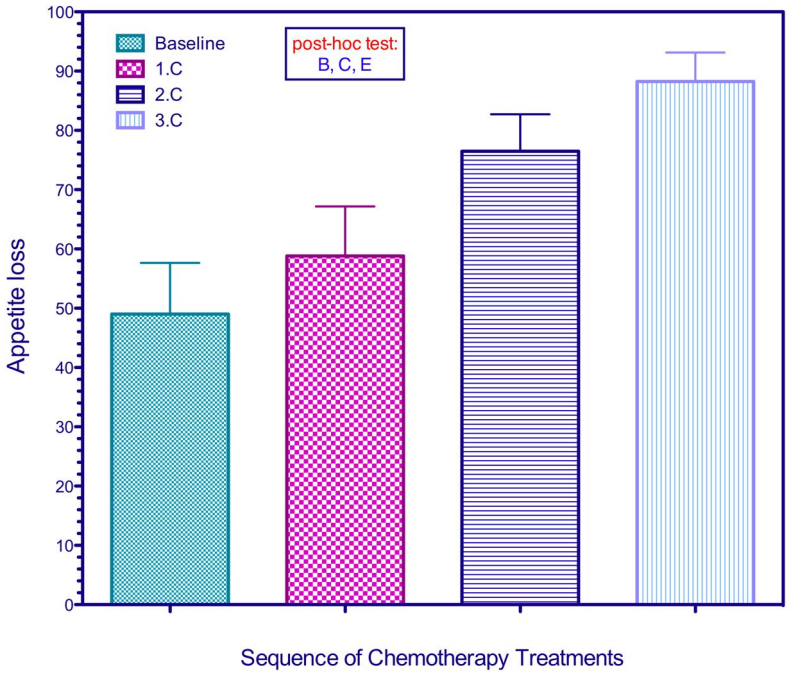


Figure 14: Appettite loss scores at the four assessments

4.2.3.7. Constipation

Regarding Constipation, the baseline mean value was 41.176 ± 6. There was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.2.3.8. Diarrhea

Regarding Diarrhea, the baseline mean-value was 19.61 ± 5. There was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.2.3.9. Financial Difficulties

Regarding Financial Difficulties, the baseline mean-value was 27.45 ± 6. There was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.3. LUNG CANCER MODULE: QLQ-LC13

4.3.1. Symptom Scales

4.3.1.1. Lung Cancer Associated Symptoms

4.3.1.1.1 Cough

The baseline mean-value was 58. 82 ± 5 and there was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.3.1.1.2. Haemoptysis

The baseline mean-value was 37.25 ± 7 and there was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.3.1.1.3. Dyspnea

There was an upward trend in dyspnea symptoms from the baseline to third chemotherapy and this increase was not significant between the baseline and third chemotherapies ($p < 0.05$, $F= 1.381$).

4.3.1.1.4. Side Specific Pain

4.3.1.1.4.1. Pain in chest

The baseline mean value was 41.18 ± 8 and there was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.3.1.1.4.2. Pain in arm or shoulder

The baseline mean-value is 52.94 ± 4 and there was not a significant change from the baseline to the third chemotherapy ($p > 0.05$).

4.3.1.1.4.3. Pain in other parts

The mean value was 29.41 ± 8 and there was not a change from the baseline to the third chemotherapy ($p > 0.05$).

4.3.1.2. Treatment-related Side Effects

4.3.1.2.1. Sore Mouth

Regarding Sore Mouth, there was an upward trend from the baseline to the third chemotherapy. The increases between the baseline and first chemotherapies, baseline and second chemotherapies, and baseline and third chemotherapies were significant ($p < 0.05$, F= 1.085).

