Dosimetric Evaluation of Deep Inspiration Breath-Hold Technique for Breast Cancer Radiotherapy: A Single-Center Experience

Öztun TEMELLİ, Mehmet DEMİRTAŞ, Berat Tuğrul UĞURLU, Eda KAYA PEPELE, Bahaddin YAPRAK, Hülya GÜLBAŞ, Fatma Aysun ERASLAN, Şimay GÜROCAK

Department of Radiation Oncology, İnönü University, Malatya-*Turkey*

OBJECTIVE

To retrospectively evaluate the absorbed doses of organs at risk, such as lungs and the heart of the patients who underwent radiotherapy (RT) using the voluntary deep inspiration breath-hold (vDIBH) technique, and to compare the results with the literature.

METHODS

In this study, 102 patients who underwent adjuvant RT for the treatment of breast cancer in our clinic between November 2018 and December 2019 were included. A breast and/or chest wall, and/or lymph node RT of 50 Gy in 25 fractions was planned for all patients, and an additional boost of 10 Gy in five fractions was planned for patients requiring an RT boost. The treatment plans included 3DCRT, Field in Field (FIF), IMRT and VMAT approaches.

RESULTS

In the group undergoing supraclavicular fossa RT, the mean V20Gy was found to be 24.8%, compared to 16% in the group not undergoing supraclavicular fossa RT (p<0.01). In the group undergoing mammaria interna RT, the mean heart dose was 3.1 Gy, compared to 2.1 Gy in the group not undergoing mammaria interna RT (p=0.04).

CONCLUSION

Respiratory motion control techniques can reduce uncertainties in the target related to respiratory motion. The irradiated volume doses of the ipsilateral lung, heart reduce.

Keywords: Breast cancer; deep breath hold technique; radiotherapy.

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Introduction

Breast cancer is the most common cancer type and the leading cause of death among women worldwide.[1] Treatment modalities include surgery, chemotherapy, hormone therapy and radiotherapy (RT). Adjuvant RT aims to eradicate tumor deposits either through mastectomy or breast-conserving surgery and has improved locoregional recurrence (LRR), breast cancer-specific survival and overall survival (OS).[2] Radiation-related toxicity is still a significant problem due to the proximity to at-risk organs, despite the use of modern techniques in RT applications. Various studies have reported an increase in cardiovascular mortality in patients undergoing breast and/or chest wall irradiation.[3,4] It has been shown that breast RT increases

Dr. Öztun TEMELLİ
İnönü Üniversitesi,
Radyasyon Onkolojisi,
Malatya-Turkey
E-mail: oztun.temelli@inonu.edu.tr

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the risk of secondary lung cancer development, pneumonia and lung fibrosis.[5]

The deep inspiration breath-hold (DIBH) technique has been developed to reduce doses of RT on the lung and heart. There are different methods and systems for the application of DIBH, including voluntary, moderate or active breathing control [ABC]. Voluntary DIBH (vDIBH) relies on patient coaching throughout the respiratory cycle, whereas ABC DIBH makes use of a spirometer-like device. Although both techniques are effective, vDIBH is reported to be better tolerated.[6]

The vDIBH technique is based on observation of the flattening of the diaphragm and the expansion of the lungs during inspiration when the heart is moved away from the chest wall. During both simulation and treatment, the patient takes a deep breath and then holds it for the duration of the treatment.[7] In two extensive studies, a relative dose reduction was recorded in the heart from 40–48%, along with a mean dose reduction of 1.7–2.5 Gy with DIBH when compared to the free-breathing technique.[8,9] Ipsilateral lung doses were also found to be lower with DIBH in patients undergoing additional internal mammary chain (IMC) RT.[10]

The present study to retrospectively analyze the doses of organs at risk, such as the lung and heart of patients who underwent RT using the vDIBH technique, and to compare them with the findings in the literature.

