

RETROSPECTIVE ANALYSIS OF PREVALENCE OF BRAIN METASTASIS IN VARIOUS CANCERS AND THEIR SURVIVAL- INSTITUTIONAL EXPERIENCE

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Abstract

Background: Brain metastasis (BM) is the most common intracranial tumor in adults, with an incidence of 20% to 40%. Though it is most common in lung cancer, 20% may present upfront with BM, as in melanoma. Multiple site metastases are commoner, with most common site being the cerebral hemisphere (80%). The study's objective is to analyse the prevalence of brain metastasis in various cancers and their survival. **Materials and Methods:** One hundred thirty-six patients diagnosed with brain metastasis in our institution from 2018 to 2022 were analysed retrospectively. The prevalence, progression-free survival (PFS) and overall survival (OS) were calculated. **Result:** The median age of presentation was 56 years, with female preponderance. Of 136 patients, 47% had lung primary, and 29% had breast primary. The most common sites of brain metastasis are the cerebral hemisphere (85%), cerebellum (32%) and brain stem (7%). About 28% had solitary brain metastasis, most in the frontal region. On analysis, the prevalence of brain metastasis in lung cancer has increased from 9% in 2018 to 16% in 2021. PFS for cervix, lung and breast carcinoma were 2-3 years, ten months and 1-4 years respectively and for ovary and rectum carcinoma ranges from 3 to 8 years. Of 76 patients who received whole brain radiotherapy, OS for lung cancer is less than 12 months, breast carcinoma is 2-5 years, and melanoma is six months. **Conclusion:** The factors like the primary site, upfront presentation, multiple-site brain metastasis, molecular markers and extracranial metastasis affect PFS and OS.

INTRODUCTION

The most common intracranial neoplasm in adults is Brain metastases (BM). The incidence of BM is 20% to 40%^[1] and there is no difference between males and females, except in a few studies.^[2] The most common primary with BM is lung (20-50%), followed by breast (5-20%), melanoma (7-10%), kidney (4-6%) and colorectal (2-5%). Moreover, about 20% of patients may present upfront with brain metastasis. Though the highest numbers of brain metastases come from the lung, melanoma has the highest propensity of all malignant tumors to metastasize to the brain.^[3] The median interval between cancer diagnosis and identification of brain metastases ranges from 2 to 9 months for lung and 1 to 3 years for breast, respectively. The development of brain metastases is a complex process. First, the

primary cancer cells must invade the surrounding tissue and vessels and enter the circulatory system. Finally, cross the blood-brain barrier, colonize, and grow in the brain parenchyma.^[4,5]

The selective pressure in brain parenchyma makes brain a preferential site of metastasis. The common sites of BM are the cerebral hemisphere (80%), cerebellum (15%) and brain stem (5%), with multiple sites being commoner than single site. It is a complication of systemic malignancy contributing to overall morbidity and mortality in our country and is considered a poor prognosis. The frequency of detection of brain metastasis is thought to be rising due to longer survival after a primary cancer diagnosis. Moreover, due to improved imaging detection and the availability of newer systemic treatments and emerging targeted therapeutics, the

prevalence of BM is increasing as the mortality rates are declining.^[6,7]

Solitary BM is common in breast cancer in about 50% of individuals with BM. Hence surgical resection is reserved for lesions causing life-threatening complications, requiring pathologic confirmation or in patients with good performance status [i.e., Karnofsky Performance Status (KPS) ≥ 70] with controlled extracranial disease burden. Stereotactic Radiosurgery(SRS) is indicated for 1 to 3 metastases with a maximum diameter of 4 cm for the largest lesion and additional lesions not exceeding 3 cm. SRS achieve excellent local control because of the penumbra dose beyond the periphery of the metastatic lesion, sterilizing microscopic disease. However, as these patients have a short life expectancy, the treatment options are intended to achieve local control of the metastatic lesion, improve their quality of life, and prevent death from neurological disease.^[6] Whole brain radiotherapy (WBRT) is the standard of care in patients with diffuse brain metastasis (≥ 5 brain metastases) with overall response rates of 70% to 93% with significant decline in learning and memory function. However, Hippocampal avoidance WBRT (HA-WBRT) preserved memory-related dysfunction. The study aims to understand the prevalence of brain metastasis in various cancers and their survival.

