Isolated System Towards A Successful Radiotherapy Treatment

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Abstract

Purpose Establishment of the specifications and standards for successful radiotherapy treatments through identifying three objectives: administering the appropriate low-waste dose, developing dose-delivery skills and monitoring an earlier response to therapy.

Methods The appropriate low-waste dose is administered via the work-energy principle, considering the interaction between the drug and the tumor as an isolated system. Then, chelated with any compound that could form a lipid-soluble complex with the radioactive metal ions, it is injected directly into the tumor via a multihole needle to improve the distribution of the injectate solution. This can be detected by monitoring the tumor response through newer imaging techniques that combine single photon emission computed tomography (SPECT) with computed tomography (CT), or positron emission tomography (PET) with CT, so that nonresponding tumors can be identified early to modify the administered dose.

Results The accuracy of estimating the initial effective radioactive dose depends on the equivalence of the growth energy of the tumor estimated from the CT scan and the decay energy of the effective radioactive dose. Besides earlier or more accurate assessment of the tumor response by PET with the glucose analogue ^{18}F -fluoro-2-deoxyglucose (^{18}F -FDG), this contributes to the most safe and low-cost successful treatment. This approach assessed the therapeutic significance of lipid-soluble compounds with the radioactive metal ions in

protecting system isolation, which plays a major role in targeted tumor therapy.

Conclusion Treatment success shows that the three identified objectives are completely dependent objectives. It should also be taken into consideration that radionuclide decay-generated Auger electrons may be more effective in very small tumors to avoid a cross dose.

Keywords Isolated radiotherapy · Growth energy · Emad · Work-energy principle

Introduction

Effective use of radiotherapy treatments requires that nonresponding tumors be identified early in the course of therapy, as early identification of nonresponding patients could lead to modifying the administered dose to avoid complications caused by tumor progression, and also lead to considerable costs savings, since many new drugs are expensive. In the United States, for example, 1 month of treatment with cetuximab costs more than \$16,000 [1]. The high costs for new cancer drugs are largely due to the failure of drug candidates in late phase III studies [2]. New imaging biomarkers of tumor response that correlate better with patient outcome than do size measurements could thus significantly reduce the costs of drug development and thereby eventually decrease drug costs in clinical practice [2]. Then tumor response is a fundamental concept in clinical oncology, where most anticancer drugs are seemingly effective only in subgroups of patients. However, our current understanding of tumor biology allows us to predict accurately which patient will benefit from a specific therapeutic regimen, through techniques have been developed for three important objectives: administering the appropriate low-waste dose to

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decrease drug costs, injection skills to ensure optimized uniform absorption of the dose by the tumor [3], and monitoring its response to therapy [4]. Treatment success shows that these three objectives are completely dependent. Decreasing the loss of dose energy per unit of its path way, which is known by (dE/dX) [5, 6], can be achieved through targeting a high delivery rate. Using injection skills by new devices with lipid-soluble complexes, that substantially improve the distribution of the injectate solution over the regular rates, as it binds to proteins within the cells, and once bound, remains bound to proteins [3]. This enables consideration of the interaction between the drug and the tumor as an isolated system suitable for applying the law of conservation of energy. In other words, it allows considering only the drug decay energy per unit of decreasing mass, which is known by the tumor response or (dE/dm) . While monitoring tumor response to therapy is an essential part of the clinical management of cancer patients, where the primary goal is to identify the nonresponding tumors early, in order to stop ineffective therapies and avoid complications caused by tumor progression.

Materials and methods

This section is divided into five parts, which show the methodology of the three objectives to reach the case of the isolated system treatment (isolated radiotherapy), followed by an experiment that can be considered as a practical proof for the isolated system efficacy, and finally, the dose modification for the relapsed tumors.

1. Estimating and calculations of the equivalent radioactive doses through the concept of the work-energy principle

Taking into consideration that the interaction between the drug and the tumor is an isolated system, for which no energy crosses the system boundary by diminishing (dE/dX) as mentioned in the introduction. The estimation of the required dose from a decaying system [radioactive isotope] to destroy the biological cells of a growing system (tumor) needs to apply the law of conservation of energy, which is known in mechanics as the work-energy principle [7]. It states that “the work done against the biological culture (tumor) growth will be equal to the loss in radiation energy [decay energy] of the used dose.” Thereafter, the relation of the disintegration energy of the radioactive isotope and its decay constant $[\frac{dA}{dN_{isotope}}]$, and the relation of the growth energy of the biological cell and its growth constant $[\frac{dG}{dC_{BiologicalCell}}]$ should be derived and proved, such that both relations can be expressed in the same units. Therefore, we have to reconsider the concept of mass and energy conversion, $E=mc^2$, by using a new concept in the cases that need to relate the decay or growth energies by their activities. The following is a proof

for such a concept for mass and energy conversion (Emad’s formula) starts with the definition of the natural decay of isotopes to reach its final form.

1.1. Natural decay of isotopes

The activity of the radioactive isotopes through the process of natural decay, which is expressed also by the rate of emission of particles, $\frac{dN}{dt}$, is directly proportional to the number of the available particles (N) in the substance, which also varies with time.

$$\text{i.e. } \frac{dN}{dt} \propto N \rightarrow \frac{dN}{dt} = -KN [7] \quad (1.1.1)$$

[7], where K is constant, and the negative sign indicates that N decreases in time, $\frac{dN}{dt} = -K \cdot dt \Rightarrow \int \frac{dN}{N} = \int -K \cdot dt \Rightarrow \ln N = -Kt + c$ where c is the integration constant that can be determined by replacing the initial number of particles = N_0 at $t=0$

$$\Rightarrow \ln N = -Kt + \ln N_0 \text{ At half - life time } t = t_{1/2} \Rightarrow N = \frac{1}{2} N_0$$

Then, $\ln \frac{1}{2} N_0 = -Kt_{1/2} + \ln N_0$, consequently $K = \frac{\ln N_0 - \ln \frac{1}{2} N_0}{t_{1/2}}$

$$\Rightarrow K = \frac{\ln \frac{N_0}{1/2 N_0}}{t_{1/2}} = \frac{\ln 2}{t_{1/2}} \text{ From (1.1.1), i.e. } \frac{dN}{dt} = \frac{-\ln 2}{t_{1/2}} N \quad (1.1.2)$$

Also, N as a function of time can be calculated as follows: from (1.1.2) $\Rightarrow \int \frac{dN}{N} = \int \frac{-\ln 2}{t_{1/2}} dt \Rightarrow \ln N = \frac{-\ln 2}{t_{1/2}} t + c$ where c is a constant that can be calculated by replacing N by N_0 when $t = 0 \Rightarrow c = \ln N_0$

$$\text{Then: } \ln N - \ln N_0 = \frac{-\ln 2}{t_{1/2}} t \Rightarrow \ln \frac{N}{N_0} = \frac{-\ln 2}{t_{1/2}} t \Rightarrow \frac{N}{N_0} = e^{\frac{-\ln 2}{t_{1/2}} t} \Rightarrow N = N_0 e^{\frac{-\ln 2}{t_{1/2}} t} \quad (1.1.3)$$

$$\Rightarrow \ln (1.1.2) \frac{dN}{dt} = \frac{-\ln 2}{t_{1/2}} N_0 e^{\frac{-\ln 2}{t_{1/2}} t} \quad (1.1.4)$$

That is, the more the activity (rate of emission of particles) the shorter the normal half-life time and vice versa.

