

# Effects of Radiation Dose on Liver After Free-breathing Volumetric Modulated Arc Therapy for Breast Cancer

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**Abstract.** Background/Aim: To evaluate the early effect of radiation dose on liver function in breast cancer patients undergoing free-breathing volumetric modulated arc therapy (FB-VMAT). Patients and Methods: Medical records of 125 patients with breast cancer who underwent curative surgery followed by postoperative radiotherapy using FB-VMAT during 2018-2021 were reviewed. Results of the liver function test (LFT), performed within 1-week before and 6-months after radiotherapy, were collected and compared. The LFTs analyzed albumin, total and direct bilirubin, aspartate transaminase, alanine transferase, and alkaline phosphatase levels. The mean dose and relative liver volume receiving at least 10 Gy, 20 Gy, or 30 Gy were calculated. Results: Median follow-up time was 21.4 months. One

patient experienced locoregional and distant failures. The mean liver irradiation dose was 325.9 centigray (cGy) for all patients. The liver irradiation dose was higher in patients with right breast cancer than in those with left breast cancer (mean, 434.1 cGy vs. 260.6 cGy,  $p < 0.001$ ). Direct bilirubin and aspartate transaminase levels showed significant differences after FB-VMAT. LFT results outside normal limits were noted in 31 patients at follow-up, but nobody met the criteria of radiation-induced liver disease. Underlying liver disease, breast laterality, systemic treatment, or dose-volume histogram parameters were not associated with abnormal LFT results. Conclusion: FB-VMAT can deliver radiation doses safely without adversely affecting the liver. The mean dose  $\leq 4$  Gy could be a useful dose criterium of the liver for FB-VMAT plans.

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Radiotherapy (RT) is the mainstay of locoregional treatment for breast cancer and is routinely performed following breast-conserving surgery (BCS) (1) or selectively administered after total mastectomy (TM) (2) to reduce locoregional recurrence and breast cancer mortality. Because the breasts are located on the anterior surface of the chest wall, radiation doses can be delivered in a relatively simple manner using a technique consisting of two opposite angles, called traditional tangential-field radiation therapy (TFRT). However, TFRT inevitably passes through several organs at risk (OARs), such as the heart, lung, and liver. Concerns of risks including the ischemic heart disease (3) and radiation pneumonitis (4) have motivated the introduction of advanced RT techniques that can spare OARs.

Intensity-modulation radiation therapy (IMRT) has the advantages of better dose conformity and target coverage compared to conventional RT techniques. Volumetric modulated arc therapy (VMAT) is a type of rotational IMRT with a faster dose delivery than static IMRT (5). The use of VMAT for breast cancer is increasing in many fields of adjuvant RT, such as hypofractionated whole breast RT (6), regional nodal irradiation (7), and simultaneous integrated boost (8).

To emphasize on the benefit of VMAT, particularly in sparing OARs, guidelines categorizing dose-volume histogram parameters (DVPs) to mitigate toxicity risks are essential (9). The recommended DVPs for cardiac toxicity are the mean dose ( $D_{\text{mean}}$ ) and relative volume receiving at least 25 Gy ( $V_{25\text{Gy}}$ ) of radiation in the entire heart or  $D_{\text{mean}}$  for the left anterior descending artery (10, 11). For the radiation pneumonitis risk, reliable DVPs are the  $D_{\text{mean}}$  and relative volume receiving at least 20 Gy ( $V_{20\text{Gy}}$ ) of radiation in the lung (12).

Currently, the toxicity effect of breast RT on the liver is unclear. Studies analyzing liver malignancies suggest that the dose constraints for normal liver volumes are  $D_{\text{mean}} \leq 28\text{--}32$  Gy in 2 Gy fractions to prevent RT-induced liver disease (RILD) (13). However, these dose constraints are unrealistically high considering the prescribed dose for breast cancer; therefore, they are not useful in clinical settings. In this study, we evaluated the early effect of radiation dose on liver function in breast cancer patients undergoing free-breathing VMAT (FB-VMAT).

## Patients and Methods

Between October 2018 and June 2021, 185 patients underwent BCS or TM followed by adjuvant RT, using FB-VMAT for breast cancer treatment. This treatment took place in the Department of Radiation Oncology of Hallym University Sacred Heart Hospital. Of these patients, 10 patients with a history of other malignancies were excluded. We also excluded 20 patients who had liver function test (LFT) results outside the normal limits, performed within one week before the start of RT. Finally, the medical data of 125 patients, including the patient and tumor characteristics and treatment details, were reviewed for the present study.

