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Favored gyral sites of supratentorial astrocytic tumors

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Abstract

It is well known that the predilective sites of extrinsic tumors (meningiomas, chordomas, etc) are at the skull base and along the calvarium. Although intrinsic tumors or glial tumors have also been seen to have anatomic and functional predilective sites within the central nervous system, these have not been well documented. We conducted this study to investigate if supratentorial astrocytic tumors have a predilection for specific gyri. We investigated the clinical and radiological records of 60 successive patients who had been operated on at our institution and had had histologically confirmed supratentorial astrocytic tumors (36 males, 24 females, mean age: 52 years). Coronal sections were selected from the pre-operative contrast enhanced T1-weighted magnetic resonance imaging (MRI). The labeling of gyral areas for analysis of MRI was done using Yaşargil's method. Additional information obtained from 3-dimensional MRI and surgical findings was taken into account when it was difficult to distinguish the specific gyrus in which the tumor was located. The middle portions of the frontal gyri, insular gyri and the supramarginal gyrus and its surroundings were among the most common locations for the development of tumors. Interestingly, with the exception of one case, none of the tumors was situated in the precentral or postcentral gyri. It seems that supratentorial astrocytic tumors have a predilection for specific gyri and disfavor some other gyri. This cannot be explained simply by the different sizes of the cerebral lobes. A classical lobar concept of cerebral anatomy may lead to a misunderstanding of cerebral pathophysiology.

INTRODUCTION

It is well known that the predilective sites of extrinsic tumors (meningiomas, pituitary adenomas, chordomas, glomus jugulare tumors, epidermoids, etc) are at the skull base and along the calvarium.[1,2] Although intrinsic tumors or glial tumors have also been seen to have anatomic and functional predilective sites within the central nervous system, these have not been well documented.[2-5] Today, in spite of progress in understanding the molecular genetics of gliomas, the cell type(s) of origin are still uncertain, and the molecular determinants of disease aggressiveness are not well-understood.[6,7] For example, whereas high-grade gliomas account for the majority of cerebral intra-parenchymal lesions in adults, low-grade gliomas account for the overwhelming majority of such tumors in children.[8,9] Pediatric high-grade gliomas have also been reported to differ from their adult counterparts in terms of molecular abnormalities.[10-12] As another example, high-grade astrocytomas comprise only 6-11% of all spinal cord gliomas and are even less common in children and the molecular biology of pediatric astrocytomas differs according to location.[11,13-15]

Studies using magnetic resonance imaging (MRI) of the brain were first published in the literature in the 1980s.[16] The routine use of MRI in clinical practice worldwide came later. High-resolution magnetic resonance imaging became the imaging modality of choice for investigation of central nervous system neoplasms in the 1990s. Thus, surgically relevant descriptions of the sulcal anatomy in radiological studies have until recently been lacking. Brain mapping by functional neuroimaging, diffusion tensor imaging enabled a tumor resection with regard to functional boundaries.[17] Nevertheless, physiological understanding of the brain is not possible without anatomical and histological knowledge. The objective of this study was to examine the impact of anatomy on clinico-pathological correlation in astrocytic tumors, one of the most common

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primary tumors of the brain. As the first step, we investigate if supratentorial astrocytic tumors have a predilection for specific gyri, using MRI and up-to-date gyral labeling in neuroanatomy.

METHODS

Subjects

The authors retrospectively investigated the clinical and radiological records of 252 patients with histologically confirmed neuroepithelial tumors (according to the WHO classification of tumors of the central nervous system[18]) who were operated on at Göztepe Education and Research Hospital in Istanbul between December 2006 and December 2009. The inclusion criteria were patients having "supratentorial tumor", "astrocytic histopathology" and "pre-operative MR images". Oligodendroglial tumors, oligoastrocytic tumors and other neuroepithelial tumors were excluded.

Procedure

The coronal sections were selected from among the pre-operative, contrast enhanced T1-weighted scans, except for 8 patients who had recurrent tumors at the same site of the tumor's origin or for whom only T2-weighted/Flair images were available. The labeling of gyral areas for analysis of MR scans was done using Yaşargil's system.[2] Although coronal sections were predominantly used for labeling, all information obtained from the 3-dimensional MR scans and surgical findings was taken into account, especially when it was difficult to distinguish the specific gyrus in which the tumor was located. The neocortical-convoluted ribbon was subdivided by topographic criteria into 39 parcellation units in each hemisphere (Table 1). The opercular, orbital and triangular parts of the inferior frontal gyrus, uncus and temporal pole were not indicated separately.