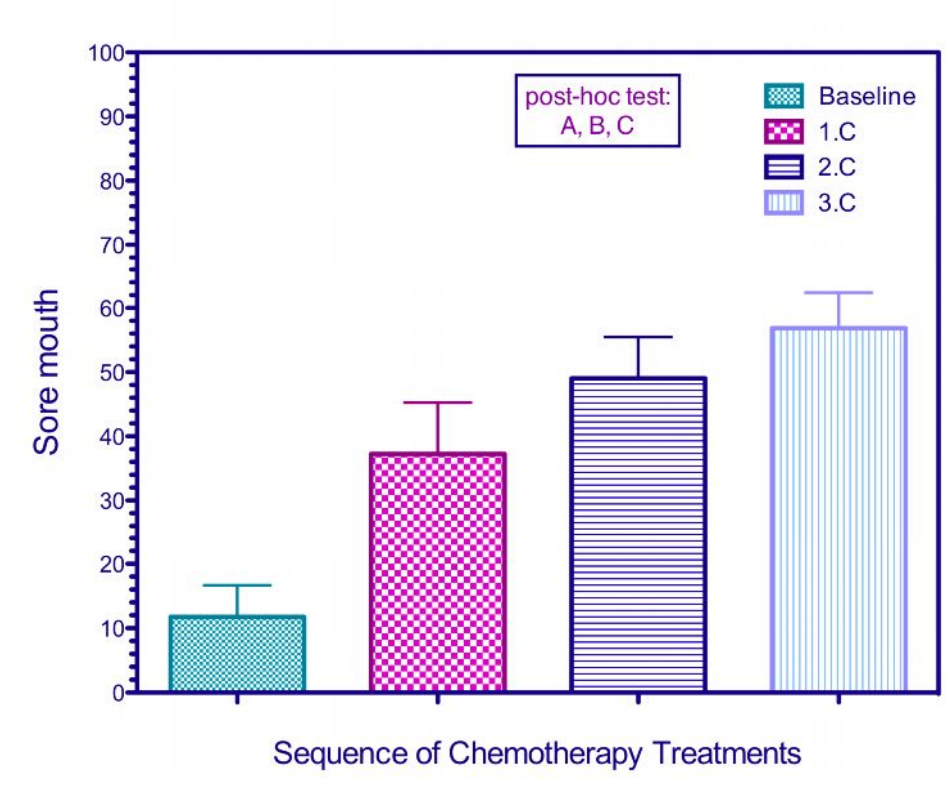


Figure 15: Sore mouth scores at the four assessments

4.3.1.2.2. Dysphagia

Concerning Dysphagia, there was an upward trend from the baseline to the third chemotherapy. The increases between the baseline and second chemotherapies and the baseline and third chemotherapies were significant ($p < 0.05$, $F= 6.559$).

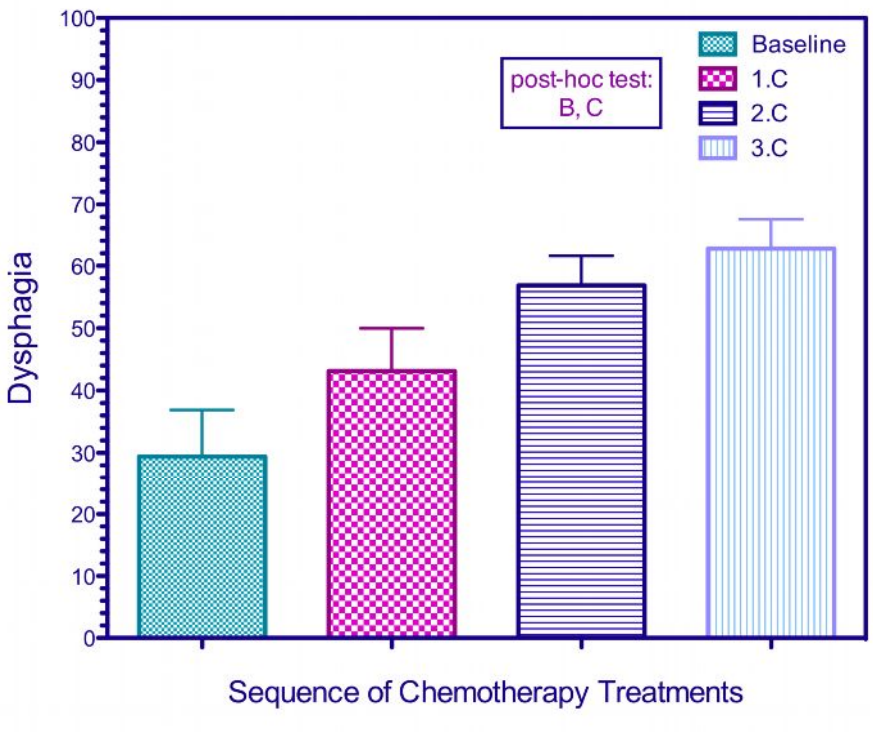


Figure 16: Dysphagia scores at the four assessments

4.3.1.2.3. Peripheral Neuropathy

The baseline mean value was 43.14 ± 6 and the third chemotherapy mean value was 76.47 ± 3. This increase was significant between the baseline and first chemotherapies, baseline and second chemotherapies, and baseline and third chemotherapies ($p < 0.05$, $F = 7.040$).

