A STUDY OF 211 PATIENTS WITH VERIFIED Glioblastoma Multiforme

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(Received for publication May 3, 1948)

... because I strongly believe that the operative mortality is higher in the case of gliomas treated merely by decompression than it is when the growth, once exposed, is removed as completely as possible, it is our invariable rule vigorously to attack a glioma of the cerebral hemisphere rather than to withdraw from it.—Harvey Cushing.

In a follow-up study of 211 patients with glioblastoma multiforme, verified microscopically, we have found a relationship between the postoperative survival time and the pathological characteristics, the various types of surgical attack, the age of the patient, the site of the tumor, and roentgen

![Chart 1](image)

and radium irradiation. There also was a tendency for some of the tumors to change their histopathological character during treatment of the patients.

We have encountered 860 patients with verified intracranial tumors from July 1, 1944, to July 1, 1947 (Chart 1). Of these, 455 patients (52.9 per cent) had gliomas. The 211 patients who had verified glioblastoma multiforme comprised 29.5 per cent of the total number of intracranial tumors, or 46.4 per cent of the gliomas. Careful follow-up studies have been done in each instance, except for 8 patients in this group, whom we have been unable to follow.
Of the 211 patients, 24 were brought into the hospital in such poor condition that they expired shortly after arrival, before any surgical procedure was done. The diagnosis in each instance was verified by autopsy. The remaining 187 patients were operated upon 225 times, and of these, 77 died in the hospital within 1 month after operation. The cause of death in many cases was directly due to the operation, but any patient dying within 1 month after the operation, regardless of the cause, was considered an operative death. The case mortality was 36.5 per cent and the operative mortality was 30.2 per cent. Included in this number are 8 patients in whom ventriculography alone was performed, and who expired before any direct surgical attack upon the tumor was made. Of the 110 patients who survived surgery, 41 lived for 6 months or less, 38 survived for 7 to 12 months, 12 survived for 1 to 2 years, and 11 survived for longer than 2 years. The longest survival time was that of a patient who lived for 41 months after operation (Chart 1).

PATHOLOGY

We have based our microscopic diagnosis of glioblastoma multiforme on a histogenetic schema according to Bailey and Cushing's classification of gliomas. This histological division was not always clear-cut, because of the frequent cytological and structural variations encountered in different sections of the same tumor, particularly when only a small fragment of tissue was first available for biopsy at operation, and later, the whole tumor was re-studied at postmortem examination. As a matter of fact, in addition to the 211 tumors studied, there were 14 which were originally classified as glioblastoma multiforme. However, when these tumors were critically and repeatedly re-examined, they were finally verified as astrocytomas (8), medulloblastomas (3), oligodendrogliaoma (1), sponggioblastoma unipolare (1), and melanomas (1).

Again, there was another group of 8 tumors in this series, 7 of which were verified as astrocytomas after operation, and 1 as an oligodendrogliaoma, which, after second operation or autopsy, showed a transition to glioblastoma multiforme (Figs. 1 and 2). These mixtures of different cytological glioma entities in one and the same tumor have been discussed previously by Carmichael, Davidoff and Ferraro, Cox, and Deery. These observers also confirmed Virchow's original observations in 1863-65 and those of Stroebel, Henneberg, and Tooth, on the transition of a so-called "benign" glioma into a more "malignant" type. Bailey and Cushing and Globus and Strauss also observed glioblastomas to dedifferentiate from astrocytomas.

In attempting to correlate the microscopic pathology of glioblastoma multiforme with the survival time of the patients, we were struck by the preponderance of proliferative vascular changes in these tumors, and, on the basis of their angio-architectural patterns, we arbitrarily divided them into two groups. The first, or angiothrombotic group, was characterized by microscopic evidence of thrombosis, both recent and organizing, with multiple large areas of infarction and hemorrhage (Fig. 3). The second, or
angioproliferative group, was characterized by adventitial or perivascular proliferations, glomerular formations or sessile bud-like outgrowths of the intima, or intravascular endothelial proliferations resembling at times even obliterative endarteritis (Gough\textsuperscript{13}), but usually without any evidence of thrombosis at the site of subdivision (Fig. 4). If any thrombi at all were seen in these tumors, or any large areas of necrosis, as distinct from minor degenerative changes, then they were all placed in the angiothrombotic group regardless of the fact that co-existing extensive proliferative changes

Fig. 1. (left). Typical astrocytoma, showing uniformity of cell types and some cyst formation. Compare with Fig. 2. (Hematoxylin-eosin, \( \times 230 \).)

