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EDITORIAL

Quantitative Autoradiography for the Study of Radiopharmaceutical Uptake and Dose Heterogeneity

The calculation of absorbed dose estimates is standard practice to help assess risk of injury or probability of therapeutic efficacy in the diagnostic and therapeutic use of radiopharmaceuticals. Even though tissues vary, the response of a single tissue type to a uniform absorbed dose delivered under identical conditions is highly correlated with dose magnitude. The Medical Internal Radiation Dose (MIRD) Committee has developed a methodology for calculating organ doses (*1*) which is often used to calculate "average" doses using the simplified assumptions of uniform activity density and homogeneous organ composition, known as the uniform isotropic model. Use of this simplified model is widespread. However, due primarily to the observed heterogeneity of radiopharmaceutical uptake in tissues (*2–5*), there is growing evidence of its inadequacy.

If the average dose calculations were a valid predictor of effect, there should be a simple relationship between external beam irradiation (XRT) and radioimmunotherapy (RIT). A recent review of XRT/RIT comparisons (*6*) listed relative efficiencies of tumor growth delay to range between 0.3 and 3.3. Possible reasons noted for a decreased efficiency of RIT relative to external beam were: (1) dose rate effect (*7*); and (2) dose heterogeneity. Possible reasons for an increased efficiency were: (1) enhanced reoxygenation with RIT; (2) RIT preferentially targeting rapidly proliferating cells; (3) cell cycle redistribution with accumulation in the radiosensitive G2 phase; (4) cell geometric effect (*8*); and (5) RIT contribution to increased tumor vascular permeability. This illustrates the current uncertainties in the use of calculated dose values using the uniform isotropic model: there appears to be a very tenuous relationship between average dose and outcome with many potential correction factors of uncertain magnitude.

The general MIRD committed methodology does allow for the use of nonuniform activity distributions in source regions and nonuniform size and density of target regions (*1*). However, the greatest obstacle for the use of more realistic models is the collection of accurate input data. A recent editorial (*9*) on the MIRD approach recommends the use of improved measurement techniques for the determination of activity density values at both the cellular and multi-cellular levels for the study of the dosimetric consequences of nonuniform activity distributions. The time variations of the activity distributions can also be significant (*5*). The MIRD methodology includes provisions for the time dependence; but, again, the calculation of a dose distribution for a time-dependent inhomogeneous activity distribution requires a substantial quantity of input data.

Quantitative autoradiography (QAR) can be used to determine the activity density distributions for the whole body, individual organs and tumors. The film optical density scale is calibrated using standards of known activity density, allowing the calculation of activity densities from the autoradiograph data. The quality of the autoradiograph is dependent on the type of film and the type of emitted radiation. The autoradiograph film is typically digitized using an imaging system or optical densitometer. The spatial resolution of the autoradiograph and the pixel size of the digitizer are important parameters. The need for high spatial resolution is dictated by the penetrating ability of the emitted radiation. The digitizer pixel size should be small compared to the distance of significant gradient of the optical density distribution due to its logarithmic dependence on relative light intensity (*10*). Very short range radiations (e.g., Auger emitters or alpha particles) require activity information at the cellular level (<10 μm) (*11*) as input for microdosimetry calculations. For longer range particles, calculations averaged over many cells (~100 μm) is adequate (multicellular dosimetry (*12*)). To obtain the required resolution, the range of the radiations used to produce the autoradiograph must be at least as short as the range of the radiations for which calculations are being performed. The use of low-energy, short-range sources for QAR requires special calibration procedures (*13*).

In this issue of *JNM*, Jonsson et al. (*14*) use whole-body quantitative macro-autoradiography (WBQAR) to study the distribution of uptake in rats

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for five ^{111}In radiopharmaceuticals and agents used for labeling. While the overall activity distributions were similar with the greatest concentrations in the rapidly dividing tissues, the localization in some critical organs was found to be radiopharmaceutical dependent. Very heterogeneous activity distributions were found in the liver, spleen, kidneys, bone marrow, lymph nodes and testes. Estimates of the magnitudes of the heterogeneities were performed by determining the fractional areas within optical density intervals. However, it is desirable and feasible to convert to activity density, determine the full extent of the organ or tissue and calculate absorbed dose distributions. The heterogeneous activity distributions found highlight the need for detailed studies of the distribution of radiopharmaceuticals for accurate absorbed dose calculations.

