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Towards Easier and Straight forward Dosimetry Always Inherits Identical Results

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Abstract

***Background:** On comparing the response of patients to the wide range of doses applied in radiotherapy in different schools of medicine all over the world puzzling observations arise. This research proves the predictability of the therapeutic response to radiotherapy that would contribute to avoid non optimal treatments or treatment failure.*

***Methods and Materials:** Models involving primary LS174T human colon cancer and pre-treated human epidermoid carcinoma cell line A431 with total delivered dose of 85 Gy xenografts in athymic mice were used. The response of primary LS174T model to a singlBRT exposure of ^{60}Co EBRT exposure of 6 Gy was predicted by determining Doubling Time-Energy Conversion (DT-EC) prior to therapy. Also, the recurrence of the pre-treated A431 model was predicted by determining DT-EC before dose delivery. The mechanical behavior of the primary model was monitored by determining the growth/or shrinkage constants after therapy, while the pre-treated model was monitored after cell injection.*

***Results:** The actual responses of the primary and pre-treated models to the presented therapies were 100% identical to the predicted responses to strengthen the confidence in predicting the patient response prior to therapy.*

***Conclusion:** To make dosimetry easier and straight forward always inherits identical results, the concept of DT-EC is reliable to administer the patient-personalized dose to avoid non optimal treatments or treatment failure.*

Keywords: *Dosimetry; Doubling Time-Energy Conversion (DT-EC); Emad formula; External beam radiotherapy (EBRT)*

Introduction

On comparing radiotherapy treatments in different schools of medicine all over the world, puzzling observations arise. One can find the same disease in nearly the same circumstances, but with completely different recurring doses [1, 2]. Hitherto no-one has a conceptual reasoning for these varying 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"! [3]. Thus there is a need to predict the tumor response by the end of a suggested therapy to check the sufficiency of the delivered dose or to modify it during therapy. The delivered dose would be sufficient for the suggested therapy whenever the actual response is not less than the predicted one and vice versa. In addition, predicting the therapeutic response to radiotherapy helps in preserving patients' rights against the randomized statistical dose assessment that ignores patient-specific factors [4]. On the other hand, a new model of clinical based staging of the cancer at the cellular level has been developed in which the effect on the cancer stage due to therapy can be estimated and consequently effectiveness of the treatment can be determined [5-8]. Moreover, recently, an accurate method for predicting the response to chemotherapy by constructing the dose energy model for the used drug has been presented [9-19]. Prediction of the therapeutic response to the energy yield by the administered dose requires to identify the histologic

grade (H_G) of the patient prior therapy (control tumor) [13, 14, 19, 20].

$H_{G\ controls}$ expresses all the genetic alterations that drove the normal cell to carcinoma and tumor formation [21-23]. Since dosimetry specifies the energy of the administered dose of radiotherapy a fortiori to predict the tumor response to radiotherapy as well to avoid treatment failure and non-optimal radiotherapy. Current approach presents applications on predicting primary tumor model response to radiotherapy and recurrence of pre-treated tumor model with accuracy of 100% to make dosimetry direct and easier.

Methods and Materials

Monitoring the Mechanical Behavior of the Tumor Response to Therapy

Comparing the mechanical behavior of tumor response of the treated groups to that of the control groups is assessed by determining the growth/or shrinkage constants of those tumors of different volumes along the corresponding periods [24, 25]. The growth/or shrinkage constant of the tumor at a certain time expresses the rate of the difference between Mitosis and Apoptosis with respect to the total number of the tumor cells (M – A) that characterize the tumor response at that time [9-11]. If rate of mitosis is greater than that of apoptosis, tumor grows by growth constant of $\frac{\ln 2}{t_D}$,

where t_D is the tumor doubling time and vice versa if rate of mitosis is less than that of apoptosis, tumor shrinks by shrinkage constant of $\frac{\ln 2}{t_{1/2}}$, where, $t_{1/2}$ is the tumor half-life time.

