BASICS OF RADIOPHARMACEUTICAL THERAPY

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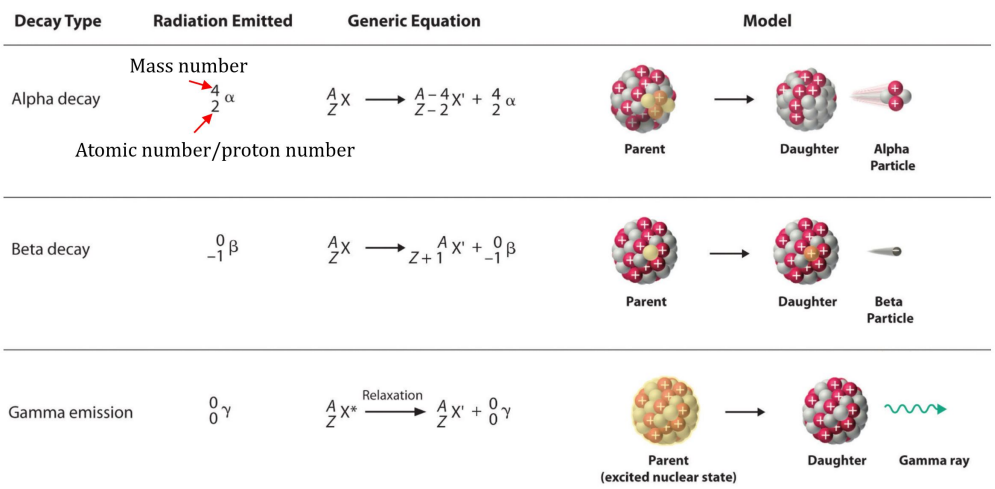


Figure 1: Modes of radioactive decay (Images were obtained from [3])

1 Modes of Radioactive Decay for Radiopharmaceutical Therapy

Radiopharmaceutical therapy (RPT) relies on the delivery of radioactive atoms to tumor-associated targets. Radionuclides with different emission properties, primarily β and α particles are used to deliver radiation, and they are described in the following subsections.

1.1 Decay by α Emission

In decay be α-particle emission, the nucleus ejects an α-particle, which consists of two neutrons and two protons (as shown in the top panel of Fig. 1). The α-particle is essentially a helium ion (or helium nuclei). Depending on the emission energy, an α-particle can travel 0.05-0.1 mm in tissue. It is positively charged and is orders of magnitude larger than an electron. The amount of energy deposited per path length traveled (i.e., linear energy transfer (LET)) is approximately 400 times more than that of an electron, which leads to substantially more damage along their path than that caused by electrons [1]. An α-particle track leads to largely irreparable DNA double-strand breaks. Therefore, α-particles are highly potent, combined with their short traveling range (which *reduces normal organ toxicity*), they have led to substantially increased interest in developing α-particle-emitting RPT agents [1].

$$\beta \text{ decay:} \quad {}^{A}_{Z}X \xrightarrow{\alpha} {}^{A-4}_{Z-2}Y \tag{1}$$

1.2 Decay by β^- And (β^-, γ) Emission

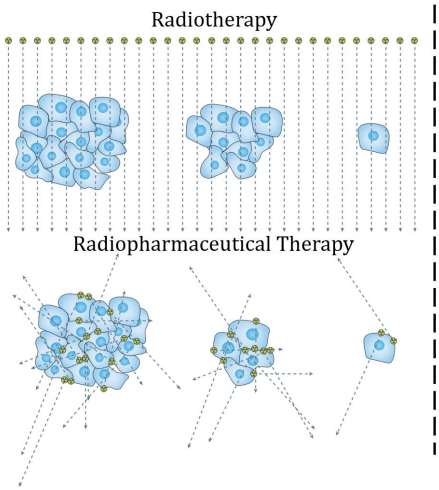
β-particles are electrons emitted from the nucleus (as shown in the middle panel of Fig. 1). They can travel a longer range in tissue than α particles (typically 1-5mm in tissue). In some causes, decay by β^- emission results in a daughter nucleus that is in a metastable state. This daughter nucleus promptly decays to a more stable nuclear arrangement by the emission of a γ ray [2].

$$\begin{aligned} \beta \text{ decay:} \quad & {}^{A}_{Z}X \xrightarrow{\beta^-} {}^{A}_{Z+1}Y \\ \beta, \gamma \text{ decay:} \quad & {}^{A}_{Z}X \xrightarrow{\beta^-} {}^{A}_{Z+1}Y^* \xrightarrow{\gamma} {}^{A}_{Z+1}Y \end{aligned} \tag{2}$$

