Impact of Dose Calculation Algorithms and Radiobiological Parameters on Prediction of Cardiopulmonary Complications in Left Breast Radiation Therapy

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ABSTRACT

Background: Breast cancer requires evaluating treatment plans using dosimetric and biological parameters. Considering radiation dose distribution and tissue response, healthcare professionals can optimize treatment plans for better outcomes.

Objective: This study aimed to evaluate the effects of the different Dose Calculation Algorithms (DCAs) and Biologically Model-Related Parameters (BMRPs) on the prediction of cardiopulmonary complications due to left breast radiotherapy.

Material and Methods: In this practical study, the treatment plans of 21 female patients were simulated in the Monaco Treatment Planning System (TPS) with a prescribed dose of 50 Gy in 25 fractions. Dose distribution was extracted using the three DCAs [Pencil Beam (PB), Collapsed Cone (CC), and Monte Carlo (MC)]. Cardiopulmonary complications were predicted by Normal Tissue Complication Probability (NTCP) calculations using different dosimetric and biological parameters. The Lyman-Kutcher-Burman (LKB) and Relative-Seriality (RS) models were used to calculate NTCP. The endpoint for NTCP calculation was pneumonitis, pericarditis, and late cardiac mortality. The ANOVA test was used for statistical analysis.

Results: In calculating Tumor Control Probability (TCP), a statistically significant difference was observed between the results of DCAs in the Poisson model. The PB algorithm estimated NTCP as less than others for all Pneumonia BMRPs.

Conclusion: The impact of DCAs and BMRPs differs in the estimation of TCP and NTCP. DCAs have a stronger influence on TCP calculation, providing more effective results. On the other hand, BMRPs are more effective in estimating NTCP. Consequently, parameters for radiobiological indices should be cautiously used s to ensure the appropriate consideration of both DCAs and BMRPs.

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Keyword

Breast Neoplasms; Radiotherapy; Tumor Control Probability; Normal Tissue Complications Probability; Dose Calculation Algorithm; Models, Biological

Introduction

Breast cancer is considered a common malignancy among women. Radiotherapy is one of the most important treatments for patients undergoing mastectomy for better tumor control and reduced recurrences in the affected area [1]. Radiation therapy aims to deliver the maximum and minimum dose to the target tissues and the normal tissues, respectively [2]. The majority of radiotherapy departments utilize

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advanced Treatment Planning Systems (TPSs) that possess high capabilities for dose calculation and prediction of normal tissue complications during treatment procedures [3]. Further, these TPSs employ Dose Calculation Algorithms (DCAs) to calculate dose values and generate three-dimensional dose distributions within the target volumes. The most current DCAs used in dedicated TPSs are correction-based, model-based, MC-based, and recently biologically-based algorithms [4]. Also, some Biological Models for Radiobiological Parameters (BMRPs) are used to calculate radiobiological indices, such as Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) and to predict normal tissue complications during and after radiation therapy [5]. The dose to tumor surrounded-tissues was computed by effective factors, such as the amount of radiation dose, irradiated field size and shape, distance to field edges, tissue inhomogeneities, and biological behaviors of tissues [6]. Monte Carlo (MC)-based DCAs can perform better than other DCAs in order to calculate dose amounts in target volume and tissues close to target volumes, such as heart and lungs in radiotherapy of the breast with tissue inhomogeneities [7]. The DCAs in TPSs are insufficient to accurately predict the complications in normal tissues because the biological response of tissues to ionizing radiation cannot be fully captured by DCAs alone. Factors, such as tissue behaviors and their biological response require additional considerations and models to better understand and predict potential complications in normal tissues exposed to radiation. Therefore, in determination of some radiobiological indicators, such as TCP and NTCP, more comprehensive information is probably obtained from tumor control and normal tissue complications. In some commercial TPSs, vendors, and companies, the design of some radiobiological indices, such as TCP and NTCP can increase their product performances. NTCP, calculated with existing dosimetry parameters and BMRPs, can lead to predicting the risk of complications in natural tissues. Accordingly, two critical factors are needed to calculate TCP and NTCP, especially for predicting tissue complications in radiation therapy, as follows: 1) the precise amount of radiation dose delivered to interested volumes and 2) the correct selection of biological models and parameters compatible with tissue response to ionizing radiations. Biologically based algorithms for predicting tissue response to radiation can lead to some serious problems and errors in predicting tissue complications because of some limitations and lack of knowledge about biological models and tissue behaviors (AAPM-TG 166) [8]. Therefore, incorrect selection of biological parameters in predicting NTCP and cardiopulmonary complications due to breast radiation therapy can lead to treatment failure and unwanted complications in the short and long term. A few DCAs and biological models and parameters were used to predict the radiotherapeutic effects of different tumors without using the MC algorithm [6, 9-11]. The use of the MC algorithm is needed due to the dose distribution in heterogeneous environments. In this study, the MC algorithm is needed and compared with other algorithms, incorporating various biological parameters in order to predict cardiopulmonary complications in left breast radiotherapy. In the current study. The current study also aimed to investigate the influence of dose calculation algorithms and radiobiological parameters on the accurate prediction of cardiopulmonary complications resulting from left breast radiation therapy.

