BJRS
BRAZILIAN JOURNAL OF RADIATION SCIENCES

doi.org/10.15392/2319-0612.2024.2532
2024, 12(4) | 01-14 | e2532
Submitted: 2424-26-06
Accepted: 2024-10-22

Effect of radiobiological parameters on the TCP for breast cancer radiotherapy

Furlan [a], L. N.; Santos [b*], M. M.; Pianoschi [a], T. A.

[a] Universidade Federal de Ciências da Saúde de Porto Alegre, 90050-170, Porto Alegre, RS, Brazil.

[b*] Instituto Federal Goiano - Campus Ceres, 76300-000, Ceres, GO, Brazil.

*Correspondence: mairon.marques@ifgoiano.edu.br

Abstract: Breast cancer remains the most prevalent malignancy affecting women globally. Among the various treatment modalities, radiotherapy stands out as a cornerstone for tumor eradication. This research explores the impact of radiosensitivity parameters on Tumor Control Probability (TCP) in breast cancer, with an emphasis on distinct radiotherapeutic techniques such as conventional, hypofractionated, and FAST, as well as the role of tumor repopulation. Based on the literature review, we obtained data on α and β radiosensitivity parameters, cell repopulation rates and standard breast cancer treatment protocols. These parameters informed the calculation of the fraction of cells surviving irradiation via the linear-quadratic model, facilitating an assessment of treatment efficacy through the Poissonian TCP model. Our findings underscore the critical influence of radiosensitivity parameters α and β on treatment outcomes, with β emerging as the predominant factor due to its quadratic contribution to the survival fraction. Moreover, our analysis indicates that tumor growth is negligible relative to the substantial cell mortality induced by radiation in the case of breast cancer. Techniques such as FAST and hypofractionated radiotherapy were identified as particularly effective, offering expedited tumor control, especially with elevated α and β values. The quadratic term β significantly enhances treatment success, while tumor repopulation exerts minimal influence on TCP, corroborating previous model comparisons. Notably, higher doses per fraction, rather than increased cumulative doses, were associated with improved TCP, providing a critical insight for optimizing radiotherapy protocols. Currently, radiobiology is not systematically integrated into clinical practice, and its analysis through PCT optimizes radiotherapy treatments, improving patient quality of life and healthcare delivery.

Keywords: breast cancer, radiobiology, tumor control probability.

BJRS
BRAZILIAN JOURNAL OF RADIATION SCIENCES

doi.org/10.15392/2319-0612.2024.2532
2024, 12(4) | 01-14 | e2532
Submitted: 2424-26-06
Accepted: 2024-10-22

Efeitos de parâmetros radiobiológicos na TCP para radioterapia de câncer de mama

Resumo: O câncer de mama continua sendo a neoplasia maligna mais prevalente que afeta as mulheres em todo o mundo. Entre as várias modalidades de tratamento, a radioterapia se destaca como uma das mais utilizadas para a erradicação do tumor. Este trabalho explora o impacto dos parâmetros de radiossensibilidade na Probabilidade de Controle do Tumor (TCP) do câncer de mama, com ênfase em técnicas radioterápicas distintas, como convencional, hipofracionada e FAST, bem como o papel da repopulação tumoral. Baseado em revisão de literatura, obtivemos dados sobre os parâmetros de radiossensibilidade α e β, taxas de repopulação celular e protocolos-padrão de tratamento do câncer de mama. Nossas descobertas ressaltam a influência crítica dos parâmetros de radiossensibilidade α e β nos resultados do tratamento, com β emergindo como o fator predominante devido à sua contribuição quadrática para a fração de sobrevivência. Além disso, nossa análise indica que o crescimento do tumor é insignificante em relação à mortalidade celular substancial induzida pela radiação no caso do câncer de mama. Técnicas como FAST e radioterapia hipofracionada foram identificadas como particularmente eficazes, oferecendo um controle rápido do tumor, especialmente com valores α e β elevados. O termo quadrático β aumenta significativamente o sucesso do tratamento, enquanto a repopulação do tumor exerce influência mínima sobre o TCP, corroborando com comparações prévias na literatura. Notavelmente, doses mais altas por fração, em vez de doses cumulativas maiores, foram associadas a uma melhora do TCP, sugerindo aspectos importantes para otimização de protocolos de radioterapia. Atualmente a radiobiologia não é integrada sistematicamente à prática clínica e sua análise, por meio da TCP, otimiza os tratamentos de radioterapia, melhorando a qualidade de vida dos pacientes e a prestação de serviços de saúde.

