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Radiobiological evaluation of hypo-fractionated breast cancer radiotherapy regimens in comparison with conventional approaches

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Abstract

Purpose: This study compares tumor control probability (TCP) and normal tissue complication probability (NTCP) across different hypo-fractionated (HypoRT) and conventional breast radiotherapy regimens using radiobiological models.

Materials and methods: Computed tomography data from 30 patients with left breast-conserving surgery were used to evaluate three HypoRT regimens (39 Gy and 41·6 Gy in 13 fractions, and 40 Gy in 15 fractions) and a conventional regimen (50 Gy in 25 fractions). Dose-volume histograms (DVHs) were extracted for radiobiological calculations using Equivalent Uniform Dose (EUD) and Poisson models for TCP, and EUD and LKB (Lyman-Kutcher-Burman) models for NTCP.

Results: Conventional treatment achieved significantly higher TCP (95%) than all HypoRT regimens ($p < 0{\cdot}001$), with no significant differences between HypoRT regimens ($p > 0{\cdot}05$. The 39 Gy/13 fraction regimen showed the lowest lung NTCP ($p < 0{\cdot}05$). HypoRT regimens had significantly lower NTCP for the lungs and heart compared to the conventional regimen ($p < 0{\cdot}01$). TCP and NTCP values from Poisson and LKB models were higher than those from the EUD model ($p < 0{\cdot}01$).

Conclusion: HypoRT regimens reduced NTCP, with the lowest values in the regime of 39 Gy/13 fractions regimen, though the conventional regimen had higher TCP.

Original Article

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Introduction

Breast cancer poses a significant global health burden, with over 2 million new cases diagnosed annually worldwide.[1,2] Radiotherapy plays a crucial role in both curative and palliative care of breast cancer.[3–5] While treatment technical developments have improved clinical outcomes, optimising the radiotherapy regimen remains challenging due to differences in individual risks and responses.[6] Hypo-fractionated radiotherapy (HypoRT) has emerged as a prominent approach, characterised by shorter treatment durations and escalated higher fractional doses.[7]

Clinical trials have underscored the safety and efficacy of hypofractionation in the treatment of breast cancer, with some studies even reporting ultra-HypoRT involving just five fractions.[7] The low α/β ratio of breast cancer cells suggests heightened sensitivity to higher fractional doses (higher dose in each fraction), further validating the HypoRT strategy.[8] Furthermore, multiple clinical trials over the past 10 years support the application of shorter treatment fractions with higher fractional doses for breast cancer radiotherapy.[7] Recent clinical trials have demonstrated that HypoRT yields comparable outcomes in terms of survival, local control and acute toxicity when compared to conventionally fractionated radiotherapy.[9] Furthermore, HypoRT suggests advantages in terms of treatment efficiency and reduced time commitment for patients. The selection of the optimal fractionation scheme remains a crucial clinical decision, considering individual patient factors.[10]

Radiobiological modelling is a multidimensional challenge that can help personalise radiation prescriptions and compare different treatment plans.[11] In this model, both aspects of an appropriate treatment including tumour control probability (TCP) and normal tissue complication probability (NTCP) need to be predicted for comparison and evaluation. These

probabilities are obtained from the dose distributions of target volume and organs at risk (OARs), considering previously obtained radiobiological dose-response parameters obtained from large groups of patients treated with radiation and receiving different doses. Therefore, the dose distribution must be calculated accurately and described with appropriate metrics.[12]

Although advanced radiotherapy techniques such as volumetric modulated arc therapy, intensity-modulated radiotherapy (IMRT) and tomotherapy improve tumour control and spare normal tissues, conventional radiotherapy remains a standard treatment technique in breast cancer.[13] Conventionally, whole breast radiotherapy involves 50 Gy over 5 weeks[5]; however, HypoRT regimens with lower total doses and fractions have shown comparable efficacy with reduced workload.[14] This approach, introduced experimentally in the UK and Canada decades ago, includes dose regimens of 41·6 Gy in 13 sessions, 39 Gy in 13 sessions and 40 Gy in 15 sessions.[15–17]

