THE GROWTH OF GLIOBLASTOMA MULTIFORME
(ASTROCYTOMAS, GRADES 3 AND 4) IN
NEUROSURGICAL PRACTICE

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In Bailey and Cushing’s original series the glioblastoma multiforme (astrocytomas, grades 3 and 4) made up about 40 per cent of their gliomas. In our series, this type of malignant glioma constitutes almost 60 per cent of the total number and more than 90 per cent of all gliomas in elderly patients.

Many pathologic investigations have been carried out regarding this type of tumor. The surgical treatment has not been solved. Attempts have been made by many neuropathologists to demonstrate the distribution of this highly malignant tumor in the brain, but their main interest has been its preferential sites and its microscopic differentiation in each location.

Ostertag described the location of the various types of gliomas, and recently Zülch published his own series of brain tumors and demonstrated preferential localization in each lobe. Ikuta suggested an embryologic reason for the location of certain gliomas in specific regions. However, few studies have been made concerning the gross aspect of growth and extension of this tumor on the laws governing structural development.

The earliest observations were made in this field by Stroebe in 1895. In 1934 Voris reported that 24 per cent of frontal-lobe gliomas have bilateral infiltration across the corpus callosum. In 1938 and 1940 Scherer worked on the forms of growth in gliomas and their practical significance. He obtained 120 gliomas at necropsy and studied the morphology of this type of tumor. At that time he said that “most investigators of the last twenty years have been fascinated by cytological and histogenetic problems to such a degree that they pay little attention to most of the other aspects of the morphology of glioma.” This curious state of things still seems to be true.

Astrocytomas, grades 3 and 4, have infiltrative characteristics of growth which make successful radical extirpation difficult. In the literature many workers frequently emphasized the fact that in a glioma “no capsule is formed.” In many cases that we have noted, astrocytomas, grades 3 and 4, have spread diffusely throughout much of the brain. Scherer said that primarily diffuse gliomas without formation of a definite mass and without pronounced destruction of the pre-existing tissue are encountered in about 25 per cent of gliomas in general.

Scherer also reported that in many glioblastomas, in medulloblastomas, in most of the oligodendrogliomas and cerebellar astrocytomas, and in the so-called polar spongio-blastomas, a narrow zone of infiltration is encountered. He thought that several factors such as an arresting of its spread at given pre-existing structures, especially in white matter at its junction with the cortex or deeper gray matter, would limit the growth of gliomas. He and others mentioned various types of growth in the glioma group and emphasized that the form of the glioma depends on the pre-existing brain tissue in which it is growing or on primary architectural properties of the brain. Recent studies
of growth and extension of gliomas have led to almost similar opinions by Russell and Rubinstein.11

Our investigation was designed to study the microscopic and gross morphology of glioblastoma multiforme (astrocytomas, grades 3 and 4) from the point of view of the feasibility of surgical excision of these neoplasms. Recent advance in neurosurgery makes it possible to locate a tumor in an early stage and to remove it widely with surrounding brain tissue. The feasibility of extensive hemispheral removal has been investigated in primates in our laboratories.6,17 The limitations of surgical excision of brain structures have been expanded to include the lenticular, caudate, amygdaloid nuclei and thalamus unilaterally.6,17 In recent years we have performed wide excision of these tumors, including removal of a portion of the basal ganglia and thalamus.9 One of us (C.S.M.) has mentioned that in most instances when a glioma had produced complete hemiplegia, the lesion had involved the internal capsule and the basal ganglia and had extended beyond the limits of operation. This concept might now be revised.

MATERIALS AND METHODS

In 100 consecutive cases of supratentorial astrocytomas, grades 3 and 4 (glioblastoma multiforme), tumors were obtained at necropsy for careful study. These tumors were from 57 males and 43 females and were investigated in the following manner:

1. Macroscopic observations were made on each brain. The clinical history of each case and the description of the tumor at the time of necropsy and photographs taken at that time were reviewed prior to examination of the brain itself.

