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Uses of Dosimetry Information in Nuclear Medicine

Diagnostic Versus Therapeutic Applications

Since the earliest days after the discovery of radiation in 1895 by Wilhelm Conrad Roentgen, it has been known that exposure to ionizing radiation can be harmful to humans. In any use of ionizing radiation, one must prevent or minimize the risks of the use of the radiation while allowing its beneficial applications. As we will discuss later in this book (Chapter 6), current research is challenging the paradigm that the quantity *absorbed dose* is the best to use in predicting biological effects. There are clearly complications that need to be considered in assessing the response of all biological systems to all kinds of radiation. Nonetheless, the quantity *absorbed dose*, which gives the energy of ionizing radiation absorbed per unit mass of tissue (or any material for that matter), is usually indicative of the probability of a deleterious biological effect, and it is the quantity that will be studied most in this text.

The history of the use of radioactive materials as biological tracers dates to Georg de Hevesy and colleagues, who, in 1924, performed radiotracer studies of the kinetics of lead-210 (^{210}Pb) and bismuth-210 (^{210}Bi) in animals. Soon thereafter in 1925, Herrman Blumgart and Otto Yens evaluated blood flow rates in humans using bismuth-214.

Iodine-131 and cobalt-60 were discovered by John Livingood and Glenn Seaborg, and Emilio Segre and Glenn Seaborg discovered technetium-99m (^{99m}Tc) in 1938. Iodine-131 (^{131}I) and ^{99m}Tc are the predominant radionuclides currently in diagnostic and therapeutic nuclear medicine studies. The ^{99m}Tc generator was developed in 1957 by W.D. Tucker and colleagues at the Brookhaven National Laboratory.[1]

When X-rays were first discovered by Roentgen, the idea that physicians could see internal structures of the body without using a scalpel was one of the most exciting moments in medicine. Similarly, the idea of using a radioactive tracer inside of the body to transmit signals to detectors outside of the body to investigate the movements of materials in the body and thus discern physiologic, as opposed to only anatomic, information was exciting and revolutionary. The first application of nuclear medicine is *diagnostic*; that is, studying structures and processes to diagnose diseases and guide medical response to potential human health issues. The majority of day-to-day practice in nuclear medicine continues to involve diagnostic procedures, but radiopharmaceuticals used in nuclear medicine may also be applied in *therapeutic* applications; that is, administering higher levels of activity with the intent of exploiting the ability of radiation to destroy deleterious tissues in the body (cancer, inflamed joints, and other applications).

In the early part of the 20th century, shortly after the discovery of radiation and radioactivity, radiation sources were used in a number of ill-advised experiments with medical applications and consumer products. Dr. Paul Frame, in a historical review of the use of such applications, notes that popular locations in the United States and elsewhere attracted visitors who could bathe in springs of radioactive water or inhale radioactivity-laden air.[2] Some of these sites are still in operation, surprisingly. Routine intentional exposures to radiation occurred, based on the belief that radiation could cure "various forms of gout and rheumatism, neuralgia, metallic or malarial poisoning, chronic Bright's disease, gastric dyspepsia, chronic diarrhea, chronic skin lesions . . . insanity, old age" and create "a splendid youthful

joyous life."[2] Dr. Frame notes that "Professor Bertram Boltwood of Yale explained the scientific basis for the cures in the following way: The radioactivity was "carrying electrical energy into the depths of the body and there subjecting the juices, protoplasm, and nuclei of the cells to an immediate bombardment by explosions of electrical atoms," and that it stimulated "cell activity, arousing all secretory and excretory organs . . . causing the system to throw off waste products," and that it was "an agent for the destruction of bacteria."[2] A series of consumer products arose that allowed people to drink radioactive water on a regular basis in their own homes without having to travel to a spa or mine many hours away. High rates of thyroid carcinoma were observed in the 1940s and 1950s in infants treated shortly after birth for thymus enlargement. In a similar time period, large doses of radiation were given to the spines of subjects suffering from ankylosing spondylitis; the treatment was effective, but it was associated with a high rate of induction of leukemia. Radiologists and radiotherapists operating in the early years of radiation medicine suffered high rates of leukemia and pernicious anemia. A particularly tragic episode in the history of the use of radiation and in the history of industrialism was the acute and chronic damage done to the radium dial painters.[3] Radium was used in luminous paints in the early 1900s, and some factory workers (mainly women) ingested large amounts of radium-226 (^{226}Ra) during the painting of the luminous dials for watches. They soon demonstrated high rates of bone cancer and even spontaneous fractures in their jaws and spines from cumulative radiation injury.

In the early years, ^{226}Ra was the principal radionuclide used in radiation therapy in which high-activity sources were placed on or near tumors to attempt to eradicate them (*brachytherapy*; with *brachy* coming from a Greek word meaning "close to"). Modern external radiation therapy still employs a number of brachytherapy techniques involving different radionuclides and radiation-producing machines that deliver high doses of radiation to malignant tissues while minimizing dose to healthy body tissues. In nuclear medicine therapy, the goal is to administer compounds systemically

that will preferentially concentrate in tumors and deliver a high dose to these tissues while hopefully having lower concentrations and faster clearance rates from other tissues. An overview of the current practice of nuclear medicine therapy is given in Chapter 5.

