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Radiation Dosimetry for Radionuclide Therapy

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Abstract

The radionuclide therapy is a protocol for tumor control by administering radionuclides as the cytotoxic agents. Radionuclides concentrated at the site of cancerous lesion are expected to kill the cancerous cells with minimal injury to the normal tissue. The efficacy of every radionuclide treatment can be evaluated by examining the toxicity to the lesion differentiated from that to the normal tissue. Radiation dosimetry is the procedure of quantitating the energy absorbed by target volumes of interest. Dosimetric information plays an indicator of the expected radiation damage and thus the therapeutic efficacy. This paper summarizes the dosimetric aspects in radionuclide therapy in terms of radionuclides of use, radiation dosimetry methodology and considerations for each treatment in practical use.

Radionuclide Classification

The radionuclides employed for radionuclide therapy can be classified according to the range of the major radiation emissions: alpha emitters, short-range beta emitters, medium-range beta emitters, long-range beta emitters and Auger electron emitters. List in Table 1 are the radionuclides of potential use in radionuclide therapy.

The alpha particles having a relatively short range (around 50~90 μ m) traverse up to 10 cell diameters from the point of radioactive decay. The therapeutic potential of alpha emitters lies in the high energy loss within this short track. The high linear energy transfer (or high LET) ranging from 80 to 100 keV/μ m of alpha particles may result in the energy deposition of 1 MeV to the cell nucleus while traversing it. The energy deposition of 1 MeV in the nucleus volume from a single track is considered to be high enough to cause multiple double strand breaks of DNA.

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Table 1. Radionuclides of Potential Use in Radionuclide Therapy.

Alpha	Beta mean range < 200μ m	Beta mean range >200μ m < 1mm	Beta mean range > 1mm	Electron capture / internal conversion
^{211}At	^{33}P	^{47}Sc	^{32}P	^{67}Ga
^{212}Bi(^{212}Pb)	^{121}Sn	^{67}Cu	^{89}Sr	^{71}Ge
^{223}Ra	^{177}Lu	^{77}As	^{90}Y	^{77}Br
	^{191}Os	^{105}Rh	^{114m}In	^{103}Pd
^{225}Ac	^{199}Au	^{111}Ag	^{188}Re	^{119}Sb
		^{131}I		^{123}I
		^{143}Pr		^{125}I
		^{153}Sm		^{131}Cs
		^{161}Tb		^{193m}Pt
		^{186}Re		^{197}Hg

Beta-emitting radionuclides of therapeutic use are classified into three groups according to their range: short-range (less than 200 μ m) beta emitters, medium-range (between 200 μ m and 1 mm) beta emitters and long-range (greater than 1 mm) beta emitters. The short-range beta emitters can be identified by the average energy lower than 200 keV of the beta particles. The range longer than 1 mm corresponds to the beta emitters having the average energy higher than 1 MeV of the beta particles.

Auger electron emitters decay by electron capture or internal conversion. Due to the very short range of Auger electrons, the biological damage to the cancerous cells occurs only if the radioactive decay takes place close to the DNA. The cell killing effect is reduced by more than 100 times when the Auger electron emission occurs around the cell membrane.[1] The therapeutic potential has been assessed for several Auger electron emitters.[2]

The radiation dose distribution around the target tissue is affected by the size of tumor mass and the potential inhomogeneity of uptake of radiopharmaceuticals in relation to the energy or the range in the medium of the radiation emissions considered. The dose distribution in a spherical volume filled with ^{131}I has been described for the sphere size volume ranging from 100 μ m to 4 cm in diameter.[3]

Radiation Dosimetry

The objective of radiation dosimetry is to obtain precise estimates of the magnitude and the spatial distribution pattern of radiation dose delivered to organs or tissues of interest.

Experimental methods

The methods of in vivo dosimetry include the autoradiography, the thermoluminescence dosimetry (TLD) and radiochromic film dosimetry. Autoradiography allows the high-resolution images of radionuclide distribution at the cellular level. The disadvantage of autoradiography is that it reads at only one single time point in a single two-dimensional section of the tumor. The single section image is of no use particularly for long-range beta-emitting sources.[4] The information provided by autoradiography can make the input to the theoretical microdosimetric calculations.

TLD makes the direct measurement of the integrated absorbed dose. The local absorbed dose can be measured by implanting the

micro-TLDs in tissue sections of interest and reading those recovered from tissue sections. The signal loss of TLDs while remaining in vivo limits the preciseness in TLD reading.[5] Also, dosimetric data can not be stored for archival purposes by using the conventional TLD readout procedures.

Radiochromic film dosimetry produces dosimetric data of high spatial resolution in permanent storage.[6] Radiochromic dosimeters color directly not requiring chemical process. Energy transferred from the photons or particulate radiation to the receptive part of the colorless photomonomer molecule initiates color formation through chemical change. The radiochromic dosimeters are insensitive to visible light offering ease of handling and preparation in room light.

