Comparison of liver dose in right chest wall radiotherapy using field-in-field, intensity-modulated radiotherapy, and helical tomotherapy

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ABSTRACT

Background: This study aims to assess the liver dose received in the absence of explicit dose considerations during right chest wall radiotherapy planning for three different treatment techniques and to contribute to thr limited literature on this topic. ***Materials and Methods:*** A total of 20 patients with indications for radiotherapy of the right chest wall following mastectomy were selected. After tomography scan images were sent to the Treatment Planning System (TPS), where a radiation oncologist delineated the target volumes and critical structures. Subsequently, a medical physicist created treatment plans utilizing three techniques. The dosimetric parameters were evaluated and compared for different treatment techniques. ***Results:*** The field-in-field (FIF) technique resulted in the lowest mean liver dose and V10 values ($p<0.001$). No significant difference was observed between helical tomotherapy (HT) and intensity-modulated radiotherapy (IMRT) techniques regarding average liver doses and V10 values. The FIF treatment technique also showed the lowest V20 value. ***Conclusions:*** In right breast radiotherapy, when comparing liver doses across different treatment plans excluding the liver, the FIF technique demonstrated significantly better results in terms of average liver dose than the other two treatment techniques. It was concluded that liver dose should be taken into account during treatment planning.

INTRODUCTION

Breast cancer is one of the most common cancers among women in the world. Advances in early detection, surgical techniques, systemic therapy, and radiotherapy have contributed to a decline in breast cancer mortality rates (1). The incidence of breast cancer is increasing day by day (2). The survival rate for women diagnosed with early-stage breast cancer is 98.9% over a 5-year period (3).

Investigating effective breast cancer treatment methodologies is essential for prolonging survival and improving the quality of life of women of suffering from breast cancer (4). The primary treatment for breast cancer which includes surgery, often supplemented with chemotherapy, hormone therapy, targeted therapy, and radiotherapy (5). Radiotherapy plays a crucial role as an adjuvant treatment, especially for patients undergoing breast-conserving surgery or those at high risk of recurrence (6, 7).

Advances in radiotherapy and systematic treatments substantially improved patient prognosis, thereby increasing the emphasis on quality of life and the preservation of normal tissues (8). In recent years, the cosmetic outcomes of these interventions, include the risk of losing the breast, have become important. Several studies have reported satisfactory outcomes with breast-conserving therapy compared with radical mastectomy (9-11).

Please replace with: "In breast cancer radiotherapy, minimizing the dose delivered to organs at risk is crucial, as long-term adverse outcomes such as secondary malignancies may arise (12, 13). There are many reports comparing dose distributions obtained with different radiotherapy treatment techniques in breast cancer (14-17). Advancements in Computerized Tomography (CT) based TPS, multi-leaf collimators (MLCs) and three-dimensional conformal radiotherapy (3DCRT) techniques have improved plan conformity and reduced critical organ doses (18, 19). Radiotherapy techniques such as 3DCRT, IMRT, and volumetric-modulated arc therapy (VMAT) are commonly used in the treatment of breast cancer. While 3DCRT delivers breast irradiation using two opposing wedges and tangential fields, protection of critical organs is achieved through the use of MLCs (20). It has been demonstrated that tangential wedge and field-in -field (FIF) techniques improve dose homogeneity in whole-breast irradiation [21-23]. IMRT, in particular, has proven its importance, especially with constraints in dose distribution and dose reductions in critical organs. Multiple institutional and randomized studies have shown that IMRT enhances dose uniformity and decreases radiation exposure to skin and contralateral breast compared with conventional wedge-based techniques [24].

Tomotherapy is a type of linear accelerator that can perform **helical tomotherapy**, a technique that integrates megavoltage computed tomography (MV-CT) with helical intensity modulation [25-27]. Despite its advantages, tomotherapy also has certain limitations. In helical delivery, the rotating gantry irradiates the patient from continuously varying angles as the table moves, enabling treatment from essentially any direction. Consequently, compared with standard non-tangential IMRT techniques, this approach results in low-dose exposure to larger volumes of normal tissue that would otherwise receive primarily scattered radiation [28].