1.2. Kinematics of radiation

From (1.1.4) $\frac{dN}{dt} = \frac{-\ln 2}{t_{1/2}} N_0 e^{\frac{-\ln 2}{t_{1/2}} t}$ by replacing $\frac{dN}{dt}$ with A and $A_0 = \frac{-\ln 2}{t_{1/2}} N_0$

$$\Rightarrow A = A_0 \times e^{\frac{-\ln 2}{t_{1/2}} t} \Rightarrow \frac{A}{A_0} = e^{\frac{-\ln 2}{t_{1/2}} t} \Rightarrow \ln \left(\frac{A}{A_0} \right) = \frac{-\ln 2}{t_{1/2}} t$$

$$\ln A = \ln A_0 - \frac{\ln 2}{t_{1/2}} t \quad (1.2.1)$$

from (1.2.1)

$$\frac{d(\ln A)}{dt} = \frac{-\ln 2}{t_{1/2}} \quad (1.2.2)$$

$$\int (\ln A) dt \Rightarrow \int \ln \left(A_0 e^{\frac{-\ln 2}{t_{1/2}} t} \right) dt \Rightarrow \int \left[\ln A_0 + \ln \left(e^{\frac{-\ln 2}{t_{1/2}} t} \right) \right] dt$$

$\Rightarrow \int \left(\ln A_0 - \frac{\ln 2}{t_{1/2}} t \right) dt = \ln A_0 t - \frac{\ln 2}{2 t_{1/2}} t^2 + C$ where C is constant. At $t=0$, $\int (\ln A) dt = 0 \Rightarrow C = 0$

$$\int (\ln A) dt = (\ln A_0) t - \frac{\ln 2}{2 t_{1/2}} t^2. \quad (1.2.3)$$

From (1.2.1) and by squaring both sides,

$$(\ln A)^2 = (\ln A_0)^2 - 2 \ln A_0 \frac{\ln 2}{t_{1/2}} t + \frac{(\ln 2)^2}{(t_{1/2})^2} t^2$$

$$(\ln A)^2 = (\ln A_0)^2 - 2 \frac{\ln 2}{t_{1/2}} \left(t \ln A_0 - \frac{\ln 2}{t_{1/2}} t^2 \right)$$

and from (1.2.3)

$$(\ln A)^2 = (\ln A_0)^2 - 2 \frac{\ln 2}{t_{1/2}} \int (\ln A) dt \quad (1.2.4)$$

Equations 1.2.1, 1.2.3, 1.2.4 are similar to laws of motion by uniform deceleration [$v = v_0 - at$ & $s = v_0 t - \frac{1}{2} at^2$ & $v^2 = v_0^2 - 2as$] [7]. Therefore, it can be concluded that the radiation process model follows the model of motion in a straight line by uniform deceleration, in which the radiation decay constant ($\ln 2/t_{1/2}$) corresponds to the deceleration of motion (a). Consequently, other characteristics of the radiation process can be derived in the same way as for motion by uniform deceleration, taking into consideration the continuous decrease for radiation over time.

1.3. Momentum of radiation

Amount of radiation:

$$m_r = \frac{-\ln 2}{[\ln A]^2} Bq^{-2}, \quad (1.3.1)$$

where the negative sign indicates that the amount of radiation decreases with time. Momentum of radiation:

$$H_r = \frac{-\ln 2}{[\ln A]^2} \times \ln A = \frac{-\ln 2}{\ln A} Bq^{-1} \quad (1.3.2)$$

Rate of change of radiation momentum from (1.3.2)

$$\begin{aligned} \frac{dH_r}{dt} &= 2(\ln A)^{-2} \left(\frac{-\ln 2}{t_{1/2}} \right) \\ &= \frac{-2 \ln 2}{(\ln A)^2 \times t_{1/2}} Bq^{-2} \text{sec}^{-1} \end{aligned} \quad (1.3.3)$$

1.4. Work of radiation

As the rate of change of the momentum of radiation is a variable where it is a function of the activity (A), which

varies with time, then the work of the radiation can be calculated as follows:

$$W_r = \int \frac{dH}{dt} \times d \left(\int \ln A dt \right) [7] \quad (1.4.1)$$

$$\text{From (1.2.3)} \quad \frac{d \left(\int \ln A dt \right)}{dt} = \frac{d \left(\ln A_0 t - \frac{\ln 2}{2 t_{1/2}} t^2 \right)}{dt} = \ln A_0 - \frac{\ln 2}{t_{1/2}} t$$

From (1.2.2),

$$\frac{d \left(\int \ln A dt \right)}{dt} = \ln A \Rightarrow d \left(\int \ln A dt \right) = \ln A dt \quad (1.4.2)$$

From (1.3.3) and (1.4.2) in (1.4.1),

$$W_r = \int \frac{-2 \ln 2}{(\ln A)^2 \times t_{1/2}} \times \ln A dt \Rightarrow \int \frac{-2 \ln 2}{t_{1/2} \times \ln A} dt \quad (1.4.3)$$

From (1.1.4), $A = \frac{-\ln 2}{t_{1/2}} N_0 e^{\frac{-\ln 2}{t_{1/2}} t}$ Then

$$\frac{dA}{dt} = \frac{-\ln 2}{t_{1/2}} \times A \Rightarrow \frac{dA}{A} = \frac{-\ln 2}{t_{1/2}} dt \quad (1.4.4)$$

From (1.4.4) in (1.4.3), $W_r = \int \frac{2}{A \ln A} dA = 2 \ln[\ln A] + C \Rightarrow \ln[\ln A]^2 + C$

At $t = 0$ $W_r = 0 \Rightarrow C = -\ln[\ln A_0]^2$

Then,

$$W_r = \ln[\ln A]^2 - \ln[\ln A_0]^2 Bq^2 \text{ or } Emad \quad (1.4.5)$$

1.5. Energy of radiation: energy of radiation per nucleus

From Eq. 1.4.5 and as $W_r = E_r - E_{0r}$ Then decay energy,

$$E_{0r} = \ln[\ln A_0]^2 \text{ & } E_r = \ln[\ln A]^2 Bq^2 \text{ or } Emad \quad (1.5.1)$$

The definition of 1 Emad is the energy of the nucleus of activity $A = e^{\pm \sqrt{e}} Bq \approx \frac{1}{5.20032576} \text{ or } 5.20032576 Bq$ and it can be converted to MeV by using the following formula:

$$E_{MeV} = \frac{c^2}{e} \times \ln \left(\ln \left(\frac{dA}{dN} \right) \right)^2 \times (\text{mass number})^{\frac{1 - \ln \left(\ln \left(\frac{dA}{dN} \right) \right)^2}{1 + \ln(\text{mass number})}} MeV \quad (1.5.2)$$

$$\text{I.e. } C^2 = 342.6774922 \times \ln \left(\ln \left(\frac{dA}{dN} \right) \right)^2$$

$$\times (\text{mass number})^{\frac{1 - \ln \left(\ln \left(\frac{dA}{dN} \right) \right)^2}{\ln(\text{mass number})}}$$

$$= 931.494 \text{ MeV & } Emad$$

$$= \frac{c^2}{e} \times (\text{mass number})^{\frac{1 - \ln \left(\ln \left(\frac{dA}{dN} \right) \right)^2}{1 + \ln(\text{mass number})}} MeV \quad (1.5.3)$$

1.6. Disintegration radiation energy: Q [7]

Or loss in the radiation energy per nucleus

When mass is expressed in atomic mass unit (u), Q can be calculated as follows:

$$Q = \frac{E_r}{\text{mass of neutral atom}} \times \text{mass loss } Bq^2 \text{ or } Emad \quad (1.6.1)$$

1.7. Applying the work-energy principle

In the previous point (Item 1.5), it was mathematically proven that the decaying energy of the nucleus of the radioactive isotope is

$$E_{D.Isotope} = \ln \left(\left(\ln \left(\frac{dA}{dN} \right)_{Isotope} \right)^2 \right) Emad \quad (1.5.1)$$

where A is the activity of the radioactive isotope and N is the number of undecayed nuclei at any one time. Similarly, the growth energy of a biological cell in a growing biological culture (tumor) is

$$E_{Biological\ Cell} = \ln \left(\left(\ln \left(\frac{dG}{dC} \right)_{Tumor} \right)^2 \right) Emad, \quad (1.7.1)$$

where G is the activity of the biological culture (tumor), C is the number of biological cells at any one time, while $Emad$ is a variable unit for measuring these energies.