Fig. 2 (right). Tumor from same patient as in Fig. 1 seven months later, showing transition to glioblastoma multiforme. (Hematoxylin-eosin, \( \times 230 \).)

may also have been present in the blood vessels. Despite this, there was still a group of 9 patients in which no clear-cut distinction could be made, and it was found impossible to classify the tumor on this angio-architectural basis.

There were 139 tumors designated as angiothrombotic, and 63 as angioproliferative. Of the 24 patients who were admitted in extremis and died without operation, 17 were in the angiothrombotic group, while 6 were in the angioproliferative group. Of the 77 patients who did not survive surgery, 60 were in the angiothrombotic group, and 14 were in the angioproliferative group (Chart 2). Of the patients who survived surgery, 10 (16.1 per cent) of
Fig. 3 (left). Angiothrombotic type of glioblastoma multiforme, showing thrombosis, hemorrhage and necrosis. (Hematoxylin-eosin, X100.)

Fig. 4 (right). Angioproliferative type of glioblastoma multiforme, showing endothelial and adventitial proliferation of the blood vessels. (Hematoxylin-eosin, X280.)

**MICROSCOPIC ANGIO-ARCHITECTURAL PATTERNS IN THE 101 PATIENTS WITH VERIFIED GliOBLASTOMA MULTIFORME WHO DID NOT SURVIVE**

<table>
<thead>
<tr>
<th>Moribund on Admission</th>
<th>Operative Deaths</th>
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<tr>
<td>Angio-Thrombotic</td>
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<td>Angio-Proliferative</td>
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Chart 2
the angiothrombotic group survived for more than 1 year, while 13 (30.2 per cent) of the angioproliferative group survived for more than 1 year. Similarly 3 (4.8 per cent) of the angiothrombotic, and 8 (18.6 per cent) of the angioproliferative group survived for more than 2 years (Chart 3). These figures are statistically significant by the law of probable error and show that the angioproliferative group survived for a significantly longer period of time following surgery.

Tooth in 1912 was the first to emphasize these vascular proliferative changes. He was able to subdivide the evolutionary process of an actively growing glioma into four stages, which he called angiomatous, intimal proliferative, thrombotic, and necrotic. Our angioproliferative group of tumors corresponded to his first two stages combined, and our angiothrombotic to his final two stages. Virchow in 1865 and Stroebel in 1895 noted these “telangiectatic” and hyperplastic blood vessels as part of the tumor process, and their significance was discussed later by Bertrand and Medakowitz, Scherer, and Bertha. The vascular patterns and reactions of these tumors were also studied by Globus and Strauss, Bailey and Cushing, Carmichael, Deery, Elsberg and Hare, and Hardman. Sahs and Alexander suggested that this awkward and inadequate vascular supply was a major factor in the causation of the frequent, widespread necrosis in glioblastoma multiforme.

Penfield has been the strongest proponent of the view that this remarkable multiplication of endothelial cells would yet prove to be the essential part of the tumor, and this viewpoint seemed to be strengthened by the fact that at least the glomerular type of proliferation was rarely ever seen in any other tumor but glioblastoma multiforme. Bailey and Cushing, Deery, Gough, and others considered these to be reactive blood vessel proliferations, perhaps on a toxic basis, since these formations in rare instances did appear in other glioma types as well, particularly in the astocytomas associated with dedifferentiation, and occasionally also outside the edges of a
metastatic carcinomatous nodule. Scherer\textsuperscript{22} noted that these angioblastic proliferations have always been observed in patients with an extremely rapid evolution of signs and symptoms. This, together with the curious fact that they not only precede the growth of the tumor, but also grow from the uninjured tissue towards the edge of the tumor, gave them a biological significance which he considered was worthy of further research.

In 1940, Scherer\textsuperscript{22} studied the evolutionary stages and growth processes of the gliomas, and as a result divided his glioblastomas into a primary type, revealing extensive necrosis, and a secondary type, revealing comparatively small or no necrosis, usually with some small areas of cystic degeneration. From his description, we believe that these strongly resembled our angi thrombotic and angio proliferative groups respectively. His latter group were also those with "long clinical evolution," whereas his primary glioblastomas did not live beyond 6 to 12 months.