Material and Methods

Patients

In this practical study, individuals referred to the radiotherapy department of Omid Urmia Hospital, Urmia, Iran for adjuvant RT after breast cancer surgery (mastectomy) participated from February 2020 to December 2021. Additionally, Computed tomography (CT)

was selected from 21 female patients, who were treated with 6 MV X-rays using an Elekta linear accelerator (Elekta, Synergy, Agility head 160, England and Sweden) with two tangential fields and a total dose of 50 Gy in 25 fractions (2 Gy per fraction).

Treatment plans and dose calculation algorithms

For all the patients, CT imaging (Somatom Sensation Open, Siemens, Forchheim, Germany) was performed in a therapeutic position with a 3-millimeter slice thickness. Then, CT images were transferred to the MONACO TPS (version 5.11.03, Crawley, UK). Next, the target volumes were defined according to the ICRU report No. 50 [12]. Gross Tumor Volume (GTV) and Organs at Risk (OARs) were determined based on clinical findings and delineated under the supervision of a radiation oncologist according to the Breast Cancer Atlas of the Radiation Therapy Oncology Group (RTOG) [13]. The Planning Target Volume (PTV) was defined by the expansion of GTV with a margin of 7 mm.

All the plans were implemented with DCAs (Pencil Beam (PB), Collapsed Cone (CC), and Monte Carlo (MC)) and the same techniques and administered dose. As a result, Dose-Volume Histograms (DVHs) were derived for each plan (Figure 1). For obtaining some required dosimetric parameters, differential Dose-Volume Histograms (dDVH) were extracted with a grid size of 0.10 cm and a dose bin of 0.25 Gy for PTV and OARs including heart and lung [6].

TCP and NTCP calculations

In the present study, the Poisson and Niemierko models were used to calculate TCP,

