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Radiation pneumonitis incidence in chest wall and regional lymph nodes with monoisocentric and dual isocentric techniques after mastectomy

N. Dahdouh[1*], Z. Chaoui[1], S. Khoudri[2]

[1]Department of Laboratory of Optoelectronics and Devices, Physics Department, Faculty of Sciences, UFAS1; Algeria
[2]Cancer Center of Setif, Algeria

► ***Original article***

Corresponding author:
Narimane Dahdouh, Ph.D.,
E-mail:
narimane.dahdouh@univ-setif.dz

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ABSTRACT

Background: Our new present study uses biological indices to predict NTCP (normal tissue complications probability) and TCP (tumor control probability) in breast cancer patients undergoing mastectomy planned with MIT (monoisocentric technique) and DIT (dual isocentric technique) in the 3DCRT (three-dimensional conformal radiotherapy). ***Materials and Methods:*** This study involved using DVH (dose-volume histograms) from randomly selected patients to calculate the NTCP and TCP with our in-house program, RADBIOFOR. We focused on specific parameters related to pneumonitis in the lungs, pericarditis in the heart, and tumor control for the targeted area. ***Results:*** The incidence of clinical symptomatic pneumonitis grade 2 is lower for MIT than DIT, with a mean difference of 6.86%, 1.39% for symptomatic radiation pneumonitis grade 2, 1.17% and 0.82% for radiation pneumonitis grade 2. Both techniques produced comparable results, with MIT showing slightly better control than DIT, resulting in a mean difference of 0.18%. Our study suggests that the mean lung dose significantly affects the incidence of radiation pneumonitis. ***Conclusion:*** MIT outperforms DIT and offers better lung and heart protection with a lower incidence of radiation complications. Similar local control rates in the chest wall and lymph node region.

INTRODUCTION

Breast cancer is a significant public health concern that requires prevention, screening, and therapeutic research. Treatment options include surgery, chemotherapy, and radiotherapy [1]. The irradiation technique is effective in controlling local disease. Still, it can be administered in two forms: to the chest wall after mastectomy or to the mammary gland as part of breast-conserving treatment. This irradiation is delivered at a rate that compromises between achieving a high local control rate and a low risk of acute toxicity and long-term sequelae [2, 3]. The total dose required to control the disease varies according to whether or not prior surgery has been performed. In this study, it is estimated that a minimum dose of 46 Gy in 23 fractions should be delivered to the whole mammary gland [4].

Since the beginning of 2021, the National Registry of Cancer in Algeria has identified data showing that there were 65,000 new cases of cancer in total, including over 14,000 new cases of breast cancer each year [5-7]. A significant rate appears before the age of 40, unlike in Western countries where breast cancer appears after the age of 60 and over [8]. This highlights the crucial importance of timely and effective treatment methods. Conventional radiation therapy for breast and adjacent lymph nodes involves the use of separate beams, each with its isocenter. This technique often results in issues at the junction between the different beams due to the uncertainty of the position of each isocenter. Various techniques have been developed to address the problem of inconsistent delineation of target volumes and organs at risk in treating both the chest wall and the internal mammary ganglion, supra- and sub-clavicular homolateral areas. These techniques include half-blocked supraclavicular and special tangential fields [9, 10]. However, these methods are complex and require couch motions and machine isocenter repositioning when switching between fields. Moreover, bone and/or metal markers are typically used. To simplify the process, researchers have devised a new method called the single-isocenter technique. This technique involves using a single isocenter to treat and prophylactically irradiate both areas (the chest wall and the internal mammary ganglion, supra- and sub-clavicular homolateral areas) [11].

It is imperative to note that none of the studies conducted so far to compare these two techniques have radiobiologically and dosimetrically compared them while assessing the toxicities associated with organs at risk in a sample of patients who have undergone mastectomy [12-16]. This is a significant gap that needs to be addressed, given that radiation