The contrast enhanced T1 weighted coronal MRI were for the most part utilized to determine the gyral localization of the tumors. The reasons were: Firstly, coronal MRI is the most useful image plane in pre-operative localization and surgical planning for intrinsic tumors, as the white matter peduncular architecture of most gyri can be most easily recognized in this plane. Secondly, the anatomical resolution is better with T1 images than with T2 images. Thirdly, contrast MRI is of great help in differentiating a tumor from perilesional changes. Four observers (2 neurosurgeons, one neurologist and one radiologist), each individually mapped the tumors in the gyri. The conflicting labels were shown in the table with an asterix. These were taken into account in the statistical analyses to avoid errors.

Table 1: The parcellation units in each hemisphere

In the lateral view

F-1-an, F-1-mi, and F-1-po: Anterior, middle and posterior portions of the superior frontal gyrus, respectively
F-2-an, F-2-mi, and F-2-po: Anterior, middle and posterior portions of the middle frontal gyrus, respectively
F-3-an, F-3-mi, and F-3-po: Anterior, middle and posterior portions of the inferior frontal gyrus, respectively
T-1-an, T-1-mi, and T-1-po: Anterior, middle and posterior portions of the superior temporal gyrus, respectively
T-2-an, T-2-mi, and T-2-po: Anterior, middle and posterior portions of the middle temporal gyrus, respectively
T-3-an, T-3-mi, and T-3-po: Anterior, middle and posterior portions of the inferior temporal gyrus, respectively
P-1, P-2 and P-3: Superior, middle and inferior parietal lobules, respectively
O-1, O-2 and O-3: Superior, middle and inferior occipital gyri, respectively
PREC-1, PREC-2 and PREC-3: Superior, middle and inferior portions of precentral gyrus, respectively
POSTC-1, POSTC-2 and POSTC-3: Superior, middle and inferior portions of postcentral gyrus, respectively

In the medial view

CI: Cingulum
IN: Insular gyri
CU: Cuneus
PRC: precuneus
LTO: Lateral temporo-occipital gyrus
MTO: Medial temporo-occipital gyrus
PARAC: Paracentral gyrus
HI: Hippocampus
PARAH: Parahippocampus

Although the middle portions of the frontal gyri were sufficiently large, they were not used for statistical analyses because we were unable to find published volumetric proportions that were suitable for our parcellation of the cortex. In the parcellation system used in this study, each of the frontal gyri was divided into three portions: anterior, middle and posterior. However, the parcellation system of Kennedy *et al.*[19], which we used in the comparison of the proportions, consisted of only two subdivisions of the frontal gyri: anterior and posterior. The supramarginal gyrus, one of the locations observed as favored, was also excluded from the analysis because of the slight concern about interobserver reliability in this complex location. Therefore, we preferred to use the term "supramarginal gyrus and its surroundings" throughout this text. Statistical analyses for the small volume gyri were not suitable because of the sample size of our series, and were not carried out.

Statistical analysis

Statistical software NCSS 2007 (Number Cruncher Statistical Systems, Kaysville, Utah, USA) and PASS 2008 (Power Analysis and Sample Size, Kaysville, Utah, USA) were used for statistical analyses. All results were expressed in mean ± standard deviation (SD). Results were given at a 95% confidence interval and significance was accepted at $p<0.05$ level. We based our analysis on the study by Kennedy *et al.*[19], who reported a volumetric characterization of the complete gyral topography of the neocortex in 24 young adult subjects using an MRI-based analysis. The total mean volume of the neocortex was 672.9 cm^3 (100%). Based on this total, the volumetric parameters of lobes were: frontal 41%, temporal 22% (including insula, 2.6%), parietal 19% and occipital 18%. The mean volumes of precentral gyrus and postcentral gyri were 6.1% and 4.6% respectively. We analyzed the frequency of tumor incidence using the *z* test for the difference between two independent proportions and compared the expected tumor frequency and observed frequency by region based on the previously published volumetric ratios of cerebral lobes and gyri. The limbic lobe was not indicated separately and the cingulate gyrus was considered as part of either the frontal lobe or parietal lobe in the statistical analysis. The hippocampus and parahippocampus were analyzed as part of the temporal lobe.

