TEACHING EDITORIAL

The Utility of Gallium-67 in Tumor Imaging: A Comment on the Final Reports of the Cooperative Study Group

The cooperative group formed to study the value of gallium-67 imaging in malignant disease has now published its final report on malignant lymphoma (*1*). This report complements two previous "final reports" on Hodgkin's disease (*2*) and genitourinary tract tumors (*3*), as well as a series of preliminary reports on Hodgkin's disease (*4*), malignant lymphoma (*5*), and lung carcinoma (*6*). The results obtained by the cooperative group illustrate the strengths and the weaknesses of this type of study.

The project was undertaken in the early 1970's to determine if Ga-67 was a useful agent in staging cancer. The cooperative study group set out to answer this question using the best techniques and instrumentation then available. However, this question was answered in large part by the preliminary reports of the cooperative group, as well as by a number of other clinical observations published between 1971 and 1975. By 1974 it had become obvious that Ga-67 imaging would be useful primarily as an adjunctive test in evaluating specific tumor.

Concern then shifted to determining the value of Ga-67 imaging in monitoring treatment of patients and attempting to improve the techniques of such imaging. Unfortunately, the cooperative group protocol did not anticipate these changes, and, therefore, did not provide for identification of followup information on individual patients. The large number of institutions involved in the study also inhibited introduction of modifications in instrumentation and other aspects of technique. As a result, some key clinical questions regarding Ga-67 imaging remain unanswered. What is the exact role of Ga-67 imaging in early detection of recurrent disease? Do new methods—e.g., high radionuclide dose and imaging with triple peak large field cameras, the Anger tomoscanner, or the multicrystal whole body imager—improve detection efficiency? Although the cooperative study does not answer these questions, it does provide important benchmarks for judging the effects of future technical improvements in imaging technique. The results obtained by the study are based in most cases on a large patient population, which is the major advantage of the multi-institutional approach.

In almost all diseases studied there was a correlation between lesion size and detectability—detectability increased as a function of size for lesions between 1 and 5 cm. Above 5 cm, however, lesion detectability again diminished. Among the lymphomas, overall lesion detectability was best in Hodgkin's disease, histiocytic lymphoma, and Burkitt's lymphoma*.

In Hodgkin's disease the lowest yield was in lesions with lymphocyte predominance, whereas in malignant lymphoma the yield was poorest in the well-differentiated lymphocytic and undifferentiated cell type tumors. Among genitourinary tumors the detection rate was best in embryonal cell testicular tumors. Metastatic sites of all genitourinary lesions were detected with greater sensitivity than primary sites.

Intra-abdominal lesions were most difficult to detect, presumably due to confusion with normal uptake in adjacent organs—e.g., liver and colon. Treatment with radiation and/or chemotherapy decreases sensitivity of lesion detection, and the effect of radiation is greater than that of chemotherapy.

The final reports of the cooperative study group help to confirm the utility of Ga-67 imaging in the evaluation of patients with Hodgkin's disease, histiocytic lymphoma, Burkitt's lymphoma, and embryonal cell testicular tumors. Since its introduction a decade ago (*7*), gallium imaging has also been shown to be effective in evaluating hepatoma, melanoma, and lung carcinoma. Only in hepatoma is gallium used to distinguish between benign (pseudo-

tumor of cirrhosis) and malignant disease (*8*). In all of the other tumors, its primary role is either as an adjunctive test in staging, a method of monitoring the effects of treatment, or a method of early detection of clinically unsuspected recurrent disease. Because of its nonspecificity, a positive finding on gallium scan usually requires confirmation. Moreover, sensitivity, even for detection of malignancies in which gallium scanning is useful, varies from 70 to 90% (*9*).

For those who would embark on further clinical studies, the following caveat is offered. The mechanism of Ga-67 localization, so poorly perceived in the past, is finally becoming understood, and this comprehension may have profound effects on the future clinical utilization of Ga-67 imaging. It now seems obvious that gallium is taken up in inflammatory lesions by a combination of direct bacterial incorporation (*10*) mediated through siderophores (*11*), local binding to tissue lactoferrin (*12*) (which is increased at the site of infection), and by neutrophil deposition (*13,14*). The neutrophils carry Ga-67 as a gallium-lactoferrin complex (*15*). The primary role of siderophores is to mediate passage of ferric ion into the pathogenic organism. The role of lactoferrin seems to be to oppose this action by competing for available ferric ion. Gallium binds to both molecules due to its similarity to the ferric ion in both charge and size. Unlike ferric ion, the high redox potential of Ga(III) prevents its reduction in biologic systems. Although gallium is easily displaced from lactoferrin by addition of ferric ion, its binding to certain siderophores is extremely avid and may in fact exceed the binding affinity for ferric ion (M. L. Thakur, personal communication).

In tumors, transferrin plays an important role in facilitating Ga-67 uptake in vitro (*16,17*). Lactoferrin levels are also increased in certain tumors (*18*) and, recently, increased lactoferrin content has been confirmed in two tumors associated with increased gallium uptake—Hodgkin's disease and Burkitt's lymphoma (*19, unpublished data*). Since lactoferrin deposition in tumor is most likely a reactive phenomenon, these tumors may also produce a siderophore-like substance. Very recently such a substance has been isolated (*20*).

It will be interesting to see if gallium uptake in specific tumors accurately predicts the presence of siderophore-like substances in these malignancies. Clinically, such tumors may be amenable to treatment with agents that produce ferric ion deprivation, a type of treatment effective in vitro with little detrimental effect on normal cells (*20*).

From the very beginning, the story of Ga-67 has been filled with useful surprises (*1,21*). Serendipity has been the key word in its exploration and utilization. Although the cooperative group deserves praise for its current effort, let us hope that the best is yet to come.

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FOOTNOTE

* Only four patient studies.

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