Original Research Article

Survival in Patients with Brain Metastases from an Unknown Primary Tumor

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Abstract

Aim: To analyze the survival rate and the prognostic factors of patients with brain metastases from unknown primary (BMUP) cancers. **Material and Methods:** We conducted a retrospective study with 55 patients (mean age- 62.8 years and range 22–80), with male 43 patients (78%) and female12 patients (22%) at the time of diagnosis, who presented to our outpatient oncology department between June 2015 and June 2019. We made the following variables as significant prognostic factors for a prominent index of patients' survival: age, gender, Karnofsky performance score (KPS), number of metastatic lesions, primary site and type of treatment. Patients' survival was evaluated from plotted Kaplan– Meier curves and the log-rank test for univariate analysis. **Results:** The mean follow-up was 13 months (range 4–60 months). The mean survival after the diagnosis of brain metastasis was 18.7 months for this study. Lung cancer was the most common primary tumor (74.5%). The KPS and number of lesions were found to have a prognostic effect on survival. Survival analysis showed no statistical significance with age, gender, primary site and type of treatment. **Conclusion:** This study showed that KPS and the number of lesions affect the survival outcomes. Therefore, BMUP cancer is indeed related to poor prognosis.

Keywords: Brain metastases, Neoplasm, Survival analysis, Unknown primary, Prognosis

Abbreviations: BMUP- Brain metastases from unknown primary, KPS- Karnofsky performance score

Introduction

Brain metastases are the most common intracranial tumors with a higher prevalence rate than primary malignant brain cancers[9]. The incidence rate of metastatic brain tumors has been increasing, mainly because brain metastasis has remained an indicator of poor prognosis with debilitating effects on many critical functions controlled by the organ and results in nearly always a fatal outcome in patients with solid cancers. Patients' survival is typically <2 years, and a few patients would survive for >4 years[2].

Intracranial metastases are regarded as end-stage cancers related to significant morbidity and mortality[4]. In the past, survival time of a patient with a metastatic cerebral tumor was approximately a month without treatment[10].Only palliative treatment was used, and personalized treatment modalities had a limited potential to increase survival times[4]. Lately, however, continuous developments in chemotherapy, notably in small cell lung cancer and breast cancer, have improved diagnostic methods that enable early detection and are expected to increase survival rates[7].

Although the primary tumor site is crucial for the choice of treatment, 15% of patients with metastatic intracranial tumors are diagnosed with the unknown primary site. Neurological symptoms of brain tumors can be the first sign of an undiagnosed metastatic disease[2]. The National Institute for Health and Care Excellence (NICE) also highlighted the scarcity of data regarding brain metastases of unknown primary[6].

We aimed to retrospectively evaluate 55 patients with brain metastases of unknown primary cancer at the time of diagnosis and evaluate potential factors (age, gender, Karnofsky Performance Score, number of metastases, treatment type) that attribute to patients' survival time.

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Material and Methods

This retrospective study was conducted at Nalanda Medical College and Hospital Patna, between June 2015 to June 2019, enrolling 55 patients with brain metastases from unknown primary tumors at the time of diagnosis with consistent followed up and enrolled in the study. Exclusion criteria were patients with brain metastases from known primary sites.

Written informed consent was obtained from all participants. Demographic and clinical characteristics were obtained from patients' medical records. The following variables as significant prognostic factors for a patients' survival: age, gender, mean survival time, performance status based on Karnofsky Performance Status (KPS; scores range: 0–100), number of metastatic lesions, the primary site that was detected in evaluations, and type of treatment (if metastasectomy performed or not). Overall survival was calculated from the date of diagnosis until death from any cause or last date of a patient known to be alive. For the detection of primary cancer, a routine diagnostic evaluation was done. Final identification of the primary tumor was based on histopathological examination of either cranial resection or tissue biopsy material from a radiologically-detected primary tumor.

Each of the parameter was divided as below 60 or above 60 years for age and male or female for gender. Patient performance which was assessed by Karnofsky score was divided as below 70 or above 70 score. Number of lesions were classified as single/two or over three for several lesions. Primary tumor site was classified as lung or another primary for primary site. Finally, treatment was classified as surgical or nonsurgical treatment of cranial metastases. The effect of each variable on survival was determined by univariate analysis.

