The Clinical Value of Direct Tumor Scintigraphy: A New Hypothesis

Thus the task is not so much to see what no one has seen yet, but to think what nobody has thought yet, about what everybody sees.

(Spinoza)

Whenever nuclear medicine is being compared with other similar methods of investigating disease, it is usual for it to be quite properly defended as providing a range of techniques which are uniquely able to provide physiological or functional information. We wish to suggest that this has not as a rule been true of our use of direct tumor scintigraphy. Such a fact may have compromised a great deal of endeavor in this context.

We define direct tumor scintigraphy as methods which seek to reflect the immediate presence of tumor deposits (e.g., gallium-67 scintigraphy, cancer radioimmunodetection) rather than reflect the epiphenomena caused by tumors (e.g., the increase in exchangeable calcium in proximity to a bone metastasis as revealed by technetium-99m methylene diphosphonate).

To date, direct tumor scintigraphic methods have nearly uniformly been validated by reference to the presence of focal radiotracer uptake at sites which are subsequently shown, by whatever methods, to represent or not represent sites to which tumor has spread. Thus various analyses, some of which we must admit to, have found various percentages of metastases detectable in one or other kind of cancer: Equally various proportions of cancers of differing cell types are reported as imaged or not imaged.

However, neither radioimmunodetection nor radiogallium scintigraphy have proved consistently capable of being used to detect tumors of less than 1.0 or 1.5 cm in diameter (*1*,*2*). Such tumor masses represent enormous cell populations of the order of 10^{13} cells. While immunoscintigraphy, in particular, is probably capable of refinement, an increase in detection sensitivity of even two orders of magnitude will mean that tumor masses of up to 10^{11} cells will be undetectable. Not only are such lesions the cause of serious disease but it is self-evident that even one malignant cell is potentially lethal.

As tumor scintigraphy is refined during the next two decades, we will be driven by our oncologist colleagues to detect ever smaller tumor-cell masses. We submit that there is no realistic technology that can be anticipated in the near future which might allow us to achieve scintigraphic techniques to meet these morphological constraints of cancer medicine.

Now to predict that something is impossible in science is to risk being overtaken by events. It seems to us, however, that, within the lifetimes of present investigators, the existing goals of tumor scintigraphy are simply unrealistic. Moreover, we believe that they are capable of being replaced now by realistic and relevant goals which are the subject of this Editorial.

We propose that the validation of direct tumor scintigraphy should not be based upon methods which document tumor size and number, and which record the success or failure of tumor scintigraphy in these morphologic terms. Rather, we should exploit the power of nuclear medicine to reflect some of the pathophysiological characteristics of a tumor. We need to know the invasiveness of a cancer, its anaplasticity or whatever other characteristics are necessary to understand if a given tumor is likely to have metastasized and, in effect, have escaped from the potential for local cure. This definition of the local curability or incurability of cancers is, after all, what determines treatment: On the one hand by surgery or radiation or both, and on the other by systemic treatment such as chemotherapy. Thus we suggest that research be directed to replacing the present morphological or anatomical scintigraphic methods of tumor staging by a "functional staging." Indeed there is already evidence that gallium scintigraphy may have had some effectiveness in this context, when it was being more widely used to answer other clinical questions (*3–6*).

Some exceptions to this strategy may remain. It appears, for example, that in patients with melanomas at sites of lymphatic watersheds it is important in planning regional node

dissection to know the anatomical pattern of lymph drainage from a given tumor. It remains uncertain if this information must be provided by some method of direct tumor scintigraphy, or, for example, scintigraphy with a radiocolloid (*7*).

In effect it seems to us that the question most often to be answered by tumor scintigraphy is not:

> Does this patient have morphological evidence of metastases—most of which is impossible to ever hope to demonstrate physically (anatomical staging)?

But rather should be:

> Does this patient's tumor have demonstrable behavioral characteristics (of anaplasticity, invasiveness, or otherwise) which lead me to expect that it will metastasize whether or not I can demonstrate such metastases (functional staging)?

If scintigraphic techniques are to be directed to this second question not only will the answers be intrinsically more powerful in patient care but they will require quite different approaches to validation. Research must be directed to determining the relationship between tumor uptake (preferably quantitative) of a given radiopharmaceutical, or radiopharmaceuticals, and the subsequent behavior of that tumor in terms of patient outcome, rate of disease progression, or similar parameters.

Present programs to develop tumor scintigraphic agents may still be relevant but their success or failure must thus be judged by different criteria. Also, if the present initiatives in immunoscintigraphy lead to agents which localize in tumors to an adequate degree, then their labeling with α or β emitters may permit the treatment of tumors which are occult to present physical means of detection. Yet the administration of such powerful agents for therapy, particularly at that early stage in the evolution of a tumor when they are most likely to be effective, must be predicated on some rational anticipation of how any given tumor is likely to behave biologically.

Nor need this be idle speculation pending the development of yet other radiopharmaceuticals. Radiolabeled bleomycin may already reflect DNA mass, and tracers serving as analogs of DNA precursors have been investigated. Radiolabeled hematoporphyrin analogues possibly serve as markers of cell-division rates. Conceivably existing labeled monoclonal antibodies, if measured in quantitative terms proportional to a tumor mass, reflect its degree of cellular differentiation or anaplasticity; other such tracers may reflect invasiveness or other crucial functional characteristics of a cancer. There is already evidence that phosphorus-31 in vivo tumor spectroscopy is providing evidence in the context we propose, if not formally conceptualized as "functional tumor imaging" (*8*). This approach may or may not need new agents: The recognition of the goals to which tumor imaging is redirected, nevertheless, has to precede the definition of the best radiopharmaceutical agents with which to meet those goals.

In essence, we wish to see tumor scintigraphy brought into the mainstream of diagnostic nuclear medicine as a method of examining the behavior of tumors as well as recording their presence. The mere fact of their presence can, with considerable limitations, be more readily ascertained by prosaic methods such as computed tomography. Those limitations are defined by both spatial and contrast resolution and, for the foreseeable future, appear formidable. The presence of formidable obstacles upon a path which one does not wish to take is, we suggest, irrelevant.

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