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RADIOBIOLOGICAL CONSIDERATIONS ON MODERN TECHNIQUES OF EXTERNAL RADIOTHERAPY IMRT AND VMAT

BY

CAMIL CIPRIAN MIREȘTEAN[1], CĂLIN GHEORGHE BUZEA[1,*] and DRAGOȘ TEODOR IANCU[1,2]

[1]Regional Institute of Oncology, Iași
[2]“Grigore T. Popa” University of Medicine and Pharmacy, Iaşi

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Abstract. In the last decades, we witness the advancement of new external radiotherapy techniques together with significant advances in cancer biology, imaging and computerized data processing that impact on the involvement of radiobiological considerations in the therapeutic decision. Preclinical studies demonstrated significant changes in cell survival fractions under irradiation parameters, that simulate irradiation with increased and variable dose rate and total irradiation time/fraction > 30 min, similar to the situation encountered in IMRT irradiation in vitro. Inverse planning techniques allow irradiation with the integrated boost technique, irradiating target sub-volumes with fractions greater than 2Gy. In this context, the use of the linear quadratic model may be useful but requires caution both in assessing equivalent-tumoral doses and acute and late toxicities. The introduction of mathematical models that calculate TCP (tumor control probability) and NTCP (the probability of healthy tissues to develop toxicity) has simplified comparative assessment for complex irradiation plans.

Keywords: radiotherapy; therapeutic decision; inverse planning; linear quadratic model.

[*]Corresponding author; *e-mail*: calinb2003@yahoo.com

1. Introduction

In the last decades, we have witnessed a steady increase in the use of modern radiotherapy techniques, having as a prerequisite the achievement of a higher degree of target volume covering compared to conformational radiotherapy, but especially the reduction of doses received by radiosensitive organs. With all these advantages, the implementation of modern techniques and the physical characteristics of the radiation beam and the delivery mode of the dose brings a number of uncertainties and challenges regarding the radiobiological effects both on the tumor target and the healthy tissues (Nishimura *et al*., 2015).

The application of radiobiological modeling originated three decades ago and many research centers have tried to prove the utility of this instrument in clinical practice. However, mathematical models are not perfect because they do not take into account the individual variables of the radisensibility of each case, the inclusion of individual clinical biological and imaging parameters being needed to improve their predictive value. Biological modeling uses a DVH of a certain plan and certain biological features (histological type of the tumor and characteristics of the normal tissues from the organs exposed to the risk of toxicity) for the calculation of TCP and NTCP.

Consider a statistical ensemble of tumors treated with radiotherapy with dose D. Let us denote by λ the mean number of surviving clonogenic tumor cells in this tumor ensemble. The TCP is given by the probability of no surviving clonogenic cell. If the actual number of surviving clonogenic cells among the tumors is distributed according to Poisson statistics, then TCP for a tumor is calculated using the Poisson model by the following formula (Nishimura *et al*., 2015):

$$TCP(D) = exp\big(-\lambda(D)\big) \tag{1}$$

Using the LQ model

$$\lambda(D) = N_0 exp(-\alpha D - \beta D^2) = N_0 exp(-\alpha D - \beta d D) \tag{2}$$

where N_0 denotes the initial number of clonogenic cells in the tumor, and the second form corresponds to fractionated irradiation with dose per fraction d and total dose D. The TCP formula of the Poisson model combined with the LQ expression thus reads

$$TCP(D) = exp\big(-N_0 exp(-\alpha D - \beta d D)\big) \tag{3}$$

The number of clonogenic cells N_0 can be expressed in terms of clonogenic density ρ_0 and tumor volume V

$$N_0 = \rho_0 V \tag{4}$$

The clonogenic density ρ_0 has been estimated from experimental data and/or models at 10^4-10^6 cells per cm^3, significantly below the density of all cells (10^9 cells per cm^3). There is evidence even for the clonogenic density being dependent on tumor volume.