We collected the results of the LFTs performed 6 months after the end of RT to evaluate the early effect that FB-VMAT had on the liver. The LFTs included albumin, total and direct bilirubin, aspartate transaminase (AST), alanine transferase (ALT), and alkaline phosphatase (ALP) levels. The normal range is 3.8–5.3 g/dl for albumin, 0.2–1.2 mg/dl for total bilirubin, 0.0–0.4 mg/dl for direct bilirubin, 8–38 IU/l for AST, 5–43 IU/l for ALT, and 35–105 U/l for ALP tests. We also reviewed the presence of ascites on follow-up imaging studies using abdominal sonography or computed tomography (CT).

Planning CT scans were acquired with a Brilliance CT Big Bore (Philips Healthcare, Cleveland, OH, USA) or Somatom Confidence (Siemens Healthiness, Erlangen, Germany). All patients underwent non-enhanced CT simulation in the supine position under free-

breathing respiration. Slices with 3 mm thickness were acquired. Subsequently, one radiation oncologist delineated target volumes referring to atlases for breast cancer RT, as suggested by the Radiation Therapy Oncology Group (14) and the European Society of Radiation Oncology (15). In BCS cases, clinical target volumes (CTVs) included glandular breast tissue and/or regional lymph node areas encompassing the supraclavicular, infraclavicular, and axillary lymph nodes. For TM cases, the chest wall anterior to the ribs was delineated instead of the glandular breast tissue. The internal mammary lymph nodes were not routinely irradiated unless they were involved. The planning target volumes (PTVs) were expanded from the CTVs with a margin of 6 mm in all directions. We cropped the CTVs and PTVs 3 mm below the skin surface. Contoured normal organs were the contralateral breast, heart, lungs, and liver.

RayStation (RaySearch Laboratories, Stockholm, Sweden) version 4.7, 8A, 8B, and 9B were used for FB-VMAT planning, and the Collapsed Cone algorithm was applied for the final dose calculation. Two arcs in the 210° range were used. Regarding optimization constraints, we followed the dose criteria of the OARs described in the Radiation Therapy Oncology Group (RTOG) 1005 protocol (16). Since the dose limit for the liver was not presented in the RTOG 1005 protocol, we attempted to lower the liver  $D_{\text{mean}}$  to less than 3 Gy for the left breast and 4 Gy for the right breast. From the dose-volume histograms of the liver, we calculated DVPs consisting of the  $D_{\text{mean}}$  and relative volume of the liver receiving at least 10 Gy ( $V_{10\text{Gy}}$ ), 20 Gy ( $V_{20\text{Gy}}$ ), and 30 Gy ( $V_{30\text{Gy}}$ ) of radiation. Figure 1 presents the coronal and axial views of the FB-VMAT planning.

Pearson's chi-square test or Fisher's exact test was used to evaluate differences in categorical variables. Logistic regression analysis was used to verify the statistical significance between continuous and binary variables. The analytical results with a  $p$ -value of  $<0.05$ , were considered statistically significant. Statistical analysis was performed using R 4.1.1 (R Development Core Team, Vienna, Austria). The Institutional Review Board of Hallym University Sacred Heart Hospital approved this study and waived the requirement for informed consent.

## Results

*Patient characteristics and treatments.* Patient characteristics and treatments are detailed in Table I. The median patient age was 58 years (range=29–86 years). The ratios of right and left breast cancers were 37.6% and 62.4%, respectively. BCS was performed in 105 patients (84%) and TM in 20 (16%).

In patients who underwent RT for the breast alone ( $n=70$ ), the whole breast dose was 42.56 Gy in 16 fractions, and the booster dose was 10.64 Gy in 4 fractions. Patients receiving regional node RT ( $n=33$ ) were irradiated with a whole breast dose of 50 Gy and a booster dose of 10–14 Gy as a daily dose of 2 Gy. After TM ( $n=20$ ), a total dose of 50 Gy in 25 fractions, was delivered to the chest wall and regional nodal area. Two patients underwent simultaneous integrated boost VMAT: 61.6 Gy for the tumor bed and 50.4 Gy for the whole breast and regional node areas, administered in 28 fractions.