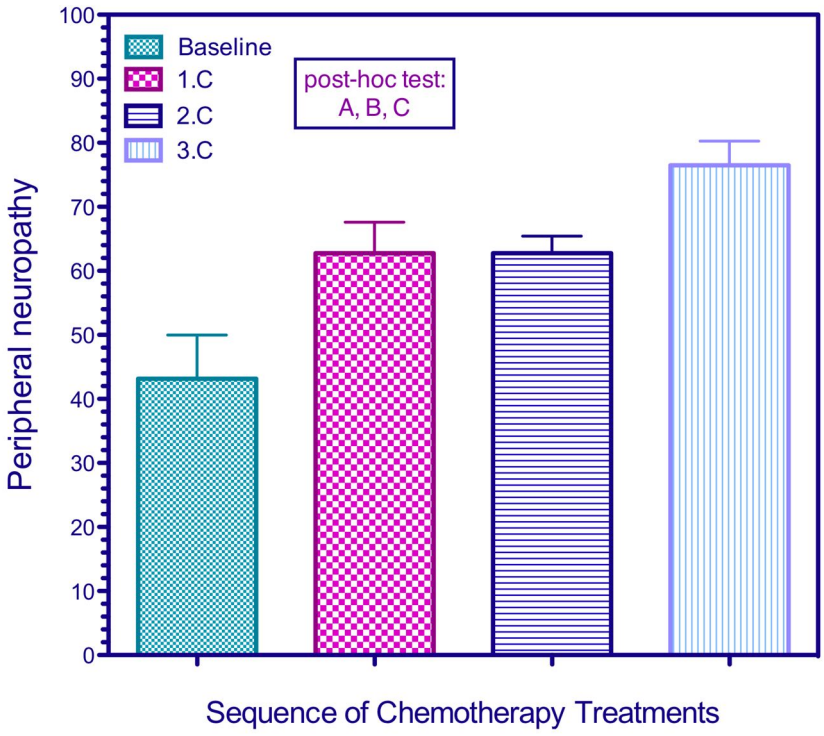


Figure 17: Peripheral neuropathy scores at the four assessments

4.3.1.2.4. Alopecia

The baseline mean value was 0 ± 0 and the third chemotherapy mean value was 86.27 ± 4. This increase was significant between the baseline and first chemotherapies, baseline and second chemotherapies, baseline and third chemotherapies, first and second chemotherapies, and the first and third chemotherapies ($p < 0.05$, $F = 0.9904$)

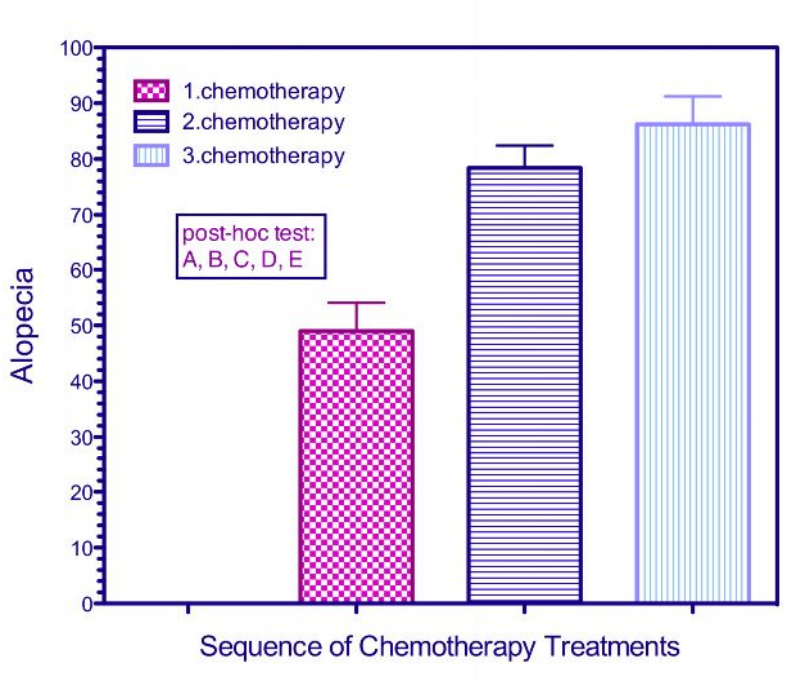


Figure 18: Alopecia scores at the four assessments

4.4 PERFORMANCE SCALES

4.4.1. ECOG PERFORMANCE SCALE

The mean ECOG performance score for the baseline was 2.05 ± 0.15 and 2.58 ± 0.11 for the third chemotherapy. There was a significant difference between the baseline and second chemotherapies and the baseline and third chemotherapies ($p < 0.05$, $F = 0.923$).

