INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in both men and women in the United States and throughout the world. The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women. Lung cancer recently surpassed heart disease as the leading cause of smoking-related mortality. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis ***(Parkin et al., 2007).***

It is the fourth most common malignancy in men after Bladder cancer, Hepatocellular carcinoma and Non hodjken lymphoma in Egypt ***(GLOBOCAN, 2002).*** This high incidence is due to high smoking prevalence among Egyptian men ***(Nadia Mokhtar and Nabil El bolkeny, 2004)***.

Signs and Symptoms of lung cancer may arise from local tumor growth, invasion of adjacent structures, or distant metastasis ***(Tarabeia et al., 2008).***

Cough is the major symptom in 75% of patients, haemoptysis has been described in 57% of patients, other common symptoms include dyspnea, chest pain in 40% of patients, or non specific initial symptoms as weight loss, weakness, anorexia, malaise in 10-15% of patients ***(Emami et al., 1998).***

Chest X-ray, C.T scan chest are the most important and valuable radiologic tools in diagnosis of Non small cell lung cancer ***(Del Regato and Spjur, 2002).***

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases and it includes four major types: Squamous cell (epidermoid) carcinoma, Adenocarcinoma, Broncho-alveolar and Large-cell carcinoma ***(Baron and Levitt, 2002)***.

The need to diagnose lung cancer at an early and potentially curable stage is obvious. In addition, most patients who develop lung cancer have been smokers and have smoking-related damage to the heart and lungs, making aggressive surgical or multimodality therapies less viable options ***(Scagliotti and Aisner, 2008).***

Advanced NSCLC encompasses metastatic disease (Stage IV) as well as locally advanced disease (Stage IIIB) that due to tumor or patient characteristics cannot be approached with curative intent ***(David et al., 2009).***

A landmark meta-analysis has shown that chemotherapy when compared with best supportive care (BSC) in advanced NSCLC was associated with high statistically significant results (an absolute survival improvement of 10% (26% in the chemotherapy arm compared with 16% in the BSC arm) and median survival increased from six months in the BSC arm to eight months in the chemotherapy arm. The goals of chemotherapy in this setting are mainly symptom palliation to improve length and quality of life. So the side effects of chemotherapy are important considerations in management of advanced stage Non small cell lung cancer ***(Green and Page, 1995).***

According to the previous clinical trials and with the emerge of new drugs as targeted therapy, a retrospective medical chart reviews were performed to evaluate the economic impact of treatment from the time of diagnosis until the time of death or the end of the evaluation period in patients with Advanced NSCLC. Results of these data show that treatment of patients leads to high medical resource consumption ***(Marjolin et al., 2009)***.

These results lead to an increase in economic arguments in medical decision making on both national and local levels concerning type, duration of chemotherapy to be given. ***(Scagliotti et al., 2006)***

The standard treatment of advanced stage NSCLC is platinum doublet chemotherapy, as Cisplatin is considered the most effective for NSCLC ***(Sandler et al., 2005).***

Gemcitabine (2',2'-difluorodeoxycytidine, dFdc), an analog of cytosine arabinoside (Ara-C), is a pyrimidine anti-metabolite. It has consistently demonstrated a favourable toxicity profile and activity in NSCLC, and its novel mechanism has encouraged its use in combination with tradional agents such as cisplatin.

Gemcitabine- cisplatin chemotherapy is considered as one of the most active regimens for advanced NSCLC, with an overall response rate (ORR) of 22-40.6% and median survival of 8.1-9.8 months in phase III trial***. (Le Chevalier et al., 2005)***.

A recent meta-analysis showed an absolute 1-year survival benefit of 3.9%for Gemcitabine - cisplatin regimen when compared with other platinum-containing regimens ***(Van Moorsel and Peters, 1997).***

Gemcitabine is usually administered intra-venously at a dose of 1,000–1,250 mg/m^2 as a 30-minute infusion on days 1 and 8 of a 21-day cycle or days 1, 8, and 15 of a 28-day cycle ***(Ruiz van Haperen et al., 1994)***. This standard Gemcitabine infusion acts through the enzyme deoxycytidine kinase(dCK) which catalyzes the phosphorylation of gemcitabine into the active gemcitabine triphosphate which then will be saturated ***(Plunkett and Huang, 1995).***

