Prognostic Factors and Survival in Patients with Non-Small Cell Lung Cancer and Brain Metastases: Single Tertiary Cancer Center Experience from Kurdistan-Iraq

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ABSTRACT

Background: Lung cancer is the second most frequently occurring cancer in the world. The global mortality-to-incidence ratio in 2020 was 0.81. Brain metastases (BM) are the most common type of intracranial malignancies. Among the non-small cell lung cancer (NSCLC), adenocarcinomas metastasize to the brain more frequently than squamous cell carcinomas. The incidence of brain metastases appears to be increasing, which may reflect improvements in diagnostic imaging and survival associated with more effective systemic therapies. The study aims to examine the survival after diagnosing BM and the prognostic factors that may affect it.

Methods: A chart review identified 59 patients with BM from histologically proven NSCLC over three years, from December 1, 2013 to November 30, 2016. Follow-up was updated from the case records and by phone contact. Patient-related variables were age, sex, histology of NSCLC, extracranial metastases, number of brain lesions, Karnofsky Performance Status, and survival from the time of the diagnosis of brain metastases. Whole Brain Radiotherapy of 20 Gray/five fractions over one week was used for all patients.

Results: The median survival after the diagnosis of BM was 6.5 months. Factors that affected survival were age, Karnofsky Performance Status, number of brain lesions, and extracranial metastases. There was no statistically significant survival correlation with sex and histological type of NSCLC.

Conclusions: Survival outcome was poor in NSCLC with BM patients. Age less than 60 years, Karnofsky Performance Status over 70, single brain lesion, and absent extracranial metastases were relatively favorable prognostic factors.

Keywords: Lung cancer, brain metastasis, radiotherapy, Kurdistan, Iraq.

العوامل النذيرة والبقاء على قيد الحياة لدى المرضى الذين يعانون من سرطان الرئة ذو الخلايا غير الصغيرة والانتشارات الدماغية: تجربة مركز سرطان ثالثي واحد من كردستان ـ العراق

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الخلاصة

الخلفية: سرطان الرئة هو ثاني أكثر أنواع السرطان شيوعا في العالم. بلغت نسبة الوفيات إلى الإصابة على مستوى العالم في عام ٢٠٢٠ ٠.٨١. النقائل الدماغية هي النوع الأكثر شيوعًا من الأورام الخبيثة داخل الجمجمة. من بين سرطان الرئة ذو الخلايا غير الصغيرة، تنتشر الأورام السرطانية الغدية إلى الدماغ بشكل متكرر أكثر من سرطان الخلايا الحرشفية. يبدو أن حدوث نقائل الدماغ آخذ في الازدياد، مما قد يعكس التحسينات في التصوير التشخيصي والبقاء على قيد الحياة المرتبط بعلاجات جهازية أكثر فعالية. تهدف الدراسة إلى فحص البقاء على قيد الحياة بعد تشخيص مرض النقائل الدماغية والعوامل النذيرة التي قد تؤثر عليه.