WBQAR offers a wealth of information not only on the distribution of the radiopharmaceuticals between organs and tissues, but also on the distribution within an organ or tissue. The resulting detailed determination of the activity distribution may be used to perform improved estimates of absorbed dose distributions, from which estimates of risk or injury or probability of tumor response can be inferred. Even the activity distribution within an organ can significantly affect the estimate of risk. The qualitative comparison of radiopharmaceuticals shows the sensitivity of this method to issues important in their selection. The quantitative assessment of the activity distributions can be used as input data for improved absorbed dose calculations.

There are many other examples of the use of QAR. Fand et al. (*15*) used high-resolution semiquantitative autoradiography to study the uptake of ^{125}I-labeled monoclonal antibodies and antibody fragments in human colon cancer (GW-39) micrometasteses in nude mice. The results showed uniform uptake in micrometasteses, while the uptake in larger solid tumors was nonuniform. Ito et al. (*16*) used QAR to show that intravenous injection of ^{90}Y-labeled immunotoxin produced a more homogeneous distribution compared to intraperitoneal injection in human colon cancer (LS174T) intraperitoneal tumors in nude mice. Roberson et al. (*5*) used QAR of serial tumor sections from nude mice injected with ^{131}I-labeled 17-1A monoclonal antibody for three-dimensional reconstructions of the activity distributions for human colon cancer (LS174T) subcutaneous tumors. Three-dimensional dose-rate distributions, calculated from the activity distributions, were more nonuniform at one day postinjection compared to 4 days postinjection. At 4 days, the dose rate still varied by more than a factor of four for significantly large partial volumes.

A challenge for the QAR techniques, or any other technique designed to provide the input data for spatially dependent dosimetric calculations, has been to develop methods for handling the large quantities of data (*5,17*). This problem continues to become less formidable as the capacity and speed of computer hardware improves.

A complete dosimetric analysis also requires knowledge of the time-dependent three-dimensional activity distribution. This is not achievable for a single tumor or organ using QAR due to the destructive procedure (dissection) required for the exposure of the film. A mathematical model of the dynamic absorbed dose distribution may be developed by studying the time dependence of representative dose-rate distributions (*18*). Use of microthermoluminescent dosimeters (*3*) for time integral dose measurements can be used for model validation. Dosimetric calculations for rapidly changing tumors (*19*) offer an additional challenge because the dose rates can vary with tumor size.

The relationship between dose and effect will not be resolved without knowing more about the space-time dependence of the dose distribution in relationship to the heterogeneous composition of the whole body, organ or tumor. There is a need for thorough investigations of the activity and dose heterogeneities produced by radiopharmaceutical uptake. Quantitative autoradiography can be an important tool for these investigations.

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SELF-STUDY TEST
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ANSWERS

of tracer from the peritoneal cavity through the shunt into the target organs (lung or liver/spleen) of the tracer employed (^{99m}Tc macroaggregated albumin [MAA] or ^{99m}Tc sulfur colloid). The most frequent cause of shunt malfunction is obstruction by fibrin deposits of the afferent limb of the shunt. Less frequently, thrombus formation occurs in the efferent portion of the tubing. When ^{99m}Tc MAA is the tracer utilized at high and low flow rates, there may be nonvisualization of the efferent shunt tubing. Hence, direct target organ visualization (i.e., tracer accumulation in the lungs) should be utilized as the criterion of shunt patency. Disease states that cause elevated right heart pressure, such as congestive heart failure, can cause false-positive studies. Thus, when only the afferent portion of the shunt is visualized, direct puncture of the efferent limb is generally necessary to locate the site of malfunction more precisely.

