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Patterns of Growth of Gliomas

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The preceding paper (1) is the most interesting and provocative paper that I have read defining the “natural history” of gliomas and the effects of various treatments, surgical and/or radiologic. Indeed, I believe that the techniques described—with modifications that will become apparent below—should become routine and “on line” so that the effects of treatments applied to every glioma patient can be measured intelligently, not just assumed heroically “as the best we can do today” or blindly “as the literature suggests today.”

I hope that the reader will bear with this pathologist’s natural tendency toward retrospective analysis: beginning at the end, and performing an autopsy—in the literal sense of the word, “to see for oneself” (ie, in this case, for myself). The end, of course, is at the point in Figure 2 of Blankenberg et al (1), where “actual death (8/86)” is indicated at about 38.3 doublings of those classical but still theoretical, spherical cells 10 μm in diameter, or 8.3 doublings of a spherical mass 1 cm in diameter or 0.523 cm³ in volume, reaching a total of about 165 cm³. Although the death was “actual,” the volume was only theoretical, obtained by extrapolation of the last 5 computed tomography (CT)-defined volumes giving an average doubling time, $V_{D_{\text{ct}}} = 56$ days. However, to my eye there is a clear slowing of the terminal growth curve, which I extrapolate to about 37.5 doublings or about 100 cm³, as shown here in Figure 4.

Is this less-than-twofold discrepancy worth arguing about? Yes!

Why? First, we need more data on radiologic-pathologic correlations to establish the “fatal volume,” on which much theoretically depends. To my knowledge this fatal volume has been defined only twice before, by Concannon et al (2) and Burger et al (3). The former measured 3 diameters of the tumors in 30 cases, allowing me to calculate a range of volumes from 15 to 351 cm³ (median, 83.5 cm³) and of average diameters from 3.1 to 8.9 cm (median 5.5 cm). The latter presented two-dimensional sketches of 11 cases, from which I could estimate a range of about 2.6 to 6.4 cm for average diameters (median, about 4.8 cm). From both sources I estimate the average fatal volume to be about 64 cm³ (about $2^6$ cm³ or, in the terminology of the present paper, about 37 doublings) and the average fatal diameter to be about 5 cm.

Second, we suspect that simple exponential growth is not correct, at least terminally, as cells use up the available metabolites; and we suspect that “logistic growth” is the better model of tumor growth. Logistic growth, so named “for some unknown reason” (4) and developed by Verhulst in 1836, is defined mathematically as $\frac{dN}{dt} = rN(1-N/K)$, where $N$ is the number of cells and $K$ the “carrying capacity of the environment, which is normally determined by the available resources” (5). While the early stages of growth are practically the same in the two models, the logistic pattern decelerates terminally and predicts that saturation of cell density occurs with about half as many total cells required for the fatal volume—exactly as the end of Figure 3 shows.

Thus, this less-than-twofold difference is of greater significance than first might meet the eye. I regard it as not a mere coincidence and would push for more radiologic-pathologic correlations at autopsy—including postmortem scans and comparisons with the gross brain—to provide some sorely needed facts. The time is long past for making simple speculations about nonexponential growth patterns of optic gliomas (6) and of cerebellar astrocytomas (7). More facts are needed to help determine which mathematical model best represents the real
Fig 3. Revision of Figure 2 of Blankenberg et al (1) to illustrate the life history of the glioma in their patient 8. The linear extrapolations back to a volume equivalent to 30 doublings and forward to a fatal volume equivalent to 38.3 doublings are correlated with each treatment. In addition, an approximately logistic extrapolation is shown terminally to a fatal volume of about 37.5 doublings. Tumor volume is expressed both in cc (cubic centimeters, cm³) and in doublings.

Fig 4. A graphic representation of some of the data in Table 2 of Blankenberg et al (1). The average patient can be represented rather accurately, as can the range of growth rates ± 1 or 2 standard deviations, but more information is needed before the comparable ranges of volumes at diagnosis and death can be placed on appropriate lines rather than merely listed. Cc indicates cubic centimeters (cm³).
world, and such simple radiologic-pathologic
correlations could easily and quickly answer the
question whether terminal glioma growth is lo-
gistic or exponential. We also need more facts
concerning the actual cell densities at biopsy
and at death. Our own most recent mathe-
matical model (8) incorporates growth of cells
proportional to cell density and diffusion pro-
portional to the gradient of cell density. Mathe-
maticians would like to see whether there is a
relationship between the carrying capacity and
the terminal cell density.

Immediately next to the end of the story is
one of the most interesting features of the whole
case: the effect of the 125I seeds. These produced
a rapid decrease in volume, by extrapolation down to
about 30.5 doublings or 0.7 cm³, followed by
very rapid regrowth. The first two of these last five
data points (from about 32 to 36.5 dou-
blings in about 30 days, equivalent to about 7
days doubling time) are compatible with the
most rapidly growing glioblastoma ever mea-
sured. The last three data points either define
my postulated logistic-type curve or just hap-
pen to fit on the forward extrapolation of the line
VDt1, as shown in Figure 3. The implication is
clear: the 125I seeds did not contribute any ad-
ditional survival time.