MATERIALS AND METHODS

Our retrospective observational analysis included patients diagnosed with brain metastasis and taken policy in our tumor board as Whole brain radiotherapy (WBRT) from Jan 2018 to Dec 2022. The data were analysed from recorded master case sheets taken from our medical records department.

Patients were staged on the basis of 8th edition of American Joint Committee on Cancer staging manual. Patients who presented upfront with BM, diagnosed to have BM during their treatment and who developed BM during follow-up were included. Patient without primary identified but had BM were included in our study. For survival analysis, patients or their attenders were contacted over phone and if could not be reached, then date of last follow up was taken.

The prevalence of BM, progression-free survival (PFS) and overall survival (OS) were calculated. Prevalence is the proportion of the population affected by brain metastasis at a given time. Progression-free survival is defined as the time from cancer diagnosis to disease progression. Overall survival is the time from cancer diagnosis to death from any cause. Multivariable logistic regression analyses were done among the patients to determine whether age, gender and primary cancer type were associated with the presence of brain metastases. Survival analyses were done using the Kaplan-Meier survival analysis method.

RESULTS

About 136 patients diagnosed to have brain metastasis were analysed retrospectively. The estimated cases of BM in various cancer in descending order is found to arise from lung (47%), breast (29%), melanoma (4%), cervix (3%), sarcoma (2%), renal (1%), colorectal cancer (2%) and unknown primary (2%) and other miscellaneous cancers (10%).

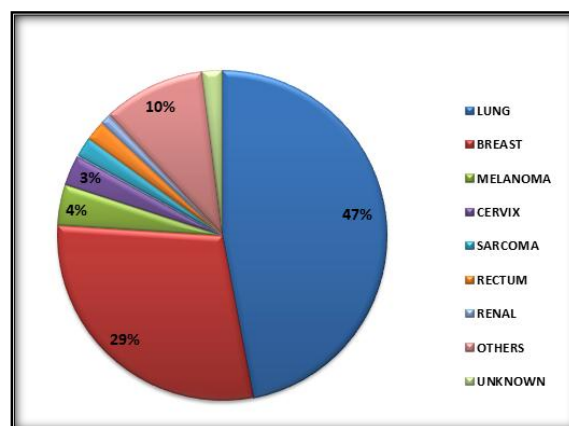


Figure 1: Partitioning of Brain Metastasis

The demographic characteristics are shown in [Table 1]. The median age with BM presentation was 56 years, with female preponderance. The median Karnofsky performance status (KPS) at BM diagnosis was 60.

Table 1: Demographic characteristics

		No of patients (%)		
		LUNG	BREAST	MELANOMA
Age	21-30	1(1.5%)	3(7.5)	
	31-40	4(6%)	5(12.5%)	1(20%)
	41-50	16(26%)	13(32.5%)	2(40%)
	51-60	30(47.5%)	15(37.5)	1(20%)
	60-70	9(14%)	3(7.5)	1(20%)
	70-80	3(5)	1(2.5%)	0
KPS / ECOG at BM diagnosis	90 – 100 / 0			
	70 – 80 / 1	7(11%)	4(10%)	1(20%)
	50 – 60 / 2	29(46%)	25(62.5%)	
	30-40 / 3	20(32%)	11(27.5%)	3(60%)
	10-20 / 4	7(11%)		1(20%)

Sex predominance	Male	39(62%)	3(7.5%)	4(80%)
	Female	24(38%)	37(92.5%)	1(20%)
Family History	Present	3(5%)	4(10%)	0
	Absent	60(75%)	36(90%)	5(100%)
Treatment details	WBRT received	36	29	4
	Completed	27	25	2
	Defaulted	9	4	2
	WBRT not received	27	11	1

Table 2: Histology and immunohistochemistry among the study.

