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ORIGINAL PAPER

Radiotherapy and risks of tumor regrowth or inducing second cancer

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Abstract Considerable research is aimed at determining the mechanism by which tumor cures, or regrows or second cancer develops, to be predictable and controllable. The wide range of doses, from low to very high, estimated statistically is responsible for such risks. A mathematical model is presented that describes both: the growth due to lower or over irradiated doses or the post therapy relapse of human cancer, and the shrinkage due to either of over irradiated doses, or appropriate irradiated doses. Simulations of the presented model showed that the initial tumor energy, administered dose energy, and their subsequent summation of tumor regrowth energy are always balanced with summation of Whole Body Cell Energy Burden during all treatment phases. Tumor regrows if its energy is higher than that of the dose, or if the increase of dose energy from that of the tumor is less than the one required to complete its shrinkage path. Patient-specific approaches that account for variations in tumor energies should enable more accurate dose estimates and, consequently, better protection against either lower or over irradiation that could lead to tumor regrowth and increase risks of second cancer.

Keywords Curing time · Summation of tumor growth energy · Whole Body Cell Energy Burden · Lower irradiated dose treatment · Over irradiated dose treatment

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1 Introduction

Since, the number of cancer survivors increases, prediction of radiotherapy induced second cancer risks becomes a considerable issue. The lifetime risk of radiation-induced second cancers in these subjects can't be neglected (Brenner et al. 2007), and these second cancers can result in morbidity or high death rates. For instance, it is evident that breast cancer radiotherapy can cause lung cancer (Brenner et al. 2000; Ron 2006), and secondary rectal cancer rates are higher in prostate cancer patients (Harlan et al. 2001a). Consequently, second malignancies induced by radiotherapy are becoming a growing concern such that radiation is considered a potential cause of cancer but, at the same time, this risk is greatly outweighed by the reduction in risk that occurred due to treating the original tumor (Schneider and Besserer 2010). Many studies dealing specifically with some related problems like relapsed cases have conducted such risks, but most of them have not introduced a conceptual reasoning to this issue for its statistical analysis nature, or could not show how to predict the time necessary for either curing or regrow. Yet, none of these latter-day scientists could propose a theory or a concept for the mechanism of the treatment kinematics of such an unlikely appearing event as the curing or regrowth time of radiotherapy treatment. Strategy of cancer treatments is to include all cancer phases: phase I prior to the treatment, to phase II during it and to phase III afterwards. Phase I clinical trials are conducted to find recommended doses, where toxicity of the agent is typically assessed to determine what dose is appropriate for subsequent trials. Since, the statistical power of phase I drug trials is inadequate to assess antitumor efficacy, currently, Emad Moawad presents a promising physical power approach of phase I, contributing to the safest and low cost successful

treatment. It linked the radiobiology associated with dose delivery and viewed dose from a purely physical model of energy deposition (Moawad 2010). The equation of such an approach that can be applied for all types of radio therapies is as follows:

$$A_0 \times Q_{Iso} \times t_{1/2} = G_0 \times (E_{Cell} \times h\% \times Emad_{131I}) \times t_D, \quad (1.1)$$

where

$$Emad_{131I} = \frac{C^2}{e} \times 131^{1-\frac{1-\ln E_{131I}Emad}{\ln 131}} = 23234.59MeV, \quad (1.2)$$

A_0 & G_0 are the initial activities of each of administered doses and the tumor, respectively, Q_{Iso} is the used isotope decay energy, $t_{1/2}$&t_D are the half-life time of the used radionuclide and the tumor doubling time, respectively, while E_{Cell}&h% are the tumor cell growth energy in Emad and the percentage of the hypoxic cells, respectively (Gillies and Gatenby 2007; Sullivan and Graham 2007; Brown 1999). Knowing that a tumor of 1 g converted into 10^9 ng contains 10^9 cells, it would be more convenient to express the tumor cell growth energy by nanoscale as equivalent to the growth energy of a tumor of 1 ng or one nanoparticle investigating whether we can directly control matter on the molecular scale. Hereby, in all sections of the current approach the nanoparticle will be expressed by the cell itself ($E_{cell} = E_{ng}$), i.e.,

$$A_0 \times Q_{Iso} \times t_{1/2} = G_0 \times \left(E_{Tumor.of.1.ng} \times h\% \times 23234.59\right) \times t_D \quad (1.3)$$

This relation enables us to test all the background of medical dosimetry experiments that, based on the statistical analysis as well as prior successful treatments, had been conducted in different schools of medicine. In an effort to assist in the understanding of recurrent cancer and the energy balance processes that mediate this disease, this approach provides a framework for using mathematical techniques to study novel therapeutic strategies aimed at controlling this disease and tries to relate the cancer therapeutic drugs course of phase I prior the treatment to tumor response of phases II and III.

2 Methods and materials

2.1 Mathematical model

A mathematical investigation of the multiple pathways to recurrent cancer is covered: there are two reasons for tumor regrowth; these reasons are either underestimation or overestimation of the administered dose. The curves of energies of treated tumors by either of Lower Irradiated Dose Treatments LIDT or Over Irradiated Dose Treatment OIDT would have different attitudes for each case. An important aspect of the model is that tumor size may vary during treatment; if rate of growth is faster than that of cell killing, the tumor volume will increase. Conversely, if rate of cell killing is faster than that of the growth, the tumor volume decreases. The tested hypothesis of the current mathematical model is that summation of tumor growth energy along the studied duration $\sum_{T=o}^{T} E_{Tumor.Growth}$ results from the balance between initial tumor energy $E_{0.Tumor}$, initial drug energy $E_{0.Doses}$, and, finally, amount of energy that the whole body disposed of by rate of radionuclide decay constant within the same duration, which is known by summation of Whole Body Cell Energy Burden ∑WBCEB, such that:

$$\sum E_{Tumor.Growth} = \left|(E_{0.Tumor} + E_{0.Dose}) \mp \sum WBCEB\right| \quad (2.1.1)$$

Provided that the way of whole body self adaptation, according to the whole-culture measurement approach point of view, is that radiation effects propagate gradually by radionuclide decay constant circularly from internal nanoparticles (cells) to be released in the neighborhood and so on till the outer nanoparticles (cells) and then to the surrounding environment. This recovery operation lasts till Whole Body Cell Energy Burden (WBCEB) for all body nanoparticles (cells) reaches the Natural Background Radiation (NBR) level settled by the Committee on the Biological Effects of Ionizing Radiations (BEIR) of the National Research Council, and shown by Emad Moawad that it is equivalent to (E_{NBR} = 0.0000538132 Emad) (Moawad 2011). Thus, all body nanoparticles (cells) were involved in recovery burden, and then ∑WBCEB = the Whole Body Cell Energy Burden (WBCEB) gained due to radiotherapy × C_0 (the total number of the body nanoparticles (cells)). Negative or positive sign (∓) to cover all types of treatments with respect to dose energy, negative for either of the Over Irradiated Dose Treatment OIDT or treatments that follow work–energy principle WEPT (Moawad 2010), and positive for the Lower Irradiated Dose Treatment LIDT. The main features and assumptions of the mathematical model describing the response of the tumor to radiotherapy are as follows: the tumor is viewed as a densely packed, radially symmetric sphere. Cell movement is produced by the local volume changes that accompany cell proliferation and death. The spheroid expands or shrinks at a rate that depends on the balance between cell growth and division and cell death within the tumor volume (O'Donoghue 1997). Controlled tumors follow a growth curve by an exponential function of

growth constant equivalent to $\ln 2/t_D$, where t_D is the tumor doubling time; the initial tumor cell energy can be determined by Emad's formula (Emad 2010):

$$E_{Tumor.of.1ng} = E_{Tumor.Cell} = \ln\left[\left(\ln\frac{\ln 2}{t_D}\right)^2\right] \quad (2.1.2)$$

