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Teaching Case

New Technologies and Multidisciplinarity as Strategic Factors to Cope With Challenges in Postmastectomy Breast Cancer Radiation Therapy

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Introduction

Postmastectomy radiation therapy (PMRT) reduces the risk of breast cancer recurrence and mortality in patients with node-positive breast cancer.[1] However, PMRT to the left chest wall and regional lymph nodes often poses technical challenges owing to irregular surface contours, large curvature, and a near-surface target. Adequate irradiation of target volumes should never penalize the sparing of the adjacent organs at risk (OARs).

Modern technologies such as the Active Breathing Coordinator (ABC) device,[2-4] the AlignRT surface imaging system (by VisionRT), volumetric arc therapy (VMAT),[5,6] and the automated planning (AP) module of the Pinnacle3 treatment planning system[7] represent key tools to overcome several hurdles in this complex setting. To our knowledge, the simultaneous use of these techniques and devices has not been reported.

Case report and presentation

The case of a 71-year-old White woman with a history of left breast cancer treated by radical mastectomy and lymphadenectomy is reported. In 2017, the patient had a cancer in the left lung treated by lobectomy, removing about 67 cm^3 of lung with the tumor. Moreover, she had positive family anamnesis for cardiovascular diseases and had experienced valvular disease with left atrial dilatation, for which a mechanical mitral valve had been implanted in December 2011. The patient's ejection fraction was approximately 50% to 55%. Her pharmacologic therapy consisted of chronic anticoagulant oral therapy, digitalis drugs, and calcium channel blockers.

In February 2020, the patient discovered a lump in her left breast. A breast ultrasound examination and mammography revealed a category 4 plaque (Breast Imaging Reporting and Data System) in the periareolar region with negative axillary nodes. Excision biopsy revealed the presence of invasive breast cancer—no special type, grade 2 (Nottingham system), involving surgical margins. Owing to the infiltrative margin, 2 months later, the patient received radical surgery with axillary nodal dissection (level I and II), revealing a 2.1-cm lesion getting to the skin without ulcer, as per invasive breast cancer—no special type, grade 3 (Nottingham system), negative for perineural and perivascular invasion and positive for lymphocyte infiltration. Metastases with extracapsular extension were detected in 3 of 7 lymph nodes removed. The patient's cancer stage was pT2N1a, and her hormonal status was as follows: Estrogen Receptor, 95%; Progesterone Receptor, 40%; Ki-67, 30%; and a score ≥2 for Her2. An echocardiogram showed the presence of the

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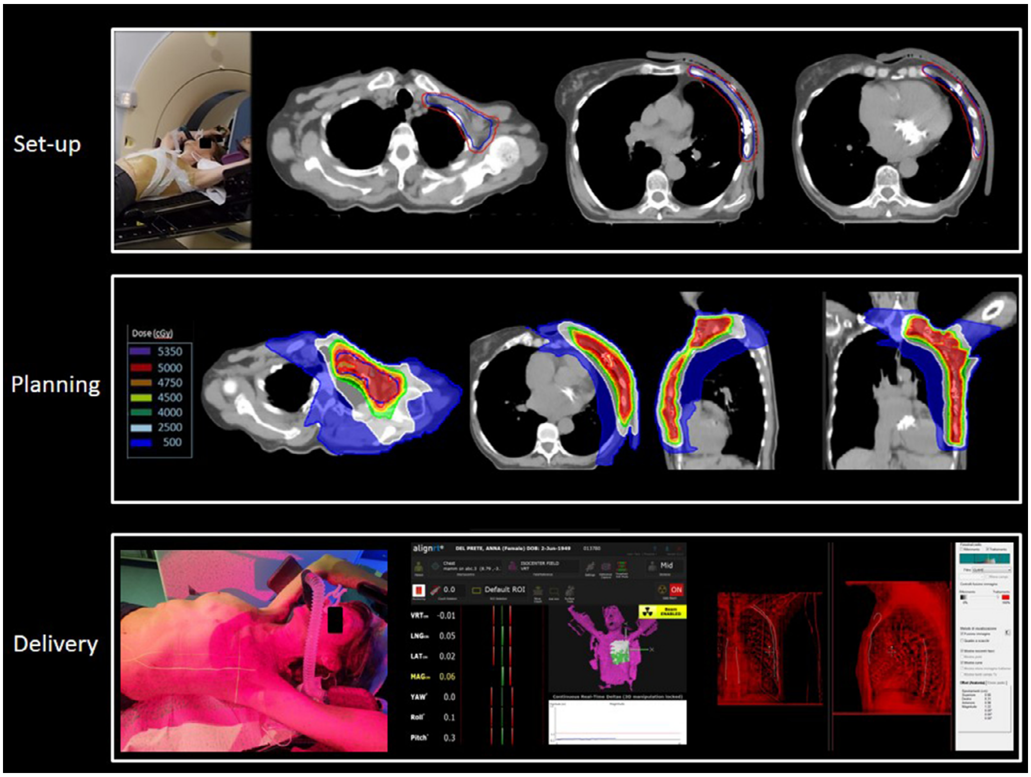