A radiation dose analysis is fundamental to the use of either diagnostic or therapeutic radiopharmaceuticals. For diagnostic compounds, the U.S. Food and Drug Administration (FDA) studies a number of safety issues during the drug approval process, and internal dosimetry* is one issue of high importance (see Chapter 7). Radiation dose estimates are not often of direct interest in day-to-day practice in the clinic, but they are often referred to when comparing advantages and disadvantages of possible competing drug products, by radioactive drug research committees (RDRCs) in evaluating safety concerns in research protocols, and in other situations. In therapeutic applications, the physician should perform a patient-specific evaluation of radiation doses to tumors and normal tissues and design a treatment protocol that maximizes the dose to tumor while maintaining doses to healthy tissues at acceptable levels (i.e., below thresholds for direct deleterious effects), as is always done in external radiation therapy treatment planning. Unfortunately, this is not routinely practiced in most clinics at present, and patients are generally all treated with the same or similar protocols without regard to their specific biokinetic characteristics.

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*_Dose assessment_ is actually the correct, formal name for this process. In day-to-day use, however, the terms external and internal *dosimetry* are used. This is the classic, historical usage since the Manhattan Project in the 1940s. The term *dosimetry* contains the suffix *metry*, which relates to metrology, which implies the measurement of physical quantities. Much of external dose assessment does have to do with measurements, so the term *dosimetry* is mostly accurate, although some assessment is done with theoretical models. The science of *internal* dose assessment is almost entirely founded in theoretical calculations and models, with no measurements being involved. This field is, however, most often referred to as *internal* dosimetry, to be a correlate to *external* dosimetry.

Model-Based Versus Patient-Based Approaches

As noted above, internal dose estimates are performed via calculations, not measurements. Usually, they are based on standardized models of the human body and often on standardized models of radiopharmaceutical behavior in the body as well (see Chapter 3). This approach results in a calculation that is easily traceable and reproducible. One of the important aspects of model-based internal dose calculations is that the output (calculated dose estimates) is only as good as the input (assumptions and models employed). With very good data, one can obtain good dose estimates, but one must always remember that what has been calculated is dose to a *model*, not dose to a *person* (patient, research subject, etc.). In diagnostic applications, this is generally acceptable. All of the input data has some associated uncertainty, and the calculated results reflect both this inherent uncertainty in the data as well as uncertainties related to the application of standardized models of the body to a variety of patients who vary substantially in size, age, and other physical characteristics. When the radiation doses are low, this kind of uncertainty is tolerable because, if the calculated answers are incorrect by tens of percent or even factors of 2 or more, the consequences for the patient are small or nonexistent (depending on what you believe about radiation risk models at low doses and dose rates; see Chapter 6). In therapeutic applications, however, the tolerance for uncertainty needs to be lower, as the doses are higher, and the chances of reaching or exceeding an organ's threshold for expressing radiation damage are real.

The use of model-based dosimetry for therapy with radiopharmaceuticals must be abandoned and replaced with a patient-specific modeling effort that considers both the unique anatomic and physiologic characteristics of the patient, as has been done in external beam radiotherapy for decades. It is true that such attention to detail for the patient's benefit requires significantly more effort in data gathering and dosimetric modeling, but the effort is worthwhile in providing the patient with a better quality of care

and expectancy for a positive outcome from the therapy. Radiopharmaceutical therapy must advance beyond its roots in pharmaceutical therapy dosage (e.g., using a quantity of drug per unit measure of patient size) and become more like radiotherapy dose delivery (e.g., employing understandings of energy deposited per unit mass of tissue).

Practical Dosimetry: Balancing Benefits and Risks

As we study the details of dose calculations, we will develop carefully the minimum requirements for performing an adequate calculation of radiation dose. Natural progress will ensure that more and more technology can be brought to bear in analyzing the problem. With more and more data constantly gathered, the quality of the results and approaches will improve. Data gathering for dosimetry requires that the subject spend perhaps 10 to 40 minutes in a fixed geometry in a detector counting system, which involves some discomfort and difficulty. The data analysis requires the time and attention of skilled professionals. There is obviously a balance that needs to be struck between an excellent analysis and logistical concerns. After the absolute minimum of data is obtained, additional data may be taken as is possible, given the concurrence of the physician and patient and availability of the counting systems. When only fixed dosages of radiopharmaceuticals are administered to all patients with no study whatsoever of the radiation doses received, it is impossible to optimize individual subjects' therapies or to advance our understanding of dose-effect relationships and how to provide the best treatments for our patients.

Clinical Utility: Interface of Patient, Physician, and Physicist

The patient-physician relationship is a special one, involving trust, weighing and balancing of very significant decisions, exposure of highly personal information, and usually significant expenses. Decisions about medical procedures and

follow-up, use of medications, planning, and lifestyle are very personal and often difficult. The physicist, who provides just one piece of information that the physician must weigh and convey to his or her patients, plays a very peripheral but nonetheless pivotal role in the case of therapeutic use of radiation. In diagnostic applications, the physicist is separate from the process and just provides dose calculations that are used by regulatory and other bodies to make very broad recommendations about the general use of radiopharmaceuticals in clinical practice and research. Only rarely does a flawed diagnostic study (e.g., a misadministration) necessitate the physicist's attention to dosimetry in a particular patient's situation. These three individuals must work closely, however, in this ongoing process to provide the highest quality medical care possible in every circumstance. Ultimately, the patient (or research subject) makes the final decisions about the progress of the medical care and must be given high-quality information, clearly and unambiguously communicated by the physician and/or physicist. It is important that radiopharmaceutical therapy begin to involve the physicist more than it has in the past, as is modeled in external beam radiotherapy.

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