Brain metastases in Non Small Cell Lung Cancer (NSCLC): Retrospective analysis of risk factors and treatment outcome.

Thesis

Submitted for partial fulfillment of M.SC degree of clinical oncology by:

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Abstract Text:

Background: Incidence of cerebral metastasis is increasing among lung cancer patients. Many factors have been reported associated with increase risk of brain metastasis. The aim of this retrospective analysis is to investigate the predictive factors for the development of brain metastasis in lung cancer patients.

Methods: We retrospectively analyzed histologically proven lung cancer patients radiologically diagnosed of having brain metastases who presented to Kasr Al-Eini Center for Oncology (NEMROCK) in the period from 2004 till 2010, with follow up period of 6 months at least. The following factors were analyzed: age, gender, PS, smoking history, tumor size & grade preceding development of brain metastasis.

Results: Our study included 403 patients. 67 patients (16.6%) experienced brain metastasis during the course of their disease. 40 (10%) patients had brain metastasis among other sites of distant spread at first presentation which represent 88.9% of patients presented with metastatic disease. In a median follow-up of 17.1 months (6-77) the time to develop brain metastasis (TTBM) for the whole group was 5 months (range 2-22 months) (95% CI : 4.3-7.7). The most important factor affecting the TTBM was the use of chemotherapy before developing brain metastasis with a median TTBM of 5.9 months (95%CI : 3.2-6.8) among those who received chemotherapy compared to 2 months among the patients who didn't receive chemotherapy (P= <0.0001). The second factor was PS at time of initial diagnosis (P= 0.027). The median OS after brain metastasis was 6 months (95% CI : 4.26-7.74). On univariate analysis, PS and use of chemotherapy after developing brain metastases showed statistically significant difference affecting OS.

Conclusions: We concluded that PS as well as use of chemotherapy are the 2 main factors associated with shorter time to develop brain metastasis. PS and use of chemotherapy after developing brain metastases showed longer OS after developing brain metastases.

Keywords: NSCLC, Brain metastasis, Egypt , oncology,cancer

بسم الله الرحمن الرحيم

"اقرأ و ربك الأكرم * الذي علم بالقلم *
علم الإنسان ما لم يعلم"

(العلق: آيات من ٣ - ٥)

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Hussam Hamdy Zawam

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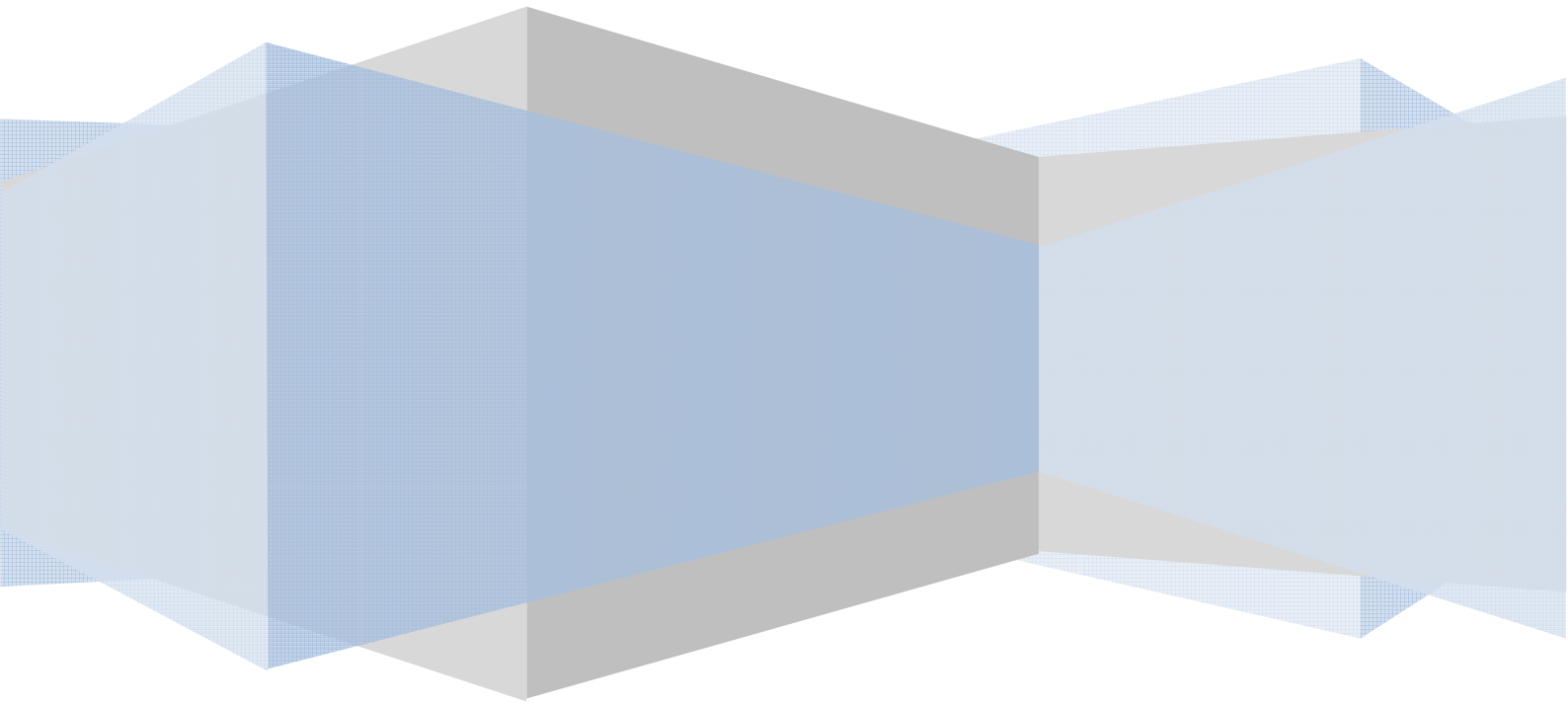
CHAPTER (1)
INTRODUCTION



