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Commentary

Virchow's Shackles: Can PET-FDG Challenge Tumor Histology?

Giovanni Di Chiro[1] and Michael J. Fulham[1]

When in April 1980, after some 2 years of preparations, our team carried out the first brain tumor positron emission tomography (PET) study using [^{18}F]2-fluoro-2-deoxyglucose (FDG), skepticism among colleagues was prevalent. Computed tomography (CT) scanning had solved all diagnostic problems related to brain tumors. Also, the first magnetic resonance (MR) imaging paper on the brain had just appeared (1), hinting at soon-to-come, even more tantalizing structural imaging advances. Why, then, use PET, a "sophisticated" procedure, to assess such a "mundane" pathology as cerebral neoplasms? What could we possibly learn from a functional analysis of neoplasms? Some 13 years later, the scene has changed. "The use of FDG for the qualitative and quantitative evaluation of tumor metabolism is currently the fastest growing area of clinical PET," we read in a recent editorial (2).

The fact is that any expert in tumor management familiar with Warburg's concept that neoplasms display higher rates of aerobic glycolysis with increasing degree of malignancy (3), and with Sokoloff's [^{14}C]deoxyglucose measurement of regional cerebral glucose utilization (4), would have considered a Warburg-Sokoloff "marriage" obvious. Therefore, when Reivich et al (5) transferred Sokoloff's laboratory breakthrough to human applications by introducing FDG as a PET radiopharmaceutical, the use of PET-FDG for studying brain tumors appeared to us, given the above compelling theoretical framework, as a logical—indeed, the most logical—clinical application of this method. Although we were eager advocates and practitioners of CT, and open-minded about the just-being-introduced MR image, we were also keenly aware that unanswered diagnostic and management questions abounded (and are still with us): When should therapy (surgery, radiotherapy, or chemotherapy) be started? Should therapy be delayed as long as possible in low-grade tumors? Is open surgery necessary in all high-grade gliomas? How reliable is stereotactic sampling? Should stereotactic radiosurgery be used for suspected high-grade, deep lesions, even in the absence of histologic confirmation? How can primary brain tumors be graded? How do we manage renewed clinical deterioration after radiotherapy, considering that CT, MR, and arteriography do not allow confident differentiation between tumor recurrence and radiation necrosis? Do we proceed with additional surgery or interstitial radiotherapy, pass to chemotherapy, or abstain from further treatment? When is histologic confirmation needed? Should histology be the definitive guide at every stage of management? Does histology consistently help in prognosis? The list of questions seemed inexhaustible (6).

The paper by Davis et al (7) in this issue addresses some of these questions, related to tumor grading and differentiation of radiation necrosis from tumor recurrence. The diagnostic tools used and compared are gadolinium-enhanced MR imaging and PET-FDG. The article is appropriately guarded in its conclusions. Nevertheless, we are struck by the fact that, in three of the five cases illustrated, PET-FDG showed a strong superiority. In two patients, the metabolic information provided by PET-FDG gave critical information not supplied by gadolinium-enhanced MR, revealing the malignancy of an astrocytoma in one, and distinguishing the different nature of two (bilateral) lesions—a focus of tumor recurrence and an area of predominant radionecrosis—in the other. In a third patient, MR gave a false-positive diagnosis (attributed to surgical trauma), whereas PET-FDG, which initially showed high uptake caused by recognized seizure activity, gave a true negative after the patient

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was placed on anticonvulsant medication. In the two remaining illustrated examples (one malignant, one not), both methods gave equally valid information.

PET-FDG provides new parameters for recognizing critical features of brain tumors. To convince ourselves of this, let us return to the case of the patient with bilateral gadolinium-enhancing posttreatment lesions in the white matter. A similar case from our own files is shown in Figure 1. Here, in the very same individuals, we have an ideal comparison of two different lesions which appeared the same on MR. In each case, PET-FDG alone was able to distinguish the recurrent tumor from the region of radiation necrosis. If one reflects on the underlying pathophysiology, this is to be expected: *gadolinium is a marker of the blood-brain barrier status, whereas FDG measures tissue glucose utilization.* In radionecrotic brain, the blood-brain barrier is disrupted, with ensuing gadolinium enhancement, but the glucose consumption is massively reduced. This can be seen not only in necrotic, tumor-invaded tissue, but also in irradiated normal brain tissue (Fig. 2).