This result differs from one element to another, depending on the mass number of the said element, as shown previously in Eq. 1.5.3. As measuring the growth and decaying energies in Emads produces different converting factors from one element to another, according to their mass number, then there is a second need to equalize the converting factor of the growing energy of the biological cell by the converting factor of the decaying energy of the commonest safely used radioactive isotope, namely iodine-131 [8]. This means that iodine-131 will be considered as a reference for estimating the required activity of the radioactive dose, according to the work-energy principle concept, which will then make it easy to calculate its equivalent dose from any other radioactive isotope. This will be shown in the next point (Eq. 1.8.2). Alternatively, it may be possible to derive a formula to estimate the activity of the required dose of any other radioactive element directly in one-step, as shown later in Eq. 1.9.7.

1.8. Estimating the required dose of iodine-131 according to the theory of mass-radiation energy conversion and the work-energy principle:

- a. It is believed that cell hypoxia contributes significantly to treatment failure because cells in the hypoxic zones resist traditional chemical disinfection. This happens for at least two reasons. First, most agents cannot penetrate beyond 50–100 μm from capillaries [9], therefore never

reaching the cells in the hypoxic regions. Second, the lower nutrient and oxygen supply to cells in the hypoxic zones causes them to divide more slowly than their well-oxygenated counterparts. Therefore, hypoxic cells exhibit greater resistance to chemical treatments, as well as radiation that targets rapidly dividing cells or requires oxygen for efficacy [10–13]. Drugs used to target hypoxic cancer cells, using redox-activation, utilize the large quantities of reductase enzyme present in hypoxic cells to convert the drug into its cytotoxic form, essentially activating it [12, 14]. Consequently, if the percentage of hypoxic cells is $h\%$, the work done against the tumor growth can be calculated as the total growth energy of the hypoxic cells, as follows:

from (1.7.1) $\Rightarrow W_{r,T} = \ln \left(\ln \left(\frac{dG}{dC} \right)_{Tumor}^2 \right) \times C_0 \times h\% Emad$, where C_0 is the initial number of tumor cells, h is the percentage of the hypoxic cells, and $\left[\ln \left(\ln \left(\frac{dG}{dC} \right)_{Tumor} \right)^2 \right]$ is the tumor growth energy/cell in $Emad$ units. Meanwhile, the decay energy of the effective dose of iodine-131 can be calculated as follows: from (1.6.1), $\Rightarrow Q_{r,131I} = \ln \left(\ln \left(\frac{dA}{dN} \right)_{Nuclei}^2 \right) \times \frac{\text{mass loss}}{\text{mass number}} \times N_0 Emad$, where N_0 is the initial number of the undecayed nuclei of iodine-131, while the mass loss and the mass number of iodine-131 in atomic unit weight (u) are 130.9061246 u and 0.0010422 u, respectively [15, 16]. While $\ln \left(\ln \left(\frac{dA}{dN} \right)_{Nuclei}^2 \right)$ is the Iodine-131 decay energy/nucleus in $Emad$ units, $\frac{dA}{dN} = \lambda = \frac{\ln 2}{t_{1/2}}$ is the decay constant [7], $t_{1/2}$ is the half-life time of the iodine-131, which is 8.04 days [15, 16].

Hint Formula (1.5.3) can be used to convert the calculated decay energy Q from $Emad$ to MeV to check the accuracy of the calculations, as shown in the following:

$$\Rightarrow Q_{r,131I} = \ln \left(\ln \left(\frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right)^2 \right) \times \frac{0.001}{131} \times \frac{931.494}{e} \\ \times (131)^{1 + \frac{1 - \ln \left(\ln \left(\frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right)^2 \right)}{\ln 131}} = 0.97 \text{ MeV}$$

This is 100% identical to the value of Q for iodine-131 when calculated by the Einstein's formula, $E=mc^2$ [5, 15, 17, 18]. Nevertheless, there is a need to use $Emad$ formula in decay energy calculation from the decay constant to be able to calculate the growth energy of the biological cultures (tumors) from the growth constant in same unit ($Emad$), to apply the work-energy principle.

- b. By applying the law of conservation of radiation energy, the work done against the biological culture (tumor) growth will be equal to the loss in radiation energy of the used dose of iodine-131, $\Rightarrow W_{r,T} = Q_{r,131I}$ [7].

$$\ln \left(\ln \left(\frac{dG}{dC} \right)_{Tumor}^2 \right) \times C_0 \times h\% = \ln \left(\ln \left(\frac{dA}{dN} \right)_{Nuclei}^2 \right) \times \frac{\text{mass loss}}{\text{mass number}} \times N_0$$

$$\Rightarrow A_{0^{131}I} = \lambda \times h\% \times C_0 \times \frac{\text{mass number}}{\text{mass loss}} \times \frac{\ln \left(\ln \frac{dG}{dC} \right)^2_{\text{Tumor}} Bq}{\ln \left(\ln \frac{dA}{dN} \right)^2_{\text{Nuclei}}} \quad (1.8.1)$$

which can be simplified as follows:

$$\Rightarrow A_{0^{131}I} = \frac{\ln 2}{t_{1/2^{131}I}} \times h\% \times C_0 \times \frac{131}{0.001} \times \frac{\ln \left(\ln \frac{\ln 2}{I_{D,\text{Tumor}}} \right)^2}{\ln \left(\ln \frac{\ln 2}{t_{1/2^{131}I}} \right)^2} Bq \quad (1.8.2)$$

1.9. Equivalent radioactive doses

If it is required to estimate two equivalent doses of P and I, which are two different radioactive isotopes, then both of them should contain the same amount of the decaying energy:

$$\text{i.e. } Q_I \times N_{0I} = Q_P \times N_{0P} \quad (1.9.1)$$

where Q is the decay energy per nucleus and N_0 is the initial number of the undecayed nuclei.

$$\text{As } A_{0I} = \frac{-\ln 2}{t_{1/2I}} \times N_{0I} \& A_{0P} = \frac{-\ln 2}{t_{1/2P}} \times N_{0P} \quad (1.9.2)$$

$$\text{From (1.9.2) in (1.9.1) } Q_I \times \frac{A_{0I}}{-\ln 2} \times t_{1/2I} = Q_P \times \frac{A_{0P}}{-\ln 2} \times t_{1/2P}$$

$$\Rightarrow Q_I \times A_{0I} \times t_{1/2I} = Q_P \times A_{0P} \times t_{1/2P} \quad (1.9.3)$$

$$\text{i.e. } A_{0P} = \frac{Q_I}{Q_P} \times \frac{t_{1/2I}}{t_{1/2P}} \times A_{0I} \quad (1.9.4)$$

From (1.8.1)

$$\Rightarrow A_{0I} = \frac{|\ln 2|}{t_{1/2I}} \times h\% \times C_0 \times \frac{(\text{mass number})_I}{(\text{mass loss})_I} \times \frac{\ln \left(\ln \frac{dG}{dC} \right)^2_{\text{Tumor}} Bq}{\ln \left(\ln \frac{dA}{dN} \right)^2_I} \quad (1.9.5)$$

As the energies of the biological culture (tumor) and radioactive dose are:

$$E_{\text{Tumor}} = h\% \times C_0 \times \ln \left(\ln \frac{dG}{dC} \right)^2_{\text{Tumor}} E_{\text{mad}} \& E_{r,131I} \quad (1.9.6)$$

$$= \ln \left(\ln \frac{dA}{dN} \right)^2_I E_{\text{mad}}$$

From (1.9.6) in (1.9.5)

$$\Rightarrow A_{0\text{Isotope}} = \frac{|\ln 2|}{t_{1/2\text{Isotope}}} \times \frac{E_{\text{Tumor}} \times E_{\text{Iodine-131}}}{Q_{\text{Isotope}} \times E_{r\text{Iodine-131}}} Bq \quad (1.9.7)$$

where: $A_{0\text{Isotope}}$, $t_{1/2\text{Isotope}}$, and Q_{Isotope} are the activity, the half-life time and the decaying energy of the used radioactive isotope, E_{Tumor} is the total energy of the tumor, while $E_{\text{Iodine-131}}$ and $E_{r\text{Iodine-131}}$ are the stored and radiation

energies of the iodine-131 nucleus which is considered in this method as a base for estimating the required dose from any radioactive isotope.