2 Concepts of Radiopharmaceutical Therapy

2.1 Pharmacokinetic And Biodistribution

There are two important concepts in RPT, namely the pharmacokinetics and biodistribution of an RPT agent inside the patient body. Their definitions are:



Radionuclide	Therapeutic emission	Approximate emission range in tissue (mm)	Radionuclide half-life
Yttrium-90	β^-	5.30	64.1 hours
Iodine-131	β^-	0.8	8.0 days
Samarium-153	β^-	0.4	46.5 hours
Lutetium-177	β^-	0.62	6.6 days
Astatine-211	α	0.05	7.2 hours
Lead-212/bismuth-212	β^-/α	<0.1/0.05	10.6 hours/1.0 hours
Radium-223	α	0.05–0.08	11.4 days
Actinium-225	α	0.05–0.08	10.0 days
Thorium-227	α	0.05–0.08	18.7 days

Figure 2: Left: RPT vs radiotherapy. Right: Radionuclide properties. (Images were obtained from [1])

- **Pharmacokinetics** is described as what the body does to a drug, refers to the movement of the drug into, through, and out of the body—the time course of its absorption, bioavailability, distribution, metabolism, and excretion [4].
- **Biodistribution** is a method of tracking where compounds of interest travel in an experimental animal or human subject [5].

They describe the movement of an RPT agent inside the human body. RPT agents emit α- and β-particles that are highly cytotoxic, meaning that they can cause nonrepairable double-strand DNA breaks, which leads to cell death. While the cytotoxicity of RPT agents is desired for killing cancerous cells, RPT agents cause damage to normal cells. Therefore, the pharmacokinetics and biodistribution of the RPT agents are very important. Ideally, RPT agents should be highly localized to tumor regions, where the absorbed dose for the tumor should be maximized while retaining a minimal normal organ absorbed dose.

2.2 Emission Range in Tissue

Unlike radiotherapy, for which the radiation particles or photons have to hit normal tissue to get to tumors, radiations emitted from RPT agents are localized to tumor regions (as shown in the left panel of Fig. 2). In order to be localized, the distance a particle can travel should be limited. As described in the previous section, radiation photons (e.g., x-ray and γ-ray) can travel 140-380mm in tissue, which is not suitable for localized delivery of cytotoxic radiation. Whereas α-particles travel 0.05-0.1mm in tissue and β-particles travel 1-5mm. Therefore, RPT agents are predominantly developed based on α- and β- particles, owing to the strong ionizing power and the short range of these particles. The size of the tumor or the tissue mass to be treated should be matched with the appropriate, effective radiation range.

β-particle Radionuclides emitting beta particles are effective for large tumors owing to their large millimeter range and crossfire. However, they are less effective in treating smaller metastatic tumors due to the deposition of a larger fraction of the particle energy outside the tumor volume.

α-particle On the other hand, α-particles have a shorter travel path. Therefore, they are effective for small tumors, small metastases, and micrometastases.

2.3 Natural Affinity

The radioactive compounds of RPT agents travel to cancer cells by natural affinity (i.e., RPT agents are concentrated in tissue through natural physiological mechanisms). For example, radioiodine (a β-particle emitter, as shown in the right panel of Fig. 2) has been used to treat metastatic differentiated thyroid cancer (DTC) because iodine naturally accumulates in thyroid cells for thyroid hormone production and metastases of DTC retain the ability to concentrate iodine [6]. The radioiodine is then able to kill nearby cancer cells by β-particle irradiation. Another example is radium 223 dichloride (Xofigo), which was approved in 2013 to treat metastatic prostate cancer. When cancer cells grow in

Decay	Particles (#)[a]	$E_{(min)}$–$E_{(max)}$	Range	LET (KeV/μm)
α^{++}-particle	He nuclei (1)	5–9 MeV[b]	40–100 μm	~80
β^{-}-particle	Energetic electrons (1)	50–2300 keV[c]	0.05–12 mm	~0.2
EC/IC	Nonenergetic electrons (5–30)	eV–keV[b]	2–500 nm	~4–26

[a]Number of particles emitted per decaying atom
[b]Monoenergetic
[c]Average (>1 % intensity); continuous distribution of energy

Figure 3: General characteristics of therapeutic radionuclides. (Table was obtained from [9])

the bone, they cause the bone tissue to break down. The body then attempts to repair this damage by replacing that bone — a process called bone turnover [7]. The radioactive element radium is chemically similar to calcium in being a bone-seeking element in areas of active bone remodeling (i.e., bone turnover) - where the metastasis are growing. The radioactive radium localized to bone lesion regions and kill nearby cancer cells by α-particle irradiation.