Materials and Methods

Patient Selection
In this study, 102 patients who underwent adjuvant RT for the treatment of breast cancer in our clinic between November 2018 and December 2019 were evaluated retrospectively. The inclusion criteria were no hearing problems, no known respiratory disease, able to perform the given commands and an ECOG performance score of 0–1. The exclusion criteria were unable to perform the breath-hold technique, bilateral breast cancer, patients undergoing palliative breast RT and those treated with hypofractionated RT. This study was approved by the local ethics committee and was carried out in accordance with the Helsinki Declaration. Patient data is provided in Table 1.

Simulation, Treatment Planning and Delivery
The breath-hold technique was described to all patients by a training nurse before the simulation. All patients were placed in the supine position on the breast board. The surgical scar and palpable breast tissue were marked with radiopaque wire. A Varian RPM (real-time po-

sition management) system (Varian Medical Systems, Palo Alto, CA, USA) was used for the vDIBH technique. The RPM box, placed on the patient's chest wall, detects vertical displacements during the respiratory cycle, and the patient is instructed to hold their breath during a computer tomography (CT) (Aqullion LB TSX-201A, Toshiba Medical Systems, Japan) scan. A specific cut-off value for the upper and lower values of vertical displacement of the patient's chest wall was determined. A CT scan at 3 cm thickness was performed from the level of the larynx to the center of the abdomen.

Target volume contouring and organs at risk (OARs) (such as lungs, heart, esophagus, spinal canal and contralateral breast) contouring were performed in accordance with the Varian Eclipse planning system (version 13.7 - Varian Medical Systems, Palo Alto, USA) in accordance with the RTOG atlas.[11] A breast and/or chest wall, and/or lymph node RT of 50 Gy in 25 fractions was planned for all patients, and an additional boost of 10 Gy in five fractions was planned for the patients requiring an RT boost. The 3DCRT, Field in Field (FIF), IMRT, and VMAT techniques were used in the treatment plans. The CTV coverage was required to be between 90% and 110% of the prescribed dose.

The Anisotropic Analytical Algorithm (AAA) photon dose calculation algorithm was used for all plans. The maximum dose rate was 400 MU/min for the IMRT and 3DCRT plans, and 600 MU/min for the VMAT plans. The dose calculation grid was selected to be 0.25 cm. Treatment was delivered using a Varian linear accelerator (Clinac IX, Varian Medical Systems, Palo Alto, CA, USA).

The normality of the data was evaluated using a Shapiro-Wilk or Kolmogorov-Smirnov test, depending on the sample size. Since the data did not meet the normality criteria, it was summarized as median, minimum and maximum values. A Mann-Whitney U test was used for between-group comparisons, and a Kruskal-Wallis test was used for the comparison of more than two groups. After the Kruskal-Wallis test, pairwise comparisons were performed using the Conover method. The significance level was set at 0.05 for all analyses.

Results

The mean age of the patient group was 49 (range: 31–86) years; three had ductal carcinoma in situ while the others had invasive breast cancer; one patient was male; 12 patients were at stage 1; 39 patients were at stage 2; 47 patients were at stage 3 and two patients

Table 1. Patient characteristics

Characteristics	n (102)
Age	49 (Range:31-86)
T stage	
Tis (Carcinoma in situ)	3
T1	30
T2	53
T3	14
T4	2
N stage	
N0	31
N1	27
N2	25
N3	19
Stage	
0	3
I A	12
II A	26
II B	13
III A	27
III B	1
III C	18
IV	2
Pathology type	
Invasive ductal carcinoma	38
Invasive lobular carcinoma	7
Medullary carcinoma	7
Mucinous carcinoma	3
Metaplastic carcinoma	1
Invasive carcinoma of no special type	43
Ductal carcinoma in situ (DCIS)	3
Tumor side	
Right	42
Left	60
Surgery	
Mastectomy	57
Breast-conserving surgery	45
Axillary dissection	
Yes	70
No	32
Neoadjuvant chemotherapy	
Yes	21
No	81
Molecular subtypes	
Luminal A	56
Luminal B	22
Triple-negative/basal-like	19
HER2-enriched	5

had oligometastatic cancer at the time of diagnosis. The metastatic patients underwent surgery followed by adjuvant RT once their metastases had disappeared following neoadjuvant chemotherapy.

Table 1. Cont.