Fig. 1 Overview of the treatment setup, planning, and delivery.

mechanical valve, slight parietal hypertrophy of the left ventricle, an ejection fraction of 50% to 55%, and deficits in the aortic (slight deficit) and tricuspid (moderate deficit) valves.

The case was discussed by the multidisciplinary tumor board. The medical oncologist firmly excluded chemotherapy or radiation therapy and suggested only hormonal therapy (letrozole was promptly started) and follow-up. However, in light of the PMRT indication, the radiation oncologist proposed a dosimetric study for assessing the radiation therapy feasibility of all cutting-edge technologies available in our arsenal, despite the patient's comorbidities. The patient was counseled to inform her about the radiation therapy indication and the concerns related to this approach in terms of both feasibility and toxicities. Then the patient was immobilized on the C-Qual Breastboard system (by CIVCO Radiotherapy) and was simulated in moderate deep inspiration breath-hold with both arms abducted above the head. A bolus 1 cm thick was positioned on the chest wall, and the planning computed tomography images were acquired with a 5-mm slice thickness. The chest wall plus an 8-mm margin, as well as the axillary and supraclavicular nodes (level I-IV) plus a 5-mm margin, were contoured according to the Radiation Therapy Oncology Group's breast cancer atlas volumes and internal guidelines.[8] Two planning target volumes (PTVs), 1 for the chest wall and 1 for the supraclavicular nodes, were combined as an integrated PTV (Fig 1). For the sake of completeness, internal mammary nodes (IMNs) were also outlined, although in such situations, we do not irradiate the IMNs. The OARs included the heart, homolateral and contralateral lung, and contralateral breast. To reduce the dose to the OARs, especially the lungs and heart, the moderate deep inspiration breath-hold technique using the ABC device was used (Fig 1).

The total dose was 50 Gy over 25 fractions for the integrated PTV; target coverage criteria followed the recommendations of the International Commission on Radiation Units & Measurements' Report 62.

Owing to the patient's comorbidities, stringent objectives were applied to spare healthy organs. Keeping the mean dose less than 4 Gy was the main objective for heart preserving, as per the NSABP B-51/RTOG1304 breast cancer trial.[9]

Furthermore, it is well known that the heart volume receiving 25 Gy <10% has been correlated with a very low probability of cardiac mortality (<1%) at 15 years after radiation therapy.[10] To be more conservative, we pursued the objective of V20 ≤10% for the heart[11] and V5 <50%, V10 <35%, and V20 <20% for the homolateral lung (12). The mean dose and the dose to 1cc of the contralateral breast volume (D1cc) was requested to be <2 Gy and 5 Gy, respectively.[12]

Normal tissue complication probabilities (NTCPs) for the lung and heart were calculated by the Lyman-Kutcher-Burman probit model.[13] The considered endpoints for heart and lung toxicity were pericarditis, long-term mortality, and pneumonitis.

Four different plans were generated and compared to pursue the best dosimetric result: a plan mixing 3-dimensional (3D) and intensity modulated radiation therapy, a plan mixing 3D and volumetric arc techniques, a fully manual VMAT plan, and a fully automated VMAT (AP-VMAT) plan.