2.4 Linear Energy Transfer

Particles released from radionuclide deposit their energy to nearby tissues. This process damages the DNA of nearby cancer cells (and normal cells). Moreover, when a cell's DNA is irreparably damaged, that cell dies. The amount of energy deposited per path length traveled is known as linear energy transfer (LET). LET of α-particles is approximately 400 times greater than that of electrons (i.e., β-particles) (as shown in the table of Fig. 3). This leads to more damage along the path of α-particles than that caused by electrons [1]. Radiation can possess either high linear energy transfer or low linear energy transfer. The spectrum of LET can be relatively broad and does not necessarily follow a Gaussian distribution (normal distribution) [8].

2.5 Radionuclide Decay And Half-life

The half-life of a radionuclide should be well matched to the biolocalization of a radiolabeled compound (e.g., radium-223 can be localized within 10 minutes in bone [10]). If the half-life is too short, the activity of the radionuclide decreases before the radiolabeled compound reaches and has sufficient residence time at the target site. On the other hand, a long residence time could cause unnecessary radiation dose to normal tissue. The decay product of a radionuclide should be stable (i.e., non-radioactive).

2.6 Gamma Photon Emission

Emission of gamma rays is useful to visualize targeted uptake, biokinetics, and monitor response to therapy. However, gamma rays contribute to the whole-body radiation burden of the patient without significantly damaging the target (i.e., tumor) [9].

3 Dosimetry

3.1 Mean Absorbed Dose

Response and toxicity prediction are very important for the rational implementation of cancer therapy. The biological effects of RPT are described by the absorbed dose (D). Dosimetry analysis is performed by calculating tumor versus normal organ absorbed dose, and the likelihood of treatment success [1]. In *diagnostic imaging*, dose prediction is used for estimating the risk of cancer. Whereas, in *RPT*, dose prediction estimates the efficacy and toxicity of an RPT treatment. In general, the absorbed dose for a target region r_T from the total number of radionuclide decays (i.e., radio-activity), $\tilde{A}(r_S)$ that have occurred in the source region r_S is given by:

$$D(r_T \leftarrow r_S) = \tilde{A}(r_S) S(r_T \leftarrow r_S), \tag{3}$$

where

$$\tilde{A}(r_S) = \int_0^\infty A(r_S, t) dt \tag{4}$$

is the time-integrated activity (TIA). The activity in the source region at time t (i.e., $A(r_S, t)$) is given by: $A(r_S, t) = A_0 \times f_S \times e^{-\lambda_e \times t}$, where A_0 is the injected activity, f_S is fraction in the source region, λ_e is the clearance rate that is

TABLE 2. Recommended Tissue-Weighting Factors

Tissue	w_T	$\sum_T w_T$
Active bone marrow, colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, esophagus, liver, thyroid	0.04	0.16
Endosteal tissues, brain, salivary glands, skin	0.01	0.04
Total		1.00

*Remainder tissues are adrenal glands, extrathoracic airways, gallbladder, heart, kidneys, lymphatic nodes, skeletal muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, and uterus/cervix (♀). Data are taken from ICRP publication 103 (8).

Figure 4: Tissue-weighting factors. (Table was obtained from [11])

the sum of the biological clearance rate and the physical decay rate of the radionuclide (i.e., $\lambda_e = \lambda_B + \lambda_P$). Finally, $S(r_T \leftarrow r_S)$ is the absorbed dose per TIA:

$$S(r_T \leftarrow r_S) = \frac{\sum_i \Delta_i \times \phi(r_T \leftarrow r_S)}{M(r_S)}, \tag{5}$$

where Δ denotes the total emitted energy in the target region per unit disintegration in the source region, $\phi(r_T \leftarrow r_S)$ denotes the fraction of the enrgy emitted from a source region that is absorbed in the target region, $M(r_S)$ is the mass of the target. Finally, the absorbed dose from each source region is summed to give the total absorbed dose:

$$\begin{aligned} \dot{D}(r_T, t) &= \tilde{A}(r_{S_1})S(r_T \leftarrow r_{S_1}) + \tilde{A}(r_{S_2})S(r_T \leftarrow r_{S_2}) + \tilde{A}(r_{S_3})S(r_T \leftarrow r_{S_3}) + ... \\ &= \sum_{r_S} \tilde{A}(r_S)S(r_T \leftarrow r_S). \end{aligned} \tag{6}$$