i.e. $(M - A) = \frac{\ln 2}{t_D} S^{-1}$ in case of tumor growth,

&

$(A - M) = \frac{\ln 2}{t_{1/2}} S^{-1}$ in case of tumor shrinkage

where t_D and $t_{1/2}$ in seconds Eqt (1)

The clinical staging model presented by Moawad showed that the tumor histologic grade (HG) that expresses tumor response can be identified through the concept of Doubling time-Energy Conversion (DT-EC) by Emad formula [4-23] as follows:

In Case of Tumor Growth

$$H_G = \ln\left(\ln\frac{\ln 2}{t_D}\right) \times C_0 \times h \times 23234.59\ \text{MeV} \quad \text{Eqt (2)},$$

where $C_0 \times h$ is number of the hypoxic cells in the tumor or number of the inoculated cells in the transplanted tumor in xenografted models.

In Case of Tumor Shrinkage

Radiotherapy affects the tumor cells such that the more the dose the less of mitotic cells or the more of apoptotic cells. Since the portion of tumor cells underwent apoptosis due to anti-microtubule agents therapy had been prevented first from mitosis. Thus to apply equation 2 in the shrinking case, the apoptotic tumor portion of half-life time ($t_{1/2}$) would be replaced by virtual growing portion of doubling time (t_D) which had been prevented first from mitosis. The greater the shrinkage portion of the tumor, the more the efficiency of the treatment and hence replaced by a smaller virtual growing portion and vice versa. Thus, rate of the virtual growth would be inversely proportional to the rate of the tumor shrinkage as follows:

$$\left(\frac{V_{Initial} - V_{Final}}{V_{Initial}}\right)_{Shrinkage} = \left(\frac{V_{Initial}}{V_{Final} - V_{Initial}}\right)_{Virtual\ growth} \quad \text{Eqt (3)},$$

where V is the tumor volume. Accordingly from equations (1) and (2), the alteration in the treated tumor H_G to that of the control tumor induced by the drug dose would be equivalent to the energy yield by the drug dose according to the following model:

$$E_{Dose} = \left[\ln(\ln(M\text{-}A)_{Treated})^2 - \ln(\ln(M\text{-}A)_{Control})^2\right] \times C_0 \times h \times 23234.59\ \text{MeV} \quad \text{Eqt (4)}$$

Predicting Primary Tumor dose Response to External Beam Radiotherapy (EBRT)

As conducted and described by Buchsbaum et al [26, 27];

Athymic nude mice (25g) bearing (5×10^6 cells) LS174T human colon cancer xenografts were treated with a single ^{60}Co EBRT exposure of 6 Gy.

Doubling time estimates taken from unirradiated or irradiated tumor growth curves near the 1-cm tumor diameter size were ~4days. Response of LS174T human colon tumor model to EBRT exposure was predicted using DT-EC formula.

Predicting the Recurrence of Pre-Treated Tumor Xenografted by a Radioresistant Isogenic Cancer Cell Line

As conducted and described by Josep Balart et al [28]; an experimental development of a radioresistant isogenic cancer cell line was performed. Human

epidermoid carcinoma cell line A431 were maintained as a monolayer under standard cell culture conditions. Cells growing in 100-mm plastic dishes were irradiated at room temperature (RT) using 6-MV X-rays at dose rate of 2.7 Gy/min. The procedure was continued until a total of 85 Gy had been delivered. These cells were denominated as A431-R (Resistant) cell line and both cell lines (A431-P and A431-R) were used to generate a two tumor mouse models. 10^6 of A431-P cells or 10^6 of A431-R cells suspended in 100 µL of medium were injected into subcutaneous tissues on the right thigh of six to eight week old female athymic Swiss nu/nu mice to generate tumor xenografts models. A431-P model represented a primary tumor and A431-R model represented a pre-treated recurrent tumor. Tumor size was measured twice/week, and the doubling time (t_D) of tumor growth was determined in each model. Recurrence of A431-R tumor model was predicted using DT-EC formula. Tumor size was calculated using the formula: π/6 x (large diameter) x (small diameter)^2.