Radiation-induced damage to liver cells ranges from asymptomatic to visible through elevation in liver function tests and radiological imaging of focal parenchymal damage [29, 30]. Chemotherapy, the volume of irradiation, and fraction doses increase liver toxicity [31].

Although extensive research exists on patients with left-sided breast cancer, studies on right-sided breast cancer remain limited and insufficient [32]. The available literature has largely focused on left-sided radiotherapy due to cardiac risks, leaving the dosimetric impact of right-sided chest wall radiotherapy - especially liver exposure-underexplored. The primary objective of the present study is to provide a comprehensive dosimetric comparison of FIF, IMRT, and HT treatment techniques for right-sided chest wall irradiation, with a specific focus on liver dose. By highlighting liver exposure differences among three widely used radiotherapy modalities, this study offers novel and clinically relevant insights that can contribute meaningfully to the limited existing literature on right-sided breast radiotherapy.

MATERIALS AND METHODS

Patient selection

In our retrospective study, twenty patients diagnosed with breast cancer between January 2011 and December 2021 who received radiotherapy were selected from the Radiation Oncology Department of Necmettin Erbakan University Medical Hospital (The institutional review board approval for this retrospective study was obtained from the Ethics Committee of Necmettin Erbakan University Medical School, approval number 2023/4645). All patients were female and classified as stage II–III. The age of the individuals ranged from 33 to 72 years. When selecting patients, we ensured that the tomography scans included the liver. All patients had undergone right-sided chest wall radiotherapy using the 3DCRT field-in-field technique. Table 1 presents the patient characteristics.

Table 1. Patient characteristics.

Median age	54 (33-72)
Median PTV volume (cc)	684.6 (344.7-1088.2)
Median liver volume (cc)	1397.3 (728.0-1877.7)
Median right lung (cc)	1465.3 (1152.5-1789.6)
Histological type	
Ductal	18 (90)
Lobular	2 (10)
T Stage	
T1	11(55)
T2	8 (40)
T3	-
T4	-
Tx	1 (5)
N Stage	
N0	10 (50)
N1	6 (30)
N2	
N3	
Nx	4 (20)

PTV: Planning target volume.

We utilized a breast board to immobilize patients. The patients were positioned in the supine position, with both arms placed on arm holders above the head area. Markers were attached over the skin for precise immobilization. Computed tomography data were acquired using a Siemens Emotion Duo scanner (Siemens Somatom Duo, Germany) with a slice thickness of 5 mm. The scan usually covers area over the mandibles to the end of the liver for these patients. After the CT scanning, we transferred data to the Eclipse TPS (version 8.9.08, Eclipse, Varian Medical Systems, Palo Alto, CA, USA) for target volume and critical organ delineation.

Simulation and Contouring

All patients involved in the study were positioned supine, utilizing a chest board with arm support. The simulation process included imaging that captured the liver for simulation purposes. The liver was outlined according to the Radiation Therapy Oncology Group (RTOG) guidelines, covering the entire range of liver abdominal window levels in the cross-sectional area [33].

Target and critical structure delineation

Following transfer of the computed tomography data to the TPS via DICOM, the liver, heart, ipsilateral lung, contralateral lung, and spinal cord were delineated by a dosimetrist. Some structures were initially generated using automatic contouring and subsequently reviewed. The clinical target volumes (CTV) were delineated including the entire chest wall and regional lymph nodes, with supraclavicular, infraclavicular, and axillary lymph nodes by the radiation oncologist according to the RTOG [33]. The

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chest wall CTV was contoured to the muscle–rib junction to encompass the pectoralis muscles and the entire surgical scar margin. The cranial border was defined at the caudal border of the clavicular head, determined clinically using simulation markers and guided by the contralateral breast. The lateral border was typically contoured to the midaxillary line, while the medial border extended to the sternum–rib junction to avoid crossing the midline. The PTV was created by expanding the CTV with a 5-10 mm margin [34]. A 5 mm isotropic margin was applied to the CTV and cropped 3 mm from the skin surface. Each PTV contour was then reviewed slice by slice by a radiation oncologist and modified when necessary.

