EDITORIAL

Prognosis by Nuclear Medicine: Can Functional Staging of Cancer Patients Predict Therapeutic Response and Survival?

Clinical oncologists, by tradition, use a number of baseline factors to predict outcome of patients with cancer. Guidelines have been proposed for such studies and include concerns about the assembly of a cohort and referral pattern, blinded assessment of outcome, completeness of follow-up, adjustment for other factors and statistical methods employed (*1*). However, determining the impact of a relatively straightforward factor such as age can be difficult and multiple studies can be performed with quite different results (*2*).

Historically, cancer has been one of the major areas for nuclear medicine practice. In the beginning, it was thought that therapy of cancer would be possible with unsealed sources of radioactivity. However, the use has largely been diagnostic, which in a broad sense includes detection, staging, prognosis and follow-up. Many studies attest to the usefulness of nuclear imaging procedures for this purpose; particularly, one can point to the use of bone scintigraphy, which is one of the most frequently performed nuclear medicine procedures based on its sensitivity and total body imaging technique (*3*). Recent trends have emphasized the ability of nuclear imaging procedures to reflect pathophysiological changes to perform what has been called "functional staging" (*4*).

With that in mind, there is an article in this month's issue that evaluates the effectiveness of ^{67}Ga and ^{99m}Tc-MDP uptake in primary tumors in determining prognosis for children with Stage IV neuroblastoma (*5*). In this report, the authors have studied 35 children to see if tumor uptake of these tracers could be used as an indicator of survival. However, even if the gallium-avid or MDP-avid tumors did have a slightly poorer prognosis than those that are not avid, pediatric oncologists are not likely to add routine gallium scans to the initial evaluation unless it were shown that it could also predict tumor response. Predicting response is becoming more important in these patients because new or more aggressive treatment regimens are being proposed for these children who face a very dismal life expectancy with conventional therapies. In fact, as this report demonstrates, survival in children over one year of age with advanced disease is less than 20%, thus prompting efforts to detect disease at an early stage (*6*). Some patients do respond well to conventional therapy and so it would be helpful to be able to separate at the onset those who might respond from those who will probably not respond.

In addition, as evaluation of tumor response in bone is very difficult in neuroblastoma, nuclear medicine studies that improve on the ability to discriminate healing from progressive bone lesions would also be very valuable.

The study is straightforward in its concept. Patients were scanned conventionally with ^{99m}Tc-MDP and ^{67}Ga-citrate and the results were compared with the subsequent survival of the patients. This type of study has been done in the past with contradictory results. Technetium-99m-MDP uptake in primary neuroblastomas was found not to reflect survival (*7*). Gallium-67 uptake was found to be a useful prognostic indicator, albeit in a small series of 10 patients (*8*). In the present study, such usefulness cannot be substantiated statistically. Technetium-99m-MDP bone scans were found to be useful in staging disease, although this was not examined directly, and, in fact, ^{99m}Tc-MDP was used in some cases to establish that the patients were Stage IV. The authors conclude that further study using large numbers of patients from multicenters is desirable.

The statistical aspects of this study show how the examination of small numbers of patients limits conclusions. First, the confidence limits for uptake of ^{67}Ga includes the number five, which indicates that the study lacks sufficient statistical power to detect a fivefold increase in risk. Thus, one can readily agree with the authors that large differences in risk could have been missed by this study. In fact, the confidence intervals in the study are uniformly too wide for reliable conclusions to be drawn. Too few patients were studied and no amount of analysis can compensate for this lack.

I have consulted with the statisticians at my institution who have found considerable question with the analysis of survivorship in this study. They point out that it is improper to report death (and relapse for that matter) as a simple proportion. Treatment completion as a study endpoint is also problematic, especially since no time frame for completion is specified in this study. The Kaplan-Meier method can be used to calculate median survival by taking censoring into account, but it is not valid to compare survivors to nonsurvivors when they have different lengths of follow-up. Also the use of Cox proportional hazards regression analysis (a large sample method) on a sample of 35 patients with multiple study factors is cause for skepticism.