	LUNG	BREAST	MELANOMA
Histology	Adenocarcinoma – 46 (73%)	Infiltrating ductal carcinoma – 38 (95%)	Malignant melanoma – 5 (100%)
	Adenosquamous – 3 (5%)	Metaplastic carcinoma – 1 (2.5%)	
	Small Cell – 5(8%)	Mixed Lobular & Ductal – 1 (2.5%)	
	Large cell – 1 (1.5%)		
	Squamous cell carcinoma – 8 (12.5%)		
Immunohistochemistry		ER/ PR –ve& Her 2 +ve – 9(22.5%)	
		ER/ PR +ve& Her 2 –ve - 3(7.5%)	
		Triple Negative – 13(32.5%)	
		Triple positive – 11(27.5%)	
		Not Known – 4(10%)	

The development of BM was not associated with patients who had a strong family history. About 11% defaulted treatment due to poor general conditions like Anemia. About 29% patients did not receive WBRT because they were not willing for treatment or defaulted to follow-up after diagnosis or had poor general condition. The common metastatic sites in the brain are as shown in Figure 2. The most common site of brain metastasis in the cerebral region was the Frontal lobe. Cerebellar (12%) metastasis was seen predominantly in breast carcinoma patients. Melanoma, Ovarian and Small cell carcinoma lung patients also had metastasis in the brainstem. In cervical carcinoma with BM, patients (100%) had poorly differentiated squamous cell histology.

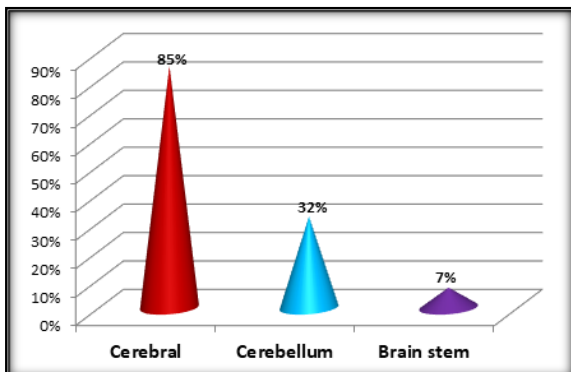


Figure 2: Sites of Brain Metastasis

Though multiple extracranial site metastases were predominant, breast(6%), lung(3%), ovarian(0.7%), prostate(0.7%), and head and neck carcinoma patients(1.5%) had solitary brain metastasis. About 28% of patients had single-site brain metastasis, which was predominant in breast carcinoma(15%) patients. The predominant single site of brain metastasis in breast carcinoma patients was in the cerebral region in the Frontal lobe (9%).

Melanoma patients presented predominantly with brain metastasis upfront, followed by Sarcoma and Lung carcinoma. Cervical, rectal, head and neck carcinoma patients developed brain metastasis during their follow-up period [Figure 3].

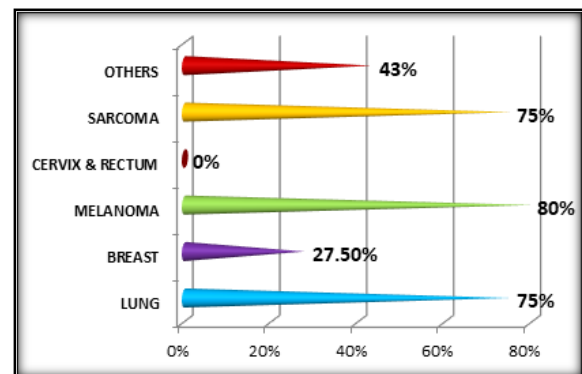


Figure 3: Brain metastasis as upfront presentation

BM prevalence in lung cancer increased from 9% in 2018 to 16% in 2021 and in Breast cancer from 2% in 2018 to 6% in 2021. PFS for cervix – 2 to 3 years, lung – 10 months, breast carcinoma – 1 to 4 years, and ovary and rectal carcinoma ranges from 3 to 8 years.

Overall survival analysis by Kaplan Meir curve is depicted in Figure 4. We can see that overall survival is low for melanoma, about six months, and highest for breast carcinoma, about five years and still, two breast carcinoma patients treated in 2018 are surviving. However, OS for breast carcinoma varies depending upon the molecular subtypes. In descending order OS for Triple positive, Luminal type, and Triple-negative breast carcinoma is 4-5 years, 2-3years and two years, respectively. Moreover, the patients who had BM upfront had low survival compared with those who progressed during treatment. The improved survival did not correlate with patients who underwent WBRT. But they were symptomatically better. However,

improved survival was seen in patients who received systemic chemotherapy.

