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Risks to Normal Tissues From Radionuclide Therapy

Ruby Meredith, MD, PhD,* Barry Wessels, PhD,† and Susan Knox, MD, PhD‡

The development of radionuclide therapies during the past few decades provides a growing body of data on radiobiologic effects, including normal tissue toxicities and antitumor efficacy. Information on normal tissue toxicity from radionuclides is more limited than that from external beam radiation and appears to be more variable. Much of the increased variability is attributed to heterogeneous distribution, which complicates the potential for whole-organ toxicity, and the differences in dosimetry methodology. Although new tools are becoming available, quantitation of heterogeneous dose for radionuclides is usually less precise than dosimetry that is used in external beam radiation practice. The correlation between reported dose estimates and toxicity has improved during the past 2 decades, partly as the result of increased accuracy and standardization of dosimetry techniques and to adjustment for biologic effects. This review provides an updated compendium of dose–response relationships and consideration of dosimetry as well as radiobiologic factors that influence the reported results. Data presented are mainly derived from studies involving deliver of radiation to adults with malignancies, with most experience from radionuclides that predominantly emit beta radiation.
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Therapeutic applications of radionuclides for malignancy have expanded in the past few decades and have led to increasing concern about normal tissue toxicity and an awareness of the need to be able to better predict side effects.[1] Despite much progress, less information has been reported on normal tissue tolerance and antitumor efficacy of radionuclide therapy than is generally available for external beam radiation. Information from studies directly comparing radionuclide therapy with external beam radiation is available from laboratory experiments but not from controlled clinical studies[2,3] With radionuclide therapy the tolerance of normal tissues often appears greater but more variable. Much of the increased variability is attributed to differences in dosimetry methodology and to heterogeneous distributions of the radionuclides, which complicates the potential for organ toxicity. Even with improved detection techniques, the quantification of a heterogeneous dose for radionuclides is usually less precise than for applications involving external beam radiation. With increasing use of intensity-modulated radiation (IMRT) treatment planning systems that provide dose–volume histograms, an increased understanding of partial organ tolerances for external beam radiation, comparison with heterogeneous radionuclide dose deposition will improve.

Heterogeneity of dose deposition at the cellular level will remain of more concern for radionuclides.[4] However, some true difference is expected between radiation dose delivered by photon and radionuclide radiation as the result of biologic mechanisms, in addition to factors such as overall treatment time and dose rate, that tend to be widely divergent between these modalities.[5] Radiobiologic factors need to be considered in terms of how they affect tolerance for both radionuclide and external beam radiation therapy but, in the past, have usually only been considered in special circumstances or limited reports.[6-9] Different forms of radionuclide therapy may also have variable effects as suggested by comparison of gene expression after alpha versus beta radiation.[10] The Wellcome Trust Case Control Consortium at www.wtccc.org.uk continues to study genetic differences in health and disease of a large population. Their data may allow application of meta-analysis to various models to arrive at the best estimate of tolerance. The compilation of radionuclide normal tissue toxicity data provided here includes examples that show the approximate range of doses that may result in low to severe toxicity; this collection is not intended to include all pertinent references or extremes of range. The following review of data, primarily from irradiation of adults with malignancy, describes (1) normal tissue toxicity reported for radionuclides and compares this with tolerance for external beam

*University of Alabama at Birmingham, Birmingham, AL.
†Case Western Reserve University, Cleveland, OH.
‡Stanford University, Stanford, CA.
Support for some clinical trials was from NIH M01 RR-00032.
Address reprint requests to Ruby Meredith, MD, PhD, Department of Radiation Oncology, University of Alabama at Birmingham, 1824 6th Ave South, Birmingham, AL 35249. E-mail: rmeredith@uabmc.edu

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radiation, and (2) considerations of radiobiologic factors that impact outcome.[11] A more detailed review of radiobiologic factors by A. Kassis appears as a separate article in this issue.