2. Isolating the system “dose delivery”

The primary treatment against cancer remains surgery, chemotherapy, radiation therapy, and radionuclide therapy. Treatments on the horizon are vaccine therapy that spurs the immune system, gene therapy that introduces genes to eradicate malignant cells, and targeted drug therapy that is designed to take advantage of certain specific receptors that are overexpressed on tumor cells. Although the surgical removal of tumors followed by therapeutic intervention is the mainstay of cancer management, not all tumors can be radically or even partially dissected without serious consequences that can severely degrade the quality of the patient's life. Brachytherapy, in which the implanted radioactive seeds may not deliver a uniform radiation dose, is supplemented by external radiation therapy. With external-beam radiation therapy, the dose to the surrounding normal tissues could be high, and therapy could be less effective if the tumor is hypoxic, which consequently leads to high waste energy destroying the surroundings to region of interest (ROI). This violation to isolated system principle can be reformed using three correction factors used to correct or to modify the administered dose by the work-energy principle, which are: (1) energy loss external to the tumor (2) effect of dose non-uniformity on cell survival and (3) effect of correlation of dose nonuniformity with cell proliferation rate [19]. At the same time, there is a need for another technique that promises to induce a significantly smaller radiation dose to tissues in the immediate vicinity of the target, applicable to all tumors, including those that may be refractory to chemo—or radiotherapy. This approach suggests that injecting any radionuclide of therapeutic importance chelated with any compound that could form a lipid-soluble complex with the radioactive metal ions, directly into a tumor can deliver a high radiation dose and arrest tumor growth without excessive radiation dose to normal organs and adjacent tissues, weight loss, or bone marrow toxicity. Care must be taken, however, that the agent distributes uniformly within the tumor. This agent needs to be injected directly into the tumor (or the residual portion of a tumor not removed by surgery) via a multihole needle. This technique substantially improved the distribution of the injectate solution over the regular end-hole needle, where the radioactivity injected using the end-hole needle covered a small tumor area, only around the end-hole, whereas almost the entire tumor area was covered by the radioactivity injected through the multihole needle. However the solution should slowly injected after inserting the multihole needle only at one site, horizontally into the tumor, then the needle should be withdrawn very slowly, in

the presence of light pressure applied on the needle holes to prevent any solution oozing out of the tumor. This simple technique—introduced by Thakur and Coss [3]—has numerous potential advantages over the current systemically given chemo- or radiotherapeutic agents. A radionuclide with suitable physical and chemical characteristics that will distribute uniformly within the tumor and bind to cell cytoplasmic components until completely decayed will deliver a high radiation dose to the tumor cell nucleus, eventually leading to cell death, while sparing normal tissue. Such a treatment, in principle, is desirable, and may be more effective, and safer than the current treatments by which patients with tumors that are too risky to resect or cannot be radically extirpated are managed. Such radionuclide therapy should also be applicable to most solid tumors and metastatic lesions, such as those in the liver, lungs, or brain. Furthermore, theoretic calculations suggested that the radiation dose to normal organs adjacent to the tumor might also be negligible, compared with external-beam therapy or interventions with any other forms of radionuclides, as more than 85% of the used radionuclide will remain in tumors, bound to cell cytoplasmic components. Because of this characteristic, radiation dose to adjacent normal organs, besides all forms of waste energy, including heat, will be within 5–10% of the radiation dose to the tumor, which is promising towards the isolated system.

3. Monitoring tumor response

Monitoring tumor response to therapy is part of the clinical management of cancer patients. It is considered the third objective during successful treatment, as mentioned in the introduction, to follow-up and to check the other two objectives for decreasing loss of dose energy per unit of its pathway (dE/dX), and consequently for realizing the efficiency of estimating the administered dose based on the assumption of conservation of energy for the closed system. Hereby the primary goal of monitoring tumor response is to identify non-responding tumors early, i.e., the drug decay energy per unit of decreasing mass (dE/dm), in order to stop ineffective therapies and avoid complications caused by tumor progression [4]. In drug development, there is generally more interest in responding tumors because tumor response is considered an objective marker of drug activity. The ultimate goal in drug development is to use tumor response as a surrogate for clinical benefit, because response is generally faster to assess and less confounded by covariates such as patient status at the start of the clinical trial or the effects of second-line therapy. Taking into consideration the most important parameter that affects (dE/dm), which is the rate of tumor growth (dm/dt), for its reflection on the growth energy calculation (1.7.1). Accordingly, it does not make any sense to compare the

response towards equivalent doses by two different tumors of equal masses but having different doubling times, as they would have different growth energy, consequently they would need different administered doses with different decay energies. This is illustrated practically [4] in a study for the response of two exponentially growing spherical tumors. Tumor A is growing with a volume doubling time of 90 days, whereas tumor B is growing more slowly, with a volume doubling time of 200 days. Such volume doubling times have been observed in several studies of patients with untreated non-small cell lung cancer [4]. Both tumors are assumed to be diagnosed at the same time, when the diameter has reached 3 cm. Then, a treatment is administered for 3 months, in the beginning the diameter of tumor A decreases by one-third, whereas tumor B is unaffected; afterwards, tumor A regrows quickly and exceeds tumor B in size within about a year. This experiment can be explained from point of view of this paper as follows: according to current response criteria, as the growth rate of A is greater than that of B, inversely the growth energy of tumor A would be less than that of B, so that tumor A responded while tumor B did not respond. Nevertheless, at the same time as the drug energy supplied was insufficient for the tumors, the faster tumor A relapsed, regrows quickly, and exceeds tumor B in size within about a year. This simple example illustrates that tumor shrinkage after therapy may mislead those expected inaccuracies inherent in dosimetry methods, and propose that disease stabilization may be a better parameter than shrinkage for monitoring tumor response to therapy, which is simply incorrect [4]. It is, therefore, challenging to differentiate between growth rate (dm/dt) and growth energy $E_{\text{Biological Cell}} = \ln(\ln \frac{dG}{dC})^2$, as for same mass the fast-growing tumor needs less drug energy than that of the slowly growing one. This can be an answer for puzzling observations on comparing radiotherapy treatments in different schools of medicine all over the world. Although one can find the same disease in nearly the same circumstances, but with completely different recurring doses, hitherto no-one has had a conceptual reasoning for these invariant doses. Although statisticians and physicians classify characteristics of patients more specifically, even whether white or black, they finally concluded that “dosimetry never inherits identical results,” ignoring the most important parameter, which is the tumor doubling time (t_D), as explained before. Hereby I suggest giving this parameter a higher consideration in estimating the administering doses prior to treatment.

Current Approaches for Monitoring Response

Tumor size can be measured bidimensionally with calipers in nude mice experiments, and the volume is calculated

assuming elliptic or spherical geometry, while in human treatments, the tumor self-absorbed radiation dose (TSARD) is determined from scintillation-camera conjugate views, and the tumor volume is measured using computed tomography (CT) or magnetic resonance imaging (MRI) [4]. Although response assessment on CT has been refined over many years, fundamental limitations remain in measuring tumor shrinkage on CT. In radio-immunotherapy treatment (RIT), cumulated activity and tumor volume/mass are the principal quantities necessary for the calculation of the absorbed dose to the tumor, as explained in Item 1.8 [5]. To assess the tumor mass (m) [20], clinical RIT protocols usually include a CT investigation before the start of therapy to calculate the mass (m), (dm/dt), and consequently the tumor doubling time (t_D), which is the most important parameter required to determine growth energy of the tumor cell $E_{G.Tumor} = \ln \left(\left(\ln \left(\frac{dG}{dC} \right)_{Tumor} \right)^2 \right) Emad.$ (1.7.1). These initial tumor parameters estimated from the CT scan are used routinely throughout all of the dosimetric calculations, as shown in Eq. 1.9.7. For these limitations in the current approaches for response prediction, the need for techniques to monitor tumor response to therapy is apparent. The common goal of these techniques is to evaluate the effectiveness of therapy earlier than is feasible through symptoms or other clinical parameters furthermore, the techniques aim to measure tumor response more objectively. Among several pursued molecular imaging approaches for treatment monitoring, positron emission tomography (PET) with the glucose analogue ^{18}F -fluoro-2-deoxyglucose (^{18}F -FDG) is currently the clinically most advanced. In numerous studies, ^{18}F -FDG PET has been shown to be a robust imaging technique not requiring sophisticated protocols for data acquisition and analysis. Furthermore, within the last 5 years, PET has become clinically available at almost all major hospitals. In a variety of solid tumors, single-center studies have indicated that ^{18}F -FDG PET may provide earlier or more accurate assessment of tumor response than CT, as it provides several highly reproducible quantitative parameters of tumor glucose metabolism [4, 21]. Suggesting that ^{18}F -FDG PET could play a significant role in personalizing the treatment of malignant tumors, where the tumor response might be identified earlier through changes in the ^{18}F -FDG signal than through changes in measured size [22–25]. However, generally accepted criteria for response assessment in solid tumors are missing, which makes it frequently impossible to compare the results of different studies.