INTRODUCTION:

Lung cancer was uncommon before the advent of cigarette smoking; it was not even recognized as a distinct disease until 1761.[1] Different aspects of lung cancer were described further in 1810. In Germany in 1929, physician Fritz Lickint recognized the link between smoking and lung cancer, which led to an aggressive antismoking campaign.[2] The British Doctors Study, published in the 1950s, was the first solid epidemiological evidence of the link between lung cancer and smoking.[3] As a result, in 1964 the Surgeon General of the United States recommended that smokers should stop smoking.[4]

Nowadays Lung cancer ranks among the most common and most lethal malignancies worldwide. It remains the leading cause of cancer mortality in both women and men, being responsible for 25% of all cancer mortality. Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases.[5]

Lung cancer is rapidly emerging as a major cause of mortality in the Middle East, Africa, and Asia as well. According to El-Bolkainy et al, The leading cancers in Egyptian patients are; breast: 24.3%, GIT:18.4%, urinary bladder:18.2%, lymphomas:9.8%. In group of 11,614 patients with solid tumors presented to NCI between 1994-1997 , lung cancer represented 8.6% of the whole group. But a selection bias exists in this material since it is a specialized center in bladder and head & neck cancer but lacks service departments for chest surgery and neurosurgery.[6]

Intraparenchymal brain metastases (BMs) are the most common neurological complication related to cancer and represent the most common brain cancer, exceeding gliomas in prevalence by nearly tenfold, and occur in 20–25% of all patients with systemic cancer. Lung cancer accounts for 60% of all BMs and 25% of patients with lung cancer will develop BMs. The incidence of the brain as the first site of relapse is 15–30% in non-small-cell lung cancer (NSCLC) and in 33% of patients, the brain is the only site of recurrent disease.[7]

Brain metastasis has increasingly become a major problem in the treatment of patients with NSCLC for two reasons: (1) The routine use of magenetic resonance imaging (MRI) for staging purposes, even in asymptomatic patients with metastatic NSCLC, has resulted in the identification of small asymptomatic lesions that