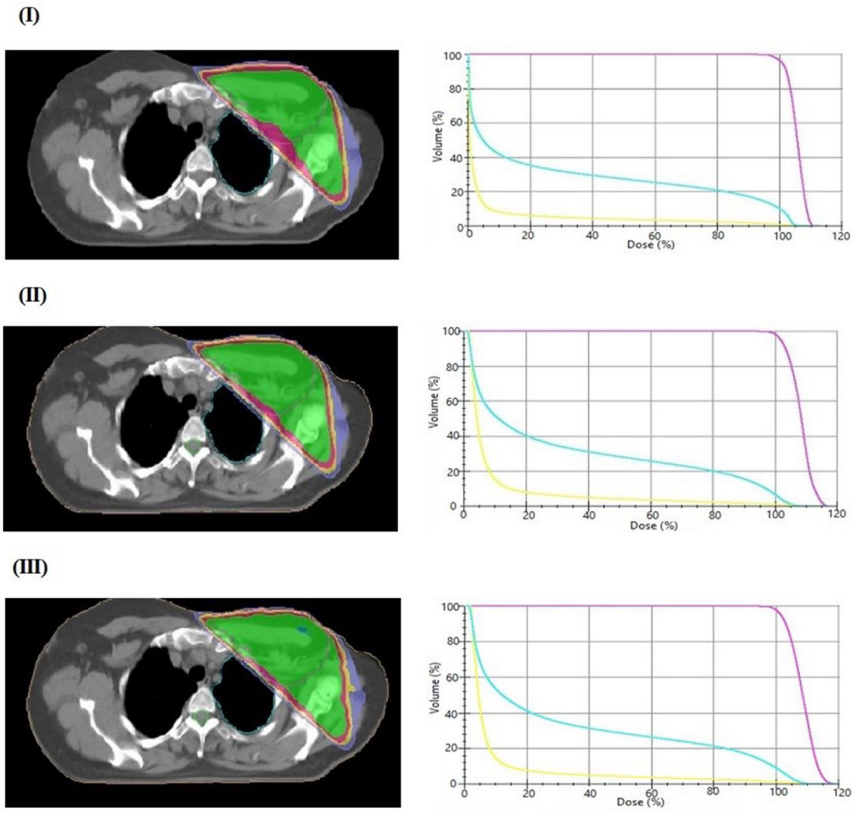

Figure 1: Isodose and DVH (Dose Volume Histogram) for dose calculation algorithms (**I**) PB (Pencil Beam), (**II**) CC (Collapsed Cone) and (**III**) MC (Monte Carlo) for a patient as an example

and the Lyman-Kutcher-Burman (LKB) and Relative-Seriality (RS) models were applied to calculate NTCP. Formulas to calculate each index are included in Equations 1 to 8 [5, 10]. The Poisson model can be expressed by the Equation (1):

$$TCP = \left(\frac{1}{2}\right)^{\sum_i V_i \exp\left(2\gamma_{50}\left(1-\frac{D_i}{TCD_{50}}\right)/\ln 2\right)} \quad (1)$$

TCP, according to Niemierko, can be determined by the equations (2) and (3):

$$EUD = \left(\sum_i v_i D_i^a\right)^{1/a} \quad (2)$$

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

where TCD_{50} is a uniform dose increasing the probability of tumor control by 50%, v_i is the volume irradiated with a uniform dose of D_i, γ_{50} is the slope of the dose-response curve in TCP, D_i shows the dose per voxel, and a is the defined specific parameter-tumor tissue describing the dose-volume effect (a=-7.2 for PTV) [14]. For the PTV, the TCP is used for breast cancer based on the Possion and Niemerico models. The radiobiological parameters for calculating the TCP for breast cancer included values α/β=4 [15], TCD_{50}=30.89 Gy, and γ_{50}=1.3, obtained by Okunieff P et al. [16]. For each DCA, TCP was measured for each patient and averaged.

NTCP, according to the LKB model, is expressed by the formula (4-6):

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \quad (4)$$

$$t = \frac{EUD - TD_{50}}{m \cdot TD_{50}} \quad (5)$$

$$EUD = \left(\sum_i v_i D_i^{\frac{1}{n}}\right)^n \quad (6)$$

where TD_{50} is a uniform dose causing a 50% probability of complication, m is the curved slope, and n is a parameter describing the importance of the volume effect.

The RS model can be determined by the equations (7) and (8):

$$NTCP = \left[1-\prod_{i=1}^{M}\left(1-(P(D_i))^s\right)^{v_i/v}\right]^{1/s} \quad (7)$$

$$P(D_i) = 2^{-\exp\left(e\gamma\left(1-\frac{D_i}{D_{50}}\right)\right)} \quad (8)$$

where D_{50} is a uniform dose causing a 50% complication probability, γ is defined as the slope of the curve, M is the total number of voxels, S is the relative model serial, and V shows the total volume of the organ.

Consequently, the required data have been calculated in two ways to calculate the values of TCP and NTCP with the mentioned models, as follows: 1) dosimetric parameters extracted from TPS, such as dose bin (D_i, V_i) for each patient by three dose calculation algorithms and 2) published radiobiological parameters according to the models in this study, for each organ (GTV, lung, and heart).