According to the work–energy principle, the accuracy of estimating the initial effective radioactive dose depends on the equivalence of the initial growth energy of the tumor and the initial decay energy of the effective radioactive dose (Moawad 2010), i.e.,

$$E_{0.WEPT} = E_{0.Tumor} \quad (2.1.3)$$

Such Work–Energy Principle Treatment WEPT posits that the tumor will be cured such that the tumor shrinkage constant will be identical to the decay constant of the used radionuclide. This means that in such a case, the value of the used radionuclide half-life time will be an approximate value for the half-time of doomed cell loss:

$$t_{1/2Shrinkage} = t_{1/2Isotope}, \quad (2.1.4)$$

i.e., the treated tumor according to WEP will be cured and shrunken exponentially by the decay constant of the used radioactive dose. This provides a hypothesis that curves of energies of each of the treated tumor according to WEP, and the radioactive dose as functions of time are congruent along the whole treatment. This means that energy of the tumor E_{Tumor} along the WEPT is

$$E_{Tumor} = E_{0.Tumor} \times e^{\frac{-\ln 2}{t_{1/2.Isotope}}\times t} \quad (2.1.5)$$

Accordingly, the ratio of the dose released energy during a certain time to summation of tumor energy along the shrinkage stage $\sum_{t=o}^{T} E_T$ in the same duration is equivalent to the radionuclide decay constant, i.e.,

$$\sum_{t=o}^{T} E_T = E_{0.D}\left(1 - e^{\frac{-\ln 2}{t_{1/2.Isotope}}\times t}\right) \times \frac{t_{1/2.Isotope}}{\ln 2} \quad (2.1.6)$$

Such a hypothesis can be tested by integrating the function of the tumor energy pathway along the studied duration. In addition, this approach posits that in case of WEPT treatments, the time passed for the WBCEB under a successful cancer therapy, without tumor regrowth $\left(\sum_{T=o}^{T} E_{Tumor.Growth} = 0\right)$ to reach the E_{NBR} is the curing duration. Then, in such a case, from Eq. (2.1.1), summation of Whole Body Cell Energy Burden is equivalent to the sum of energies of each of the dose and the tumor, i.e.,

$$\sum WBCEB = E_{0.Dose} + E_{0.Tumor} \quad (2.1.7)$$

$$\Rightarrow WBCEB = \frac{E_{0.Tumor} + E_{0.Dose}}{C_{0.Whole.Body}} \quad (2.1.8)$$

since $E_{0.Tumor} = E_{0.Dose}$ in WEPT as shown in Eq. (2.1.3), then $WBCEB = \frac{2\times E_{0.Dose}}{C_{0.Whole.Body}}$. Such curing time should be minimized as much as possible to reduce serious normal tissues toxicities (Schneider and Besserer 2010). Therefore, radionuclides with short half-lives offer advantages over those with longer lives; advantages over existing techniques include extremely low radiation dose because of the short half-life of the isotope ease. After passing n radionuclide half-life times the WBCEB will be decreased to the E_{NBR}. Accordingly, $E_{NBR(Cell)} = \frac{WBCEB}{2^n} = \frac{2\times E_{0.Dose}}{2^n \times C_{0.Whole.Body}}$, and then curing time of the radiotherapy treatments is:

$$T_{Curing} = t_{1/2.Isotope} \times \log_2\left(\frac{WBCEB}{E_{NBR}}\right)$$
$$\Rightarrow T_{Curing} = t_{1/2.Isotope} \times \log_2\left(\frac{2 \times E_{0.Dose}}{C_{0.Whole.Body} \times E_{NBR}}\right) \quad (2.1.9)$$

The significance of the above relation shows the possibility to decrease time of both of phase II and phase III in which the treated body disposes dose and tumor energies and comes back to ENBR or in other words: disposes tumor and drug toxicities to decrease the risks for inducing second cancer (Schneider and Besserer 2010). The remission duration is taken as the time between the start of treatment and tumor regrowth to some size or cell number threshold (O'Donoghue 1997). In either of LIDT or OIDT, summation of WBCEB will be decreased by energy consumed for regrowth, and then from Eqs. (2.1.7) and (2.1.1)

$$\sum WBCEB = \left|(E_{0.Tumor} + E_{0.Dose}) - \sum E_{Tumor.Growth}\right| \quad (2.1.10)$$

Also, for time of tumor regrowth from Eq. (2.1.9)

$$T_{Growth} = t_{1/2} \times \log_2\left(\frac{|E_{0.Tumor} + E_{0.Dose} - \sum E_{Tumor.Growth}|}{C_{0.Whole.Body} \times E_{NBR}}\right) \quad (2.1.11)$$

This equation is not applicable for tumor regrow time prediction as $\sum E_{Tumor.Growth}$ must be known first, but it contributes to prove that the energy balances during radiotherapies for all types of tumor responses in accor-

dance to the given experimental data. In addition, the physical quantity, ∑WBCEB, introduced in the presented mathematical model can be calculated according to the whole body measurement approach point of view, by considering that whole body cells gain energy after exposure to radiation, which leads to the increase of their growth energy exponentially by the growth constant of used radionuclide. Accordingly, if a healthy subject has been exposed to radiation dose for a certain duration (T), then

$$\mathrm{WBCEB} = \mathrm{E_{NBR}} \times e^{\frac{\ln 2}{t_{1/2}} \times T},$$

from Eq. (2.1),

$$\Rightarrow \sum_{t=0}^{T} \mathrm{WBCEB} = C_0 \times \mathrm{E_{NBR}} \times e^{\frac{\ln 2}{t_{1/2}} \times T}. \tag{2.1.12}$$