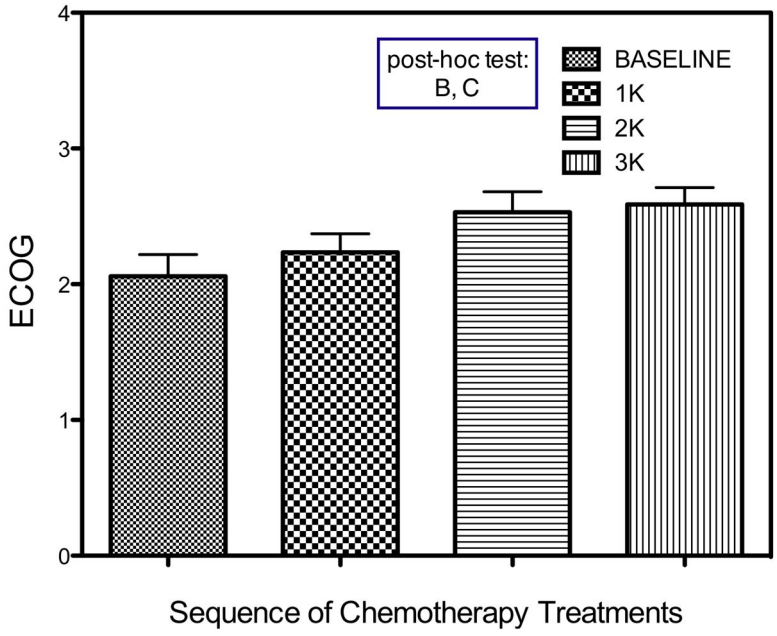


Figure 19: ECOG performance scores at the four assessments

There was a significant negative correlation between ECOG performance scale and GHS (r= - 0.71, p< 0.05).

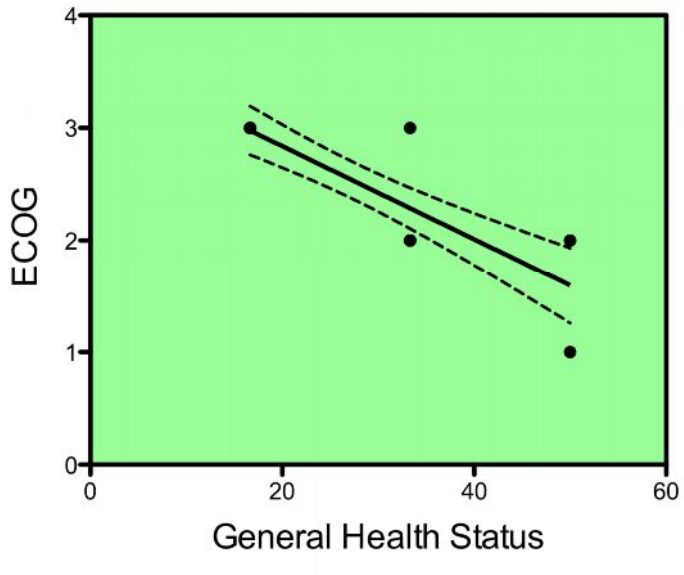


Figure 20: Correlation between ECOG performance scale and Global Health Status

4.4.2. KARNOFSKY PERFORMANCE SCALE

The mean KPS performance score for the baseline was 60.00 ± 4.11 and 45.29 ± 2.58 for the third chemotherapy. There was a significant difference between the baseline and second chemotherapies, baseline and third chemotherapies, and first and third chemotherapies ($p < 0.05$, $F = 9.507$).