2. The brains had been cut mainly by frontal sections at the time of necropsy, but further sectioning was done to determine the extent of the tumor. It was difficult to determine the gross limitations of most tumors because of their indistinct boundaries.

3. The macroscopic demarcation of tumor infiltration was carefully traced in so far as possible, with attention particularly to the relationship to anatomical brain structures such as external capsule, basal nuclei, internal capsule, diencephalon, mesencephalon, and especially the corpus callosum. Numerous microscopic sections were made from the tissue at the margin of each tumor.

4. Specimens for microscopic examination also were obtained from the normal-appearing areas at the edge of the macroscopic demarcation, especially the corpus callosum, basal ganglia, diencephalon, and mesencephalon.

On gross observation it was found that the tumor had not spread to the opposite hemisphere in 66 of the 100 cases. Microscopic preparations, however, showed infiltration into the opposite hemisphere, mesencephalon, or metencephalon in 13 of the 66 cases. The tumors in these 13 cases therefore were considered anatomically inoperable.

Consequently in 53 cases the tumor was limited to a single hemisphere, but 2 cases were included in which the tumors involved the hypothalamus unilaterally. Thus there were 51 cases in which macroscopically and microscopically the tumor appeared to be confined to one hemisphere without involvement of the hypothalamus.

It is well known that brain tumors spread along fiber tracts such as the corpus callosum or internal capsule.8 Gross inspection of the astrocytomas revealed that infiltration by the tumors is found frequently in some particular direction and that the anatomical background of the brain has a great influence on the spread of the tumor. For example, an astrocytoma of either grade 3 or 4 of the frontal lobe often spreads through the genu corporis callosi to the opposite hemisphere. However, an astrocytoma, grade 3 or 4, in the parietal or temporal regions is found more commonly with wide anteroposterior extension. Furthermore, the growth of the tumor is not infrequently retained from lateral spread by an internal or external capsule.

The 53 tumors involving a single hemisphere are classified and described according
to their spread from an anatomical viewpoint.

**Classification and Description of Astrocytomas, Grades 3 and 4, in Single Hemisphere**

*Tumors Located in White Matter and Cortex.* No involvement of basal ganglia, diencephalon, or mesencephalon.—Thirty-six tumors belonged in this category. They were sufficiently superficial to be excised from a purely technical aspect with acceptance of the possible excision of portions of such structures as the lenticular nucleus, the caudate nucleus, the internal capsule, and the lateral thalamus in an endeavor to excise normal tissue around the neoplasm. This is a fairly large number; however, it should be emphasized that we have included in this category those tumors that had microscopic infiltration near but not across the midline of the corpus callosum.

In our study tumors were located as follows: 9 in the frontal lobe (anterior to central sulcus and above sylvian fissure); 6 in the parietal lobe (posterior to central sulcus and above sylvian fissure); 5 in the temporal lobe (below sylvian fissure); 2 in the occipital lobe (originated behind parieto-occipital fissure); 0 in frontal and parietal lobes (crossed rolandic fissure); 2 in frontal and temporal lobes (crossed sylvian fissure); 4 in parietal and occipital lobes (crossed parieto-occipital fissure); 1 in parietal and temporal lobes (crossed sylvian fissure); 3 in temporal and occipital lobes, and 4 in frontoparietotemporal lobes.

As would be anticipated, the tumors of the tip of the frontal lobe have less tendency to involve other parts of the brain. Tumors in the parietotemporal and frontoparietal regions tend to invade neighboring parts of the brain as will be mentioned later; however, in this series, we encountered 4 tumors that were limited to the frontoparietotemporal regions and 2 that were limited to the frontotemporal regions. Careful observation of these tumors revealed that all had spread through the inferolateral aspect of the white matter and had invaded the three lobes along the uncinate fasciculus and its correlated fiber bundles in the white matter, but none were found in the superolateral aspect of the hemisphere. Tumors of the white matter are considered to grow in all directions; therefore, not infrequently a seemingly well-demarcated tumor is found.