While conventional treatment planning systems can calculate equivalent doses, our study offers a unique and clinically relevant contribution by employing a comparative approach within the same patient group. We leverage radiobiological models, including the Lyman-Kutcher-Burman LKB, EUD and Poisson models, to predict and compare both TCP and NTCP for different hypo-fractionated regimens (41·6 Gy in 13 sessions, 39 Gy in 13 sessions and 40 Gy in 15 sessions). This approach allows us to assess the relative performance of each model in predicting not only tumour control but also the potential for complications in healthy tissues. By comparing the models' predictive power for both TCP and NTCP within a consistent clinical context, our study offers a more robust and internally controlled evaluation compared to analyses across diverse patient populations.

Materials and Methods

Patients

This cross-sectional study was conducted under the recommendations and regulations of the national ethical committee. The consent forms were waived due to the retrospective nature of the study. In this study, 30 patients in T2 and T3 stages without positive nodes and metastasis (N0M0) were selected who had been diagnosed with early-stage invasive ductal carcinoma of the left-sided breast cancer and showed no signs of involvement in the supraclavicular and axillary lymph nodes. The patient's computed tomography images (Somatom Sensation 16, Siemens Healthcare, Erlangen, Germany), treatment plans, calculated dose distributions and demographic information were obtained from the radiation oncology department of Golestan Ahvaz Hospital (Ahvaz, Iran).

Treatment approach

The selected patients received whole breast radiation therapy using the 3D-conformal technique (3D-CRT). The whole breast with 2 cm inferior to the inframammary line and 1 cm superiorly above the breast tissue superiorly was considered as the planning target volume. The medial and lateral margins for PTV were defined as the mid-sternum and mid-axillary lines, respectively. The ipsilateral lung and heart were also contoured adhering to the criteria outlined by Radiation Therapy Oncology Group.[18] The entire treatment planning process was carried out using ISOgray treatment planning system (DOSI soft corporation, edition 4·2·3·65L, France). One treatment plan for each patient was considered and the prescribed dose was altered to obtain the HypoRT, determining the dose distribution of the target volume and OARs. Details of the treatment planning can be found in Banaei et al.'s study.[4] The prescribed conventional treatment regimen consisted of a total dose of 50 Gy, administered in 25 fractions, using photon irradiation with the energy of 6 MV and employing two tangential fields (medial and lateral fields). Furthermore, three commonly used HypoRT regimens,[19] with the dose levels of 41·6 Gy (13 fractions), 39 Gy (13 fractions) and 40 Gy (15 fractions) were considered for patients. It should be noted that we did not evaluate the ultra- HypoRT regimens (such as five fraction short-course techniques) in the current study. Regarding the calculated dose distribution, 95% of the PTV received 95% of the prescribed dose in all the patients. After the planning procedure and dose calculations, dose-volume histograms (DVHs) for each patient in various treatment regimens were exported as the input data for TCP and NTCP calculations.

Radiobiological modelling and parameters

To assess the radiobiological impact of treatment regimens on the target volume and OARs (lung and heart), TCP and NTCP values were calculated using various models regarding the DVHs derived from the treatment plans as the input data. Two models based on equivalent uniform dose (EUD) and the Poisson model for TCP and two models based on EUD and LKB for NTCP calculations were considered.

NTCP and TCP: EUD model-based

EUD can be computed from the dose distribution of a structure and is defined as a uniform dose that produces similar biological effects to an actually delivered non-uniform dose distribution for the structure. It can be used when dealing with inhomogeneous dose distributions in tissues and is essentially regarded as a uniform dosage that mimics the same radiobiological effects of a non-uniform dose distribution. To adapt the concept of EUD for normal tissues, Niemierko[20] introduced a mathematical formula (Equation 1):

$$EUD = \left[\sum_{i=1}^{M} \left(v_i . EQD_{2,i}{}^{a}\right)\right]^{1/a}$$
$$EQD_{2,i} = D_i \frac{(\alpha/\beta) + d_i}{(\alpha/\beta) + 2} \quad (1)$$

In this formula, v_i signifies the fraction of the i^{th} volume of an organ receiving a dose of D_i, while M represents the number of histograms. The parameter 'a' is a dimensionless factor characterised by a negative value for tumour tissues and a positive value for normal tissues, reflecting its volumetric impact.