Palavras-chave: câncer de mama, radiobiologia, probabilidade de controle tumoral.

1. INTRODUCTION

Breast cancer is the most common cancer in the world, regardless of the country's level of development [1]. Furthermore, excluding non-melanoma skin tumors, breast cancer ranks first in terms of cancer incidence and mortality in women, with 66,280 new cases estimated for 2022 in Brazil [2]. Early diagnosis of the disease is essential for a positive prognosis, and mammography is considered the most effective method of detection [3].

Cancer is a disease of uncontrolled proliferation by transformed cells subject to evolution by natural selection [4]. Treatments include surgery, radiotherapy, and systemic chemotherapy, whether or not these modalities are used together [5, 6]. There are approximately 66,000 new cases for the three-year period 2020-2023 [7].

The goal of radiotherapy is to use ionizing radiation to destroy tumor cells in a planned manner, using protocols that minimize damage to adjacent healthy tissues. Radiotherapy techniques can be divided into three: conventional, which has a lower daily dose, ranging from 1.8 to 2.0 Gy, with an average total dose of 45 to 60 Gy, and the technique with the highest number of fractions, divided into 25 to 30 [8]. Hypofractionated is the technique with doses above 2.0 Gy, resulting in a lower accumulated dose of 40 Gy, as it is fractionated into 15 and 16 fractions [9]. Finally, the FAST technique uses the highest daily dose of the three, 5.2 Gy, with a total dose of 26 Gy delivered in 5 uninterrupted fractions [10].

Mathematical modeling plays an important role in understanding and optimizing treatment, whether in comprehending tumor dynamics or the quality of diagnostic and therapeutic systems [11, 12], as it provides insight into tumor dynamics and the treatment itself without experimental costs [13, 14], making it very important for patient care. The linear quadratic model (LQM) is the most widely used representation for quantifying the fraction of cells that survive a given dose of radiation [14]. Although it was discovered empirically by

experimental fitting, over time its parameters have gained a mechanistic interpretation related to the damage caused to DNA strands [15 - 17]. The LQM is expressed as a function of the alpha (α) and beta (β) radiosensitivity parameters of the tissue according to Equation 1:

$$F(D) = e^{-\alpha D - \beta D^2} \quad (1)$$

where α refers to the one hit event on the DNA and is designated as a linear parameter (αD), and β refers to the multiple hit on the DNA and is designated as a quadratic parameter (βD^2) [18].

Some mathematical probability models make it possible to estimate the treatment success of a given protocol, widely known in the literature as the Tumor Control Probability or TCP. The TCP makes it possible to compare radiotherapy protocols and techniques to optimize clinical decisions [20, 21]. However, to obtain more realistic responses, the rate of cell repopulation between irradiations must be taken into account, since cells are constantly proliferating. This study investigates the effects of radiosensitivity on the Poissonian Tumor Control Probability (TCP), in terms of α and β parameters, considering conventional, hypofractionated and FAST radiotherapy techniques, as well as tumor repopulation. Therefore, this study is concerned with the effect of radiobiological parameters on the response to TCP.

2. MATERIALS AND METHODS

2.1. Gathering data from the literature

To perform the calculations and visualize the results graphically, this work was based on the literature review conducted by van Leeuwen et al.[21], which in turn was based on the work of Qi et al.[22]. From which the values of the radiosensitivity parameters α and β derived from the linear-quadratic model were obtained, as shown in Table 1. All parameters were taken from the work of Leeuwen et al. [21], as they are based

on a large review of randomized clinical trials for breast irradiation, while the literature is vague regarding more recent studies.

Table 1 : Radiosensitivity parameters α and β according to the work of Leeuwen and coworkers [21].

