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Original Research Article

SURGICALLY RESECTED INTRACRANIAL METASTASES- NEUROPATHOLOGICAL STUDY IN CONCOMITANT WITH CLINICAL AND IMMUNOLOGICAL PROGNOSTICATION

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ABSTRACT

Background: Intracranial metastases (ICM) are more frequent than primary malignancies arising within adult brain. Primary malignant tumors mainly from lung, breast, gastrointestinal tract followed by the kidney are known to cause ICM in Asian population. **Objectives**: To study clinicopathological and immunohistochemical prognostic parameters in patients with intracranial metastases alongwith survival data analysis. **Material and Methods:** Retrospective study was undertaken for patients' that underwent surgical resection of intracranial metastasis from January 2006 to December 2022. Tabulation of histomorphological parameters and immunoprognostication was carried out using representative paraffin sections. SPSS software version 25 was utilized for calculating the statistical parameters. **Results:** Thirty six patients constituted the study group, of which majority presented in 6th decade (47.2%) with male (69.4%) preponderance. Intracranial metastases were usually solitary (89%) and affected predominantly cerebral hemispheres (75%) followed by cerebellum (16.7%). Brain metastasis especially from lung resulted in precocious neurological symptoms (66.7%) in a significant subset of patients. Overall mean and median survival duration was 20.5 months and 12 months. Statistical analysis showed that primary site of malignancy (p=0.006) and p53 (p<0.001) had significant correlation with survival. Her 2 Neu score 2+ (22.2%) and 3+ (16.7%) were observed in ICM from lung, GIT and breast. Six months, 1 year, 2 year and 5 year survival rates were 83.3%, 46.6%, 30% and 6.6% respectively. **Conclusion** Primary tumor location (Lung and GIT) and p53 overexpression was associated with poor survival. Her2neu amplification in substantial number of patients opens the door for upcoming combined targeted therapeutic regimes.

INTRODUCTION

Brain metastases (BM) account for the most common intracranial malignancies (tumors) in adult population with a variable frequency of 3 to 10 times when compared to primary brain tumors.[1] Brain metastasis with neurological symptoms are often the first presenting features in patients with otherwise previously undiagnosed cancer. In Approximately 15% of patients with BM, primary tumor remains unidentified despite extensive workup.[1,2] According to the research data, among Asian population primary malignancies from lung, breast, gastrointestinal tract and kidney often metastasize to brain.[3] Development of brain metastases has been regarded as end stage complication of systemic malignancy.[4] However, in the recent era introduction of effective systemic therapies and advanced imaging modalities has resulted in increasing numbers of patients with intracranial progression. Existing treatment protocol includes surgical resection, whole brain radiotherapy and or combined surgery and radiotherapy.[5] With

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the evolution of precision medicine, druggable molecular targets such as Epidermal growth factor receptor (EGFR), Human epidermal growth factor recepror 2 (Her 2), Platelet-derived growth factor receptor (PDGFR) and Vascular endothelial growth factor receptor (VEGFR) are being utilised for individual tumor types.[6] In recent decades expanding neurosurgical services for central Indian population, patient's inclination towards surgical resection and increased patient's compliance towards chemotherapeutic drugs has resulted in better survival. A critical analysis of intracranial metastases was carried out to study the clinico-radiological, neuropathological and immunohistochemical prognostic markers alongwith survival data in affected patients.