RESULTS

Sixty patients who had a supratentorial astrocytic tumor and who had coronal MR images taken were included in the study. The mean age of the patients (36 males, 60% and 24 females, 40%) was 52 ± 13.9 SD years (range: 15-76). According to the 2007 WHO classification of tumors of the central nervous system, the histopathological diagnosis was glioblastoma-grade IV in the majority of the cases (41 cases, 68.3%). The other histopatologies were pilocytic astrocytoma-grade I in 4 cases (6.7%), fibrillary astrocytoma-grade II in 12 cases (20%), gemistocytic astrocytoma-grade II in one case (1.7%) and anaplastic astrocytoma-grade III in 2 cases (3.3%).

The tumors were located in the left hemisphere in 33 cases (55%) and in the right hemisphere in 27 cases (45%). The tumors were located in the frontal gyri in 18 cases (F-1, F-2, F-3, precentral gyrus, part of the paracentral gyrus, part of the cingulate gyrus), in the temporal gyri in 12 cases (T-1, T-2, T-3, hippocampus, parahippocampus and parts of the MTO and LTO gyri), in the parietal gyri in 12 cases (P-1, P-2, P-3, postcentral gyrus, part of the cingulate gyrus, precuneus), in the occipital gyri in 8 cases (O-1, O-2, O-3, cuneus and parts of the MTO and LTO gyri), and in the insula in 9 cases (Table 2). One of the cases, histopathologically diagnosed to be a glioblastoma, was seen to be diffuse on the MRI, but seemed to be limited to the right hemisphere. This case had to be excluded from the statistical analysis because it could not be mapped to a single gyrus. Hence, 59 cases were suitable for statistical analyses. The middle portions of the frontal gyri, insular gyri and the supramarginal gyrus and its surroundings were among the most common locations for the development of tumors (Figure 1).

There was a statistical significance of tumors' predilection for the insular gyri ($p=0.001$) (Figure 2). In total, 21 tumors (21 in 59 cases, 35.5%) were located in the limbic-paralimbic areas (insula, hippocampus-parahippocampus and cingulate gryus, fronto-opercular, temporo-opercular and temporal pole). The limbic areas, including the cingulate gyrus and hippocampus, were also observed to be favored locations (6 in 59 cases, 10.1%). In contrast, the paracentral gyrus, precentral gyrus, and postcentral gyrus were among the relatively least frequent sites for tumor location. Only one tumor was mapped to the primary sensorimotor gyri. We could not definitively map the case to the pre- or post-

Table 2: Summary of the cases

Patient No	Age	Sex	Histopathology	Side	Site	Surgery
1	59	M	GB	L	F-2-Mi	1st
2	67	M	GB	R	F-2-Mi	1st
3	54	F	GB	R	F-3-An	1st
4	32	M	PA-G1	R	IN	1st
5	43	F	FA-G2	R	HI-PARAH*	1st
6	40	M	AA-G3	L	P-2	1st
7	15	M	PA-G1	L	P-2	1st
8	70	M	GB	R	CU	1st
9	41	F	GB	R	F-2-Mi	2nd
10	50	F	GB	R	O-3	1st
11	54	M	GB	R	P-1	1st
12	32	M	GB	L	F-3-Mi	1st
13	68	M	GB	L	F-1-Po	1st
14	73	M	PA-G1	L	T-2-mi/T-2-po*	1st
15	44	F	FA-G2	L	PRC	1st
16	65	M	GB	R	IN	2nd
17	68	M	AA-G3	L	T-3-Mi	1st
18	56	M	GB	L	T-1-Mi	1st
19	44	F	FA-G2	R	P-1	1st
20	61	F	GB	R	P-3	1st
21	53	F	GB	L	IN	1st
22	64	F	GB	L	P-3	1st
23	50	F	GB	R	F-1-Mi/F-2-Mi*	2nd
24	49	F	FA-G2	R	IN	1st
25	56	F	GB	R	PREC-POSTC*	1st
26	73	M	GB	L	O-2	1st
27	72	M	GB	L	T-1-Po	1st
28	50	M	GB	R	P-2	1st
29	63	M	GB	L	IN	1st
30	46	M	GB	R	CI	1st
31	52	M	GA-G2	R	F-2-Mi	1st
32	35	M	FA-G2	R	F-2-Po	1st
33	39	F	FA-G2	L	CI	1st
34	53	F	GB	L	PARAC	1st
35	57	M	GB	L	CI	1st
36	51	M	GB	R	P-3	1st
37	52	M	GB	R	F-3-Mi	1st
38	48	M	GB	R	Diffuse	2nd
39	75	F	GB	R	IN	1st
40	42	M	GB	L	F-1-An	1st
41	51	M	GB	R	P-2	1st
42	57	F	GB	R	IN	1st
43	50	M	FA-G2	L	T-2-Mi	1st
44	50	M	GB	L	O-2	2nd
45	76	M	GB	R	P-3	1st
46	48	F	GB	R	HI-PARAH*	1st
47	26	M	FA-G2	L	T-3-Mi	1st
48	53	M	GB	L	O-2	1st
49	16	M	FA-G2	L	IN	1st
50	44	F	PA-G1	L	O-1	1st
51	63	F	GB	R	P-3	1st
52	45	F	FA-G2	L	O-3	1st
53	57	M	GB	L	T-3-An	1st
54	62	M	GB	L	IN	1st
55	72	F	GB	L	T-1-Mi	1st
56	18	F	FA-G2	L	T-2-Po	1st
57	54	M	FA-G2	L	F-1-Mi	1st
58	64	M	GB	L	T-3-Po	1st
59	53	F	GB	L	CU	1st
60	57	F	GB	L	CI	1st