Quite frequently microscopic sections revealed infiltration of the tumor beyond the gross demarcation. Therefore, the extension of the tumor was naturally greater than that observed grossly; it also was found to take a particular direction in the white matter. Although some tumors involved extensive areas of white matter, they did not invade the basal ganglia, cerebral peduncle, or the wall of the ventricle. Macroscopically it appeared as though the tumors were retained by these structures and that their growth was confined to the white matter between the cortex and these parts of the brain (Figs. 1–3).

Furthermore, in many cases we were able to trace the tumor in a specific direction in the white matter. Neuroanatomical investigation of the neoplastic extension revealed a close correlation of fascicular architecture of white matter to growth or extension of the tumor. Not all fiber bundles such as uncinate fasciculus, fasciculus longitudinalis superior or inferior, occipitofrontalis inferior, auditory or visual bundle, or corona radiata of the corpus callosum were free of tumor, and from this point of view it should be possible at operation to anticipate the paths of extension of gliomas in most instances (Fig. 4).

The cortex and the walls of the ventricle frequently were free from tumor growth and, histologically, this freedom of the ventricular wall or cortex was confirmed in spite of extensive tumor growth in some cases (Fig. 5).

*Tumors that Invaded the Basal Nuclei (Caudate and Lenticular Especially).* No involvement of diencephalon.—Six tumors were included in this category with the following localizations: 1, frontotemporal lobes; 2, frontoparietal lobes; 2, parietotemporal lobes, and 1, frontotemporoparietal lobes. These tumors were similar to those located in the white matter and cortex, except that they infiltrated the basal nuclei.
FIG. 1 (left). Infiltration of tumor outside of internal capsule. Tumor cells are infiltrating into the capsule through small vascular wall and between the fasciculous tissues. However, the malignant-cell density is significantly low in the capsule (hematoxylin and eosin, ×50).

FIG. 2 (right). Sharp demarcation between tumor in parietotemporal regions and retrolenticular part of internal capsule (hematoxylin and eosin, ×25).

Microscopic examination showed that tumors in the basal nuclei had significantly decreased cellularity compared to those outside of the basal nuclei. It is well known that the shape of neoplastic cells varies with the anatomical background. Outside of the basal nuclei, the neoplastic cells frequently are elongated or spindle-shaped in the direction of the fibers of the capsular bundles. These spindle-shaped tumor cells are found between the fibers, not only around the basal nuclei but also in any fasciculous neural tissue (Fig. 6). However, in the tissues of the basal ganglia the tumor cells as a rule are not elongated (Fig. 7).

Tumors that Invaded the Internal Capsule.
—Six tumors belonged to this group: 1 in the

Fig. 3. Tumor in uncus and normal cerebral pedicle. Relatively sharp demarcation between the two tissues (hematoxylin and eosin, ×120).
temporal lobe, 1 in the parietotemporal lobes, 1 in the parieto-occipital lobes, and 3 in the frontotemporalparietal lobes.

These tumors spread rather widely along the internal capsule. Three of them had infiltrated into the retrolenticular part of the internal capsule; however, microscopic sections showed that they had not invaded the basal nuclei. Each of the 3 tumors was in the parietotemporal and neighboring regions. It is possible that a tumor in this region had a greater tendency to invade the deeper structure of the brain, that is, the diencephalon.

_Tumors that Involved the Thalamus and Hypothalamus._—Five tumors were included in this group. One of them was a tumor of
thamic origin and was without bilateral
involvement. The other 4 tumors were
located in the parietotemporal regions. This is
consistent with the tumors that invaded the
internal capsule and that had a greater ten-
dency to involve the deeper structure of the
brain. The tumor of the thalamus had not
spread beyond the external capsule so that it
was sharply circumscribed, but it involved
the fornix and septum pellucidum, although
it did not extend across the midline.

TUMORS OF BOTH HEMISPHERES
AND THE BRAIN STEM

Forty-seven tumors had extended to the
opposite hemisphere, into the brain stem,
and had become implanted on the spinal
cord, or had produced meningeal gliomato-
sis. Classification and description of these
47 tumors follow.