MATERIALS AND METHODS

A retrospective analysis of surgically resected brain metastasis of patients aged 34 to 71 years who were operated in the tertiary care institute at Bhopal between January 2006 to December 2022 were included in the study. Hematopoietic and spinal malignancies were excluded from the study. Institutional ethical committee approval (IEC) was obtained for the study. The clinical details including age, sex, clinical features, radiological findings, histopathology, and follow-up data of these patients were extracted from the patient's record files. Radiological parameters assessed were size, distribution, tumor border and echotexture. Routine Hematoxylin and eosin-stained 3-micron sections of formalin fixed tissue were reviewed by three histopathologists (H.G, S.K, G.V). Histopathological parameters assessed were tumor morphology, differentiation, mitosis, necrosis, and tumor infiltrating lymphocytes. Tumor grading and differentiation was done using the latest CAP protocol for breast, lung, kidney, and gastrointestinal tract. Immunohistochemical (IHC) studies were done for characterization of the original site of malignancies in cases of unknown primary. IHC was carried out on 3-micron paraffin sections on poly-l-lysine coated slides using Ready to use and diluted antibodies with appropriate positive and negative controls by polymer horse radish peroxidase IHC detection system following the manufacturer's instructions. Antibodies used for detection of primary malignancy in unknown cases were Pancytokeratin (RTU, Monoclonal, Quartett), LCA (RTU, Monoclonal, Biogenex), GFAP (RTU, Monoclonal, Leica), Vimentin (RTU, Monoclonal, Biogenex), CK-7 (RTU, Monoclonal, Quartett), CK-20 (RTU, Monoclonal, DAKO), TTF-1 (RTU, Monoclonal, Quartett), p63 (RTU, Monoclonal, Quartett), CA-125 (1: 10 dilution, Monoclonal, Thermofisher), ER (RTU, Monoclonal, Genome me), PR (RTU, Monoclonal, Genome me), CD10 (RTU, Monoclonal, DAKO).

Prognostic immunohistochemical markers Ki-67 (1:100 dilution, Monoclonal, Quartett), p-53 (RTU, Monoclonal, Leica), and Her 2 Neu (RTU, Monoclonal, Genome me) were performed in all the cases on representative sections. Ki-67 proliferative index was calculated by manual counting method wherein an initial slide scan was performed on low power to identify the 'hot spot' areas in the tumor. Microscope was then focused on the 100 x objective and Ki-67 positive tumor nuclei per 2000 tumor cells were counted in real-time. Every brown-stained nucleus was considered as positive irrespective of intensity; necrotic and vascular endothelium were excluded from counting. Immunostain for p53 was scored as follows: < 10% tumor cells positive-0, 10-50% strong nuclear positivity of tumor cells-1+, >50% strong nuclear positivity of tumor cells -2+. Immunostain for Her 2 Neu was scored using the latest CAP guideline devised for breast as follows: No staining is observed or Membrane staining that is incomplete and is faint/barely perceptible and in ≤10% of tumor cells (0), Incomplete membrane staining that is faint/ barely perceptible and in >10% of tumor cells (1+ Negative), Weak to moderate complete membrane staining observed in >10% of tumor cells (2+ equivocal) and Circumferential membrane staining that is complete, intense and in >10% of tumor cells (3+ positive).[7] Statistical analysis was performed using SPSS version 25. Continuous and categorical parameters were calculated. Statistical significant value was used as 0.05. Kaplan-Meier test was performed to calculate survival analysis and comparison was done by log rank test. Univariate analysis was done for prognostic factors evaluation.

RESULTS

Resected histopathology specimens received from neurosurgery department accounted for a total of 1615 cases. Of these 1212 were neoplastic and amongst these non-hematopoietic intracranial metastases were reported in 36 cases. The clinical and demographic details of these patients have been summarized in table 1. Patient's age ranged from 34 to 71 years with a mean age of 49.8 years. Most of the patients were in 6th decade (47.2%). There was male preponderance (69.4%) and male to female ratio was 2.27:1. The presenting signs and symptoms varied depending on the intracranial location of the tumor. Symptoms of raised intracranial pressure such as headache (44.4%) and vomiting (16.6%) were frequently observed. Chronic (> 1 month, 69.5%) presentation was more common than subacute (>1 week to 1 month, 25%) and acute (<1 week, 5.5%). Neuroimaging was performed in all the patients that comprised of CECT and MRI. Although majority of metastatic lesions were solitary (89%); multiple intracranial metastases were observed in 4 patients. Amongst the later, three patients had primary lesion in lung whereas one female patient had primary in

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breast. Radiological imaging of brain metastases revealed findings such as ring enhancement (19.4%), solid cystic lesion (14%), hydrocephalus (8.3%) and dural attachment (8.3%). (Fig 1A) Previous history of known primary malignancy was provided in 12 (33.3%) patients. Duration between primary tumor detection and development of brain metastases ranged between 5 months to 4 years. A significant number of patients (66.7%) had precocious clinical presentation with neurological symptoms due to brain metastases. Primary tumor site could not be identified in two of the cases. Histopathological examination revealed adenoid-cystic morphology in one of these patients. However, she succumbed to death before the primary site of tumor could be searched for. The other case exhibited poorly differentiated tumor morphology and even after extensive clinicoradiological workup primary tumor origin remained undetermined.