Adjuvant chemotherapy was administered to 81 patients. Anthracycline-based regimens were administered to 76 patients, taxanes were administered to 48 patients, and the

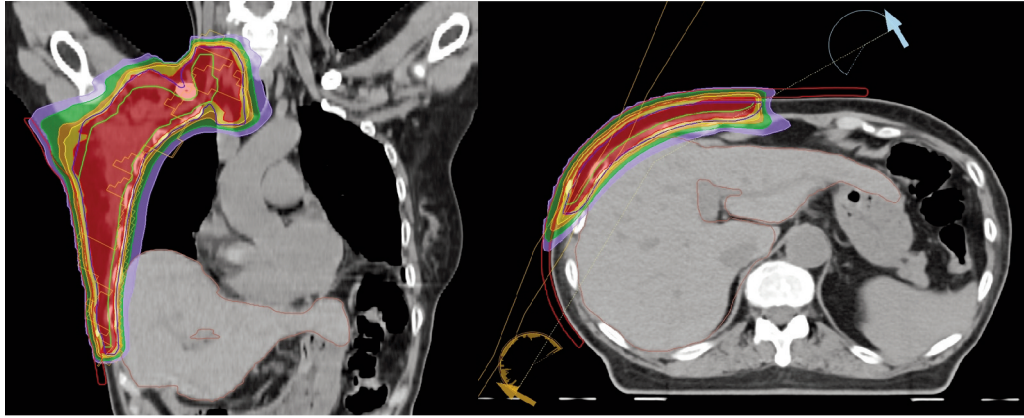


Figure 1. Coronal and axial views of free-breathing volumetric modulated arc therapy planning for right breast cancer.

remaining five patients received cyclophosphamide, methotrexate, and fluorouracil regimens. Neoadjuvant chemotherapy, based on anthracyclines, was administered to nine patients.

Of the 95 patients with hormone receptor-positive breast cancer, 94 received hormone therapy. Of the 28 human epidermal growth factor receptor 2 (HER2)- positive patients, 24 underwent HER2-targeted therapy.

**Treatment outcomes and liver DVPs.** The median follow-up time was 21.4 months (range=5.4-42.9 months). One patient experienced locoregional and distant failures. All patients survived during the study period. The mean liver volume was  $1291 \pm 322$  ml for all patients. The mean value of  $D_{\text{mean}}$  was  $325.9 \pm 147.1$  centigray (cGy) for all patients. The  $D_{\text{mean}}$  was significantly different according to the laterality of the tumor; the  $D_{\text{mean}}$  was 260.6 cGy and 434.1 cGy ( $p < 0.001$ ) for left and right breast cancer, respectively. The median values of  $V_{10\text{Gy}}$ ,  $V_{20\text{Gy}}$ , and  $V_{30\text{Gy}}$  were 3.0% (range=0-28.3%), 1.0% (range=0-5.8%), and 0% (range=0-2.6%), respectively.

The mean values of the LFTs performed before the start of FB-VMAT were  $4.3 \pm 0.3$  g/dl for albumin,  $0.44 \pm 0.19$  mg/dl for total bilirubin,  $0.17 \pm 0.05$  mg/dl for direct bilirubin,  $23.2 \pm 5.3$  IU/l for AST,  $20.2 \pm 7.7$  IU/l for ALT, and  $72.7 \pm 16.5$  U/l for ALP. After the completion of FB-VMAT, the mean LFT result values were  $4.3 \pm 0.3$  g/dl for albumin,  $0.41 \pm 0.20$  mg/dl for total bilirubin,  $0.21 \pm 0.05$  mg/dl for direct bilirubin,  $29.6 \pm 14.6$  IU/l for AST,  $25.6 \pm 20.0$  IU/l for ALT, and  $72.8 \pm 30.2$  U/l for ALP. Among the results of LFTs, direct bilirubin and AST levels showed significant changes after FB-VMAT (Figure 2).

A total of 31 patients were recorded to have LFT results outside normal limits: 16 had abnormal AST levels, 15 had abnormal ALT levels, 11 had abnormal ALP levels, and five had abnormal albumin levels. However, no patient had  $\geq 2$

Table I. Patient characteristics and treatments.