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pneumonitis has been reported as the most common lung disease following radiotherapy to the thorax in patients with breast and lung tumors [17]. It is generally reported that the mortality rate from radiation pneumonitis is less than 2%. However, if the pneumonitis is of a higher grade (grade ≥ 2), it can significantly impair the patient's quality of life. On the other hand, if the pneumonitis is of lower grade (grade ≤ 2), it does not affect the patient's daily activities but medical intervention is indicated. The current study aims to predict these toxicities using valuable tools [18]. Biological indices are assessed to determine the occurrence of different grades of resulting toxicities, with a variety of identified parameters established for a specific clinical endpoint [19]. These predictions are estimated here using the LKB (Lyman-Kutcher-Burman) model; as new, we investigated whether the treatment technique MIT and DIT affect this incidence using biological indices, namely the NTCP and TCP. Note that we classified the radiation pneumonitis according to clinical scales criteria: SWOG (Southwest Oncology Group), CTCAE (Common Terminology Criteria for Adverse Events), and CTCNCIC. Furthermore, we calculated the NTCP predictions for pericarditis, and TCP for the PTV (planning target volume) using corresponding parameters that have been selected from the literature for this type of cancer [20]. In this analysis, we aim to comprehensively evaluate the impact of radiotherapy on the lung, heart, and PTV, which will help us improve the overall patient outcomes from MIT and DIT treatment techniques. Concerning lung, different endpoints [21-24] have been chosen to evaluate their NTCP; the corresponding parameters are shown in table 1. For the heart, we have used identified parameters to predict pericarditis [25]. Furthermore, we have utilized identified parameters of tumor control to evaluate the PTV [20, 26, 27].

MATERIAL AND METHODS

Subjects and treatment planning

We conducted a study of four selected left breast patients who had undergone mastectomy. For each patient, we created two treatment plans using MIT and DIT. To ensure accurate comparison, we used the same CT (computed tomography) images treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA, USA) in the Setif radiation therapy center [28, 29]. Each patient received the same treatment indications, which included the prescription of 46 Gy in 23 sessions of 2 Gy per fraction. This involved the irradiation of two PTVs: PTV1, which encompassed the left chest wall, and PTV2, which covered the volume of the supra- and sub-clavicular lymph node areas. In MIT, a single isocenter was used between two PTVs (PTV 1 and PTV2), whereas with DIT, two isocenters were used, the first in PTV1 and the second in PTV2. We focused on the left lung and the heart as organs at risk. In addition, we compared the two techniques based on the (SD) standard deviation and the mean dose difference.

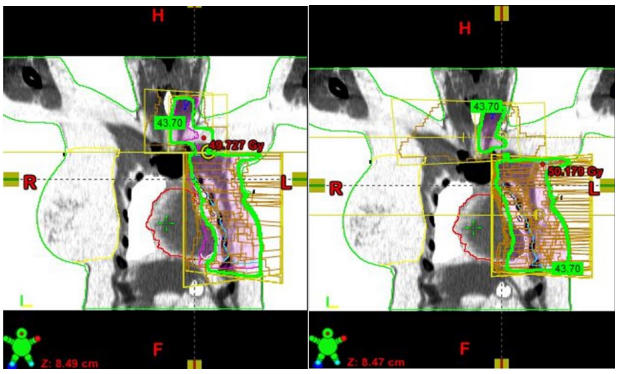

Figure 1. (A) The monoisocentric technique uses a single isocenter positioned between the left chest wall and the supra - and sub-clavicular lymph node areas. **(B)** The dual isocentric technique involves two isocenters, the first in the middle of the left chest wall and the second in the middle of the supra- and sub-clavicular lymph nodes.

Radiobiological analysis

We elaborated an in-house calculation program RADBIOFOR to assess and predict early and late effects during the treatment planning. To carry out the present calculations, we have chosen the LKB model to calculate the NTCP and the logit by EUD based TCP [30]. The program incorporates in tabular format the cumulative DVH of the structure of interest (tumor or organ at risk). It uses the inserted parameters identified in the literature, corresponding to each treatment plan technique.

The LKB model

The model describes the sigmoidal dose-response curve of normal tissues using the equations (1, 2, and 3) [31-33]:

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

$$t = \frac{D_{eff} - TD_{50}}{m\, TD_{50}} \quad (2)$$

$$D_{eff} = (\sum V_i D_i^{1/n})^n \quad (3)$$

Where: TD_{50} is the radiation dose delivered to the entire organ or a specific volume of tissue that would result in a 50 percent probability of complications; m is the slope of the response curve; n is a parameter reflecting the biological properties of the organ, indicating volume dependence; D_i is the total dose in the subvolume V_i. The effective dose D_{eff}. To evaluate equation (1), a simple form is used given in equation (4) [21].

$$NTCP = \frac{1}{2}\left[1 + erf\left(\frac{t}{\sqrt{2}}\right)\right] \quad (4)$$

We have used the nearly-best rational approximations to evaluate the error function provided by Cody [34].