Overall analysis of the residual thirty four cases showed that the commonest primary malignancy leading to brain metastases was lung followed by gastrointestinal tract and genitourinary tract. (Detailed in table 2) Depending on the primary site of tumor, brain metastasis revealed varied tumor morphological patterns on surgical pathology examination. Adenocarcinoma was commonest histopathological subtype followed by squamous cell carcinoma. (Fig 1B-D, 2A-C) The various histomorphological and prognostic parameters have been summarized in table 2. Differentiation of tumor based on cytoarchitectural and nuclear grading system was possible in 32 cases. Poorly differentiated tumor morphology was most frequently observed.

Postoperative status was uneventful in thirty five patients. One patient died due to cardiac arrest two days after surgery. Follow-up was available in thirty patients. Twenty four of the patients died whereas six were alive during the study period. Follow-up duration ranged from 2 days to 120 months. Overall mean and median survival was 20.5 months and 12 months. (Fig 3A) Patient's survival rate for durations of six months, 1 year, 2 year and 5 year were 83.3%, 46.6%, 30%, and 6.6% respectively. Immunological markers assessed for prognostication were Ki-67 proliferation index, tumor suppressor gene p53 and Her 2-Neu. Median survival analysis for nuclear p53 immunological score <10% was 14 months and for >50% ;7 months (p value-<0.001). (Fig 3B) Depending on the primary site of tumor, malignancies from lung and GI tract had median survival of 7 months after the metastases of tumor to brain (p value-0.006).(Fig 3C) Other parameters like tumor differentiation (p value=0.180), Ki-67 proliferation index (p value= 0.922) and necrosis (p value=0.715) were not found significant. Immunoscores for Her2-Neu protein showed 3+ intense complete membranous staining in 16.7 % cases. In addition, an equivocal score of 2+ was observed in eight (22.2%) cases. (Fig 4A-D) Primary tumor site in 3+ Her 2 Neu scores were Lung (4), GI tract (1), Breast (1) and 2+ equivocal were Lung (6), GI tract (1) and Unknown (1). Various treatment modalities were used in these patients such as systemic chemotherapy (22.2%), radiotherapy (16.6%) and whole brain radiotherapy (8.3%).

Table 1: Clinical characteristics and demographical profile of the patients (n=36) with intracranial metastases

Age (years)	
31-50 yr	11 (30.6%)
51-70yr	23 (63.9%)
>70yr	02 (5.5)
Sex % Male Female	 25 (69.4%) 11 (30.6%)
Clinical features	Headache (44.4%), weakness (30.5%), Seizure (22.2%), Vomiting (16.6%), Altered sensorium (11.1%)
Location-	
Cerebrum	75%
Cerebellum	16.7%
Others	8.3%
Distribution Solitary	89%
Multiple	11%
Laterality	Left (16)> Right(15), Bilateral – (4) Midline-(1)

Table 2: Histomorphology features and immunohistochemical markers expression observed in the patients

Primary site-	**Known (n=12) Unknown primary(n=24)**
Lung	1 (8.3%) 16 (66.6%)
Gastrointestinal tract	4 (33.4%) 2 (8.3%)
Breast	2 (16.7%) 1 (4.2%
Ovary	2 (16.7%) 1 (4.2%)
Kidney	1 (8.3%) 1 (4.2%)
Thyroid	0 (0%) 1 (4.2%)
Others-	
Parotid	1 (8.3%) 0 (0%)
Sarcoma	1 (8.3%) 0 (0%)
Unclassified	0 (0%) 2 (8.3%)

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Histomorphology- Adenocarcinoma and its subtype	23 (63.9%)
Squamous cell carcinoma	4 (11.1%)
Serous papillary cystadenocarcinoma	3 (8.4%)
Clear cell renal cell carcinoma	2 (5.5%)
Undifferentiated carcinoma	2 (5.5%)
Follicular carcinoma	1 (2.8%)
Alveolar soft part sarcoma (Fig 2D)	1 (2.8%)
Grading/differentiation- Well differentiated	08 (25%)
(n=32) Moderately differentiated	06 (19%)
Poorly differentiated	18 (56%)
Mitosis- <5/HPF	14 (39%)
5-10/HPF	18 (50%)
>10/HPF	04 (11%)
Necrosis- 1+	19 (52.8%)
2+	11 (30.5%)
3+	06 (16.7%)
Ki-67 Index-<10%	14 (38.9%)
10-30%	08 (22.2%)
>30%	14 (38.9%)
P53- <10%	17 (47.2%)
10-50%	05 (13.9%)
>50%	14 (38.9%)
Her2-Neu- 0	13 (36%)
1+	9 (25%)
2+	8 (22.2%)
3+	6 (16.7%)