Theoretical Radiobiologic Models for Radionuclide Therapy

The linear quadratic (LQ) model that is now used extensively in clinical radiobiology was outlined by Fowler and Stern in 1960.[12,13] The model is based on a single-hit cell kill (Type A event), which corresponds to a lethal single-ionization event and is thus independent of dose rate. A second (Type B) event can only be induced by 2 separate ionization interactions and is thus a function of dose rate. The LQ equation for the surviving fraction (*SF*) of cells after an instantaneously delivered absorbed dose (*D*) is as follows:

$$SF(D) = e^{(-\alpha D - \beta D^2)} \quad \textbf{(1)}$$

where αD is attributed to cell kill from Type A events, and βD^2 from Type B events. If *D* is delivered over a protracted time, as with long-lived radionuclides, Type B events must be corrected for repair of sublethal damage as described by:

$$SF(D) = e^{(-\alpha D - g(T)\beta D^2)} \quad \textbf{(2)}$$

where $g(T)$ is a dimensionless function expressing the decrease in Type B events with increasing treatment time (T).[13,14] When the duration T of the protracted dose becomes significantly long compared with the repair half-time then, for a dose delivered at constant dose-rate, $g(T)$ can be approximated by the expression:

$$g(T) = \frac{2}{\mu T}\left[1 - \frac{1 - e^{-\mu T}}{\mu T}\right] \quad \textbf{(3a)}$$

where μ is the rate of repair of sublethal damage ($\mu = \ln 2/T_{Rep}$, where T_{Rep} represents the repair half-time constant).[15-20] For most organs, T_{Rep} ranges between 0.25 and 3.0 hours,[21] which supports the use of Eq 3a for most radionuclide therapy, the notable exceptions being the alpha-emitters ^{213}Bi, ^{212}Bi, and ^{211}At[22,23] In addition, high relative biologic effectiveness associated with high linear energy transfer radiation has been ignored here but can be incorporated using the method described by Dale.[24]

Radiation dose given with radionuclides is delivered over a protracted time, with kinetics following an exponentially declining curve with an effective decay constant λ, assuming that single-exponential kinetics are observed. In this case, the factor $g(T)$, expressed as a function of the elapsed time T after injection of the radionuclide is obtained by double integration of Eq 3a with exponential decay term included[17,25]:

$$g(T) = \frac{\lambda}{\lambda + \mu}\left\{\frac{1 - 2\frac{\lambda}{\lambda - \mu}e^{-(\lambda+\mu)T} + \frac{\lambda + \mu}{\lambda - \mu}e^{-2\lambda T}}{(1 - e^{-\lambda T})^2}\right\} \quad \textbf{(3b)}$$

Eq 3b reflects the overall effect of Type B damage over the whole selected time period, rather than the instantaneous effect at any instant. For radionuclides with long effective half-lives in comparison with the repair half-time, $g(T)$ becomes very small and the quadratic term in Eq 2 diminishes. With short effective half-lives, $g(T)$ is not negligible, especially in the initial time after injection of a radionuclide and the onset of radiation exposure to various organs.

Within the LQ model, the concept of biologically effective dose (BED) may be used to quantify the magnitude of the biological effect. Calculation of tissue-specific BEDs should make possible the prediction of the impact of different treatment modalities including targeted radiotherapy regimes, based on knowledge derived from the effects of external beam treatments. The BED is considered to be the product of the total dose (D_T) and a biological factor designated as the relative effectiveness per unit dose (RE). The main radiobiologic parameters important in conventional radiotherapy are assumed to be equally relevant for targeted radionuclide therapy. Thus, with temporal variations in dose-rate included, the LQ formulation may be applied to this modality also. For continuous therapy at low dose-rate, late-responding normal-tissue BEDs may be expressed by:

$$\text{BED} = R^*T[(1 + 2R)/(\mu(\alpha/\beta))] \quad \textbf{(4)}$$

where R is the dose-rate, T the elapsed treatment time after administration, and D_T has been expressed as RT[17,15,26]

For continuous therapy with an exponentially decreasing dose-rate BED may be given as:

$$\text{BED} = R_0/\lambda[(1 + R_0)/(\mu + \lambda)(\alpha/\beta)] \quad \textbf{(5)}$$

where R_0 is the initial dose-rate, and λ is the effective rate constant describing the loss of activity (assumed to be exponential) from the organ in question, being the sum of the radioactive decay constant and the organ clearance constant.[15,17] For exponentially decreasing radiation, D_T has been expressed as R_0/λ, which accounts for the complete radionuclide decay where time goes to infinity. Similarly, the exact expression for organ-specific BEDs generated over a specific time interval of irradiation for radionuclide therapy to account for potential cellular repopulation is provided by Fowler and Dale.[15,17]