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The EUD-based TCP model

This model is known as the Niemierko model [35]. It assumes that the dose-response follows a logical pattern, uses logistic functions, and considers counts as a parameterization of dose-response properties, expressed in equation (5) [30, 36];

$$TCP = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (5)$$

TCD_{50} is the dose giving a 50% probability of complications if the organ is irradiated uniformly and γ_{50} describes the slope of the dose-response curve. EUD is the effective uniform dose [30].

Table 1. Identified parameters of the evaluated lung end-points used in this study.

Reference	Endpoints	Scale	Fractionation dose	n	m	TD50
Rancati 2007 [23]	Clinical Symptomatic Pneumonitis Grade≤2	CTCNCIC	2 Gy	1	0.41	29.9
Semenenko 2008 [21]	Symptomatic Radiation Pneumonitis Grade 2	CTCAE	2 Gy	0.99	0.37	30.8
Seppenwoolde 2003 [22]	Radiation Pneumonitis Grade≥2	SWOG	1.4-1.9 Gy (normalized to 2 Gy), α/β = 2.5-3 Gy	0.86	0.36	16.4
Kwa 1998 [24]	Radiation Pneumonitis Grade≥2	SWOG	1-2.7 Gy (normalized to 2 Gy), α/β = 2.5-3 Gy	1	0.30	30.5

RESULTS

Lung analysis

Figure 2 shows the predicted incidence of radiation pneumonitis for all patients using both MIT and DIT treatments. In figure (2A), the analysis was based on the parameters identified by Rancati *et al.* [23]. Both MIT and DIT exhibit remarkably high NTCP values (> 25%). However, the MIT outperforms the DIT with a significant mean dose difference of 6.86% and SD of 0.15 see (table 2).

The figure (2B) presents an accurate calculation of the predicted value of symptomatic radiation pneumonitis grade 2 for all patients using the parameters identified by Semenenko *et al.* 2008 [21] (table 1). The calculated values indicate a low prediction (<14%) for all patients compared to clinical symptomatic pneumonitis grade≤2. It is noteworthy that MIT has demonstrated lower values than DIT, with a mean dose difference of 1.54% and SD of 0.15.

Another endpoint was chosen for assessing and comparing the incidence of radiation pneumonitis grade ≥ 2, we employed the parameters identified by Seppenwoolde *et al.* [22] and Kwa *et al.* [24] (table 1). The corresponding results are shown in figures (2C) and (2D). We found that the NTCP values do not exceed 10 % and 6% for both sets of parameters, respectively. In the context of predicting both endpoints, it has been observed that MIT outperforms the DIT, with a mean dose difference of 1.17% and 0.82%, respectively. The SD difference between MIT and DIT is 0.18 and 0.24 for the two endpoints, respectively.

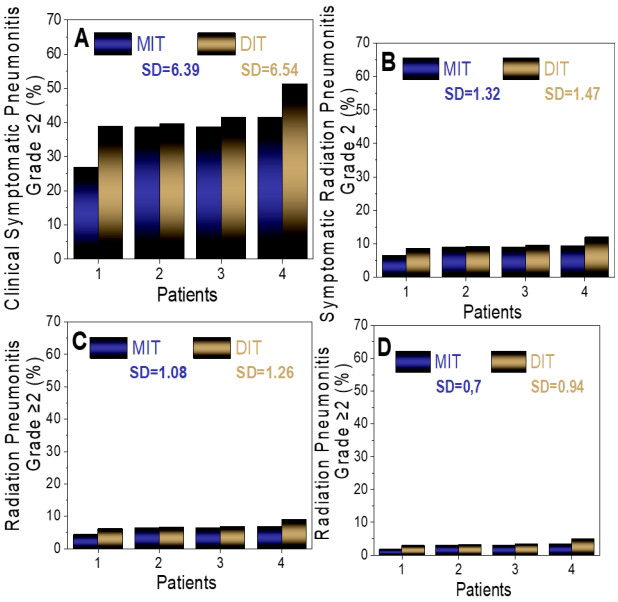

Figure 2. The SD and the NTCP predictions of radiation pneumonitis incidence with MIT and DIT using identified parameters of **A)** Rancati 2007 [23], **B)** Semenenko 2008 [21], **C)** Seppenwoolde 2003 [22], and **D)** Kwa 1998 [24].