α (Gy^{-1})	β (Gy^{-2})
0.04	0.01
0.06	0.02
0.08	0.03
0.10	0.04
0.13	0.05
0.16	0.06

The initial tumor size, N_0= 10^9, and the cell repopulation rate, R_p=0.0481 $days^{-1}$, are based on studies by Wang & Xa [23]. The value of Rp was obtained using the expression $Rp = \frac{ln2}{td}$, where 'td' is the potential doubling time of the cell (td = 14.4) [22].

In addition, values were collected in the literature [24] for the clinical dose deliberation parameters used in practice for the conventional, hypofractionated, and FAST techniques in terms of total dose, fractions, and dose per fraction, as shown in Table 2. A escolha desse documento [24] se deu por se tratar de um documento guia para prática de oncologia clínica, baseada nas revisões da mais recente literatura.

Table 2 : Radiotherapy protocols used in clinical practice.

Technique	Total Dose (Gy)	# of fractions (days)	Dose per fraction (Gy/day)	Reference
Conventional	50	27	1.8	[24]
Hypofractionated	42.5	16	2.65	[24]
FAST	26	5	5.2	[24]

2.3. TCP calculation

The probability calculations were implemented in Python on a conventional computer using the free Google Colab platform. From the survival fraction described in equation 1, one can derive the Poisson TCP model in equation 2,

$$TCP = e^{-N_0 F(D)} \quad , \tag{2}$$

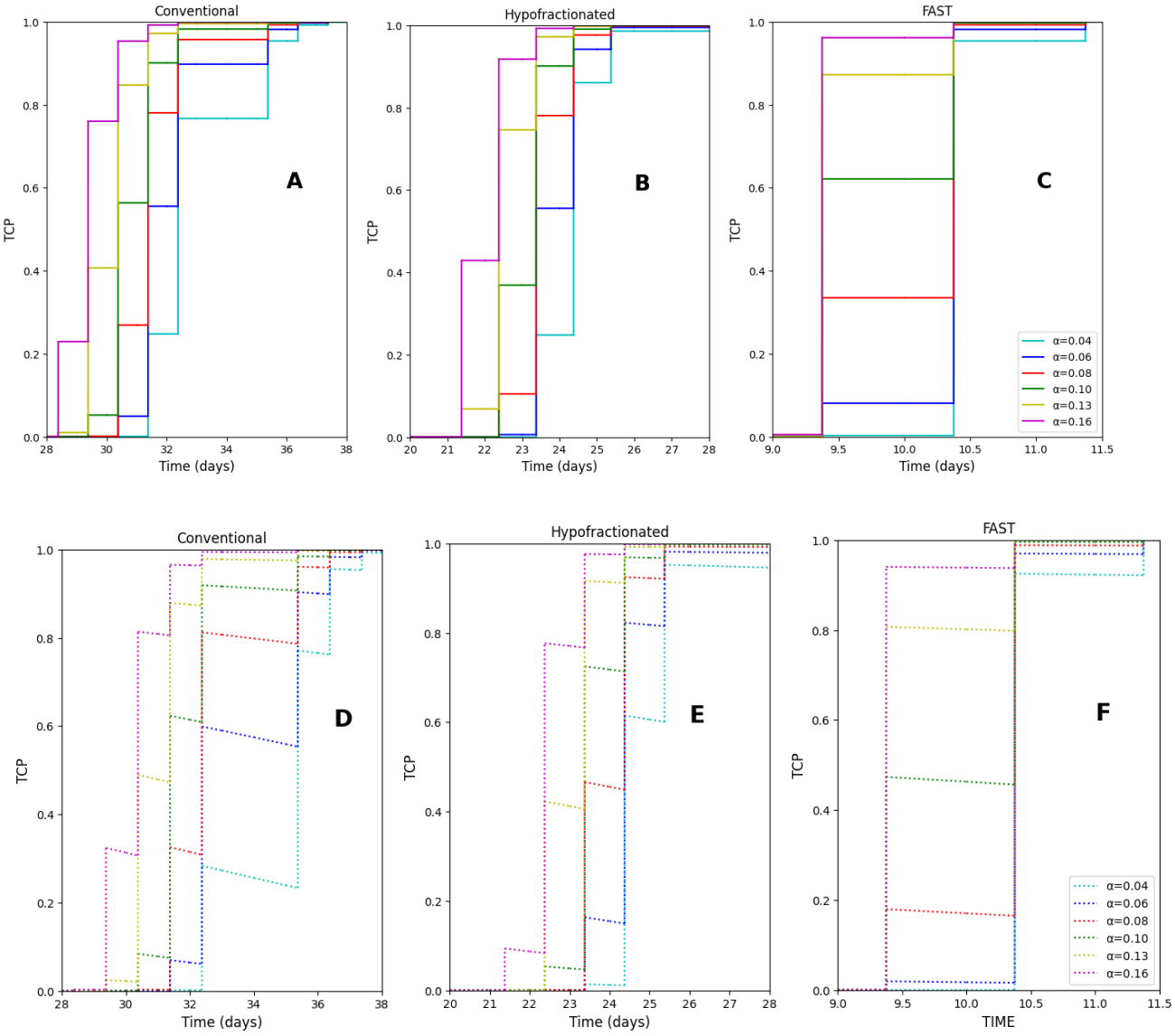
in which Gong and colleagues [26] showed that for low proliferation tumors, such as breast and prostate, more sophisticated TCP approaches lead to basically the same results as simple approaches, such as the Poisson approach. Therefore, this paper focuses on the use of the Poisson TCP.