Preclinical studies in human tumor cell lines and xenografts showed that intracellular accumulation of gemcitabine triphosphate (dFdCTP), the active metabolite of gemcitabine, is dependent on the total exposure time and rate of administration of gemcitabine ***(Smit et al., 2003)***. So, the brief 30-minutes infusion of Gemcitabine at 1000mg/m2 might not result in higher concentrations of its active metabolite ***(Xu et al., 2007).*** Therefore, prolonging the infusion time at lower dose levels of gemcitabine, such as moderately prolonged 100min infusion (Fixed dose rate 10 mg/m2/min) ***(Von Deluis, 2007)*** and the low dose infusion lasting for 3, 6,24 hours have been studied in different clinical trials, and demonstrated good efficiency in different tumors, as it leads to the maintenance of plasma gemcitabine concentrations at levels at which dCK is

saturated for prolonged periods of time which increases intracellular accumulation of Gemcitabine triphosphate ***(Capuzzo and Novello, 2007)***. This strategy was hypothesized to result in a higher antitumor activity of gemcitabine in patient with nsclc ***(Soo and Wang, 2006).***

AIM OF THE WORK

To compare the efficacy and safety of the combination of Gemcitabine at low dose (250mg/m^2 over 6-hours prolonged infusion) with cisplatin in chemo-naive patients with advanced non-small cell lung cancer (NSCLC) versus the standard infusion (1000mg/m^2 over 30 minutes infusion).

Also, to evaluate the cost benefit ratio of giving this novel combination versus the standard one.

Primary end point is assessment of Efficacy and Tolerability to the 6 hours infusion of gemcitabine in comparison to the standard infusion.

Secondary end point is time to disease progression and overall survival in both arms.

EPIDEMIOLOGY AND PATHOGENESIS

The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women ***(Parkin et al., 2007***). Based on Global Cancer Statistics , it is estimated that 222,520 men and women (116,750 men and 105,770 women) were diagnosed with and 157,300 men and women died of cancer of the lung and bronchus in 2010 ***(Jemal et al., 2011)*.**

SEER Cancer Statistics (*Howlader et al., 2011).*

SEER Incidence of Lung Cancer by Age, Sex and Race

From 2004-2008, the median age at diagnosis for cancer of the lung and bronchus was 71 years of age. Approximately 0 % were diagnosed under age 20, 0.2% between 20 and 34, 1.6% between 35 and 44, 8.8% between 45 and 54, 20.9% between 55 and 64, 31.1% between 65 and 74, 29.0% between 75 and 84 and 8.3% 85+ years of age.

The age-adjusted incidence rate was 62.0 per 100,000 men and women per year. These rates are based on cases diagnosed in 2004-2008 from 17 SEER geographic areas.

Table (1): Incidence Rates by Race

Race/Ethnicity	Male	Female
All Races	75.2 per 100,000 men	52.3 per 100,000 women
White	75.3 per 100,000 men	54.6 per 100,000 women
Black	99.8 per 100,000 men	54.7 per 100,000 women
Asian/Pacific Islander	53.2 per 100,000 men	28.5 per 100,000 women
American Indian/Alaska Native	51.2 per 100,000 men	39.5 per 100,000 women
Hispanic	39.6 per 100,000 men	24.5 per 100,000 women