Based on this formulation, a methodology was proposed for calculating the probability of producing complications in healthy tissues and assessing TCP.[9] This calculation relies on the concept of EUD and was introduced in the following equations (Equation 2):

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}}$$
$$TCP = \frac{1}{1 + \left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (2)$$

Where TD_{50} is the uniform tolerance dose of normal tissues that leads to a 50% of complications within a specified time

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interval. TCD_{50} is the tumour control dose that, if uniformly delivered to the tumour, achieves 50% control, and γ_{50} is a dimensionless parameter that represents the slope of the dose-response curve at the point of TD_{50} dose.

NTCP: LKB model-based

In our effort to compare the outcomes derived from the EUD model when estimating the complication probability in healthy tissues, we turned to the LKB model. This model features a volume-dose relationship that effectively characterises these side effects.[21,22] The complication probability for a uniform dose (D) to the total volume of normal tissue (V_{total}) is expressed by the Equation 3:

$$NTCP(D) = 1/\sqrt{2\pi}\int_{-\infty}^{t}\exp(-x^2/2)dx$$
$$\therefore \quad t = \frac{D - TD_{50}(V_{total})}{m \cdot TD_{50}(V_{total})} \tag{3}$$

Where TD_{50} is the dose to the total volume of the organ that leads to 50% complication and m is a parameter that describes the slope of the dose-response curve. This model integrates fractionation and DVH parameters and takes into account the uniform irradiation of a portion of normal tissue (v_i). This involves calculating the effective volume (V_{eff}) and the tolerance dose for the effective volume, $TD(V_{eff})$. This calculation is outlined in the following equation (Equation 4):

$$V_{eff} = \sum_{i=1}^{M} v_i \left(\frac{D_i}{D} \times \frac{1 + [d_i/(\alpha/\beta)]}{1 + [d/(\alpha/\beta)]}\right)^{1/n}$$
$$TD_{50}(V_{eff}) = \frac{TD_{50}(V_{total})}{{V_{eff}}^n} \tag{4}$$

Where v_i denotes the fraction of volume that receives total doe D_i and dose per fraction d_i, M is the number of fractional volumes and n is a parameter that represents the volume's power, relating the tolerance doses to the total organ volume and a portion of the organ volume that is irradiated.[23] The parameter 'a' (Equation 1) and the parameter 'n' from the LKB model have an inverse relationship with each other, expressed as '$a = 1/n$'.

TCP: Poisson model-based

To compare the results obtained from the EUD model for tumour control calculations, the Poisson model was used, and the results were compared with available clinical trial data. This model is based on the assumption that the remaining clonogenic cells in the tumour after receiving a uniform dose D follow a Poisson distribution. The Poisson linear-quadratic (Poisson LQ) radiobiological model[24] considers that the probability of overall tumour control is equal to the product of the probabilities of controlling each voxel as follows (Equation 5):

$$TCP = \prod_{i=1}^{M}\left[\exp\left(-N_0\exp\left(\sum_{k=1}^{Fr}\{-\alpha d_{k,i} - \beta d_{k,i}^2\}\right)\right)\right]^{v_i} \tag{5}$$

Where v_i denotes the fraction of volume that receives dose D_i, M is the number of volumes, $D_{k,i}$, is the dose delivered to the i^{th} voxel within k^{th} fraction and Fr is the total number of fractions. α and β stand for the LQ model parameters, and N_0 signifies the initial number of cells. The exact value of N_0 is often unclear, thus, we adopted the following equation for TCP estimation (Equation 6):

$$TCP = \prod_{i=1}^{M}\left[\exp\left(-\exp\left(e.\gamma - \frac{EQD_{2,i}}{TD_{50}}(e.\gamma - \ln(\ln 2))\right)\right)\right]^{v_i} \tag{6}$$

Where TD_{50} corresponds to the dose yielding a 50% response probability, γ denotes the maximum normalised gradient of the dose-response curve, and $EQD_{2,i}$ represents the equivalent dose in voxel i when delivered in a 2 Gy per fraction regimen.