TCPs were calculated by varying the radiosensitivity, growth rate, and dose deliberation parameters according to the protocols described in Tables 1 and 2, respectively. The values were substituted into Equation 1, which corresponds to the function F(D) in Equation 2, multiplied by the initial number of cells ($N0 = 10^9$) [20].

3. RESULTS AND DISCUSSIONS

The plots in Figure 1 A, B, C, D, E and F evaluate the effect of the α parameter on TCP for three different breast radiotherapy protocols: conventional, hypofractionated, and FAST. Thus, $\alpha = [0.04; 0.16]$ Gy^{-1}, while the β parameter is kept constant and corresponds to 0.028 Gy^{-2}. These values for α e β were used according to Leeuwen et al. [21] and Qi et al.[22]. The solid curves represent the TCPs without repopulation, while the dashed curves include cell repopulation.

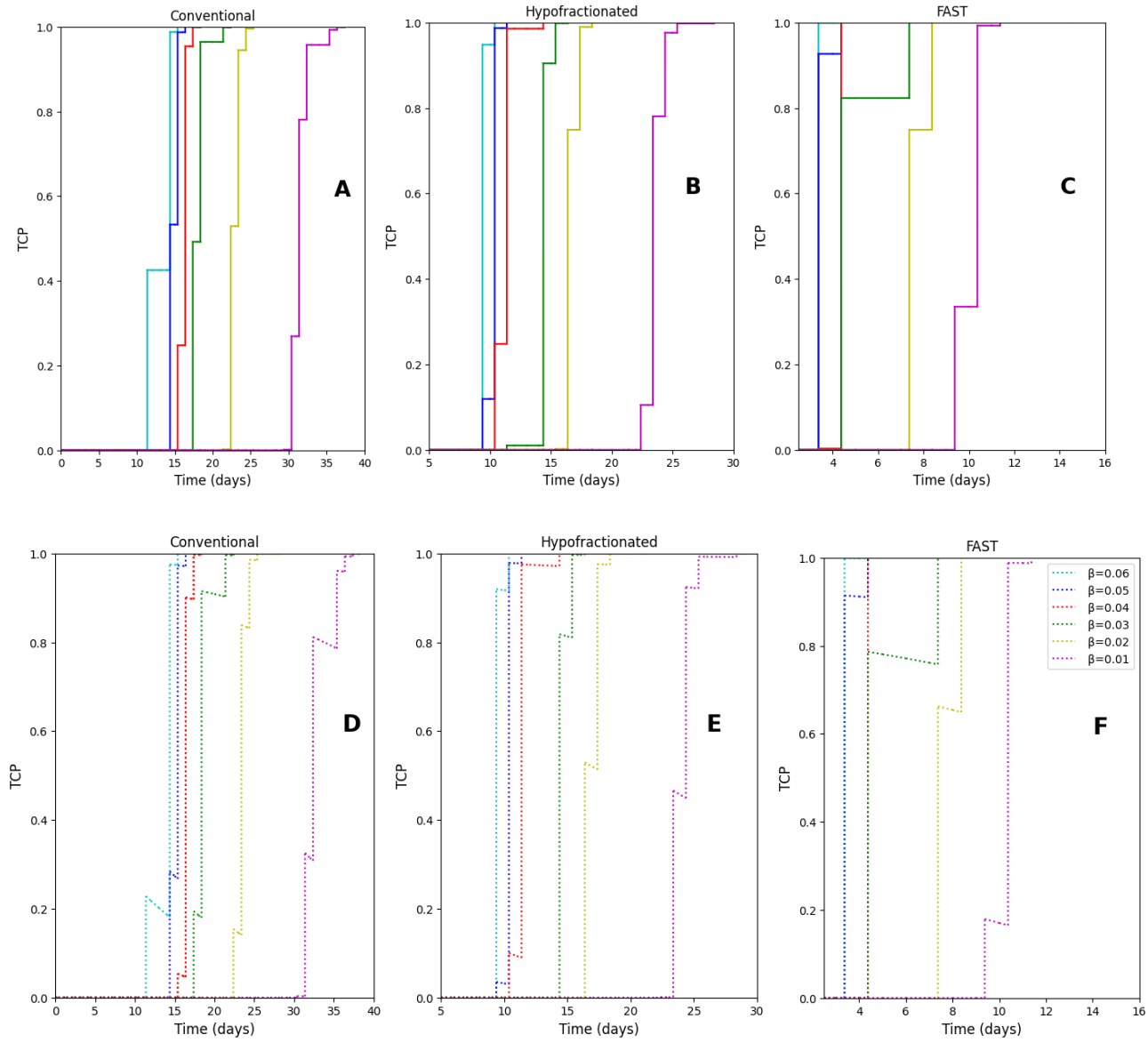
Figure 1: A, B, C, D, E and F represent the TCPs for the conventional, hypofractionated, and FAST techniques, respectively, varying the parameter α = [0.04; 0.16] Gy-¹ and keeping β = 0.028 Gy-². Solid curves consider Rp = 0 and dashed curves consider Rp = 0.0481 d-¹.



Fonte: authors

