

# CNS Metastases of Lung Tumours -An Immunohistochemical Approach to Diagnosis

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## ABSTRACT

**Background:** The aim of this study was to establish the relative frequency of primary as well as metastatic CNS tumors and the role of immunohistochemistry in diagnosing the primary site of CNS metastasis.

**Material and Methods:** A 3 year retrospective hospital-based study of patients with CNS neoplasms was performed. Primary and metastatic brain tumors were recorded. The primary sites of metastatic CNS tumors were detected by applying immunohistochemistry panel on the CNS biopsies. The panel comprised

TTF1, CK5/6, CK7, CK20, CDX2, synaptophysin, ER and PR.

**Results:** A total of 96 cases of CNS neoplasms were recorded. Out of these 41(43%) were astrocytomas, 22(23%) were meningiomas, 12(13%) were schwannomas, 10(10%) were pituitary adenomas, 4(4%) were of ependymomas, 1(1%) was oligodendroglioma, 2(2%) were medulloblastoma and 4(4%) were of metastasis to CNS. Of the 4 cases of CNS metastasis in which IHC was done; all showed primary site as lung.

**Conclusion:** The most frequent type of CNS tumors in this study were astrocytomas and the least frequent was oligodendroglioma. Male to female ratio was 1.3:1. Females outnumbered males in meningioma (1:3.4). In cases of metastasis, lung was the most common primary site, as deduced by IHC findings.

**Key Words:** Lung Tumours, CNS Metastasis, Immunohistochemistry.

## INTRODUCTION

The central nervous system neoplasms comprise a heterogenous group which includes both benign as well as malignant tumors. The tumors of central nervous system are reported to be less than 2.0% of all malignancies [1]. In India, CNS tumors constitutes about 1.9% of all tumors.<sup>2</sup> The age predilection of CNS tumors is said to be bimodal, with one peak in children and another at 45-70 years of age [2]. Males are involved more frequently with meningiomas

being an exception, having a higher rate in females.

According to the WHO classification, tumors of CNS comprise more than 50 clinico-pathological entities, out of which the major categories include the tumors of neuroepithelial tissue, cranial and paraspinal nerves, meninges, sellar region, lymphomas, haematopoietic neoplasms, germ cell and metastatic tumors [3]. Among the primary sites, the common ones are lung cancer, breast cancer, and melanomas [4]. Data is available regarding the diagnosis of metastatic tumors in CNS by immunohistochemical methods [5]. Various immunomarkers can be applied to know the site of primary tumor [5,6]. In our study we used a combination of immunomarkers like CK5/6, CK7, CK20, TTF-1, CDX2, ER, PR and synaptophysin.

## MATERIAL AND METHODS

A 3 year retrospective hospital-based study was conducted, during which a total of 96 CNS neoplasms were diagnosed. All biopsy specimens which were fixed in 10% buffered formalin, paraffin embedded, cut into 3-4 $\mu$  sections and finally stained with haematoxylin and eosin were used for the study. For metastatic brain tumors, immunohistochemistry using monoclonal antibodies against TTF1, CK5/6, CK7, CK20, CDX2, synaptophysin, ER, PR was performed to know the site of the primary tumor.

## RESULTS

Age of the patients in our study ranged from 6 to 79 years, with a mean age of 43 years. Peak incidence was seen in 41-50 years of age (42.0% cases). Males slightly outnumbered females with a ratio of 1.3:1. However the male: female ratio in case of meningioma was reversed with

female predominance (1:3.4). Majority of tumors were intracranial, 82 (85.4%) whereas the remaining 14 (14.6%) were spinal.

Out of a total of 96 cases, including the brain and spinal cord, 92 (96%) were primary, and 4 (4%) were metastatic. Among the primary CNS tumors the most frequent tumour was astrocytoma (41 cases, 43%), followed by meningioma (22 cases, 23%), schwannoma (12 cases, 13%), pituitary adenoma (10 cases, 10%), ependymoma (4 cases, 4%), medulloblastoma (2 cases, 2%) and the least common was oligodendroglioma (1 cases, 1%). (Table 1)

2 (4.8%) cases of astrocytoma were in WHO grade I, 11 (26.8%) in grade II, 9(21.9%) in grade III and 19 (46.3%) cases were in WHO grade IV (glioblastoma multiforme).

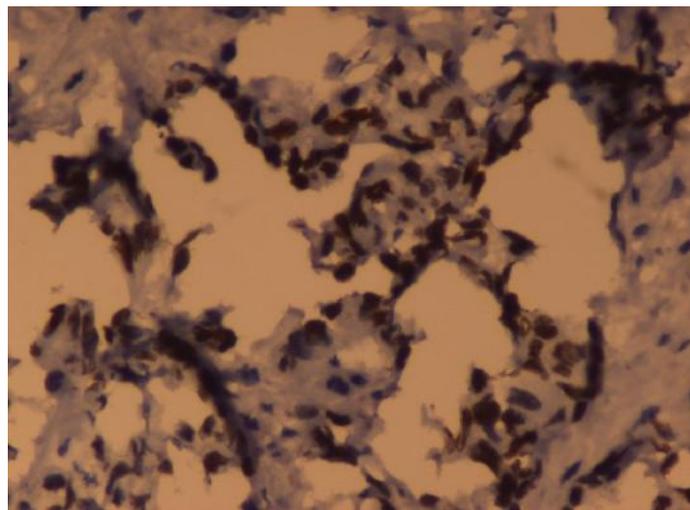
Meningioma comprised the second most common group of tumors (23% of all tumors). Out of 22 cases of meningioma, 17 were intracranial and 5 spinal.