Blankenberg et al (1) averaged all of these
last five points in Figure 2 to find VDt3 = 56
days, which they say is not statistically signifi-
cantly different from the first two rates (75 and
79 days). Well, I tend to ignore statistics when
they do not fit with what I think is right biologi-
cally! The five points clearly are not on a
straight line—and almost as clearly fit on a de-
celerating logistic curve.

There are probably no specifically 125I-resis-
tant cells; the surviving cells are probably the
same radiation therapy–resistant cells that had
already diffused beyond the reaches of the lo-
cally destructive 125I. This phenomenon of growth of
cells still existing beyond the surgical or local-radi-
logic resection dramatically illustrates how our cur-
rent approaches to the treatment of gliomas resemble
the ineffectual attempts to control a spreading
forest fire by dropping fire fighters into the burned
out center. The action is on the outer edge. The
central mass of a glioma actually contributes very
little or nothing to the continued growth of the dif-
fusing glioma, as we have shown mathematically
(9, 10) (Cook J, Woodward DE, Tracqui P, et al,
“Resection of Gliomas and Life Expectancy,” pre-
sented at the Satellite Symposium on Brain Tu-
mours, September 1994, Ottawa; Woodward DE,
Bartoo GT, Tracqui P, Cruywagen GC, Murray JD,
Alvord EC Jr, unpublished data; Cook J, Woodward
DE, Alvord EC Jr, unpublished data). Very exten-
sive resections are necessary to achieve any signif-
icant postponement of death from gliomas (9)
(Cook J et al, “Resection”; Woodward et al, unpub-
lished data; Cook et al, unpublished data).

The next point that caught my eye in Figure 2
was the beginning of the story, where the initial
volume is indicated by an isolated point at
about 34.5 doublings or about 11 cm³. Just how
real this point is seems to be in some doubt
since there is a statement: “(1st CT scan outside
not available)”. In any event, there must be such
a point, whatever the initial preoperative vol-
ume of some size at that time, through which
one can easily draw a line parallel to the subse-
quently defined growth rate, VDt1 = 75 days, as
shown in Figure 3. This new line can be ex-
tended back to about −240 days, when it was
only 1 cm in diameter, and forward to about 400
days (depending on how one represents the
terminal growth, as discussed above), to esti-
mate the patient’s prognosis if not treated at all,
surgically or radiologically.

This total “size-adjusted survival time” of
about 640 days is what should be correlated
with the histologic type of tumor, grade I oli-
goastrocytoma, and its site, in this case the
frontal lobe, which has twice as good a progno-
sis as other sites (11). Neither the actual “sur-
vival” times nor the “size-adjusted survival”
times in Table 3 (1) can be correlated with
anything histologic or biological other than the
particular treatment or sequence of treatments
that have preceded the patient’s death and, it is
hoped, have prolonged the patient’s life.

Returning to the beginning of Figure 2 and
accepting the probability that the neurosurgeon
removed some significant volume of tumor al-
 lows one to draw a vertical line down to inter-
cept the backward extrapolation of VDt1 at
about 31.5 doublings or about 1.3 cm³, repre-
senting the volume of residual tumor left behind
postoperatively on 1/84, as shown in Figure 3.
Extrapolating VDt1 forward yields the “theoreti-
cal time of death” with surgery, without radia-
tion therapy (not “without therapy” as stated in
Figure 2) and intersecting the same 37.5 or
38.3 lines (not the 38.0 line as shown in Figure
2) at about 600 days. In other words, the sur-
gery provided the patient about 200 extra days
survival, which again cannot be correlated with
the histologic or DNA characteristics of the tumor. The type of tumor defines the slope (i.e., the rate of growth). The treatment defines the amount of the shift of the line to the right (i.e., the theoretical survival time) if all goes well. If less had been removed, the theoretical duration would have been shorter; if more had been removed, the theoretical duration would have been longer.

Figure 2 also has a middle, where a number of questions and interpretations arise:

1. The volume before “radiation therapy (5500 rads)” of about 35 doublings or 17 cm³ could have been asymptomatic, defined only by routine scanning on follow-up, or it could have been symptomatic. In either case, ignoring the doubt expressed above, this volume appears to be larger than the initial volume of 11 cm³, suggesting that the patient's brain has accommodated to a larger volume, presumably also to a deeper mass. On both of these scores the tumor was likely to have invaded more "eloquent" tissue. If true, this would be of considerable interest to neuroanatomists, physiologists, and clinicians interested in "plasticity" of the nervous system as well as to theoreticians. It was, after all, Collins et al (12) who postulated that a recurrent tumor should be symptomatic when it reached the same size as it had been when originally diagnosed, and that survival past the longest possible time to reach this size indicated cure: "Collins's law." The competing forces of diffusion and plasticity were, of course, ignored at that time, 4 decades ago.