One of the most used models is Lyman-Kutcher-Burman (LKB). In the LKB model, NTCP is defined as:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{u} e^{-t^2/2} dt \tag{5}$$

where

$$u = \frac{D - TD50(V)}{m \times TD50(V)} \tag{6}$$

$$TD50(V) = TD50(1)/V^n \tag{7}$$

where *TD*50(V) is the tolerance with 50% probability of complications caused by uniform irradiation in volume *V* where *TD*50 is the probability of complications in healthy tissue caused by uniform irradiation of volume *V* and where *n* is the exponent of the volume and *m* is a parameter that is inversely proportional to the slope of the dose-response curve (Warkentin *et al*., 2004).

2. Discussion

For example, Basu *et al*. compares in 10 cases of prostate adenocarcinoma, TCP and NTCP calculated for plans with conventional four-field box techniques, plus conformational boosts with three fields (3D + 3DCRT), 3D-CRT plans followed by IMRT boost (3D + IMRT), IMRT plans followed by IMRT boost (IMRT + IMRT) and simultaneosly integrated boost plan (SIBIMRT). In the case of integrated boost, equivalent doses were calculated using the biological equivalent dose, assuming the alpha/beta ratio is 1.5 Gy, and NTCP was calculated using the Lyman-Kutcher-Burman (LKB) model. SIMBIMRT provided the lowest NTCP with 3 weeks of reduced treatment time, being considered as a feasible technique for dose escalation (Basu and Bahl, 2009).

Hardcastle *et al*. comparatively evaluate IMRT and VMAT irradiation plans for prostate neoplasm with the objective of assessing the risk of rectal toxicity. With similar coverage of the target volume, the VMAT technique offers a lower risk of late rectal complications (Hardcastle *et al*., 2011).

Comparative study on plans obtained for the same patients through different techniques has revealed difficulties in assessing the advantages and disadvantages of each and every case. Significant dosimetric differences do not

always translate into advantages in tumor control, the biological properties of tumor and healthy tissue may play an important role in the irradiation response. The TCP and NTCP mathematical models simplify these differences by providing precise values for the possibility of obtaining tumor control and the risk that the treatment will be accompanied by acute and delayed toxicity. In many cases, minimal differences between these values save time-consuming optimization of plans with no benefit in clinical practice. The purpose of increasingly use of radiobiological models was to have a predictive tool for the biological effects of variations of different parameters in the treatment plan, to evaluate the consequence of geometric errors and to compare the plans obtained with modern radiotherapy and those with conventional techniques, to achieve a clinical-benefit dosimetric benefit correlation (Jiang *et al*., 2013; Mesbahi and Oladghaffari, 2017).

The IMRT technique is characterized by a prolonged delivery time of the irradiation dose per fraction. In a study focused on the delivery effect at different times on the A549 cell line, of the same dose on A549 tumor growth in mice, Jiang and co-workers demonstrate using the formalism of the linear quadratic model and the incomplete lesion repair model to generate cell survival curves. Radiation was delivered with one fraction per day simulating a clinical model. Delivery times over 40 minutes diminished the tumoricidal effects of irradiation but in clinical practice the disadvantage of the risk of cellular repopulation associated with long delivery times of each fraction characteristic to the IMRT technique could be compensated by the radiosensitizing effects of reoxygenation (Jiang *et al*., 2013; Mesbahi and Oladghaffari, 2017). Another study is aimed at exploring the impact of prolonged dose delivery times similar to IMRT irradiation on (HCC) HepG2 and Hep3B human hepatocellular carcinoma cell line destruction. Simulating dose delivery conditions similar to IMRT technique significantly decreased the effect of HepG2 cell destruction, but not Hep3B. The ability to repair sublethal lesions was the predominant factor determining the decrease of the HepG2 cells tumorigenic randament, effect proven by clinical trials also. Based on the analysis of clinical data, it was concluded that dose-modifying factors of 1.08-1.16 should be considered when total irradiation time is 20-30 min (Zheng *et al*., 2005, Shibamoto *et al*., 2012).