4. Comparing results of experiments in nude mice bearing human tumors performed under the circumstances of the isolated system by results of applying the work-energy principle

What follows in this section is the analysis of an experimental treatment entitled “The role of lipid-soluble complexes in targeted tumor therapy” that was conducted in different hospitals and universities. The techniques and results of the study are described by Thakur and Coss [3], and are here going to be tested and compared by the isolated system objectives. Experiments on nude mice bearing human tumors were performed and are summarized briefly as follows:

Methods and materials for experiments in nude mice bearing human tumors Approximately 5×10^6 viable human prostate (DU145), breast (T47D), or colorectal cancer (LS174T) cells were implanted into nude mice in groups of ten mice each, and tumors were allowed to grow to 0.5 cm in diameter. Approximately 18.5 MBq (500 μCi) ^{111}In -oxine or ^{111}In -Merc in 100 μl of 10% ethanol in isotonic saline were injected per tumor of mass 0.5 g (0.61 cm in diameter) by the use of a multihole needle. Tumors in some mice were dissected, and 20- μm -thick sections were autoradiographed. In additional mice, tumor diameter was measured daily, mice were imaged and weighed, and blood samples were drawn for determination of neutrophil counts for up to 28 days after injection. Some mice were killed at predetermined times for quantitative tissue distribution of ^{111}In . Additionally, tumor cells were labeled with ^{111}In -oxine and homogenized, and ^{111}In associated with cell components was determined using polyacrylamide gel electrophoresis. The radiation dose that could be delivered to adjacent tissues was estimated. The ^{111}In absorbed dose as a function of radial position r in a 1-g tumor was theoretically compared with those of β -emitting radionuclides ^{90}Y and ^{177}Lu .

Calculations for Radiation Dose to Tumor and Adjacent Normal Organs [3]

For a 1-g tumor containing 10^9 cells, 37-MBq (1 mCi) intratumoral injection results in an average of 13,028 decays per cell after ten half-lives have elapsed. Thus, an absorbed dose of 17.55 Gy (1,755 rad) was obtained, which represents the self-dose to the cell. Their calculations were based on the assumption that 37 MBq (1mCi) ^{111}In will be uniformly distributed in a spherical tumor of mass 1 g (1.24 cm in diameter for unit density matter) and will undergo a complete decay with its physical half-life (T_p) of 67.9 h. The tumors treated with nonradioactive placebo continued to grow, irrespective of their type—breast, prostate, or colorectal. Within 28 days after injection, the prostate tumors with the placebos grew to nearly 100% of their initial size, whereas the tumors of 0.5 gm (0.61 cm initial diameter) treated with 16.7 MBq (450 μCi) ^{111}In -oxine grew, on average, only 17%. Both increases appeared linear

over days, but the slope for the control group was steeper than that for the treated (relapsed) group. The cumulated activity $A\sim$ for a 37-MBq (1 mCi) intratumoral administration with no biologic clearance is $1.44 A_0$, T_p 1.44 (37 MBq [1,000 μ Ci]) (67.9 h) 9.778×10^4 μ Ci-h. Finally, the total mean absorbed dose to the 1-g tumor is $D A\sim S$ 2.43 Gy/MBq injected (9,000 rad/mCi injected). For many tumor cells, this dose is lethal [26]. The calculation above represents the mean absorbed dose to a stable tumor (not growing or shrinking). If the tumor grows and subsequently shrinks during the decay of ^{111}In , then the absorbed dose calculations will require modification. If shrinkage is observed during the decay of ^{111}In , we can revise our dose estimates by taking into account the reduction in mass as a function of time after injection. This calculation is readily handled by the methods described by Goddu et al. [27] and Howell et al. [28–30].

Results of Experiments in Nude Mice Bearing Human Tumors

Thakur and Coss showed that more than 85% of ^{111}In remained in tumors, bound to cell cytoplasmic components of apparent molecular weights 250 and 6 kDa. ^{111}In in tumors was uniformly distributed. Only 2% of the injected ^{111}In was in the liver, kidneys, and carcass. Statistical analysis showed that on day 28, control tumors grew 100%, whereas treated tumors either had growth arrested or grew only slowly (17%). The estimated radiation dose per megabecquerel (millicurie) injected was 90 Gy/g (9,000 rad/g), of which 64% was from conversion electrons, 16% from Auger electrons, and 20% from γ -photons and X-rays, respectively. Radiation dose to adjacent normal organs was 5–10% of the radiation dose to the tumor and negligible to the liver and kidneys. Neutrophil counts remained unchanged; the radioactivity remaining was excreted in the urine within the first 24 h, as was evident by the daily whole-body radioactivity measurements. The bone marrow radioactivity was negligible. As a result, the white blood cell counts in all animals remained practically unchanged from the levels before the initiation of treatment [3].

Testing the Tumors Responses by the Work-Energy Principle

a. For the cured tumors

Tumor model The following are the data of a (RIT) for approximately 5×10^6 viable human prostate (DU145), breast (T47D), or colorectal cancer (LS174T) cells were implanted in nude mice in groups of ten mice each, and

spherical tumors of mass 1 g (1.24 cm in diameter for unit density matter). The growth doubling time of 28 days [3], having a percentage of the hypoxic cells of 10% [19]. (Assumed as it was not given.)

Dosimetry model The proposed isotope is the indium-111; its half-life is 67.9 h, while its decay energy is 0.865 MeV [31].

Step 1—Tumor model calculations: The mass of the tumor is 1 g; as number of cells/gram = 10^9 cells [32], then number of cells of the tumor, $C_0 = 0.5 \times 10^9$. This is the initial activity of the tumor.

Step 2—Dosimetry model calculations: (Radiotherapy dosage efficiency through the concept of theory of radiation energy-mass conversion):

According to the iodine-131 decay process, Work-Energy principle [7]: $\Rightarrow W_{rEmad} = Q_{rEmad}$

$$\begin{aligned} \ln \left(\ln \frac{dG}{dC} \right)_{\text{Tumor}} \times C_0 \times h\% &= \ln \left(\ln \frac{dA}{dN} \right)_{\text{Nuclei}} \times \frac{\text{mass loss}}{\text{mass number}} \\ &\times N_{0I-131} \\ \ln \left(\ln \frac{\ln 2}{28 \times 24 \times 60 \times 60} \right)_{\text{Tumor}}^2 \times 1.0 \times 10^9 &\times \frac{\text{cell}}{131} \\ \times 10\% &= \ln \left(\ln \frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right)_{\text{Nuclei}}^2 \times \frac{0.001}{131} \times N_{0I-131} \\ N_{0I-131} &= 1.2999 \times 10^{13} \text{ nuclei}, \Rightarrow N_{0In-111} = 1.2999 \\ &\times 10^{13} \times \frac{0.97}{0.865} = 1.4577 \times 10^{13} \text{ nuclei} \\ A_{0In-111} &= 1.4577 \times 10^{13} \times \frac{\ln 2}{67.9 \times 60 \times 60} = 41.33 \text{ MBq} = 1.1 \text{ mCi}, \end{aligned}$$

which is 10% more than postulated for a 1-g tumor lethal dose of ^{111}In (1 mCi), shown by Thakur and McAfee [26]. Taking into account that Thakur and McAfee stated that it should be borne in mind that the quantity of ^{111}In they administered in this feasibility study was chosen arbitrarily and was not optimal, to demonstrate its therapeutic effectiveness [3].