The LQ model has also been extended to large doses per fraction for application in stereotactic radiation and there are efforts to compare large dose/fraction treatments to the equivalent at conventional fractionation.[27,28] Data suggests tolerance may vary with tissue. For instance, neural tissue may have less tolerance for higher dose per fraction of external beam radiation than other normal tissues, such that the term neuret has been coined.[29] In contrast, the effects of ^{131}I treatment of thyroid cancer may be less than the equivalent dose by standard external beam fractions.[30]

Other biologic effects such as low dose rate and radiation-induced bystander effects are under study.[11,31-34] Bystander effects have been noted in the study of various radiopharmaceuticals, including alpha, beta, and Auger emitters.[35] Radio-

biologic principles that provide further basis for this contribution are reviewed in detail in this issue by A. Kassis.

Toxicity Monitoring

There are accepted standard toxicity scoring criteria that have been applied to various therapeutic agents, including cytotoxic chemotherapy agents, biologics, gene therapy, external beam radiation, and radionuclides. The most common types of toxicity may vary with modality, such as fibrosis associated with radiation and peripheral neuropathy that may result from chemotherapy. Because chemotherapy or other agents (such as biologics or radiation sensitizers/protectors) are frequently used with radiation, it may not be possible to entirely separate side effects of radiation from that of other agents. Unfortunately, the use of various scoring systems adds to the difficulty of comparison between studies. Efforts to improve the capture of adverse events have included 2 conferences sponsored by the International Atomic Energy Agency (IAEA).[36] These conferences found that radiation-induced toxicity tends to be underreported in radiation therapy. More toxicity was found when both physicians and patients assessed outcome, and the length of follow-up was adequate to determine late toxicity. It was confirmed that there was heterogeneity of adverse event reporting between institutions and individual clinicians even when there was an effort to be consistent. The use of various grading systems hampered comparison of results. Thus, although limitations were noted in the National Cancer Inst. Common Terminology Criteria for Adverse Events version 3.0 (CTCAE), the conferences recommended adoption of these criteria for comparison between trials (see http://ctep.info.nih.gov).[37] One of the strengths of the CTCAE is that it allows capture of both acute and late effects. Despite this recommendation, most of the data in this document uses toxicity scoring of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer as that was the scale frequently used to report the data available.[38] As a result of their conferences, IAEA made a number of recommendations, and future directions were proposed for improving the capture of adverse events.[36]

Late effects, even from radiation associated with diagnostic procedures, include induction of malignancy assessed as an increased stochastic risk, not as a graded toxicity. Tools to assist in predicting such risk are available and take into account some known influences such as age and sex.[39,40] The Radiation Dose Assessment Resource, RADAR, at www.doseinfo-radar.com provides links to some potentially valuable aids. Increased risk for multiple organs that receive a low dose of radiation from radionuclide therapy and IMRT is of concern but has not been well quantified.[41] Among the carcinogenic concerns for ^{131}I therapy is myelodysplasia syndrome (MDS), thyroid cancer, colon cancer,[42] and stomach cancer, whereas bone and hematologic malignancies have stronger association with bone-seeking radionuclides. Despite the short-term effects on the menstrual cycle, ^{131}I therapy has not been associated with infertility or birth defects in offspring.[43] Some risk of second malignancy among thyroid cancer patients that is attributed to ^{131}I therapy may be caused by genetic predisposition, and the risk actually decreases for lung and cervix cancer.[44] Although the potential risk of MDS after radionuclide therapy is being studied, development of MDS has also been associated with chemotherapy (especially alkylators) and external beam radiation. For instance, Brown and coworkers report an incidence of second malignancy of 21% by 10 years (10% non-MDS) after cyclophosphamide + total body radiation and autologous bone marrow transplant for non-Hodgkin's lymphoma (NHL).[45] Age was a factor in the increased risk of second malignancy.[45] The influence of previous chemotherapy and/or radiation makes it difficult to quantify any increased risk for myelodysplasia due to radionuclides. It is also noted that some patients have shown evidence of dysplasia before radionuclide therapy.[46] Interaction between the agents may also be a factor as the long-term risk of MDS appears to be less when ^{131}I-anti-CD20 antibody therapy was used initially rather than after several chemotherapies.[47] Age can be a factor in the induction of nonhematologic malignancy as well, as noted in the observed increased incidence of thyroid cancer in children affected by the Chernobyl accident.[40] Other influences such as nutritional status, exposure to carcinogens and individual radiosensitivity have not been included in risk assessments.[30]