الطريقة: حددت مراجعة الرسم البياني ٥٩ مريضًا يعانون من النقائل الدماغية من سرطان الرئة ذو الخلايا غير الصغيرة المثبت تشريحيًا على مدى ثلاث سنوات، من ١ ديسمبر ٢٠١٣ إلى ٣٠ نوفمبر ٢٠١٦. تم تحديث المتابعة من سجلات الحالة وعن طريق الاتصال الهاتفي. وكانت المتغيرات المتعلقة بالمريض هي العمر والجنس وعلم الأنسجة في سرطان الرئة ذو الخلايا غير الصغيرة، والانبثاثات خارج الجمجمة، وعدد آفات الدماغ، وحالة أداء كارنوفسكي والبقاء على قيد الحياة من وقت تشخيص نقائل الدماغ. تم استخدام العلاج الإشعاعي الكامل للدماغ بنسبة ٢٠ جراي / خمسة أجزاء على مدى أسبوع واحد لجميع المرضى.
النتائج: كان متوسط البقاء على قيد الحياة بعد تشخيص النقائل الدماغية ٦.٥ أشهر. العوامل التي أثرت على البقاء كانت العمر، وحالة أداء كارنوفسكي، وعدد آفات الدماغ، والانبثاث خارج الجمجمة. ولم تكن هناك علاقة ذات دلالة إحصائية للبقاء على قيد الحياة مع الجنس والنوع النسيجي لسرطان الرئة غير صغير الخلايا.
الاستنتاجات: كانت نتائج البقاء على قيد الحياة سيئة في سرطان الرئة ذو الخلايا غير الصغيرة مع مرضى النقائل الدماغية. العمر أقل من ٦٠ عامًا، وحالة أداء كارنوفسكي أكثر من ٧٠ عامًا، وآفة دماغية واحدة وغياب النقائل خارج الجمجمة كانت عوامل تشخيصية مواتية نسبيًا.

الكلمات المفتاحية : سرطان الرئة، ورم خبيث في الدماغ، العلاج الإشعاعي، كردستان، العراق.

INTRODUCTION

Lung cancer is the most frequently diagnosed cancer in 2022, responsible for almost 2.5 million new cases, or one in eight cancers worldwide (12.4% of all cancers globally) [1]. Overall, up to 30% of patients with non-small cell lung cancer (NSCLC) will present with or develop brain metastasis (BM) subsequently [2]. For patients with stage III disease treated with curative intent who achieve a partial or complete radiological response, the risk of later developing brain metastases is 50% [3]. Lung cancer is the most common cause of BM, constituting 50–65% of patients within published epidemiological studies and brain radiotherapy trials [4,5].

Historically, survival rates after the development of metastatic BM in patients with NSCLC have been consistently lower than for patients with other primary cancer sites, such as breast cancer [6], and range from 2 to 6 months [7,8]. In recent years, the potential treatment options for metastatic brain disease from NSCLC have continued to evolve, including neurosurgery, stereotactic radiosurgery, and systemic treatments. Thus far, only patients with solitary brain metastasis have been shown to attain statistically significant survival benefit when whole brain radiotherapy (WBRT) is combined with focal (surgical or stereotactic) management of the intracranial disease [9]. The absence of level 1 evidence for a survival improvement from focal management for patients with more than one brain metastasis might be obscured by the competing risk of death from extracranial disease [10]. Survival outcomes for NSCLC patients with multiple BM are poor with radiation, radiosurgery, or chemotherapy, alone or in combination, and have hardly changed since the original publications of the 1980s [11]. Thus, the historically developed treatment of steroids and WBRT continues to be a very widely used option, mainly when other methods are not feasible [12-14].

In this work, we aim to examine the survival outcomes of our NSCLC patients who have BM and determine the prognostic factors that may affect their survival.

PATIENTS AND METHODS

Methods

This study employed a retrospective design, focusing on the evaluation of patient charts to identify a cohort of 66 consecutive patients with BM originating from histologically confirmed NSCLC. These patients were treated at a public, tertiary-level radiotherapy center over a period spanning from December 1, 2013, to November 30, 2016. Due to either incorrect contact information in the patient's chart or inability to reach them by phone, seven participants were eliminated from this study at the time of data entry. Consequently, the analysis was conducted on a revised cohort comprising 59 patients.

The age range was between (39-79) years, with no history of previous cranial irradiation. Patients who had presented with BM during the initial presentation of NSCLC and those who showed BM during follow-up after initial treatment were included in this study. Patients were staged according to the 2010 seventh edition of the American Joint Committee on Cancer (AJCC 7th edition) using standard staging investigations depending on the results of bronchoscopy, histopathology report, and diagnostic imaging studies. The diagnosis of BM was mainly based on clinical-radiological correlation, and histopathological confirmation of BM was not mandatory. Follow-up was updated from the case records and by telephone contact whenever necessary.