Currently, age, stage and N-myc copy number are the most significant prognostic factors in neuroblastoma. In fact, a good model might be found for future studies of this type in the report by Seeger et al., which establishes the association of N-myc onco-

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gene with early tumor progression after diagnosis (*9*). Correlation of tumor uptake of a radionuclide with the presence or absence of this oncogene might be a way of getting an early "fix" on whether or not the nuclear medicine procedure shows promise as a prognostic factor.

Another model for examination of therapeutic response would be the studies that correlate the results of ^{67}Ga imaging in predicting the outcome in lymphoma (*10,11*). The important difference in these reports is that it is the presence or absence of uptake *after* the initiation of chemotherapy, not before, that correlates with outcome. These comments should be taken into account in the design for future studies. The results of the MacDonald study do suggest that we need to do a larger study, possibly a multicenter study, since the incidence of this disease does not lend itself to a large, single institution investigation. Alternatively, multiple individual studies pooled by meta-analysis may be a way of answering these questions (*12*).

In the future, studies employing gallium scanning and bone scintigraphy should be done not just before but also after treatment. It is also suggested that SPECT imaging be employed because it is becoming more available and may improve sensitivity and specificity (*13*). There is also a question as to whether ^{99m}Tc-MDP and ^{67}Ga are optimal in these patients. Other tracers could be examined. Recent studies with ^{201}Tl and ^{99m}Tc-sestamibi have suggested that these agents may be of value in monitoring tumors under treatment (*14,15*). Iodine-131-metaiodobenzylguanidine has also been found useful (*16*). Finally, PET scanning with ^{18}F-fluorodeoxyglucose (*17*) and ^{11}C-methionine (*18*) or SPECT with radiolabeled monoclonal antibodies (*19*) could be considered.

The decision of what studies to perform and when to perform them is critical. At a time when medical care costs are increasingly coming to the forefront, the expense involved in such investigation must be closely scrutinized. This calls for close cooperation between oncologists and nuclear medicine specialists, which may take numerous conferences, drafts and discussions before these questions can be resolved. As previously mentioned, a comparison of scintigraphic results with other prognostic indicators known to have significance, such as the presence of N-myc oncogene amplification, may have a role in determining the aggressiveness of neuroblastomas.

Discussions I have had with a pediatric oncologist reveal areas where cooperation could refine our clinical parameters and lead to better patient care. For example, except for children under one year of age, there are no good Stage IV patients with neuroblastoma. All need aggressive treatment and another prognostic parameter within Stage IV may not be that helpful. A study of earlier Stage II or Stage III patients might be more rewarding. For pediatric oncologists, a better way to follow bone lesions to determine if healing is occurring may be even more important, and nuclear medicine techniques could probably help with that.

Ultimately, with all of the various technologies at our disposal today, and with the limited resources that are likely to be present in the future, we have to be aware of our decision-making habits and where we may be going astray or overdoing. Schoenbaum points out in an editorial discussing concensus by experts as a means of eliminating unnecessary care that "there are so many potential patient scenarios that it would be virtually impossible to perform all of the outcome studies that would be needed to ground all appropriateness assessments in outcomes data" (*20*).

One would have thought by this time that most of the clinical questions regarding the use of bone scintigraphy and gallium scanning in patient care would have been fairly well worked over and settled. With the number of articles in the literature and patient populations that have been imaged over the last 20 years, one would be skeptical that very much new data could be revealed. However, this is not the case. There are presently many techniques in routine use and practice whose basis in decision making is shaky. This is partly because techniques change from year to year, and thus patient studies have a rather short half-life for their relevancy to current practice. Additionally, our concepts of how to analyze the effectiveness of clinical procedures is changing. An analysis that at one point in time would be considered exemplary may later be judged as totally inadequate. It is therefore important to continuously examine our practice and our research to be sure that we are on solid ground, or at least doing the best we can with current ideas and techniques. One has only to look at the recent controversy over the use of mammography for screening of breast cancer to see how difficult that can be (*21*).

In summary, we all would like nuclear medicine to grow in its application in cancer and other diseases for the betterment of patient care. However, we hope that growth will be orderly and functional. Studies such as those reported by MacDonald et al. are important in reminding us how difficult it is in the clinical environment to research and analyze patient care while we are performing it. They also remind us of the need to constantly examine and reexamine so that we can ultimately conduct our care with the fewest possible procedures and with the best outcomes.

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