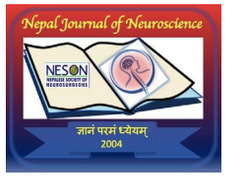
Brain Metastases: Outcome Related to Prognostic Indices: Critical Review a Single Institutional Experience



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Abstract

Introduction: Brain metastases are the most common brain tumour. There are various prognostic indicators which determine the overall outcome and survival of the patient.To study the outcome of the patients of cerebral metastases based on various indices and to correlate the prognostic significance of these indices.
Material and Methods: A total of 123 surgically resected cases of brain metastases from July 2007 to July 2017 were included in the study. The clinical details including the age, gender, clinical features, location of the primary, status of control of primary disease, Karnofsky performance status, number and intracranial location of the metastases were obtained. The follow up period for the study was at least 36 months.
Results: The prognostic factors associated with better survival were KPS > 60 (p value < 0.0001), controlled status of the primary malignancy (p value < 0.0001), age < 50 yrs(p value< 0.0001) and number (<3) of metastases (p value < 0.000). Gender (p value = 0.902), primary site (P = 0.758) and location of intracranial metastases (P = 0.575) had no significant impact on the survival.
Conclusion: Of the various prognostic indices, patients with KPS > 60, well controlled primary malignancy, age <50 yrs. and number of metastases less than 3, were related to statistically significant better prognosis and survival.

Key words: Brain metastases, prognostic indices, KPS score.
Key Message: Patients with KPS > 60, younger than <50 yrs. of age, with well controlled primary malignancy and less than 3 cerebral metastases do well with surgery.

Introduction

Cerebral metastases are the most common type of intracranial tumour. It accounts for more than half of brain tumours. In patients with primary malignancies, brain metastases occur in 10 to 30 percent of adults and 6 to 10 percent of children 1 [https://doi:10.1038/s41572-018-0055-y]. This includes in the order of precedence lung, breast, gastrointestinal tumours and melanoma followed by unknown primary.[2] The early diagnosis of cerebral metastases has increased in due course of time with increase in imaging modalities.[2] However, these imaging modalities may not be able to differentiate metastatic lesions from primary malignant lesions and non-neoplastic lesions.[3] Definitive histological diagnosis is required for the commencement of chemotherapy and radiotherapy even if it is a surgically non-resectable lesion.[3] The overall survival is determined by the stage of systemic disease and neurological manifestations.[4] As per literature, the various prognostic indices which determine the overall survival are preoperative Karnofsky score, number of metastases, age, and status of primary disease, primary pathology and gender. Surgical resectability requires consideration of the above prognostic factors.[5] In good prognostic scores combination of surgery with radiotherapy is superior to WBRT alone including in single brain lesion6. In an emergency situation, a total surgical excision is indicated if the lesion is in the posterior fossa compressing the ventricle leading to clinical features of increased intracranial tension. Another alternative is radiosurgery if the size of the lesion is < 3 cm and deep seated.[7]

This study was conducted to assess the clinical outcome of the patients based on the prognostic indices like number of metastases, KPS Score, status of primary disease and other clinical parameters like age, gender, signs and symptoms, the

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histological diagnosis and the primary pathology. This article reviews the strength and weakness of different prognostic indices and highlights the broader perception of the clinical outcome based on the above indices.

Materials & Methods

This was a retrospective cum prospective study of ten years duration on patients who underwent surgical resection for cerebral metastases at our institution (Jul 2007 to Jul 2017) and patients were followed up for a minimum period of 36 months. Inclusion criteria include non haematological solid tumour malignancies. Haematological, lymphoid and meningeal tumours were excluded. The clinical details of the patients including the factors mentioned above were collected and analysed to look for their impact on the overall outcome and survival. The statistical methodology used was SPSS Version 24 (Free version)