Toxicity Reporting and Tolerance Dosing

Whole and Partial Organ Tolerance

In most instances, tolerance information is useful to avoid irreversible organ compromise, whereas in some instances dysfunction is the desired effect, such as ^{131}I for thyroid ablation. The concept of minimal and maximal tissue tolerance dose was introduced by Rubin and Caserett and applied to whole or partial organ volume that received a uniform dose of external beam radiation at conventional high dose rate (>100 cGy/min) daily fractionations of 1.8 to 2Gy.[48] Data were compiled from experience to predict a tissue tolerance dose (TD) that was associated with a 5% rate of complications within 5 years ($TD_{5/5}$) or a maximum tolerance dose, $TD_{50/5}$, which resulted in a 50% complication rate by 5 years. A subsequent tabulation by Emami and coworkers provided $TD_{5/5}$ and $TD_{50/5}$ values for selected complications from radiation of 1/3, and 2/3 as well as the whole organ.[49] These early tables are based on patients being treated with radiation alone, usually after biopsy only or incomplete resection, with the use of fractionated external beam radiation. Also, the partial organ tolerances were based on a segment receiving full dose, whereas the remainder was shielded. This is contrary to current IMRT or stereotactic radiation that delivers a gradient of doses to an organ, with the dose to the entire organ being less than whole organ tolerance but often none of the organ completely spared. Now with differential partial organ volumes and dose volume histograms reported, trends for external beam radiation toxicity assessment are moving beyond simple tables to normal tissue complication proba-

bility (NTCP) calculations. Similar NTCP may be applicable for radionuclides, especially for heterogeneous distribution such as that of microspheres to liver lesions.[50]

NTCP Modeling and Dose/Volume Histogram Analysis

The Lyman NTCP model, which is being used extensively in external beam therapy planning, assumes that the probability of complication after irradiation of a specified volume of an organ at risk follows a sigmoid dose response relationship.[51,52] For expression using this model, $TD_{50}(v)$ designates the 50% tolerance dose for uniform irradiation of v, the fraction of the organ irradiated or the volume relative to some reference volume. The tolerance dose is expressed in a functional form with volume (ie, TD(v)), and the calculation includes a parameter associated with the slope or steepness of the dose-response curve.[51]

NTCP and alpha/beta radiobiologic models are useful for comparing dose/fractionation schedules and assessing complication probability using dose–volume histograms.[51,52] A recent compilation of information about complication probabilities from the era of 3D treatment planning, where fractions of organs receive varying dose levels, has been provided by Milano and coworkers.[53] This provides a more useful tool for current practice than the earlier tables from Emami and coworkers[49] and Rubin and coworkers.[48] Although the database for NTCP is growing for IMRT outcomes, there are a number of caveats.[54,55] Glatstein described the current status as inadequate. His concerns are that the postradiation follow-up is too short to detect the true rate of complications, and NTCP models are mostly neglectful of many other potentially influential factors.[56,57] However, failure to account for potentially influential factors applies to nearly all toxicity scoring systems currently in use. Most systems fail to account for factors such as age, existing medical conditions, genetic variants and other therapies.[56] Even NTCP models generally do not take into account dose rate effects, overall treatment time and the influence of other therapy effects such as chemotherapy, or other sensitizers/protectors. The Random Forests Technique is another statistical tool recently applied for identification of predictors of toxicity and may be especially useful when there are multiple variables in a limited clinical data set.[58] Efforts to improve quantitation and correlation with normal tissue toxicity have resulted in the organization of QUANTEC, a collaborative group sponsored by the American Society for Therapeutic Radiology and Oncology and the American Association of Physicists in Medicine. Models for assessing toxicity of combined modality therapy have also been proposed.[59]

