by Blasberg et al. in animals (8), specific and nonspecific uptake (the latter mainly related to pathophysiologic parameters such as permeability, blood volume, etc.) can be clearly differentiated by a quantitative analysis or by evaluating kinetics of specific and nonspecific radiolabeled antibodies.

This approach would not be practical for clinical use in humans. In this respect, in order to avoid mistakes, the knowledge of the "pathophysiologic state" of a patient (i.e., the knowledge of the presence of conditions that could create nonspecific uptake) is mandatory. In this way it could be possible to minimize false-positive results, particularly in the differential diagnosis of recurrences, that is, in the main clinical utilization of RIS. Furthermore, an opposite conclusion could be derived from the article of Kairemo et al. False-negative results at RIS could be explained not only in terms of lack of expression of the specific antigen but also because of pathophysiologic conditions (blood-brain barrier, basal membranes, low blood flow, etc.) that do not permit the access of the radiolabeled antibody to its target. In this sense, RIS can anticipate the efficacy of a therapeutic strategy utilizing antibodies by demonstrating the in vivo tumor/nontumor ratio. Tumoridical effect cannot be obtained if the uptake is not present at the level of one or more neoplastic lesions. In conclusion, RIS could be proposed as a necessary preliminary step to all immunologic therapeutic approaches in oncology using MoAbs, also without radionuclides.

REFERENCES


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Quo Vadis Radioimmune Imaging?

TO THE EDITOR: The editorial by Fischman, Khaw, and Strauss (1) in the November 1989 issue of The Journal of Nuclear Medicine represents a substantial effort to provide insights into the explosively developing area of radioimmune imaging. There is much to be learned from this editorial, and it is understandable that certain topics were over simplified and others provoked some difference of opinion. In recognition of the need for diversity at this stage of development of radioimmune imaging, we would like to provide the following perspectives: Our major purpose is to provide additional information that has become available relative to the efficacy of radioimmune imaging for cancer since the original editorial was in preparation, and which has dramatically altered circumstances to the point where we, and others, are now convinced that radioimmune imaging (and treatment) will soon play a major role in the management of patients with cancer.

Before considering this topic let us address a few concepts developed in the original editorial.

The in vivo situation is very different from the in vitro situation so that the association formulae provided in the editorial are not necessarily relevant to the in vivo situation. Indeed, Weinstein (2) has shown that a high avidity constant may actually decrease permeation and tumor uptake of the antibody.

It is unlikely that the quantity of antigen will be a limiting factor for most radioimmune imaging wherein the amount of administered antibody is not large (3–5). The quantity of antigen on the target could be a factor when large amounts of unconjugated antibody are used for direct treatment of cancer. While the amounts of antibody ordinarily used for radioimmune imaging are unlikely to saturate the target antigen, this possibility should always be considered. However, for many antibodies, the amount of administered antibody has to be increased to saturate nonspecific antibody receptor sites, circulating antigen and cross-reacting tissue antigen in order to optimize the results of imaging (6–12). We do not believe that indiscriminate increases in the amount of administered antibody beyond this level improve localization (13).

Several studies reported recently have substantially increased our knowledge of the human anti-mouse antibody (HAMA) response (14–18). These data indicate, as one would expect, that the Fc region of the antibody is the more likely site for reaction with a HAMA, but it is not correct to suggest that Fab fragments do not elicit any immune response. The Fab region, whether administered as part of the intact antibody or as the fragment, has been shown to elicit a HAMA response (19). It is less likely to do so than the intact antibody and radioimmune imaging with small amounts of Fab fragments of murine monoclonal antibodies which has been performed repeatedly without eliciting a HAMA response (20,21).

L

Luigi Mansi
Secondo Lastoria

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It is important to expand upon the comments of the editorial relative to tumor imaging. We agree that an intravascular target, such as a venous thrombus is an ideal one because of its ready availability to an intravenously injected antibody. An obstacle to successful imaging (and treatment) with radio-labeled antibody is represented by delivery problems. The problem is greater when these extravascular targets are poorly perfused. This is true of extravascular cancer as well as other extravascular targets, such as myocardial infarcts. However, recent studies clearly document remarkable efficacy for radioimmune imaging of cancer despite this problem.

Until 2–3 yr ago data suggested that radioimmune imaging of cancer lacked sensitivity, and even the specificity originally anticipated. Not only were small lesions missed, but many other “lesions” were imaged that could not be corroborated by conventional imaging procedures. However, it has become apparent that radioimmune imaging of cancer is more sensitive and more specific than all other existing, conventional imaging methods (19,20,23–33). Results reported earlier have proven to reflect the deficiencies of the conventional imaging methods more than those of radioimmune imaging. While the sensitivity of radioimmune imaging of cancer is not complete, it is now regularly reported to be 80%–90% when conventional imaging methods or surgical confirmation are used. More importantly, apparent false-positives in earlier reports have mostly proven to be additional lesions detected by radioimmune imaging and undetected by conventional imaging methods. These lesions have been reported to be about equal in number to all the lesions detected by conventional imaging methods. Lesions have been found earlier by radioimmune imaging than by other methods.

