



PREDICTING PATTERNS OF BRAIN METASTASES IN NSCC LUNG

Dr Vansh Arora	3rd year resident , SPMC Bikaner
Dr Kapil Soni	Medical Officer , GMC Kota
Dr Saroj Dhaka*	Senior Resident Bikaner. *Corresponding Author
Dr Bhuvnesh Narayan Purohit	Senior Resident , SPMC Bikaner

ABSTRACT The estimated global BM incidence was 9.6%, in descending order arising from lung (19.9%), melanoma (6.9%), renal (6.5%), breast (5.1%) and colorectal cancer (1.8%). In other studies, the incidence of BM ranged from 5% to 20% in breast cancer.

Of all NSCC lung 16 to 20 percent will develop brain metastases in course of their disease .This incidence is higher in patients whose cancers harbor epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, in whom up to 50 to 60 percent will develop brain metastases over the course of their disease .

There is a possibility to select high risk patients for NSCC Lung which then may receive prophylactic cranial irradiation in the future .

MATERIAL AND METHODS: A total of 100 patients were retrospectively selected from our institutional data who underwent Palliative cranial Radiotherapy where the primary was NSCC Lung with no metastases except Brain . Data of previous all investigation were collected for same and patients were divided on the basis of following categories

1. Gender
2. Site of primary tumour
3. T and N stage of primary tumour at first diagnosis
4. Site of metastases in Brain

Our aim was to distribute patients as per these above mentioned criterias and see if we could decode a pattern to select which region of primary along with stage is most susceptible for brain metastases . we also attempt to know which is the most common site for brain metastases

RESULTS: Total of 100 patients who had NSCC Lung with only brain metastases and underwent prophylactic cranial irradiation were taken for the study where they were distributed among groups according to above mentioned criterias .

Our result show that 92% were male , 8 % were females .

When distributed amongst region of the primary, 48% of patients had disease in Right lung , 36% had disease in left lung and 16% had central bronchus disease.

Amongst 90 patients who had disease in the lung specially ,upper lobe of lung appeared to be the region of disease in 54% . middle lobe in 16% and lower lobe in 30%

When categorized on the basis of nodal status of primary disease , 12% had N0 status , 18% had N1 status , N2 appeared in 52 % of cases and N3 in 18 % of cases

Distribution as per T category of AJCC 8th edition showed none of the patients had T1 status , 16% had T2 , 36% had T3 and 48% had T4 tumours .

When distributed according to site of primary disease , Frontal and temporal area were the region of mets in 36% , parietal was in 24% , occipital was in 16% and others including basal ganglia , cerebellum were in 18% . Here , if patient had fronto-parietal region as primary , it was counted both in frontal as well in parietal separately

KEYWORDS : Brain , metastasis , NSCL**INTRODUCTION**

Metastases to the brain remains the most intractable issue for patients , it not only effects the physical function , independence , personality and quality of life but also greatly increases mortality when compared to other organs .¹ The estimated global BM incidence was 9.6%, where lung is the primary in 19.9% of cases for brain metastases²⁻⁶ .

Histologically Brain metastases are detectable in at least 18% of SCLC patients at diagnosis⁷ and eventually are diagnosed in another 20% to 25%, with an increasing likelihood seen with lengthening survival.^{8,9} Actuarial analysis reveals a probability of brain metastases ranging from 50% to 80% in patients who survive 2 years. At post-mortem examination, brain metastases are found in up to 65% of SCLC patients.¹⁰ Because these metastases are sometimes the sole site of clinical relapse and are frequently clinically disabling, PCI has been recommended by many¹¹ .

For NSCC lung 16 to 20 percent will develop brain metastases in course of their disease .This incidence is higher in patients whose cancers harbor epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement, in whom up to 50 to 60 percent will develop brain metastases over the course of their disease¹²⁻¹⁴ . Although some, but not all, data have suggested patients with c-ROS oncogene 1 (ROS1)-positive NSCLC have lower rates of brain metastases than those with ALK rearrangements, the incidence in

this subtype is approximately one-third¹⁵⁻¹⁷ .