3.2 Equivalent Dose

The equivalent dose is a radiation protection quantity used to relate absorbed dose to the probability of stochastic health effects (risk of getting cancer) in a population exposed to radionuclides or radiation fields, which include a mixture of radiation particle types of varying linear energy transfer (LET) [11]. The equivalent dose $H(r_T)$ is defined as:

$$\begin{aligned} H(r_T) &= \sum_R w_R D_R(r_T) \\ &= \tilde{A}(r_S) \sum_R w_R \frac{\sum_i \Delta_i \times \phi(r_T \leftarrow r_S, E_R)}{M(r_S)} \\ &= \tilde{A}(r_S) \sum_R w_R \frac{\sum_i E_{R,i} Y_{R,i} \times \phi(r_T \leftarrow r_S, E_R)}{M(r_S)}, \end{aligned} \tag{7}$$

where $E_{R,i}$ and $Y_{R,i}$ are the energy and yield of radiation type R and i^{th} nuclear transitions, and w_R is the radiation-weighting factor for radiation type R. w_R is obtained based on the relative biological effectiveness (RBE) of the radiation type R. RBE is calculated as:

$$\text{RBE} = \frac{\text{Dose of 250 kVp X-rays for } \textit{observed biological effect}}{\text{Dose of test radiation for the } \textit{same biological effect}}. \tag{8}$$

The values of w_R are 1.0 for photons, electrons, positrons, and β-particles and 20 for α-particles.

The equivalent dose, given as the product of the absorbed dose and w_R values, is reserved for use in risk assessment associated only with radiation-induced stochastic effects [11].

3.3 Effective Dose

The effective dose is another radiation protection quantity for establishing annual limits of exposure to workers and members of the general public [11]. This quantity takes into account radionuclide sources that contribute to low-dose

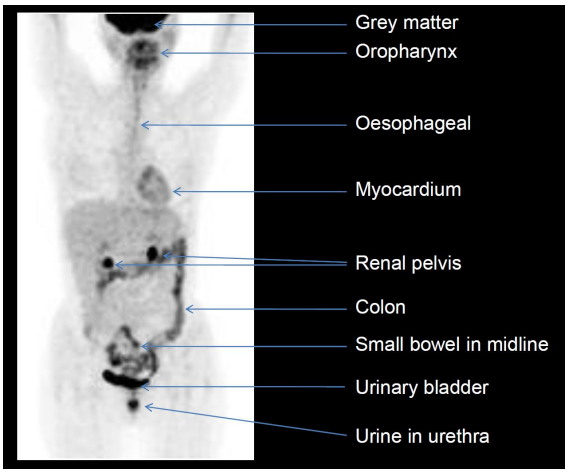


Figure 5: Normal distribution of FDG. (Image was obtained from [12])

irradiation of tissues and organs:

$$\begin{aligned} E &= \sum_T w_T H(r_T) = \sum_T w_T \sum_R w_R D_R(r_T) \\ &= \sum_T w_T \sum_R w_R \frac{\sum_i E_{R,i} Y_{R,i} \times \phi(r_T \leftarrow r_S, E_R)}{M(r_S)}. \end{aligned} \tag{9}$$

where w_T is a tissue-weighting factor which reflects the total harm to health (given in the table of Fig. 4).

The effective dose is an appropriate quantity for assessing stochastic risk as delivered in diagnostic exposures to populations of patients whose age and sex distribution do not significantly differ from those considered in the derivation of w_T.

3.4 Stochastic Effects

For diagnostic nuclear medicine procedures, radiation-absorbed doses to tissues of the patient are relatively low, and the resulting stochastic risk of cancer is correspondingly low. In therapeutic nuclear medicine, however, absorbed doses to normal tissues can be high and can result in both an increased stochastic risk of cancer and the induction of deterministic effects such as hematologic toxicity, renal failure, gastrointestinal tract toxicity, or lung fibrosis [11].

4 Questions

4.1 Why cannot F-18-FDG be used for radiopharmaceutical therapy?

4.1.1 Dosage for RPT

Generally, the dose of radiopharmaceutical used for RPT is often much higher than that used for diagnostic imaging. For instance, the injected activity of radioiodine for treating differentiated thyroid cancer can be 3000 to 35000 MBq [13]. However, in PET diagnostic imaging, the recommended activity of ^{18}F-FDG for imaging an adult is within the range of 185 to 379 MBq [14]. If FDG is used for RPT, the injected activity needs to be increased, which leads to a higher absorbed dose than that for radioiodine to the patient. Because an ^{18}F decay emits a positron and *two* high energy gamma photons, whereas a radioiodine decay emits a β-particle and *one* gamma photon. Assuming the injected activities for FDG and radioiodine are the same, the extra gamma photon from a ^{18}F decay may[1] contribute to an increased irradiation to normal tissues.