Table 1: Clinical and demographic profile of the patients

TOTAL NUMBER OF PATIENTS (n=123)				
VARIABLE		**MALE (n=43) (34.9%)**	**FEMALE (n=80) (65.04%)**	**TOTAL (n=123)**
1.	**AGE (in years)**	03 (6.9%)	03 (3.7%)	06 (4.8%)
a.	**<50**	18 (41.8%)	25 (31.2%)	43 (34.9%)
b.	**50 – 60**	20 (46.5%)	51 (63.7%)	71 (57.7%)
c.	**60 – 70**	02 (4.6%)	01 (1.2%)	03 (2.4%)
d.	**>70**			
2.CLINICAL PRESENTATION				a. Headache- 115 (93.4%) b. Focal weakness- 83 (67.4%) c. Vomiting- 73 (59.3%) d. Seizures- 42 (34.1%) e. Cerebellar Signs- 15 (12.1%)
3.	**PRIMARY SITE**			
a.	**Lungs**	31 (72%)	35 (43.7%)	66 (53.6%)
b.	**Breast**	00 (0.0%)	36 (45.0%)	36 (29.2%)
c.	**Esophagus**	03 (6.9%)	01 (1.2%)	04 (3.2%)
d.	**Melanoma**	02 (4.6%)	03 (3.7%)	05 (4.0%)
e.	**Colorectal**	03 (6.9%)	02 (2.5%)	05 (4.0%)
f.	**Others**	04 (9.3%)	03 (3.7%)	07 (5.6%)
4.	**No. of Metastasis**			
a.	**<3**	18 (41.8%)	48 (60.0%)	66 (53.6%)
b.	**Equal to or >3**	25(58.1%)	32 (40.0%)	57 (46.3%)
5.	**Lobar involvement**			
a.	Supratentorial	18	32	50 (40.6%)
i)	Frontal	08	14	22 (17.0%)
ii)	Parietal	05	17	22 (17.8%)
iii)	Temporal	33	47	80 (65.04%)
iv)	Multiple	12	17	29 (24.3%)
b.	**Infratentorial**			
6.	**Primary disease controlled**	28 (65.1%)	53 (66.2%)	81 (65.8%)
a.	**YESb. NO**	15 (34.8%)	27 (33.7%)	42 (34.1%)
7.	**KPS Score**			
a.	**< 60**	08 (18.6%)	13 (16.2%)	21 (17.0%)
b.	**>60**	35 (81.3%)	67 (83.7%)	102 (82.9%)
8.	**Outcome**	07 (16.2%)	11 (13.7%)	
a.	**Survived**	05 (11.6%)	22 (27.5%)	18 (14.6%)
b.	**Loss to follow up**	31(72%)	47 (58.7%)	27 (21.9%)
c.	**Dead**			78 (63.4%)

Results

Table 1 summarises the demographic profile of the patients. There was a slight female predominance with female to male ratio 1.86: 1.Most patients were in the sixth decade. The age of the patients ranged from 37-78 years and the mean age of presentation was 60.91 years. Majority of the patients manifested with features of raised intracranial pressure which included headache (n= 115, 93.4%) associated with focal weakness (n= 83, 67.4%) and vomiting (n=73, 59.3%). The most common primary was lungs (n= 66, 53.6%) followed by breast (n=36, 29.2%). Most patients presented with <3 metastases (n=66, 53.6%). Most of the metastases were supratentorial (n=94, 76.4%) with predominant involvement of frontal lobe (n=50, 40.6%).The primary malignancy was well controlled in 81 (65.8%) patients. KPS score was > 60 in 102 (82.9%) patients. Of 123 patients included in the study, 78 patients (63.4%) died, 27 patients (21.9%) were lost to follow-up and only 18 patients (14.6%) survived over a follow up period of 36 months.The median survival time from the diagnosis of the primary tumour was 11 months (95% CI 8.046-13.594).

Table 2 shows the survival data as per different variables. Median survival in patients with a KPS >60 was 13 months (95% CI 11.254-14.746) as compared to 06 months (95% CI 4.711-7.289) in patients having KPS<60.

The median survival in patients with well controlled primary malignancy was 14 months (95% CI 12.457-15.543) as compared to 08 months (95% CI 6.061-9.939) in cases in which primary disease was not controlled. The median survival for patients having <3 metastases was 13 months while in cases which have equal to or more than 3 metastases it was 11 months. We analyzed the affect of number of metastases using different groups (for example single metastasis, 2-3 metastases and more than 3 metastases). However, we found that the survival outcomes were significant only when we compared <3 metastases with equal to or more than 3 metastases.

The median survival in cases of males was 13 months as compared to 11 months in females. The two most common primary sites (that is lungs and breast) were compared for any survival difference. There was no significant difference.

On applying Log Rank test to each variable independently in our study it was found that, KPS score >60,number of metastases <3 and controlled status of primary disease has a significant impact on the survival of the patient (p values= 0.000, 0.015 and 0.000 respectively).Whereas, gender, primary site and intracranial location of lesion do not have a significant impact on the patient's survival (p values= 0.902, 0.758, 0.575 respectively).