In contrast with the evidence offered in the illustrations, the text of the Davis article takes a "balanced" approach, and reaches a verdict of equivalence. Complementarity of the techniques is stressed—an even-handed, uncontroversial conclusion.

The illustrative evidence from this paper is in accord with our own experience in over 1500 PET-FDG brain-tumor studies (a specific comparison of PET and gadolinium-enhanced MR imaging in 160 of these cases has been presented previously (8)). Indeed, we have come to believe that PET-FDG may even take us a step further, to challenge the conventional unshakable reliance on histology as the ultimate tumoral assessment. Undoubtedly, in 1858, and for one century afterward, the lessons contained in Rudolf Virchow's *Die Cellularpathologie* have been invaluable for the progress of medical science (9). Lately, however, we feel that Virchow's guidelines have been transformed into shackles, preventing us from moving forward. Histology is important, but it should not dogmatically dominate our judgment. After all, the really critical issue is the biological behavior of a tumoral lesion—a dynamic feature which may or may not be reflected in the static histologic features. *Biological behavior, more than histology, will eventually determine the patient's fate.*

Currently, our group's efforts are dedicated to, and we have been reporting on, the possibility of advancing beyond histology in the prognostic assessment of brain tumors (10–13). It is somewhat disappointing that Davis et al have not included a deeper analysis of other nosologic aspects of the tumoral lesions, besides histology. We invite them, and any other group working with PET-FDG in brain tumors, to have a new look at their material. Follow your patients, over and beyond the histologic judgment. You will be surprised at how often PET-FDG will eventually prove to be the best predictor of final outcome. PET-FDG, being a "functional" method, gives us

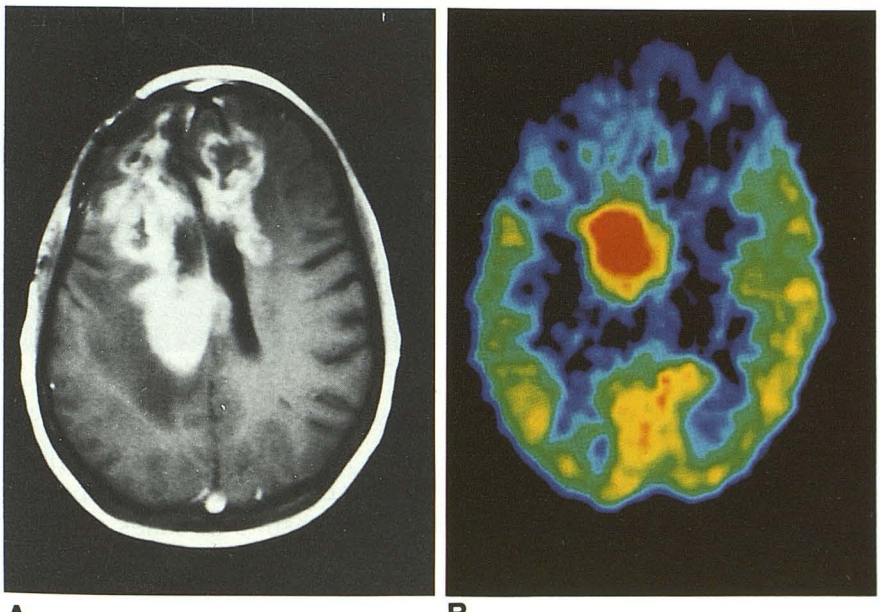

Fig. 1. Recurrent tumor and radiation necrosis histologically verified (autopsy).

A, Postcontrast MR image shows a deep central region of "solid" gadolinium enhancement, as well as enhancement in both frontal lobes.

B, PET-FDG shows hypermetabolic focus (recurrent glioblastoma multiforme) of increased FDG uptake, corresponding to solid area of enhancement on MR. Left frontal lobe is hypometabolic (radiation necrosis of normal brain), but there is heterogeneous FDG uptake in right frontal lobe (radiation necrosis and recurrent tumor). The color scale for FDG uptake in this and the following PET images corresponds to the visible color spectrum (red = high FDG uptake, violet = low FDG uptake).