In this study we tend to observe patterns in brain metastases for NSCC in terms of site of presentation both in brain and lung, T and N staging of lung carcinoma .Therein the end ,we would try to innumerate factors which make patients with NSCC lung most susceptible to brain metastases

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DISCUSSION

Brain metastases are the most common intracranial tumours in adults, accounting for significantly more than 50% brain tumours. In patients with systemic malignancies, brain metastases occur in 10 to 30 percent of adults and 6 to 10 percent of children²⁻⁵

Brain Metastases remains the most dreadful issue for patients and only affect the physical function, independence, personality, quality of life, and self-awareness of the patients but also increases the mortality rate compared with metastases to other organs, are as high as 80% within one year. BM accounts for most CNS tumours, but the incidence varies depending on the type of primary malignancy^{18,19} .

It can be said that due to new and improved detection technique ,brain metastases may be increasing.

In adults, the most common primary tumours that can lead to brain metastases are carcinomas, and include lung, breast, kidney, and colorectal cancers, and melanoma. Whereas, carcinomas of the prostate, oesophagus, and oropharynx and non-melanoma skin cancers rarely metastasize to the brain. In children, the most common sources of brain metastases are sarcomas, neuroblastoma, and germ cell tumours²⁰⁻²¹

The occurrence of BM requires that tumor cells cross the Blood Brain Barrier The BBB is a structure formed by brain endothelial cells (BECs), pericytes, and astrocyte foot processes. It is a highly selective barrier and is necessary to maintain brain homeostasis. The passage of solutes through the BBB is limited by their molecular weight and charge.²⁶ Tight junction (TJ) proteins are restrict the paracellular diffusion of substances between the blood and the brain . Damage to TJs can lead to a leaky BBB and the continuous exposure of the CNS to harmful substances in the circulation. Additionally, changes in intracellular transport in BECs contribute to BBB disruption and disease progression.²⁷ The BBB plays a dual role in cancer cell BM, both forming a tight barrier to protect the CNS from invading tumor cells, while also protecting metastatic cells during extravasation and proliferation in the brain.²⁸ The loss of BBB integrity due to neuroinflammation, upregulation of proteolytic enzymes, and direct destruction by TNBC cells may promote metastatic invasion.²⁹ The partial destruction of the BBB leads to increased invasion of tumor cells and related molecules, thereby potentially promoting tumor cell brain colonization. When tumor cells enter the brain, they mainly gather at the branching points of cerebral vessels and further exude and invade. Metastatic tumor cells interact with BECs through surface molecules, including selectins, integrins, and chemokines. This is accompanied by the secretion of growth factors such as vascular endothelial growth factor (VEGF), neuropeptide, chemokines and cyclooxygenase 2 (COX2), which further weaken the BBB and allow tumor cells to penetrate the brain parenchyma.³⁰

Several studies have also questioned the incidence and prevalence of BM according to the primary cancer. In a population-based study from the Metropolitan Detroit Cancer Surveillance System, Barnholtz et al. collected data from 16,210 patients diagnosed with BM from various primary tumours between 1973 and 2001. The estimated global BM incidence was 9.6%, in descending order arising from lung (19.9%), melanoma (6.9%), renal (6.5%), breast (5.1%) and colorectal cancer (1.8%). In other studies, the incidence of BM ranged from 5% to 20% in breast cancer²²⁻²⁵

Lung cancer remains the most common reason for brain metastases , where in exploring lung cancer specifically , it has been divided into two groups on the basis of histology .

First being SCLC and the other in NSCL . With a lot of evidence based statistically significant studies , we now very well prescribe prophylactic cranial irradiation in chemo responsive cases of SCLC as it is estimated that a patient with SCLC has a a probability of brain metastases ranging from 50% to 80% who survive 2 years.

For NSCLC a lot of studies have identified risk of 16 to 20 percent during the course of the disease , which rises to 50 percent in patients whose cancers harbor epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement .

The purpose of our study was to observe a pattern in incidence of brain metastases in patients of NSCLC bases on their primary location , T and N staging and also to determine which region in the brain is most vulnerable to get brain metastases and if possible to conclude combining the categories and coming up with a region and stage of NSCLC where the probability of getting brain metastases is highest .

Based on our result , we concluded that Male patient with primary in the right lung , upper lobe with T3-4 , N2-3 disease has the highest chance to get brain metastases in the future However our study was limited to 100 patients that were retrospectively selected from data of single institutuion situated in north-western India and didn't take into account the genetic variation amongst patients.

Yet , it might be useful for early prediction of high risk patients , most vulnerable to brain metastases prior to the development of disease . where in we might prescribe prophylactic RT to cranium as we do for SCLC

CONCLUSION

Our primary aim was to observe a pattern of spread according to the primary in NSCC lung with only brain metastases .