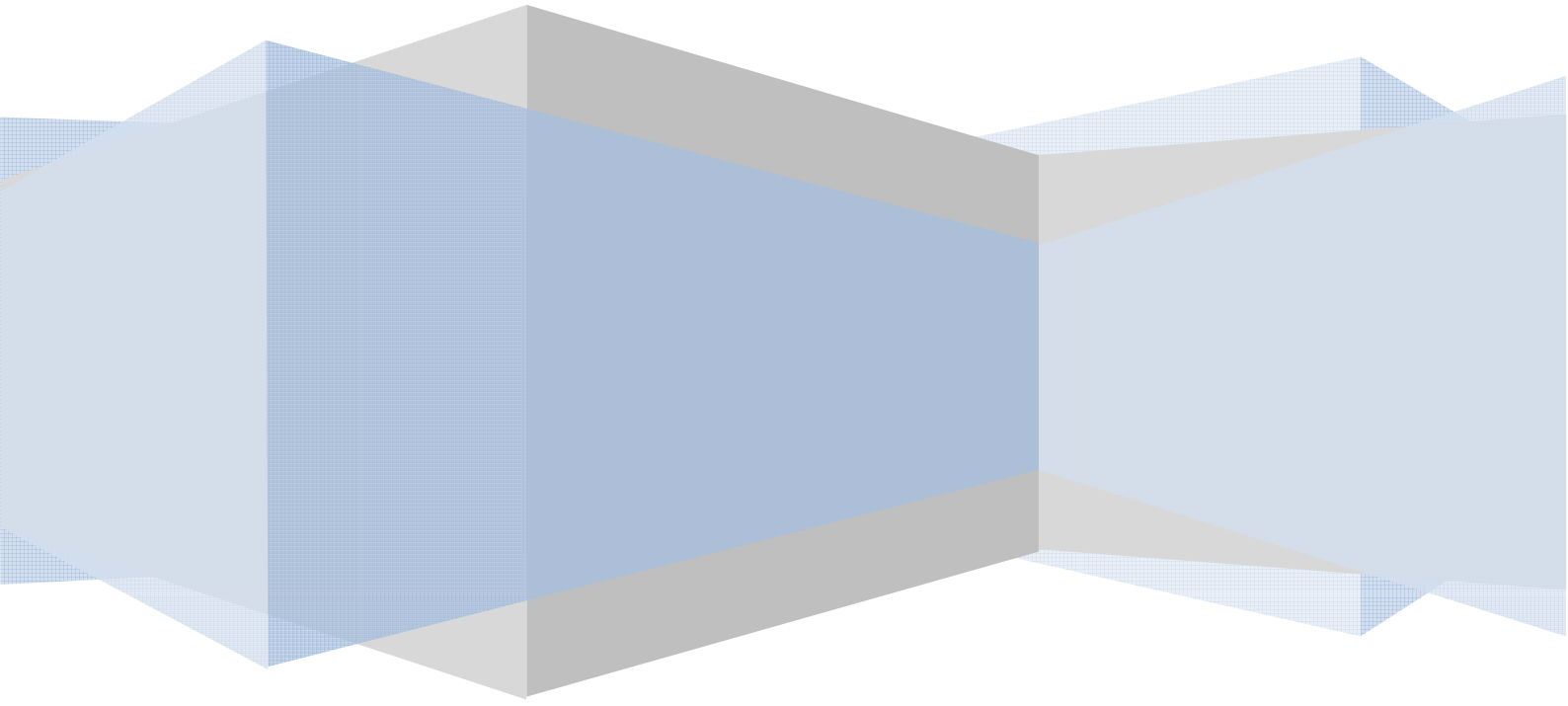
would otherwise have gone unnoticed for some time. (2) With the availability of more effective systemic therapy for patients with resected NSCLC and locally advanced NSCLC, the brain as a single site or as the first site of relapse is becoming more common. It is not surprising, therefore, that the rate of brain metastasis in NSCLC is now approximately 30%.[8-9]

The symptoms resulting from brain metastases may be ameliorated with corticosteroids or osmotic therapy for the peritumoral edema or with anticonvulsants for seizure control. Direct antitumor therapies include surgery, radiotherapy (external beam radiotherapy, radiosurgery, and brachytherapy), chemotherapy, and molecular targeted drugs.[10]

In general, brain metastases are associated with a poor prognosis. In the pre-CT era, the median survival time of patients with symptomatic brain metastases was approximately 1 to 2 months without treatment, 2 to 2.5 months with corticosteroid therapy, and 3 to 6 months with WBRT. Despite some major advances in cancer diagnosis, cancer treatment, and brain imaging, the overall survival time of unselected patients with brain metastases treated with WBRT has remained at 3 to 6 months since the 1950s. [11]