Results and Analysis

Predicting Tumor dose Response to External Beam Radiotherapy (EBRT) using Concept of DT-EC by Staging the Control Tumor

Tumors averaged ~1 cm in diameter (range, 0.5-1.7) and ~0.6 g in weight [27]. Doubling time estimates taken from unirradiated or irradiated tumor growth curves near the 1-cm tumor diameter size were ~4 days [26].

According to the concept of DT-EC (Eqt 26), the histologic grade ($H_{G\ Control}$) of the control tumor xenograft of transplanted 5×10^6 LS174T human colon cells was identified as follows:

$$H_{G\ Control}=\ln\left(\ln\frac{\ln 2}{4x24x60x60}\right)^2 x\ 5\ x\ 10^6 x\ 23234.59071=$$

$5.980824132x10^{11}$MeV.

Mice (25 g) were exposed a single ^{60}Co EBRT exposure of 6 Gy. Thus, the energy yield by exposure to EBRT of 6 Gy in tumor xenograft of transplanted 5×10^6 LS174T human colon cells is equivalent to (6 Gy × 0.0006 kg × 6.242 × 10^{12} MeV) 2.24712 × 10^{10} MeV. Thus, the histologic grade (H_G) of the exposed LS174T human colon tumor model to a single ^{60}Co EBRT of 6 Gy is supposed to be:

$H_G=5.980824132x10^{11}+2.24712\times10^{10}=6.205536132\times10^{11}$ MeV.

Thus from Eqt 26, H_G /(Transplanted cell) = 6.205536132×10^{11}MeV/5×10^6cells=124110.7226MeV/23234.59071 =5.341635848 Emad. Accordingly from Eqt 20, LS174T human colon tumor model would be predicted to grow with $(t_D)_{Predicted}=\ln2x\ e^{\sqrt{5.341635848\ Emad}}=1.30965158x$

10^6 sec = 15.15800754 days which is ~100% identical to that quoted by Buchsbaum et al. about the actual regrowth time delay to LS174T human colon tumor doubling to be 15 days ±1 day (^{60}Co EBRT of 6 Gy) [24, 25]. This clarifies the accuracy of Emad formula to identify DT-EC during tumor formation and strengthens the confidence in predicting the therapeutic response of tumors to EBRT according to the concept of DT-EC during radiotherapy.

Predicting the Recurrence of Tumor Xenografted by a Radioresistantisogenic Cancer Cell Line using Concept of DT-EC by Staging the Primary Tumor

Seven days after cell injection all animals exhibited tumor growth in the subcutaneous tissues of the right thigh. The average tumor size grew from 1 mm^3 to 51.30 ± 8.8 mm^3 in the control tumor model (A431-P) in 7 days ($p<0.0001$) [26], with doubling time (t_D) of 1.23220196 days. According to the concept of DT-EC (Eqt 26), the histologic grade ($H_{G\ Control}$) of the control tumor xenograft of transplanted 1×10^6 A431cells was identified as follows:

$$H_{G\ Control}=\ln\left(\ln\frac{\ln 2}{1.23220196\ x\ 24\ x\ 60\ x\ 60}\right)^2 x\ 1x10^6 x23234.59071$$

$=1.152466606x10^{11}$ MeV. A total of 85 Gy had been delivered to develop a radioresistant isogenic human epidermoid carcinoma cell line A431 that xenografted in mice to generate A431-R tumor model. Thus, the energy yield by exposure to 85 Gy in tumor xenograft of transplanted 1×10^6 A431cells is equivalent to

$$(85Gy\ x\ \frac{1x10^6\ cells}{1x10^{12}\ cells/kg}\ x\ 6.242x10^{12}\ MeV)\ 5.3057x10^8\ MeV.$$

Thus, the histologic grade (H_G) of the resistant tumor model (A431-R) is supposed to be: $H_G=1.152466606\times10^{11}$ $+5.3057\times10^8=1.15777231\times10^{11}$ MeV.