Busch and Christensen\textsuperscript{4} subdivided their glioblastomas into three main pathological groups. These groups were: (1) angionecrotic, characterized by pleomorphism of cells, necrosis, hemorrhage and increased vascularity, with proliferation of intima and adventitia, as well as thrombosis, fibrosis, and hyaline degeneration; (2) multicellular, characterized by less vascularity, less polymorphism, and greater richness of cells; and (3) magnocellular, characterized by large, plump cells with eccentric nuclei and the more frequent occurrence of multinuclear giant cells. We attempted to classify our 211 glioblastoma multiforme tumors in this manner, but the attempt was only partially successful because in many cases there was no clear-cut differentiation between the types, and frequently there was merging of one type into the other in different sections of the same tumor. In our study, 96 tumors were angionecrotic, 68 multicellular, 38 magnocellular, and 9 unclassifiable. Of the patients who survived surgery, 8 (17.0 per cent) of the angionecrotic lived for 1 year or longer, as contrasted with 11 (39.6 per cent) of the multicellular, and 4 (33.7 per cent) of the magnocellular group. This was in general agreement with the findings of Busch and Christensen,\textsuperscript{4} but our results were not as dramatic as theirs.

**AGE INCIDENCE**

Over half of the patients were between 40 and 60 years old, the greater number being in the 40 to 50 year age group. However, the ages ranged from 3 years to 75 years, and there were 4 patients below the age of 10. Of the 4 patients in the 3 to 10 year group, it should be noted that none survived surgery, and the 2 over 70 years old were in extremis on admission and died without operation. There were 19 patients between the ages of 61 and 70 years, but none of these survived for more than a year. The patients in the third decade of life generally survived longer than the others. Of the 25 patients in the above three extreme age groups, 20 were classified as angi thrombotic. Again this seems to indicate that this group is the more malignant one.
SEX INCIDENCE

Several of the patients in this series were treated at a Veterans Administration Hospital, where there is a high preponderance of male patients. Therefore, we do not believe that our figures relative to sex incidence are representative.

LOCATION OF THE TUMOR

Of the 211 tumors, 103 were confined to either the frontal, parietal, or temporal lobe, most of them being in the latter location. In only 1 patient was the tumor confined to the occipital lobe. Seventy-eight tumors occupied more than one lobe but were unilateral, while 26 were bilaterally located in the cerebrum. Three tumors definitely verified as glioblastoma multiforme were infratentorial in location. One of these was located in the brain stem of a 51-year-old male and only a surgical biopsy was taken because of the inaccessibility of the tumor. He expired in the hospital shortly after operation and the tumor could not be classified definitely as angiothrombotic or angio proliferative. Another was located in the right cerebellar hemisphere, with extension into the pons, of a 12-year-old boy, who also died in the hospital shortly after operation. A subtotal resection of the tumor was done and the tumor was classified as angiothrombotic. The third tumor was located in the right cerebellar hemisphere of an 8-year-old boy, who died on the operating table during the induction of anesthesia, before the tumor was attacked. This tumor was angioproliferative.

Of the 30 tumors confined to the frontal lobe, 3 survived for more than 2 years, while of the 73 confined to either the temporal or parietal lobe, only 2 survived for more than 2 years. The operative mortality was only 27 per cent in the tumors confined to one lobe, while it was 44 per cent in the multilobar tumors, and 50 per cent in the bilaterally located tumors. Four patients with multilobar tumors lived for more than 2 years, while 2 with bilaterally located tumors lived for more than 2 years.

SURGICAL TREATMENT

It has been our invariable rule to operate through a large osteoplastic craniotomy in order to have adequate exposure of the tumor for removal and to provide, if necessary, a thorough decompressive effect. Even when there was good reason preoperatively to suspect the tumor of being glioblastoma, we have never followed the practice of performing a trephine opening to obtain a small amount of tissue by means of a ventricular needle or a small forceps. The histologic nature of any tumor should not be judged by such limited tissue study, and on several occasions we have found that the tissue so obtained and diagnosed elsewhere as "glioblastoma" or "probably glioblastoma" proved, on later removal of the tumor, to have been merely the softening with glial proliferation around a benign tumor or a glioma of much less malignant character than a glioblastoma. Neither do we feel that the discovery of cystic fluid in a softened area in the brain by such methods is sufficiently diagnostic of glioblastoma to deny the patient any benefit of
complete surgery. Were only such limited operative approaches persistently made to the surgical problem of the glioblastoma, the solution of this admittedly difficult situation would never be attained. The electrosurgical unit, improved instruments, adequate suction apparatus, and hemostatic agents have facilitated the radical removal of these tumors during the last 20 years.