| Variables           |                   | n   | (%)    |
|---------------------|-------------------|-----|--------|
| Laterality          | Left              | 78  | (62.4) |
|                     | Right             | 47  | (37.6) |
| Surgery             | Breast Conserving | 105 | (84.0) |
|                     | Mastectomy        | 20  | (16.0) |
| Histology           | Ductal            | 111 | (88.8) |
|                     | Lobular           | 5   | (4.0)  |
|                     | Others            | 9   | (7.2)  |
| T                   | Tis               | 25  | (20.0) |
|                     | T1                | 51  | (40.8) |
|                     | T2                | 45  | (36.0) |
|                     | T3                | 4   | (3.2)  |
| N                   | N0                | 73  | (58.4) |
|                     | N1                | 26  | (20.8) |
|                     | N2                | 19  | (15.2) |
|                     | N2                | 7   | (5.6)  |
| Molecular subtypes  | ER/PR-positive    | 95  | (76.0) |
|                     | HER2-positive     | 28  | (22.4) |
| Systemic treatments | Neoadjuvant       | 6   | (4.8)  |
|                     | Adjuvant          | 81  | (64.8) |
|                     | Hormone           | 94  | (75.2) |
|                     | Targeted          | 24  | (19.2) |

ER: Estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2.

times the upper limit of ALP or  $\geq 5$  times the upper limit of AST or ALT, which is the general criteria defining RILD (17). In addition, liver DVPs, liver  $D_{\text{mean}}$ , laterality, systemic treatments, and underlying liver disease were not associated with an LFT result outside the normal range after FB-VMAT.

## Discussion

RILD is often noted within 2-3 months after RT completion. RILD is generally defined by a  $\geq 2$ -fold increase in the level