Both the sensitivity and specificity of peritoneovenous shunt scintigraphy appear to be high. In a study of 40 patients, six of whom were evaluated when their shunts appeared to be malfunctioning, no false-positive or false-negative studies were encountered.

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ITEMS 16–19: Scintigraphy for Meckel's Diverticula

ANSWERS: 16, F; 17, T; 18, F; 19, F

The histamine-2 receptor antagonist, cimetidine, enhances imaging of Meckel's diverticulum by causing continued accumulation of [^{99m}Tc] pertechnetate in ectopic gastric mucosa and by reducing secretion of ^{99m}Tc activity into the bowel. By decreasing the amount of pertechnetate entering the small bowel, cimetidine helps to reduce the frequency of false-positive studies.

Up to 73% of menstruating women have been shown to demonstrate a uterine "blush" following [^{99m}Tc] pertechnetate administration during the menstrual or secretory phase of their menstrual cycle. This may lead to a false-positive interpretation. In general, premenarchal, postmenopausal, and menstruating patients in the proliferative phase do not show this uterine "blush."

Small bowel duplications occasionally contain ectopic gastric mucosa and may simulate Meckel's diverticulum on scintigraphy with [^{99m}Tc] pertechnetate. Because the position within the abdomen of a small bowel duplication can mimic that of Meckel's diverticulum and because both anomalies contain ectopic gastric mucosa, it usually is not possible to distinguish Meckel's diverticulum from a small bowel duplication by [^{99m}Tc] pertechnetate imaging.

Autoradiographic studies have shown that, after intravenous administration, [^{99m}Tc]pertechnetate is selectively concentrated by the mucous-producing cells of gastric mucosa, rather than by parietal cells or chief cells. Experimental animal studies have demonstrated that at least 2 cm^2 of functioning ectopic gastric mucosa is necessary for visualization.

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ITEMS 20–22: Meckel's Diverticula in Adults

ANSWERS: 20, F; 21, F; 22, F

Although Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, with a prevalence of approximately 1%, most are not symptomatic. Additionally, those that cause symptoms usually do so in the first 2 yr of life. Ectopic gastric mucosa is more frequently encountered in symptomatic Meckel's diverticula, but may also be present in asymptomatic Meckel's diverticula. Lower gastrointestinal bleeding is the most frequent presentation of symptomatic Meckel's diverticulum in the pediatric population. In adults, the most common presentation is acute inflammation (Meckel's diverticulitis). Obstruction is seen less often, and gastrointestinal bleeding occurs rarely. Several studies have clearly shown that the sensitivity of [^{99m}Tc] pertechnetate scintigraphy for Meckel's diverticulum is greater than 80% in the pediatric population. In adults, however, the sensitivity of Meckel's scintigraphy is approximately 60%. The precise reasons for this are unclear.

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ITEMS 23–26: Red Blood Cell Labeling with ^{99m}Tc

ANSWERS: 23, F; 24, F; 25, T; 26, F

In vivo red blood cell labeling is the most frequently utilized method because it is the simplest approach. It is not the most satisfactory method, however, for gastrointestinal bleeding scintigraphy. Because of the variability in labeling efficiency, significant amounts of unbound, free ^{99m}Tc can be secreted into the stomach and bowel, causing false-positive studies. Additionally, much of the activity not bound to red blood cells is excreted by the kidney as labeled small proteins and reduced technetium complexes. This urinary activity may cause problems in interpretation (e.g., a rectal bleeding site may be obscured) and renders the bladder as the critical organ with this labeling method (approximately 2.4 rads/20 mCi). When in vivo techniques are used, the "cold" stannous pyrophosphate should be injected directly into a vein. The precise reason for this is unclear, but if the cold pyrophosphate is injected via an indwelling catheter, poor red blood cell labeling can occur, and this may result in a nondiagnostic examination.

The basic theory underlying red blood cell labeling with ^{99m}Tc is as follows. The stannous ion complex freely diffuses into the red blood cell and binds to cellular components. Pertechnetate ion also freely diffuses into and out of red cells. Once the pertechnetate ion is inside the red

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