[1]The energy of the two gamma photons from a ^{18}F decay are 511 keV, which is higher than 364 keV (i.e., the energy of the gamma photon from a ^{131}I decay). Therefore, photons from ^{18}F decay have a high probability of escaping from the patient body, which may not increase the absorbed dose of normal tissues.

4.1.2 Calculation of Approximated Dose

Radioactive Decay Law The average decay rate of N radioactive atoms of a certain radionuclide is given by:

$$\frac{\Delta N}{\Delta t} = -\lambda N = A(Bq), \tag{10}$$

where $\lambda = \frac{\ln 2}{T_{1/2}}$ is the decay constant, and A represents the activity (disintegrations per second or dps). The exact mathematical expression for the number of atoms at time point t can be obtained by integrating equation above:

$$\begin{aligned} \frac{\Delta N}{\Delta t} = -\lambda \Rightarrow \frac{\Delta N}{N} = -\lambda \Delta t \Rightarrow \frac{dN}{N} = -\lambda dt \\ \int_{N_0}^{N_t} \frac{dN}{N} = \int_0^t -\lambda dt' \Rightarrow \ln N_t - \ln N_0 = -\lambda t \Rightarrow \ln N_t = \ln N_0 - \lambda t \\ N_t = N_0 e^{-\lambda t}. \end{aligned} \tag{11}$$

Approximated Dose As described in 4.1.1, the injected activity of radioiodine for treating DTC can be about 35000 MBq (or 35 GBq). Assuming that the biodistributions of ^{18}F-FDG and radioiodine are similar, the total number of atoms (i.e., N) of them needs to be matched for treating DTC:

$$\begin{aligned} \frac{A_{^{18}F}}{A_{^{131}I}} &= \frac{\lambda_{^{18}F} N_{^{18}F}}{\lambda_{^{131}I} N_{^{131}I}} \qquad \text{we let } N_{^{18}F} = N_{^{131}I} \\ A_{^{18}F} &= \frac{\lambda_{^{18}F}}{\lambda_{^{131}I}} A_{^{131}I} = \frac{\ln 2/T_{1/2}^{F-18}}{\ln 2/T_{1/2}^{I-131}} A_{^{131}I} = \frac{T_{1/2}^{I-131}}{T_{1/2}^{F-18}} A_{^{131}I} \\ A_{^{18}F} &= \frac{T_{1/2}^{I-131}}{T_{1/2}^{F-18}} A_{^{131}I} = \frac{24 \text{ hrs} \times 8.0197 \text{ days}}{1.83 \text{ hrs}} \times 35000 \text{ MBq} \\ &= 3681173.77 \text{ MBq} = 99.49 \text{ Ci} \end{aligned} \tag{12}$$

Assuming β-particle and positron have the same travel range, we still need to compensate the activity of $A_{^{18}F}$ by the difference in energy of the emitted particles. The postrition emission of ^{18}F-FDG has an energy of 249.8 keV, and the β emission of ^{131}I has an energy of 606 keV, thus, their ratio is $\frac{606}{249.8} = 2.426$. The final activity is:

$$\begin{aligned} A_{^{18}F} &= \frac{24 \text{ hrs} \times 8.0197 \text{ days}}{1.83 \text{ hrs}} \times 35000 \text{ MBq} \times \frac{606 \text{ keV}}{249.8 \text{ keV}} \\ &= 3681173.77 \text{ MBq} \times 2.426 = 8930527.56 \text{ MBq} = 241.36 \text{ Ci} \end{aligned} \tag{13}$$

If we assume the decay of the radioisotopes emits a single β-particle or positron, the absorbed dose of bladder and brain to the patient would be (using the information from the table in Fig. 6):

$$\begin{aligned} D_{bladder} &= 8930527.56 \text{ MBq} \times 0.13 \text{ mGy/MBq} = 1160968 \text{ mGy} \\ D_{brain} &= 8930527.56 \text{ MBq} \times 0.038 \text{ mGy/MBq} = 339360 \text{ mGy} \\ D_{liver} &= 8930527.56 \text{ MBq} \times 0.021 \text{ mGy/MBq} = 187541 \text{ mGy} \\ D_{heart\ wall} &= 8930527.56 \text{ MBq} \times 0.067 \text{ mGy/MBq} = 598345 \text{ mGy} \end{aligned} \tag{14}$$

These values are too high, leading to severe damage to normal tissues.