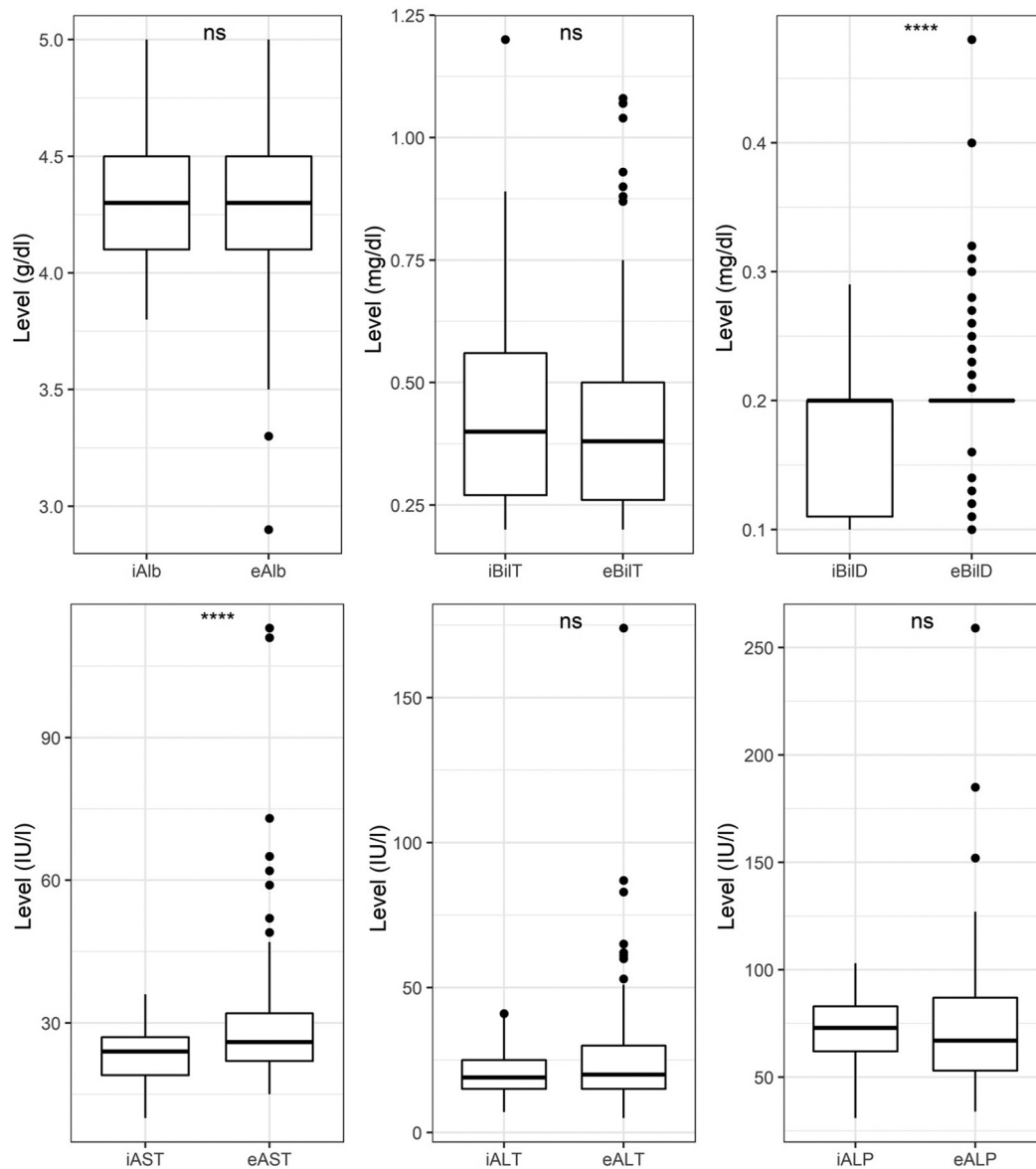


Figure 2. The mean values of the liver function tests performed before the start of free-breathing volumetric modulated arc therapy and after the completion of free-breathing volumetric modulated arc therapy.

of ALP (classic type) or  $\geq 5$ -fold increase in the level of AST/ALT (non-classic type) following RT. Pathophysiologically, classic RILD is characterized by hepatic veno-occlusive disease. Non-classic RILD is associated with an underlying chronic liver disease (17). Generally, dose constraints for the liver predicting a 5% chance of RILD consider a  $D_{\text{mean}}$  of 28-32 Gy in 2 Gy fractions (13). However, considering the dose prescribed to the whole breast in addition to the anatomical location of the liver, the recommended  $D_{\text{mean}}$  for a normal liver is too high, and thus, clinically not meaningful for breast cancer treatment. Our study could be useful for analyzing DVPs for

liver toxicity using FB-VMAT, which can modulate liver dose. Importantly, this is the first study to evaluate the association between the radiation dose used in breast cancer and the early effects on the liver.

TFRT is a traditional RT technique used in patients with breast cancer. It has a limitation in reducing the liver dose, given that the radiation doses are delivered by only two opposite tangential beams. If the liver is pushed away using the deep inspiration breath-hold (DIBH) technique, TFRT could reduce the liver dose significantly compared to free-breathing (18-20). However, DIBH is a complex technique that requires the dedication and cooperation of patients or

elaborate computer control. One benefit of using voluntary DIBH is that it does not require expensive instruments; rather, additional skin markers are required (21). Despite its cost-benefit, voluntary DIBH has inherent limitations since it is patient-dependent and has an ambiguity in 3-dimensional dose distribution (22). Additionally, breathing volume controlled DIBH has been reported to significantly reduce the irradiation dose to normal organs (23). However, interfractional instabilities in the chest wall position can occur owing to differences in the breathing maneuvers of patients, such as abdominal and costal respiration (24). Optical surface imaging can reduce setup error non-invasively and dynamically monitor the DIBH status. Nonetheless, the potential disagreement between the surface and internal anatomy of the chest wall may hinder its widespread adoption, as well as the cost of surface-guided RT systems (25).

Contrarily, FB-VMAT can deliver radiation dose to the breast and regional nodes without compromising RT target coverage and normal organs sparing (26, 27). For breast cancer, FB-VMAT has been applied to shorten treatment courses (6, 8), and reduce skin toxicity (28) and cardiac dose (7, 29). At our institution, we administer FB-VMAT with the aim of hypofractionation or regional irradiation in patients with breast cancer.

In this study, no patients experienced symptoms or signs associated with RILD or had LFT results meeting the criteria for RILD within six months after the completion of FB-VMAT for breast cancer. LFT results outside of the normal range were observed in 31 patients (24.8%). Underlying liver disease, the laterality of breast cancer, and systemic treatment, such as tamoxifen, aromatase inhibitors, and trastuzumab, were not associated with mild changes in LFT. Therefore, FB-VMAT can be administered safely to patients with breast cancer, without severe adverse effects on the liver.

We could not find any association between the DVPs and LFT results outside the normal range. Several studies analyzing patients with hepatocellular carcinoma and treated with RT have revealed that  $V_{30\text{Gy}}$  can be used to predict RILD. Severe liver toxicities were observed more frequently when  $V_{30\text{Gy}}$  was >40-60% (30-32). In our study,  $V_{30\text{Gy}}$  was 0% in 67 patients (53.6%) and the highest value of  $V_{30\text{Gy}}$  was 2.6%. Considering that a very limited volume of the liver received a clinically meaningful radiation dose related with RILD, this likely explains why our results suggest that there were no DVPs related to abnormal results in LFT. Therefore, the liver  $D_{\text{mean}} \leq 3$  Gy or 4 Gy for the left and right breast cancer could be a helpful dose criterion that can be easily adopted for the FB-VMAT planning.