In LIDT, in the absence of energy equilibrium between initial tumor energy, $E_{0.Tumor}$, and that of administered dose, E_{LIDT}, tumor growth will be the resultant of the activated nuclear transmutations, as shown by Emad Moawad (2010); LIDT curve would be grown to a level of tumor energy equivalent to

$$\mathrm{E_{Tumor}} = \mathrm{E_{0.Tumor}} + \Delta \mathrm{E_{Doses}}, \tag{2.1.13}$$

where ΔE_{Doses} is the difference between the initial tumor energy and that of insufficient dose administered in LIDT, i.e., $\Rightarrow E_{Tumor} = E_{0.Tumor} + (E_{0.Tumor} - E_{LIDT})$. In addition, summation of tumor response growth energy after dose delivery would be: $\sum_{T=0}^{T} E_{Tumor.Growth} = E_{0.D} + E_{0T} + \sum_{T=0}^{T} \mathrm{WBCEB}$ as postulated in Eq. (2.1.1). Then, from Eq. (2.1.12)

$$\sum_{T=0}^{T} \mathrm{E_{Tumor.Growth}} = \mathrm{E_{0.D}} + \mathrm{E_{0T}} + C_0 \times \mathrm{E_{NBR}} \times 2^{\frac{T}{t_{1/2Isotope}}}, \tag{2.1.14}$$

and can be checked through integrating the area shown in Fig. 1 between tumor energy curve of LIDT and that of the initial energy level. While for OIDT compared to WEPT in case of tumor shrinkage, the difference between their released energies would be equivalent to the summation of the difference of their tumor energies along shrinkage duration $\Delta E_{Doses} = \sum \Delta E_{Tumor.Shrinkage}$, i.e.,

$$\Rightarrow \mathrm{E_{0.OIDT}} - \mathrm{E_{0.WEPT}} = \sum (\mathrm{E_{Tumor.WEPT}} - \mathrm{E_{Tumor.OIDT}}). \tag{2.1.15}$$

To test the previous hypothesis, the tumor energy progression should be determined along the whole treatment for OIDT and WEPT. The accumulated difference of the tumor energies along both treatments, which is the sum of difference of energies of the faster shrunken than the slower one, should be equivalent to the accumulated difference of energy of the administered doses in both treatments, i.e.,

$$\mathrm{E_{0.OIDT}} - \mathrm{E_{0.WEPT}} = \mathrm{E_{0.T}} \times \left(\int_0^T e^{\frac{-\ln 2 \times t}{t_{1/2.Isotope}}} dt - \int_0^T e^{\frac{-\ln 2 \times t}{t_{1/2.Shrinkage}}} dt \right). \tag{2.1.16}$$

The different tumor responses along treatments of different dose energies with respect to that of the tumor are represented graphically in Figs. 1 and 2.

For OIDT, curve of tumor response energy would be compressed, following a higher decay constant than that of the used radionuclide, of half-life time $t_{1/2.Shrinkage} > t_{1/2.Isotope}$, leading to faster shrinking than that of the WEPT as shown in Figs. 1 and 2, i.e.,

$$\mathrm{E_{Tumor}} = \mathrm{E_{0.Tumor}} \times e^{\frac{-\ln 2}{t_{1/2.Shrinkage}} \times t}.$$

At the same time, this model enables to predict the shrinkage half-life time during a certain time T in either WEPT or OIDT according to the following equation:

$$t_{1/2Shrinkage} = \frac{2^n}{2^n - 1} \times \left[1 - 2^{\frac{-T}{t_{1/2Isotope}}}\right] \times \left[t_{1/2Isotope} - \ln 2 \left(1 - \frac{E_{0.OIDT}}{E_{0.Tumor}}\right)\right], \tag{2.1.17}$$

where $E_{0.OIDT} \geq E_{0.Tumor}$. Hence, by trial and error method, assuming values of n satisfies

$$T = t_{1/2Shrinkage} \times n, \tag{2.1.18}$$

since

$$\lim_{n \to \infty} \left(\frac{2^n}{2^n - 1} \times \left(1 - 2^{\frac{-T}{t_{1/2.Isotope}}}\right) \right) = 1 \Rightarrow$$

then Eq. (2.1.17) can be simplified for long-term radiotherapy effects to $t_{1/2Shrinkage} = t_{1/2Isotope} - \ln 2 \left(1 - \frac{E_{0.OIDT}}{E_{0.Tumor}}\right)$. Moreover, Eq. (2.1.17) shows that for WEPT: $E_{0.Tumor} =$

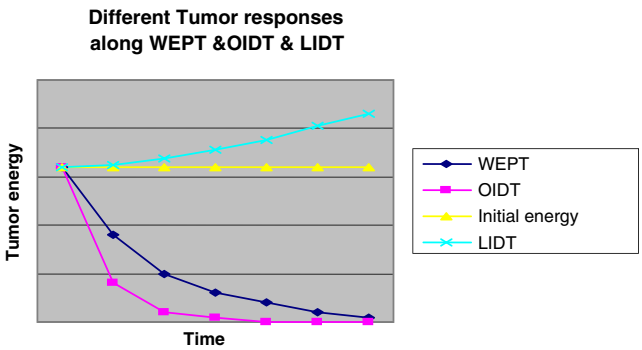

Fig. 1 Different tumor responses in LIDT and WEPT and OIDT

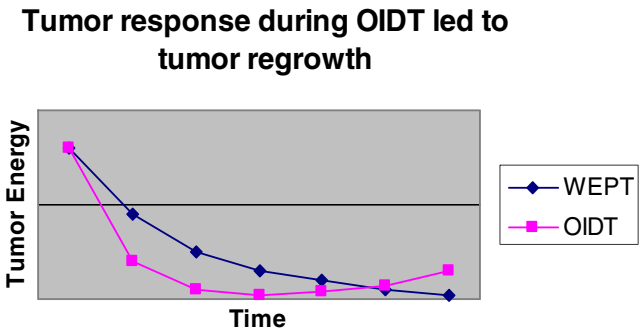

Fig. 2 Tumor response in OIDT led to tumor regrowth

$E_{0.WEPT} \Rightarrow t_{1/2Shrinkage} = t_{1/2Isotope}$ as postulated for the presented mathematical model. This fast shrinkage will last, under the condition that the difference of the total decay energies that are released from both treatments, OIDT and WEPT, is higher than the accumulated difference of the tumor energies along both treatments, i.e., $\Delta E_{Doses} \geq \sum \Delta E_{Tumor.Shrinkage}$, as shown in Fig. 2. Once these differences become close to each other, as the shrinkage slows gradually to the minimum tumor size of OIDT, and then reverses its response, regrows to achieve the balance with that of WEPT according to its time course when $\Delta E_{Doses} = \sum \Delta E_{Tumor.Shrinkage}$. Afterwards, the tumor energy curve of the OIDT will continue to regrow negatively above that of the WEPT as shown in Fig. 2 to a level of energy such that this accumulated tumor response energy would be equivalent to $\sum_{T=0}^{T} E_{Tumor.Growth} = E_{0.D} + E_{0T} - \sum_{T=0}^{T} WBCEB$ as previously postulated for the mathematical model in Eq. (2.1.1); from Eq. (2.1.12)

$$\sum_{T=0}^{T} E_{Tumor.Growth} = E_{0.D} + E_{0T} - C_0 \times E_{NBR} \times 2^{\frac{T}{t_{1/2Isotope}}} J, \quad (2.1.19)$$

which can be checked through integrating the area shown in Fig. 2 between the tumor energy curve of OIDT and that of WEPT starting from their intersection.