Our observation was limited to 100 patients falling into our criteria and was a retrospective study limited to a single institutional data in a north western regional cancer centre

With our observation we could make following conclusion

1. Male patients are on much higher risk for lung cancer with brain metastases.(92% vs 8%)
2. Upper lobe of lung (Right and Left) is most susceptible to get brain metastases (54%)
3. Patients with T3 ,T4 disease as primary are most susceptible to get brain metastases (84%)
4. N2 status and onwards is a high risk factor for brain metastases (70%)
5. Fronto parietal region of brain is most susceptible region (36% for each), however parietal region also doesn't lack behind (24%)
6. Right sided lung cancer is more common to have disease mets in brain than left

It is a well proven fact that mutation with ALK are more susceptible to brain metastases , with all these things in background in the near future with more larger group study we might come up with some scoring system which would tell us most susceptible patients which might have possibility of brain metastases , where we may prescribe prehand prophylactic irradiation like in term we do with Small Cell Carcinoma Lung .

Like with our study we may conclude that Male patients , primary with T3-4 N2-3 , right upper lobe masses are the most susceptible patients to get brain metastases .

However a much larger study group would be needed to finally get on a more evidential study and adding genetic studies would also enhance our accuracy for the same.

TABLES

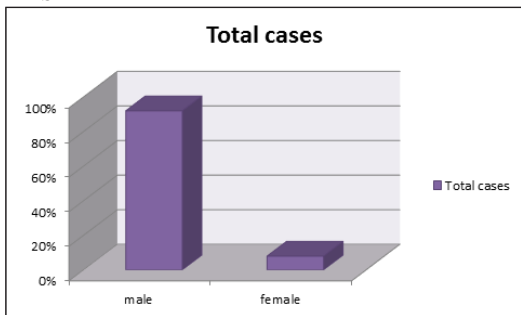


Table 1 : Division On Basis Of Gender

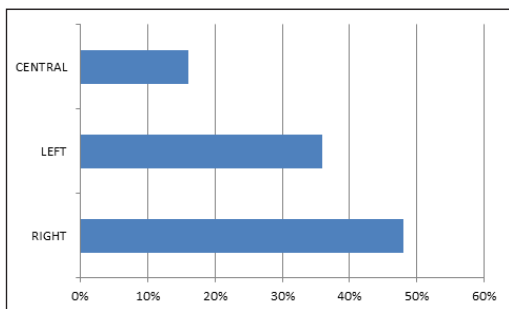


Table 2 : division on basis of right , left and central region of lung

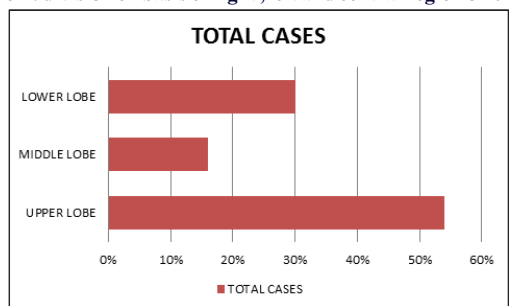


Table 3 : Lobe Wise Division Of Patients

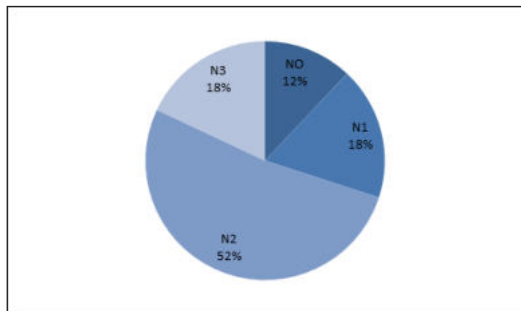


Table 4: Nodal Division Of Patients

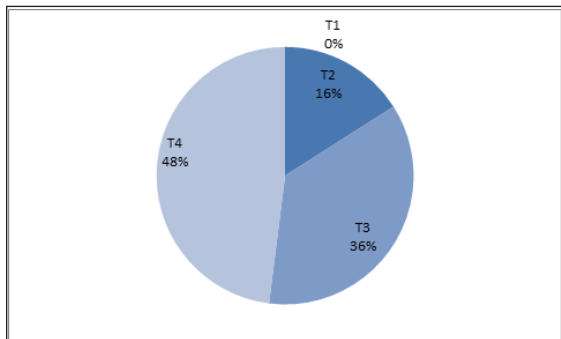


Table 5 : Distribution Of T Staging

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