Treatment planning

All patients had previously undergone treatment using the Siemens Primus plus radiotherapy machine (Siemens Primus Plus, Germany) with 6 MV photons energy, utilizing the 3DCRT with FIF technique. A total dose of 50 Gy, fractionated into 25 sessions, was prescribed to right-sided breast cancer patients using the Eclipse TPS. To deliver an optimal dose to the PTV, two opposing tangential beams and four field-in-field (FIF) beams were used. The beam's-eye-view (BEV) window was utilized to position the MLCs to minimize doses to critical organs, implement FIF to reduce hot spots, and improve plan conformity. A 2 cm skin fall-off region for the PTV margin was created using MLCs in the breast area. The tangential isocenter was positioned approximately at the mid-portion of the right breast and adjusted to one-third of the distance from the skin surface. For the supraclavicular field (SCF), the isocenter was placed near the superior border of the tangential field to reduce beam divergence, and anterior-weighted anterior–posterior fields were created. Additionally, a 4–5° table rotation adjustment was applied to the tangential field to minimize hot or cold junction points.

Subsequently, IMRT plans were generated using 6 MV photon energy with nine static gantry angles (55°, 40°, 25°, 5°, 330°, 280°, 265°, 250°, and 235°) within the Eclipse TPS. Treatment plans were also created using the Accuray Precision TPS (version 2.0.1.1; Accuray Incorporated, Madison, WI, USA), which employs a superposition/convolution algorithm. Tomotherapy systems deliver only 6 MV photon beams. Plans were generated using a 2.5 cm field width, a pitch of 0.435, and a modulation factor of 3.0. To ensure consistency across all plans, every treatment plan was prepared by the same medical physicist.

During the treatment planning process, efforts were made to ensure that at least 95% of the PTV volume received a minimum of 95% of the prescribed dose, provided that the doses to critical organs did not exceed their respective tolerance limits. It was also ensured that the maximum dose did not surpass 110% of the prescription. However, maintaining critical organ doses within clinically acceptable limits remained a priority while achieving adequate PTV coverage. The right lung was constrained such that no more than 30% of its volume received 20 Gy or more (V20 ≤30%), and the heart dose was maintained below 4 Gy. For the left lung, dose constraints were preserved as much as possible while fulfilling the primary planning objectives.

The CI and HI were calculated according to the definitions of Radiation Therapy Oncology Group (RTOG) as equations 1 and 2:

$$CI = V_{RI} / TV \tag{1}$$
$$HI = I_{max} / RI \tag{2}$$

with V_{RI} as the volume of the prescribed dose, TV is the total volume of the PTV, I_{max} is the maximum dose and RI is the prescribed dose.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS), version 25.1 (SPSS, Inc., Chicago, IL, USA). Analysis of variance (ANOVA) was utilized to analyze the differences between the three techniques. The Tukey test was used to emphasize the order of each method in case a noticeable difference was found between each method. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The transverse and coronal dose distributions for all three treatment techniques at the same coordinates are shown in Figure 1. Additionally, Table 2 presents the comparison of the mean values and standard deviations of all evaluated parameters across the three radiotherapy techniques. Dosimetric data for right breast irradiation were analyzed using FIF, IMRT, and HT techniques.

In comparing these three treatment techniques for right-sided breast radiotherapy, the FIF technique demonstrated the highest average maximum PTV dose. Although the average maximum PTV doses were similar between the FIF and IMRT techniques, the FIF technique showed a significantly higher average maximum dose compared with HT (p=0.001). Conversely, the HT technique yielded the lowest average maximum PTV dose relative to IMRT.