2.2 Lower irradiated dose treatment

This application shows that tumors under LIDT will grow or gain energy equivalent to the difference in energy of WEPT from that of LIDT, i.e., $E_{Tumor} = E_{0.Tumor} + \Delta E_{Doses}$, $\Delta E_{Doses} = E_{WEPT} - E_{LIDT}$ as shown in Eq. (2.1.13). Furthermore, it tests the hypothesis of the LIDT mathematical model $\sum E_{Tumor.Growth} = |(E_{0.Tumor} + E_{0.Dose}) + \sum WBCEB|$ as shown in Eq. (2.1.1). Thakur et al. (2003) showed 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 (0.61 cm in diameter) 5×10^8 ng and treated with 16.7 MBq (450 μCi). 111In-oxine grew, on the average, only 17% irrespective of their type—breast, prostate, or colorectal, within 28 days after injection (Thakur and Ron Coss 2003), while those treated by 18.5 MBq (500 μCi) did not grow within the same duration as shown in Figs. 3 and 4.

To test whether the lower administered dose (16.7 MBq of 111In) was appropriate or not, the tumor cell growth energy, $E_{0.Cell}$, and its doubling time, t_D, which is adequate for such a dose can be derived from the equations

$$E_{0.ng} = E_{0.Cell} = \frac{N_{0.Iso} \times Q_{Iso}}{m_0 \times 10^9 \times h\% \times Emad_{131I}} Emad,$$

$$t_D = \ln 2 \times e^{\sqrt{e^{E_{0.Cell}}}} s$$

(Moawad 2010), which show that this dose was appropriate for tumor cell (nanoparticle of 1 ng) growth energy equivalent to $E_{o.Cell}=E_{o.ng}=4.385$ Emad, corresponding to tumor doubling time, $t_D=5384.51$ s=0.06 days, while the presented data shows that t_D was equivalent to 28 days. This great difference in dose energy supply from that of the tumor allows tumor growth through the phenomenon of transmutation that permits transformation of elements in live organisms [9 s]. For growth calculations, Emad Moawad explained (2010) that those little doses were not sufficient. The growth energy of the untreated (controlled) tumor was 1.0091 J, while the decay energy of the insufficient dose from In-111=0.816 J only. Tumor growth energy (17%) + dose decay energy (insufficient dose) = 0.1717+0.8161=0.988 J, which achieves an accuracy of 98% of the growth energy of the untreated (control) tumor (1.0091 J). In addition, $\Delta E_{Doses} = 1.0091J - 0.816J = 0.1931J$. At the same time, the regrowth energy, $\Delta E_{Regrowth}$,

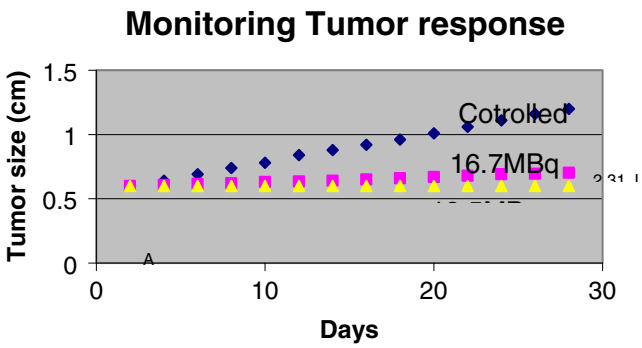

Fig. 3 Monitoring tumor responses for different doses [none, 16.7 MBq and 18.5 MBq] (Thakur and Ron Coss 2003)

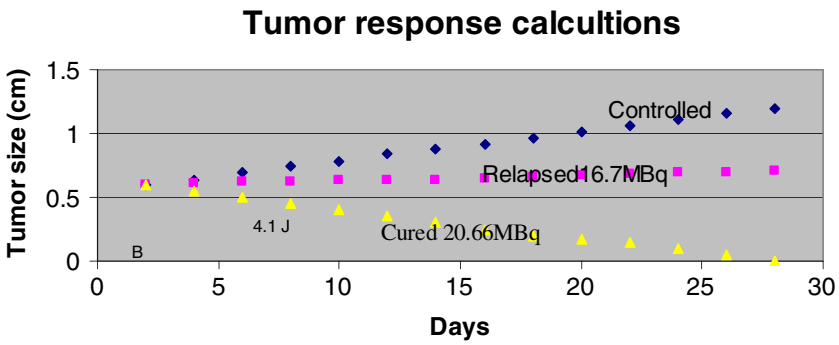

Fig. 4 Calculations of the tumor groups [controlled, relapsed and cured] responses over 28 days (Moawad 2010)

was $17\% \times 1.0091\text{J} = 0.1717\text{J}$, following a doubling time of 123.6156238 days. This indicates that the tumor regrowth energy due to LIDT is less than the difference between WEPT and LIDT dose energy. To check the hypothesis of the mathematical model: summation of tumor growth energy, $\sum E_{\text{Tumor.growth}}$, can be calculated along time of growth 28 days as presented in the experimental data as follows: from Eq. (2.1.1 & 2.1.14)

$$\sum_{T=0}^{T} E_{Tumor.\text{Response}} = 0.81612302 + 1.0091 + 25 \times 10^{8} \times \frac{0.0000538132 \times 23234.59}{6.242 \times 10^{12}} \times 2^{\frac{28\times 24}{67.9}} = 2.303\,\text{J}.$$

Tshis value can be reached by integrating the presented experimental observations by Thakur et al. as follows: $\sum_{T=0}^{T=28} E_{Tumor.\text{Regrow}} = 1.0091\times\left(\int_{0}^{28} e^{\frac{\ln 2}{123.6156238}\times t}dt - \int_{0}^{28} dt\right) = 2.317747\,\text{J}$ as shown in Fig. 3 (Fu et al. 2004). This is nearly 100% identical to the experimental data that presented by Thakur et al.'s measurement (2003). In addition, from Eq. (2.1.17), if the administered dose would be 20.66 MBq (1.0091 J), as shown by Emad Moawad, instead of the applied ones (16.7 MBq, 18.5 MBq) by Thakur et al. to satisfy the WEPT, the shrinkage half-life time is supposed to be

$$t_{1/2Shrinkage} = \frac{2^{n}}{2^{n}-1} \times \left[1 - 2^{\frac{-28\times 24}{67.9}}\right] \times \left[\frac{67.9}{24} + \ln 2\left(1 - \frac{1.0091}{1.0091}\right)\right] \Rightarrow \frac{2^{n}}{2^{n}-1} \times \frac{679}{240},$$

by trial and error method. The value of n that satisfies Eq. (2.1.18) is n=9.9 as it gives $t_{1/2.\text{Shrinkage}}$ equivalent to 2.83 days; this rate corresponds to the summation of tumor energy

$$\sum_{t=0}^{28} E_T = 1.0091\times \int_{0}^{28} e^{\frac{-\ln 2}{2.83}\times t}dt = 4.1\,\text{J}$$

along 28 days as shown in Fig. 4 (Brown 1999); this is also nearly 100% identical to the ratio of the dose released energy during the same period by the decay constant of the radionuclide, as previously postulated for the features of the mathematical model in Eq. (2.1.6) for WEPT, where $E_{0.D}\left(1 - e^{\frac{-\ln 2}{t_{1/2.Isotope}}\times t}\right) \times \frac{t_{1/2.Isotope}}{\ln 2} = 1.0091\times \left[1 - e^{\left(\frac{-\ln 2}{67.9}\times 24\times 28\right)}\right] \times \frac{67.9}{24\times \ln 2} = 4.11\,\text{J}$.

