Dose compensation algorithm in radiotherapy planning

Neda Milosavljević[1,2*], Marija Živković Radojević[1,2], Darko Stojanović[2,] Marko Spasić[3]

[1]University of Kragujevac, Faculty of Medical Sciences, Department of Clinical Oncology, Kragujevac, Serbia; email: neda.milosavljevic@yahoo.com, makizivkovicmarija@gmail.com,

[2]University Clinical Center Kragujevac, Kragujevac, Center for Radiation Oncology, Krgujevac, Serbia; email: kgkid.ds@gmail.com

[3]University of Kragujevac, Faculty of Medical Sciences, Department of Surgery, Kragujevac, Serbia; email: drmspasic@gmail.com

* *Corresponding author*

DOI: 10.46793/ICCBI23.188M

Abstract: Pauses in radiotherapy treatment is a significant problem that affects overall treatment time - a predictor of tumor proliferation and definitive patient outcome and demands a decision-making tool for optimizing doses between healthy tissue and target volumes.

During prolonged radiotherapy interruptions, linear-quadratic model showed inadequacy in predicting tumor proliferation. We have developed a radiobiology algorithm applied for dose compensating, providing multiple options for dose compensating due to prolonged pauses. Based on linear-quadratic (LQ) model providing, in specific cases, orientational values for tumors and organs at risk (OAR), we developed a radiobiology calculator that can be used in dose compensation, giving more than one option in correcting biological effective dose (BED) due to prolonged pauses. Generic OAR offers the opportunity to individualize α/β ratio for any organ at risk or tumor. Seven cancer patients who experienced radiotherapy treatment delays, for more than two weeks, are included in this research.

The developed algorithm offers the radiation oncologist optimal modality choice and can be a helpful tool for overcoming long delays, except for patients whose treatment interruptions occur at the end of radiation treatment and for patients with fast proliferating tumors. During this course of treatment, none of the included patients manifested severe acute radiotherapy adverse events.

The dose compensating algorithm can be a useful tool for dose calculations with optimal healthy tissue sparing, but large prospective studies are necessary to confirm the benefit.

Keywords: radiotherapy, dose compensation, algorithm

1. Introduction

Radiotherapy is an integral part of the multidisciplinary treatment of oncological patients, where over 50% of oncology patients undergo radiotherapy during their treatment [1, 2]. For local control of the disease, compliance in treatment, as well as the development of acute and chronic adverse events, it is necessary that radiotherapy treatment be carried out in an adequate time frame depending on the goal of radiotherapy (neoadjuvant, adjuvant, radical or palliative approach) and fractionation regime [2]. Deviations from the recommended regimens can lead to inadequate local control of the disease, which affects the time to disease progression (Disease free survival, DFS), or overall survival (OS) [3]. Fowler et al showed that prolonging radiotherapy treatment in patients with head and neck cancer reduces local tumor control by 1.4% per day of missed treatment [4]. Pauses in radiotherapy treatment are not rare, and the most common reasons for this are of a technical nature (device failure), personal reasons of the patient or manifestations of acute radiation toxicity, grade 3 and higher [5-7].

The current recommendations for overcoming this, regardless of the type and intention of the radiotherapy treatment, according to the recommendations of The Royal College of Radiologists (RCR), are an increase in the daily tumor dose or use of hyperfractionated regimes [8]. Although the mentioned methods are adequate in reimbursing the dose to the target volumes, the surrounding healthy tissues receive a higher dose than recommended [8]. In the previous years, models have been developed for the assessment and recalculation of the effects of delaying radiotherapy, where most of them relied only on $\alpha\beta$ ratio, the relationship between the tumor and surrounding healthy tissues in response to the applied radiotherapy dose [9], where it should be borne in mind that the $\alpha\beta$ value differs between different healthy and tumor tissues.

In the era of the Covid-19 pandemic, it has become clear that there are also unforeseen circumstances that would cause prolonged breaks in the implementation of radiotherapy, which is why it is necessary to define guidelines for the compensation of missed therapeutic doses and the correction of the total time required for the delivery of a radiotherapy dose [10].

2. Material and method

The linear quadratic (LQ) model, which represents the correlation between cell survival and delivered dose, is widely used to analyze and predict responses to ionizing radiation in vivo and in vitro, but not designed to provide responses to cell proliferation during prolonged intervals. This model can provide orientational parameters for tumor proliferation [11]. Based on the LQ model disadvantages to predict tumor proliferation, during prolonged radiotherapy interruptions, but providing, in certain cases, orientative values for tumors and organs at risk (OAR), a collaboration between radiation oncologists and medical physicists developed a radiobiology calculator that can be used to compensate radiotherapy dose - more than one option in correcting biological effective dose (BED) due to pauses more than two week period, with the possibility to individualize α/β ratio for any organ at risk or tumor.

2. Results

In a newly created algorithm, we included all cancer patients who experienced radiotherapy treatment delays, for more than two weeks, regardless of primary malignancy. During the period of one year, there have been seven patients whose characteristics, as well as data on the planned radiotherapy treatment, are shown in Table 1.