The IMRT technique is beneficial to irradiate the sub-volumes from a target volume with different doses/fraction by using the integrated boost. The necessity of evaluating the equivalent dose from the standard fractionation as both tumoricidal and toxicity has led to the need for frequent use of the linear-quadratic model (n2d2/n1d1 = (1+ d1/[a/b]) / (1+ d2/[a/b]) (where d1 and d2 are doses per fraction and n1 and n2 the number of fractions). The Linear Quadratic Model is useful for converting between relatively low dose fractions used in conventional radiotherapy, but studies have shown errors in assessing the equivalent dose for large fraction of doses per day or for a small number of fractions. The validity of its use for hypofractionation schemes, stereotactic radiosurgery or single session irradiation should be validated by clinical trials (Brenner, 2008).

Guerrero and Li propose a modified version of the modified linear quadratic model for evaluating equivalent doses in extracranial stereotactic radiosurgery by evaluating the proposed equation for doses >15Gy. The new parameter introduced is valid in vitro, on the cell survival curves of several human tumor cell lines and in vivo for animal-validated iso-effect curves. For high dose per fraction, the modified linear quadratic model appears to provide predictive accuracy and correspondence with the clinical reality superior to the linear quadratic model for calculating the isoefect dose (Guerrero and Li, 2004).

At low doses per fraction (<1Gy), the hyper-radiosensitization effect described in both tumor and healthy tissue may result in underestimating the response to treatment and toxicity using the linear quadratic model. It is the case of IMRT and VMAT techniques in which large volumes of tissue are irradiated with doses per fraction situated in this interval characteristic to the effect of hyper-radiosensitization. Validation of some equations that more accurately characterize the small dose per fraction effects on cells, opens new horizons of approaching radioresistant tumors at doses of 2Gy. Joiner, Marples *et al*. describe that most cell lines have hyper-radiosensitivity (HRS) at very low doses of radiation (<10 cGy) and around 30 cGy, increases the radioresistance (IRR), around 1 Gy/fraction, the radiosistance becomes maximum (Joiner *et al*., 2001).

3. Conclusions

Technological development, the implementation of intensity modulated techniques and the image guided radiotherapy led to the increase of reproducibility of the treatment plans and irradiation accuracy. From a radiobiological point of view, the use of high dose rates, long dose delivery times, and dose distribution in healthy tissue volumes (reducing high dose irradiated volumes and increasing volumes that will receive low doses) are factors that alter cell survival curves and it is necessary to validate the mathematical models through clinical studies. The use of TCP and NTCP can provide an intuitive solution in the selection and comparison of different treatment plans in terms of tumor control and toxicity.

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CONSIDERAȚII RADIOBIOLOGICE ASUPRA TEHNICILOR MODERNE DE RADIOTERAPIE EXTERNĂ IMRT ȘI VMAT

(Rezumat)

În ultimele decade asistăm la un avânt al noilor tehnici de radioterapie externă simultan cu progrese semnificative înregistrate în biologia cancerului, în imagistica și în prelucrarea computerizată a datelor cu impact asupra implicării raționamentelor radiobiologice în decizia terapeutică. Studiile preclinice au demonstrat modificări semnificative în fracțiile de supraviețuire celulară în condițiile parametrilor de iradiere care simulează o iradiere în pulsuri cu debit crescut și cu timp total de iradiere/fracțiune > 30 minute asemănator situației întâlnite în iradierea IMRT in vitro. Tehnicile de planificare inversă permit iradierea prin tehnica boostului integrat, iradiind subvolume din ținta cu fracțiuni mai mari de 2Gy. Utilizarea modelului liniar pătratic în acest context poate fi utilă, dar necesită precauții atât în evaluarea dozelor echivalente tumoricide cât și al toxicităților acute și tardive. Introducerea modelelor matematice care calculează TCP (probabilitatea de control tumoral) și NTCP (probabilitatea țesuturilor sănătoase de a dezvolta toxicități) a simplificat evaluarea comparativă a planurilor complexe.