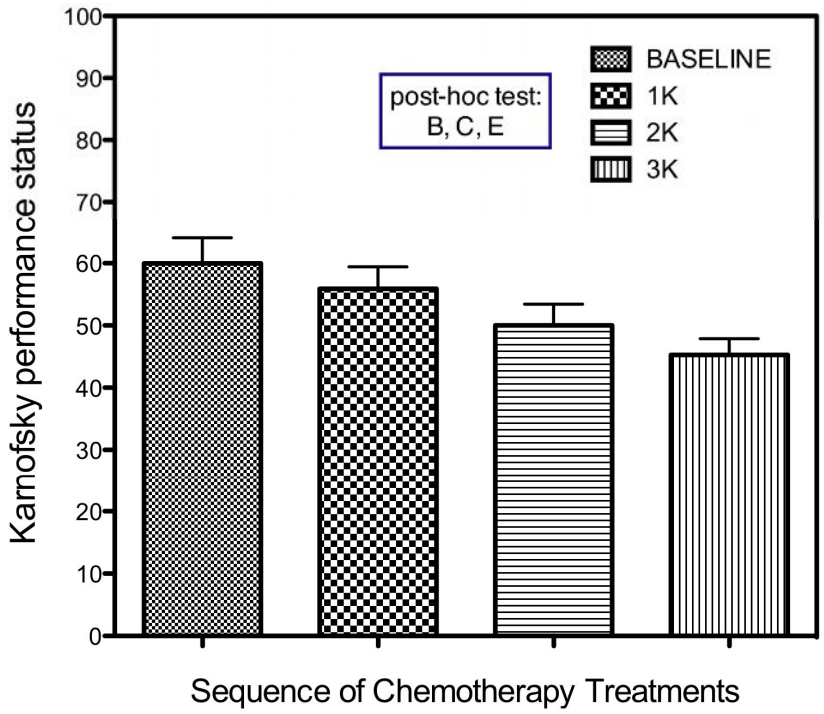


Figure 21: Karnofsky performance scores at the four assessments

There was a significant positive correlation between KFS performance scale and GHS ($r = 0.74$, $p < 0.05$).

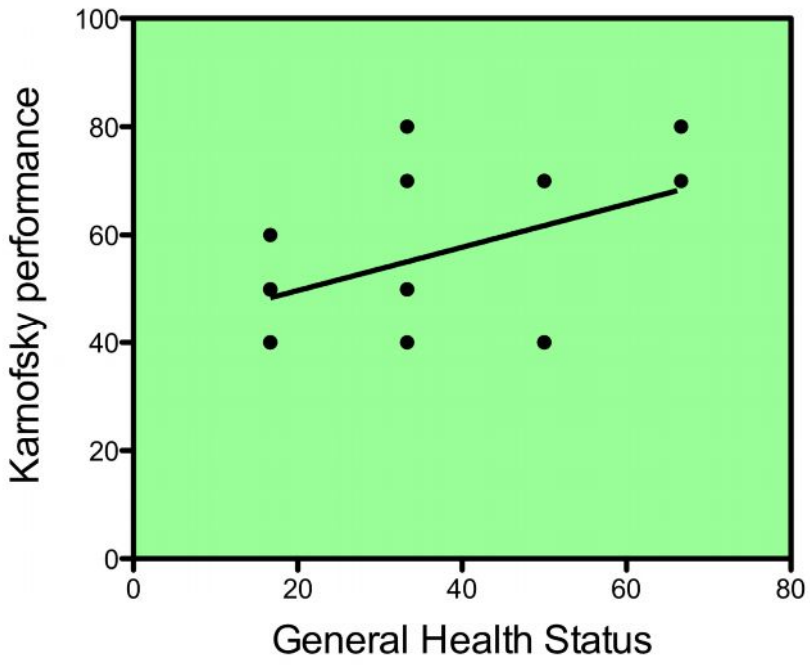


Figure 22: Correlation between Karnofsky performance scale and Global Health Status

4.5. AGE & GENERAL HEALTH STATUS

The mean age was 59.29 ± 1.73 and there was not a significant correlation between age and GHS ($p > 0.05$).

5. DISCUSSION

Advanced lung cancer has a grave prognosis; data from recent randomized clinical trials indicate that patients with metastatic disease still survive only a median of 8 to 10 months with modern combination therapy, showing that the status of modest improvement in survival with chemotherapy has still not changed [98].

On the other hand, there is sufficient evidence to suggest that initial QOL is a strong prognostic factor for survival in lung cancer. Ganz et al. demonstrated the predictive value of QOL [assessed by Functional Living Index-Cancer (FLI-C)] for survival in 40 patients receiving either chemotherapy or radiotherapy [99].

Most studies show that patients in advanced stages of the disease (III and IV) score less in all domains compared with their counterparts in early stages (I and II) [100].

Matsumoto et al [101] analyzed the factors that affect quality of life. In their study, there was an increase of the quality of life in patients over 65 years. Mohan et al [80] evaluated QOL in 76 newly diagnosed lung cancer patients and demonstrated that QOL did not correlate with age. Also in our study, mean age of the patients was 59 and there was not a correlation between age and quality of life. Matsumoto et al concluded that this lack of correlation might be partly due to the fact that median age in the study population was 55 years, which was considerably less compared with most other studies. It can be concluded that our study was consistent with Mohan et al [80], but not consistent with the study carried out by Matsumoto [101]. However, further research including a large sample in each age group may be needed to confirm these results.