Of the 187 patients who were operated upon, the tumor was not directly attacked in 39. These patients were those in whom there was an error in localization of the tumor, or on whom ventriculography was performed with death occurring before operation could be done, or those on whom subtemporal decompression alone was done. In the early years of our treatment of these tumors, and especially before the now common use of preoperative pneumoencephalography, subtemporal decompression was occasionally done as a first-stage operation, or to relieve the patient of his increased intracranial pressure while awaiting the appearance of further localizing signs or an improvement in his general condition. In the remaining 148 patients in whom the tumors were directly attacked, the involved lobe was completely resected in 7. Forty-one patients had resection of all grossly visible tumor and in many instances this amounted to over 100 grams of tissue. From 1 woman with a glioblastoma of the right frontal lobe 106.6 grams of tissue were removed at the first operation, and 90 grams more were removed at a second operation almost 2 years later. Seventy-one patients had subtotal removal of the tumor and 28 patients had smaller amounts of tumor removed for microscopic verification only when for special reasons a more radical operation was deemed unwise. Such partial removal of the tumors was done when the lesion lay adjacent to a vital area of the brain, when the tumor extended widely through the corpus callosum into the opposite hemisphere, or when the patient was in such poor condition that wide removal of the tumor could not have been tolerated.

As with tumors elsewhere in the body, it is a general rule that the wide removal of a glioblastoma undoubtedly prolongs the life of the patient. Of those patients who had complete removal of a lobe and survived surgery, 50 per cent lived for more than a year after operation. Twenty-six per cent of those who had resection of all grossly recognizable tumor, 21 per cent of those who had subtotal removal, and 18 per cent of those who had surgical biopsy only, survived for more than a year after surgery. Of the 39 patients in whom the tumor was not directly attacked, only 1 patient survived for more than a year.

The immediate postoperative state of the patient, as well as his survival time and his comfort and well-being during that period, is markedly affected by surgical decompression of the brain. At the time of operation the bone flap was removed in 90 patients, while the usual decompression in the flap was made in 80 others. There were 33 per cent operative deaths among those patients in whom the bone flap was removed, while in those in which the usual decompression in the bone flap was made the operative mortality was
45 per cent. The bone flap was always removed in those instances where the
tumor was obviously of a highly malignant and infiltrative nature, or when
the brain appeared to remain under tension even after resection of the tumor.
The usual decompression in the bone flap was performed when the tumor
appeared to be more benign in nature, when all visible tissue had been re-
moved from a lesion that appeared to be fairly well circumscribed, or when,
following removal of the tumor, the brain appeared to be relieved of its ten-
sion and not likely to undergo marked postoperative swelling. It is note-
worthy that the postoperative mortality was actually lower in that group
of patients with the most severe lesions and in whom the widest possible
decompressive effect was obtained by removal of the bone flap. However,
fewer patients in this group survived for more than a year after surgery than
among those in whom a decompression in the bone flap was performed, indi-
cating that with succeeding months the malignant and destructive charac-
teristics of the tumors outweighed the immediate good effects of decompres-
sion. The approximate histologic nature of the tumor was verified by frozen
section or by a rapid vital staining technique but these methods are not
completely reliable.

The story of surgical accomplishment in this most difficult group of in-
tracranial tumors is not a pleasing one. It should challenge the surgical con-
science and ability of every neurosurgeon. New methods must be devised to
supplant the present crude surgical techniques of glioma removal. The
challenge cannot be met by adopting procedures which hasten rather than
retard the clinical progression of the gliomas.