2.3 Over irradiated dose treatment

O'Donoghue et al. (2000) showed the temporal behavior of a surviving fraction for a tumor of (1×10^{11} ng) initial mass with the baseline response parameters. The t_D of the tumor cells was taken as 4 days. This represents a central estimate of values measured by bromodeoxyuridine labeling in human tumors (Terry et al. 1995; Tsang et al. 1995; Bolger et al. 1996; Bourhis et al. 1996). The single, large administrations of LSA treatment consists of an administration of 8.25 GBq (223 mCi). A value of 3 days was used as an approximate value for the half-time of doomed cell loss (Ts). The time courses of tumor regression and recurrence for the treatment showed that the minimum tumor size reached was (7.2×10^{8} ng) at 27.6 days for LSA. If remission duration is defined as the time to regrow to a tumor mass of (5×10^{9} ng), then this was 53.2 days counted from the start of dose delivery (O'Donoghue et al. 2000); these experimental data are shown in Fig. 5.

Checking the thesis of this approach and mathematical model accuracy:knowing that t_D=4 days, from Eq. (2.1.13), the growth energy of tumor nanoparticle (cell), E_{ng}, can be determined by Emad's formula from Eq. (2.1.2) as follows:

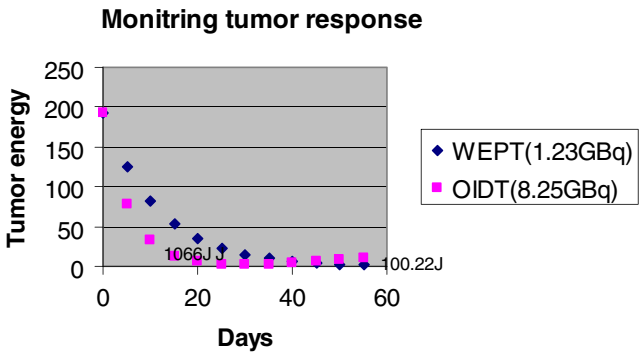

Fig. 5 Tumor response in both of OIDT and WEPT

$$E_{ng} = E_{Cell} = \ln\left[\left(\ln\frac{\ln 2}{4\times 24\times 60\times 60}\right)^2\right]\text{Emad}.$$

Then, the total tumor growth energy

$$E_{0Tumor} = \frac{C_0 \times h\% \times E_{Cell} \times Emad_{131I}}{6.242\times 10^{12}}\text{J} = \frac{\text{mass}_{ng}\times h\% \times E_{ng}\times \text{Emad}_{131I}}{6.242\times 10^{12}}\text{J},$$

$$\Rightarrow E_{0Tumor} = \frac{(1\times 10^{11}\text{ng})\times 10\%}{6.242\times 10^{12}} \times \ln\left[\left(\ln\frac{\ln 2}{4\times 24\times 60\times 60}\right)^2\right]\times 23234.59 = 192.065\,\text{J}.$$

While the administered dose was 8.25 GBq, of decay energy.

$$E_{0.Dose} = \frac{8.25\times 10^9\text{Bq}\times 8.04\text{d}\times 24\text{h}\times 60\text{min}\times 60\text{sec}\times 0.97\text{MeV}}{\ln 2\times 6.242\times 10^{12}\text{MeV/J}} = 1284.837\,\text{J},$$

which is obvious much more than $E_{0.Tumor}$ representing an OIDT, as from the point of view of this approach the initial decay energy of the administered dose was supposed to be 192.065 J, instead of 1284.837 J, and all such energy difference (1092.772 J) is considered an over irradiated dose, responsible for the consequent tumor regrowth. During this treatment, the initial tumor size shrunk, and the time courses of tumor regression and recurrence for the treatment showed that the minimum tumor size reached was 7.2×10^8 ng at 27.6 days. The corresponding half-life time of tumor decay was 3.87761 days. The first hypothesis of the OIDT mathematical model in which the accumulated difference of the tumor energy along OIDT from that of WEPT will be equivalent to the accumulated difference of energy of the administered doses in both treatments, i.e.,

$$E_{0.T}\times\left(\int_0^T e^{\frac{-\ln 2\times t}{t_{1/2.\text{Isotope}}}}dt - \int_0^T e^{\frac{-\ln 2\times t}{t_{1/2.\text{Shrinkage}}}}dt\right) = E_{0.D} - E_{0.T}$$

as shown in Eq. (2.1.16) can be tested as follows: the tumor energy progression should be determined along the whole treatment for both administrations, OIDT and WEPT. The accumulated difference of the tumor energies along both treatments, which is the sum of the difference of energies of the occasional faster shrinkage than the slower one, and the consequent regrow, should be equivalent to the accumulated difference of the energy of the administered doses in the same interval from treatment start until equivalence of tumor energies in either treatment, i.e., until their curve intersection (balancing point). Firstly, from t=0 to t=27.6 days, the stage of the fast shrinkage, size of the over irradiated tumor decreased faster than the size of the one irradiated according to WEP, due to the over irradiated dose, the difference between its decay energy, and the decay energy administered by WEP released within this interval, ΔE_{Doses}, where

$$\Delta E_{Doses} = (1284.837\text{J} - 192.065\text{J})\times\left(1 - e^{\frac{-\ln 2}{8.04}\times 27.6d}\right) = 991.58\,\text{J}.$$

While the accumulated energy differences between tumor energies along the same period is $\sum_0^{27.6}\Delta E_{\text{TumorResponse}} = \sum_0^{27.6}(E_{\text{Tumor.WEP}} - E_{\text{Tumor.Overirradiated}})$, then

$$\sum_0^{27.6}\Delta E_{\text{Tumor.Response}} = 192.065\times\left(\int_0^{27.6} e^{\frac{-\ln 2}{8.04}\times t}dt - \int_0^{27.6} e^{\frac{-\ln 2}{3.8776}\times t}dt\right) = 954.774\,\text{J} \quad (2.3.1)$$

Secondly, from t=27.6 days to t=53.2 days, the time courses of the over irradiated treatment showed that the tumor size regrow from 7.2×10^8 ng and reached 5×10^9 ng. This shows that the regrowth doubling time was

9.1564 days. The WEP treatment showed that the tumor size decayed exponentially following the decay constant of the used radionuclide. Consequently, the time courses of both treatments showed that tumor energy would get the same energy in both treatments after their start by 43.419 days. At this balancing point, the accumulated differences between tumor energies along the same period [from start till balancing point] is $\sum_{0}^{43.419} \Delta E_{Tumor.Shrinkage} = \sum_{0}^{43.419} (E_{Tumor.WEP} - E_{Tumor.Overirradiated})$, where

$$\sum_{27.6}^{43.419} \Delta E_{Tumor.Shrinkage} = -192.065 \times \int_{27.6}^{43.419} e^{\frac{-\ln 2}{8.04} \times t} dt - 1.373 \int_{0}^{43.419-27.6} e^{\frac{\ln 2}{9.156} \times t} dt = 111.616\,J. \quad (2.3.2)$$