4.1.3 Biodistribution

The tumor to non-tumor absorbed dose ratio is low for ^{18}F-FDG because this radiopharmaceutical is not localized to cancer tissues. ^{18}F-FDG is a glucose analogue taken up by cells (both benign and malignant) according to the glycolytic rate (Warburg effect) and as a result of the expression of cellular membrane glucose transporters and enhanced hexokinase enzymatic activity in both cancer tissue cells and normal proliferating cells [15]. While cancer cells take up more FDG, ^{18}F uptake distributes not only in cancer tissue but also in normal and benign tissue, such as brain, myocardium, and bladder (as shown in Fig. 5), leading to a small f_S (i.e., the fraction of the activity in the cancer tissue). As mentioned in section 2.1, electron radiation can cause irreparable damage to a cell's DNA. Therefore, the positron and gamma photon radiation from ^{18}F contribute to unnecessary irradiation to normal tissue, leading to an increment of normal tissue dose, thus, decreasing the tumor to non-tumor absorbed dose ratio. If we consider the

case in treating DTC (assuming the tumor is located in the thyroid) with RPT, in which it is desirable to concentrate (or localize) the radioactivity to the thyroid region in order to maximize the tumor versus non-tumor absorbed dose. However, as shown in Appendix A, the percentage of the absorbed dose of thyroid for ^{18}F is very small, where the main absorbed dose is deposited in the bladder. Whereas the absorbed dose for ^{131}I is primarily concentrated in the thyroid, making it more suitable for treating thyroid cancer.

It is also worth mentioning that the irradiation to normal tissue can also cause a long-term effect - an increased effective dose - that increases the probability for the patient to get harmful diseases.

4.1.4 Half-life And Pharmacokinetic

The half-life of 1.83 hours of ^{1}8F may be too short for an effective RPT, and the reasons are described in the following paragraphs.

Biologically effective dose (BED) is a quantitative assessment of the tissue-specific biological effects that accounts for dose rate variations. For continuous therapy with an exponentially decreasing dose rate, its BED is given by [16]:

$$BED = \frac{R_0}{\lambda}[1 + \frac{R_0}{(\mu + \lambda)(\alpha/\beta)}], \tag{15}$$

where α and β are tissue specific coefficients for radiation damage, μ is the repair constant, and λ is the decay factor for activity ($\lambda = \frac{0.693}{T_{1/2}}$). The half-lives for ^{131}I and ^{1}8F are, respectively, 8 days and 2 hours, therefore the decay factor, λ, for ^{131}I is much smaller than that for ^{18}F, resulting in a larger BED for ^{131}I compared with that for ^{18}F. In order for ^{131}F to achieve the same biological effects (i.e, cytotoxicity) to cancer tissues as ^{131}I, the only way is to increase the dose (or dose-rate, R_0). However, for the reasons described in section 4.1.3, an increased ^{18}F dose contributes to more damage to normal tissue, which is highly undesirable.

Another reason is related to the pharmacokinetics of ^{18}F relative to its half-life. For diagnostic PET imaging, the recommended interval between FDG administration and the start of scanning is 50 to 75 minutes [17], which implies that it requires 50-75 minutes for FDG to get to target tissues. This interval is too high compared with its 2-hour half-life, where the radioactivity deposits most of its energy (or dose) before it reaches the target tissue (e.g., cancer tissue). Other radiopharmaceuticals, such as Radium 223 (half-life of 11 days) and Iodine 131 (half-life of 8 days), localize to target tissue in about 10 and 60 minutes [10, 18], respectively, which are very short compared with their half-lives.

4.2 Which specifics aspects would you ask nature to change so that FDG were as effective in treating all cancers as radioiodine is in treating thyroid cancer?

Biodistribution - Since FDG is taken up by both cancer and normal cells, the biodistribution of FDG is suboptimal for its application in RPT. One thing if nature could change is the biodistribution of FDG. If only the cancer cells take up glucose, the ^{18}F-FDG would be highly localized to cancer tissue, making it suitable for treating all types of cancer.

Pharmacokinetics - The pharmacokinetics of ^{18}F-FDG is also suboptimal. It takes about two-thirds of its half-life to get to the target tissue. Thus, a large amount of its energy is lost on the way. Things, if nature could change, are the pharmacokinetics of FDG or the half-life of ^{18}F. Making the localization process faster or the half-life longer would concentrate the absorbed dose to target tissue (e.g., cancer tissue) better, leading to the increased tumor versus non-tumor absorbed dose.