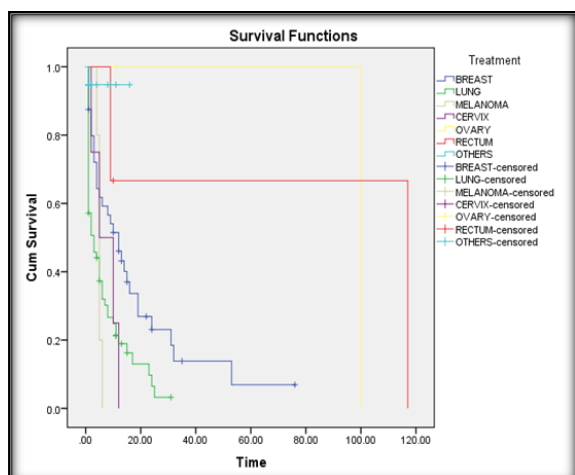


Figure 4: Overall survivals

DISCUSSION

This retrospective study analysed the prevalence of BM in various cancers, as shown by many studies.^[2] Lung cancer is the most common cancer to metastasize to the brain, followed by breast and melanoma, and this trend has been proven in our study. This is because, as per the study by Kromer et al., cancer cells from most primaries must reach the brain through the lungs. However, in lung cancer, cancer cells travel directly from the pulmonary venous system to the brain through the heart, which makes it the most common to metastasize to the brain.^[8]

Though melanoma has the highest propensity to metastasize to the brain,^[9] it accounted for 4% of BM in our study. It is much lower than the Western studies, with an incidence of 40%.^[10,11] The lower incidence in our population and the lack of autopsies could account for this finding. Our result is similar to studies conducted by Patnayak et al. and Singh et al., accounting for 5% and 4.8%, respectively.^[12,13] There was also a difference in sex distribution. Melanoma and lung cancer were common in men, and breast carcinoma in females. Our study also shows a rising trend in the female population being diagnosed with lung carcinoma with BM.^[14] As per study by Posner et al., lung cancer and melanoma are more likely to be associated with multiple brain metastases, whereas breast, renal, and colorectal cancers have a slightly higher likelihood of developing a single brain metastasis which has been shown in our study.

In 40 patients with breast cancer and brain metastases in our study, 32.5% were found to have triple-negative cancer. BRCA1 mutations are often associated with triple-negative breast cancer.^[15] In a study by Albiges et al., 67% of patients with BRCA1 mutation developed brain metastases.^[16] In our study, 22.5% belong to HER 2 positive subtypes, and 27.5% are triple positive. Above 25%

of all breast cancers will show HER2 amplification, an independent prognostic factor for developing brain metastases, as per a study by Anders et al.^[15]

In a study by Kim et al., only 1% of Renal cell carcinoma (RCC) accounts for brain metastasis.^[17]

In our study, 2(1.5%) patients with RCC had been documented because they probably had not survived due to hemorrhagic metastasis. An autopsy had not been carried out to document the brain metastasis. The prevalence of brain metastasis has increased because of imaging modalities available and improved patient survival due to novel treatment methods.^[6] Due to improvements in Her2-directed regimens, the overall survival is better than in older studies.^[18-20] The survival report for lung cancer by Melosky et al. shows a survival benefit of 47 months with EGFR-directed therapy.^[21]

Our study showed an overall survival benefit of only nine months. This may be because of late presentation to our hospital with poor general condition and drug non-compliance due to the long distance from home to our centre. Moreover, patients who were evaluated for driver mutation were low in our study. This may be because many patients in our study are below the poverty line and are not covered under insurance. Brain metastasis is an important cause of morbidity and mortality for patients with cancer. Hence, early detection of brain metastases may minimize morbidity, mortality, and treatment-related toxicity.

CONCLUSION

Thus, primary site, upfront presentation, multiple site brain metastasis, molecular markers, and extracranial site metastasis affect PFS and OS. The limitations of our study are vast data and each can be analyzed separately in future studies. It's a retrospective analysis, and future prospective studies can help assess these patients neurocognitive status and treatment outcomes. If required, MRI brain can be done prophylactically in future in patients with high-risk features. This can help in early diagnosis of BM, thereby improving survival. Moreover, all patients in our study had been treated only by WBRT. In the future, steps to cover all common driver mutations under insurance can help choose targeted therapy to improve their survival.

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