The plots in Figure 2 A, B, C, D, E and F evaluate the effect of the β parameter on TCP for three different breast radiotherapy protocols: conventional, hypofractionated, and FAST. The β parameter varies in the range β=[0.01; 0.06] Gy-², while α is kept constant and corresponds to 0.08 Gy-¹. Again, the solid curves exclude tumor repopulation during treatment, while the dashed curves include tumor repopulation.

Figure 2: A, B, C, D, E and F represent the TCPs for the conventional, hypofractionated, and FAST techniques, respectively, with the parameter $\alpha = 0.08$ Gy^{-1} held constant and the parameter β=[0.01; 0.06] Gy^{-2} varied. Solid curves consider Rp = 0 and dashed curves consider Rp = 0.0481 d^{-1}.



Fonte: authors

When tumor repopulation is taken into account, TCP values decrease in the absence of treatment, leaving a sloping profile as tumor growth becomes dominant in the face of radiation death. As an example, we have the blue and purple dotted curves in Figure 1D. The same behavior is repeated for all dashed curves in Figures 1 and 2.

For the curves without repopulation, represented by the solid lines, there is only a less accentuated horizontal plateau or staircase profile: the TCP remains constant because there is no death due to radiation or tumor growth. This behavior is more evident in the purple curves in Figures 1D and 1E, although it is repeated in the others, except for the cyan curve in Figure 1F, which quickly reaches TCP=1 due to the high values of α and β.