Montazeri at al [90] evaluated the impact of gender on quality of life in 129 lung cancer patients (range was equal for women and men) and there was not a significant difference. Tanrikol et al [102] assessed the factors that affect quality of life and showed that men have significantly higher quality of life scores than women (p=0,001). In our study group, we did not evaluate the effect of gender on quality of life because there were only 3 women. This possibly explains the lack of correlation of QOL in gender.

Analyses using statistical modeling techniques show a tight association between national mortality rates and smoking [103]. The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per/year. In some studies, it was found that patients who continue smoking after diagnosis have a poor QOL score [104, 105]. In our study, none of the patients were smoking after diagnosis, but all had a smoking history. (mean = 27.94, SD = 12.75). There was not a significant correlation between duration of smoking and QOL scores. This result is similar to the findings of a study conducted by Sarna et al [103].

Cancer-specific QOL is distinct from measures of performance status, which have been used by oncologists for many years. Performance status measures are typically completed by the physician or interviewer and include a single item that provides a composite description of physical activity and symptoms. In contrast, QOL instruments are typically completed by the patient, and include multiple items that cover two or more of life's domains. In studying 139 patients with lung cancer, Schaafsma and Osoba [106] reported that QOL was a much broader concept than that reflected by KPS, and they found only a weak correlation between the two. However, in our study, the mean ECOG performance was 2.05 ± 0.15 and KPS was 60.00 ± 4.11. There was a strong significant negative correlation ($r= -0.71$, $p< 0.05$) between ECOG performance and all domains of the EORTC QLQ-C30. There was a strong significant positive correlation ($r= 0.74$, $p< 0.05$) between KPS

and all domains of the EORTC QLQ-C30, which was similar to results found by Mohan et al [80]. Performance status is the patient's ability to do certain physical activities, especially related to mobility, work, and self-care. Compromised performance status leads to decreased performance of activities of daily living and infringes on the independent functioning of the patient. Thus, although performance status is not a true measure for QOL, it should be seen as an important predictor of QOL of the patient and should be routinely assessed by physicians.

The association of QOL with chemotherapy has been evaluated in several studies. Helsing et al compared platinum based chemotherapy with best supportive care and demonstrated significant survival benefit in the chemotherapy group (29 weeks *vs.* 11 weeks; 1-year survival, 28% *vs.* 8%) along with significant improvement in dyspnea, pain, insomnia, and social function [107].

Bente et al [108] assessed the QOL of 170 patients with limited and advanced SCLC as well as with stages III and IV NSCLC at three different times during the treatment and follow-up. The global health status/QLQ (baseline mean= 66.67) showed no significant difference over the 6 months. Emotional function increased between baseline and 3 months later (p= 0.009). Concerning nausea and vomiting, a significant decrease was identified over time (p= 0.003), especially between baseline and 3 months after and from baseline to 6 months after. In this study, performance status of the patients was not measured.

In contrast, Huinink et al [109] determined the response rates, survival rates, and toxicities of single-agent gemcitabine and a combination of cisplatin/etoposide in patients with non-resectable, locally advanced, or metastatic non-small cell lung cancer. One hundred and forty-seven patients were enrolled: 72 in the gemcitabine and 75 in the cisplatin/etoposide arm. Clinical and haematologic toxicity was more pronounced in the cisplatin/etoposide arm. Quality-

of-life measures indicated a significant worsening of symptoms in the cisplatin/etoposide arm for hair loss, nausea/vomiting, and appetite loss. This study showed that platinum-containing chemotherapy is associated with more side effects in patients with non-resectable, locally advanced, or metastatic NSCLC. Hakan et al (makale sekiz) assessed the quality of life in patients with advanced disease with an ECOG performance status of $\leq$2. They also showed that the patients receiving non-platinum containing, single- agent chemotherapy experienced less fatigue.

In our study, all of the patients (n= 17) with ECOG PS=2 and KPS=60 were receiving platinum-based chemotherapy (35.29% paclitaxel + carboplatin, 47.05% cisplatin + etoposide, 11.76% cisplatin + gemcitabine, 5.88% docetaxel + cisplatin). From the baseline to the third chemotherapy, there was a significant increase in treatment-related side effects including sore mouth ($p < 0.05$, F= 1.085), dysphagia ($p < 0.05$, F= 6.559), peripheral neuropathy ($p < 0.05$, F= 7.040), and alopecia ($p < 0.05$, F= 0.9904). At the same time, there was a significant decrease in GHS (and Functional Scales including physical functioning, role functioning, emotional functioning, cognitive functions, and social functioning. There was also an increase in symptom scales including nausea and vomiting, dyspnea, insomnia, and appetite loss.