F : Female, M: Male, GB: Glioblastoma, L: Left, R: Right, A: Astrocytoma, PA: Pilocytic astrocytoma, FA: Fibrillary astrocytoma, GA: Gemistocytic astrocaytoma, AA: Anaplastic astrocytoma, G: Grade, F (in the 6th column): frontal, PRC: Precuneus, IN: Insula, P: Parietal, T: Temporal, PREC: Precentral, PARAC: Paracentral, O: Occipital, CU: Cuneus, HI: Hippocampus, PARAH: Parahippocampus, CI: Cingulate, POSTC: Postcentral, An: Anterior, Mi: Middle, Po: Posterior
* Interobserver conflict

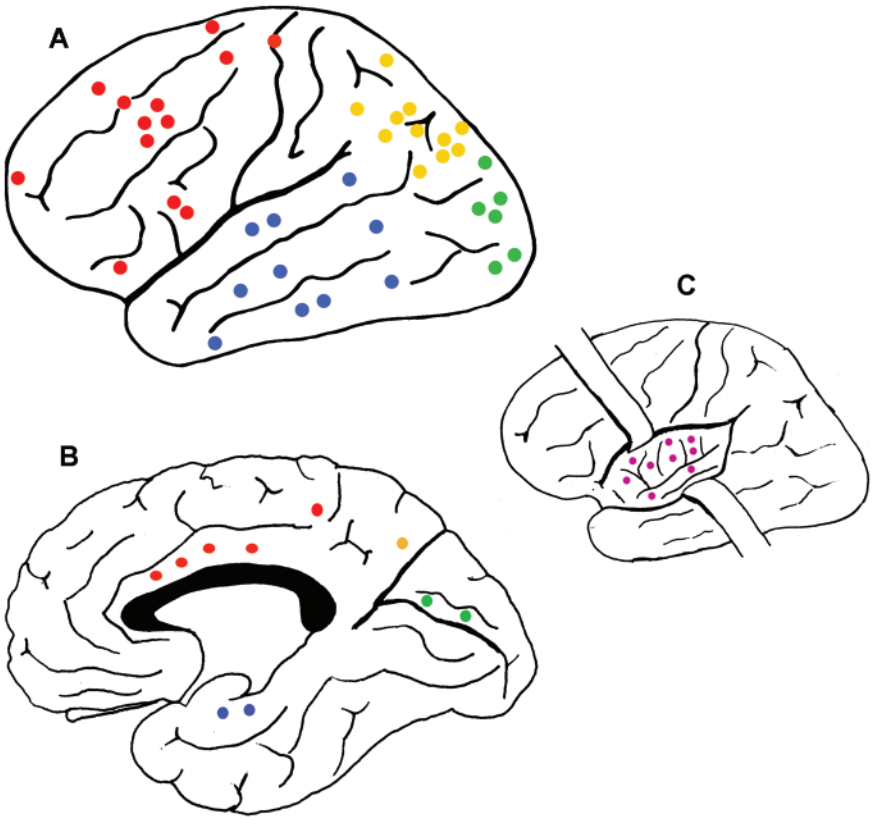

Figure 1: The locations of 59 supratentorial astrocytic tumors in lateral (A), medial (B) and lateral-insular views (C). Separate indication of right and left-sided tumors was disregarded in the figure.