A homemade computer code was developed in MATLAB (MathWorks Inc, MATLAB-Rb2018) to calculate TCP and NTCP parameters, and these two series of data were used as input data for this program. Four sets of parameters were used to calculate the NTCP of cardiac complications, and three parameters were used to predict cardiac pericarditis, and one to evaluate late cardiac mortality [17-19]. Also, in the case of the lungs, six sets of parameters were used for the risk prediction of developing pulmonary pneumonitis [20-25]. Also, a parameter set obtained from different studies was used to calculate TCP [16]. Table 1 shows the values of radiobiological parameters used for NTCP calculations.

Statistical analysis

Analysis of variance and comparison of the mean NTCP obtained for DCAs were performed using the ANOVA test. The Tukey

Table 1: Radiobiological parameters of NTCP (Normal Tissue Complication Probability) calculation for the breast cancer plans.

		NTCP Parameters			
Structure	**Model**	**D_{50} (Gy)**	**m/γ**	**n/s**	**Reference**
lung	**LKB**	24.5	0.18	0.87	[21]
		30.5	0.30	1	[22]
		30.8	0.37	0.99	[23]
	RS	34	0.9	0.06	[23]
		30.1	0.96	0.012	[24]
		24.5	2.1	0.0061	[20, 25]
Heart	**LKB**	48	0.10	0.35	[19]
		50.6	0.13	0.636	[17]
	RS	52.4	1.28	1	[18, 19]
		49.2	3	0.2	[20, 25]

LKB: Lyman Kutcher Burman, RS: Relative Seriality, NTCP: Normal Tissue Complication Probability, D_{50}: uniform dose causing a 50% complication probability, γ: slope of the curve, m: curved slope, n: a parameter describing the importance of the volume effect

HSD test was used to compare DCAS pairs. For a limited number of parameters due to heterogeneity of variance, the Kruskal-Wallis nonparametric test was used to analyze variance. SPSS statistics (version 22; IBM) was used for data analysis with the significant mean difference at the 0.05 level.

Results

Table 2 presents the mean TCP and NTCP values for the 21 patients, along with their corresponding standard deviations, used to quantitatively evaluate the performance of the applied DCAs and BMRPs in estimating TCP and NTCP. The optimal results were achieved when TCP estimations were close to 1, showing a higher probability of tumor control, and NTCP estimations were close to 0, showing a lower likelihood of complications in normal tissues.

TCP analysis

Table 2 and Figure 2 present the TCP results of PB, CC, and MC algorithms for 21 breast cancer patients, averaged across the patient cohort. The percent mean TCP values for the Niemierko model, estimated using PB, CC, and MC algorithms, were 84.38, 88.17, and 89.84, respectively (P-value>0.05). Regarding the Poisson model, the percent mean TCP values for PB, CC, and MC algorithms were 94.05, 95.08, and 94.82, respectively (P-value<0.05). The PB algorithm consistently demonstrated lower TCP values compared to CC and MC algorithms. Conversely, the MC algorithm yielded similar TCP results as the CC algorithm (P-value<0.05).

NTCP (Lung, Heart) analysis

Table 2 and Figure 2 provide the NTCP results for heart and lung structures obtained using the PB, CC, and MC algorithms. Additionally, Table 2 presents the mean lung NTCP values for pneumonitis prediction using two LKB and RS models with three DCAs, utilizing the BMRP. Based on the RS model and the published radiobiological parameters (D_{50}=24.5, γ=2.1, S=0.0061) for the lung, there was no significant distinction among the PB, CC, and MC algorithms in terms of NTCP

Table 2: Statistical description of TCP (Tumor Control Probability) and NTCP (Normal Tissue Complication Probability) with different biological models and parameters for three dose calculation algorithms

	Radiobiological Models	PB Average±SD	CC Average±SD	MC Average±SD	*P*-value
TCP (PTV)	Niemierko Model	84.38±4.25	88.17±1.70	89.84±1.74	0.384
	Poisson Model	94.05±0.21	95.08±0.15	94.82±0.26	*0.005
NTCP (Lung)	LKB Model	3.47±1.17	5.36±1.87	7.88±2.53	*0.0001
		2.35±0.37	7.06±0.84	7.21±1.06	*0.0001
		4.98±0.53	11.58±0.87	11.01±1.14	*0.0001
	RS Model	4.71±0.74	10.61±0.89	11.05±1.04	*0.0001
		3.64±0.60	11.29±1.07	11.02±1.38	*0.0001
		3.47±1.17	5.36±1.87	7.88±2.53	0.281
NTCP (Heart)	LKB Model	0.027±0.01	0.16±0.06	0.088±0.04	0.061
		0.011±0.003	0.055±0.01	0.036±0.01	*0.005
	RS Model	1.80±0.32	2.01±0.52	1.01±0.82	0.248
		2±0.33	3.37±0.50	2.90±0.42	0.078