Furthermore, our data is in agreement with previous reports in which patients with metastatic disease and ECOG PS=2 appear to experience more toxicity and treatment- related side effects than patients with PS=1 [4]. Thus, PS=2 patients with advanced disease may be harmed by platinum-based chemotherapy.

When the results of such trials are compared to previously published data, the percentage of PS-2 patients in the older trials should be taken into consideration. Comparative trials, especially in advanced NSCLC, generally lead to very small differences (for example, a 4% or 5% gain in survival at two years). This small

benefit may be either overestimated or underestimated if populations are not comparable (i.e., same percentage of PS-2 patients). The American Society for Clinical Oncology (ASCO) clinical practice guidelines recommend the use of chemotherapy in selected patients with advanced NSCLC (i.e., PS-0 or -1, and possibly -2). However, we believe that PS-2 patients are generally candidates for systemic treatment in addition to best supportive care, but should be treated with singe agents which have less side effects than combination therapy [4].

The right management decision would appear to be treatment with active singe agents. In this regard, single agent regimens such as vinorelbine was found to be active and well tolerated in Stage IV NSCLC patient [110].

From the above evidence, it is clear that the benefit of chemotherapy over best supportive care is still questionable. A clear answer to this question would be difficult since most chemotherapeutic regimes have produced benefits in different aspects of the disease such as survival, symptomatic relief, tumor regression, and QOL.

5.CONCLUSION

This study demonstrates that there were significant differences in QOL from the baseline to the third chemotherapy and a strong correlation between performance scales (ECOG and KPS) and Global Health Status.

In addition, we believe that assessments of QOL should also be routine for all patients with advanced NSCLC and SCLC. This information may be useful in developing treatment programs that minimize chemotherapy side effects while maximizing the well being of patients.

Larger multi-central studies may help in providing a more comprehensive evaluation of the effect of various demographic and clinical variables on QOL in this setting.

This information may be useful in developing treatment programs that minimize chemotherapy side effects while maximizing the well being of patients. The formation of a oncology care team consisting of physicians, clinical pharmacists and nurses is very important in order to provide good pharmaceutical care to the lung cancer patients. These problems might be managed with the contribution of a clinical pharmacist. Further studies could focus on defining the role and benefits of the clinical pharmacist within the Oncology team.

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APPENDIX A: EORTC QLQ C-30 Questionnaire (English)

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX B: EORTC QLQ C-30 Questionnaire (Turkish)

TURKISH

EORTC QLQ-C30 (version 3.0)

Siz ve sağlığınız hakkında bazı şeylerle ilgileniyoruz. Lütfen soruların tamamını size uygun gelen rakamı daire içine alarak yanıtlayınız. Soruların "doğru" veya "yanlış" yanıtları yoktur. Verdiğiniz yanıtlar kesinlikle gizli kalacaktır.

Lütfen ad ve soyadınızın başharflerini yazınız: ⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Doğum gününüz (Gün, Ay, Yıl): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Bugünkü tarih (Gün, Ay, Yıl): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

		Hiç	Biraz	Oldukça	Çok
1.	Ağır bir alışveriş torbası veya valiz taşımak gibi zorlu hareketler yaparken güçlük çeker misiniz?	1	2	3	4
2.	Uzun bir yürüyüş yaparken herhangi bir zorluk çeker misiniz?	1	2	3	4
3.	Evin dışında kısa bir yürüyüş yaparken zorlanır mısınız?	1	2	3	4
4.	Günün büyük bir kısmını oturarak veya yatarak geçirmeye ihtiyacınız oluyor mu?	1	2	3	4
5.	Yemek yerken, giyinirken, yıkanırken ve tuvaleti kullanırken yardıma ihtiyacınız oluyor mu?	1	2	3	4

Geçtiğimiz hafta zarfında:		**Hiç**	**Biraz**	**Oldukça**	**Çok**
6.	İşinizi veya günlük aktivitelerinizi yapmaktan sizi alıkoyan herhangi bir engel var mıydı?	1	2	3	4
7.	Boş zaman aktivitelerinizi sürdürmekten veya hobilerinizle uğraşmaktan sizi alıkoyan bir engel var mıydı?	1	2	3	4
8.	Nefes darlığı çektiniz mi?	1	2	3	4
9.	Ağrınız oldu mu?	1	2	3	4
10.	Dinlenme ihtiyacınız oldu mu?	1	2	3	4
11.	Uyumakta zorluk çektiniz mi?	1	2	3	4
12.	Kendinizi güçsüz hissettiniz mi?	1	2	3	4
13.	İştahınız azaldı mı?	1	2	3	4
14.	Bulantınız oldu mu?	1	2	3	4
15.	Kustunuz mu?	1	2	3	4