Regarding minimum PTV doses, the FIF technique produced the lowest average values, while the HT technique yielded the highest. When examining the mean PTV doses, the IMRT technique resulted in the highest average dose, followed by HT and FIF, respectively. The right lung was constrained such that no more than 30% of its volume received 20 Gy or more (V20 ≤30%). Additionally, IMRT demonstrated significantly higher mean PTV doses

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compared with FIF (p<0.001).

The mean D95 value, representing the dose delivered to 95% of the target volume, was highest in the HT technique and lowest in the FIF technique. Although no significant difference was observed between HT and IMRT for D95, both techniques yielded significantly higher values than FIF (p<0.001).

The lowest mean conformity index (CI) and homogeneity index (HI) values for the PTV were obtained with the HT technique. While no significant difference was detected between HT and IMRT for CI, both HT and IMRT achieved significantly better CI values than FIF (p<0.001).With respect to monitor units (MU), the HT technique exhibited the highest average MU value, whereas no significant difference was observed between the FIF and IMRT techniques (p=0.717).

When evaluating the liver, the FIF technique demonstrated significantly lower mean dose and V10 values (p<0.001). No statistically significant difference was observed between the HT and IMRT techniques with respect to mean liver dose or V10 values. Although the FIF technique achieved the lowest mean liver dose and V20 values with statistical significance, no significant differences were found among the techniques for V30 values.

For the right lung, the FIF technique yielded the highest average maximum dose, mean dose, V20, and V30 values, whereas the lowest average V5 and V10 values were observed with this technique. In terms of V5, the FIF technique showed a significantly lower value compared with the other techniques (p<0.001).

Additionally, the FIF technique exhibited significantly lower mean V10 values than both HT and IMRT (p<0.001), while no significant difference in mean V10 was detected between HT and IMRT. Regarding the maximum mean dose to the right lung, both HT and IMRT demonstrated significantly lower values compared with the FIF technique (p=0.002 and p=0.017, respectively). For mean right lung dose, the HT technique was significantly lower than FIF (p=0.017).The FIF technique resulted in significantly lower doses (p<0.001) compared with the other techniques with respect to the mean dose to the contralateral lung and both the mean and maximum doses to the heart. Moreover, the IMRT technique produced significantly lower values (p<0.001) than the HT technique for both means left lung dose and maximum heart dose. However, the HT technique demonstrated a significantly lower mean heart dose than IMRT (p<0.001).

For the spinal cord, another critical organ, the IMRT technique yielded the lowest average maximum dose, with a clear distinction from the FIF and HT techniques. Furthermore, IMRT showed significantly lower average maximum spinal cord doses (p<0.001) compared with both FIF and HT.

Table 2. Comparison of mean values and standard deviation of all parameters according to the three radiotherapy techniques. A p-value determines significance.

p-values of subgroup comparisons*						
Dosimetric parameter	**HT(1)**	**FIF(2)**	**IMRT(3)**	**p-value**		
				1 Vs 2	**1 Vs 3**	**2 Vs 3**
PTV50						
Dmax	5435.76±33.95	5472.82±21.55	5465.76±26.14	0.001	0.008	0.739
Dmin	4142.18±221.57	2500.46±547.67	3724.40±255.68	0.000	0.005	0.000
Dmean	5145.41±24.00	5102.18±35.05	5183,92±34,85	0.001	0.003	0.000
D95	4925.29±54.56	4757.00±75.57	4903.53±54.34	0.000	0.569	0.000
CI	1.277±0.087	1.662±0.233	1.331±0.113	0.000	0.581	0.000
HI	1.117±0.0134	1.191±0.117	1.192±0.179	0.000	0.000	0.000
MU	7455.9±749.7	452.2±10.4	568.2±25.9	0.000	0.000	0.717
Organ at risk						
Right lung						
Dmax	5084.00±186,57	5306.93±96.10	5134.68±219.38	0.002	0.678	0.017
Dmean	1262.53±164.92	1381.05±117.99	1334.25±51.81	0.017	0.204	0.501
V	73.29±7.62	39.45±3.31	87.64±2.68	0.000	0.000	0.000
V_{10}	46.00±9.42	31.81±2.30	43.88±4.42	0.000	0.588	0.000
V_{20}	23.98±2.86	26.46±2.88	22.05±8.77	0.405	0.575	0.065
V_{30}	13.37±3.37	22.76±2.90	11.90±1.23	0.000	0.251	0.000
Left lung						
Dmean	433.35±58.84	60.28±9.82	307.41±40.77	0.000	0.000	0.000
Liver						
Dmax	5060.41±306.46	5070,06±96,26	875.88±170.59	0.990	0.360	0.026
Dmean	1057.35±241,7	385.15±227.7	1024.25±179.98	0.000	0.898	0.000
V_{10}	45.96±12.56	8.44±5.91	39.78±9.09	0.000	0.155	0.000
V_{20}	18.36±5.91	6.18±7.73	12.05±3.68	0.000	0.001	0.003
V_{30}	6.43±2.73	4.78±3.91	4.65±2.10	0.256	0.209	0.256
Heart						
Dmax	2456.18±535.93	486.21±298.48	1892.03±455.84	0.000	0.001	0.000
Dmean	389.00±44.58	116.45±22.22	523.81±66.51	0.000	0.000	0.000
ms						
Dmax	2719.53±230.59	2892.85±678.75	1893.09±306.70	0.505	0.000	0.000