Out of 12 cases of schwannoma, 8 were intracranial at the cerebellopontine angle and 4 spinal. On microscopy, these neoplasms showed either cellular Antoni A areas or a mixture of Antoni A and Antoni B areas.

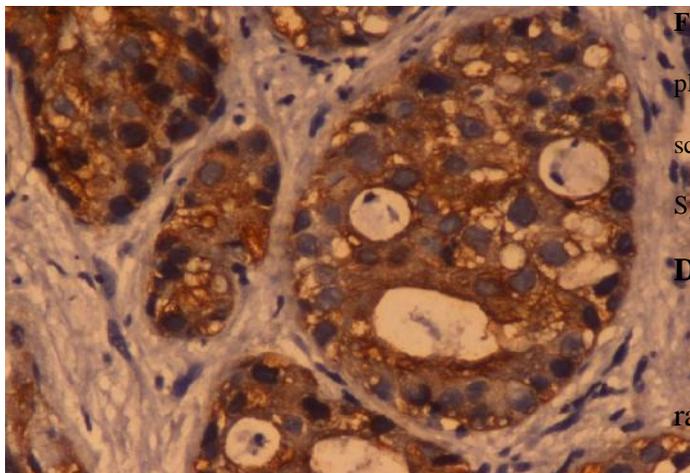
All cases of pituitary adenoma were intracranial in location. 4 cases of ependymoma were also seen in the age group of 21 to 50 years. Medulloblastoma constituted 2% (2 cases) of all CNS neoplasms and both were seen in children. Histologically all the cases showed classic pattern of small blue carrot - shaped cells. A single case of oligodendroglial tumor was reported in a male aged 41 years.

Among the 4 metastatic tumors, the most common histologic type was

adenocarcinoma (3 cases, 75%) along with a single case of small cell carcinoma. The antibodies used to identify the primary site were thyroid transcription factor-1 (TTF-1), CK5/6, CK7, CK20, CDX2, synaptophysin, estrogen receptor (ER) and progesterone receptor (PR). All the three adenocarcinomas were positive for TTF1, CK7 (Figure 1 and 2) and negative for CK20, CDX2, ER and PR, confirming lung cancer as the primary site of metastasis.

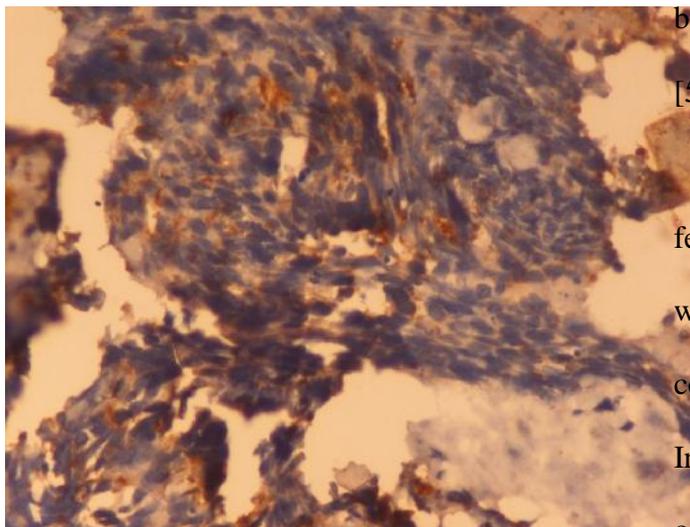


**Figure 1:** Adenocarcinoma showing nuclear positivity for TTF1 in cells lining malignant glands. IHC TTF1 x500



**Figure 2:** Adenocarcinoma showing glands lined by malignant cells with strong cytoplasmic CK7 positivity. IHC CK7 x500

A single case of metastatic small cell carcinoma was positive for synaptophysin (Figure 3) and TTF1, which again confirmed lung as the primary site.



**Figure 3:** Small cell carcinoma showing pleomorphic, hyperchromatic moulded nuclei and scant cytoplasm with synaptophysin positivity. IHC Synaptophysin x500

## DISCUSSION

Central nervous system tumors are rare neoplasms constituting less than 2% of all malignancies. A bimodal peak of CNS tumors is reported, one in children and other in 45-70 years age group [3]. This was not observed in our study, which may be due to less number of cases. However the peak incidence was seen between 41-50 years and majority of cases (42.7%) were seen between 41-60 years, similar to other studies [5,7].