Repopulation has a direct impact on treatment time, as the tumor may grow again over the weekend or between radiation sessions during the week. Eradication is delayed due to repopulation. However, as shown in a previous study [25], tumor repopulation was observed to be subtle mainly in tumors with high α and β values, such as glioblastoma, head and neck cancer.

Figures 1A, 1B and 1C show the conventional, hypofractionated and FAST techniques, respectively. For the same protocol, the curves follow the same behavior in terms of time to TCP for different values of the parameter. One can observe that the pink curve with the highest α value (0.16 Gy^{-1}) is always the first to reach treatment success (TCP=100%) compared to the cyan curve (= 0.04 Gy^{-1}). The horizontal time difference for TCP=1 between these curves is $\Delta t \sim 4$ days. This parameter weights the effect of radiation in the low-dose regime such that the higher its value, the faster TCP=1 is reached. In this regime, according to the mechanistic interpretation, one DNA hits predominate.

In Figures 2A, 2B, and 2C, one can see that in each protocol, the effect of the β parameter on TCP is more drastic compared to the effect of the parameter (from Figure 1). This is most evident when looking at the horizontal distance between the cyan and pink curves in Figure 2A: when β varies from 0.01 to 0.06 Gy^{-2}, the time to tumor control varies from $\Delta t \sim 20$ days. In its equivalent, Figure 1A, the horizontal difference is only $\Delta t \sim 4$ days, showing the drastic effect of the β parameter on TCP. This is typically related to the multiple-hit events on the DNA [31]. In Figures 2B and 2C, such difference is not evident for the dose accumulates very quickly due to the hypofractionation and FAST protocols.

In terms of protocols, comparing Figures 1A, 1B and 1C with their equivalents 2A, 2B and 2C, one can see that TCPs achieve success more quickly when the protocol provides a higher dose per fraction and more fractions. In particular, the effect of a higher dose per fraction outweighs the effect of a higher cumulative dose, contradicting the intuition that the total dose would dominate treatment success. Thus, the FAST technique guarantees faster tumor control, followed by the hypofractionated technique and finally the conventional technique. However, it should be noted that successful treatment must include the optimization of maximum doses in tumors and minimum doses in healthy tissue.

4. CONCLUSIONS

This analysis highlights the significant influence of the radiosensitivity parameters α and β in the calculation of Tumor Control Probability (TCP), where subtle variations result in significant changes in tumor control times, with $\Delta t \sim 4$ days and $\Delta t \sim 20$ days for variations in α and β, respectively, in conventional protocols.

In addition, the β parameter emerges as the most important factor in TCP formulation due to its quadratic weight in the survival fraction, because it decreases the function faster and thus increases tumor control faster.

The tumor repopulation rate has minimal influence on tumor control, as it is superimposed on the cell death rates induced by the radiation doses according to Equation 1. This observation is consistent with studies comparing TCP models in tumors of varying aggressiveness.

In protocol comparisons, higher doses per fraction accelerate treatment, contrary to the intuition that a higher total dose would lead to faster control, which is consistent with findings from previous studies. TCP analysis can aid in the selection of treatment

protocols by highlighting techniques or protocols that are more likely to lead to faster treatment success.

We encourage that radiobiology needs to systematically integrate into clinical practice [27, 28], regardless of the tissue involved. The evaluation of TCP optimizes radiotherapy treatments, improving the quality of life of patients and the delivery of healthcare services.

ACKNOWLEDGMENT

The authors would like to thank the Instituto Federal Goiano (IF Goiano) and also the Universidade Federal de Ciências da Saúde de Porto Alegre for providing materials and space along this research.

CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

REFERENCES

[1] ARNOLD, M.; MORGAN, E.; RUMGAY, H.; MAFRA, A.; SINGH, D.; LAVERSANNE, M.; VIGNAT, J.; GRALOW, J. R.; CARDOSO, F.; SIESLING, S; SOERJOMATARAM, I. Current and future burden of breast cancer: Global statistics for 2020 and 2040. **Breast,** 2022 Dec;66:15-23.