Characteristics	n (102)
Estrogen receptor status	
Positive	78
Negative	24
Progesterone receptor status	
Positive	67
Negative	35
Her-2	
Positive	27
Negative	75

A total dose of 50 Gy was administered to 57 patients, and a boost treatment was administered to 46 patients as an additional 10 Gy in five fractions. The 3DCRT-FIF, IMRT and VMAT plans were delivered to 82, 3 and 17 patients, respectively. The mean CTV-50Gy volume was found to be 859 cc. The treatment and CTV parameter characteristics are specified in Table 2.

Table 2. CTV parameters

CTV mastectomy	
Volume (cc)	859.8
Dmax (Gy)	55.3
Dmean (Gy)	50.9
V95	97
V100	70.2
V105	17.9
Radiotherapy volume	
Breast	25
Breast/chest wall+SCV+Ax	19
Breast/chest wall+SCV+Ax+IMC LN	58
Radiotherapy technique	
FIF	82
IMRT	3
VMAT	17
Boost	
Yes	45
No	57
CTV boost	
Volume (cc)	86.86
Dmean (Gy)	
V95	99.4
V100	90.4
V105	23.07
Boost technique	
FIF	17
IMRT	7
VMAT	3
Electron	18

FIF: Field in field; IMRT: Intensity-modulated radiation therapy; VMAT: Volumetric modulated arc therapy

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The mean lung volume was 4373 cc. The administered ipsilateral lung V20 and OAR doses are presented in Table 3. In the group receiving supraclavicular fossa RT, the mean V20Gy was found to be 24.8%, compared to 16% in the group not receiving supraclavicular fossa RT (p<0.01). In the group receiving mammaria interna (MI) RT, the mean ipsilateral lung V20Gy was found to be 26.2%, compared to 18.6% in the group not treated with MI RT (p<0.01). In the group treated with MI RT, the mean heart dose was 3.1 Gy, compared to 2.1Gy in the group not given MI RT (p=0.04). The mean ipsilateral lung V20Gy dose was found to be 16.5% in 25 patients who underwent breast RT alone, and 24.6% in the patients who underwent additional chest wall RT. The heart Dmean was found to be 2.5 Gy in 11 patients with left breast cancer who only underwent breast RT.

The detailed comparison of the techniques and the associated OAR doses is presented in Table 4.

Discussion

Breast cancer can be detected at an early stage. The frequency of treatment with RT following breast-conserving surgery has increased in recent years. There have been many young breast cancer patients with long survival expectancy, and so the amount of radiation received by healthy tissue becomes significant,[12] and this has led to the development of different respiratory management strategies in recent years.[13] For instance, ABC DIBH uses a spirometer-like device,[14] while Percussion-Assisted Radiation Therapy (PART) aims to suppress respiratory motion, while maintaining adequate oxygen diffusion and carbon dioxide removal