Ethical approvals were obtained from the Sulaimani Directorate of Health and the Ethical Committee of the College of Medicine at the

University of Sulaimani. Patient consent was unnecessary in this retrospective study, based mainly on chart review of previously treated patients.

Variables

Patient-related variables were age, sex, histology of NSCLC [adenocarcinoma, Squamous cell carcinoma (SCC), large cell carcinoma (LCC), and NSCLC not otherwise specified (NOS)], extracranial metastases (ECM), number of brain lesions [single, multiple], Karnofsky Performance Status (KPS) [≥70 and <70] and survival [in months from the time of the diagnosis of BM and also from the time of the diagnosis of the primary lung cancer]. Extracranial metastases were recorded depending on imaging studies as part of metastatic workup. KPS was based either on the chart review recorded by the physician at the time of the diagnosis of BM or by telephone contact, depending on the information given by the relatives of the patients. KPS of 70 was selected to define the patients according to this category: (Cares for self; unable to carry on normal activity or do active work). Patient age was meticulously recorded and subsequently dichotomized into two categories: ≤60 years and >60 years. This stratification diverges from most sources surveyed in the current literature, which conventionally utilize 65 years as the demarcation threshold. The rationale for adopting a lower age criterion in this study stems from the observation that less than one-fourth of the patient population exceeded 65 years at the diagnosis of brain metastases. In contrast, approximately half of the patients were over the age of 60 years. Hence, an age cut-off of 60 years was deemed more representative for this analysis. Survival was calculated from the date of radiological diagnosis of brain metastases to the date of death, or for those who were alive at the end of May 2016, which is the date of the last collection of information from the relatives.

Treatment

All patients underwent a detailed neurological assessment in the outpatient clinic. Radiotherapy was started as a priority, depending on the available space at the treatment machines. Whole brain radiotherapy using two lateral opposed techniques was used for all patients. All cases received 20 Gray/five fractions over one week. Supportive care in the form of medical decompression, anti-epileptics, and physiotherapy was given to patients with or without hospitalization, depending on clinical symptoms. All patients were re-assessed once during treatment and finally after radiotherapy.

Statistical Analysis

The primary endpoints for this analysis were survival outcomes (in months) and prognostic factors affecting it. The Kaplan Meier method was used in (IBM® SPSS® version 23). The Log-rank test with a p-value of ≤ 0.05 was used to indicate statistical significance.

RESULTS

In this study, 59 patients were included. The age ranged from (39-79) with a median age of 62 (Table 1). The median survival after the diagnosis of BM was 6.5 months. The range is between (2-18) months (Figure 1).

Age, KPS, ECM, and number of brain lesions were statistically significant prognostic factors in patients with BM from NSCLC. In contrast, there was no statistically significant correlation between the survival with sex and histology. The findings can be summarized as follows:

- The older the age at the diagnosis of BM, the less the survival outcome (Figure 2).
- Patients with a KPS of 70 or more had higher survival than those with a KPS of less than 70 (Figure 3).
- Patients with single brain lesions survived more than those with multiple lesions (Figure 4).
- Patients with only BM had more prolonged survival than those with ECM (like bone, liver, adrenals, etc.) (Figure 5).
- There was no significant association between the sex or the histology with the survival outcome, P = 0.84 and 0.34, respectively (Figures 6 and 7).

DISCUSSION

Brain metastasis is an essential cause of NSCLC-associated morbidity and mortality. The overall prognosis after the detection of BM is dismal, except for a subset of patients with a solitary BM and those with positive molecular markers, where we can use specific targeted therapies [15]. Historically, BM from NSCLC was felt to represent a poor outlook [16,17]. More recently, there has been a shift toward more aggressive local management in selected patients to maximize survival and neurologic function [18]. The present study investigated the survival outcome in patients with BM from NSCLC after WBRT and the prognostic factors affecting it. The median survival after the diagnosis of BM was 6.5 months. Several prognostic factors affected survival after the BM diagnosis, while others did not.

