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Commentary

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 retrospectroscopic 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 cm^3 in volume, reaching a total of about 165 cm^3. 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, VD_{t3} = 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 cm^3, 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 cm^3 (median, 83.5 cm^3) 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 cm^3 (about 2^6 cm^3 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 $dN/dt = rN(1-N/K)$, 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

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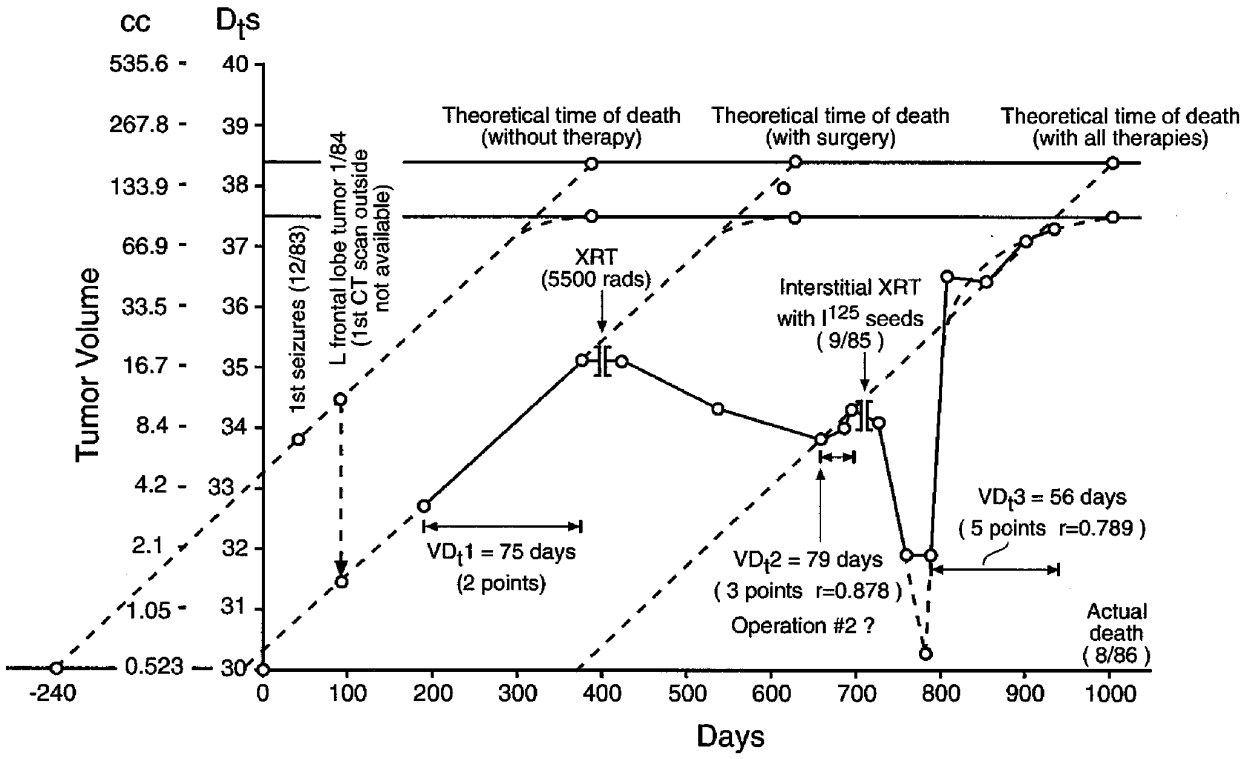

Fig 3. Revision of Figure 2 of Blankenberg et al (1) to illustrate the life history of the glioma in their patient 8. The linear extrapolations back to a volume equivalent to 30 doublings and forward to a fatal volume equivalent to 38.3 doublings are correlated with each treatment. In addition, an approximately logistic extrapolation is shown terminally to a fatal volume of about 37.5 doublings. Tumor volume is expressed both in cc (cubic centimeters, cm^3) and in doublings.