Table 2: Log Rank Test

VARIABLE	MEDIAN SURVIVAL	SE	95%CI	'p' VALUE
KPS score				0.000
>60	13 months	0.891	11.254-14.746	
<60	6 months	0.658	4.711-7.289	
Primary controlled				0.000
Yes	14 months	0.787	12.457-15.543	
No	8 months	0.989	6.061-9.939	
No. of metastases				0.015
<3	13 months	2.318	8.457-17.543	
>3	11 months	1.318	8.417-13.583	
Gender				0.902
Male	13 months	1.828	9.418-16.582	
Female	11 months	1.132	8.780-13.220	
Primary site				0.758
Lungs	11 months	1.507	8.046-13.594	
Breast	11 months	1.668	7.731-14.269	
Location of lesion				0.575
Supratentorial	11 months	0.919	9.198-12.802	
Infratentorial	14 months	1.369	11.317-16.683	

SE: Standard Error, CI: Confidence Interval

The Cox Proportional Hazard Model (Table 3) was used in addition to evaluate different variables and their effects which were studied.

The hazard or the chance of the event (death) was 0.86 times in males as compared to females or in other words the chance of death was 14% lower in males as compared to females. This gender difference however was found to be statistically insignificant.

Subjects with KPS >60 had 0.382 times chances of death or 62% decrease in hazard as compared to the patients having KPS<60. This difference was found to be statistically significant (p<0.05)

Subjects with well controlled primary malignancy as compared to those with poorly controlled primary malignancy had 0.598 times chances of death or 40% decrease in hazard. However, this difference was found to be statistically insignificant using the above model (p>0.05 i.e. 0.089).

With each year increase in age the hazard or the chances of death increased by 1.18 times. The hazard or the chances of death were 18% higher with each year increase in age. This difference was found to be statistically highly significant (p<0.01) using the Cox proportional Hazard model.

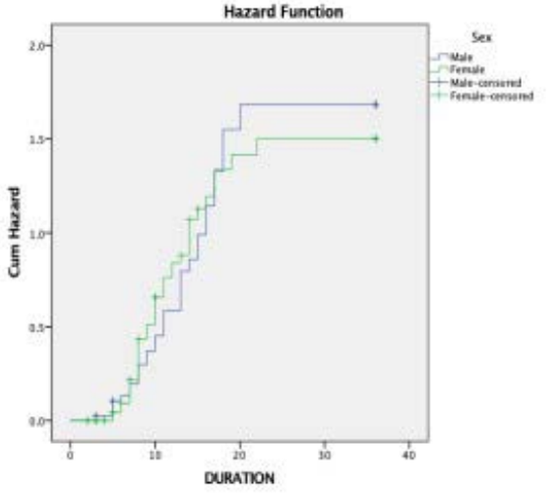
Subjects having number of metastases three or more than three had 1.83 times more chances of death as compared to those having metastases <3. This difference was found to be statistically non-significant using this model (p>0.05 i.e. 0.22). However, this difference was statistically significant using Log Rank test.

Table3: Cox proportional hazard model

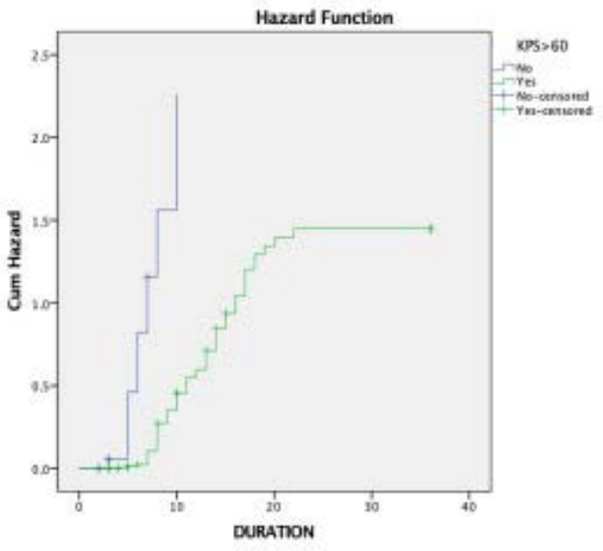
Variable studied Exp(B)	B	SE	Sig.		95.0% CI for Exp(B)	
					Lower	Upper
Sex	-.151	.237	.525	.860	.540	1.369
KPS>60	-.962	.405	.018	.382	.173	.846
Primary controlled	-.514	.303	.089	.598	.330	1.082
Age in years	.173	.025	.000	1.189	1.131	1.250
Number of metastases	0.606	0.264	0.22	1.832	1.093	3.072