Tumors Having Bilateral Involvement
Through the Corpus Callosum. (a) Without
involvement of basal nuclei or diencephalon.
—The 10 tumors of this type were found in
the following locations: 5 in the frontal lobe,
2 in the parietotemporal lobes, 1 in each of
the frontotemporal, temporo-occipital, and
occipitoparietotemporal lobes.

Three tumors of this group showed only
microscopic extension beyond the midline
of the corpus callosum. The basal nuclei and
deeper structure of the brain were not in-
vaded.

Tumors of the frontal lobe had the butter-
fly shape in the bifrontal region. As would be
expected, the number present in the temporoo-
occipital and parietotemporal regions which
had bilateral involvement through the corpus
callosum was relatively small. However,
these tumors more frequently involve the
basal ganglia and deeper structures.

(b) With involvement of basal nuclei or
other parts of deeper structure of brain.—
Localization of the 15 tumors in this group
was as follows: 4 in the frontoparietal lobes,
3 in each of the frontotemporal and parieto-
temporal lobes, 2 in the frontotemporo-
parietal lobes, and 1 in each of the frontal, temporo-occipital, and parietal lobes.

Tumors in the frontal lobe showed involvement of the deeper structure of the brain; however, the degree of invasion was not so extensive as that of tumors in the parieto-temporal regions. A significantly larger number occurred in the parietotemporal regions. Many of these tumors were associated with involvement of the brain stem.

**Tumor Spread Without Tumor Tissue Continuity.**—Seven astrocytomas, grades 3 and 4, had spread from a single hemisphere but with an undetermined pathway. They possibly were multifocal or had spread by way of the cerebrospinal fluid or the blood stream. One of the tumors was in each of the following locations: temporal lobe and aqueduct of Sylvius, occipital lobe with meningeal gliomatosis involving the brain stem, temporo-occipital lobes and spinal cord with meningeal gliomatosis, frontotemporal lobes with involvement of the diencephalon and meninges, temporal lobe and meninges with ependymal gliomatosis, temporal lobe and hypothalamus, and frontal lobe, aqueduct of Sylvius, brain stem, cerebellum, and spinal cord.

In addition, in one patient two separate tumors were found in a single hemisphere on the same side and another patient had a coincidental meningioma.

**Tumors of the Diencephalon (Including Basal Nuclei).**—There were 11 tumors in this group, 10 of which showed spread to the opposite side or to the brain stem or to both.

It is important that all tumors involved the brain stem. Some tumors were limited by the internal or external capsules and by the corpus callosum, and some crossed the midline through the septum pellucidum and fornix. The high incidence of invasion of the brain stem could be explained from an anatomical viewpoint by the close connection of the diencephalon and the mesencephalon.

**Corpus Callosoal Tumor.**—Five tumors which had originated in the corpus callosum were available for study. All of these tumors had extensive infiltration throughout the corpus callosum itself and bilaterally into the hemispheres or thalamus.

### TABLE 1

<table>
<thead>
<tr>
<th>Lobe Involved</th>
<th>Theoretically Operable</th>
<th>Not Operable</th>
<th>Total</th>
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<tbody>
<tr>
<td>Frontal</td>
<td>9</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Parietal</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Temporal</td>
<td>5</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Occipital</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Frontoparietal</td>
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<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Frontotemporal</td>
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<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Parieto-occipital</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Parietotemporal</td>
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<td>3</td>
</tr>
<tr>
<td>Temporo-occipital</td>
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<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Frontotemporoparietal</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Occipitotemporoparietal</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

**Total**          | 36                     | 48           | 84    |
GROWTH OF GLIOBLASTOMA MULTIFORME IN PRACTICE

parietal lobe. Therefore, it must be recognized early so that lobectomy or radical resection might be employed before the tumor has extended deeply or widely. Since the tumors in these 36 cases were microscopically outside of the diencephalon and the midline of the corpus callosum was not invaded, radical resection should have been wide enough to expose the deeper structure.