Statistical Analysis

All analyses were carried out in Statistical Package for the Social Sciences (SPSS). Numerical data were presented as a mean and standard deviation. Relative frequencies were described as percentages. Kaplan–Meier curves were plotted for evaluation of survival, and the log-rank test was used for univariate analysis. The

level of significance was set at p<0.05.

Results

During the study period, 222 patients with brain metastasis were admitted to the hospital. Among these, 60 (27%) patients were diagnosed with unknown primary tumor. Fifty five (n=55, 91%) out of 60 patients with unknown primary tumors had regular follow-ups and were enrolled in the study. Forty two (n=43, 78.0%) out of 55 patients were male, and the remaining 12 (22.0%) were female. The mean age of the patients was 62.8 years (range 22–80). Mean age of men = 63.8 ± 10.3 years and for female = 59.4 ± 14.9 years respectively. The primary cancer type was determined with histopathological examination of either resection material of cerebral metastasis (n=7, 12.7%) or tissue biopsy material of radiologically-detected primary tumor (n=48, 87%). Seven patients (n=7) were treated with cranial metastasectomy and radiotherapy; 48 patients only received cranial radiotherapy as a local treatment. All patients received palliative systemic chemotherapy based on primary tumor pathology.

After the diagnostic examinations, the most common primary site for cancer was found to be the lung (n=41, 74.5%), followed by breast (n=6, 10.9%), kidney (n=2, 3.6%), colon (n=1, 1.8%), gastric (n=1, 1.8%), rectum (n=1,1.8%), and laryngeal (n=1, 1.8%), and melanoma (n=2, 3.6%).

Twenty seven (n=27, 49%) out of 55 patients were below 60 years, and the remaining 28 (51%) subjects were above 60 years. Regarding functional status, 35 patients were assigned a KPS≥70 (n=35, 63.6%), while 20 patients had a KPS<70 (n=20, 36.4%). Twenty nine (n=29, 52.7%) out of 55 patients had one or two metastatic lesions, and the remaining 26 (47.2%) subjects had ≥3 lesions. In 7 (12.7%) patients metastasectomy was performed, and in 48 (87.2 %) patients, no surgical treatment was performed (Table I).

The death occurred in 14 patients (25%). Lung tumors accounted for most deaths (n=11), followed by melanoma (n=1). One gastric tumor and one colon cancer were responsible for the other two deaths.

The mean follow-up was 13 months (range 4–60 months). Mean survival after diagnosis was 18.7 months (range 16.35– 21.17) (17.7 months for men and 19 months for women). From the factors evaluated, KPS and the number of metastatic lesions were found to have a prognostic effect on survival time. Mean survival time, according to KPS, was 22.1 months for KPS≥70 and 15.4 months for KPS<70 (p=0.006). Mean survival time according to the number of metastatic brain lesions was 21.7 months for <3 lesions and 14.5 months for ≥3 lesions (p=0.002).

Mean survival time did not differ among the age groups below or over 60 years (p=0.373). There was also no significant difference in mean survival time according to gender (p=0.184), tumor site (p=0.245) and type of treatment (p=0.582).

Discussion

Total 55 Patients with brain metastasis of unknown primary location at diagnosis were retrospectively evaluated in our study to determine the prognostic factors affecting these patients survival time. The mean survival time was 18.7 months. Demographic data age, gender, KPS, number of metastatic lesions, the primary tumor type, and type of treatment were evaluated in univariate analysis. From the factors examined, only KPS below 70 and cerebral metastases number at least or more than three correlated with decreased survival rates.

The frequency of metastatic cerebral tumors is increased due to improved systemic disease control, advanced imaging modalities,and increased use of routine screening for staging.

