and levels of cellular and intratumor extravascular antigen as tumor size increases. In addition, the presence of circulating tumor-derived antigen can influence tumor deposition and blood survival of antibody (4). In this latter context particularly one can envisage that with small doses of antibody a sufficient amount may be neutralized in animals with larger tumors to significantly reduce tumor uptake and therefore destroy any correlation between tumor size and extent of antibody deposition. It is possible in these circumstances that if antibody dose was increased, a correlation would become apparent. In the osteosarcoma system, circulating antigen has not been detected (1) and this mechanism cannot operate; this might explain why here a good correlation between tumor size and antibody deposition can be seen. Moreover tumors used in our studies were not 1 g, but with larger tumors this relationship could well break down as tumors become necrotic.

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References


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Effect of Tumor Size on Monoclonal Antibody Uptake in Tumor Models

TO THE EDITOR: The article “Tumor Size: Effect on Monoclonal Antibody Uptake in Tumor Models” by Hagan et al. (1) primarily addresses the problems of the effect of tumor size on the uptake of “tumor specific” antibodies, but does not relate this to tumor imaging. Mann et al. (2) utilized nude mice with two implanted tumors (melanoma and lung carcinoma) and the simultaneous injection of differently labeled monoclonal antibodies for each of these two tumors. Iodine-125 and iodine-131 (131I) were utilized and these labels were reversed in half of the experiments. In vitro studies demonstrated that these two monoclonal antibodies were almost completely specific for their corresponding melanoma or lung carcinoma. Total uptake in vivo increased linearly with tumor size, but this appeared to be secondary to increased nonspecific uptake with increased tumor size. The largest tumor tended to be better visualized, even if the 131I-labeled antibody was “specific” for the smaller tumor. Both tumors were often visualized and large tumors were also easily imaged with a nonspecific, nonimmune IgG.

The use of percent administered dose per gram of tumor (% admin dose/g) may be misleading because the uptake in small tumors must be multiplied to normalize it for 1 g. This approach tends to ignore biological changes that may occur in tumors with increasing size, e.g., necrosis. This is probably the reason that the highest % admin dose/g in the literature are almost invariably reported to occur in small tumors that then are scaled up to 1 g. Percent admin dose per mg or per 100 mg would probably be a more reliable measure of uptake that could be used for comparisons in tumors of all size.

Hagan’s comparison of nonspecific versus specific uptake in animals bearing both a melanoma and a colon carcinoma is distorted by the fact that the melanoma is three to four times the size of the colon carcinoma and is “by far the more necrotic of the two.” Nonspecific uptake increases directly with increased tumor size, but is decreased by necrosis (3). Mann et al. (2) utilized nude mice that were inoculated with the slow growing melanoma 2–3 wk prior to inoculation with the pulmonary carcinoma. This tends to result in mice with two different, but similar sized tumors. Under these conditions both nonspecific uptake and total tumor uptake increased with increasing tumor size. We find that imaging studies complement and tend to clarify the results of tissue counting studies.
REFERENCES


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REPLY: Doctors Cohen, Saxton, and Mann make the point in their letter that while we have addressed the problems of tumor size on the uptake of tumor-specific monoclonal antibodies (MoAbs), we did not relate this to tumor imaging. They further state that in their own studies (1) using doubly implanted mice (one tumor specific for the MoAb, the other not), total uptake increased linearly with tumor size, but that the increase was due to nonspecific mechanisms. They imaged these tumors and found that the larger ones were better visualized regardless of specificity.

It is true that nonspecific uptake of antibody occurs in tumors and that the clearance of these antibodies from the tumor will be relatively slow. Part of this is because the venous return from tumors is sluggish and secondly there are no lymphatics to allow a second avenue of escape. Thus what goes into tumors has a slow egress and will be imaged provided the label does not escape. Normal tissues tend to rid themselves of iodinated antibodies (which Mann et al. used in labeling), slightly faster than will tumors. Given this fact, it is not surprising that nonspecific tumors will be “seen” by imaging technique if they are large enough. Nonspecific MoAb uptake in human studies has been poor in our experience. Tumors can be enormous and not take up enough indium-111-labeled MoAb to be detected. Part of the reason for this is probably that the background remains relatively high with indium as it does not leave the normal tissues easily, but on the other hand it does not leave the tumor tissue either.

In the report published by Mann et al. (1), the time of imaging and dissection ranges from 3 to 9 days postadministration of the radiopharmaceutical. Seventy-five percent of the label had been removed by 3 to 4 days and it has been our experience that the rate of dehalogenation can vary from tumor to tumor. For this reason it’s a little difficult to interpret these data. In fact, if internalization of the radiolabeled antibody occurred in the tumors for which the specific antibody was used, removal of the label would have been extremely fast (Larson S, Carrasquillo J, unpublished data) has shown. Regardless of label, however, nonspecific uptake of radiolabeled antibodies does occur in tumors.

Doctors Cohen, Saxton, and Mann also comment on the need to present the data in smaller units than percent injected dose per gram. The undersigned do not feel that it makes any difference as long as the units are constant; however, we do feel that it is important to put the basic data in an article such as shown by Pimm and Baldwin (see letter).

The manuscript by Mann et al. (1) referred to in their letter is excellent. Unfortunately, the tissue distribution data are shown as comparative ratios. One cannot take such data and determine the absolute concentration in the tumors. If the absolute data is given, however, one can make any calculations one wishes and compare it with that from their own laboratory.

Finally, the authors state that the imaging studies complement and tend to clarify the results of tissue-counting studies and in this, we agree. It should also be remembered, however, that when the radiopharmaceutical is unstable at the tissue level, the imaging results can be very misleading. This is especially true in organs such as the liver in which dehalogenation can be rapid. When iodine isotopes are used and the animals are imaged more than a few days from the time of administration, it can appear that the radiopharmaceutical has almost totally concentrated in the tumor with little remaining in the rest of the body. In short, imaging may be worthwhile, but only when the tissues have been counted and quantified.

REFERENCES


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Sensitivity of Positron Detection for a Pair of Opposed Detectors Compared with Ring Scanners Using Image Reconstruction

TO THE EDITOR: In a recent report, Bice et al. (1) described a simple dual detector coincidence counting system for brain imaging of neuroreceptor studies. We agree that such an approach may prove valuable for test-retest studies where subjects act as their own baseline controls. However, we disagree with one of their principle claims for the high efficiency annihilation detection system (HEADS) scanning device—that it represents an advance in sensitivity over positron emission tomography (PET) scanners allowing multiple studies to be performed at a much lower radiation dose than otherwise possible. The remaining advantages of simplicity and low cost seem more than sufficient, however, to justify developing this new application of an old approach.

Their claim of high sensitivity relative to PET scanners seems to be based on a comparison of relative signals from very different tissue volumes. In addition, in claiming a solid