Thus from Eqt 26, H_G / (Transplanted cell)=1.157772 $31x10^{11}$MeV/1×10^6cells=1.15777231×10^5MeV/2323 4.59071= 4.98296837 Emad.

Accordingly from Eqt 20, A431-R tumor model would be predicted to grow with

$(t_D)_{Predicted}=\ln 2 x e^{\sqrt{e^{4.98296837Emad}}}=1.22110012x10^5$ sec=1.41331033 days to 30.97 mm3 which is ~100% identical to that quoted by Josep Balart et al about the actual growth of A431-R tumor model from 1 mm^3 to 30.73 ± 7.4 mm^3 in 7 days ($p<0.0001$) [28], with t_D of 1.416552168 day. This also boosts the confidence in predicting the recurrence of the pretreated (resistant) tumor through the concept of DT-EC and provides a clear cut criterion to establish Emad formula as a reliable tool for dosimetry measurements.

Discussion

The aim of this research is to prove the predictability of the therapeutic response to radiotherapy that would contribute to avoid non optimal treatments or treatment failure. The primary goal of administering the appropriate dose is to optimize radiotherapy that significantly inhibit tumor growth besides reducing the risks of inducing a second cancer and decreasing the costs of the drug dose [20, 29 and 30]. Dose assessment by ignoring patient-specific factors and using standard models is responsible for wide range of doses, and consequently tumor regrowth and second cancer risks. The relation of the growth energy (E_G) of the biological systems and its growth constant [$\ln 2/t_D$] has been confirmed to add a new concept for energy conversion in the biological systems [31-33]. Thus, administering the optimal radioactive dose and predicting its effectiveness should depend on monitoring DT-EC during tumor formation clinically by means of medical imaging or pathologically by means of ^3H -TDR incorporation [5-8]. This study used in vivo tumor models in athymic mice which are commonly used to study tumorigenesis and assay efficacy of novel radiotherapies [34]. A clinical methodology for staging tumors was conducted to predict their responses to therapies as described before in earlier studies [5-8]. Accuracy of the presented model to predict tumor response to therapy has been confirmed to provide a clear cut criterion to accuracy of Emad formula for measuring DT-EC takes place during tumors formation and therapy [9-21]. It is, challenging to differentiate between growth rate (dm/dt) and growth energy (E_G) of the tumor. For same mass the fast growing tumor (higher dm/dt) needs less drug energy than that of the slowly growing one [20]. While E_G expresses the tumor H_G such that tumor of higher E_G needs more drug energy than that of the lower one. This can be an answer for the puzzling observations on comparing radiotherapy treatments in different schools of medicine all over the world, and introduce a conceptual reasoning for their invariant doses. The actual responses to the presented therapies identified by different research institutes were 100% identical to the predicted responses by our thesis to boost the confidence in the current approach. Those matching responses provides also a clear-cut criterion for accepting the hypotheses of the equivalence between the effect on the tumor H_G induced by and the energy of those doses as described before in earlier studies [9-21]. The therapeutic response to radiotherapy was predicted by knowing the histologic grade (H_G) of the control tumors as shown in section of Results and Analysis. Such technique is valid for predicting the therapeutic responses of the patient to the administered dose to check dose sufficiency prior therapy and to modify the administered dose whenever the actual response differs from the predicted one. Applying the concept of DT-EC is not exclusive to optimize radiotherapy; it has been applied successfully to optimize chemotherapies, in conducting an energy balance test through a nutrition diet for cancer screening and preventing tumor formation [8]. In addition this new concept has been applied in optimizing processes of producing bio-fuels in biotechnology [31-33]. Thereby together with these findings and analysis current approach suggests settling down a new protocol for the proper ranges of radionuclide doses to make dosimetry easier and straight forward always inherits identical results.

Conclusion

On the contrary of dosage by standard models, applying concept of doubling time-energy conversion in dose assessment identifies patient-personalized dose that makes dosimetry straight forward always inherits identical results.

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