Table 2. The mean dose results calculated for MIT and DIT for lung, heart, and PTV target for all patients.

Dose	Mean dose					
Organ at risque	Lung				Heart	PTV
References	Rancati *et al.* [23]	Semenenko *et al.* [21]	Sppenwoolde *et al.* [22]	Kwa *et al.* [24]	Burman *et al.* [25]	Okunieff *et al.* [20]
MIT	36.39	8.46	6.06	2.85	$1.41^{\wedge}10^{-8}$	76.24
DIT	43.25	9.84	7.23	3.66	$6.09^{\wedge}10^{-8}$	76.07

Heart analysis

The figure 3 displays the predicted incidence of pericarditis on the heart for all patients using both MIT and DIT treatments using the LKB model including the well-known parameters of Burman 1991 [25]. NTCP values shown in figure 3 are not exceeding 10^{-6} %. It ensures that the heart is well-preserved during the treatment planning. The mean dose and SD calculated for MIT are less than DIT (table 2).

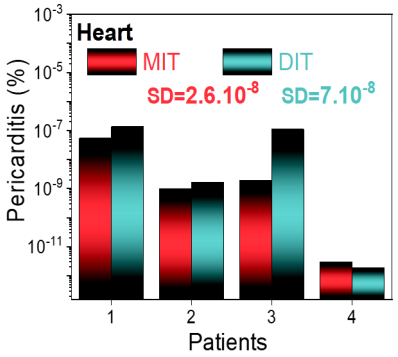

Figure 3. The SD and the calculated NTCP predictions of pericarditis in the heart for MIT and DIT.

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PTV analysis

Logistic regression was used with data collected from various institutions' local control data on the chest wall and regional lymph nodes treatment post-mastectomy, using identified parameters that locally control 50% of tumors (loco-regional recurrences, distance metastasis, and treatment failure) where the mean follow-up period was 16 years (range: 13-19 years). The dose of radiation administered was 46 Gy and 45 Gy, with 1.8-2.2 Gy/Fx, 5 days a week [20, 26, 27]. However, the values were not always comparable due to differences in the method of prescribing doses. The second parameter, γ_{50}, was employed by Brahme to analyze the dose-response curves of human tumors. It is considered a descriptor of the slope of these curves and represents the percentage increase in the probability of tumor control for every 1% increase in dose. Therefore, the γ_{50} value is essential in determining the effectiveness of radiation therapy in treating tumors [37]. Figure 4 displays calculated TCP results; the two techniques produced similar results with slightly better control of MIT than DIT, and a mean difference of 0.18%.

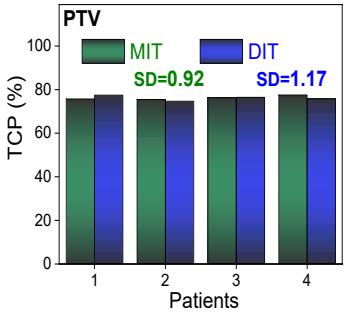

Figure 4. The SD and the calculated TCP results from the MIT and DIT of all patients treated with the 3DCRT technique.

Table 3. Comparison of the calculated lung dose constraints with both DIT and MIT.