2. The slow decrease in volume after the 5500 rads nicely illustrates the expected slow, delayed effects of radiation therapy. More demonstrations of the rates of change after radiation therapy would be very helpful in future mathematical modelling of such treatments, even though I would expect that these effects may vary widely from extremely radiosensitive to completely radioresistant.

3. Where is the second operation? Table 4 (1) indicates it occurred in 8/85, when a grade III astrocytoma was resected. Perhaps it was only a biopsy just preceding the three points defining VD₁. Why only a biopsy? Because the first CT (also dated 8/85 in Table 5) is so large, about 33.7 doublings or 7 cm³, that there is no room for a significant resection to be included in the figure. But it should be indicated more accurately in both Figures 2 and 3.

So much for Figures 2 and 3—except one final comment about clinicopathologic correlations. Which histologic grade should be correlated with which survival time? In this particular case there were two grades (I and III) and there were two types of glioma (oligoastrocytoma and astrocytoma). The natural histories of these four combinations are already known to be sufficiently different (13, 14) that I would not lump them together. In addition, there were four treatments (surgery 1, radiation therapy, surgery 2, and ¹²⁵I). Comparing this case with a frontal lobe tumor with the others in various sites, including one or more other lobes, "suprasellar" (optic chiasmal), cerebellar, and pontine, seems to ignore the literature available on site, type, and grade—to say nothing of the adequacy of sampling, which is always the bugaboo of this subject. Did the tumor really change its appearance and/or behavior, or was the sample not representative of what was left behind in the patient to "recur," really to continue its course?

I would suggest that VD₂ can be better interpreted as evidence of a second clone of glioblastoma cells arising near the end of the patient's life. Others might interpret it as a "change" or "dedifferentiation" from a low-grade mixed oligoastrocytoma to a high-grade astrocytoma. The words and concepts may be slightly different, but it must have been those cells that had diffused distal to the effects of the ¹²⁵I seeds, cells that grew so much more rapidly and terminated in a typical "logistic" pattern of deceleration. Assuming a doubling time of about 1 week for the earlier growth allows an estimate of about 30 weeks before 12/85 (as noted in Table 5), or about 4/85, when this new clone arose—ironically, just in the middle of the apparent radiation therapy-induced regression of the tumor. However, logistic growth is sigmoid, both ends approaching their values asymptotically, so there may be considerable error in this estimate of the origin of the second clone.

The data in Table 2 are also interesting from several different points of view:

1. Although Blankenberg et al (1) used the histologic grading scheme of Daumas-Duport et al (15), they did not confirm the expected differences in growth rates in grades I to III, all of which averaged 140 to 145 days doubling time. Only grade IV grew about twice as fast (69.7 days). Perhaps the small numbers of cases explains the discrepancy, but, even so, the treatment of individual cases is frequently dictated by the histologic appearance, and I would have hoped for at least a trend.

2. The sizes at diagnosis and death are remarkably constant, about 35 and 38 doublings on the average, respectively. However, there is considerable variation, about twice as much at the time of diagnosis as
at the time of death. This may reflect the difference in “eloquence” of the sites affected, producing symptoms early or late, as contrasted with the greater diffusion and relatively constant mass to kill.

3. However, the variations must be important. Considering the “averages of the 16 patients with supratentorial gliomas with both preoperative and premortem scans” led to the formulation of Figure 4. The average patient presents with 22 cm³ of tumor measured at diagnosis (equivalent to 35.4 doublings), survives for 303 days (2.9 doublings with the tumor doubling every 105 days, ln = 4.65), and dies with 165 cm³ of tumor (extrapolated from the last scan at the same doubling time and equivalent to 38.3 doublings). The implication is that the average patient received no benefit from treatment. The standard deviations of the doubling times allow an accurate demonstration of the range of growth rates starting from 30 doublings (as in the calculation of the “size-adjusted survival time”) but it is not obvious on which lines in Figure 4 the ranges of 1 or 2 standard deviations for the volumes at the time of diagnosis and at the time of death should be placed. Perhaps Table 3 should include a column for the initial volumes so that the reader could reconstruct the life history of each patient and see just how the variables combine.

Finally, a helpful hint: I think better in base 2, where 2₁₀ = about 1,000 or 10³ cells, 2₃⁰ = 1 g or cm³, 2₂⁰ = 1 mg, 2₄⁰ = 1 kg, and 2₂⁶.₅ = 100 g. I find it much easier to calculate powers of 2, simply multiplying serially by 2 on my fingers, if necessary, than to consider e = 2.71828 or natural logs (where ln 2 = 0.693). Besides, base 2 is built for doubling times. And especially with gliomas, in which the cells are usually irregularly shaped, multibranched, and much larger than those classical 10-μm spherical cells, I find it most convenient to begin with 2₃⁰ = 1 g or cm³, thereby using cubes rather than spheres to fill the volume and eliminating that 0.523 factor. However, one must note that the volume equivalent to number of doublings in Figures 2 and 3 are doubled in this scheme. Furthermore, equation 1 in the Appendix (1) becomes much simpler: x = 30 + log₂(vol.).

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References