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The helical tomotherapy (HT), field-in-field (FIF), and intensity modulated radiotherapy (IMRT) groups are represented by the numbers 1-3, respectively, in the subgroup analysis. PTV: planning target volume; D_{max}, maximum dose; Dmin, minimum dose; D_{mean}, mean dose; D_{95}, dose delivered to 95% of the PTV; CI, conformity index; HI, homogeneity index; MU, monitor unit; V_x, percentage of X(Gy) dose received by the tissue in the total volume of the tissue. A p-value of less than 0.05 was considered statistically significant.

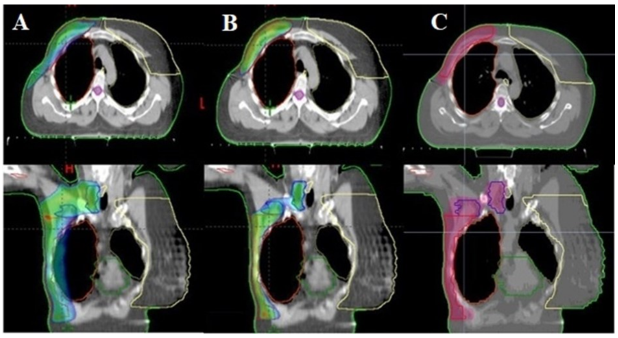

Figure 1. 95% of the prescribed dose distributions of a patient on a transverse and coronal plane for **a)** FIF technique, **b)** HT technique **c)** IMRT technique.

DISCUSSIONS

Historically, liver doses in right-sided breast radiotherapy have not been considered clinically significant. The range of liver doses in breast irradiation is broad; however, high-dose exposure is more commonly observed in patients with markedly larger breasts [35]. The relationship between liver size and breast size may be influenced by factors such as breast shape, breast volume, and gravitational effects [36]. Anatomically, the liver lies in close proximity to the treatment field in breast irradiation, making it a potentially vulnerable organ. Recommended mean liver dose limits for right-sided breast irradiation range between 28-32 Gy [37]. Our study supports the need for contouring the liver and incorporating it into dose calculations for right-sided breast radiotherapy. Moreover, it was observed that the liver may still receive a substantial amount of radiation regardless of the technique used. Treatment plan analyses further revealed that liver doses may be even higher under certain conditions, particularly when IMRT techniques are employed, as these approaches prioritize minimizing radiation exposure to the heart and ipsilateral lung.