Table 3. OAR doses

| | Left | | Right | |
	Mastectomy (n=34)	BCS* (n=26)	Mastectomy (n=23)	BCS* (n=19)
Right lung				
V5	8.1 (0-32.7)	2.3 (0-38)	48 (39-74)	39.9 (23-61)
V10	1.3 (0-7.7)	0.5 (0-8)	33.5 (28-47)	25.7 (15-40)
V20	0.05 (0-0.9)	0.02 (0-0.08)	25.3 (16-35)	17.7 (11-29)
Dmean (Gy)	1.4 (0-4.5)	0.67 (0-5)	13.6 (10-18)	10.9 (7-16)
Left lung				
V5	54 (34-76.5)	46.7 (23-69)	2.2 (0-35)	0.01
V10	36.6 (19-53)	30.4 (12-44)	0.43 (0-6)	0
V20	24.3 (12-35)	21.7 (7-34)	0	0
Dmean (Gy)	13.5 (7.94-18.29)	12.6 (6-18)	0.41 (0-5)	0.33 (0-1)
Heart				
Dmax (Gy)	39.5 (4.2-55.3)	36.4 (6-56)	12.9 (4-51)	9.2 (3-29)
Dmean (Gy)	4 (0.6-17.6)	2.9 (0-8)	1.08 (0-6)	1.03 (0-3)
V20	2.3 (0-9.7)	2.13 (0-12)	0.12 (0-2)	0
V25	1.7 (0-6.68)	1.6 (0-11)	0.09 (0-2)	0
V30	1.2 (0-5.9)	1.4 (0-10)	0.07 (0-2)	0
V40	0.6 (0-4.2)	0.92 (0-9)	0.05 (0-1)	0
Esophagus				
Dmax (Gy)	38.2 (7.1-52.6)	24.2 (1-48)	32.6 (8-49)	8.3 (1-50)
Contralateral breast				
Dmax (Gy)	9.7 (1.6-35.7)	7.3 (2-26)	8.25 (2-40)	5.2 (1-21)
Dmean (Gy)	1.1 (0.04-3.2)	0.37 (0-3)	0.29 (0-3)	0.3 (0-1)
Spinal canal				
Dmax (Gy)	10.6 (0.4-29.95)	6.67 (1-37)	11.2 (2-36)	3.02 (0-20)
Liver				
Dmean (Gy)	0.4 (0-3.9)	0	2.38 (0-8)	1.3 (0-7)
V20	0.1 (0-4.6)	0	3.3 (0-15)	1.2 (0-12)

BCS*: Breast-conserving surgery
'()' minimum and maximum values are given inside the parenthesis

Table 4. OAR doses according to treatment techniques

Parameters	FIF-3DCRT	IMRT	VMAT	p
Ipslateral lung				
Dmean	12.9 (6.7-18.29)	14.2 (11.9-14.39)	13.5 (5.6-18.1)	0.7328
V5	45.65 (23.4-63.8)[a]	73.4 (57.3-76.5)[b]	63.5 (23-73.5)[b]	<0.001
V10	30.9 (14.5-44)[a]	46.3 (34.7-49.5)[b]	40.3 (11.8-53.1)[b]	<0.001
V20	22.85 (10.8-35.7)	23.7 (18.1-25.4)	22.3 (6.9-33.5)	0.997
Kontralaterallung				
Dmean	0.2 (0.1-3.3)[a]	1.9 (1.8-3)[b]	3.78 (0.2-4.9)[b]	<0.001
V5	0 (0-20.1)[a]	10.5 (5.5-25.8)[a]	21.1 (0-37.9)[b]	<0.001
V10	0 (0-4.3)[a]	0.2 (0-1.2)[b]	3.7 (0-7.9)[b]	<0.001
V20	0 (0-0)[a]	0 (0-0)[a]	0.06 (0-0.9)[b]	<0.001
Heart				
Dmean	1.35 (0.19-17.61)[a]	6.1 (4.5-9.1)[b]	4.5 (0.2-6.8)[b]	<0.001
Dmax	17.84 (3.36-56.07)	49.2 (38.6-49.6)	31.6 (6.4-55.3)	0.0965
V20	0 (0-12)[a]	6.6 (2.4-9.7)[b]	0.9 (0-5.9)[b]	0.0035
V25	0 (0-11)[a]	4.2 (1.1-6.4)[b]	0.01 (0-3.8)a	0.0242
V30	0 (0-10.3)[a]	2.7 (0.6-3.8)[b]	0 (0-2.24)[a]	0.036
V40	0 (0-8.5)	0.4 (0-1)	0 (0-1.1)	0.4342
Esophagus				
Dmax	28.48 (0.5-49.8)[a]	51.3 (46.3-52.6)[b]	39.8 (2-50.7)[b]	0.002
Contralateral breast				
Dmax	3.8 (1.2-40)[a]	13 (5.4-22.9)[b]	15 (5.2-35.7)[b]	<0.001
Dmean	0.18 (0-2.3)[a]	3.2 (0.6-16.6)[b]	2.3 (0.04-2.96)[b]	<0.001
Liver				
Dmean	0.25 (0-8.09)	0 (0-0.7)	0 (0-7.4)	0.2845
V20	0 (0-14.9)	0 (0-0)	0 (0-9.8)	0.095
Spinal canal				
Max	3.28 (0.4-36.7)[a]	17.1 (11.3-29.95)[b]	16.66 (1.9-35.9)[b]	<0.001