Theoretical methods

The theoretical approach includes Monte Carlo simulation[7] and the point kernel integration method.[8] The Monte Carlo simulation requires the information on the physical characteristics of radiation interaction with the medium. The point kernel integration method is based on dose estimates for the combinations of point source and point target volumes. The Monte Carlo simulation tools of popular use in dosimetry for radiation therapy include EGS4[9] and MCNP.[10] The point kernel data for beta emitting radionuclides are available from various sources.[8]

MIRD scheme

The MIRD scheme was introduced by the Medical Internal Radiation Dose (MIRD) Committee of The Society of Nuclear Medicine as a methodology for estimating doses to organs or tissues from internal radionuclides.[11] The MIRD scheme comprises of the following steps: (1) to identify all the source and target organs, (2) to calculate the absorbed dose of target k, D_k, due to the activity in the source organ h

$$D_k = \tilde{A}_h \cdot S_{k \leftarrow h}$$

where $\tilde{A}_h$ is the cumulated activity in *Bq-sec* in the source organ h; $S_{k \leftarrow h}$ is the S-value implying the absorbed dose in *Gy/Bq/sec* of the target organ k due to unit activity in the source organ h.

The cumulated activity $\tilde{A}_h$ in each source organ can be determined by:

(1) performing a tracer study prior to therapy using a radioisotope suitable for gamma-ray imaging,
(2) injecting dual radionuclides for both imaging and therapy,
(3) imaging the bremsstrahlung radiation from beta emitters or
(4) using tomographic imaging (SPECT or PET).

The radionuclide pairs for imaging and therapy include $^{123}I/^{131}I$, $^{124}I/^{131}I$, $^{51}Cr/^{32}P$, $^{85}Sr/^{89}Sr$, $^{64}Cu/^{67}Cu$ and $^{86}Y/^{90}Y$. With ^{131}I as the therapy agent, the radioactive concentrations can be determined by ^{131}I SPECT, ^{123}I SPECT or ^{124}I PET tracer study prior to the therapeutic administration.

The MIRD is the method of choice when the beta-emitters are uniformly distributed in source volumes and the target of interest is relatively large. When small targets (mm in scale) and non-uniform source distributions are involved, the MIRD is less useful. Computer simulation using information from autoradiography and TLD measurements allows better assessment of tumor and normal tissue doses.

Dosimetry Classification

Radiation interaction with the medium and the amount of energy delivered to the medium are controlled by statistics. The consequential radiation dose distribution may be uniform or non-uniform over the whole target volume. The radiation dose data should be presented in a form pertaining to the purpose of their use.

Macrodosimetry

Macrodosimetry is to provide the radiation dose estimate averaged over the target volume. Macrodosimetry is efficient when the dose level is relatively high and thus the energy absorption is uniform over the tatget volume. The application of macrodosimetry includes the estimation of average doses to organs and the whole body. The estimate by macrodosimetry is notated by D.

Microdosimetry

Microdosimetry is to describe the statistical variation in energy delivery to a specific target volume. Dose estimate that varies due to the statistical property of radiation interaction is termed *specific energy z*. Microdosimetry is particularly valuable in assessing the radiation dose distribution for inhomogeneous depositions of short-range emitters. The estimate by microdosimetry is notated by f(z).

Radionuclide Therapy in Practical Use

Iodine therapy of the thyroid

^{131}I has been used in the treatment of thyrotoxicosis[12] and differentiated thyroid cancer.[13] Iodine is a precursor of thyroxin and is taken up in the follicular cells of the thyroid. Table 2 contains the summary of the physical properties of ^{131}I. The range of about 0.6 mm limits the toxic effect to the thyroid sparing the adjacent tissues. Dose calculations for thyrotoxicosis and thyroid cancer treatment requires the following factors be taken into account: (1) accurate measurement of the functioning mass of thyroid, (2) the assessment of the percentage uptake of the administered dose into the gland and (3) the rate of clearance of radioiodine from the gland. The dose contribution of high-energy gamma emissions should be taken into consideration.

Table 2. Physical Properties of ^{131}I

Half-life	8.04 days	
Principal gamma-energies	80 keV	(0.026)*
	284 keV	(0.054)
	364 keV	(0.820)
	637 keV	(0.026)
	723 MeV	(0.068)
Principal beta E_{max}	0.61 MeV	(0.016)

* yield

Treatment by local injection of radiopharmaceuticals

Direct intravascular, intracavitary or intralesional injection of radiopharmaceuticals into inflammatory sites creates the differential concentrations of radioactivity between tumor or cavity fluid and the surrounding normal tissue, which results in the effective treatment while with minimal radiation damage to the normal tissue.