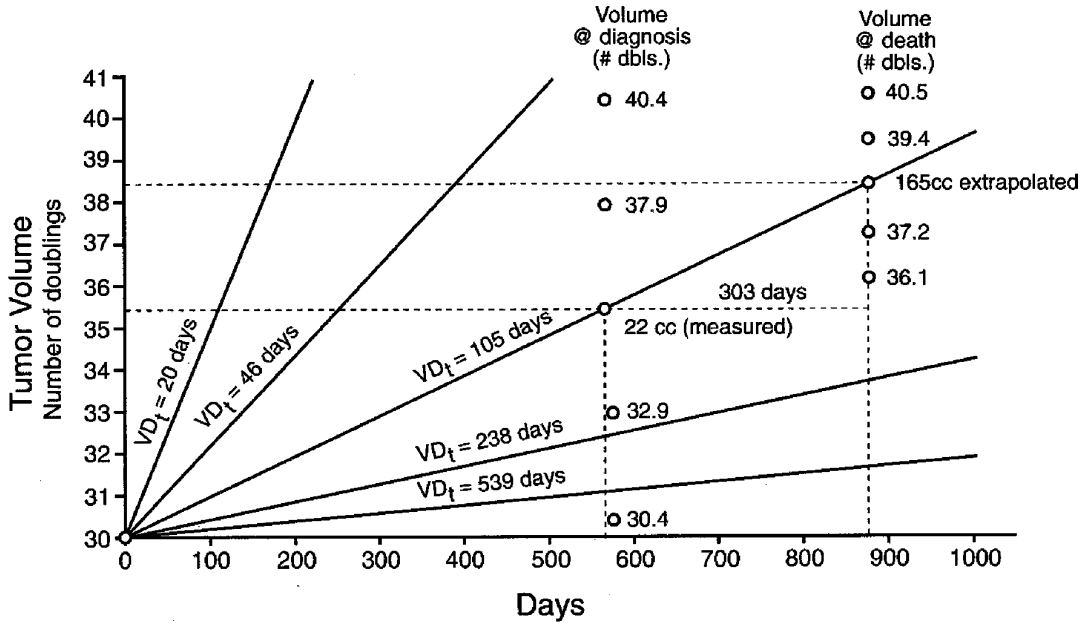

Fig 4. A graphic representation of some of the data in Table 2 of Blankenberg et al (1). The average patient can be represented rather acm^{3}urately, as can the range of growth rates ± 1 or 2 standard deviations, but more information is needed before the comparable ranges of volumes at diagnosis and death can be placed on appropriate lines rather than merely listed. *Cc* indicates cubic centimeters (cm^3).

world, and such simple radiologic-pathologic correlations could easily and quickly answer the question whether terminal glioma growth is logistic or exponential. We also need more facts concerning the actual cell densities at biopsy and at death. Our own most recent mathematical model (8) incorporates growth of cells proportional to cell density and diffusion proportional to the gradient of cell density. Mathematicians 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 ^{125}I seeds. These produced a rapid decrease in volume, by extrapolation down to about 30.5 doublings or 0.7 cm^3, followed by very rapid regrowth. The first two of these last five data points (from about 32 to 36.5 doublings in about 30 days, equivalent to about 7 days doubling time) are compatible with the most rapidly growing glioblastoma ever measured. The last three data points either define my postulated logistic-type curve or just happen to fit on the forward extrapolation of the line VD_{t2}, as shown in Figure 3. The implication is clear: the ^{125}I seeds did not contribute any additional survival time.

Blankenberg et al (1) averaged all of these last five points in Figure 2 to find VD_{t3} = 56 days, which they say is not statistically significantly 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 biologically! The five points clearly are not on a straight line—and almost as clearly fit on a decelerating logistic curve.

There are probably no specifically ^{125}I-resistant cells; the surviving cells are probably the same radiation therapy–resistant cells that had already diffused beyond the reaches of the locally destructive ^{125}I. This phenomenon of growth of cells still existing beyond the surgical or local-radiologic resection dramatically illustrates how our current 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 diffusing glioma, as we have shown mathematically (9, 10) (Cook J, Woodward DE, Tracqui P, et al, "Resection of Gliomas and Life Expectancy," presented at the Satellite Symposium on Brain Tumours, 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 extensive resections are necessary to achieve any significant postponement of death from gliomas (9) (Cook J et al, "Resection"; Woodward et al, unpublished 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 cm^3. 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 volume of some size at that time, through which one can easily draw a line parallel to the subsequently defined growth rate, VD_{t1} = 75 days, as shown in Figure 3. This new line can be extended 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 estimate 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 oligoastrocytoma, and its site, in this case the frontal lobe, which has twice as good a prognosis as other sites (11). Neither the actual "survival" 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 allows one to draw a vertical line down to intercept the backward extrapolation of VD_{t1} at about 31.5 doublings or about 1.3 cm^3, representing the volume of residual tumor left behind postoperatively on 1/84, as shown in Figure 3. Extrapolating VD_{t1} forward yields the "theoretical time of death" with surgery, without radiation 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 surgery 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 (ie, the rate of growth). The treatment defines the amount of the shift of the line to the right (ie, 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 cm^3 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 cm^3, 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 VD_{t2}. Why only a biopsy? Because the first CT (also dated 8/85 in Table 5) is so large, about 33.7 doublings or 7 cm^3, 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 ^{125}I). 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 VD_{t3} 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 ^{125}I 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 cm^3 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 cm^3 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 $\pm$ 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 volume 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 2^{10} = about 1,000 or 10^3 cells, 2^{30} = 1 g or cm^3, 2^{20} = 1 mg, 2^{40} = 1 kg, and $2^{36.5}$ = 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 2^{30} = 1 g or cm^3, 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: $x = 30 + \log_2(\text{vol.})$.

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