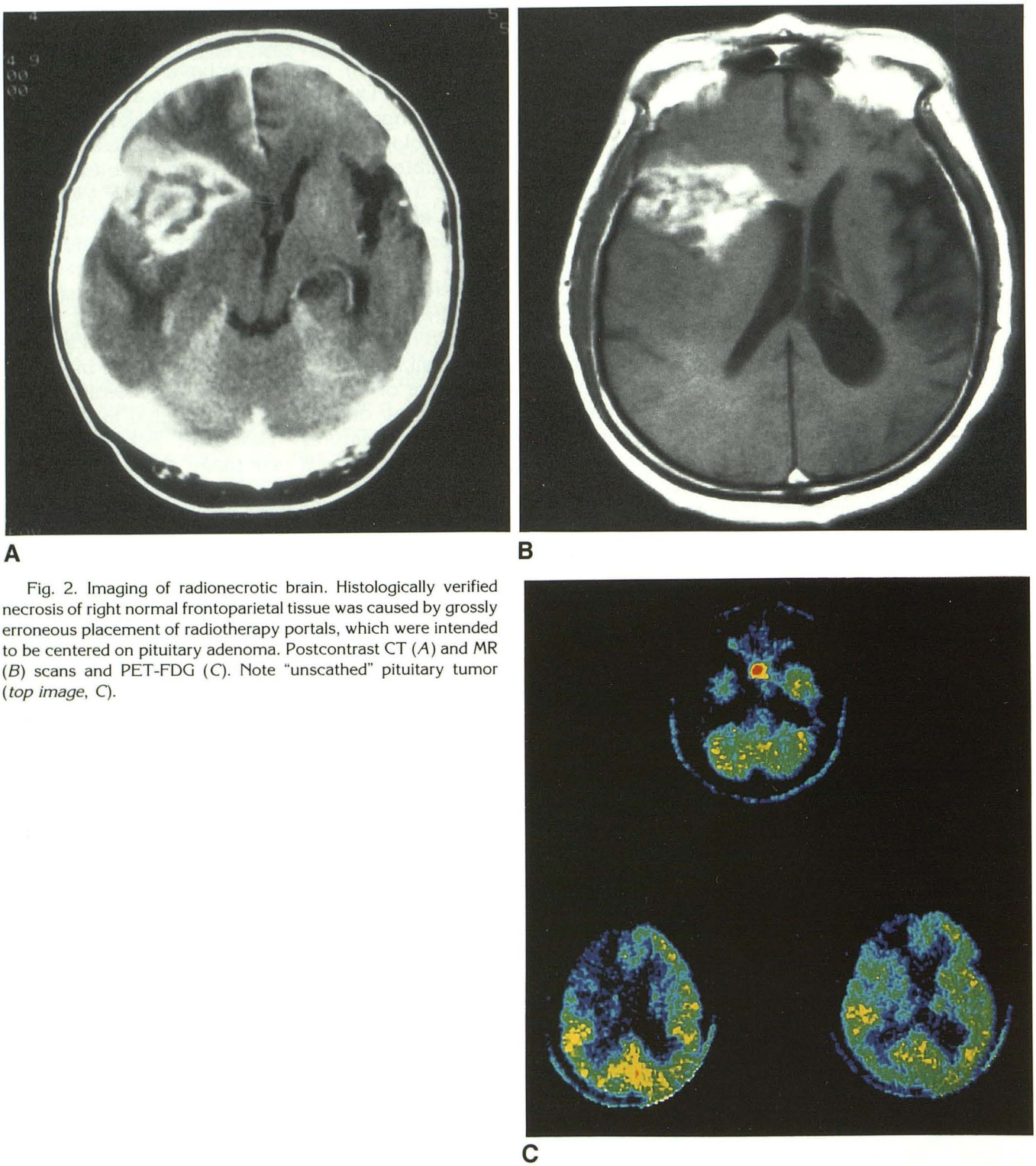

Fig. 2. Imaging of radionecrotic brain. Histologically verified necrosis of right normal frontoparietal tissue was caused by grossly erroneous placement of radiotherapy portals, which were intended to be centered on pituitary adenoma. Postcontrast CT (*A*) and MR (*B*) scans and PET-FDG (*C*). Note "unscathed" pituitary tumor (*top image*, *C*).

information that gadolinium-enhanced MR cannot approach, and that histology may miss.