US Mortality By Age, Sex and Race

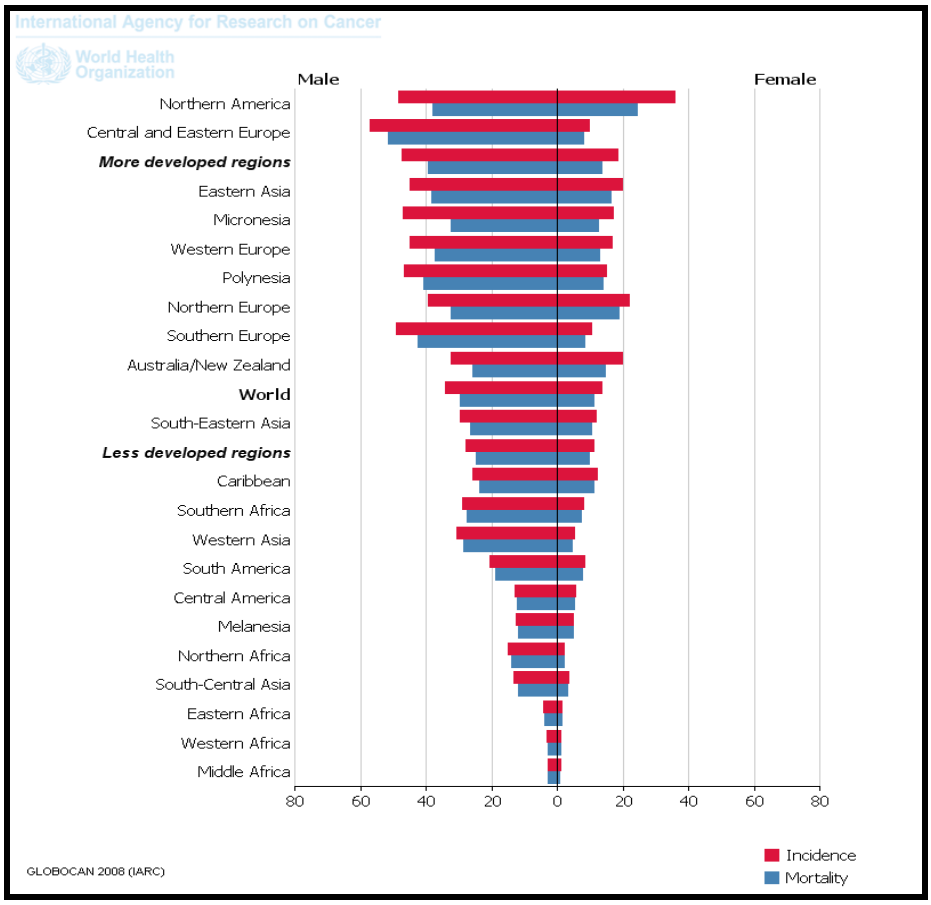
From 2003-2007, the median age at death for cancer of the lung and bronchus was 72 years of age. Approximately 0 % died under age 20, 0.1% between 20 and 34, 1.4% between 35 and 44, 7.9% between 45 and 54, 19.7% between 55 and 64, 30.6% between 65 and 74, 30.7% between 75 and 84 and 9.6% 85+ years of age.

The age-adjusted death rate was 52.5 per 100,000 men and women per year. These rates are based on patients who died in 2003-2007 in the US.

Mortality data for the current data year is not yet available.

Table (2): Death Rates by Race

Race/Ethnicity	Male	Female
All Races	68.8 per 100,000 men	40.6 per 100,000 women
White	68.3 per 100,000 men	41.6 per 100,000 women
Black	87.5 per 100,000 men	39.6 per 100,000 women
Asian/Pacific Islander	36.7 per 100,000 men	18.5 per 100,000 women
American Indian/Alaska Native	48.1 per 100,000 men	33.3 per 100,000 women
Hispanic	32.5 per 100,000 men	14.4 per 100,000 women



Estimated age-standardised rates (World) per 100,000

Figure (1): Lung Cancer Incidence and Mortality Worldwide ***(Globocan, 2008)*.**

Lifetime Risk (*Howlader et al., 2011)*

Based on rates from 2005-2007, 6.95% of men and women born today will be diagnosed with cancer of the lung and bronchus at some time during their lifetime. This number can also be expressed as 1 in 14 men and women will be diagnosed with cancer of the lung and bronchus during their lifetime. These statistics are called the lifetime risk of developing cancer. Sometimes it is more useful to look at the probability of developing cancer of the lung and bronchus between two age groups. For example, 2.89% of men will develop cancer of the lung and bronchus between their 50th and 70th birthdays compared to 2.27% for women.

Updated lifetime risk statistics for the current data year is not available until the mortality data is released.

