EDITORIAL

Clinical Applications of Positron Emission Tomography In Cancer: The Good, The Bad and The Ugly

SIMPLER IS BETTER

In the immediate future, I believe that the most promising clinical role of PET will be to help guide the therapeutic management of patients with cancer. The paper by Okada et al. (*1*) brings PET one small step closer to achieving this goal. In order to be clinically practical, PET must be simplified. In their paper, the authors demonstrate that noninvasive semiquantitative, prognostic indices derived from PET correlate with pathologically derived prognostic indices. The correlation of a more invasive, more complicated PET index with pathologically derived prognostic indices was not significantly better than the simpler PET indices.

As is usually the case, this paper answers only a few of the important questions. From the information provided, it is not possible to determine if the prognostic information provided by PET was unique. It is likely that the poor prognosis of some patients with lymphoma could have been predicted from other available clinical or pathologic information.

Despite its promise, research into the clinical applications of PET in oncology has, until recently, lagged behind research in the clinical application of PET in cardiac and neurological diseases. I suspect that the late start was partly due to the limited field of view of PET scanners, which made it much easier to image a small (<10 cm) organ in a well-defined location than to search for tumors of variable size in unknown locations.

The increasing interest of PET applications in oncology is encouraging. In order to achieve the goal of providing clinically useful information with PET in oncology patients, we have to understand the nature of the problems clearly. I have outlined below what I perceive as the potential promise of PET in oncology (The Good), the scientific hurdles that must be overcome (The Bad), and the economic and regulatory shackles that must be broken (The Ugly).

THE GOOD: THE POTENTIAL OF PET

According to the American Cancer Society, 22% of Americans will die from cancer. It is the second most common cause of death in the United States (*2*). Therapies designed to combat this enemy abound. The techniques available to assess the effectiveness of therapies are primitive. In the clinical setting, the patient is typically treated for several weeks with therapies that induce considerable morbidity. The effectiveness of the therapy in the individual patient is determined by waiting until there is a change in the size of the tumor. This change in size can take weeks to months to occur.

Since it is logical that changes in the physiology of the tumor will occur long before changes in the structure, PET thus might serve as a noninvasive tool capable of distinguishing patients who will respond to treatment from those who will not. If this information could be obtained very early in the course of treatment, the morbidity of ineffective treatments could be avoided and other more aggressive treatment could be initiated sooner.

Other potential clinical applications of PET in cancer include more accurate staging, guiding of biopsies and grading of tumors. Although PET may eventually be used in a clinical setting for these applications in some patients, demonstrating that more accurate staging, biopsy and/or grading will result in decreased patient morbidity or mortality will be difficult. If such benefits are demonstrated, will they be attained for a justifiable cost?

THE BAD: SCIENTIFIC HURDLES

Anyone working with PET recognizes that there are a number of formidable scientific problems that complicate the use of PET in a clinical setting for oncologic applications. Fundamental problems include the efficient design of scientific studies designed to measure the clinical benefit of PET studies in patients with cancer and the limitations imposed by current PET instrumentation.

Several important decisions must be made when designing a study to measure the clinical benefit of PET in cancer. First, a particular type of tumor must be selected. In order to increase the chances of demonstrating clinical benefit, types of tumors that respond well to chemotherapy or radiation therapy should be chosen. It will be difficult to convince anyone that PET is clinically useful if there is no efficacious treatment for the tumor.

Second, a practical potentially useful radiopharmaceutical must be chosen. A large number of radiopharmaceuticals have been described for tumor imaging. Although the ability to label a large number of biologically important chemicals is a great strength of PET, it is also a great curse. A strong theme in PET research is to perform small exploratory studies using novel compounds. It is difficult to draw any conclusions from the plethora of studies reporting the initial results of a new radiopharmaceutical in a few patients. Larger studies focusing on fewer radiopharmaceuticals will provide more useful scientific information that can then be used to

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help define the clinical role of PET in the management of cancer patients. The radiopharmaceutical of choice for clinical oncologic PET will be determined not only by its biological behavior but also by its ease of preparation as well as by the logistics of imaging. In the short term, FDG appears to be the imaging agent of choice for tumor imaging.

Third, large, well-designed multicenter studies are needed to allow for collection of enough data to achieve adequate statistical power in a timely fashion. When introducing an expensive technology, it will not be sufficient to only demonstrate that PET is accurate. PET must be shown to add unique information that would not have been obtainable by evaluation of other clinical factors. Knowledge of this unique information must ultimately be shown to affect patient outcome.

PET instrumentation must also be improved for clinical oncologic PET to become a reality. Most PET scanners image a very limited portion of the body (typically 10 cm in the z-axis). Furthermore, sampling in the z-axis is often incomplete. Incomplete z-axis sampling makes it much more difficult (often impossible) to re-orient the images. Re-orientation is very helpful (sometimes essential) for comparison of low-resolution functional images with high-resolution anatomic images.

The study by Okada et al. (*1*) provides a good example of the shortcomings of many PET scanners. Their scanner acquires only three slices simultaneously. The thickness of each slice is 1.65 cm and the field of view is limited. This limited field of view of most PET scanners nullifies one of the major advantages of nuclear medicine, the fact that the tracer is distributed throughout the entire body and the entire body can be imaged. Fortunately, this limitation is being overcome with state-of-the-art PET scanners providing larger fields of view and the ability to obtain a whole-body planar survey (*3*).

Increasing the volume that is imaged tomographically is not a simple task. For most PET scanner designs, increasing the number of transaxial slices means increasing the number of rings of crystals, thus making a complex machine even more complicated and more expensive.