Table 1 depicts the parameters used for the radiobiological models for calculating the side effects on healthy heart and lung tissues as well as tumour control for the left breast tissue.[9,22,25–28] The endpoints of the NTCP models for the heart and lung were pericarditis and pneumonitis, respectively. BIOPLAN version 1·3·3 (BIOlogical evaluation of PLANs) was used for TCP and NTCP calculation.

Statistical analysis

We used the SPSS version 26 software (IBM Corporation, USA) to analyse our radiobiological results and previous clinical data. A normality statistical assessment was conducted using the Kolmogorov-Smirnov test. Since all data exhibited a normal distribution, we applied the Repeated Measurement statistical test to compare the different treatment regimens. The significance level, namely, a P-value was considered to be lower than 0·05.

Results

Table 2 presents the mean ± standard deviation values of TCP in addition to 95% confidence interval (between brackets) values obtained from Poisson and EUD models for two different sets of radiobiological parameter values (including $^{\alpha}/_{\beta}(Gy)$, $TCD_{50}(Gy)$, γ_{50}, *and* a across the evaluated breast radiotherapy regimens, along with comparison results among treatment regimen.

The statistical analysis showed that the differences between the TCP values obtained from Poisson and EUD models were significant ($p < 0{\cdot}001$) in both sets of radiobiological parameter values. The results showed that different radiotherapy regimens had significant differences in TCP values. The dose fractionation of 50 Gy in 25 fractions had the highest TCP values in both EUD and Poisson-based calculation models. Furthermore, delivering 41·6 Gy in 13 fractions had the lowest TCP values in both of TCP models and considering the radiobiological parameters of $^{\alpha}/_{\beta} = 4Gy$, $TCD_{50} = 28Gy$, $\gamma_{50} = 2$, *and* $a = -7.2$. In the other set of radiobiological parameters, the 41·6 Gy in 13 fractions had the lowest TCP values in the EUD-based model; without a significant difference with 40 Gy in 15 fractions.

The mean and standard deviation values (as error bars) of ipsilateral lung NTCP values obtained from LKB and EUD models for the evaluated breast radiotherapy regimens, along with comparison results among these regimens are provided in Figure 1. The results showed that all the NTCP values obtained from the LKB model had significantly higher values compared to values obtained with the EUD model ($p < 0{\cdot}001$). The 50 Gy in 25 fraction regimens showed significantly higher lung NTCP values compared to 39 Gy in 13 fraction regimens for EUD NTCP modelling. In addition, for LKB NTCP modelling, the 50 Gy/25

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Table 1. The parameters used for the radiobiological models. The reference numbers are presented in the parenthesis

Radiobiological modelling parameters						
	Poisson Model			EUD Model	LKB Model	
	$\frac{\alpha}{\beta}$ (Gy)	TCD_{50}/TD_{50} (Gy)	γ_{50}	a	m	n
Breast	**4** (25)	**28** (9)	**2** (9)	**−7·2** (9)	–	–
		30·89 (26)	**1·3** (26)			
Heart	**3** (27)	**48** (9)	**3** (9)	**3** (9)	**0·1** (22)	**0·35** (22)
Ipsilateral Lung	**3** (27)	**24·5** (9)	**2** (9)	**1** (9)	**0·3** (28)	**1** (28)

TCD50/TD50 is derived from clinical data based on conventional fractionation (typically 2 Gy per fraction). Therefore, it adjusted for a specific HypoRT regimen using an equivalent uniform dose (EQD) concept (Eq. 2).