From Eqs. (3.2.1) and (3.2.2),

$$\sum_{0}^{43.419} \Delta E_{Tumor.Shrinkage} = \sum_{0}^{27.6} \Delta E_{Tumor.Shrinkage} + \sum_{27.6}^{43.419} \Delta E_{Tumor.Shrinkage} = 954.77 + 111.616 = 1066.39J \quad (2.3.3)$$

as shown in Fig. 5. While the difference of the released energy between the over irradiated dose and the WEP one is

$$\Delta E_{Doses} = (1284.837J - 192.065J) \times \left(1 - e^{\frac{-\ln 2}{8.04} \times 43.419d}\right) 1066.9\,J. \quad (2.3.4)$$

From Eqs. (2.3.3) and (2.3.4), it can be deduced that in the same period, from t=0 to t=43.419 days, the difference between the decay energy of the over irradiated dose and that administered by the WEP that was released within this interval, ΔE_{Doses}, is equivalent to the accumulated differences between tumor energies, $\sum \Delta E_{Tumor.Shrinkage}$, i.e., $\Delta E_{Doses} = \sum \Delta E_{Tumor.Shrinkage}$, along the same period [from start till balancing point] as previously postulated by Eq. (2.1.15). To check the second hypothesis of the OIDT mathematical model: summation of tumor growth energy, $\sum E_{Tumor.growth}$, can be calculated along the time of growth, 53.2 days, as shown by O'Donoghue et al. as follows: from Eqs. (2.1.1) and (2.1.19)

$$\sum_{T=0}^{T} E_{Tumor.Regrow} = 1284.8 + 192.065 - 70 \times 10^{12} \times \frac{0.0000538132 \times 23234.59}{6.242 \times 10^{12}} \times 2^{\frac{53.2}{8.04}} = 100.6\,J$$

This value can be reached by integrating the presented experimental observations (O'Donoghue et al. 2000) as follows:

$$\sum E_{Tumor.Regrow} = 1.373 \times \left(\int_{0}^{53.2-27.6} e^{\frac{\ln 2}{9.156} \times t} dt - \int_{0}^{53.2-27.6} e^{\frac{-\ln 2}{3.877} \times t} dt \right) = 100.22\,J \quad (2.3.5)$$

as shown in Fig. 5. This is nearly 100% identical to the experimental data that was presented by O'Donoghue et al.'s measurement (2000). This test can be executed conversely; by knowing $\sum E_{Tumor.Regrowth}$, duration of such tumor response can be determined from Eq. (2.1.11) as follows:

$$T_{Regrow} = 8.04d \times \log_2 \left(\frac{|1284.837J + 192.065J - 100.22J| \times 6.242 \times 10^{12} MeV/J}{0.0000538132 Emad/Cell \times 23234.59 MeV/Emad \times 70 \times 10^{12} Cell/(Adult_{70Kg})} \right) = 53.2\,days,$$

as previously presented in the experimental data. This success in determining $\sum E_{Tumor.Growth}$ enables us to predict whether tumor will regrow or be cured after a certain time due to cancer treatment. In addition, to check the third hypothesis of OIDT mathematical model for fast shrinkage rate, the shrinkage half-life time can be predicted from Eq. (2.1.17) as follows:

$$t_{1/2Shrinkage} = \frac{2^n}{2^n - 1} \times \left[1 - 2^{\frac{-27.6}{8.04}}\right] \times \left[8.04 + \ln 2 \left(1 - \frac{1284.837}{192.065}\right)\right], \Rightarrow \frac{2^n}{2^n - 1} \times 3.716974,$$

by trial and error method. The value of n that satisfies Eq. (2.17) is n=4.6 as it gives $t_{1/2.Shrinkage}$ equivalent to 3.877 days, which is also 100% identical to O'Donoghue et al.'s presentation (2000). As the goal of our model development is second cancer risk prevention, this approach, hereby suggests that WBCEB should be less than the Low Dose Radiation (LDR) effect that was settled by BEIR and that was shown by Emad Moawad to be equivalent to E_{LDR} = 0.000538132 Emad or 12.503 MeV or $2.0030088 \times 10^{-12}$ J (Moawad 2011). In application 2.3-, $\sum$WBCEB has been increased from $(2 \times 192.065) \times C_0$ J in WEPT to $(2 \times 192.065 + 1130) \times C_0$ J in OIDT; this led to prolongation of the curing time shown in Eqs. (2.1.8) and (2.1.9) from 38.39 days in WEPT to 54.3 days in OIDT that could lead to serious normal tissue toxicities and contribute in increasing

second cancer risks. Therefore, OIDT is also considered one cause of second cancer.

2.4 Estimating the WEPT from the tumor response through the LIDT or the OIDT

This application for checking the efficacy of radiotherapies after their execution helps in preserving patients' rights against the randomized statistical dose assessment that ignores patient-specific factors. It shows that as the tumor sizes and their doubling time in patients varied widely, as these differences produced significant differences between doses assessed physically even for the same sizes (Rajendran et al. 2004). Barendswaard et al. (Barendswaard et al. 2001) showed that 4- to 6-week-old athymic female Swiss (*nu*/*nu*) mice, body weight $20-25\times10^9$ng, from their in-house nude mouse facility were injected with 10×10^6 SW1222 cells in the left thigh muscle. After 5–7 days, mice bearing tumors of $1.40–9.0\times10^8$ ng were selected. A total of 169 mice were divided into groups of 4–9 mice. Fourteen groups were administered varying amounts of mAb A33 labeled with 131I. The activities of 131I-A33 ranged from 0.925 to 18.5 MBq (0.025–0.5 mCi). Tumor size was measured bidimensionally with calipers, and the volume was calculated assuming elliptic geometry. Initial tumor sizes were between 0.14 and 0.90 cm^3 (mean, 0.44 cm^3), i.e., initial tumor masses were between 1.4 and 9.0×10^8 ng, mean 4.4×10^8 ng. Mice with tumors of differing sizes were divided into groups such that the tumor size spectrum for each group was similar. The tumors were measured every 3 or 4 days for 100 days or until the death of the animal. Mice were killed when the tumor caused apparent discomfort in walking or when its volume exceeded 2 cm^3, i.e., when tumor mass exceeded 2×10^9 ng. Observations showed that tumor growth was retarded after treatment to an extent that was dependent on the amount of activity administered. Barendswaard et al. showed that "tumors were considered cured if they failed to regrow over the period of observation (100 d after treatment), while occasional tumor cures were seen at intermediate administered activities of 131I (3.7–11.1 MBq), but a higher value (14.8 sMBq) did not produce any cures. Four of five tumors in this group became temporarily undetectable but subsequently recurred between day 40 and day 80. The highest activity of 131I administered (18.5 MBq) resulted in tumor cures in all four animals in that group." (Barendswaard et al. 2001). Barendswaard et al. showed that the maximum tolerated activities of 131I were 18.5 MBq (0.5 mCi) in this model system. Activities of 18.5 MBq 131I caused petechiae, which became apparent after 2 days and confluent after 4 days; these activities also caused progressive weight loss. Median tumor volume, normalized to initial volume, as a function of time in nude mice bore SW1222 xenografts when treated and shown in Fig. 6 as presented by Barendswaard et al. (2001).