PB: Pencil Beam, CC: Collapsed Cone, MC: Monte Carlo, PTV: Planning Tumor Volume, LKB: Lyman Kutcher Burman, RS: Relative Seriality

Significant *P*-values marked by *. *P*-value<0.05 shows that there is a significant difference between the two DCAs (Dose Calculation Algorithms) in calculating TCP (Tumor Control Probability) and NTCP (Normal Tissue Complication Probability)

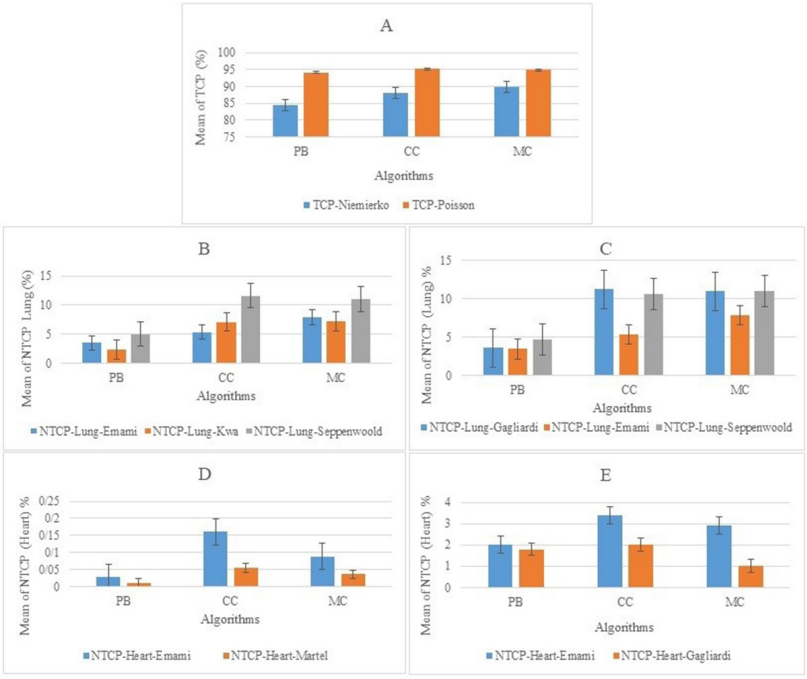

Figure 2: Mean values of Tumor Control Probability (TCP) (%) and Normal Tissue Complication Probability (NTCP) (%) as a function of different biological parameters, in different dose calculation algorithms [Pencil Beam (PB), Collapsed Cone (CC) and Monte Carlo (MC)] for 21 patients, in graphs (**A**), (**B**), (**C**), (**D**) and (**E**) are given.

results (*P*-value>0.05) [20, 25].

Table 2 also shows the mean heart NTCP for radiation-related cardiac complications, such as pericarditis with three DCAs for LKB and RS models using BMRPs. There is no significant difference between PB, CC, and MC algorithms in terms of NTCP results based on LKB and RS models for all the radiobiological parameters used in Table 2 except the Martel parameter (D_{50}=50.6, m=0.13, n=0.636) for the heart (*P*-value>0.05).

In analyzing other biological parameters, a significant difference was observed. Specifically, in the calculation of TCP, lung NTCP (pneumonitis), and heart NTCP (pericarditis and cardiac mortality), pairwise comparisons were made between the algorithms using Tukey and Mann-Whitney tests. The results demonstrate that there is no significant difference between the CC and MC algorithms (*P*-value>0.05). However, there is a statistically significant difference between the PB-CC and PB-MC algorithms (*P*-value<0.05).