[2] MINISTÉRIO DA SAÚDE. Dados e números sobre câncer de mama [Internet]. Rio de Janeiro: INCA; set 2023, 36 p. Avaliable in: https://www.inca.gov.br/publicacoes/relatorios/dados-e-numeros-sobre-cancer-de-mama-relatorio-anual-2023. Acesso em: 14 maio 2024.

[3] CAMPOS, L.; SANTOS, J. R.; SOUZA, D. N.; ATTIE, M. R. P. Relevant aspects of hypofractionation in breast and prostate radiotherapy. **Res Soc Dev.** 2021 May 5.

[4] BROWN, J. S.; AMEND, S. R.; AUSTIN, R. H.; GATENBY, R. A.; HAMMARLUND, E. U.; PIENTA, K. J. Updating the Definition of Cancer. **AACR Journals.** 2023 Nov.

[5] O'SHAUGHNESSY, J. A. Treating breast precancer. **Clin Breast Cancer.** 2000 Sep;1 Suppl 1:S74-9

[6] LIMA, B. D.; COSTA, C. L.; CAVALCANTE, K. A.; PEREIRA, S. M.; BRITO, M. A.; JIMENEZ, K. L. Desenvolvimento de protocolo de acompanhamento farmacoterapêutico a pacientes em tratamento de câncer de mama/ Development of a pharmacotherapeutic follow-up protocol for patients undergoing breast cancer treatment. **Braz J Health Rev.** 2021 May 24;4(3):11321-40.

[7] DOURADO, C. A.; SANTOS, C. M.; SANTANA, V. M.; GOMES, T. N.; CAVALCANTE, L. T.; DE LIMA, M. C. Câncer de mama e análise dos fatores relacionados aos métodos de detecção e estadiamento da doença. Cogitare Enferm. 2022 May 27;27.

[8] KIM, N.; KIM,Y. B. Journey to hypofractionation in radiotherapy for breast cancer: critical reviews for recent updates. **Radiat Oncol J.** 2022 Dec; 40(4): 216–224. Published online 2022 Dec 26. doi: 10.3857/roj.2022.00577.

[9] FANG, M.; MARTA, G. N.; Hypofractionated and hyper-hypofractionated radiation therapy in postoperative breast cancer treatment. Rev Assoc Bras. 2020 sept; 66 (9).

[10] Brunt AM, Haviland JS, Wheatley DA, et al. One versus three weeks hypofractionated whole breast radiotherapy for early breast cancer treatment: the FAST-Forward phase III RCT. **Southampton (UK): National Institute for Health and Care Research**; 2023 Nov. (Health Technology Assessment, No. 27.25.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK597550/ doi: 10.3310/WWBF1044.

[11] BRADY, R.; ENDERLING, H. Mathematical Models of Cancer: When to Predict Novel Therapies, and When Not to. **Bull Math Biol.** 2019 Oct;81(10):3722-3731. doi: 10.1007/s11538-019-00640-x. Epub 2019 Jul 23.

[12] PAIXÃO, L.; OLIVEIRA, B. B.; VILORIA, C.; DE OLIVEIRA, M. A.; TEIXEIRA, M. H.; NOGUEIRA, M. D. O. Monte Carlo derivation of filtered tungsten anode X-ray spectra for dose computation in digital mammography. **Radiol Bras.** 2015 Nov-Dec;48(6):363-7.

[13] VIEIRA, L. C.; COSTA, R. S.; VALÉRIO, D. An overview of mathematical modelling in cancer research: fractional calculus as modelling tool**. Fractal Fract [Internet]**. 2023 Aug 11;7(8):595.

[14] CUI, M.; GAO, X. S.; LI, X.; MA, M.; QI, X.; SHIBAMOTO, Y. Variability of α/β ratios for prostate cancer with the fractionation schedule: caution against using the linear-quadratic model for hypofractionated radiotherapy. **Radiat Oncol**. 2022 Mar 18;17(1).

[15] LEA, D. E.; CATCHESIDE, D. G. The mechanism of the induction by radiation of chromosome aberrations inTradescantia. **J Genet [Internet]**. 1943 Dec 44(2-3):216-45.