Dose/volume histogram analysis of some radionuclide therapies with heterogeneous distributions, such as ^{90}Y-microsphere treatment of liver lesions, is under study.[50,60,61] As predicted from the NTCP model and noted with external beam experience, this shows that greater doses can be tolerated from heterogeneous distribution than as a uniform dose to the whole organ. Arterial administration of ^{90}Y-microspheres can selectively provide a high dose to liver tumors with much less radiation to normal liver than for a uniform distribution of the ^{90}Y throughout all liver tissue. Normal liver tolerance for this type of selective arterial delivery appears higher than for ^{90}Y-antibody conjugates given intravenously.[62] Although the mechanism for this difference has not been extensively reviewed, it is expected to mainly result from more heterogeneous distribution of microspheres that would provide a relative sparing of much of the normal liver. Study of surgical specimens and dose/volume histogram analysis of heterogeneous distribution has facilitated calculation of microdosimetric dose distributions at selected time points.[50,63] However, changes in the uptake and retention of ^{90}Y over time at the cellular level complicate dosimetry. Potentially dose-limiting radioactivity can also be delivered to portions of the liver by shunting from intralesional radionuclide treatment of pancreas cancer. The liver shunting appeared to be improved by injection of dexamethasone before the radionuclide.[64] This regimen allowed delivery of extremely high doses (up to 17,000 Gy) to pancreas lesions.[64]Results from initially analyzed dose volume histograms for the human liver after ^{90}Y-microsphere therapy were consistent with increased liver radiation tolerance when much of the organ receives less than the mean calculated dose.[60,65] A more recent dose volume histogram analysis showed that only 16% of the liver received the nominal whole liver dose of 110 Gy and the mean normal liver dose was 58 Gy.[50] Because of the parallel nature of the liver, data from stereotactic radiation therapy confirms the elevated partial organ tolerance as with radionuclides, and suggests that the *volume* of liver receiving radiation within tolerance may be more important than the maximum dose to the portion receiving a dose above the usual whole organ tolerance level.[66]

^{90}Y-microsphere therapy has also contributed to knowledge of tolerance in adjacent organs.[67] Dose-limiting radiation pneumonitis has occurred when ^{90}Y-microsphere shunting results in $>$ 30 Gy to lung in a single treatment, and a higher dose with fractionated delivery.[61] The portion of stomach adjacent to the liver has tolerated 60 Gy and the adjacent portion of the right kidney has tolerated 25 Gy.[50]

Another site in which radionuclide therapy can provide a high dose to tumor by restriction of the volume affected is brain. Direct injection into resection cavities or use of a device for contained infusional radionuclide treatment (eg, Gliasite from Proxima Therapeutics, Inc, Alpharetta, GA) has allowed dose escalation while minimizing radiation to normal surrounding brain.[68-70] The Duke University experience shows that 44 Gy to 2 cm beyond the resection margin of the tumor cavity is tolerated with initial dose rate $<$0.4 Gy/h.[70] Additional tolerance data are available from alpha-emitting radiopharmaceuticals.[71] Stereotactic external beam radiation to the brain has shown decreased tolerance with increasing volume.[72,73] As with some other organs such as the kidney, it is known that certain portions of the central nervous system are more radiosensitive than others.[74] For example, with single fraction stereotactic radiation, tolerance of the acoustic nerve is less than that of the facial nerve.[75]

Urinary Tract Toxicity Reported for Radiopharmaceutical Use in Therapy

In most instances, tabulations of normal organ toxicity from radionuclide therapy are less extensive than for external beam, but for the kidney radionuclide therapy has provided significant information about radiation toxicity. Renal toxicity from radionuclide conjugates is under intense investigation because it has caused fatal consequences in a few cases and moderate toxicity in others. This toxicity has occurred with antigenic targeting and small molecular weight radionuclide conjugates, such as those targeting neuroendocrine receptors.[6,76] Analysis from peptide-radionuclide conjugate therapy has shown prolonged exposure to the proximal tubules and that radiation tolerance of subunits of the kidney varies.[77] Renal toxicity has decreased as infusion of amino acids has reduced kidney uptake, resulting in less radiation dose to the kidneys.[6,78] Six new age-dependent Medical Internal Radiation Dose models are available that allow for radionuclide dose calculation for subregions of the kidney to aid in further defining subregion tolerance.[79-82]