4.3 Why is radioiodine so effective at treating thyroid cancer?

Thyroid tissue has the ability to take up iodine from the blood. Thyroid cells trap iodine to generate thyroid hormones based on their membrane sodium-iodide transporter. Like iodine, radioiodine is also taken up by thyroid cells and concentrated in thyroid cells, where the β-radiation emitted from radioiodine can destroy the thyroid cells, including the cancer cells that take up iodine. Thyroid cancer metastases retain this ability to concentrate iodine. Because of this, radioiodine can also be used to treat metastases of thyroid cancer.

4.4 What makes the radioiodine beta-particle emitter so effective for metastatic thyroid cancer?

Radioiodine for thyroid RPT is an unconjugated RPT (i.e., does not depend on the conjugated or tumor-targeting agent). This RPT uses the biology the fact that metastases of thyroid cancer retain the ability to trap iodine for producing thyroid hormones. The advantages of this radiopharmaceutical for metastatic thyroid cancer are two-fold:

1. **Biodistribution** - Thyroid tissues (both cancer and normal tissues) and the metastases of DTC have the ability to trap iodine from the blood. Because of this, 70–80% of iodine in a healthy adult is in the thyroid [19]. Radioiodine is taken up by thyroid cancer cells (in both main tumor and metastases), and therefore effectively destroys the cancer cells' DNA by β-particle irradiation.
2. **Pharmacokinetics** - Radioiodine is an unconjugated radiopharmaceutical. Unconjugated radiopharmaceutical can usually get to the target tissues using shorter amounts of time than antibodies or tumor-targeting agents. This reduces the unnecessary radiation dose to the normal tissues, which enhances tumor versus non-tumor absorbed dose.

4.5 When radioiodine fails, why does it do so?

Biodistribution - Radioiodine may fail to treat thyroid cancer. There are cases where thyroid cancer cells no longer trap and concentrate iodine, and hence are refractory to radioiodine, due to the loss of thyroid differentiation features in the thyroid cancer cells, such as iodide uptake and organification [20]. It is found that 5% to 15% of DTC and 50% of metastatic DTCs are refractory to radioiodine treatment [21, 22]. In those cases, external-beam radiation therapy is commonly used for treating thyroid cancer and sometimes in combination with surgery in bone and central nervous system metastasis of thyroid cancers [20].

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Appendix

Appendix A: Absorbed Dose for ^{18}F-FDG

Table C.31. Absorbed doses for ^{18}F-fluoro-2-deoxy-D-glucose.

	Absorbed dose per unit activity administered (mGy MBq^{-1})				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	1.2E−02	1.6E−02	2.4E−02	3.9E−02	7.1E−02
Bone surfaces	1.1E−02	1.4E−02	2.2E−02	3.4E−02	6.4E−02
Brain	3.8E−02	3.9E−02	4.1E−02	4.6E−02	6.3E−02
Breast	8.8E−03	1.1E−02	1.8E−02	2.9E−02	5.6E−02
Gallbladder wall	1.3E−02	1.6E−02	2.4E−02	3.7E−02	7.0E−02
Gastrointestinal tract					
Stomach wall	1.1E−02	1.4E−02	2.2E−02	3.5E−02	6.7E−02
Small intestine wall	1.2E−02	1.6E−02	2.5E−02	4.0E−02	7.3E−02
Colon wall	1.3E−02	1.6E−02	2.5E−02	3.9E−02	7.0E−02
(Upper large intestine wall	1.2E−02	1.5E−02	2.4E−02	3.8E−02	7.0E−02)
(Lower large intestine wall	1.4E−02	1.7E−02	2.7E−02	4.1E−02	7.0E−02)
Heart wall	6.7E−02	8.7E−02	1.3E−01	2.1E−01	3.8E−01
Kidneys	1.7E−02	2.1E−02	2.9E−02	4.5E−02	7.8E−02
Liver	2.1E−02	2.8E−02	4.2E−02	6.3E−02	1.2E−01
Lungs	2.0E−02	2.9E−02	4.1E−02	6.2E−02	1.2E−01
Muscles	1.0E−02	1.3E−02	2.0E−02	3.3E−02	6.2E−02
Oesophagus	1.2E−02	1.5E−02	2.2E−02	3.5E−02	6.6E−02
Ovaries	1.4E−02	1.8E−02	2.7E−02	4.3E−02	7.6E−02
Pancreas	1.3E−02	1.6E−02	2.6E−02	4.0E−02	7.6E−02
Red marrow	1.1E−02	1.4E−02	2.1E−02	3.2E−02	5.9E−02
Skin	7.8E−03	9.6E−03	1.5E−02	2.6E−02	5.0E−02
Spleen	1.1E−02	1.4E−02	2.1E−02	3.5E−02	6.6E−02
Testes	1.1E−02	1.4E−02	2.4E−02	3.7E−02	6.6E−02
Thymus	1.2E−02	1.5E−02	2.2E−02	3.5E−02	6.6E−02
Thyroid	1.0E−02	1.3E−02	2.1E−02	3.4E−02	6.5E−02
Urinary bladder wall	1.3E−01	1.6E−01	2.5E−01	3.4E−01	4.7E−01
Uterus	1.8E−02	2.2E−02	3.6E−02	5.4E−02	9.0E−02
Remaining organs	1.2E−02	1.5E−02	2.4E−02	3.8E−02	6.4E−02
Effective dose (mSv MBq^{-1})	1.9E−02	2.4E−02	3.7E−02	5.6E−02	9.5E−02

