

# Patterns of brain metastasis in anaplastic lymphoma kinase - rearranged and epidermal growth factor receptor-mutated lung cancer patients in magnetic resonance imaging

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## Abstract

**Introduction:** The optimal management of neuroparenchymal lesions in cases of lung cancer is exigent as this frequent yet notorious complication negatively impacts the morbidity and mortality index. **Aims:** This study is aimed at recognizing various patterns of neuroparenchymal metastasis in patients of lung cancer with epidermal growth factor receptor (EGFR)- and anaplastic lymphoma kinase (ALK)-positive mutations. **Material and Methods:** The radiological findings of the neuroparenchymal lesions were analyzed and the statistical data were charted. We identified two groups of patients with neuroparenchymal lesions among a cohort of 340 patients having EGFR-positive (68) and ALK-positive (24) mutations (total: 24 + 68 = 92). **Results:** We observed that among the ALK group, leptomeningeal spread was less compared to EGFR group (2/24 as opposed to 18/68). Morphological heterogeneity and central necrosis in the parenchymal lesion which were associated with unfavorable outcomes were predominant in ALK group (8/24) as opposed to EGFR group (2/68). Ancillary findings but pertinent to survival and morbidity such as presence of perilesional edema, hemorrhage, and hydrocephalus on magnetic resonance imaging were also analyzed. The mutation-specific differential imaging spectrum could be attributed to biological differences between these cancers.

**Key words:** Anaplastic lymphoma kinase mutation, epidermal growth factor receptor, lung cancer, magnetic resonance patterns, neuroparenchymal

## Introduction

Early detection of brain metastasis (BM) in patients of lung cancer has reaped survival benefits. A rising trend is observed in the incidence of BM, probably due to improved management and prolonged survival, as well as due to superior imaging techniques. These asymptomatic metastases have been found to be less significant and less in figure than those with symptoms.

The epidermal growth factor receptor (EGFR) transmembrane receptor tyrosine kinase is involved in signal transduction, regulation of DNA synthesis, and cell proliferation. Mutations in the EGFR gene can result in constitutive activation of the tyrosine kinase that can lead to tumorigenesis.<sup>[1]</sup> In NSCL, overexpression of EGFR has an impact on the biologic behavior of the disease, affecting survival and treatment response with EGFR tyrosine kinase inhibitors (EGFR-TKIs).<sup>[2,3]</sup>

An essential and well-studied oncogene as a therapeutic target is EGFR as patients positive for EGFR mutations show superior response rates and prolonged progression-free survival on management with EGFR-TKIs compared to those treated with standard platinum-based chemotherapy.<sup>[2,4]</sup>

Anaplastic lymphoma kinase (ALK) is an additional emerging oncogene that has come to attention. Lung cancer with ALK rearrangement (ALK+), which is commonly reported as an echinoderm microtubule-associated protein-like 4-ALK translocations, is a subgroup that exhibits a remarkable response to specific targeted drugs such as crizotinib, an oral small-molecule inhibitor of ALK.<sup>[5,6]</sup>

The presence of EGFR and ALK mutations could have a significant outcome on the pattern of metastatic disease spread. Further, differences in metastatic temperament could have a differential effect on morbidity and mortality. The consequential information could help to foresee disease conduct and to direct investigations or modify therapy.

## Materials and Methods

A retrospective analysis of 340 (60 ALK-positive and 280 EGFR-positive mutations) patients with histopathologically confirmed lung cancer and proven mutations by sequencing FISH/IHC technique was undertaken. Magnetic resonance imaging (MRI) brain was not done routinely in all cases. Patients underwent contrast-enhanced MRI of brain (done on 1.5 T MR System (MAGNETOM EXPERT, Siemens, Germany) in all symptomatic cases.

Imaging protocol included fluid attenuation inversion recovery, T1 spin echo (SE) sequences in axial plane, and T2-weighted images in axial and sagittal planes.

Postcontrast T1 SE images were obtained after administration of 0.1 mmol/kg body weight of gadobenate dimeglumine. An additional axial gradient-recalled echo sequence to detect magnetic susceptibility effect was taken to rule out any hemorrhage in the lesion. In all cases, slice thickness was 5 mm with 10% interslice gap and matrix size of 256 × 256.