Although liver irradiation doses after FB-VMAT are regarded as clinically acceptable and safe, the current methods may not be sensitive enough to detect the effect of

RT on the liver. Therefore, a limitation of this study was the lack of other sensitive studies and techniques available to identify RT-induced liver changes. Although FB-VMAT did not result in significant liver toxicity, molecular or functional imaging studies may visualize liver changes more apparently (33, 34). In addition, the absence of serial LFT results during FB-VMAT is another limitation, which resulted from the retrospective nature of this study. The dynamics of LFT during and after FB-VMAT could be worth examining to evaluate the effects of the radiation dose on the liver.

Herein, clinically significant liver toxicities were not observed in patients with breast cancer after FB-VMAT. Mild LFT changes outside normal limits were noted in 25% of patients when the liver  $D_{\text{mean}}$  was  $\leq 4$  Gy. Mild changes in LFT were not associated with underlying liver disease, laterality, post-RT systemic treatment, or DVPs. Thus, FB-VMAT is a safe modality that can deliver radiation to the breast with relevant modulation of the liver dose.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

TK conceptualized and designed this study. HJP, KHC, and TK collected and analyzed data. MYL, KK, SP, TH, SKK, BH, JWY, MYK, and HB participated in the interpretation of results. HJP and KHC drafted the article, and TK revised the article. All Authors read and approved the article.

## References

- 1 Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, Cutter D, Davies C, Ewertz M, Godwin J, Gray R, Pierce L, Whelan T, Wang Y and Peto R: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 378(9804): 1707-1716, 2011. PMID: 22019144. DOI: 10.1016/S0140-6736(11)61629-2
- 2 EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, Gray R, Mannu G, Peto R, Whelan T, Wang Y, Wang Z and Darby S: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 383(9935): 2127-2135, 2014. PMID: 24656685. DOI: 10.1016/S0140-6736(14)60488-8
- 3 Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C and Hall P: Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 368(11): 987-998, 2013. PMID: 23484825. DOI: 10.1056/NEJMoa1209825