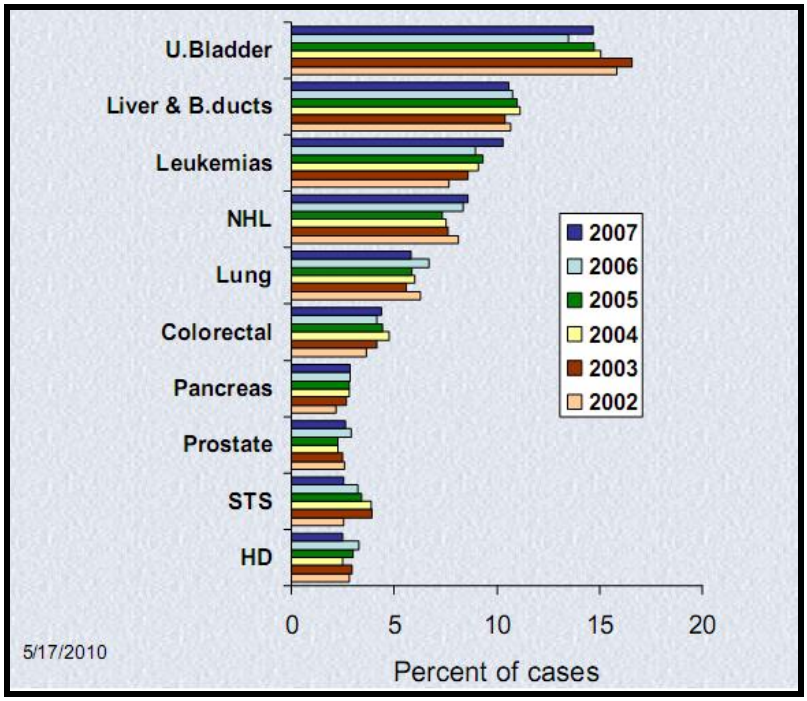


Figure (2): Top Cancers in Egypt from 2002-2007 ***(GLOBOCAN, 2008).***

Table (3): Most Common Cancer Sites in Selected Arab Countries, Males.

Country	1st	2nd	3rd	4th	5th
Egypt	Bladder	Liver	NHL	**Lung**	Colorectal
Tunisia	**Lung**	Bladder	Prostate	Larynx	Colorectal
Algeria	**Lung**	Bladder	Stomach	Prostate	Colorectal
Jordan	**Lung**	Bladder	Prostate	NHL	Skin
KSA	NHL	Liver	Leukemia	Colorectal	**Lung**
Kuwait	Colorectal	NHL	Prostate	**Lung**	Liver
Lebanon	Bladder	**Lung**	Prostate	Colorectal	Stomach

(GLOBOCAN, 2002)

Table (4): Age of Lung Cancer Male Cases in Selected Arab World

Country	**Median (years)**	**Age % <45 years**
Egypt (NCI)	60.0	12.1
Egypt (Gharbiah)	62.5	6.3
Saudi Arabia	65.8	6.6
Kuwait	70.0	5.0
Jordan	63.2	7.5
Bahrain	69.5	0.0
Oman	61.2	2.7
USA	70.0	3.0

(Gharbiah, 2007, NCI 2004, GLOBOCAN, 2008)