Age: The present study had a statistically significant association between age and survival. The results from other studies also compared age with survival and found age to be an important predictor for survival [19,20]. However, in our analysis, we couldn't collect information about associated comorbid diseases like ischemic heart disease, hypertension, and diabetes mellitus, especially in elderly patients, that could have an impact on survival.

Primary tumor control: In this study, primary tumor control was not included in the materials of this study because it depended mainly on the telephone calls and patients' chart reviews, which, at the time of data collection, most patients had already died, and it was challenging to get this information from the relatives. Some studies found that controlling the primary tumor will strongly affect survival. Reviewing these studies showed longer median survival time in patients with controlled primary tumors through surgical resection, chemotherapy, and radiation therapy [19,21].

Karnofsky performance status (KPS): The KPS had a statistically significant correlation with the survival rate of BM patients from NSCLC. Patients with good performance status (KPS ≥ 70) had better survival. However, KPS will be strongly affected by other extracranial metastases, as well as the number and size of brain lesions. The presence of ECM and multiple brain lesions will result in low KPS and poorer survival [4,19-22]. However, the Rotterdam score used another scale for performance status instead of KPS, Eastern Cooperative Oncology Group (ECOG), which uses a different scoring system (a 0-4 score for ECOG, while KPS uses a 0-100 score).

Number of brain lesions: Our analysis showed a statistically significant relationship between the number of brain lesions and survival. Patients with single brain lesions showed better survival in comparison to those with multiple brain lesions. Other studies have also demonstrated better survival in patients with fewer brain lesions [19,20].

Histology: The present study showed no significant association between survival and histology of NSCLC. In analyzing 190 patients with NSCLC, Kepka et al. reported a lack of prognostic significance of histology on survival. However, excluding patients with a non-specific histological subtype showed better survival for adenocarcinoma on univariate analysis [23].

Sex: The results of our study support no available association between sex and survival in NSCLC BM patients. There is a large number of publications suggesting that women diagnosed with NSCLC and SCLC have a better prognosis than men [24-28]. With specific reference to BM and NSCLC, retrospective studies suggest that the female sex may positively impact outcomes [29-31]. Two reports indicate no association between sex and survival [32,33].

The basis for this provocative relationship between female sex and lung cancer outcomes remains unclear. Still, it seems to transcend stage or some patient-related variables and tends to support an intrinsic biological basis for the improved survival of women [34].

The prognostic significance of sex in NSCLC, especially in the setting of BM, needs systematic evaluation at the molecular level, exploring the biological differences in the natural history of lung cancer between men and women [35].

Limitations of this study: The main limitations of this study were the retrospective design, small sample size, single-institutional cohort, and single treatment arm without any other available treatment arms to be compared. Additionally, targeted therapies that can effectively address brain lesions in the modern era of systemic treatments are insufficiently available.

Strengths of this study: It is the first in the Kurdistan (Northern Iraq) region.

CONCLUSIONS

Survival after the diagnosis of BM is generally poor, with a median survival of 6.5 months. The age, number of brain lesions, performance status, and active extracranial disease are the significant indicators of outcome following therapy in BM from NSCLC. The sex and histology do not affect survival outcomes.

Further work is needed to find detailed prognostic scores, and there will probably be a group of patients with poor prognostic features who might need the best supportive care without radiotherapy. Future computer-based data archiving is required for easy access to all patients' information regarding their entire history and examination, as well as investigations done for them and medications given to them. Research on survival and prognostic factors in cancer patients should be done with a bigger sample size, prospective design, and the inclusion of other cancer institutions in Iraq for better results and also different types of primary tumors with BM to be studied.

Table 1. Patient and tumor characteristics.