The physical half-life of ^{18}F is 1.83 h.

Figure 6: Absord dose for ^{18}F-FDG (table was obtained from [23])

Appendix B: Absorbed Dose for ^{131}I

SUMMARY OF ESTIMATED ABSORBED DOSES FROM RADIOIODINE AFTER A SINGLE ORAL ADMINISTRATION OF SODIUM IODIDE TO A EUTHYROID ADULT

Target organ	Maximum thyroid uptake (%)	Absorbed dose (rads/mCi of radioiodine administered)						
		^{123}I	^{124}I	^{125}I	^{126}I	^{130}I	^{131}I	^{132}I
Liver	5	0.029	0.36	0.087	0.25	0.32	0.20	0.14
	15	0.028	0.45	0.22	0.45	0.30	0.35	0.13
	25	0.027	0.55	0.36	0.65	0.29	0.48	0.13
Ovaries	5	0.036	0.33	0.029	0.14	0.34	0.14	0.14
	15	0.034	0.31	0.033	0.15	0.31	0.14	0.14
	25	0.031	0.30	0.039	0.15	0.29	0.14	0.13
Red marrow	5	0.030	0.27	0.044	0.16	0.23	0.14	0.094
	15	0.030	0.36	0.077	0.26	0.23	0.20	0.092
	25	0.030	0.46	0.12	0.37	0.23	0.26	0.091
Stomach wall	5	0.25	2.4	0.27	1.5	2.4	1.7	1.2
	15	0.23	2.2	0.26	1.4	2.2	1.6	1.2
	25	0.21	2.0	0.26	1.3	2.0	1.4	1.1
Testes	5	0.013	0.18	0.015	0.088	0.18	0.084	0.078
	15	0.012	0.18	0.018	0.094	0.17	0.085	0.076
	25	0.012	0.17	0.024	0.10	0.16	0.088	0.074
Thyroid	5	2.4	180.0	140.0	320.0	22.0	260.0	2.3
	15	7.5	530.0	450.0	960.0	68.0	800.0	7.4
	25	13.0	890.0	790.0	1,600.0	120.0	1,300.0	13.0
Total body*	5	0.025	0.36	0.11	0.28	0.25	0.24	0.10
	15	0.027	0.59	0.29	0.61	0.27	0.47	0.10
	25	0.029	0.83	0.49	0.95	0.29	0.71	0.11

* Includes dose from source organs plus dose from radioiodine assumed to be distributed uniformly in the total body.

Figure 7: Absord dose for ^{131}I (table was obtained from [24]).

	Maximum thyroid uptake	Absorbed Dose (rads/mCi)	Absorbed Dose (mGy/MBq)
Liver	5	0.2	5.4E-02
	15	0.35	9.5E-02
	25	0.48	1.3E-01
Ovaries	5	0.14	3.8E-02
	15	0.14	3.8E-02
	25	0.14	3.8E-02
Red marrow	5	0.14	3.8E-02
	15	0.2	5.4E-02
	25	0.26	7.0E-02
Stomach wall	5	1.7	4.6E-01
	15	1.6	4.3E-01
	25	1.4	3.8E-01
Testes	5	0.084	2.3E-02
	15	0.085	2.3E-02
	25	0.088	2.4E-02
Thyroid	5	260	7.0E+01
	15	800	2.2E+02
	25	1300	3.5E+02
Total body	5	0.24	6.5E-02
	15	0.47	1.3E-01
	25	0.71	1.9E-01

Figure 8: Absord dose for ^{131}I in mGy/MBq based on Fig. 7.