b. For the relapsed tumors and the law of conservation of energy:

Thakur and McAfee showed that tumors of 0.5 g (0.61 cm in diameter) treated with 16.7 MBq (450 μ Ci) ^{111}In -oxine grew, on the average, only 17% [3]. This provides a good chance to check whether this process violates the law of conservation of energy for an isolated system or otherwise [7]. Thus, the sum of both of the growth energy of the relapsed tumor—after receiving the insufficient dose— $[E_{\text{Relapsed Tumor}}]$, and the decay energy of such a dose $[E_{\text{Insufficient Dose}}$ of 16.7 MBq], should be equivalent to either of the decay energy of the lethal dose that has been administered for the cured tumors $[E_{\text{Cured Tumor}}$ of 20.665 MBq], or to the growth energy of the untreated (control) tumors which grew to nearly 100% of their initial size within 28 days $[E_{\text{Untreated Tumor}}]$; i.e., $[E_{\text{Insufficient Dose}} + E_{\text{Relapsed Tumor}}] = E_{\text{Cured Tumor}} = E_{\text{Untreated Tumor}}$

Check calculations A tumor growth energy of 17% can be converted to its corresponding decay energy from iodine-131 as follows from (8.2.2)

$$N_{0I-131} = \frac{\ln \left[\left(\ln \left(\frac{\ln 2}{28 \times 24 \times 60 \times 60} \right) \right)^2 \right]}{\ln \left[\left(\ln \left(\frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right) \right)^2 \right]} \times 0.17 \times 0.5 \times 10^9 \times 10\% \times \frac{131 \times 931.494}{0.97}$$

$$N_{0I-131} = 1.104901936 \times 10^{12} \text{nuclie}$$

$$[\text{GrowthEnergy}]_{\text{RelapsedTumor}} = 1.104901936 \times 10^{12}$$

$$\times \frac{0.97 \text{MeV}}{6.242 \times 10^{12}} = 0.1717 \text{Joule}$$

Decay energy of the insufficient dose from indium-111

$$= 16.7 \times 10^6 \times \frac{67.9 \times 60 \times 60}{\ln 2} \times \frac{0.865 \text{MeV}}{6.242 \times 10^{12}} = 0.8161 \text{Joule}$$

Growth energy of the untreated (control) tumor

$$= \frac{\ln \left[\left(\ln \left(\frac{\ln 2}{28 \times 24 \times 60 \times 60} \right) \right)^2 \right]}{\ln \left[\left(\ln \left(\frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right) \right)^2 \right]} \times 0.5 \times 10^9 \times 10\% \times \frac{131 \times 931.494}{6.242 \times 10^{12}} = 1.0091 \text{ Joule}$$

Growth energy (17%) + decay energy (insufficient dose) = 0.1717 + 0.8161 = 0.988 Joule, which achieves an accuracy of 98% Of the growth energy of the untreated (control) tumor (1.0091 Joule) or the decay energy of the lethal dose has been administered for the cured tumors with the prior experimental treatment, i.e., ($E_{\text{Cured Tumor}}$ of 20.665 MBq) . Then this process did not violate the law of conservation of energy. The previous calculations of the tumors responses are expressed in Fig. 1.

5. Dose modification

From the earlier assessment of the tumor response, it is possible to modify the dose administered prior the treatment. From Fig. 1, the radius of the treated tumor at any time follows the formula $r_{\text{Treated}} = r_{\text{Initial}} \times \left(1 + \frac{\Delta E}{E_{\text{Tumor}}} \times \frac{t}{t_D} \right)$ cm

$$t_D = \frac{0.62}{0.6413 - 0.62} \times \frac{135.8}{24} = 164.7 \text{days} \Rightarrow E_{\text{BiologicalCell}} = \ln \left(\ln \frac{\ln 2}{164.7 \times 24 \times 60 \times 60} \right)^2 = 5.64 \text{Emads},$$

$$E_{\text{Tumor}} = \frac{\ln \left(\ln \frac{\ln 2}{164.7 \times 24 \times 60 \times 60} \right)^2 \times 0.5 \times 10^9 \times 1.034 \times 10\% \times 131 \times 0.97}{\ln \left(\ln \frac{\ln 2}{8.04 \times 24 \times 60 \times 60} \right)^2 \times 0.001 \times 6.242 \times 10^{12}} = 1.1317 \text{ Joules}$$

Fig. 1 Calculations of the tumor groups [control, relapsed, or cured] responses over 28 days

(5.1), where $\Delta E = E_{\text{Tumor}} - E_{\text{Dose}}$ represents the energy of the dose that should be added in the case of the relapsed tumors. From Eq. 5.1, the formula of the modified dose at any time during the treatment will be $D_{\text{Modified}} = D_{\text{Administered}}(\text{MBq}) + \Delta D$, where

$$\Delta D = \left(\frac{r_{\text{Treated}}}{r_{\text{Initial}}} - 1 \right) \times E_{\text{Tumor}}(\text{Joule}) \times \frac{t_D}{t} \times \frac{\ln 2}{t_{1/2\text{Isotope}}} \times \frac{6.242 \times 10^6}{Q_{\text{Isotope}}(\text{MeV})} \text{MBq}. \quad (5.2)$$

Consequently

$$D_{\text{Modified}} = D_{\text{Administered}}(\text{MBq}) + \left(\frac{r_{\text{Treated}}}{r_{\text{Initial}}} - 1 \right) \times E_{\text{Tumor}}(\text{Joule}) \times \frac{t_D}{t} \times \frac{\ln 2}{t_{1/2\text{Isotope}}} \times \frac{6.242 \times 10^6}{Q_{\text{Isotope}}(\text{MeV})} \text{MBq} \quad (5.3)$$

Where t is the elapsed time from the treatment start until measuring the tumor response, and t_D is the tumor doubling time. This can be applied in the previous experimental treatment for the relapsed tumor as follows: the administered dose was 16.7 MBq, while from the earlier determination of the tumor response through the ^{18}F -FDG PET imaging technique, the size of the treated tumor grows by 3.4% from 0.62 cm to 0.6413 cm after two half-lives (135.8 h for ^{111}In) have elapsed. Therefore, the modified dose at this time, $t=135.8$ h, can be calculated by using formulae (5.2) and (5.3), as follows:

$$\text{From (5.2)} \quad \Delta D = \left(\frac{0.6413_{Treated}}{0.62_{Initial}} - 1 \right) \times [1.1317_{(Joule)}] \times \frac{28 \times 24}{135.8} \times \frac{\ln 2}{67.9 \times 60 \times 60} \times \frac{6.242 \times 10^6}{0.865_{(MeV)}} = 3.87 \text{ MBq}$$

From (5.3)

$$D_{Modified} = 16.7_{(MBq)} + \left(\frac{0.6413_{Treated}}{0.62_{Initial}} - 1 \right) \times [1.1317_{(Joule)}] \times \frac{28 \times 24}{135.8} \times \frac{\ln 2}{67.9 \times 60 \times 60} \times \frac{6.242 \times 10^6}{0.865_{(MeV)}} = 20.64 \text{ MBq}$$

This calculation is 99.9% of the administered dose calculated for the group of the cured tumors (20.665 MBq) in the provided experimental treatment, where the greater the accuracy of the used imaging technique, the greater the accuracy of the calculation of the dose modification.