Characteristics	Category	Number	Percentage
Age	≤ 60	27	45.8
	> 60	32	54.2
Sex	Male	43	72.9
	Female	16	27.1
KPS*	≥ 70	32	54.2
	< 70	27	45.8
Histology	Adenocarcinoma	39	66.1
	Squamous cell carcinoma	12	20.3
	large cell carcinoma	1	1.7
	Non-small cell lung cancer	7	11.9
Extracranial metastasis	Yes	19	32.2
	No	40	67.8
Number of brain lesions	Single	24	40.7
	Multiple	35	59.3
Status	Alive	7	11.9
	Dead	53	88.1
Total		59	100

KPS: Karnofsky performance status

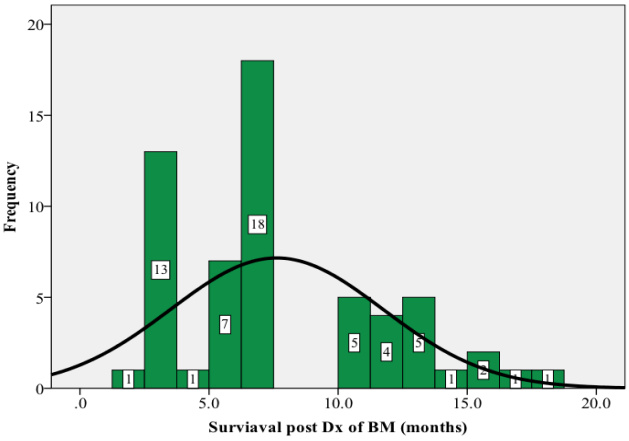

Figure 1. Survival curve of patients from the time of the diagnosis of BM to death

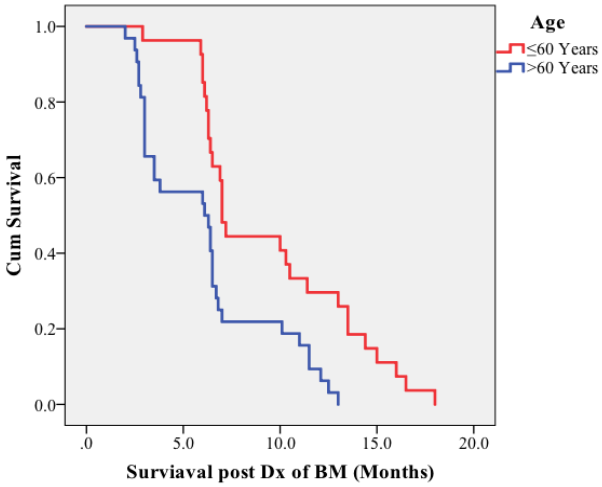

Figure 2. Survival outcome with the age at diagnosis of BM.

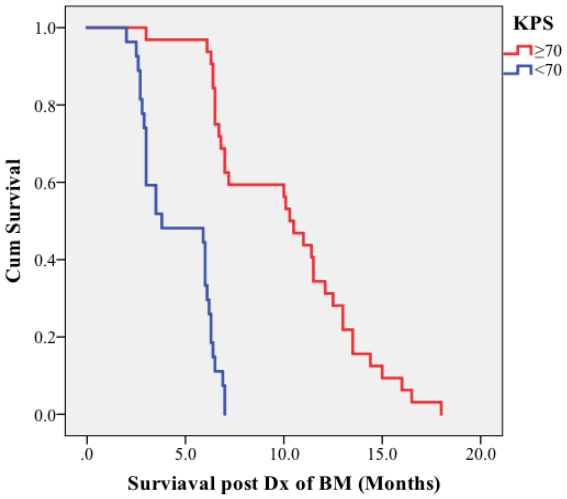

Figure 3. Survival outcome with KPS.