Discussion

The present study aimed to evaluate the influences of DCAs and BMRPs on NTCP and TCP in cancer patients with left breast radiotherapy. TCP and NTCP, two radiobiological indicators, evaluate patient plans before radiotherapy, optimize, and improve the quality of patient treatment. TCP and NTCP are used for evaluating tumor control and predicting normal tissue complications following radiation therapy, respectively. Cardiopulmonary complications are considered one of the main side effects of breast cancer radiotherapy, especially in patients with left breast involvement. DCA-based TPSs have undergone significant advancements in both radiotherapy techniques and software enhancements, leading to more accurate and efficient dose calculations for better treatment planning and delivery. As a result, radiotherapy has progressed in terms of precision, effectiveness, and patient outcomes. Different DCAs, such as correction-based, model-based, and MC-based algorithms, help physicians and physicists ensure the accuracy and precision of dose-delivery systems [26]. Along with TPS improvements, radiobiological-related studies were performed for assessments of tumor cells and normal cell response to ionizing radiations, leading to the introduction of numerous BMRPs, which reflect the response of tumor and normal cells against radiations. Missing some BMRPs led to overestimating or underestimating predicted values of TCP and NTCP [27]. Meanwhile, AAPM-TG 166, as substantial scientific evidence, emphasized that the use of biologically related models and parameters as the main tool can be dangerous in the clinic due to various limitations in models and extracted parameters [8]. Thus, TPSs must be used as a collection of algorithms and organ-specific models for optimizing plans and estimating radiobiological indices, such as TCP and NTCP. In this study, the influences of main DCAs and available BMRPs were evaluated on estimating TCP and NTCP in patients with left breast cancer. Numerous BMRPs were carefully extracted from previous studies and used for TCP and NTCP calculations accompanied with DCAs [16-25]. TCP was calculated using Poisson and Niemierko models with no significant difference between all DCAs for Niemierko model. However, there was a statistically significant difference between TCP calculation with PB and CC algorithms, and also between PB and MC algorithms using the Poisson model (*P*-value<0.05) in the present study. Meanwhile, there was no significant difference between CC and MC results (*P*-value>0.05). These results are consistent with studies by Chetty et al. and Liu et al., showing that correction-based algorithms underestimated TCP more than model-based algorithms [28, 29]. In addition, the 85th report of AAPM-TG 65 showed that only 5% of changes in dose calculation by DCAs without correction could lead to noticeable variations in TCP and NTCP estimation [30]. The results confirmed

that advanced DCAs, such as CC and MC did not lead to a significant influence of BMRPs on TCP calculation. However, the impact of BMRPs on TCP calculation was statistically considerable using undeveloped model-based DCAs, such as PB (P-value<0.05).

Our results showed that NTCP calculation with the PB algorithm led to lower values than NTCP recalculation with the CC algorithm in predicting cardiopulmonary complications. Studies conducted by Bufacchi et al. and Chiakh et al. have shown that undeveloped model -based algorithms estimate NTCP for lungs less than model-based algorithms, which is compatible with our results [6, 31]. Although PB, an undeveloped model-based algorithm, calculates dose in less time than other algorithms, it does not accurately consider the distribution of secondary electrons in heterogeneous environments via simulation of electron dispersions in one dimension. Therefore, this algorithm is known as a flounce map in the TPS, used in IMRT treatment for plan optimization, but it is not widely used in 3D-CRT plans [32, 33]. In contrast, the CC algorithm performs better in modeling secondary electron dispersions, especially in longitudinal and lateral directions. Thus, the CC algorithm will have a more reliable performance than the PB algorithm [34]. The findings also demonstrated a statistically significant difference between PB and MC algorithms in TCP and NTCP calculation by most of BMRPs (P-value<0.05). Lu et al. and Elcim et al. showed significant differences between MC and PB algorithm calculations, which is consistent with our results and recommended using the MC algorithm in heterogeneous environments [35, 36]. Accordingly, in calculating NTCP, the PB algorithm estimates cardiopulmonary complications in less time than the MC algorithm. Zhuang et al. and Liu et al. showed the same results during the application of PB and MC for calculating NTCP in radiotherapy of heterogonous fields, which are compatible with our results [37, 38]. The MC-based DCA has been recognized as a gold standard method for particle transport and dose calculation in dosimetric studies and also used progressively in advanced TPSs [39]. Since the radiation target volume in left breast radiation therapy is adjacent to some tissues with different densities, such as bony thorax, pectorals' muscles, fats, and lungs, the MC algorithm considers electron disequilibrium due to tissue heterogeneities. Thus, the MC algorithm calculates radiobiological indices more accurately than the CC algorithm. However, the obtained results of the current study demonstrated no significant differences in NTCP calculation between CC and MC algorithms in MONACO TPS (P-value>0.05), which can be due to the definition of electron cutoff criteria in TPS. Therefore, the reduction of the NTCP value related to MC, especially for organs irradiated outside the target volume, is due to the limitation in defining the cutoff criterion for secondary electrons. By considering all organs for the calculation of NTCP, this uncertainty in the calculations must be carefully considered. Consequently, in large organs, such as lungs and heart, the cutoff criterion considered by TPS may be insufficient for the entire volume of these organs. Therefore, increasing the distance from the edges of the radiation field decreases the accuracy of NTCP calculation [40].