A postcontrast magnetization transference sequence was done to look especially for leptomeningeal disease.

The study included analyzing the lesions with regard to number, site (parenchyma/meningeal), nature (with or without necrosis), and ancillary findings such as presence or absence of intralesional hemorrhage, perilesional edema, and development of hydrocephalus.

## Results

Among the above cohort of 340 patients, brain as a sanctuary for metastasis was documented in 92 patients who underwent MRI due to symptoms suggestive of central nervous system (CNS) involvement. The median age group of cohorts was 25–80 years.

Incidence of BM is higher in ALK group (24/60) as compared to EGFR group (68/280).

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Among the ALK group, leptomeningeal spread was less compared to EGFR group (2/24 as opposed to 18/68).

Morphological heterogeneity and central necrosis in the parenchymal lesion which were associated with unfavorable outcomes were predominant in ALK group (8/24) as opposed to EGFR group (2/68).

Ancillary findings but pertinent to survival and morbidity such as presence of perilesional edema, hemorrhage, and hydrocephalus on MRI were also analyzed.

The mutation-specific differential imaging spectrum could be attributed to biological differences between these cancers.

## Discussion

Approximately 25%–30% of patients with lung cancer develop BM at some stage, and the incidence at the initial workup has been reported to be between 12% and 18%.<sup>[7,8]</sup>

Because of the blood–brain barrier (BBB), antineoplastic drugs commonly are barred from entering into the brain; therefore, the CNS has been a plausible site for many types of cancer. However, studies have shown that the BBB can be disrupted by BMs, and targeted therapies, such as EGFR and ALK TKIs, have shown enormous potential in treating BMs.<sup>[9–12]</sup> Crizotinib is a first-generation ALK inhibitor approved by the United States Food and Drug Administration because of its effectiveness in the treatment of ALK-rearranged nonsmall cell lung cancer (NSCLC).<sup>[13]</sup>

In our study, we analyzed different features of BMs according to mutation status. To eliminate the impact of histology, this study was restricted to information on pulmonary carcinoma.

To date, there have been few studies that focused on the implications of EGFR and ALK mutation on BM in a homogeneous population of lung cancer.

Some investigators have shown clinical substantiation for the impact of EGFR mutation on distant metastasis. Preliminary results from a Chinese study suggested diverse metastatic patterns in the brain.<sup>[14]</sup> In a study evaluating three different oncogenes (EGFR, V-Kiras2 Kirsten rat sarcoma viral oncogene homolog, and ALK), EGFR mutation was not significantly associated with BM.<sup>[15]</sup> However, differential diagnostic timing of metastatic presentation and histological heterogeneity in the preceding studies should be taken into consideration. It would be biased to chalk out conclusions from preceding data about the clinical implication of EGFR mutation on BMs.

Further analysis of data from patients with BMs showed that among the ALK group, leptomeningeal spread was less compared to EGFR group. Morphological heterogeneity and central necrosis in the parenchymal lesion which were associated with unfavorable outcomes were predominant in ALK group as opposed to EGFR group. However, the size of BMs was not associated with mutation status.

Our study has few limitations. First, the retrospective nature of our study was one of the potential pitfalls. Second, we could not evaluate other clinically relevant information such as symptoms at the time of initial presentation. Third, we have not charted a follow-up response evaluation criterion of these BM based on treatment modalities.

Despite these limitations, our study is valuable in view of new insights into the clinical association between EGFR and ALK mutation status and BM in patients of lung carcinoma.

## Conclusion

We believe that the prognostic impact of EGFR and ALK mutation on BMs is worth examining in further studies. In a recent study,<sup>[16]</sup> correlation between mean Apparent diffusion coefficient (ADC) values measures from solid component of brain lesions correlated well with the mutational subtype (especially EGFR) of the lung carcinoma, though they did not correlate well with histological type. Could we possibly use these advances of functional MRI techniques and get away with the time and financial consuming mutational analysis pathway. The question remains to be answered by further future substantial number of randomized trials.

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## Conflicts of interest

There are no conflicts of interest.

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