Dose constraints	Patient 1		Patient 2		Patient 3		Patient 4	
	DIT	MIT	DIT	MIT	DIT	MIT	DIT	MIT
V10	33.07	28.10	35.97	35.86	36.47	34.18	40.98	36.94
V20	26.77	22.41	28.52	28.27	29.46	27.61	33.21	29.46
V30	22.48	18.39	22.07	21.50	22.46	22.57	26.32	22.12

DISCUSSION

The increase in the obtained NTCP value (more than 26.86% and 38.92% for MIT and DIT) of the first endpoint (grade≤2) is acceptable and does not cause a serious problem in the validation of treatment plans, because it has remained as asymptomatic and no slight radiological changes (radiological changes assessed with diagnostic chest X-ray:) [23]. Upon reviewing the previous studies, it can be observed that the probability of experiencing a complication (symptomatic pneumonitis) following the irradiation is 5%, 10%, and 20% dependent on the dose constraints V20 with thresholds of less than 22%, 31%, and 40% and mean doses of 7 Gy, 13 Gy, and 20 Gy, respectively [38]. Given that the recommended threshold of V20 mentioned in RTOG guidance is 35% [39]. In this study, table 2 displays the calculated V20 and mean dose for each patient, with all results falling below 31% and 14 Gy, except for one instance where the calculated V20 with DIT was 33.21% and the mean dose was 15.49 Gy.

According to the analysis, the calculated NTCP of the symptomatic radiation pneumonitis falls within the same range as the Emami et al study [38] with a range of 5% - 10% for required V20 and mean dose, where mean NTCP values calculated by DIT and MIT were 9.85% and 8.46% respectively. Additionally, it is noted that the mean dose value in patient 4 is 15.49 Gy, and the calculated NTCP is 11%, which is a significant finding.

In the context of predicting radiation pneumonitis toxicity (grade ≥2), which is graded based on the severity of symptoms, grade 2 requires steroids or tapping of effusion, grade 3 requires oxygen, grade 4 requires assisted ventilation, and grade 5 results in death [40], it was observed that using the parameters identified by Kwa *et al.* [24] and Seppenwoolde *et al.* [22] resulted in lower NTCP values despite the identical clinical scale used for toxicity classification. However, this discrepancy in values can be attributed to the method employed for identifying the radiobiological parameters that constitute this endpoint. However, in a study conducted by Kwa *et al.* [24], the incidence of radiation pneumonitis was evaluated in 481 cancer patients, including 59 breast cancer patients. In comparison to the study conducted by Seppenwoolde *et al.* [39], they included 382 malignant lymphoma and inoperable non-small-cell lung cancer patients from two centers, including 42 breast cancer patients. The results showed a mean difference of 3.65 % and 3.21 % using the parameters identified by Seppenwoolde *et al.* [22] and Kwa *et al.* [24] for patients treated with DIT and MIT, respectively. These differences could be attributed to variations in patient characteristics such as age, chemotherapy use, and volume effect. In contrast, the insufficient statistics and diversity of clinical data pose significant challenges in defining narrow confidence intervals for parameter estimates, resulting in difficulty in generating precise radiobiological predictions. In a study conducted by Kwa *et al.* [24], fixing the parameter n = 1 led to tighter confidence intervals for the other two parameters, m, and D50, unlike Seppenwoolde *et al.* [22], which converged the parameter value of n to 0.99. These findings highlight the importance of considering various factors that may affect confidence intervals when generating radiobiological predictions.

An extensive analysis was conducted by Hurkman *et al.* [41] to evaluate the likelihood of radiation pneumonitis incidence based on parameters identified by Kwa *et al.* [24]. During this study, it was found that the patient who received 8 Gy did not observe this complication, despite the mean dose

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received by the lung. Although the mean dose value in this study exceeded 13 Gy, it was observed that the NTCP values calculated were less than 6%, which aligns well with the Hurkman *et al*. study [41]. Therefore, it can be concluded that even a 5 Gy difference in the received mean dose could significantly impact the NTCP value downward. Additionally, MIT is ahead of its counterparts, offering significant improvement in eliminating hot spots and enhancing the junctions between beams. With its ease of use and efficient handling see figure 1, this innovation provides a considerable reduction in positioning uncertainties throughout the treatment, making it the obvious choice for patients seeking quality care.

CONCLUSION

The findings of our research show that the MIT technique provides better lung protection than DIT, with a relatively lower incidence of radiation pneumonitis. Additionally, our study suggests that the mean lung dose plays a crucial role in determining the incidence of radiation pneumonitis.

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***Conflicts of interests*:** Declared none.

***Ethical considerations*:** None.

***Author Contribution*:** This research work is the result of equal contributions from both (N. D) and (Z. C) who have put in their best efforts to make it successful. Moreover, (S. K) has played a vital role by providing the necessary input for the dose-volume histogram (DVH) analysis.

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