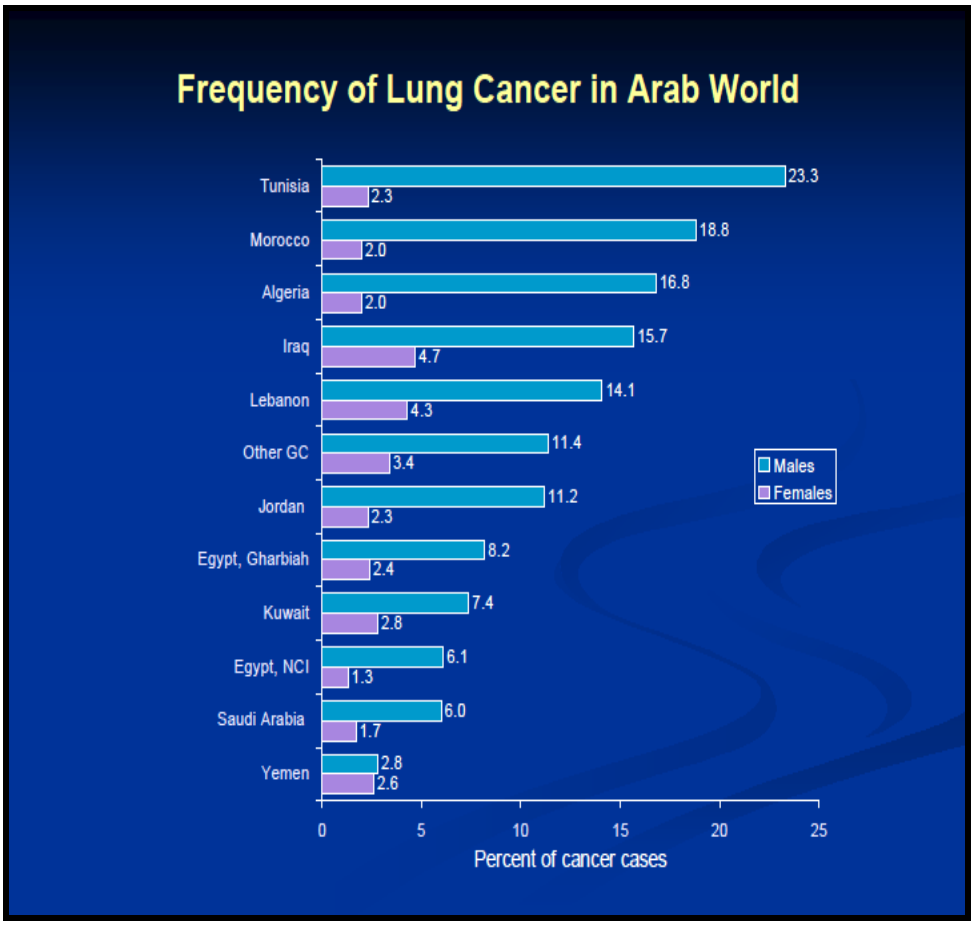


Figure (3): Frequency of Lung Cancer in Arab World
(Gharbiah 2007, NCI 2004, Globocan, 2008).

Lung cancer is the Fifth most common malignancy among males in Egypt after Bladder cancer, liver and biliary duct carcinoma, leukemias and Non Hodjken Lymphoma and the third most common solid malignancy after bladder cancer, liver and biliary duct carcinoma ***(Globocan, 2008).*** Accurate epidemiological data on lung cancer in Egypt is not available since a comprehensive national population-based cancer registry is lacking. However, official statistics as well as institution and hospital- -based studies were able to release some data, where the average incidence of lung cancer among

the Egyptian population was about 6.1 /100,000 new cases diagnosed each year according to the NCI cancer statistics on year 2004, with median age among males 60 years. This incidence have been increased in the last few years due to high tobacco consumption among egyptian men especially younger ages. This may reflect a cohort effect of rising rates in this younger population ***(Nadia Mokhtar and Nabil El bolkeny, 2004)***. The average incidence of Lung cancer new cases in AIN SHAMS Hospital was about 8.2/100,000 in year 2010 while in KASR AINY Hospital was 3.8/100,000 in the same year. In addition, the incidence in GHARBIA Hospital was 8.2/100,000 for both sexes (13.6/100,000 for male population, 3.6/100,000 for female population) in year 2000-2002.