While still challenging, detection of lesions smaller than one centimeter in diameter is now common, reflecting better radionuclides and greater experience. There is also evidence, albeit early, that detection of lesions missed by other methods is relevant and therapeutically meaningful to the management of the patients (19,20,23–26,30,31,33).

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**REPLY:** We would like to thank Drs. Halpern et al., Lawrence, the DeNardos, Massuger et al., and Mansi et al. for their comments on our recent editorials (1,2). We agree with the concepts expressed by Massuger et al. and Mansi et al., since they provide additional data in support of our position.

We offer the following reply to the points raised by the other correspondents. The terms sensitivity and specificity are used in a sense that would imply clinical utility of radioimmunooimaging. Inspection of the articles cited by Halpern et al. and the DeNardos (that have been published in peer reviewed journals and refer to data on lesion detection in patients) indicates the results of Table 1.

From the data in Table 1, it is clear that some lesions can be localized with radioimmunooimaging techniques, however, the methodology cannot identify all sites of antigen producing documented disease. Although some studies have reported sensitivities of >90% for tumor detection this is not the norm. In those studies in which large numbers of patients were evaluated (melanoma and colorectal carcinoma), sensitivity is closer to 70%–80%. In a study with PAY-276, for example, a total of 11/81 lesions were seen on radioimmunooimaging. These findings indicate that the technique may be useful for localization of particular types of tumor, but needs further development prior to implying that wide application is in order.

As suggested by Halpern et al., the case for antimonyosin imaging is much stronger. For example, overall sensitivity was 93% in three studies evaluating 132 patients (3,4,5). In a phase 3 multicenter trial, sensitivity was 94% for 202 patients with transmural infarction and 84% for 57 patients with non-transmural infarction (6). In the case of radioimmuno imaging for infection, the data are sparse. Similarly, imaging of thrombus also gets mixed reviews.

Concerning the important point raised about the number and affinity of binding sites for radioimmunooimaging. Dr. Denardo states (7): "In the absence of heterogeneous expression of the antigen or obstacles to delivery of the antibody to the cell membrane antigenic sites, the 10^10 to 10^12 antibody molecules can be accumulated in 1 gram of cancer tissue." This suggests that up to 250 μg of antibody (25% of the injected dose after administration of 1.0 mg of antibody) could be concentrated in a single gram of tumor. These attractive assumptions, unfortunately, have not been borne out by clinical experience. In practice, lesions rarely concentrate more than 0.01% of the injected dose.

We agree with the authors that the relative mass of antibody administered to a mouse or man is not the sole determinant for the different levels of accumulation of radiolabeled antibody in tumors in these species. Imaging studies performed following radioimmuno therapy, where large amounts of protein and radioactivity are administered, rarely identify lesions that were not seen with smaller diagnostic doses. These observations do not favor the prospective of Dr. Lawrence that scaling the mass and associated radioactivity of an antibody preparation to the weight of the subject (mouse versus man) would result in similar imaging results. The author's statement that "no application of nuclear tracers has consistently demonstrated a sensitivity significantly greater than 80% in tumor

**TABLE 1**

<table>
<thead>
<tr>
<th>Primary effect tumor</th>
<th>Antibody</th>
<th>No. Patients</th>
<th>Detection rate</th>
<th>Ref.</th>
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<tr>
<td>Colorectal</td>
<td>ZCE-025</td>
<td>24</td>
<td>34%</td>
<td>3H</td>
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<tr>
<td>&quot; (Fab)</td>
<td>ZCE-025</td>
<td>16</td>
<td>83%</td>
<td>3H</td>
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<td>Mab35,Fab</td>
<td>57</td>
<td>82%</td>
<td>24D</td>
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<td>F023C5</td>
<td>509</td>
<td>79%</td>
<td>33D</td>
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<td>Melanoma</td>
<td>ZME-018</td>
<td>28</td>
<td>43%</td>
<td>3H</td>
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<td>96.5</td>
<td>21</td>
<td>56%</td>
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<td>HMWA</td>
<td>10</td>
<td>74%</td>
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<td>31</td>
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<td>16H</td>
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<td>225.28S</td>
<td>554</td>
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<td>25D</td>
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<td>Prostate</td>
<td>PAY-276</td>
<td>10</td>
<td>15%</td>
<td>3H</td>
</tr>
</tbody>
</table>

* % of all known lesion sites identified in the radioimmuno images;  
† % of known lesions >1.5 cm in diameter; in this study, greater sensitivity was achieved with higher doses of antibody;  
‡ Sensitivity of 29% for 2.5 mg of antibody (n = 4) and 74% for 20 mg (n = 6);  
§ The false-positive rate in this study was 50%.  
** = reference from Halpern et al. and D = reference from DeNardo and DeNardo.  

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