Results

According to the principle of conservation of energy, the work done against the tumor growth will be equal to the loss in radiation energy of the used dose, where—after converting the units—the disintegration energies derived by the concept of radiation decay energy $E_r = \ln \left(\ln \frac{dA}{dN} \right)^2$ are identical by 100% to those derived by the conversion formula, $E = mc^2$. Similarly, the growth energy of the biological cell is calculated $E_{Biological \text{ Cell}} = \ln \left(\ln \frac{dG}{dC} \right)^2$, where it is challenging to differentiate between tumor growth rate and its growth energy, as for the same mass the fast growing tumor needs less drug energy than that of the slowly growing one. Hereby, I suggest giving the tumor doubling time, t_D , a higher consideration in estimating the administering doses prior the treatment. Accordingly, the formula for estimating the effective dose activity is: $W_r = Q_r \Rightarrow \ln \left(\ln \frac{dG}{dC} \right)^2_{Biological \text{ Cell}} \times C_0 \times h\% = \ln \left(\ln \frac{dA}{dN} \right)^2_{Nuclei} \times \frac{\text{mass loss}}{\text{mass number}} \times N_0$. Considering ^{131}I as a reference for dose calculation, allowing expression of the tumor growth energy in MeV or Joules, which enables the efficacy of the isolated radiotherapy to be checked. Consequently, to estimate the required dose from the ^{131}I according to the new concept of mass-energy conversion and the work-energy principle, the formula is simplified to $\Rightarrow A_0 = 2.48892 \times 10^{-8} \times h\% \times C_0 \times \ln \left(\ln \frac{dG}{dC} \right)^2_{Biological \text{ Cell}} \text{ MBq}$, whereas to replace the ^{131}I by another in a differential absorption treatment $\Rightarrow Q_I \times A_{0I} \times t_{1/2I} = Q_P \times A_{0P} \times t_{1/2P}$, where P is the other radioactive isotope. Moreover, to estimate the required dose directly from any radioactive isotope, the previous formula is generalized to $\Rightarrow A_{0Isotope} = \frac{[-\ln 2]}{t_{1/2Isotope}} \times \frac{E_{Tumor} \times E_{Iodine-131}}{Q_{Isotope} \times E_{Iodine-131}} \text{ Bq}$.

The accuracy of the work-energy principle calculations has been checked against prior experimental treatments,

which is considered to be a fully accepted measurement in which to make a comparison to determine the accuracy of the dose calculation, taking into consideration that Auger electrons from radionuclide decay may be more effective in very small tumors to avoid a cross dose, while they would be ineffective against radionuclide-void tumor cells. Conversely, in large tumors with an uneven distribution of radionuclide, a β -decay radionuclide would be more effective. While the accuracy of the initial tumor parameters [mass (m), doubling time (t_D), and growth energy (E_G)] are estimated from the CT scan, besides earlier or more accurate assessment of tumor response by PET with the glucose analogue ^{18}F -FDG, allows the administered doses for the relapsed tumors at any time t to be modified during the treatments according to the following formula $\Delta D = \left(\frac{r_{Treated}}{r_{Initial}} - 1 \right) \times E_{Tumor(Joule)} \times \frac{t_P}{t} \times \frac{\ln 2}{t_{1/2Isotope}} \times \frac{6.242 \times 10^6}{Q_{Isotope(MeV)}} \text{ MBq}$, which contributes to the safest and lowest-cost successful treatment. Monitoring the responses of the controlled and the relapsed tumors shown by Thakur and Coss [3] is congruent to that shown by the calculations of this approach, which implies harmony between the physical calculations and the results of the statistical analysis. With promising efficacy, lower risk, and a lower relatively affordable cost of a lipid-soluble complex, this approach assessed the therapeutic significance of lipid-soluble compounds with the radioactive metal ions. It passively diffuses through the cell membrane, binds to cytoplasmic components, and remains cell-bound until decay, protecting system isolation by a measure of 98%, which plays a major role in targeted tumor therapy.

Discussion

This paper describes a methodology to determine dose equivalency between different radionuclides used for therapeutic interventions. The approach is obviously appropriate for all conditions and can be extrapolated to all instances and all nuclides. It linked the radiobiology associated with dose delivery and views dose from a purely physical model of energy deposition, through the use of three correction factors used to correct or to modify the administered dose in case of isolated system violation. These factors are: (1) energy loss external to the tumor, (2) effect of dose non-uniformity on cell survival, and (3) effect of correlation of dose nonuniformity with cell proliferation rate [19], or as presented in the provided application, using the isolated system technique. The manuscript posits that total energy deposited in a known volume for one nuclide can be made equivalent to another nuclide for the same volume. This is true when only dE/dm is considered; however, both the biological issues and physical issues should be considered to assess the effectiveness of dose delivery, such as type of ionizing radiation (photon versus

particle), path length, range as shown by Meiring et al. [33], number of ion pairs created per unit length, subsequent production of free radicals during ionization, dose rate versus dose, necrosis versus viable tissue, mechanism of nuclide delivery to specific cells (blood delivery, cellular diffusion), relationship between cell cycle and energy deposition all must be taken into consideration. For example, the issue of minimizing dE/dX or energy lost per unit pathway—to satisfy closed system conditions—depends on the injection materials used and the technique, which should ensure dose delivery to the tumor to be fully absorbed within the permitted constraints of lost energy. This was clear in the provided application using ^{111}In , which bound to transferrin, or lactoferrin clears rapidly via urinary excretion and minimizes radiation dose to the whole body or other normal tissues, which is an additional advantage of this radionuclide. The path lengths of the Auger electrons emitted by ^{111}In range from 0 to 8.6 μm , those of the conversion electrons are from 200 to 600 μm , and the mean free paths for the two γ -rays are approximately 6.5 and 8 cm, respectively [29, 34]. Furthermore, this approach is applicable to all tumors, regardless of the tumor type, its receptor density, the receptor heterogeneity, and the vascularity, its hypoxic status, including those that may be refractory to chemo— or radiotherapy. The list of lipid-soluble complexes of ^{111}In is not limited to ^{111}In -oxine. Other lipid-soluble complexes, such as ^{111}In —Merc and ^{111}In -tropolone, could be equally effective. ^{111}In -oxine is predominantly preferred, not only because it is commercially available but also because the intracellular behavior of this compound is more thoroughly investigated than that of ^{111}In -Merc [3] or any other ^{111}In compound that can be used for this application. However, this targeted approach is not limited to the use either of ^{111}In or to its oxine, Merc, or tropolone complexes. Any other radionuclide of therapeutic importance chelated with any compound that could form a lipid-soluble complex with the radioactive metal ions would serve the purpose. For example, ^{177}Lu and ^{90}Y are possible candidates for this purpose, where the protein-bound such radionuclide then remains within the cell [3]. Because this agent needs to be injected directly into the tumor or the portion of it that would not be safely extracted, the technique of using a multihole needle in the presence of light pressure on the needle holes to prevent any solution oozing out of the tumor, ensures uniformity of the dose distribution. The dose may not fully reach the active tumor volume [5], when decay is by alpha or other charged particle, where dE/dX is enlarged if primary decay occurs by high energy gammas, also if the ionization, and free radical creation may occur outside the ROI. In either case, this would negate the primary premise of the energy equivalency, so doses in these cases cannot be denoted or meant an effective doses. However, it is suggestive that