The ability to enhance or modulate certain metabolic effects by pharmacologic means, as illustrated in one of the cases mentioned by Davis et al, can also be a valuable diagnostic aid. Figure 3 shows a different example, from our files, documenting the power of pharmacologic manipulation on the PET-FDG results in cases of brain tumor (14). Finally, functional, distant tumoral effects—diaschisis—can be depicted and assessed by the PET-FDG technique (15, 16).

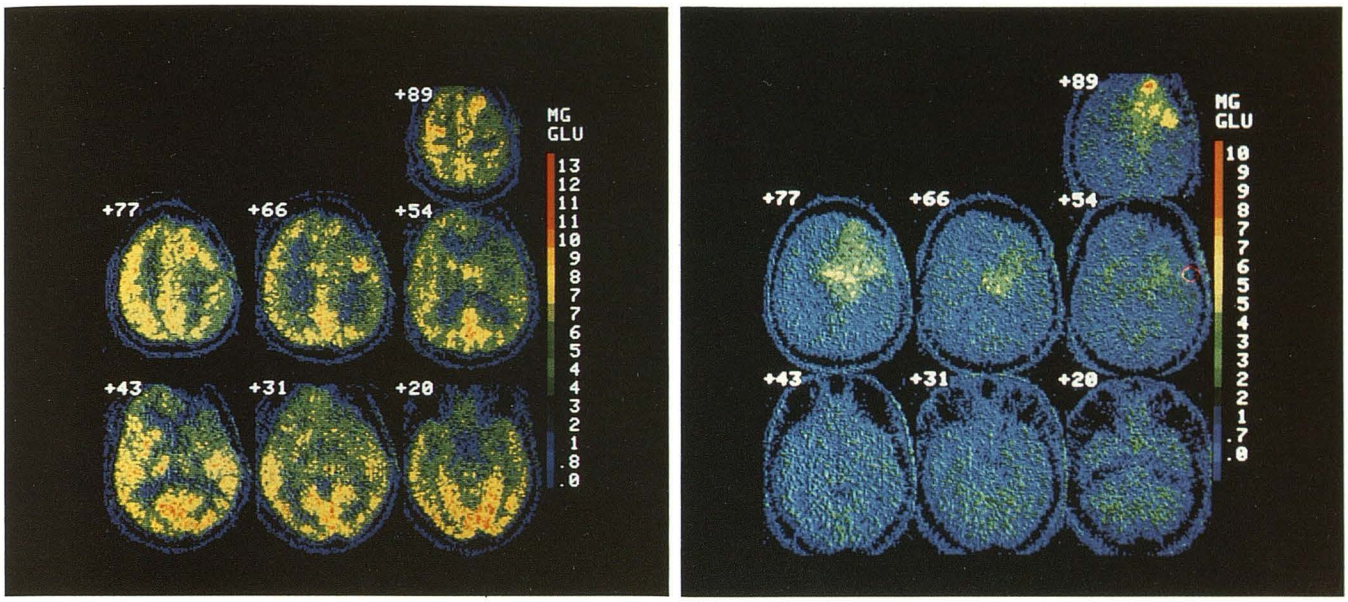

Fig. 3. PET-FDG studies of a cortical and deep-seated high-grade glioma.

A, Scans in the awake state.

B, Subsequent study during barbiturate coma shows suppressed glucose utilization in nontumoral tissue, while glucose consumption by the neoplasm continues unabated. Color scale is identical in awake and anesthetized states.

Histologic appraisal is still of great importance; its rigid findings, however, are no match for the versatility of the information generously offered to us by the PET-FDG method. One day—who knows?—we may loosen or even get rid of Virchow's shackles.

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