Table 3: Comparative analysis of Prognostic parameters and their significance (n=30)

Parameters	Patients No.	Median survival	*p* value
Gender- Male	19	8 months	0.146
Female	11	24 months	
Age- <60 year	24	10 months	0.669
>60 year	6	12 months	
Primary site- Lung and GI tract	18	7 months	**0.006**
Others	12	30 months	
At the time of presentation Primary- Known	10	8 months	0.066
Unknown	20	14 months	
Location-Cerebrum	21	10 months	0.549
Cerebellum	5	12 months	
Others	4	24 months	
Distribution-Solitary	27	12 months	0.331
Multiple	3	2 months	
Histomorphology- Adenocarcinoma	19	8 months	0.099
Others	11	14 months	
Grading- Well differentiated	09	30 months	0.180
Moderately differentiated	05	1 months	
Poorly differentiated	16	12 months	
Necrosis- 1+	17	12 months	0.715
2+	10	8 months	
3+	03	12 months	
Ki-67 index-<10%	10	10 months	0.922
10-30%	07	14 months	
>30%	13	8 months	
P53- <10%	13	14 months	**<0.001**
10-50%	3	2 months	
>50%	14	7 months	

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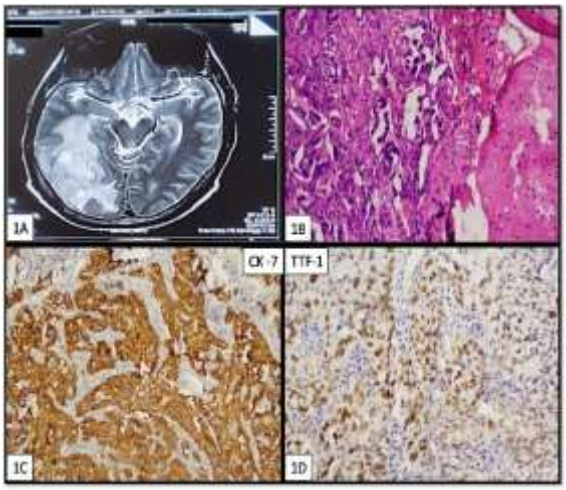

Figure 1: A) MRI image- ill-defined heterogeneously enhancing large solitary mass, B) Metastatic Poorly differentiated adenocarcinoma from lung localized in cerebral cortex (H&E,10x), Diffuse and strong immunopositivity for cytokeratin 7 C) and TTF-1 D)

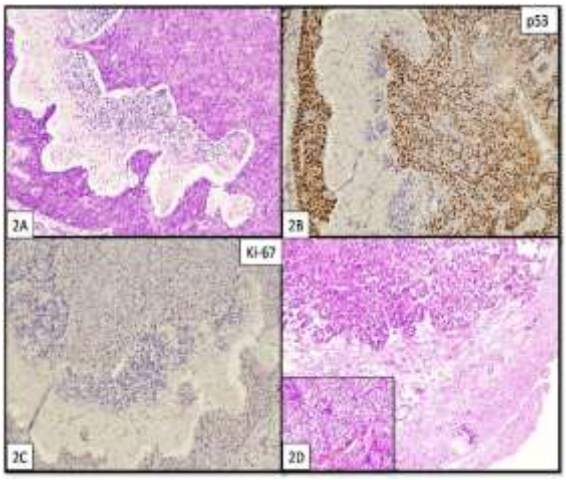

Figure 2: A) Metastatic Squamous cell carcinoma from esophagus infiltrating cerebellar hemisphere (H&E,40x) B) Strong nuclear positivity for p53, C) Ki67 proliferation index (10-15%), D) Alveolar soft part sarcoma from hand metastasized to cerebral parenchyma (H&E,4x, Inset-High power field 40X)