Table 2. Mean ± standard deviation values of TCP in addition to 95% confidence interval

		TCP Modelling (%) (α/β(Gy), TCD_{50}(Gy), γ_{50}, a)			
		4 Gy, 28 Gy, 2, −7·2		4 Gy, 30·89 Gy, 1·3, −7·2	
Total Dose	Fractions (weeks)	Poisson-Based	EUD-Based	Poisson-Based	EUD-Based
50 Gy	25[5]	92·5 ± 8·6 (89·2, 95·7)	55·4 ± 43·2 (39·3, 71·5)	91·2 ± 8·2 (89·8, 92·6)	46·6 ± 35·6 (33·3, 60·0)
41·6 Gy	13[5]	88 ± 10·5 (84·1, 92·0)	44·7 ± 39·6 (29·9, 59·5)	90·7 ± 9·6 (89·2, 92·1)	35·7 ± 29·4 (24·0, 47·5)
39 Gy	13[5]	90·88 ± 10·2 (87·0, 94·6)	50·3 ± 42·7 (34·4, 66·3)	86·9 ± 9·8 (85·5, 88·3)	41·5 ± 37·2 (28·5, 54·6)
40 Gy	15[3]	88·7 ± 10·3 (84·8, 92·5)	45·1 ± 39·9 (30·2, 60·0)	85·5 ± 10·1 (84·0, 86·9)	36·2 ± 28·9 (24·3, 48·0)

fractions regimen had significantly higher values compared to the 40 Gy/15 fractions regimen. Other radiotherapy regimens had no significant differences between these regimens and each other.

Heart NTCP values were also calculated based on the EUD, and LKB models. The obtained heart NTCP values for LKB model were zero for all the evaluated radiotherapy regimens. Therefore, we only presented the NTCP values obtained from EUD NTCP modelling (Figure 2). Although the heart NTCP values were very low and negligible, the statistical analysis showed that the radiotherapy regimen with 50 Gy dose delivered in 25 fractions had the highest heart NTCP compared to other regimens ($p < 0{\cdot}01$).

Discussion

Radiobiological models like the ones employed in this study (Poisson and EUD) offer valuable tools for evaluating the impact of different fractionation regimens on TCP and NTCP in various cancers.[8] Our study aimed to assess these radiobiological effects using standardised treatment plans with identical target coverage and dose homogeneity across all fractionation schemes. While this approach allowed us to isolate the influence of fractionation on TCP and NTCP predictions, it did not account for potential variations in dosimetric parameters for OARs like the ipsilateral lung and heart. These OAR parameters, such as mean dose and volume receiving specific doses, are known to influence NTCP.[9] Therefore, we focused on presenting the radiobiological results (TCP and NTCP) in this analysis.

Randomised trials involving over 7,000 patients have demonstrated no significant differences in treatment efficacy, late post-radiotherapy complications, or cosmetic effects between standard and moderately HypoRT regimens with 5–10 year follow-up.[29–31] Notably, Miller et al.'s[32] extended follow-up strengthens the evidence supporting the non-inferiority of HypoRT compared to conventional fractionation. These findings are further reinforced by results from three large UK research projects.[29–31] While these studies provide robust evidence for the safety and efficacy of HypoRT in many patients, some ongoing research areas remain. Potential long-term effects of administering only five large fractions over five weeks require further investigation. Additionally, specific patient sub-groups, such as those with underlying health conditions or certain tumour characteristics, may warrant a more cautious approach to HypoRT implementation. Future research should focus on these areas to refine patient selection criteria and optimise treatment personalisation.

Our study compared the performance of the Poisson and EUD models in predicting TCP for breast cancer patients undergoing conservative radiotherapy. When benchmarked against data from the START trial,[14] the Poisson model yielded superior predictive accuracy. The START trial reported a HypoRT regimen (40 Gy in 15 fractions) as having the highest TCP (96%), while the 39 Gy regimen achieved the lowest (92%).[15] In contrast, our findings using the Poisson model showed a narrower range of TCP values (3%) across the evaluated fractionation schemes. Conversely, the EUD model exhibited a wider range of TCP values (over 11%) between regimens. This discrepancy may be attributed to differences in the 'a' parameter, which plays a critical role in how each model responds to changes in fractionation.