Checking the postulates of this approach:

First: from tumor response of the controlled group, the tumor doubling time was 4 days; consequently, from Eq. (2.1.2) the cell (nanogram or nanoparticle) growth energy was

$$E_{ng}=E_{Cell}=\ln\left(\ln\frac{\ln2}{4\times24\times60\times60}\right)^2=5.14\,\text{Emad}\qquad(2.4.1)$$

Second: as the initial tumor size was not provided by Barendswaard et al., numerical simulations of Eq. (2.1.16) can be applied to investigate the tumor's initial size, which can be estimated from the thesis of the equivalence of the difference between areas under the curves of tumor response during WEPT and OIDT and the difference between drug released energy and that of the tumor, i.e.,

$$E_{0.T}\times\left(\int_0^T e^{\frac{-\ln2\times t}{T_{1/2.Isotope}}}dt-\int_0^T e^{\frac{-\ln2\times t}{T_{1/2.Shrinkage}}}dt\right)=E_{0.D}-E_{0.T}$$

as shown in Eq. (2.1.16). Then, by substituting data of this experiment, shown by Barendswaard et al. (2001) (shrinkage half-life time was 6.5 days along 20 days, for 18.5 MBq initial dose activity of 131I that corresponds to 2.881 J) in Eq. (2.1.16), calculation of the initial tumor energy shows that

$$E_{0.T}=1.2721\,\text{J},\qquad(2.4.2)$$

that corresponds to 8.168 MBq only. This means that the administered dose of WEPT was supposed to be 8.168 MBq; consequently, the doses of 14.8 MBq and 18.5 MBq are considered OIDT.

$$m_0=\frac{E_{0T}}{\sum\left(E_{0.HypoxicCell}/ng\right)}=\frac{1.2721\times6.242\times10^{12}}{5.14\times10^{-1}\times23234.59}$$
$$=6.6\times10^8 ng,$$

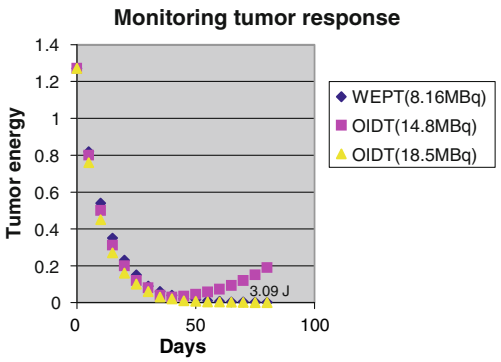

Fig. 6 Tumor response due to different doses

which is accepted as a median value for the set of treated tumors ranged (1.4–9.0)×10^8 ng, with a mean of 4.4×10^8 ng, as given by Barendswaard et al. (2001).

Forth: a dose–response relationship has been studied for the different administered doses. The highest activity of 131I administered (18.5 MBq) resulted in tumor cures in all animals, but the value of 14.8 MBq did not produce any cures and tumor regrowth was between day 40 and day 80. The tumor response after dose delivery followed an exponential shrinkage of half-life time of 6.5 days, continued only for the tumor that was assigned to the 18.5 MBq of 131I dose, and cured. On the contrary, the tumor that has been assigned to a dose of 14.8 MBq reached its minimum size after 40 days; afterwards, it relapsed, following an exponential growth of 14.46 days doubling time, and reached a relative tumor size of 6.8 with respect to the minimum size after 80 days from the dose delivery. To check the hypothesis of OIDT mathematical model for fast shrinkage rate of the 14.8 MBq (2.305 J) dose, the shrinkage half-life time can be predicted from Eq. (2.1.17) as follows:

$$t_{1/2Shrinkage} = \frac{2^n}{2^n-1} \times \left[1 - 2^{\frac{-40}{8.04}}\right] \times \left[8.04 + \ln 2\left(1 - \frac{2.305}{1.2721}\right)\right] = \frac{2^n}{2^n-1} \times 7.239463111$$

by trial and error method. The value of n that satisfies Eq. (2.1.18) is n=5.5 as it gives $t_{1/2.Shrinkage}$ equivalent to 7.4 days. This rate causes the tumor energy to decrease from 1.2721 J to 0.028 J after 40 days as

$$1.2721 \times e^{\frac{-\ln 2}{7.4}\times 40} = 0.028\,\text{J}.$$

Consequently, summation of tumor growth energy, $\sum E_{Tumor.growth}$, can be reached by integrating the presented experimental observations by Barendswaard et al. as follows:

$$\sum \mathrm{E_{Tumor.Regrow}} = 0.028 \times \left(\int_0^{80-40} \mathrm{e}^{\frac{\ln 2}{14.46}\times \mathrm{t}}\mathrm{dt} - \int_0^{80-40} \mathrm{e}^{\frac{-\ln 2}{7.4}\times \mathrm{t}}\mathrm{dt} \right) = 3.09\,\text{J}$$

as shown in Fig. 6. The postulate of the provided mathematical model summation of tumor growth energy, $\sum E_{Tumor.growth}$, can be calculated by determining the required time of regrowth as follows: from Eq. (2.1.1 & 2.1.19)

$$\sum_{\mathrm{T=0}}^{\mathrm{T}} \mathrm{E_{Tumor.Regrow}} = 2.305 + 1.2721 - 25 \times 10^8 \times \frac{0.0000538132 \times 23234.59}{6.242 \times 10^{12}} \times 2^{\frac{80}{8.04}} = 3.08\,\text{J}.$$

This is 100% identical to Barendswaard et al.'s presentation, and shows that $\sum_{\mathrm{T=0}}^{\mathrm{T}} \mathrm{E_{Tumor.Regrow}}$ is the resultant of tumor and dose energies against $\sum WBCEB$.

Fifth: to check the hypothesis of OIDT mathematical model for fast shrinkage rate, also for the 18.5 MBq (2.88 J) dose, the shrinkage half-life time can be predicted from Eq. (2.1.17) as follows:

$$\mathrm{t_{1/2Shrinkage}} = \frac{2^{\mathrm{n}}}{2^{\mathrm{n}}-1} \times \left[1 - 2^{\frac{-20}{8.04}}\right] \times \left[8.04 + \ln 2\left(1 - \frac{2.88}{1.2721}\right)\right] \Rightarrow \frac{2^n}{2^n-1} \times 5.8865$$

by trial and error method. The value of n that satisfies Eq. (2.1.18) is n=3 as it gives $\mathrm{t_{1/2.Shrinkage}}$ equivalent to 6.72 days, which is also 97% identical to Barendswaard et al.'s presentation (6.5 days) (2001).

3 Results

Numerical simulations of Eqs. (2.1.1)–(2.1.19) are performed to investigate the tumor's response to radiotherapy for various parameter values. The fit of the mathematical model to the experimental data [2.2-, 2.3-, 2.4-] is based on the tumor's response to radiotherapy according to the balance of the dose released energy and the summation of tumor energy. During shrinkage stage, these energies are in equilibrium, and once balance is violated, tumor will be grown. During growing stage, summation of tumor growth energy $\sum_{\mathrm{T=o}}^{\mathrm{T}} \mathrm{E_{Tumor.Growth}}$, results from the balance between initial tumor energy $E_{0.Tumor}$, initial drug energy $E_{0.Doses}$, and, finally, summation of Whole Body Cell Energy Burden $\sum WBCEB$, such that $\sum E_{Tumor.Growth} = |(E_{0.Tumor} + E_{0.Dose}) \mp \sum WBCEB|$. Negative or positive sign (∓) to cover all types of treatments with respect to dose energy: negative for the OIDT and positive for the LIDT. Despite OIDT may cure the primary tumor in certain cases as shown in 2.4- for the higher dose (18.5 MBq), it contributes in increasing WBCEB to levels higher than that tolerated. The best fit of the model to the experimental data allows for the estimation of the cure or the regrowth at both low and high radiation doses to be used for optimization of radiotherapy protocols.