- Intracystic injection

Some intracerebral tumors are characterized by a cystic component. Neurosurgery is not the treatment of choice for theses tumors due to high morbidity and mortality afterwards. The efficacy of fluid aspiration is declined by rapid reaccumulation of fluid. Intracystic injection of

the radiolabelled colloids can be chosen as an alternative, enabling high radiation energy delivery to the tumor with minimum systemic resorption. ^{186}Re and ^{32}P have been used to ablate the epithelial lining of the cyst preventing fluid reaccumulation.[14,15] The absorbed dose to the epithelial lining of the cyst is contributed by the radiocolloids both uniformly-dispersed in the fluid and adhered to the cyst wall. In the preliminary dosimetry study with ^{166}Ho, the relative significance in terms of dose contribution to the cyst wall is described.[16]

- Intraperitoneal injection

Intraperitoneal instillation of radiolabelled pharmaceuticals has been performed as adjuvant therapy in patients with ovarian carcinoma to prevent tumor expansion. Direct injection into serous cavity of patients with malignant effusion is to control the effusion and to kill malignant cells or cell clusters. Slow egress from the cavity and rapid systemic clearance are the requisites for ideal radiopharmaceuticals. The estimated doses to the peritoneum are informed for ^{32}P colloid[17] and for ^{166}Ho-chitosan.[18]

- Intraarterial injection

Treatment of hepatic tumors by direct injection of radiopharmaceuticals into the hepatic artery is rationalized by the fact that the most vascular supply of hepatic tumors derives from the hepatic artery (~95 %) while the normal liver is supplied by the portal venous system (~70 %). The intraarterial injection of ^{131}I-labelled lipidol has been observed to be valuable for the treatment of small tumors (< 5 cm in diameter).[19] Intraarterial injection of microspheres labelled with ^{90}Y also has shown some evidence of prolongation of survival.[20] Dosimetric aspects in applying ^{166}Ho-chitosan to the treatment of hepatic tumors have been compared for by intraarterial injection and direct point injection.[21]

Treatment with non-injected sources

Radiation treatment of the abnormality characterized by uncontrolled cell proliferation can be accomplished not only by local injection of the radiopharmaceuticals into the treatment site but also by having radiation sources just contact the treatment site. Restenosis control after percutaneous transluminal coronary angioplasty by using radioactive stent or radionuclide-filled balloon and skin cancer treatment using radioactive patch are the latter cases. Their therapeutic efficacy in clinical applications has been studied in relation to the dosimetric aspect.[22-24]

Radioimmunotherapy (RIT)

Monoclonal antibodies or their fragments have the capacity to locate tumoral antigens. Labelled with radionuclides emitting non-penetrating radiation, these antibodies can deliver radiation energy to the tumor cells within a distance corresponding to the maximum range of the radiation emissions. Radioimmunotherapy (RIT) has its rationale on this. Biodistribution studies have shown that the tumor uptake values are lower than 0.02% injected dose per gram by systemic injection of radiolabelled antibodies into patients with bulky tumors.[25] Therefore, bulky tumors are not suitable targets for RIT. The tumoricidal effect of RIT is enhanced with small or microscopic tumors since small tumors are less necrotic and more accessible by radiopharmaceutical agents. The most practical assumption in geometrical modelling for dosimetry relates to monoclonal antibodies being attached to the cell membrane. RIT, a targeted radiation therapy modality, strongly calls for the microdosimetric approach in dose assessment.[26]

Table 3. Comparison of the Tumoricidal Absorbed Doses in Radioimmunotherapy and External Beam Therapy.[27]

	(10^9 cells) 1 cm	(10^6 cells) 1 mm	(10^3 cells) micrometastasis
External beam radiotherapy	60~70	40~47	20~23
Radiommunotherapy	72~84	48~56	24~28

An important factor in radionuclide therapy is the low dose rate administered as compared to the external beam therapy. In order to compensate for the repair of sublethal damage in low dose-rate treatment, a higher total dose should be prescribed in radionuclide therapy to produce the same effect as the external beam therapy (see Table 3).

Other Dosimetric Considerations in Radionuclide Therapy

Radiation toxicity to the non-target organs and tissues

No radiopharmaceutical is entirely tissue specific and some portion of administered radiopharmaceuticals concentrate in other parts of the body. The organs of concern with relatively high concentration of radiopharmaceuticals include the liver, thyroid and the urinary tract. The normal tissue lying adjacent to the treatment site is at risk as well. The radiation damage to these non-target tissues is enhanced with long-lived radiopharmaceuticals or with free radionuclides released into the circulation. The use of radiopharmaceuticals for therapeutic purpose should be justified by the non-target organs and tissues whose radiation damage is kept below tolerance level.

Dosimetry for dose-limiting organ

The dose prescription for tumors is limited by the maximum dose that can be tolerated by normal tissues. The dose-limiting organ in radionuclide therapy varies depending on the route of administration and the radiopharmaceutical of use. In systemic radionuclide treatment, the bone marrow is the most possible dose-limiting organ. The assumptions recommended to be made for estimation of the absorbed dose to red bone marrow from non-specific uptake of radiolabelled antibodies include:

(1) the specific activity in the marrow is one-third of that in the blood;
(2) the clearance of activity from the bone marrow is equal to that from the blood;
(3) the activity distribution in the marrow is uniform.

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