**ROENTGEN IRRADIATION**

Forty-three patients received roentgen irradiation and 15 received ra-
dium therapy. Of those who received more than 4,000 r units, 12 survived
for more than 1 year, while of those who received less than 4,000 r units, none
survived. Of those patients who survived surgery and received no irradiation,
only 5 survived for more than 1 year. Only 3 of those who received radium
irradiation survived for the same period, while the other 12 succumbed within
the year. From our findings it would appear that those patients who re-
ceived adequate roentgen irradiation therapy survived for a longer period
of time than those who did not. However, despite these figures, it must be
remembered that those who had inadequate roentgen irradiation therapy
may not have lived long enough following surgery to either start, or com-
plete, their courses, because of the relatively very malignant nature of their
respective tumors.

We also studied the microscopic sections of 12 tumors both before
and after roentgen irradiation therapy (Figs. 5 and 6), and our findings
were as equivocal as those of other investigators\(^1,6,7,9,16,17,24\) of this prob-
lem. As Deery\(^10\) found, some of the glioblastomas showed striking hist-
opathological changes, while others were less convincing, and still others
showed no distinct changes at all. In 5 cases we found a striking increase in
the number of pyriform, undifferentiated, and giant cells, with marked bizarreness and hyperchromaticity of their nuclei. The stroma showed an increased number of extensive hemorrhages, and areas of necrosis and degeneration, with foci of replacement fibrosis, as well as of small round cell infiltration. The blood vessels in areas also showed more extensive changes, particularly in intimal proliferation to the point of obliteration, hyalinization, and at times necrosis of the blood vessel walls themselves; with many recent and old thromboses scattered about. However, it is difficult to determine whether these same changes could not occur within the normal range of variation in such a variegated tumor as glioblastoma multiforme at some stage during its lifetime. One tumor without roentgen irradiation, in which microscopic sections were examined first at operation and then at autopsy 7 months later, had changes similar to those which might be construed as evidence of tumor regression, resulting from irradiation therapy.

Davis and Weil\(^9\) also found no real evidence that X-ray had decisively prolonged the survival period of patients beyond the average of those with histologically similar tumors without such therapy. Tarlov\(^24\) noted the fact that histological changes were unimpressive as indications of regression due to irradiation therapy. He, among others, called attention to the stimulative effect of roentgen rays and the possibility of subsequent dedifferentiation
of tumor cells with eventual transition to a more rapidly growing malignant type of glioma, noted particularly at the edges of the tumor mass.

SOCIAL AND ECONOMIC REHABILITATION

Over 1/5 (23) of the patients who survived surgery survived for more than 1 year, and 1/10 (11) for more than 2 years, during which time the patients were not only more comfortable than they had been but were able to fulfill both economic and social obligations. Many of these patients were able to return to work for many months after operation. One patient returned to office work for 9 months after operation, while another returned to work as an executive for 13 months after surgery. The patient who lived for 41 months after surgery became interested in the Oxford Group Movement and was active in this work for most of that time. One patient who had a high-grade papilledema and was blind on entrance to the hospital was operated on and over 100 grams of tumor tissue removed. She made an excellent recovery and her intelligence quotient after operation was 118. She learned Braille and was able to work around the house and care for her two children. She made baskets and leather belts for sale and learned to do dictaphone typing. She divorced her husband, who was a drunkard, and provided for the future care of her children by her parents before she was readmitted to the hospital with a recurrence of her tumor almost 2 years later. She was re-operated upon and almost 100 grams more of tumor tissue removed. She lived for 3 more months.

SUMMARY

Two hundred eleven patients with verified glioblastoma multiforme have been studied. Of these, 187 were operated upon and 110 survived surgery. Twenty-three patients lived for more than 1 year following surgery, and 11 for more than 2 years, during which time many of them were able to fulfill economic and social obligations. On the basis of the microscopic characteristics the tumors were divided into angiothrombotic and angiproliferative groups. The survival time was longer in the latter group. The patients in the extreme age groups had a poor prognosis. The operative mortality was higher if more than one lobe was involved or if the tumor extended into the opposite hemisphere. The patients in whom all or most of the tumor was removed survived for longer periods of time than those in whom only a surgical biopsy was taken. If the bone flap was removed, there were fewer operative deaths than if only the usual decompression was done. There was a longer survival period in those patients who received adequate roentgen irradiation. There were definite microscopic differences before and after roentgen irradiation in 5 tumors. Seven tumors showed a transition from a more benign glioma to glioblastoma multiforme during treatment of the patients.

REFERENCES