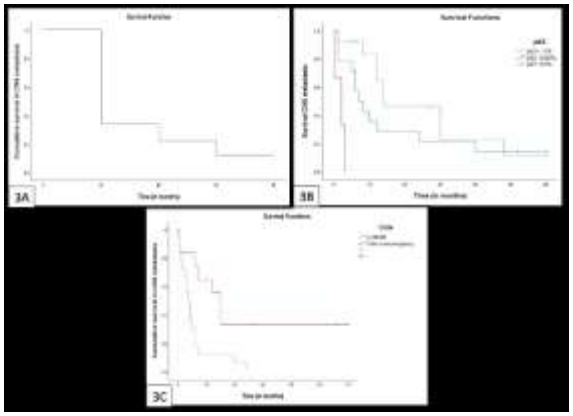

Figure 3: Kaplan- Meier A) Overall survival curve B) Survival according to p53 overexpresion and, C) Comparative survival in patients from Lung/GIT and other sites

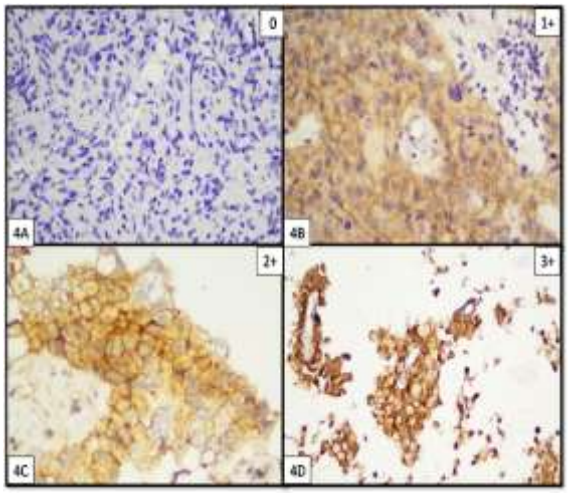

Figure 4: Immunohistochemical expression of Her2Neu A) Score 0 (Negative), B) Score 1+ (Negative), C) Score 2+ (Equivocal), D) Score 3+ (Positive)

DISCUSSION

Intracranial metastases constitute one of the most frequent complications of systemic malignancy. Rising incidence of carcinoma is reported in recent times due to early detection and better diagnostic imaging modalities.[8] Thus, resulting in a need to elaborate the relevant predictive markers for the patient's survival with distant brain metastasis. In the present study, detection of intracranial metastases as the first manifestation of primary cancer was observed in 66.7% of the patient's. Similarly a significant proportion (52.7%) of such cases have also been noted among the surgically resected metastatic lesions of brain.[3] Solitary metastatic lesions in brain parenchyma as per our analysis were generally small and ranged in maximum diameter from 1cms to 4cms. Comparative analysis of data as observed in present study vs previous research studies showed that solitary lesions (89%; 50.8-81%) were far more common than multiple metastatic deposits; location of metastases were frequent in cerebral cortex (75%; 80%) followed by cerebellum (16.7%; 15%) and others (8.3%; 5%).[9]

Overall pulmonary malignancies are among the commonest site of primary tumor site resulting in intracranial metastases. Apart from lung, tumors arising from gastrointestinal tract, breast, ovary, renal cell carcinoma and head and neck frequently metastasized to brain. Additionally in west metastases from melanomas are far more common than Asian population.[10] Hematogenous spread from sarcomas to intracranial region is rare occurrence and is observed in approximately 1-6% of cases.[11] Amongst these, metastases from alveolar soft part sarcoma is still rarer and constitutes less than <1 % of cases.[12] One each individual case from thyroid and soft tissue from hand (alveolar soft part sarcoma) was observed in the present study. The latter case presented with brain metastasis after 6 months of diagnosis of primary in hand. Twelve cycles of whole brain radiotherapy were administered

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to the patient and it again recurred with brain metastases after 5 years of treatment. Patient was still alive during the study.