Cerebral metastases constitute 10–35% of all cerebral metastatic lesions[9]. These metastatic tumors had different characteristics of complicating treatment, prognosis, and treatment responses. Nevertheless, cerebral metastases, typically, are considered to be related to poor prognosis[8]. Treatment options might differ with the number of metastases, cerebral location, patients performance status, and primary cancer type. The use of steroids is the first step of treatment after diagnosis. Surgery or radiosurgery might be prioritized in patients with a single metastatic lesion. In the case of multiple metastatic tumors (>3), whole-brain radiotherapy with or without a combination of chemotherapy is generally preferred. The efficacy of systemic chemotherapeutics is limited and might be suggested in the selected cases [2,9.]

Overall, most of the metastatic lesions to the brain were primary from lung, breast, and melanoma. Other cancers that tended to migrate to the brain included colorectal carcinoma, renal cancers and gastrointestinal malignancies[4] Majority of the primary tumors identified in our study were lung, breast and renal carcinoma consistent with reports in the literature. The lung was the major primary location of the metastatic disease (74.5%); however, breast cancer constituted only a small part (10.9%). In previous publications, the rate of breast cancer was reported to be higher and was attributable to the heterogeneity of our study population [11,12].

As per Gaspar et al. involving 1200 patients from three different brain metastasis trials, reported that the most favorable prognosis was observed in patients who were younger than 65 years old, who had a higher KPS than 70, who had the primary disease under control and who had only isolated brain metastasis[5]. If these all four factors were present, patients had a 52% probability of survival for at least 200 days. Similarly, studies with 2000 patients by Sperduto et al. reported four prognostic factors regarding improved survival in brain metastases. These four factors included patients' performance status (KPS≥70), age (<60), the number of brain metastases(<3), and metastases limited to the brain. A graded prognostic assessment classification is established with these factors [13].

However, high KPS and a low number of lesions had a statistically significant prognostic effect on survival in this study despite previous publications[11]. In Rotta et al. a study with 71 subjects, reported that only gender affects survival, without any noticeable effects of age, histological type, KPS, location of cerebral metastases, and treatment type on survival[11]. Similarly our results showed that surgically (metastasectomy) treated patients had similar outcomes and survival rates with those not treated with surgery. Although the sample size is unbalanced, and the metastasectomy group had very few patients (n=7, 12.7%) These findings suggested that local treatment of cerebral metastases does not significantly change the disease course. D'Ambrosio and Agazzi also supported that survival was not related to the known and unknown location of the primary tumor (4.5 months for diagnosed and 6 months for undiagnosed primary cancer). For a study that enrolled 342 patients, the authors reported that age (<65 years), treatment status at discharge, asymptomatic brain metastasis, and isolated brain metastasis improved survival[3]. Bartelt and Ruttelbach evaluated 916 patients with brain metastases. Among those, 47 patients displayed unknown primary at diagnosis. The authors reported a 4.8 month median survival time for BUMP cancer and also showed that KPS status and resection surgery status were independent prognostic factors of survival[1].

The limitations of this study are that it is a retrospective study, data acquired were from a single-center with relatively small sample size due to the scarcity of BUMP cancer patients. Thus, prospective observations without selection biases and randomized controlled trials are needed to individualize the treatment options, especially with end-stage cancer patients diagnosed with cerebral metastases to improve survival.

Table I: Univariate Analysis Characteristics on Survival in Patients' with Brain Metastases of an Unknown Primary Site

Parameter	Subgroup	Number of Patients n (%)	Survival (months)
Age	< 60	27(49)	17.8
	>60	28(51)	20
Sex	Male	43(78)	19

	Female	12(22)	17.7
KPS	<70	20(36)	15.4
	>70	35(64)	22.1
Number of Lesions	<3	29(53)	21.7
	>3	26(47)	14.5
Primary Tumor Site	Lung	41(75)	17.7
	Others	14(25)	21.4
Surgical Treatment (Metastectomy)	Yes	7(13)	17.5
	No	48(87)	18.9

KPS - Karnofsky Performance Status

Conclusion

Patients with metastatic tumors at the time of cancer diagnosis have approximately 18.7 months of survival. This study showed that KPS and the number of lesions affected survival outcomes. However, treatment response and survival outcomes substantially depend on patients' overall status and aggressiveness of the systemic disease.

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