- 4 Lingos TI, Recht A, Vicini F, Abner A, Silver B and Harris JR: Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 21(2): 355-360, 1991. PMID: 2061112. DOI: 10.1016/0360-3016(91)90782-y
- 5 Teoh M, Clark CH, Wood K, Whitaker S and Nisbet A: Volumetric modulated arc therapy: a review of current literature and clinical use in practice. *Br J Radiol* 84(1007): 967-996, 2011. PMID: 22011829. DOI: 10.1259/bjr/22373346
- 6 De Rose F, Fogliata A, Franceschini D, Navarria P, Villa E, Iftode C, D'Agostino G, Cozzi L, Lobefalo F, Mancosu P, Tomatis S and Scorsetti M: Phase II trial of hypofractionated VMAT-based treatment for early stage breast cancer: 2-year toxicity and clinical results. *Radiat Oncol* 11(1): 120, 2016. PMID: 27639373. DOI: 10.1186/s13014-016-0701-z
- 7 Zhao XR, Fang H, Tang Y, Hu ZH, Jing H, Liang L, Yan XN, Song YW, Jin J, Liu YP, Chen B, Tang Y, Qi SN, Li N, Lu NN, Men K, Hu C, Zhang YH, Li YX and Wang SL: P0stmastectomy radioThErapy in Node-posiTive breast cancer with or without Internal mAmmary nodaL irradiation (POTENTIAL): a study protocol for a multicenter prospective phase III randomized controlled trial. *BMC Cancer* 21(1): 1185, 2021. PMID: 34742270. DOI: 10.1186/s12885-021-08852-y
- 8 Hörner-Rieber J, Forster T, Hommertgen A, Haefner MF, Arians N, König L, Harrabi SB, Schlamp I, Weykamp F, Lischalk JW, Heinrich V, Weidner N, Hüsing J, Sohn C, Heil J, Hof H, Krug D and Debus J: Intensity modulated radiation therapy (IMRT) with simultaneously integrated boost shortens treatment time and is noninferior to conventional radiation therapy followed by sequential boost in adjuvant breast cancer treatment: Results of a large randomized Phase III trial (IMRT-MC2 Trial). *Int J Radiat Oncol Biol Phys* 109(5): 1311-1324, 2021. PMID: 33321192. DOI: 10.1016/j.ijrobp.2020.12.005
- 9 Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK and Yorke ED: Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 76(3 Suppl): S3-S9, 2010. PMID: 20171515. DOI: 10.1016/j.ijrobp.2009.09.040
- 10 Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM and Marks LB: Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 76(3 Suppl): S77-S85, 2010. PMID: 20171522. DOI: 10.1016/j.ijrobp.2009.04.093
- 11 Duma MN, Baumann R, Budach W, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Hehr T, Krug D, Piroth MD, Sedlmayer F, Souchon R, Sauer R and Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO): Heart-sparing radiotherapy techniques in breast cancer patients: a recommendation of the breast cancer expert panel of the German society of radiation oncology (DEGRO). *Strahlenther Onkol* 195(10): 861-871, 2019. PMID: 31321461. DOI: 10.1007/s00066-019-01495-w
- 12 Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, El Naqa I, Hubbs JL, Lebesque JV, Timmerman RD, Martel MK and Jackson A: Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 76(3 Suppl): S70-S76, 2010. PMID: 20171521. DOI: 10.1016/j.ijrobp.2009.06.091
- 13 Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M and Ten Haken RK: Radiation-associated liver injury. *Int J Radiat Oncol Biol Phys* 76(3 Suppl): S94-100, 2010. PMID: 20171524. DOI: 10.1016/j.ijrobp.2009.06.092
- 14 Breast cancer atlas for radiation therapy planning: Consensus definitions. RTOG (Radiation Therapy Oncology Group). Available at: [https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/BreastCancerAtlas\\_corr.pdf?ver=2018-04-18-144201-270](https://www.nrgoncology.org/Portals/0/Scientific%20Program/CIRO/Atlases/BreastCancerAtlas_corr.pdf?ver=2018-04-18-144201-270) [Last accessed on March 7, 2022]
- 15 Offerens BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, Kirova YM, Pignol JP, Remouchamps V, Verhoeven K, Weltens C, Arenas M, Gabrys D, Kopek N, Krause M, Lundstedt D, Marinko T, Montero A, Yarnold J and Poortmans P: ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 114(1): 3-10, 2015. PMID: 25630428. DOI: 10.1016/j.radonc.2014.11.030
- 16 A Phase III trial of accelerated whole breast irradiation with hypofractionation plus concurrent boost *versus* standard whole breast irradiation plus sequential boost for early-stage breast cancer. RTOG-1005. Available at: <https://www.nrgoncology.org/Clinical-Trials/Protocol/rtog-1005> [Last accessed on March 7, 2022]
- 17 Kim J and Jung Y: Radiation-induced liver disease: current understanding and future perspectives. *Exp Mol Med* 49(7): e359, 2017. PMID: 28729640. DOI: 10.1038/emmm.2017.85
- 18 Lin CH, Lin LC, Que J and Ho CH: A seven-year experience of using moderate deep inspiration breath-hold for patients with early-stage breast cancer and dosimetric comparison. *Medicine (Baltimore)* 98(19): e15510, 2019. PMID: 31083193. DOI: 10.1097/MD.00000000000015510
- 19 Pandeli C, Smyth LML, David S and See AW: Dose reduction to organs at risk with deep-inspiration breath-hold during right breast radiotherapy: a treatment planning study. *Radiat Oncol* 14(1): 223, 2019. PMID: 31822293. DOI: 10.1186/s13014-019-1430-x
- 20 Haji G, Nabizade U, Kazimov K, Guliyeva N and Isayev I: Liver dose reduction by deep inspiration breath hold technique in right-sided breast irradiation. *Radiat Oncol* 14(4): 254-258, 2019. PMID: 31918462. DOI: 10.3857/roj.2019.00206
- 21 Bartlett FR, Colgan RM, Donovan EM, Carr K, Landeg S, Clements N, McNair HA, Locke I, Evans PM, Haviland JS, Yarnold JR and Kirby AM: Voluntary breath-hold technique for reducing heart dose in left breast radiotherapy. *J Vis Exp* (89): 51578, 2014. PMID: 25046661. DOI: 10.3791/51578
- 22 Boda-Heggemann J, Knopf AC, Simeonova-Chergou A, Wertz H, Stieler F, Jahnke A, Jahnke L, Fleckenstein J, Vogel L, Arns A, Blessing M, Wenz F and Lohr F: Deep inspiration breath hold-based radiation therapy: a clinical review. *Int J Radiat Oncol Biol Phys* 94(3): 478-492, 2016. PMID: 26867877. DOI: 10.1016/j.ijrobp.2015.11.049
- 23 Eldredge-Hindy H, Lockamy V, Crawford A, Nettleton V, Werner-Wasik M, Siglin J, Simone NL, Sidhu K and Anne PR: Active Breathing Coordinator reduces radiation dose to the heart and preserves local control in patients with left breast cancer: report of a prospective trial. *Pract Radiat Oncol* 5(1): 4-10, 2015. PMID: 25567159. DOI: 10.1016/j.prro.2014.06.004
- 24 Mittauer KE, Deraniyagala R, Li JG, Lu B, Liu C, Samant SS, Lightsey JL and Yan G: Monitoring ABC-assisted deep inspiration breath hold for left-sided breast radiotherapy with an optical tracking system. *Med Phys* 42(1): 134-143, 2015. PMID: 25563254. DOI: 10.1118/1.4903511