If it were permissible to remove the thalamus and the hypothalamus on the same side, it is possible that 53 per cent of tumors were surgically approachable. We should concede, however, that hypothalamic and extensive thalamic resection in the human being is not practical. Thus the tumors in 36 of our patients would appear to have been technically resectable. However, on the assumption that extensive resection of the dominant hemisphere is not carried out, the number probably should be divided by two.

Bilateral extension was observed in 47 tumors: 25 were located principally in the white matter of one hemisphere; 7 seemed to have multifocal areas of origin, and the major involvement in 15 was the diencephalon or the corpus callosum.

Eighty-four of the 100 tumors were readily visible in the cortex or white matter of the hemisphere by the usual surgical approaches; 16 were principally deep tumors of the basal ganglia and other deep structures not readily visible at operation and ordinarily considered to be incurable. Of the 84 tumors readily visible at operation, 32 proved to involve both hemispheres bilaterally, either grossly or microscopically, and were therefore, according to our criteria, not resectable. Of the remaining 52 tumors there were 16 which were not bilateral but which had extended deeply and were therefore considered inoperable. Thus 36 patients might have been considered as acceptable surgical candidates for block resection or hemispherectomy. As indicated previously, it is our opinion that such radical surgical measures should be confined to the nondominant hemisphere. We therefore assumed that approximately 18 of the 100 astrocytomas, grades 3 and 4, might have been extirpated successfully, but in practically all instances serious neurologic defects would have resulted. In our study of the 36 operable tumors 9 appeared principally in the frontal lobe, 6 in the parietal lobe, 5 in the temporal lobe, 2 in the occipital lobe, 2 in the frontotemporal lobes, 4 in the parieto-occipital lobes, 1 in the parietotemporal, 3 in the temporo-occipital and 4 in the frontotemporoparietal lobes.

It is apparent to us that the frontal lobe is the most favorable location for these tumors to originate inasmuch as 9 such tumors in our series were theoretically resectable and 8 were not. Depending, therefore, on the surgical philosophy of the physician, as many as 9 might be resected; on the other hand, as few as 5 or 4 might be resected, depending on the attitude toward resection of a dominant frontal lobe.

Only one of the 13 tumors that involved both the parietal and temporal lobes has been considered to be resectable. Unfortunately, in this particular instance the tumor we studied was in the dominant hemisphere and was not considered operable.

Five of 9 gliomas in the temporal lobe were resectable and therefore this is a relatively favorable location, as is the frontal lobe. However, resection of the dominant temporal lobe is even less practical than resection of the dominant frontal lobe because of the overwhelming neurologic sequelae. The same might apply to the parietal lobe, where 6 out of 7 tumors were found to be resectable.

None of the tumors involving the frontal and parietal lobes in our studies was resectable. Two of 3 tumors involving chiefly the occipital pole were resectable, and 3 of 6 involving the temporo-occipital lobes were technically resectable. Two of 7 frontotemporal tumors and 4 of 5 parieto-occipital tumors were technically resectable.

Once a favorably located tumor has been identified, particularly in the nondominant hemisphere, it has been our practice for many years to try to remove the tumor by block resection, lobectomy, or subtotal hemispherectomy, including, if necessary, the ventricular walls and more superficial basal nuclei. On occasions we have encroached on the thalamus in our efforts to "get around" these neoplasms.
CONCLUSIONS

A study was made of 100 necropsy specimens of brain containing astrocytomas, grades 3 and 4, in the supratentorial area. Anatomic criteria were established arbitrarily to ascertain resectability of these tumors. The arbitrary boundaries were the midline of the corpus callosum, the lateral aspect of the thalamus and the region adjacent but above the hypothalamus and the mesencephalon. We found 36 tumors of a single hemisphere that did not involve these boundaries and, therefore, by our criteria were resectable. If it is assumed that in a large population these tumors would occur equally in either hemisphere, the conclusion is reached that about 18 per cent might be considered for radical resection, depending on the physician’s philosophy about wide resection of a dominant hemisphere.

REFERENCES