[16] SINCLAIR, W. K. **Biophysical Aspects of Radiation Quality.** International Atomic Energy Agency; Vienna, Austria: 1966. The shape of radiation survival curves of mammalian cells cultured in vitro. [Google Scholar]

[17] LYON, M. F.; PHILLIPS, R. J.; FISHER, G. Dose-response curves for radiation-induced gene mutations in mouse oocytes and their interpretation. **Mutat Res**. 1979 Nov;63(1):161-73.

[18] MCMAHON, S. J. The linear quadratic model: usage, interpretation and challenges. **IOPscience**. 2018 Dec. Institute of Physics and Engineering in Medicine. Available from: https://iopscience.iop.org/article/10.1088/1361-6560/aaf26a.

[19] O'SHEA, K.; COLEMAN, L.; FAHY, L.; KLEEFELD, C.; FOLEY, M. J.; MOORE, M. Compensation for radiotherapy treatment interruptions due to a cyberattack: An isoeffective DVH-based dose compensation decision tool. **J Appl Clin Med Phys**. 2022 Jul 22.

[20] SANTOS, M. M. **Probabilidade de controle tumoral: modelos e estatísticas** [Internet]: Universidade de São Paulo; 2014 [citado 15 maio 2024]. Avalilable from: http://www.teses.usp.br/teses/disponiveis/59/59135/tde-05012015-160705/.

[21] van Leeuwen, C.M., Oei, A.L., Crezee, J. *et al.* The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. *Radiat Oncol* 13, 96 (2018). https://doi.org/10.1186/s13014-018-1040-z

[22] QI, X. S.; WHITE, J.; LI, X. A. Is α/β for breast cancer really low? **Radiother Oncol**. 2011 Aug;100(2):282-8.

[23] WANG, J. Z.; LI, X. A. Impact of tumor repopulation on radiotherapy planning. **Int J Radiat Oncol Biol Phys**. 2005 Jan 1;61(1):220-7.

[24] The Royal College of Radiologists. Radiology dose fractionation, third edition. London: The RoyalCollege of Radiologist, 2019.

[25] HAUSSMANN, J.; CORRADINI, S.; NESTLE-KRAEMLING, C.; BÖLKE, E.; NJANANG, F. J. D.; TAMASKOVICS, B.; ORTH, K.; RUCKHAEBERLE, E.; FEHM, T.; MOHRMANN, S.; SIMIANTONAKIS, I.; BUDACH, W.; MATUSCHEK, C. Recent advances in radiotherapy of breast cancer. **Radiat Oncol**. 2020 Mar 30;15(1):71.

[26] HENNEQUIN, C.; BELKACÉMI, Y.; BOURGIER, C.; COWEN, D.; CUTULI, B.; FOURQUET, A.; HANNOUN-LÉVI, J. M.; PASQUIER, D.; RACADOT, S.; RIVERA, S. Radiotherapy of breast cancer. **Cancer Radiother.** 2022 Fev;26(1-2):221-30.

[27] GONG, J; DOS SANTOS, M. M.; FINLAY, C.; HILLEN, T. Are more complicated tumour control probability models better? **Math Med Biol.** 2013 Mar;30(1):1-19.

[28] HE, R.; DUGGAR, W. N.; YANG, C. C; VIJAYAKUMAR, S. Model development of dose and volume predictors for esophagitis induced during chemoradiotherapy for lung cancer as a step towards radiobiological treatment planning. **BMC Pulm Med**. 2023 Oct 9;23(1).

[29] LIU, F.; VERVERS, J. D.; FARRIS, M. K.; BLACKSTOCK, A. W. JR.; MUNLEY, M. T. Optimal Radiation Therapy Fractionation Regimens for Early-Stage Non-Small Cell Lung Cancer. **Int J Radiat Oncol Biol Phys**. 2024 Mar 1;118(3):829-838.

[30] COOPER, GM. The Cell: A Molecular Approach. 2nd Edition. **National Library of Medicine**. 2000. Available in: https://www.ncbi.nlm.nih.gov/books/NBK9963/.

[31] Joiner M, Van der Kogel A, editores. **Basic clinical radiobiology**. 4th ed. London: Hodder Arnold; 2009. p.50.

LICENSE