Males were affected more than females, meningiomas being an exception with higher frequency in females, a finding concordant with other authors [8,9]. Intracranial cases of meningiomas constituted 85.4% and spinal 14.6%, similar

to the observations by Hadidy et al and Lee et al [7,8].

Astrocytomas were the commonest tumors, 41 cases (43%) of all CNS neoplasms in our study, a finding concordant with Hadidy et al and Pentheroudakis et al [7,9]. However Lee et al observed meningiomas to be the largest subgroup of CNS neoplasms [8]. Glioblastoma Multiforme was the commonest subtype of astrocytoma, seen in 46.3% cases, finding similar to Pentheroudakis et al [9].

Meningiomas were the second commonest tumors, comprising 22 cases (23%) of all CNS neoplasms. Similar observations were made by Lantos et al [10]. Ten cases (10%) of pituitary adenomas were reported by us, findings similar to that of Sroden & Wester [11]. Ependymoma constituted 4% of all CNS neoplasms, which is comparable to 4.3% and 3.96% incidence

reported by Hadidy et al and Lantos et al [7,10]. Medulloblastoma constituted 2% of all CNS neoplasms which is concordant to the findings of Patty [4]. Oligodendroglial tumors represented only 1.0% of the CNS neoplasms, which was comparable to that reported by Jalali and Datta [2].

The most common primary sites for brain metastases was lung (20.0%) followed by breast (6.8%), skin (6.5%), kidney (5.0%) and gastrointestinal tract in 1.8%.

Lung can be the most common primary site for both systemic and CNS metastases presenting as metastatic neoplasm with unknown primary [12,13]. TTF-1 is positive in majority of carcinomas of lung origin including adenocarcinoma, small cell carcinoma, poorly differentiated non-small cell carcinomas, and neuroendocrine carcinoma whereas pulmonary squamous cell carcinomas are typically negative [14,15].

A greater specificity is obtained by combining markers, with most primary lung adenocarcinomas being CK7-positive, CK20-negative, and TTF-1-positive [15,16]. In our study all the three cases of metastatic adenocarcinoma were positive for TTF1 and CK7, which confirmed lung as the primary site.

A single case of metastatic small cell carcinoma was positive for TTF1 and synaptophysin, which signified lung as the primary site. The most common primary site of small cell carcinoma is the lung, although extra-pulmonary sites should also be considered including urinary bladder, larynx, gall bladder and rectum. In a retrospective study, brain metastasis was the first presentation of small cell lung carcinoma in 11% of the cases [16]. Small cell carcinomas are positive for neuroendocrine markers such as chromogranin, synaptophysin, and CD56.

Thyroid transcription factor 1 (TTF-1) which is positive in lung adenocarcinoma, is also a useful marker for small cell carcinomas of lung origin [14,15].

Like pulmonary adenocarcinomas, breast carcinomas being the next common primary site are CK7-positive and CK20-negative; however, they are negative for TTF-1 [16]. Colon adenocarcinomas can be another common primary site for CNS metastasis. They are CK7-negative and CK20-positive, hence can be easily differentiated from pulmonary and breast adenocarcinomas. CDX2 is a transcription factor which shows strong nuclear expression in up to 90% of colorectal and duodenal adenocarcinomas [16].

## CONCLUSIONS

Lung can be the most common primary site for both systemic and CNS metastases presenting as metastatic neoplasm with unknown primary.

Immunohistochemistry plays an important role in diagnosing the primary site of CNS metastasis.

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**TABLE 1: Histological Types of CNS Neoplasms**

<b>HISTOLOGY</b>	<b>MALE</b>	<b>FEMALE</b>	<b>TOTAL (%)</b>
Astrocytoma	26	15	41 (43)
Oligodendroglioma	01	-	01 (1)
Pituitary adenoma	06	04	10 (10)
Medulloblastoma	01	01	02 (2)
Meningioma	05	17	22 (23)
Schwannoma	08	04	12 (13)
Ependymoma	03	01	04 (4)
Metastasis	04	-	04 (4)
<b>Total</b>	<b>54</b>	<b>42</b>	<b>96(100)</b>

**TABLE 2: Age wise distribution of CNS tumors**

<b>HISTOLOGY</b>	<b>&lt;10yrs</b>	<b>11-20</b>	<b>21-30</b>	<b>31-40</b>	<b>41-50</b>	<b>51-60</b>	<b>61-70</b>	<b>&gt;70yrs</b>	<b>Total</b>
Astrocytoma	3	1	1	12	10	7	6	1	41
Oligodendroglioma	-	-	-	-	1	-	-	-	1
Pituitary adenoma	-	-	2	4	3	1	-	-	10
Medulloblastoma	2	-	-	-	-	-	-	-	2
Meningioma	-	-	3	2	9	5	3	-	22
Schwannoma	-	2	1	-	5	3	1	-	12
Ependymoma	-	-	1	1	2	-	-	-	4
Metastasis	-	-	-	-	1	3	-	-	4