3.1 Effects of changing model parameters

The stability of the conclusions of the modeling study was investigated by varying the radiobiologic and pharmacokinetic parameters associated with tumor response. The effects on tumor response of varying the radiobiologic parameters lower

and over the initial tumor energy were covered. In all cases, cure responses were for WEPT and OIDT, which satisfied the model energy balances of Eq. (2.1.7), whereas remission responses were similar for all LIDT and OIDT that satisfied Eq. (2.1.1). This was done for both macroscopic and microscopic tumors. It should be noted that the tumor response model is applicable for all kinds of cancer radiotherapies. All variations of radiobiologic factors are explained in only four parameters (a) initial tumor energy, (b) initial dose energy, (c) summation of Whole Body Cell Energy Burden and (d) summation of tumor energy, which arises as a result of the unbalance between the sums of the first two parameters against the third one. The possibility of adaptation of shrinkage pathway is considered by changing the parameter of the drug released energy to maintain the equation of energy balances of this model. Notice that when $\Delta E_{Doses} \rightarrow 0$, which represents the amount by which the dose energy differs from that of WEPT, its resultant which is the difference in the summation of tumor energy of either OIDT or LIDT from that of WEPT $\sum \Delta E_{Tumor.Shrinkage} \rightarrow 0$ too, which is the optimal targeted cancer radiotherapy. Moreover, the model relates all types of tumor response to the difference between energies of OIDT or LIDT from that of WEPT, with the capability to predict the tumor pathway. This was done to keep the number of model parameters at a minimum, but at same time, this simulation shows that the model and so the tumor responses are completely controlled by energy balances. In addition, it is clear that there are specific times for which tumor response energy exceeds the difference of OIDT energy from that of WEPT, resulting in net growth. Further information regarding interval time of the tumor response, whether cure or regrowth, can be derived on the basis of the n half-life times needed for WBCEB to reach the NBR. During the regrowth period, the curve of tumor energy of OIDT surpasses that of WEPT resulting in a balance point at which the model predicts the level of tumor energy that can be reached above the curve of tumor energy of WEPT. The model also predicts that tumor relapse is associated with a decrease in released dose energy from the supposed quantity needed to allow the tumor to continue its shrinkage pathway.

4 Discussion

This article describes the application of a mathematical model of tumor response to radiotherapy. The model is used to examine energy balances that influence the therapeutic effects of alternative administration patterns. Despite this, it is easier to make administering doses simple and straightforward. It should be performed specific to patient and, further, specific to normal organs or tissues at the greatest risk for life-threatening tissue damage. As the tumor sizes vary widely, individualized patient doses are supposed to have a wide range, too. Significant differences produced between doses are assumed statistically [standard masses] and physically [individualized patient]. Since the issue of radiotherapy-related second cancers will become increasingly significant (Gold et al. 2003; Tubiana 2009), the aim of the current approach is to relate the consequence of late normal tissue damage from OIDT to a precancerous lesion. Accordingly, preventing serious toxicities to normal vital organs is not only essential but also perhaps, the ethical responsibility of all involved in treating cancer patients as a whole to ensure that these risks are made as low as possible with improved understanding of the dose–risk relationship at high doses (Sachs and Brenner 2005), with improved dose delivery technology (Miralbell et al. 2002; Balog et al. 2005; Fu et al. 2004), and with more optimized treatment planning (Mohan et al. 2000; Crooks et al. 2002; Coselmon et al. 2005): as radiation administered dose estimation techniques for internal radiation emitters continue to evolve (Stabin 1999), as shown for WEPT (Moawad 2010), accurate measurement of the uptake and retention of the radiopharmaceuticals in organs and tissues is challenging, but a reasonably accurate assessment of radionuclide pharmacokinetics is feasible with current imaging techniques (Rajendran et al. 2004). A cancer induction model for radiotherapy was used to investigate the impact of different dose energy patterns on second cancer risk. It allows controlling tumor shrinkage pathway as it is recommended to keep the shrinkage pathway congruent to that of radionuclide decay energy as described in WEPT. This means that it is not favorable for the tumor shrinkage constant to exceed the radionuclide decay constant, as it will require modifying the administered dose by more drug released energy to keep the tumor in its shrinkage pathway as described in OIDT. It was found that carcinoma as well as sarcoma risk decreases by applying WEPT or OIDT such that

$$E_{OIDT} - E_{WEPT} = E_{WEPT} \times \int_0^t \left(e^{\frac{-\ln 2}{t_{1/2Isotope}}} - e^{\frac{-\ln 2}{t_{1/2Shrinkage}}} \right) dt.$$

In such a case, tumor regrowth energy will vanish. Such an approach, unifying short- and long-term models, has some advantages over currently existing methods, as discussed in the previous articles (Moawad 2010; 2011). Reasons for tumor regrowth are either underestimation or overestimation of the administered dose. For underestimation, Emad Moawad showed that exposure to certain levels of radiation of energy less than that of the biological culture allows harmful nuclear transmutation in biological cultures, which contributes in their growth and, consequently, different kinds of cancerous tumors where growth energy gained is equivalent to energy gained of such elemental

transmutations (Moawad 2011). While overestimation is the second reason for tumor regrowth or second cancer, it can be a reply for several questions like why might secondary rectal cancer rates be higher in prostate cancer patients who had conservative treatment (Harlan et al. 2001b). Rajendran et al. showed the statistical analysis to dose assessment by ignoring patient-specific factors and using standard models is responsible for a wide range of doses and, consequently, second cancer risks (Rajendran et al. 2004). Hence, significant differences are observed between the tumor response due to the physical approach and those obtained from the statistical standard models. This shows that ignoring patient-specific factors and tumor size that was handled by WEP and depending on statistical models, lead to either underestimation or overestimation of the true tumor energy of individual patients (Fisher 1994). Therefore, patient-specific approaches that account for variations in tumor sizes along with its growth doubling time should enable more accurate dose estimates and, consequently, better protection against lower or over irradiation that could lead to tumor growth or serious normal tissue toxicities and increasing the risks of second cancer.

5 Conclusions

Radiotherapy and its subsequent are an energy balance process; tumor regrows if its energy is higher than that of the dose, or if the increase of dose energy from that of the tumor is less than the required one to complete its shrinkage path. Patient-specific approaches that account for variations in tumor energies should enable more accurate dose estimates and, consequently, better protection against either lower or over irradiation that could lead to tumor regrowth and increase risks of second cancer.

Conflict of interest The author declares that there is no conflict of interest concerning this paper.

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