central gyri but the tumor was ascribed to the pre-central gyrus and the frontal lobe for the statistical analysis. The occurrence of only one tumor in the combined pre- and post-central gyri was a statistically significant indicator that tumors disfavor the primary sensorimotor area (p=0.02) (Figure 2). All 3 tumors located in the middle temporal gyrus were of lower histopathological grades. In the majority of cases, the tumors were removed gross totally. There was no operative mortality.

DISCUSSION

A clear understanding of the histological anatomy of the brain is as important as topographical anatomy. The cerebral gyri are not homogenous. There are prominent changes in histology between adjacent areas, such as those between precentral and postcentral gyri. The degree of histological differences between different cortical areas is sometimes much greater than those between the kidney and the liver, for example. The brain can be regarded as a combination of many subunits or organs. The anatomy of cerebral hemispheres has been studied in detail by many pioneers in the field of neuroscience.[2,20-27] In practice, most neurosurgeons prefer to use classical lobar terms, which are frontal, parietal, temporal, occipital and, sometimes, insular. Lobar terminology was first introduced in 1854 by Gratiolet.[28] Gratiolet demarcated four brain lobes (frontal, parietal, temporosphenoidal, occipital) as well as a fifth central lobe or insula. Later, more detailed studies of cerebral gyri were published. In 1896, Alexander Ecker described cerebral gyri, essentially mapping them.[29] In 1909, Brodmann described more than 50 different histological areas in the cerebral cortex.[30] In 1925, Economo and Koskinas defined 107 cortical cytoarchitectonic modifications for human cerebral hemispheres.[31] There are other examples of cerebral cytoarchitectonic maps, including the atlas of Talairach and Tournoux, and Sarkisov's map.[32-34]

Neuronal subtypes in the cerebral cortex and the genetic basis for their differentiation have not been fully clarified. Tumor astrocyte migration is a complex dynamic process that involves multiple biologic characteristics,