*a and b values indicate statistically significant treatment methods. FIF-3DCRT: Field in Field-threedimensional conformal radiation therapy; IMRT: Intensity-modulated radiation therapy; VMAT: Volumetric modulated arc therapy.

without general anesthesia.[15] It has been shown that ABC DIBH could reduce doses in the bilateral lungs, heart, left anterior descending coronary artery, contralateral breast, esophagus and spinal canal.[14]Continuous positive airway pressure (CPAP) significantly reduces tumor motion and increases total lung volume, thus contributing to reduced radiation doses to the lung and heart for lung stereotactic Body Radiation.[16] The CPAP technique has also been found to reduce ipsilateral lung and heart dosage in breast cancer RT through the use of conventional tangential fields.[17] Another respiratory motion technique uses rapid swallow non-invasive ventilation to regularize and to minimize the target variations resulting from respiratory motion.[18] The present study evaluates the clinical and dosimetric results of the application of the vDIBH technique in our clinic.

The doses absorbed by the lungs have been shown to be less with DIBH when compared to free-breathing in many studies,[19,20] although Bolukbaşı et al.[21] found no significant dose reduction in the lung, while V20 and V10 doses for the heart were reduced with the help of DIBH.In the present study, ipsilateral lung doses were found to be higher than in literature, which may be attributed to the fact that our patients were not homogeneous, that most had advanced stages of the disease and that boost doses were also considered in the relevant patients.

Supraclavicular region RT increases the doses absorbed by the lungs. In the present study, the lung Dmean, V5, V10 and V20 values were statistically higher in the patients who underwent additional supraclavicular RT, and these values are consistent with the literature.[9]

The risk of cardiovascular mortality has been shown to increase after breast and/or chest wall RT.[4,22] A 30% increased risk of mortality due to heart disease was identified in the Early Breast Cancer Trialists' Col-

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laborative Group study.[2] Each 1 Gy increase in the mean heart dose leads to 4–7% increased risk of heart disease and coronary events.[23,24] The International Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines state that for partial heart irradiation, "V25Gy <10% will be associated with a 1% probability of cardiac mortality" in long-term follow-up after RT.[23] In the present study, the mean V25 value was found to be quite low, while Dmean, V10 and V20 values were compatible with the literature.[9,25]

Regional nodal irradiation increases the doses absorbed by the lungs and heart, with IMC irradiation in particular increasing heart doses compared to breast and chest wall irradiation alone.[26] In the present study, lung Dmean, V5, V10 and V20 doses, heart Dmean and V20 doses, as well as Dmax doses of the esophagus, spinal canal, and contralateral breast were found to be high in the group who underwent additional IMC-RT.

In line with our constitutional guidelines, the FIF technique was first considered for all breast cancer patients, while IMRT and VMAT techniques were applied when the appropriate doses could not be achieved by the FIF technique. Our institute criterion for ipsilateral lung V20Gy is 35%. For the patients that FIF technique could not provide this criterion VMAT or IMRT was chosen for the treatment. The patients who were treated with the IMRT and VMAT techniques were generally patients who had additional regional lymph node RT, particularly IMC-RT. Since the IMRT technique was applied only to three patients, and the VMAT technique was applied to 17 patients, the comparison was not optimal, although contralateral lung doses, contralateral breast doses, spinal canal doses and esophagus doses were higher with these two techniques compared to FIF.

The limitations of this study include: All patients had RPM, and so there was no patient group without RPM. Furthermore, the number of patients was not homogeneous for different techniques.

Conclusion

Our retrospective study showed that the vDIBH technique could reduce ipsilateral lung and heart doses in accordance with the literature. Besides, we showed that for the patients that FIF technique could not be applied due to unsatisfied OAR dose restrictions, VMAT and IMRT are feasible alternatives. Patient compliance, however, is crucial. As the method increases the duration of treatment, it can be considered an applicable and effective treatment method only if appropriate patients are selected.

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