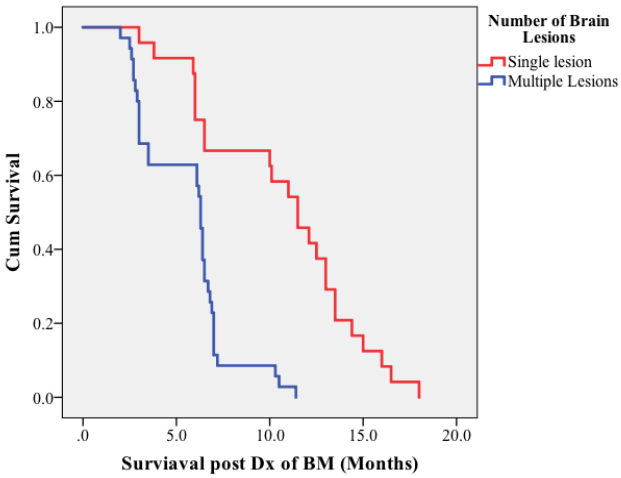

Figure 4. Survival outcome with the number of brain lesions at the time of diagnosis of BM.

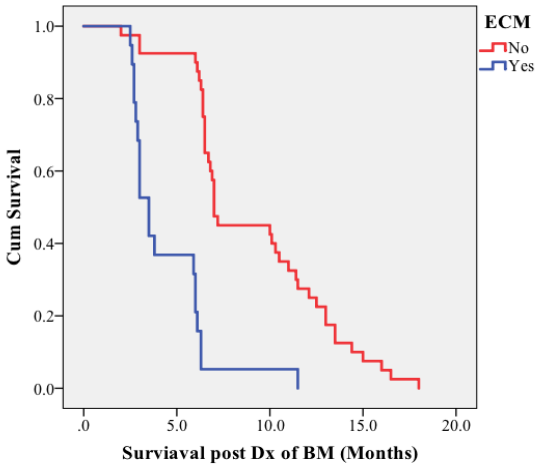

Figure 5. Survival outcome with the presence and absence of ECM.

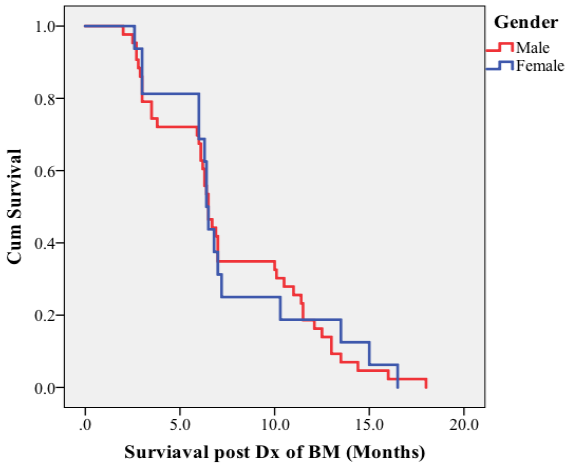

Figure 6. Survival outcome with sex

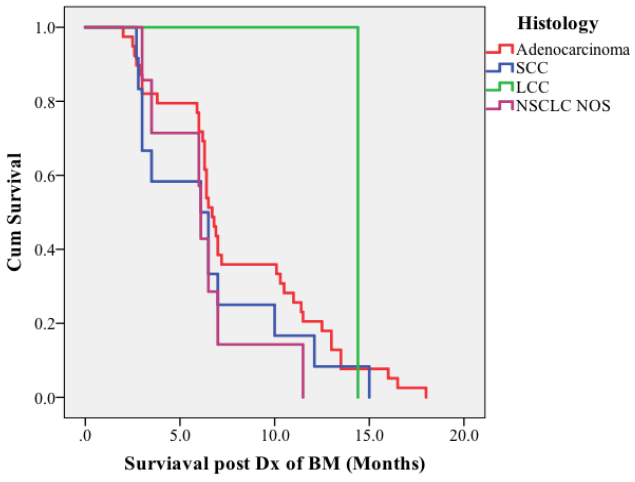

Figure 7. Survival outcome with the histology of NSCLC.

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