HAZARD FUNCTION GRAPH

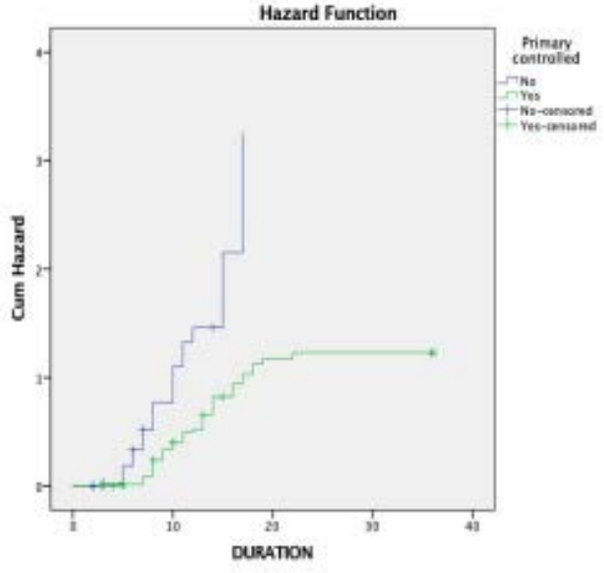
A) Sex



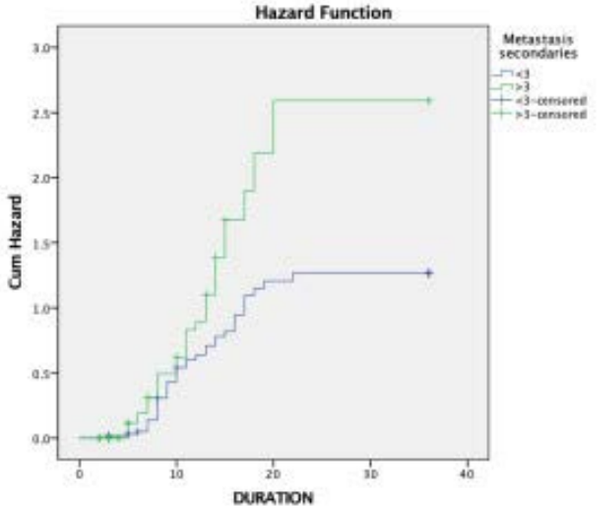
B) KPS>60



C) Primary controlled



D) Number of metastases



We found that the variables (such as controlled status of primary disease and number of metastases <3) that were statistically significant (p value= 0.000 and 0.015 respectively) on univariate analysis (Log Rank test) were found to be non-significant (p value= 0.089 and 0.22 respectively) upon multivariate analysis (Cox Proportional analysis). This effect could be explained by confounding or by small sample size.

Finally, using different tests of significance it can be inferred that, the prognostic factors associated with better survival include KPS>60, age <50 years, well controlled primary malignancy and number of cerebral metastases less than three.

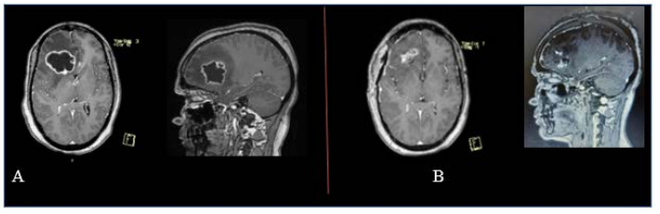


Figure 1: A case of solitary metastasis in right frontal lobe in a case of CA breast.

A. Pre-op axial and sagittal CEMRI.
B. Post-op axial and sagittal CEMRI showing complete excision.

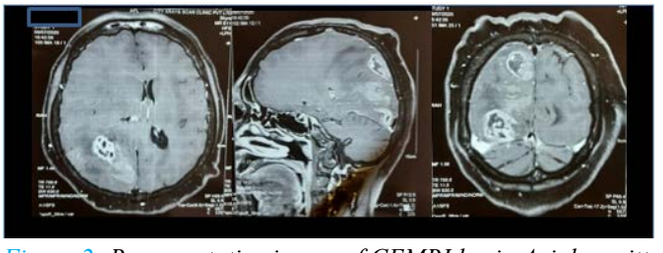


Figure 2: Representative image of CEMRI brain Axial, sagittal and coronal section showing multiple brain metastases. The patient was referred for WBRT.

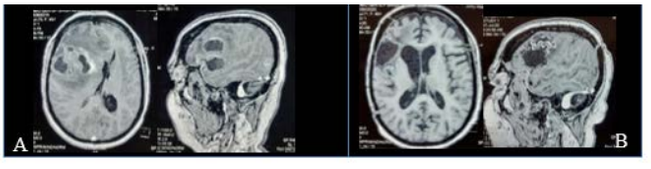


Figure 3: A case of multiple supratentorial metastases in a case of CA breast with large lesion in the right frontal lobe. Large frontal lobe lesion excision was done.