Valkema and coworkers note that other factors such as age, hypertension, and diabetes may also be influential in inducing renal toxicity after peptide-radioconjugate therapy. The radionuclide emission energy appears also to be a factor as the median decline in creatinine clearance was 7.3% per year in patients treated with ^{90}Y-DOTATOC versus 3.8% per year with ^{177}Lu -DOTATATE.[83] In an analysis from the same clinical group using patient specific dosimetry that accounted for kidney volume and dose rate effects in predicting renal toxicity from ^{90}Y-DOTATOC, Barone and coworkers found that all patients who had creatinine clearance loss $>$ 20% per year received a BED $>$ 45.[84] With a different radionuclide therapy using ^{166}Ho-DOTMP to eradicate myeloma cells in the marrow, unexpected thrombotic-mircoangiopathic nephropathy was noted in a group of patients receiving 17 to 166 GBq.[85] The etiology may have been multifactorial because toxicity did not correlate well with dose. Histologic changes could not be distinguished from radiation nephritis. Although not tested in these patients, genetic variants and other factors are associated with increased risk of a thrombotic-hemolytic uremic syndrome.[86]

Bladder toxicity, including hemorrhagic cystitis, was also noted in the ^{166}Ho-DOTMP study. This occurred in patients who did not receive continuous bladder irrigation and had a surface dose $>$40 Gy. The investigators found that bladder irrigation reduced the bladder wall dose by two-thirds.[85]

Uncertainties Associated With Reported Doses and Relation to Outcomes

Although toxicity from radionuclide therapy has not always been graded similarly to that for external beam irradiation, some comparisons are tabulated in Table 1.[87-120] O'Donoghue previously reviewed the relevance of external beam dose-response to kidney toxicity that has been associated with radionuclide therapy.[121] In assessing the radionuclide tolerances, note that doses are those reported from predominantly beta emitters without regard to dosimetry methods, which varied more than dose quantization for external beam radiation. Dose calculations for radionuclides vary in assumptions and techniques used, such as measured organ volumes versus phantom models, use of attenuation correction, and background subtraction. Brill and coworkers have recently reviewed uncertainties associated with normal organ radionuclide dosimetry.[30]

Dose estimates for radionuclide therapy are often predicted from tracer studies in which a small dose of the radionuclide agent or a surrogate is studied. Even trials that repeated dosimetry evaluations with the therapeutic administration after tracer studies show a range from very small to $>$30% change. At least part of this variation likely represents uncertainties of calculation in addition to the possibility of patient changes.[122-126] An additional potential for error is introduced when the tracer agent is not identical to the therapeutic agent and thus may not have the exact distribution and pharmacokinetics. Use of the most appropriate model can affect the dosimetry estimates by several fold as illustrated by the small intestine analysis of Fisher and coworkers for an radionuclide antibody conjugate that targeted bowel mucosa.[76,119] As operator experience grows and new techniques are implemented, toxicity considerations also change. For example, in external beam radiation, dose escalation trials for lung cancer exceed the $TD_{5/5}$ but limit the volume of nontumorous lung that receives a potentially toxic dose. V20, the volume of normal lung that receives 20 Gy, was established several years ago as a predictor of toxicity in a defined group of patients.[127] More recently, V60 and other parameters have been reported to be important as well as patient characteristics.[118,128,129] Recent reviews also indicate that pulmonary toxicity may not be detected by all postradiation pulmonary function tests, thus chronic mild toxicity may not be reported.[130] The recent review of stereotactic radiation of Chang and Timmerman provides additional information about partial organ tolerance for high dose per fraction stereotactic radiation.[131]

Biologic considerations also affect the uncertainties for dose/response relationships. In addition to biologic factors already discussed, different genetic alterations resulting from alpha versus gamma radiation, and how these may interplay in combination with other agents, is a relatively new area of study for radionuclide therapy toxicity.[10] Although reported for external beam rather than radionuclides, the analysis of Ho and coworkers demonstrate the influence of genetic variants on late toxicity risk. ATM sequence alterations were associated an increased in risk of Grade 2 to 4 late effects in breast cancer patients who underwent radiation as part of breast conservation therapy. Sequence alterations were found in 51 of 131 patients studied.[132] Of the 51 with sequence alterations 41% had Grade 2 to 4 late toxicity versus 23% among the patients who were not found to have sequence alterations, for an odds ratio of 2.4 (95% confidence interval 1.1–5.2). Fifteen patients were heterozygous for the G $\rightarrow$ A polymorphism at nucleotide 5557 of the ATM protein. Of these 15, 53% had Grade 2 to 4 late effects compared with 27% of patients without this alteration (odds ratio of 3.1, 95% confidence interval 1.1–9.4).