In order to take advantage of the improved x-y resolution of PET scanners, the z-axis resolution (slice thickness) must be improved. If z-axis resolution is improved, more transaxial slices are required if the volume is to be sampled adequately. Also, slice sensitivity decreases as the z-axis resolution improves. Decreased slice sensitivity means longer imaging times if the statistical quality of the images is to be preserved.

THE UGLY: ECONOMIC AND REGULATORY SHACKLES

The fight to move PET into the clinical arena has resulted in a "Battle Royale." Unfortunately, this attempt to introduce PET into the clinical practice of medicine comes at a time when there is great concern over the cost of medical care. Expensive high technology, in particular, has come under intense scrutiny, despite the fact that it accounts for only a small fraction of the total cost of medical care.

In addition, the rules for introducing new technology are changing almost daily. It is no longer sufficient to show that a diagnostic test is accurate. A new test must be shown to provide some unique diagnostic information and that unique information must result in improve patient outcome (i.e., longer life, less morbidity). Providing this kind of evidence is difficult, time consuming and costly. Improved patient outcome may not be apparent for months to years after a diagnostic test is performed. Attributing the improvement to one particular intervention may not be possible.

Although grants are available to support basic and developmental research, little money has been available to support studies on the effectiveness of emerging technologies. In the past, this was not such a problem because many clinical effectiveness studies were in fact supported by third-party payers. Third-party payers are no longer willing to provide this support knowingly. Other sources of support for clinical research have not materialized. Under these circumstances, PET centers must join forces and form multicenter clinical groups that can accrue patients rapidly to provide the answers to important clinical questions. Adequate funding of these multicenter groups, presumably by the federal government, is essential for clinical PET to become a reality in the near future.

Another quagmire is the current status of radiopharmaceuticals for PET. Some PET centers have taken the position that most positron-emitting radiopharmaceuticals are not under the jurisdiction of the FDA because they are compounded locally and are not introduced into interstate commerce. Others, including the ICP, have recommended submission of a new drug application (NDA) template for FDG, which could then be referenced by individual PET centers (*3*) filing their own site-specific NDAs. If NDAs must be approved for every PET center for every new positron-emitting radiopharmaceutical, progress will be further slowed.

CONCLUSIONS

Over the next few years, PET imaging will continue to test our fortitude. Given the current economic and regulatory environment, progress will be slower than we would like. Despite the dearth of funding for clinical research, it will be our responsibility to provide the scientific foundation for clinical PET. Scientifically valid multicenter studies are essential. Shortcuts will not work.

We should continue to be optimistic. PET is an exciting imaging modality with great promise. Even the most jaded observers must acknowledge the intrinsic value of a method that exploits the tracer principle, especially when biologically important molecules can be labeled and studied

noninvasively. The scientific, economic, and regulatory problems that have been discussed eventually will be solved.

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SELF-STUDY TEST

Radiobiology and Radiation Protection

Questions are taken from the *Nuclear Medicine Self-Study Program I*, published by The Society of Nuclear Medicine

DIRECTIONS

The following items consist of a heading followed by numbered options related to that heading. Select those options you think are true and those that you think are false. Answers may be found on page 344.

The anticipated effects on an individual of a whole-body radiation dose of 100 rads include:

1. a significant reduction in immune responsiveness
2. permanent sterility
3. a lifetime risk of about 1% for radiation-induced fatal cancers
4. a high likelihood of genetic effects in his or her children
5. epilation and bleeding of gums

True statements concerning nonstochastic effects of ionizing radiation include:

6. The severity of the effect varies with dose.
7. The probability of the effect varies with dose.
8. There often is a threshold dose.
9. The aim of radiation protection should be to prevent these effects.
10. They are limited by cell killing.

The genetically significant dose (GSD)

11. is the dose of radiation each person receives from birth to death.
12. is the dose of radiation that can be shown to have led to a genetic death.
13. from medical exposure in the U.S. is approximately equal to that from background sources.
14. is an index of the presumed genetic impact of radiation exposure to the population.

True statements concerning the genetic "doubling dose" for radiation-induced genetic abnormalities include:

15. It is the amount of radiation that would be expected to add as many new mutations as occur spontaneously.
16. The higher the doubling dose, the greater the risk of *mutations* for a given amount of exposure.
17. A doubling dose administered to a population would produce twice the spontaneous number of mutations in the next generation.
18. It is the reciprocal of the relative mutation risk.
19. The BEIR 1980 estimate of a doubling dose of 50–250 rads was obtained from human epidemiologic studies.

True statements concerning the genetic effects of radiation include:

20. Mutations are usually harmful.
21. Genetic effects observed in the progeny of the A-bomb survivors provide the best estimate of human risk.
22. They appear to depend very little on the stage of germ cell development at irradiation.
23. They are independent of the rate of delivery of the radiation.
24. Their likelihood decreases as the time interval between irradiation and conception increases.

Statements that support the concept of multistage development of cancer following irradiation include:

25. In irradiated populations no excess risk of breast cancer has been seen until exposed individuals reached ages at which spontaneous cancers are observed.
26. The excess incidence of radiation-induced bone cancer and leukemia appear within a few years.
27. There is a long latent period for radiation induction of most tumors.
28. Latent periods for radiation-induced cancers are reduced by "promoters."
29. Transformation to malignancy by viral oncogenes appears to require activation of more than one cellular oncogene.

Cancers induced in humans by acute whole-body radiation exposure

30. generally can be distinguished from those occurring naturally.
31. typically develop after latent periods of 10 years or more after irradiation.
32. are the most important late somatic effect.
33. are more often leukemias than solid tumors.

The risk of radiation-induced cancer is *strongly* dependent on gender for which of the following tumors?

34. breast carcinoma
35. bronchogenic carcinoma
36. leukemia
37. thyroid carcinoma
38. bone sarcomas

(continued on p. 344)