A. Pre-op axial and sagittal CEMRI.
B. Post-op axial and sagittal CEMRI showing complete excision.

Discussion

Brain metastases is the most common intra-cranial neoplasm and occurs ten times more commonly than primary brain tumours8 Demographically, most of the patients with brain metastasis in our study were females (65.05%). Cases were mostly from breast (29.26%) or from lungs (53.65%). Most studies have shown that brain metastases occur more

commonly in patients aged between 50 and 70 years.[9, 10] The mean age of patients with brain metastases in our study is about 60.91years. Patients in 6th decade constituted 57.7% followed by 5th decade 34.9 %. The most common symptom in our study was headache which was followed by focal weakness, vomiting, seizures and cerebellar signs which correlated with other studies.[11, 12, 13]

According to literature lung cancer is the leading cause of cerebral metastasis accounting to 50% irrespective of gender.[14] Similar results were found in our study. Most common primary exclusive in females was breast.[15]

As per literature 80 % of the metastatic brain lesions are found in cerebrum and 20 % in posterior fossa.[15] Similarly, in our study 75% of the brain lesions were supratentorial. The most common lobe was the frontal lobe followed by temporal lobe (Fig 1 shows a representative case with solitary metastasis in the right frontal lobe in a case of CA breast. Total excision could be achieved). The posterior fossa contributed the remaining 25 % .

According to National Cancer Institute a prognostic factor is regarded as a situation, or a characteristic of a patient which can be used to estimate the chances of recovery from a disease or chances of the disease recurring. Based on such prognostic factors, 6 different prognostic indices for adult patients with brain metastases from solid tumours have been developed (age, performance status, extracranial metastasis, controlled primary, steroid treatment, and the type of brain metastasis – number, volume and time interval detection from the primary). Based on the above prognostic indices various grading scales were formulated like Recursive partitioning analysis (RPA).[16] Score index for radiosurgery (SIR).[17] and Graded prognostic assessment (GPA).[17] However, these grading scales do not consider patients neurological condition and localisation of metastatic lesion like supratentorial or infratentorial lesions. The benefit of these scores were to guide the choice of treatment in individual patients and to avoid overtreatment in cases of limited survival (< 6 months). However, in our study we have not formulated the grading scale and statistical analysis was done for individual parameters.

In our study, number of brain metastases was used as a parameter for prognostication and we found patients having metastasis <3 was seen in 53.6 % patients (66/123) and > 3 (Fig 3) was seen in 46.3 % (57/123). There was significant difference in the median survival in the two groups (P value <0.05). Similar results were found in the study done by DiLuna et al18 who reported significantly better survival in patients with 1–3 vs > 4 brain metastases. Most literature does not recommend surgery for multiple intracranial metastases (Fig 2 shows representative image of one such case with multiple intracranial metastases which was referred for WBRT).

There are various studies in the literature which shows patients with preoperative good performance status with primary controlled (no extracranial metastasis) fared better than the patients with the poor performance status and primary not controlled (with extracranial metastasis).[19] Similar results were found in our study also.

Overall survival has been demonstrated to be higher in patients with brain metastasis who have been treated with surgical excision with cranial irradiation compared to those treated with whole brain irradiation alone.[20] Good surgical outcome in general is seen in the patients with lower number of metastatic brain lesion having good performance status and controlled status of primary disease which was also evident in our study showing significant P value (<0.05) for all three parameters.

The median survival of untreated patients is about a month, 1.6 months in patients treated with steroids only, 3.6 months in patients treated with radiotherapy and 8.9 months in. patients treated with neurosurgery followed by radiotherapy.[21 22,23,24,25] The technical difficulties in accessing and resecting multiple lesions limit the potential benefits of surgery. One of the most important purpose of this study for prognostic indices is to guide the choice of treatment in individual patients. In this context, a prognostic index should be accurate enough to avoid overtreatment in patients that actually have very short survival. Even more important, one should not withhold treatment because the index erroneously predicts an unfavourable outcome. These aspects of the indices have not been thoroughly evaluated, even in the recent GPA analysis.[26]

Conclusion

Patients with KPS > 60, well controlled primary malignancy, age<50 yrs and number of metastases less than 3 were related to significant better prognosis and survival. Using these variables, we can select the patients who will be benefited by surgical intervention, particularly in developing countries like India where the medical facilities are limited and not easily available.

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