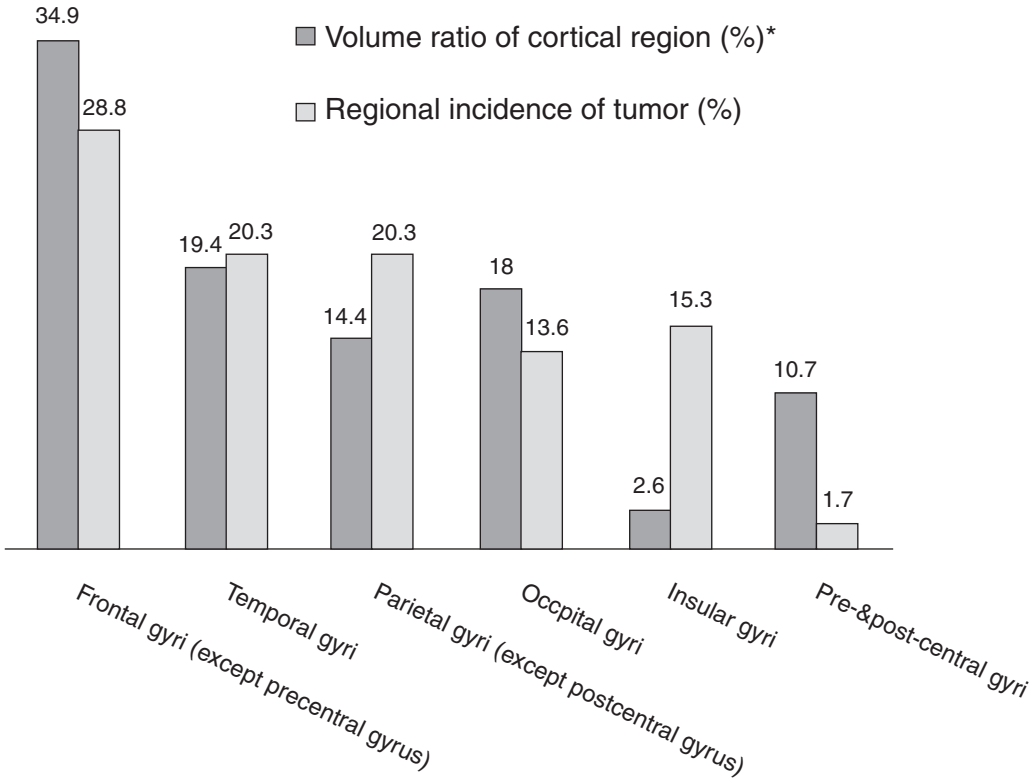

Figure 2: The expected and observed number of the cases according to the volume of the hemispheric regions. The number of tumors located in the insula demonstrated a statistical significance of tumors' predilection for the insular gyri (p=0.001). The occurrence of only one tumor in the combined pre- and post-central gyri was a statistically significant indicator that tumors disfavor the primary sensorimotor area (p=0.02) *Based on the study by Kennedy *et al*.[19]

including adhesion, motility, and invasion.[35] There is a relationship between brain locations of gliomas, especially oligodendrogliomas, and their molecular profiles.[36] Recent studies have shown that tumor growth and invasion are governed by biophysical laws, and regulated by heterogeneity in phenotypic, genotypic, and micro-environmental parameters.[37,38] Computer simulations of a human glioma over time show glioma producing finger-like extensions in the proliferative growth stage.[37]

In our study, we observed a tendency among supratentorial astrocytic tumors for the predilection for specific regions. This cannot be explained by the relative sizes of the classical lobar regions. We believe that using the classical lobar terms to locate tumors in the brain may mean that some important findings in the understanding of pathophysiology of gliomas are missed, and hence affecting the treatment outcome of gliomas. If we had used classical lobar terminology, then the study finding would have been that astrocytic tumors were seen most frequently in the frontal lobe, in line with its being the largest lobe of the cerebrum. If there were a linear relationship between the volume of the cerebral parenchyma and the regional incidence of tumors, one would have expected more tumors located in the precentral and postcentral regions among a series of 60 supratentorial astrocytic tumors. In a 622-case neocerebral intrinsic tumor series by Yaşargil, none of the tumors occurred directly within the precentral, postcentral or paracalcarine areas.[39] In practice, most neurosurgeons prefer to use classical lobar terms, which are frontal, parietal, temporal, occipital and, sometimes, insular. The growth pattern of the solid portion of malignant gliomas is largely gyral or subgyral, filling only one or two gyri.[40] This correlates with our observation that the majority (73%) of patients with glioblastoma presented first with site-specific symptoms rather than with symptoms of increased intracranial

pressure.[41] Unfortunately, the classical lobar terms are used in most of the literature about astrocytic tumors. In this study, we have used neither simple, classical lobar terminology nor the above-mentioned comprehensive cytoarchitectural maps of the cerebral hemispheres. Instead, we used the labeling of cerebral gyri, as described by M. Gazi Yaşargil.[2] This is a reduced version of the labeling of Economo and Koskinas, and not only provides ease in clinical use with MRI, but also helps avoid mistakes in surgical anatomy.

Also, in the majority of prognostic studies, 'lobar location' has been used in the methodology. Not surprisingly, cerebral location of the tumor has not been found to be a significant prognostic factor in most past studies, although various relationships between survival and lobar tumor location, deep location or eloquent location were found.[42] This may be due to a lack of precise mapping of the tumor in the cerebral gyri.

If supratentorial astrocytic tumors have a predilection for cerebral gyri, what is the reason?

The reason why intrinsic tumors show a predilection for certain localized areas of brain remains unclear. According to Yaşargil, this may be related to cytoarchitectonic structure, phylogenetic development, or vascularization patterns.[2] Yaşargil reported that there is a tendency for gliomas to occur in white matter beneath the homotypical isocortex (Table 3), in the limbic and paralimbic systems, and in the caudate nucleus, thalamus, and brain stem.[2] In our study, the favored locations of the tumor, observed and/or found to be statistically significant, are clearly in line with this. In our study, the middle portions of the frontal gyri, the supramarginal gyrus and insula as well as limbic-paralimbic areas as a whole were found to be preferential sites for astrocytic tumors. The insula itself is not homogenous and has at least three different cytoarchitectonic fields: agranular, dysgranular and granular regions.[43] The granular cortex constitutes the most posterior portion of the insula and demonstrates the highest degree of cortical differentiation. Within the insula, there are marked regional differences in vulnerability to pathologies, such as Alzheimer's disease. However, we were not able to determine the specific insular sites of the tumors.