Dumane *et al.* [38] conducted a comparison between 3D conformal radiotherapy, static IMRT, and VMAT treatment plans to find out the appropriate plan for treating right-sided chest wall and nodal case. They prescribed 50.4 Gy as the treatment planning dose for the chest wall and regional nodes. As a result of their studies, they found that the V_{20} value for the right lung was lowest with the VMAT technique (20.24%), followed by IMRT (22.33%), and 3D conformal (39.05%). The average liver doses were reported 5.12 Gy for 3DCRT, 13.7 Gy for IMRT, and 10.09 Gy for VMAT [38]. In our study, we found the average V_{20} value of the right lung to be 26.46% for 3D conformal plans, 22.05% for IMRT plans and 23.98% for HT plans. We calculated the average liver doses as 3.85 Gy for 3DCRT, 10.24 Gy for IMRT, and 10.57 Gy for HT. Regarding the left lung, Dumane *et al.* [38] found average doses of 0.55 Gy, 3.46 Gy, and 2.83 Gy for 3DCRT, IMRT, and VMAT, respectively. In our study, the corresponding values were 0.60 Gy for 3DCRT plans, 3.07 Gy for IMRT plans, and 4.03 Gy for HT plans. When comparing these findings, the V20 value of the right lung for IMRT plans was highly similar to the previously reported results, whereas our 3DCRT values were approximately 32% lower. Furthermore, the mean liver doses obtained with both the 3D conformal and IMRT techniques were lower in our study. Although the left lung doses for the 3D conformal technique were nearly identical between the two studies, their IMRT value was found to be 11% higher than ours.

Courtier *et al.* [35] reported that in 8% of right breast irradiations, the liver was included within the primary irradiation field. They demonstrated that the liver dose could be reduced using the deep breathing technique in situations where the liver dose could be elevated during treatment planning, and they determined that they could effectively minimize the side effects resulting from liver irradiation. In agreement with their findings, our study also highlights that the liver can receive a significant dose in breast radiotherapy, especially including supra and internal mammary lymph nodes are included in the treatment field. However, instead of using respiratory gating techniques, we applied different treatment techniques to reduce the liver dose, provided that we adhere to clinical constraints. Among the techniques analyzed, FIF technique resulted in the lowest liver dose compared to IMRT and HT.

Haji G. *et al.* [32] created 20 right-sided breast cancer patient plans for free breathing and deep inspiration breath hold (DIBH) techniques, each based on two separate CT scans. They created plans using the FIF technique, with a prescribed dose of 50 Gy. They reported the mean dose of liver for free breathing plans was 5.59 Gy. In comparison, our study, which employed the free breathing FIF, yielded a mean lower dose of approximately 3.90 Gy that closely aligned with their results.

In patients who underwent right breast irradiation, the average dose received by the liver was determined to be between 1.94 Gy and 4.34 Gy [8, 39-41]. Quintin *et al.* [41] developed the tomotherapy-based treatment plans for 27 right breast or bilateral breast radiotherapy plans, which required boost irradiation to the lymph node and tumor bed. As a result, they found the average liver dose to be 5.24 Gy

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(range 0.7-17.60) for right-sided breast cancer radiotherapy. According to our study all breast patients' PTVs included supraclavicular and internal mammary lymph nodes and we observed a mean liver dose of 10.6 Gy with tomotherapy. The higher liver dose in our study can be attributed to the inclusion of lymph nodes in the PTV, as well as variations in the treatment planning process concerning dose constraints.

Our study has several limitations. First, the number of patients was relatively small. Second, the clinical outcomes associated with liver doses were not evaluated in this study. In our subsequent research, we plan to investigate the relationship between liver dose and clinical outcomes.

CONCLUSIONS

In this study, three treatment planning techniques were compared for right-sided chest wall radiotherapy. All techniques resulted in notable liver exposure; however, the FIF technique yielded the lowest mean liver dose and superior V10 and V20 values compared with HT and IMRT. These findings highlight the need to account for liver dose during HT and IMRT planning for right-sided breast radiotherapy. We therefore recommend prioritizing liver dose optimization in treatment plan development.

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Author contribution: Authors contributed equally in this work.

AI Use: Artificial intelligence was utilized to support the language editing and writing processes of the manuscript.

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