CHAPTER (2)

EPIDEMIOLOGY



Epidemiology:

Lung cancer ranks among the most common and most lethal malignancies worldwide. It remains the leading cause of cancer mortality in both women and men. Non-small-cell lung cancer (NSCLC) accounts for 80%–85% of all lung cancer cases.[12]

During 2006, approximately 174,470 of an estimated 1,399,790 (12%) new cancer cases, and 162,460 of 564,830 (28%) total cancer deaths in the United States were attributable to lung cancer[12]; in Cyprus and the 38 countries comprising Europe, lung cancer accounted for 12% of approximately 3.2 million new cancer cases, and 19.7% (334,800) of cancer-related deaths.[13] Lung cancer is rapidly emerging as a major cause of mortality in the Middle East, Africa, and Asia as well. For instance, an estimated 71,228 annual cancer-related deaths will be attributed to lung cancer in Japan within 2 years.[14] During 2005, approximately 500,000 lung cancers were diagnosed in China,[15] and death rates attributable to this disease are expected to increase substantially over the next several decades.[16]

The incidence of lung cancer varies considerably among different ethnic populations throughout the world. Recently, Sano and Marugame[17] determined cumulative risks of lung cancer incidence from data derived from 22 cancer registries from 5 continents. In all registries, cumulative lung cancer risks were higher in males than females. Among men, African Americans had the highest incidence of lung cancer risk (approximately 7.5%), whereas Swedes had the lowest cumulative risk (approximately 2%). Among women, cumulative lung cancer risk was highest in African Americans (approximately 3.5%), whereas French and Korean women had very low cumulative risks (approximately 1%). Interestingly, lung cancer risks in East Asian female immigrants within the United States were comparable to those observed in native populations. The global rise in lung cancer incidence, together with the fact that the overall 5-year survival of patients with this disease is less than 15%, underscores the magnitude of the lung cancer epidemic.[16-18]

Intraparenchymal brain metastases (BMs) are the most common neurological complication related to cancer and represent the most common brain cancer, exceeding gliomas in prevalence by nearly tenfold, and occur in 20–25% of all

patients with systemic cancer. Lung cancer accounts for 60% of all BMs and 25% of patients with lung cancer will develop BMs.[19]
The incidence of the brain as the first site of relapse is 15–30% in non-small-cell lung cancer (NSCLC) and in 33% of patients, the brain is the only site of recurrent disease.[20]

Rates of brain metastases in non–small-cell lung cancer (NSCLC) are lower than those for small-cell lung cancer, but the problem of BM after treatment is significant. With improved survival after combined-modality therapy, it has been noted that the incidence of brain metastases, often as a sole site of relapse, has increased.[21-23]

Andre et al, in a retrospective review of clinical N2 patients treated with surgery, found that the cumulative incidence of brain metastases in patients treated with or without neoadjuvant chemotherapy was 32% and 18%, respectively (*P* _ .05).[22]

Ceresoli et al determined that, in stage III NSCLC patients treated with combined modality therapy, the brain was the site of first relapse in 23% of patients and, ultimately, brain metastases developed in 50% of patients at some point in the course of their disease.[23]

A retrospective review of the Southwest Oncology Group (SWOG) database was undertaken to review the incidence and timing of diagnosis of brain metastases in patients undergoing combined-modality therapy for stage III non–small-cell lung cancer (NSCLC). In this analysis Gaspar reported on 422 patients with NSCLC amongst whom 64% progressed.[24] Among the progressing patients, 26% progressed in brain (20% brain only and 6% brain plus other site). The median time to BM was approximately 6.5 months, with nearly 25% manifesting BMs during initial upfront treatment. Over 40% of patients who die of NSCLC are discovered at autopsy to have evidence of BMs.[21-24] These rates of failure of NSCLC in the brain have provided the rationale for trials utilizing prophylactic whole-brain irradiation (WBI) in stage 3a NSCLC.[25]

The rate of brain metastasis (BM) is highest in small-cell lung cancer, and multiple randomized trials and a larger meta-analysis have suggested that the problem is common enough after chemotherapy, with or without radiation, that routine prophylactic cranial irradiation (PCI) in patients with no other discernible disease is justified.[26]