Table 1 Comparison of Normal Organ Radiation Tolerance (Gy) for External Beam and Beta Emitter Radionuclide Therapy*

Organ	External Beam		Radionuclide–Mild or No Toxicity	Radionuclide–Severe Toxicity	Comment/Reference(s)
	$TD_{5/5}$	$TD_{50/5}$			
Brain, 1/3	60	75	9-89, mean = 41 to cavity wall ^{131}I-81C6[87]	111 MBq ^{90}Y to tumor cavity[88]; 440 cumulative → edema[89]; 32-97[90]	After pretargeting < 30 mGy to normal brain[91] 8/24 headache, 1/24 seizure[90] >300 Gy intra-tumor[92]
	infarction, necrosis				
Brain, STRT ≤ 10 cc		12			Gamma knife 12-Gy volume >10 mL increases risk of necrosis[73]
Meninges	54 to <1/3	? >70	Surface = 58 ^{131}I-antibody[93]; Median 33 from 3700 MBq ^{131}I-81C6[94]	Transient aseptic meningitis from 740-2294 MBq after XRT[90] 5920 MBq single, 125 cumulative tolerated[95]	Intrathecal administration, most after external beam radiation
Spinal cord, 5-10 cm	50	70	~17		Intrathecal administration[95]
	infarction, necrosis,‡[96] re-irradiation ↑				
Spinal cord, 80-100%	40-60 <5%	60-70 ≤ 50%			[53]
Thyroid	45	150	3.6 Ibritumomab, package insert; >1000 pt. mean = 2.71 Gy/GBq (range 1.4-6.2)	<150	Synthroid used; % with ↑ TSH continues with time after ^{131}I-anti-CD20 antibody (^{131}I-tositumomab package insert)[97]
	hypothyroidism			62% ↑TSH after 280-785 mCi	^{131}I-anti-B1[98]
Thyroid	Remnant ablation			25 mCi (925 MBq)	May vary with regimen rhTSH[99,100]
Lung, whole	17.5	24.5	25	27.25 Grade 3	No chemotherapy[101]
	acute and chronic pneumonitis				
Lung, 1/3	45	65		30	Microspheres[61]
Small volume	90 tolerated				[118]
Heart wall, 40, 50 pericarditis	45	55	25 ^{90}Y-Ibritumomab with short follow-up	27,[101] cardiopulmonary dose-limiting toxicity	Short FU of ^{90}Y[102]
	<20[53]				
Liver, Whole	30	40	24, ^{90}Y-CC49[62] ≤31 for ^{131}I-anti-B1[98]; ~1.5 ^{186}Re → mild nausea[103]	10.5 + ≥1.2 external beam + chemotherapy[104,105]	Transient ↑ LFT[62,104,105]
	acute and chronic hepatitis				
Liver, 1/3	50	55			[49]
			Antibody conjugate	24, ^{90}Y-CC49	No further escalation as liver toxicity projected to be DLT[62]
			Antibody conjugate	<31, ^{131}I-B1	Tolerated as cardio-pulmonary was DLT[101]
			^{90}Y-microspheres	Theraspheres 150 Gy tolerated	SIR-Spheres have different dosing
			Nonuniform distribution, mean 58 ^{90}Y-spheres[60]		Mild ↑ LFT with ≥ 45 Gy, and some serious toxicity[106]
			^{90}Y-microspheres		Mean liver dose 88 Gy tolerated from 3.5 GBq[107]

