Letters to the Editor

PET-FDG of Untreated and Treated Cerebral Gliomas

TO THE EDITOR: The recent article by Tyler et al. in the July *J Nucl Med* (*1*) contains a misunderstanding of our work on gliomas which could have serious repercussions on patient treatment. The authors report "low" metabolic rates in untreated high grade tumors, and conclude: "This finding suggests intrinsic metabolic differences between untreated tumors and tumors recurring after therapy, in which high LCMRG1 values have been observed (*2,4,42*)." All of these three references are to publications of our work on glucose utilization of cerebral gliomas studied by the PET-FDG technique.

In fact, we have consistently observed elevated FDG uptake in *both* treated and untreated high grade gliomas. Of the above references, number 2 discusses quantitative pitfalls based on our analysis of 100 cases of brain tumor, including many untreated ones, but does not present any distinction between treated and untreated tumors. Reference 4 deals with differential diagnosis (in five cases) of tumor recurrence versus radiation necrosis, and so, by definition, was limited to post-treatment tumors. Reference 42 is our original report on PET-FDG in cerebral gliomas, based on 23 in-patients at the NIH Clinical Center. This study included ten cases of high grade tumors, three of which were scanned before any therapy. In all three cases, including a rim-shaped tumor similar to Figure 1 of Tyler et al., a visually distinct "hot" area was identified within the tumor, even given the low (17 mm) spatial resolution of our scanner at the time.

After this original report we were deluged by referrals from outside neurosurgeons and neurologists and our patient population changed dramatically, with nontreated cases, including many high grade gliomas, constituting the bulk of the tumor patients studied. Also, in 1982 the Neuro-PET scanner was completed, offering 6 mm resolution. We have now studied over *400 cases* of brain tumor, more than half of them untreated, of which at least 50 were high grade neoplasms. In virtually all of the high grade lesions there was an observable elevation in FDG uptake.

We believe that the true explanation for the "low" metabolic rates seen by Tyler et al. in untreated high grade tumors lies in differences in technique.

1. Tissue of comparison. Tyler et al. use gray matter as a reference to distinguish between high and low tumoral metabolism. On the other hand, our reference is white matter. We find that the FDG uptake of high grade tumors is always greater than that of white matter, but may or may not exceed that of gray matter. The point has profound implications for diagnosis. The overwhelming majority of hemispheric gliomas are located in, or abut the white matter. Because of the high gray-white metabolic ratio (2.9 in the Neuro-PET), there is good visual contrast for high grade tumors, even if the FDG uptake is less than that of gray matter.

2. Localization of region. In analogy with the pathologist's approach to histologic grading, we look for the hottest region within the tumor area delineated by computed tomograph (CT) or magnetic resonance imaging (MRI), while Tyler et al. used average readings over the entire heterogeneous tumor region. This difference also has diagnostic implications, as the unique ability of PET-FDG to demonstrate the discrete, viable tumor areas, compared with the more diffuse and nonspecific indications on CT and MRI, provides valuable information for targeting patient management (stereotaxy, interstitial therapy).

3. Scanning technique. In the case of small or rim-shaped tumors, good spatial resolution and accurate scan placement are important. With only six images of 12 mm resolution available to the authors, it is possible that hot areas may have been missed or artifactually lowered. For example, in the rim tumor shown in Figure 1, a type of neoplasm which in our experience is *invariably* accompanied by high FDG uptake, we are convinced that the rim was either missed in the section or washed out by the partial volume artifact.

4. "Numerical" diagnosis. Tyler et al. base their conclusions on numerical measures of glucose utilization, while we look for visual contrast with surrounding white matter. Quantitation may be appropriate when comparing populations but artifacts, such as partial volume, cause numerical changes which can mask the nature of the lesion, so the human eye is preferable for individual diagnosis.

Using the techniques described above, we have achieved close to 100% accuracy in distinguishing high and low grade brain tumors. Indeed, when the methodologic differences are taken into account, the results of Tyler et al. are not in serious conflict with ours. The major discrepancy is in their two low grade tumors with reported metabolic rates comparable to gray matter. Perhaps the histology was wrong in these cases (as has happened several times in our studies), or, more likely, there was a confusion of tumor with cortical tissue. In cases where a tumor is near or within cortical areas, we have found that it takes very careful reading to separate the two structures.

Since the reported difference in metabolism between treated and untreated high grade tumors is not confirmed by our experience, we do not comment on the authors' theoretical speculations. However, we point out that the *direct* effect of radiation therapy is to reduce glycolysis (*2*), as we already observed in our original report (Reference 42 of Tyler). Indeed, the only method to differentiate between the ultimate effect of radiation (and chemotherapy as well), i.e., necrosis, and tumor recurrence is based on the difference in glucose utilization (*3,4*).