Rana et al. demonstrated that the MC-based algorithm had the same performance as other model-based algorithms in estimating NTCP for predicting heart and lung complications during breast radiotherapy, which is compatible with our results [14]. Liang et al. compared two algorithms, AAA (model-based) and AXB, to predict pulmonary pneumonitis in breast radiotherapy and used biological parameters derived from the LKB model to estimate NTCP. Their results showed no statistically significant differences between AAA and AXB algorithms in NTCP estimation [27]. Since the AXB algorithm has a similar performance to the MC algorithm in dose

calculation of heterogeneous environments, powerful algorithms, such as AXB and MC in some TPSs to calculate NTCP do not necessarily, lead to desired outcomes. The estimated TCP and NTCP were close to the expected results using CC- and MC-based DCAs. Although no significant differences were noticed in results for calculated NTCP for most BMRPs using CC and MC, some different results were observed in some cases with specific biological models and parameters (Figure 2). The parameters derived from DCAs play a significant role, while in others, the BMRPs take on greater importance.

Nielsen et al. showed that the calculated NTCP values for lungs and consequently the radiotherapy-related pulmonary complications were sensitive to types of DCAs. They also concluded that the radiation dose derived from DCA was more important than other parameters. However, they showed that NTCP for cardiac complications was less sensitive to the applied DCAs [41]. Chiakh et al. demonstrated that NTCP calculation strongly depended on the correct selection of BMRPs, whereas TCP calculation was more impressed by DCAs. They then emphasized using NTCP as a routine tool for plan evaluation and decisions in clinics [31, 42] and deduced that DCAS would be improved increasingly by advancements in computational accountings and processing. Dose calculation accuracy would increase until the effect of DCAs on estimations of radiobiological indices, especially NTCP calculation, reached constant or semi-constant values. However, the influences of biological models and parameters on NTCP estimation show complex and sometimes contradictory results. The paradox and contradiction in determining the main factor influencing NTCP estimation arise due to the limitations of biological models and related parameters, as well as the incomplete understanding of tissue response to ionizing radiation. Additionally, the availability of comprehensive and high-quality clinical data is often inadequate, further complicating the estimation process [8].

Conclusion

CC and MC algorithms in breast radiotherapy yield similar results for tumor control and cardiopulmonary complications. Accurate estimation of NTCP depends on appropriate radiobiological parameters. This study aimed to provide precise parameters for better prediction of normal tissue complications. Parameters should be obtained for new TPS and various organs to facilitate research and clinical practice.

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Authors' Contribution

A. Zinali proposed conceptualization and design, supervised modeling, edited and critically reviewed, and also interpreted the data. N. Kargar performed the conceptualization and design, collected the data and drafted the manuscript, and also provided manuscript drafting, modeling, and interpretation of the data. M. Molazadeh programmed in MATLAB and edited the draft of the manuscript. All authors read, modified, and approved the final version of the manuscript.

Ethical Approval

The Ethics Committee of Urmia University of Medical Sciences approved the protocol of the study (Ethic cod: IR.UMSU.REC.1398.100).

Informed Consent

We used patients' CT scan data, and consent was not required to conduct this study.

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Conflict of Interest

None

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