Precocious presentation of malignancy with neurological symptoms being the first manifestation, also had lung as most common primary site (66.6%). Analysis of the present study data showed that adenocarcinoma (63.9%) (Irrespective of the site) was the commonest morphological pattern observed in intracranial metastases similar to literature.[13,14] However, lung cancers patients also present late due to limited and predominantly parasympathetic innervations by pain fibre in lung. Adenocarcinomas are mostly localized in periphery of the lung and are therefore initially asymptomatic in majority of the cases until systemic spread occurs. Molecular mechanism involved in brain metastases from systemic malignancy is multifactorial process.[15,16] Prognosis after brain metastases depends on various parameters. A nomogram was prepared by Sloan-Barnholtz in 2012 based on various parameters such as status of primary disease, primary site and histology, age, metastatic spread, KPS, and number of brain lesions. They found that primary tumor site and histology significantly affected survival among the patients (p value=0.010); tumors with primary breast had better survival.[17] Study by Kavouridis et al also concluded that primary tumor origin significantly affected overall survival (p value=0.02). Patients with Colorectal malignancy had shorter median survival (10.6 months) than those with breast malignancy (22.1 months).[18] Statistical analysis of the present study revealed that patients with primary malignant tumor localized in lung or GIT had shorter median survival (7 months). At the time of data analysis, 16.6% patients were still alive with a median follow up 1185 days (120-3600 days). Median survival duration in this study was 12 months. Six months, 1 year, 2 year and 5 year overall survival rates were 83.3%, 46.6%, 30% and 6.6% respectively. According to the recent medical literature median survival after brain metastases ranges from 3 to 15 months.[18–21] Two patients were long term survivor (>5years) in present study. They had received neo-adjuvant chemo and radiotherapy for primary malignacy localized in kidney (50yr, male) and ovary (45yr, female) respectively. They presented with solitary brain metastases 6 months and 36 months after completing treatment for primary malignancy. Gross total neurosurgical resection of metastatic lesion was performed and no subsequent treatment was given to the patient. Similar to the context, previous research studies also reported that gross total surgical resection of solitary brain metastatic lesions was associated with better survival.[19,22] Long term survival is defined as survival time beyond 5 years and it ranges from 2.5 to 16%.[23–25]

Immunoprognostication markers of clinical interest that are widely available include p53 and Ki-67 proliferation index. Potential role of p53 as an indicator of prognostic marker is controversial. Main role of p53 gene is tumor suppression and it is known as guardian of genome. It helps in regulation of cell proliferation, autophagy, apoptosis and tumor microenvironment regulation. Mutation of p53 is found in various cancers and leads to increase invasiveness, cell proliferation and survival, hence promotes cancer metastasis. Some of the studies supported that overexpression of p53 found to be associated with poor survival in various cancers such as breast, head and neck, hematopoietic system and liver.[26] Similarly in the present study overexpression of p53 was associated with poor survival rate (p value<0.001). Ki-67 proliferation index had no significant impact on survival among brain metastases patients. (p value=0.922).

The rising incidence of high grade malignancy in the present era patients with brain metastasis poses significant challenge for the management of these patients. Molecular markers such as *EGFR*, *ALK*, and *HER2*, have been found to be prognostic and are being incorporated into prognostic classifications.[21,27] Cancer metastasis to brain occur relatively late in the course of disease. Her 2 amplification has been shown to predispose to brain metastasis and has been researched with special interest in breast cancer. In view of limited therapeutic options for systemic malignancy management, targeted therapy such as Her 2 inhibitors and EGFR directed against the molecular target present in primary tumor are being used increasingly.[28] In the present study Her 2 amplification was analysed, score 3+ (16.7%) and 2+ (22.2%) were observed in a substantial number of patients respectively from lung (10), gastrointestinal tract (2), breast (1) and unknown (1) malignancies. Targeted therapy against Her 2 drug oncoprotein have been administerd in various cancers such as tumor from breast, gastric, non small cell lung cancers and bladder. However, in patients with CNS metastasis several drug trials are being carried as monotherapy and combined targeted therapy for better penetration of blood brain barrier to increase the efficacy of targeted drugs.[29,30]

CONCLUSION

The present study has certain limitations; firstly, the cases studied were few. Secondly, only patients with surgically resected specimens received from Neurosurgery could be included and lastly limited treatment data was available due to lack of radiotherapy and medical oncology departments in the Institute.

To conclude, not all patients with intrancranial metastases have dismal prognosis. Approximately 6% patients were long survivors (> 5 year survival). Primary tumor site (0.006) and p53 overexpression (<0.001) had a significant impact of patient's survival. Her2 neu overexpression was observed in intracranial metastases from various tumor primaries

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and holds promising value as a druggable molecular target in this subset of patients.

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