We conclude with the outline of a glioma management guideline followed by a number of neurosurgeons who cooperate with our team: The suspected glioma, particularly if located in a functionally critical area, is treated conservatively unless the PET-FDG scan shows high uptake within the tumor

area (compared with white matter), or shows a change in repeat studies from a low to a high uptake. This documentation of metabolic change in the neoplasm, often accompanied by clinical deterioration, represents another indication of the exquisite sensitivity of the PET-FDG method, and its ability to characterize the essential tumor features. In the late 20th century, the PET metabolic studies of tumors should be considered at least on a par with, if not more important than, "static" histologic findings.

References

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Giovanni Di Chiro
Rodney A. Brooks
Department of Health & Human Services
Public Health Service
National Institutes of Health
Bethesda, Maryland

REPLY: We thank Drs. DiChiro and Brooks for their comments on our recent results (*1*) and would like to respond.

Differences in the interpretation of results for local cerebral metabolic rate of glucose (LCMRGl) in untreated gliomas exist between our centers. We reported variable, but low values of glucose metabolism in tumors, irrespective of tumor grade (*1*), compared to the gray matter LCMRGl. DiChiro et al. (*2*) reported a "correlation between the rate of glycolysis and malignancy in primary cerebral tumors"; this statement was made on the basis of 28 studies in 23 patients. Of these, 14 were preoperative PET scans, and in only seven of these cases was a histologic diagnosis of tumor grade available. In these seven cases with biopsy specimens, high-grade tumor metabolism ranged from 16 to 57 μmol/100 g/min, and low-grade tumor metabolism ranged from 15 to 35 μmol/100 g/min; indicating a considerable degree of overlap between the two groups. In their letter, Drs. DiChiro and Brooks state that "in all three (high-grade) cases . . . a visually distinct "hot" area was identified within the tumor . .". Since one of these patients was reported as having a peak LCMRG1 of 16 μmol/100 g/min, this demonstrates the discrepancy that may arise from relying on "visual" interpretation of scans as compared to quantitative analysis.

Further individual points mentioned by Drs. DiChiro and Brooks which might lead to differences in the interpretation of results between our centers may be addressed.

1. *Tissue of comparison.* We indeed used normal gray matter LCMRG1 values as a reference to distinguish between high and low tumor metabolism. The actual LCMRG1 values were given however, and even if white matter were used as a reference, over 70% of high grade tumors had metabolic rates equal to or below normal control white matter values in this laboratory (25 ± 4 μmol/100 g/min). Thus comparison with white matter would not alter our main finding that glucose metabolism in our untreated high-grade gliomas was variable, but low overall. In our opinion, it is not appropriate to compare tumor metabolic rate of glucose with that of white matter because the calculated rate constants for those tumors reported in our paper were significantly different from those for white matter (*3,4*). All of our values were calculated by using regionally measured rate constants.

2. *Localization of region.* We reported not only the average LCMRG1 values of the tumor regions, but also the range of values, due to the known heterogeneity of tumor areas, while DiChiro et al. (*5*) selected "the hottest region within the tumor area". We felt that since the heterogeneity of the tumor occurred both at the macroscopic and microscopic levels, below our scanner resolution, an average of LCMRG1 values would give more information on the overall metabolic state of the tumor. In addition, given the greater noise associated with the selection of smaller regions of interest (ROIs) when analyzing positron emission tomography (PET) data, the strategy of "peak-picking" seeks to trade increased noise for homogeneity of underlying structure. Bearing in mind that, because of image resolution limitations, any small ROI value will represent the weighted average of a substantial volume of surrounding tissue and will, of course, be much lower than the true metabolic rate at that point, there is no overwhelming reason to adopt that strategy over that of using larger ROIs. Furthermore, since tumor structure may be quite convoluted within the field-of-view of the imaging plane, the peak-picking approach is more vulnerable to artifactual local increases in apparent metabolic rate caused by differential partial volume effects through the body of the tumor. This issue demonstrates the difficulties in the use of PET to evaluate heterogeneous tissues; several different analysis techniques may be employed, depending on the physiologic information desired from the study.

3. *Scanning technique.* Again, increased scanner resolution would be expected to provide increased accuracy in quantitation. In our cases, we obtained three simultaneous slices at each of two scan positions, covering an axial distance of 54 to 72 mm. Nontumor areas were included in at least one slice above and below the tumor mass. Thus, given the number of slices available simultaneously and the resolution of our scanner, we feel that the tumors were surveyed in sufficient detail to detect hypermetabolic areas. The ability of our scanner (resolution = 12 mm transverse and axial) to detect such areas was obviously greater than that of the ECAT II (resolution = 17 mm transverse, 19.5 mm axial). Also, since the rims of some cystic tumors demonstrated high LCMRG1 values while others showed low values, we do not believe that partial volume mixing was a predominant factor in artificially lowering the results.

4. *"Numerical" diagnosis.* While the visual appearance of the scans may serve as a guide in the placement of ROI, we believe that it is preferable to utilize anatomic information from CT or MRI in the analysis of functional PET images.