We observed further discrepancies in TCP predictions when comparing our results to previous studies. Shirani et al.[33] reported a TCP of 82·8% using the Poisson model for a conventional regimen in 10 patients. In contrast, our study using the same model yielded a higher TCP (92·5%) for the conventional regimen. Similarly, Astudillo-Velázquez et al.[16] reported lower TCP values (56·04%

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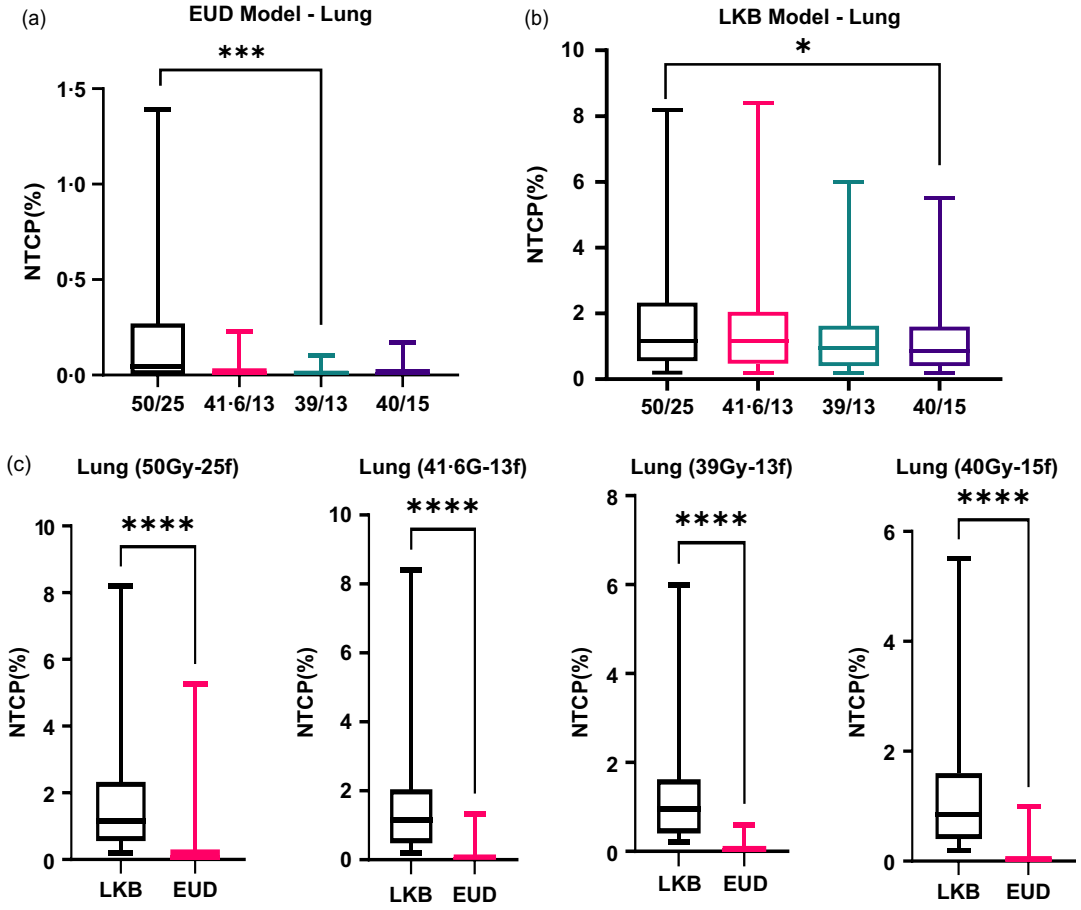

Figure 1. Mean and standard deviation values (as error bars) of ipsilateral lung NTCP values obtained from EUD (a) and LKB (b) models for the evaluated breast radiotherapy regimens, along with comparison of radiobiological models among these regimens (c).

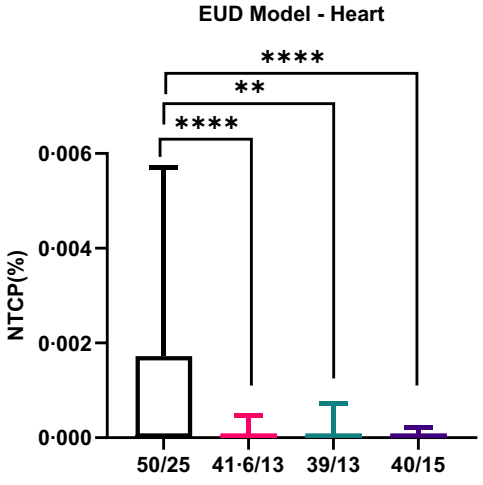

Figure 2. Mean and standard deviation values (as error bars) of heart NTCP values obtained from EUD radiobiological model for the evaluated breast radiotherapy regimens.