- 25 Hoisak JDP and Pawlicki T: The role of optical surface imaging systems in radiation therapy. *Semin Radiat Oncol* 28(3): 185-193, 2018. PMID: 29933878. DOI: 10.1016/j.semradonc.2018.02.003
- 26 Popescu CC, Olivetto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R, Wai ES and Otto K: Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys* 76(1): 287-295, 2010. PMID: 19775832. DOI: 10.1016/j.ijrobp.2009.05.038
- 27 Inoue E, Doi H, Monzen H, Tamura M, Inada M, Ishikawa K, Nakamatsu K and Nishimura Y: Dose-volume histogram analysis of knowledge-based volumetric-modulated arc therapy planning in postoperative breast cancer irradiation. *In Vivo* 34(3): 1095-1101, 2020. PMID: 32354897. DOI: 10.21873/invivo.11880
- 28 Joseph K, Vos LJ, Gabos Z, Pervez N, Chafe S, Tankel K, Warkentin H, Ghosh S, Amanie J, Powell K, Polkosnik LA, Horsman S, MacKenzie M, Sabri S, Parliament MB, Mackey J and Abdulkarim B: Skin toxicity in early breast cancer patients treated with field-in-field breast intensity-modulated radiotherapy *versus* helical inverse breast intensity-modulated radiotherapy: Results of a Phase III randomised controlled trial. *Clin Oncol (R Coll Radiol)* 33(1): 30-39, 2021. PMID: 32711920. DOI: 10.1016/j.clon.2020.07.005
- 29 Kim YJ, Kim K, Lee R, Kim J, Jung W, Paik NS, Moon BI, Lim W and Lee J: Two-year follow-up of volumetric-modulated arc therapy for treating internal mammary nodes in locally advanced breast cancer. *Anticancer Res* 36(9): 4847-4851, 2016. PMID: 27630339. DOI: 10.21873/anticancer.11047
- 30 Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, Matsumoto S, Soejima T and Sugimura K: Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 57(1): 113-119, 2003. PMID: 12909223. DOI: 10.1016/s0360-3016(03)00434-6
- 31 Liang SX, Zhu XD, Xu ZY, Zhu J, Zhao JD, Lu HJ, Yang YL, Chen L, Wang AY, Fu XL and Jiang GL: Radiation-induced liver disease in three-dimensional conformal radiation therapy for primary liver carcinoma: the risk factors and hepatic radiation tolerance. *Int J Radiat Oncol Biol Phys* 65(2): 426-434, 2006. PMID: 16690430. DOI: 10.1016/j.ijrobp.2005.12.031
- 32 Kim TH, Kim DY, Park JW, Kim SH, Choi JI, Kim HB, Lee WJ, Park SJ, Hong EK and Kim CM: Dose-volumetric parameters predicting radiation-induced hepatic toxicity in unresectable hepatocellular carcinoma patients treated with three-dimensional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 67(1): 225-231, 2007. PMID: 17056199. DOI: 10.1016/j.ijrobp.2006.08.015
- 33 Eccles CL, Haider EA, Haider MA, Fung S, Lockwood G and Dawson LA: Change in diffusion weighted MRI during liver cancer radiotherapy: preliminary observations. *Acta Oncol* 48(7): 1034-1043, 2009. PMID: 19634060. DOI: 10.1080/02841860903099972
- 34 Sanuki N, Takeda A, Oku Y, Eriguchi T, Nishimura S, Aoki Y, Mizuno T, Iwabuchi S and Kunieda E: Threshold doses for focal liver reaction after stereotactic ablative body radiation therapy for small hepatocellular carcinoma depend on liver function: evaluation on magnetic resonance imaging with Gd-EOB-DTPA. *Int J Radiat Oncol Biol Phys* 88(2): 306-311, 2014. PMID: 24411601. DOI: 10.1016/j.ijrobp.2013.10.045

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