Table 1. Patient and treatment characteristics

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**
Malignancy	Lung	Laryngs	Breast	Breast	Breast	Prostate	**Prostate**
Radiotherapy intention	P	R	P	P	P	P	**R**
Planned dose (Gy)	60	70	50	42.56	42.56	66	**72**
Pause in days	28	42	34	21	15	18	**40**
Compensating dose (Gy)	82.34	109.9	78.75	61.86	47.7	80.2	**121.1**
OAR affection %	**121.67**	**201.66**	**206.67**	**99.69**	**104.1**	**161.67**	**201.67**

Abbreviations: P- postoperative; R - radical

The calculator offers a radiation oncologist an optimal modality choice, that includes dose per fraction and number of fractions, administering dose in hyperfractionated regiment, especially in patients where $\alpha\beta$ is low ($\alpha\beta$ 3 for breast cancer) (Figure 1, left image). In patients with fast proliferating tumors regardless of tumor characteristics, the dose compensating algorithm is not applicable (Table 1; an example for one patient is shown in Figure 2, right image).

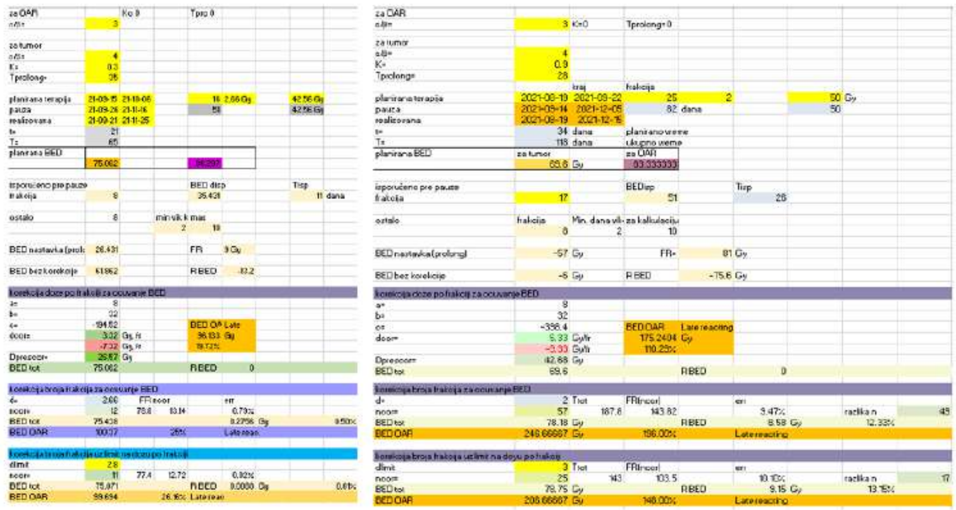

Figure 1. Example for adequate usage of dose compensating algorithm in decision making (left side) where the dose coverage is appropriate to target volumes, according to current guidelines for radiotherapy treatment; Example for patient, in which treatment delays algorithm is not useful (right side).

In collaboration with a medical physicist, the final decision is up to the radiation oncologist, to accept or decline proposed alterations in radiotherapy for each patient. As shown in Table 1, due to the high percentage of OAR affection, not all patients continued with compensated treatment. During this course of treatment, none of the included patients manifested severe acute radiotherapy adverse events and in one-year follow-up, no disease recurrence was detected.

4. Conclusions

Currently, there are no adequate recommendations or prospective studies for dose compensation for pauses that last longer than two weeks, which are individualized according to the characteristics of the patient and his primary malignancy, while taking into account all the parameters that affect the effectiveness of radiotherapy treatment.

This algorithm can be a useful tool to a radiation oncologist for dose compensation with appropriate OAR spare and it is applicable in any situation with treatment delays, but further prospective studies are needed to prove the benefit.

References

[1] Yang Y, Cameron J, Humphris G. The relationship between cancer patient's fear of recurrence and radiotherapy: a systematic review and meta-analysis. Psychooncology 2017;26(6):738-46.

[2] Siegel RL, Miller KD, Jemal A. 2020. Cancer statistics, 2020. CA: A Cancer Journal for Clinicians 70 7–30.

[3] Fietkau R, Rödel C, Hohenberger W, Raab R, Hess C, Liersch T, Becker H, Wittekind C, Hutter M, Hager E, Karstens J, Ewald H, Christen N, Jagoditsch M, Martus P, Sauer R; German Rectal Cancer Study Group. Rectal cancer delivery of radiotherapy in adequate time and with adequate dose is influenced by treatment center, treatment schedule, and gender and is prognostic parameter for local control: results of study CAO/ARO/AIO-94. Int J Radiat Oncol Biol Phys. 2007 Mar 15;67(4):1008-19.

[4] Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys. 1992;23(2):457-67.

[5] Osei E, Francis R, Mohamed A, Sheraz L, Soltani-Mayvan F. Impact of COVID-19 pandemic on the oncologic care continuum: urgent need to restore patients care to pre-COVID-19 era. J Radiother Pract. 2021 Apr 19:1–11.

[6] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31(5):1341-6.

[7] National Cancer Institute, National Institutes of Health USD. U.S. Department of health and human services. Common Terminology Criteria for Adverse Events (CTCAE). U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Published: November 27, 2017.

[8] Royal College of Radiologists. The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruptions. 2008. (Third edition).

[9] Putora PM, Schmuecking M, Aebersold D, Plasswilm L. Compensability index for compensation radiotherapy after treatment interruptions. Radiat Oncol. 2012 Dec 8;7:208.

[10] Abolfath R, Khalili M, Senejani AG, Kodery B, Ivker R. The Dependence of Compensation Dose on Systematic and Random Interruption Treatment Time in Radiation Therapy. Onco. 2022; 2(3):264-281.