If supratentorial astrocytic tumors disfavor some cerebral gyri, what is the reason?

Although precentral and postcentral gyri comprise a relatively large volumetric proportion of the total cerebral volume, only one tumor was located in these areas in our study. Two fundamental types of cortical neurons were identified by electron microscopy: pyramidal neurons and local circuit neurons. Pyramidal neurons correspond to excitatory neurons. Excitatory neurons consist of distinct cell types that create the chemical diversity of neurons in the neocortex, and are optimized for a particular function.[44] Brodmann noticed that the giant pyramidal area (precentral, area 4), postcentral area (areas 3, 1, 2) and calcarine striate cortex (area 17) are among the most differentiated structural regions of the whole human cerebral cortex.[30] He also stated that these areas were constant in the entire mammalian class. Astrocytes, which may play an important role in supporting and protecting neurons, inducing

Table 3: **Heteromodal association areas (homotypical isocortex).**

	Brodmann area
F1 middle	9
F1 anterior	10
F3 middle (pars triangularis)	45 Broca
Frontal pole	11
F1 medial rostral	9, 10, 11, 12
P2 middle (angular)	39
P3 anterior (supramarginal)	40
F2 anterior and middle	46
F3 pars orbitalis	11, 47
Insula Posterior gyri	Isocortical

F: frontal, P: parietal

From: Yaşargil MG (ed): Microneurosurgery Vol IV A, New York: Thieme medical Publishers, Inc, 1994.

neurogenesis, regulating synapse formation and synapse transmission, and initiating immune response, derive from multipotent neuroepithelial stem cells in response to both extracellular and intracellular stimuli.[45] Thus, a cell of tumor origin could be either an undifferentiated glial progenitor or a differentiated astrocyte. It should be noted that an undifferentiated cell of origin is more sensitive to various oncogenetic stimuli.[45] This may suggest that phylogenetically more differentiated and hence so-called more stable cortical areas may be more resistant to glial malignancy.

Only astrocytic tumors were included in our study. Other supratentorial neuroepithelial tumors (the subgroups of oligodendroglial; oligoastrocytic; ependymal; choroid plexus tumors; astroblastomas; neuronal and mixed neuronal-glial tumors such as dysembryoplastic neuroepithelial tumor; pineal tumors; embryonal tumors such as medulloblastomas and primitive neuroectodermal tumor) were excluded. Hence, it was sought to analyze a histopatologically homogenous group of tumors. There were two reasons for this. First, some histological types of tumors were not in sufficient number for a reliable statistical analysis. Second, some of them are already well known, in clinical practice, to have a more evident preference for specific locations, for example, oligodendrogliomas for the frontal gyri, ependymomas and medulloblasomas for the posterior fossa, dysembryoplastic neuroepithelial tumor for the temporal gyri.[46] However, the samples in our study still consisted of a heterogenous mixture of astrocytomas. Larger patient series is necessary to divide the patient groups regarding putative cell origin, histology and genetic background; for example, three distinct groups of primary glioblastomas, diffuse astrocytomas which is capable to progress into secondary glioblastomas and pilocytic astrocytomas. This may be important because secondary gliomas are much more related to oligodendrogliomas, which were excluded in our study, than to pilocytic astrocytomas. Further research is also necessary regarding histological variants of diffuse astrocytoma grade II WHO. Multi-institutional patient series may be more helpful by eliminating institution-dependent selection bias. There are recent studies on the MRI-based system for topological analysis of human cerebral cortex, observer-independent cytoarchitectonic mapping of the cerebral cortex, computer aided histological analysis, cerebral gyrification using stereology, histochemical studies, and receptorarchitecture.[47] These studies will undoubtedly provide a basis for a better correlation between tumoral site affinity and the distinct cerebral architectonic areas.

In conclusion, the distribution of astrocytic tumors in the brain is not homogenous in the cerebral gyri, nor is it proportional to the relative sizes of the classical lobar regions. In contrast, there is a preference for some areas and a disfavoring of some others. Our findings are not conclusive and need to be supported by further studies. When locating an astrocytic tumor in the cerebral cortex, all efforts should be made to find the more precise anatomical site of the tumor, instead of using classical lobar terms to locate it. Descriptions of tumor location based on lobar terminology are no longer tenable. Nor is using classical lobar location terms in the investigation of prognostic factors in the management of patients with astrocytic tumors.

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