radio immunotherapy using radionuclide with shorter ranges may have a potential role. Ultrasound or fluoroscopic guidance techniques have made precise needle insertions routinely feasible, which could be applied for intratumoral injection of these agents. Because of this possibility, intratumoral injections are gaining popularity. Because internalization of the antibody-antigen complex does not lead to rapid ionizing, this may be a rational choice for a therapeutic radionuclide [5]. The decay of radionuclide by electron capture results in the emission of a large number of low-energy Auger electrons, most of which possess ranges of 0.2 nm in tissue. These short-range electrons and the charge buildup on the daughter atom are responsible for the high linear energy transfer (LET)-type damage produced by radionuclide decays, when incorporated directly into the DNA of target cells [34–36], this resembles those produced by X-ray irradiation [5]. However, they do reach the nuclear DNA from the cell surface. Nevertheless, intracellular accumulation of the decay of radionuclide by electron capture will yield substantially greater dose to the cell nucleus (by a factor of 2–3) than cell-surface accumulation. In addition, the relative importance of cross dose (i.e., from decays outside the cell of interest) is significantly less for electron capture decay than for beta decay radionuclide, which decays within several millimeters (a vastly larger volume) and may contribute to the cross dose [18]. To investigate the therapeutic efficacy of an auger emitter and the β emissions for a comparable study, the isotopes of radioiodine are a good examples as they emit different decay energy particles [5]. ^{125}I emits ultra-short-ranged (generally less than 1 mm) auger and Coster-Kronig electrons and produces high LET cytotoxic effects, especially when ^{125}I is deposited in the proximity of the cell nucleus [5]. In small tumors, the majority of the ^{131}I β decay energy deposition occurs outside the tumor, suggesting that ^{125}I may be more effective in such circumstances. Conversely, in large tumors with an uneven distribution of radionuclide, ^{125}I may be inferior to ^{131}I , as auger electrons would be ineffective against radionuclide-void tumor cells [5, 6]. A possible interpretation of these findings is that there is a geometric enhancement of absorbed dose to the nuclei of cells that have internalized ^{125}I for example, which causes its biologic effectiveness to be greater than expected for extra cellular or surface-bound activity. Although ^{125}I decays in the cytoplasm will not result in a greater radiobiologic effectiveness per unit dose, the average dose per decay to the nucleus of an antigen-positive cell will be higher than that to an antigen-negative cell. The radiation dose from a radionuclide source decreases with distance according to the inverse square law and because of electron attenuation. Additionally, because antigen-positive tumors will accumulate radionuclide largely than antigen-negative cells, the dose enhancement will be significantly greater than from geometric factors alone. For

^{125}I , the electron emission ranges are so short that the self-dose contribution can exceed that from electron cross fire and small changes in the subcellular distribution can have a significant impact on the effectiveness of the radiopharmaceutical [5]. The geometric enhancement for β -emission radionuclide, such as with ^{131}I for example, is insignificant because the self-dose to the targeted cell is small relative to the cross-dose contribution from the longer-range β -emissions. Factors have been calculated for the dose to the nucleus from ^{125}I decays distributed uniformly in the cytoplasm and on the cell membrane, but not specifically for distributions within extracellular space [5]. Thus, ^{131}I appeared to be more efficient than ^{125}I . This is likely explained by the greater energy release in a short time interval by ^{131}I compared with ^{125}I [5]. Newer techniques of dosimetry that are now under investigation may eliminate some of these problems by fusing the structural CT or MR images with the functional nuclear images to obtain three-dimensional dosimetry [4]. Similarly, the development of imaging techniques that combine SPECT with CT, or PET with CT, may improve quantitation of targeted radiodiagnostic and radiotherapeutic agents in comparison with methods performed with conventional imaging techniques [4]. Thereby, a combined PET and CT scanner is a practical and effective approach to acquiring co-registered anatomical and functional images in a single scanning session. Since the combined PET/CT scanner post injection transmission implies that the CT images must be unaffected by the presence of radioactivity in the patient, therefore, ^{18}F -FDG PET can play a significant role in establishing response to treatment. A significant metabolic change can be established by comparing uptake values from pre—and post-treatment scans, although such comparisons can only be made accurately on attenuation-corrected, quantitative PET images. A difficulty for the interpretation of FDG PET scans, particularly in the abdomen, is the absence of identifiable anatomical structures. The low contrast and low-resolution anatomy visualized in the PET scan is insufficient for precise anatomical localization of foci of abnormal uptake. The lack of anatomical information in FDG PET scans frequently complicates interpretation, and considerable difficulty is encountered in accurately assigning functional abnormalities to specific anatomical structures [37]. The potential for more tumor-specific tracers may eliminate even the low-resolution anatomical details discernible in FDG scans. Another example for biological consideration is the issue of necrosis versus viable tissue. The mechanism of nuclide delivery to specific cells through considering the significant contribution of cell hypoxia to treatment failure is due to its high resistance to traditional chemical disinfection for penetration difficulties in the hypoxic regions and for nutrient and oxygen shortage, which lead to cells dividing more slowly than in the well-oxygenated regions. This causes higher

resistance to chemical and radiation treatments, as both target rapidly dividing cells, or requires oxygen for efficacy [9–14]—as mentioned before in Item 1.8. Consequently, taking the percentage of the hypoxic cells into account in estimating the required energy of the effective dose has contributed to the accuracy of the use of the work-energy principle, which is clear in the provided application. Using the law of conservation of energy to relate to the total decay of a radionuclide in a known and fixed volume has covered different sizes and different radionuclides as well. Even the relapsed cases followed the work-energy principle for their re-growth, which make the priority for this concept to estimate the required effective doses by the using the Emad formula, as it measures growth and decay energies in the same unit (Emad), to allow application of the work-energy principle. Such an approach in radioactive dose calculation introduces promising objectives towards treatments and experiments as well. Current studies focus mainly on statistical models to estimate the required dose for a treatment. Although such models can give good results, they lack the predictive accuracy of conceptual reasoning, in addition to the costs of such studies and the great number of animals utilized. Let us imagine how researchers reach the proper dose through the statistical analysis; thus, Thakur and Coss [3] identified the useful quantities utilized in their interesting application by citing nine previous researches and finally considered that further studies leading to administration of a calculated quantity of ^{111}In that would induce cell killing are strongly warranted. This encouraged the author of this paper to choose their application [3] to present a physical approach. This choice is considered to be like a practical proof for the application and assessment of the work-energy principle in isolated radiotherapy. Consequently, the accuracy of this physical method has been checked and compared with the statistical results of several experimental treatments conducted in different hospitals and universities [19, 39, 40], and achieved an accuracy of 97–100%. These promising results have urged the author of this study to depend on the statistical analysis of those great scientists on purpose, regarding their results as a “gold standard” or fully accepted measurement against which to make a comparison to determine accuracy of the approach.

Conclusion

Treatment success shows that administering the appropriate dose, skillful injection techniques with lipid-soluble complexes and monitoring tumor response to therapy are three completely dependent objectives towards the isolated system for which no energy crosses the system boundary by any method. Administering the appropriate low-waste dose can be performed by estimating the required dose of

the radioactive isotopes by the physical concept of the work-energy principle, considering the interaction between the drug and the tumor as an isolated system. The strategy of estimating the required dose is to estimate the required dose of iodine-131 as a reference for the required isotope decay energy, which would be replaced by the most suitable alternative radioactive isotope. The primary goal of administering the appropriate dose is to significantly reduce the costs of drug, where accuracy of estimating the initial effective radioactive dose depends on determining the initial tumor parameters (m , t_D , E_G) from the CT scan thoroughly and then equalizing the growth energy of the tumor by the decay energy of the effective radioactive dose. Even for the relapsed cases, the re-growth energy would be equivalent to the difference in the decay energies of the lethal dose and the insufficient one. Optimizing a uniform dose delivery achieved, by chelating the administered dose with any compound that could form a lipid-soluble complex with the radioactive metal ions, injected directly into the tumor, by the use of a multihole needle to improve the distribution of the injectate solution over the regular end-hole needle and to ensure uniform dose absorption, avoiding decay outside the cell of interest as well. Injection skills using ultrasound or fluoroscopic guidance techniques have made precise needle insertions routinely feasible, which could be applied for intratumoral injection of these agents to ensure maximizing the tumor dose uniform absorption while monitoring its response to therapy in order to stop ineffective therapies and avoid complications caused by tumor progression. This can be detected through monitoring the tumor response through newer imaging techniques that combine SPECT with CT, or PET with CT, may improve quantitation of targeted radiodiagnostic and radiotherapeutic agents so that nonresponding tumors can be identified early to modify the administered dose. The therapeutic efficacy of the decay of radionuclide by electron capture was compared with that of beta decay radionuclide to conclude that higher activities of electron capture donor were required for an equivalent tumor growth delay relative to that of beta decay radionuclide. On the other hand, this suggests that Auger electrons may be more effective in very small tumors, while they would be ineffective against radionuclide-void tumor cells. Conversely, in large tumors with an uneven distribution of radionuclide, beta decay radionuclide would be more effective. This is likely explained by the greater energy release in a short time interval by the β emitter compared with electron capture donor [18].

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