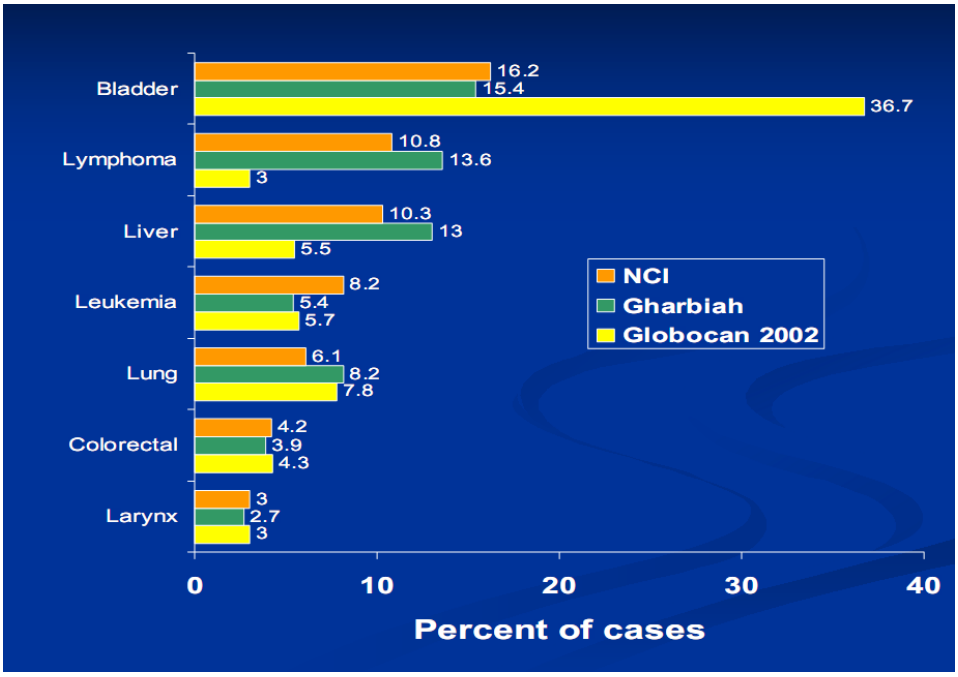


Figure (4): Most Common Sites in Egyptian males ***(NCI 2004, Gharbiah 2007 & Globocan, 2002).***

Predisposing factors

I- Smoking

The primary risk factor for lung cancer is smoking particularly of cigarettes, is by far the main contributor to lung cancer ***(Biesalski et al., 1998).*** Cigarette smoke contains over 60 known carcinogens including radioisotopes from the radon decay sequence, nitrosamine, and benzopyrene. Additionally, nicotine appears to depress the immune response to malignant growths in exposed tissue ***(Hechi, 2003).*** Across the developed world, 91% of lung cancer deaths in men during the year 2000 were attributed to smoking.In the United States, smoking is estimated to account for 87% of lung cancer cases. Among male smokers, the lifetime risk of developing lung cancer is 17.2%; among female smokers, the risk is 11.6%. This risk is significantly lower in nonsmokers: 1.3% in men and 1.4% in women ***(Sopori, 2002).***

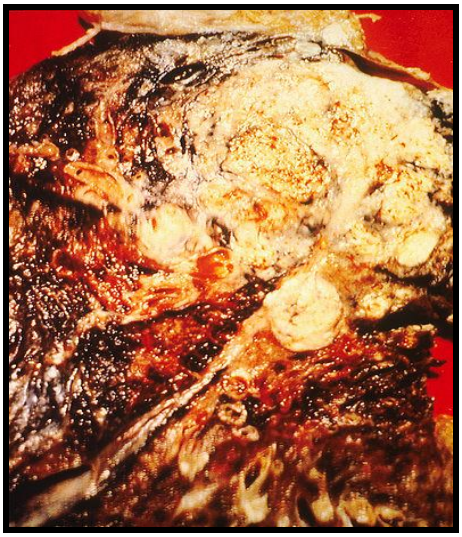


Figure (5): Cross section of a human lung. The white area in the upper lobe is cancer; the black areas are discoloration due to smoking ***(Sopori, 2002).***

Women who smoke (former smokers and current smokers) and take hormone therapy are at a much higher risk of dying of lung cancer. In a study by ***Chlebowski and Schwartz (2009)***, the women taking hormones were about 60% more likely to die of lung cancer than the women taking a placebo. Not surprisingly, the risk was highest for current smokers, followed by past smokers, and lowest for never smokers. Among the women who smoked (former or current smokers), 3.4% of those taking hormone therapy died of lung cancer compared to 2.3% for women taking the placebo.

The time a person smokes (as well as rate of smoking) increases the person's chance of developing lung cancer. If a person stops smoking, this chance steadily decreases as damage to the lungs is repaired and contaminant particles are gradually removed. In addition, there is evidence that lung cancer in never-smokers has a better prognosis than in smokers, and that patients who smoke at the time of diagnosis have shorter survival times than those who have quit ***(Peto et al., 2006).***

Passive smoking which is the inhalation of smoke from another's smoking is a cause of lung cancer in nonsmokers ***(Sun and Schiller, 2007).***

A passive smoker can be classified as someone living or working with a smoker. Studies from the U.S. Europe, the UK, and Australia have consistently shown a significant increase in relative risk among those exposed to passive smoke. Recent investigation of sidestream smoke suggests that it is more