Lütfen arka sayfaya geçiniz

Geçtiğimiz hafta zarfında:		**Hiç**	**Biraz**	**Oldukça**	**Çok**
16.	Kabız oldunuz mu?	1	2	3	4
17.	İshal oldunuz mu?	1	2	3	4
18.	Yoruldunuz mu?	1	2	3	4
19.	Ağrılarınız günlük aktivitelerinizi etkiledi mi?	1	2	3	4
20.	Televizyon seyretmek veya gazete okumak gibi aktiviteleri yaparken dikkatinizi toplamakta zorluk çektiniz mi?	1	2	3	4
21.	Gerginlik hissettiniz mi?	1	2	3	4
22.	Endişelendiniz mi?	1	2	3	4
23.	Kendinizi kızgın hissettiniz mi?	1	2	3	4
24.	Bunalıma girdiniz mi?	1	2	3	4
25.	Bazı şeyleri hatırlamakta zorluk çektiniz mi?	1	2	3	4
26.	Fiziksel durumunuz veya tıbbi tedaviniz aile yaşantınıza engel oluşturdu mu?	1	2	3	4
27.	Fiziksel durumunuz veya tıbbi tedaviniz sosyal aktivitelerinize engel oluşturdu mu?	1	2	3	4
28.	Fiziksel durumunuz veya tedaviniz maddi zorluğa düşmenize yol açtı mı?	1	2	3	4

Aşağıdaki sorular için 1 ila 7 arasındaki size en uygun rakamı daire içine alınız

29. Geçen haftaki sağlığınızı genel olarak nasıl değerlendirirsiniz?

1	2	3	4	5	6	7
Çok kötü						Mükemmel

30. Geçen haftaki hayat kalitenizi genel olarak nasıl değerlendirirsiniz?

1	2	3	4	5	6	7
Çok kötü						Mükemmel

APPENDIX C: EORTC QLQ LC-13 Questionnaire (English)

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

APPENDIX D: EORTC QLQ LC-13 Questionnaire (Turkish)

TURKISH

EORTC QLQ - LC13

Hastalar bazen aşağıdaki belirtilerın ya da problemlerin olduğunu bildirirler. Lütfen geçtiğimiz hafta zarfında belirti ya da problemleri ne ölçüde yaşadığınızı belirtin. Size uyan en iyi cevabın numarasını daire içine alarak cevaplayınız.

Geçtiğimiz hafta zarfında:	**Hiç**	**Biraz**	**Oldukça**	**Çok**
31. Ne kadar öksürdünüz?	1	2	3	4
32. Kanlı öksürüğünüz oldu mu?	1	2	3	4
33. Dinlenirken nefes darlığı oldu mu?	1	2	3	4
34. Yürürken nefes darlığı oldu mu?	1	2	3	4
35. Merdiven çıkarken nefes darlığı oldu mu?	1	2	3	4
36. Ağzınızda veya dilinizde ağrı oldu mu?	1	2	3	4
37. Yutma güçlüğünüz oldu mu?	1	2	3	4
38. El ve ayaklarınızda karıncalanma veya uyuşma oldu mu?	1	2	3	4
39. Saçlarınızda dökülme oldu mu?	1	2	3	4
40. Göğüs kafesinizde ağrınız oldu mu?	1	2	3	4
41. Kol veya omuzunuzda ağrınız oldu mu?	1	2	3	4
42. Vücudunuzun diğer kısımlarında ağrınız oldu mu?	1	2	3	4
Evet ise, nerede? _____				
43. Ağrı için hiç ilaç aldınız mı?				
1 Hayır 2 Evet				
Evet ise, ilacın ne kadar faydasi oldu?	1	2	3	4

CURRICULUM VITAE

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Beril Gulsah Kivrak was born on 25.04.1984 in Kdz. Eregli- Turkey. She graduated with a B.Sc. (Pharmacy) degree in 2006 from Marmara University Faculty of Pharmacy. She started to work as a Teaching and Research Assistant in the clinical pharmacy department in Yeditepe University Faculty of Pharmacy. In the same year, she started her M.Sc. degree in Clinical Pharmacy Programme and her M.Sc. thesis entitled *"Quality of Life Assessment in Metastatic (stage IV) Lung Cancer Patients "* under the supervision of Assist. Prof. Dr. Philip Martin Clark in the Department of Clinical Pharmacy in Yeditepe University. Beril Gulsah Kivrak is currently employed as Research Assistant in University of Maryland School of Medicine Anatomy & Neurobiology Department- USA.