Pancreas	≥45		Intra-tumor ^{32}P-MAA, ≤17,000		30 mCi × 2 followed by 60 Gy external beam; some liver shunting[64]
Small Intestine	45 perforation, ulcer, hemorrhage	55	<27, mild < ~60	N/V/D > 60, 68.5-140 → Gr4	? nausea < 27; some prior XRT in patients with diarrhea[76,108,119]
Bowel serosa		? > 55	60§	80 at tumor deposits	Rare adhesions, GI complaints[109,110]
Kidney, whole	23 acute and chronic nephro-sclerosis	28	<21.7	Delayed >21.7 ≤31†[98]	↑ creatinine ≤ 8% of patients[108]
Kidney, 1/3 or 1/2	50	45		21.2-27 cumulative of multiple infusions	>15%/year ↓ creatinine clearance[83]
Kidney, whole				16-34.5, Mean 25.3	Late toxicity in some patients[76]
Bladder, whole	60 contracture	80	<40	>40, ≤157	^{166}Ho→ hemorrhagic cystitis[85]
Ovary, whole, age dependent	3	6-12	~925 MBq ^{131}I		Transient amenorrhea[111]
Testes, whole	1 sterilization	2	>0.85 mGy		Impaired spermatogenesis[112]
Marrow[48]	2.5	4.5	0.06, ^{177}Lu-CC49[113]	0.46-0.81 = MTD ^{177}Lu-CC49 MTD < 1.85 Gy[113] for ^{131}I-CC49	Non-marrow targeting therapy[114]
	ANC Gr 0; 9/10 <0.6 Gy				Not marrow targeted[108]
				~0.13	Much prior therapy, compromised condition[115]
Marrow (L-spine)				4.45 required stem cell infusion	L-spine dosimetry[116]
Mature bone	60	100			
Skin, 10 cm^2	50	65		20-40 Gy	Necrosis[117]

ANC, absolute neutrophil count; CNS, central nervous system; DLT, dose-limiting toxicity; FU, follow-up; GI, gastrointestinal; N/V/D, nausea, vomiting, diarrhea; Gr, Grade; Gy, Gray; LFT, liver function tests; MAA, macro-aggregated albumin, pt, patients; STRT, stereotactic radiation therapy; TSH, thyroid-stimulating hormone; XRT, external beam radiation.

*External beam doses are mainly from Rubin and Casarett, Emami et al. or Milano et al. which represents late effects for 1.8-2 Gy daily fractions and may not be specifically referenced.[48,49,53] Other data sets are specified such as stereotactic radiation therapy, including gamma knife (STRT) which uses large doses per fraction. Pancreas tolerance was not listed in tolerance tables. The pancreas generally tolerates 5000 cGy to whole organ and ≥ 6000 to a lesser volume. Single-dose tolerance is ~2000 cGy. Meninges and bowel serosa have no definite tolerance in prior listing.[49] They are felt to have a higher tolerance than the adjacent tissues such as bowel mucosa and brain.

†One of 29 patients had delayed increased creatinine but dose for that individual patient was not described whereas in other studies dose estimates for each patient affected was noted and some patients received higher doses without apparent toxicity.[83,108]

‡Tolerance for re-irradiation, is increased especially after 6 months.[96]

§There is risk of complications with ^{32}P at ≥ 3000 cGy,[120] but greater doses appear to be tolerated with antibody-targeted radionuclide therapy.

Comparison of External Beam and Radionuclide Organ Toxicities

Despite all the caveats noted in this review that describe differences in methods and factors that affect dose reports, a comparison is made in Table 1 of data for normal tissue tolerance to external beam radiation and that for beta emitter radionuclide therapy. There is growing experience with use of alpha particle therapy in preclinical models and early clinical trials which may be included in future reviews.[133-135] Also, there is limited data on results from human application of Auger emitters which has not been included. An example is therapy with ^{125}I-anti-EGFR antibody, which has been well tolerated to brain tumors even after tolerance dose of external beam radiation.[136] Growing interest in this area is noted from the 6th International Symposium on the Physical, Molecular, Cellular, and Medical Aspects of Auger Processes held in July, 2007.

Conclusion

Some principles can be concluded from data reviewed here and other studies of radionuclide effects on normal tissues:

1. Dose rate affects tolerance.
2. Fractionation increases tolerance of cumulative radionuclide dose.
3. Small doses may have more carcinogenic effects compared with higher doses that may compromise organ function.
4. Heterogeneous distribution affects whole organ tolerance.
5. Subunits of organs such as kidney and central nervous system have different tolerance.
6. Tolerance varies among individuals (with influence of genetic makeup, age, and other therapies).

Future individualization may become possible as gene assays are identified that determine how a person reacts to radiation. In the meantime, prescriptions are set on probability of complication risk based on populations of patients. A useful tool achievable quickly would be a website posting where data could be updated periodically and searched by the most pertinent circumstances. Such a site could be linked to web sites such as www.doseinfo-radar.com and www.ACR.org that have been helpful in assessing carcinogenic risk from diagnostic radionuclide procedures.

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