and 55·41%) for conventional and HypoRT regimens, respectively, using the Poisson model in 10 patients. Our findings, however, showed higher TCP values (92·5% and 88·7%) for the same regimens. These discrepancies could stem from variations in model parameters, radiotherapy plans, dose distributions and fractionation. While there was a trend towards lower TCP for hypofractionation compared to conventional regimens in our study, further investigation with larger patient cohorts is warranted.

Results of the previous studies indicated a lower probability of tumour control for the hypofractionation method compared to the conventional method; and we also observed similar findings. However, we found higher NTCP values for the lung and heart in conventional fractionation. The results of Kazemzadeh et al.[34] showed lower NTCP values for the lung in conventional fractionation compared to the hypofractionation regimen. In contrast, Astudillo-Velázquez et al.[16] reported higher NTCP and TCP values for conventional treatment compared to the HypoRT regimen. Furthermore, the NTCP value in Astudillo-Velázquez et al.'s study[16] was much higher than the values of our findings and Kazemzadeh et al.'s report. The discrepancies in the NTCP results among our study and also previous reports may be justified by the different radiobiological model parameters.

Kazemzadeh et al.[34] reported the TCP values for two regimens including conventional and hypofractionation (40 Gy in 15 sessions) using the EUD model as 99·16% and 95·96%, respectively. Additionally, Shanei et al.[35] reported a TCP of 99·07% for the conventional method using the EUD model. In our study, EUD-based TCP values for conventional and hypofractionation (40 Gy in 15 fractions) regimens were 55·4% and 45·1%, respectively, showing significantly lower values compared to previous reports. Since the radiobiological model and parameters

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in these two mentioned studies were similar to our study, the lower values in our study can be related to different dose distributions resulting from different radiotherapy plans.

The heart NTCP values were consistently low and negligible across all treatment regimens. This aligns with findings from previous studies that reported similarly low or zero heart NTCP in various breast radiotherapy techniques.[30,31,33] Despite the small magnitude of heart NTCP values, statistical analysis revealed no significant differences when comparing hypofractionation regimens. However, it is noteworthy that all three HypoRT methods consistently demonstrated significantly lower NTCP values compared to the conventional method.

Our study has inherent limitations that necessitate cautious interpretation of the results. The relatively small patient cohort limit the generalizability of our findings to larger populations. Additionally, our analysis did not account for individual variations in patient radiosensitivity, a factor that could potentially influence treatment outcomes. Furthermore, the absence of long-term follow-up data precludes us from making definitive conclusions about the long-term efficacy and safety of the evaluated fractionation regimens. Finally, relying on DVHs derived from a single CT scan may not fully capture potential anatomical changes during radiotherapy, potentially introducing inaccuracies in model predictions.

Future research efforts should address these limitations by employing larger and more diverse patient cohorts. Incorporation of radiosensitivity assessments into the analysis could provide valuable insights. Additionally, implementing robust long-term follow-up protocols would strengthen the conclusions regarding treatment effectiveness and safety. Exploring advanced treatment planning techniques that account for potential anatomical variations during therapy could enhance the accuracy of model predictions and potentially lead to more personalised treatment plans.

Conclusion

Our study employed radiobiological models (Poisson and EUD) to assess the potential trade-off between TCP and NTCP for different fractionation regimens in breast cancer radiotherapy. The findings suggest that HypoRT may offer advantages in terms of reduced NTCP compared to conventional regimens. However, the model predictions also indicate a potential decrease in TCP with HypoRT compared to conventional approaches. These results highlight the importance of further research to explore strategies that optimise the balance between minimising treatment-related toxicities and achieving effective tumour control. Future investigations could involve incorporating additional biological factors or utilising advanced treatment planning techniques that personalise fractionation schemes based on individual patient characteristics.

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Competing interests. The authors declare that they have no conflict of interest.

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