In detail, the hybrid approach delivered three-fourths of the prescription dose through tangential beams and one-fourth through VMAT or intensity modulated radiation therapy (IMRT) beams; the latter was optimized by the inverse planning algorithm to satisfy the dose constraints. In the hybrid intensity modulated radiation therapy plan, a total of 4 fields were used: 2 open, tangential fields for the chest wall volume and 2 opposite half-beam fields for the nodal area. Thereafter, the plan was optimized by adding 2 modulated 6-MV beams (step-and-shoot technique) with an identical 3D conformal beams setup. No more than 10 segments and no areas smaller than 10 cm^2 were allowed. In the hybrid VMAT plan, the 3D component contributed three-fourths of the dose prescription; thereafter, 2 partial arcs, each with 210° gantry rotations delivered clockwise and counterclockwise from 320° to 170°, for the PTVs of both the chest wall and the supraclavicular nodes were added. These angles were selected to prevent the direct irradiation of the lung and the contralateral breast. The SmartArc module (by Philips) was used for optimization. The manual VMAT plan was obtained starting from the previously reported arc parameters; then we interactively tuned the optimization process of the manual VMAT plan. The AP-VMAT plan was performed using the Pinnacle3 automated planning module, version 16.0, in which all beam details, dose prescriptions, and planning aims for targets and healthy organs must be specified up front. Starting from these details, the automated planning software iteratively optimized planning parameters, with the aim to reach the planning objectives. Meanwhile, during this process, dummy structures and new objectives to the planning goals were automatically generated to enhance the dose conformity, the dose fall-off outside the targets, and the OAR sparing. The 2 target priorities were defined by numbers near to prescription doses to avoiding potential peripheral dose fall-off. The healthy-organ priorities included maximum dose, mean dose, and dose-volume histogram points with 3 different priority levels (from high to low). The heart received a priority higher than that of the target. A priori, we set up in the planning template (1) the balance tuning, (2) the Cold-Spot region of interest, and (3) the dose fall-off margin.

After comparing the plans, the automated plan was the best at reducing the homolateral lung and heart doses (full range). The AP-VMAT plan alone fulfilled the objective of a 4-Gy mean heart dose, lowered the NTCP estimates for lung pneumonitis to less than 1%, and was able to reduce the heart and homolateral lung doses to less than 5 Gy. No differences were found among the different techniques in terms of the mean dose to the contralateral breast.

The dosimetric comparisons of the different treatment plans for target-organ and OAR coverage are reported in Table 1. For a complete dosimetric overview, we also compared the AP-VMAT plan with a rival AP-VMAT plan including IMNs plus a 5-mm margin. As expected, the larger PTV resulted in a slight worsening of planning aims; however, the plan including IMNs was feasible (Table 1). A comparison between automated plans with or without IMNs is shown in Figure 2.

Ultimately, the AP-VMAT plan without IMNs was proposed for patient treatment. An overview of the AP-VMAT treatment plan and delivery by the AlignRT surface imaging system is shown in Figure 1. The patient underwent PMRT to the chest wall and lymph-nodal area without severe acute toxicity according to the Common Terminology Criteria for Adverse Events, version 5.0.[14] Six months later, no adverse events (eg, skin fibrosis or heart failure) or disease recurrence had been reported.

Discussion and Conclusion

This article highlights how modern technology may help in the treatment of complex clinical situations such as left-sided chest wall irradiation in a patient with several cardiopulmonary comorbidities.

The decision to irradiate the patient was strictly conditioned by the possibility of tracking and reproducing the patient's position before and during radiation therapy and by the chance to obtain a treatment plan able to reduce, at most, irradiation to the OARs. Among all the plans considered, the best coverage and homogeneity were obtained in the AP-VMAT plan. In terms of the dose-volume evaluation and the NTCP estimates, the manual plans provided values too high to be acceptable, whereas the AP-VMAT parameters were the closet and the safest according to plan objectives (Table 1).

Literature emphasizes the need for cardiac dose reduction in breast cancer radiation therapy, especially for patients with cardiac risk factors that put them at greater absolute increased risk from radiation therapy.[15] Darby et al retrospectively reported that the rate of coronary events increased by 7.4% for every 1-Gy increase to the heart,[16] whereas the NSABP 51 study recommended a mean cardiac dose of less than 4 Gy for left-sided breast irradiation.[9]

Respiratory management strategies are being used to reduce cardiac and homolateral lung doses in breast cancer irradiation. The moderate deep inspiration breath hold technique using the ABC device, which changes the internal anatomy, is an effective strategy that can be used to improve cardiac sparing.[17,18] Moreover, the association of ABC with a system that tracks a patient's position before and during radiation therapy (AlignRT)

Table 1 Dosimetric comparisons of rival treatment plans for coverage of targets organs and organs at risk

Structure	Metric	Objective	Plan				
			HMRT	HVMAT	MP-VMAT	AP-VMAT	AP-VMAT* (IMN)
PTV CW	D95 (Gy)	≥47.5	47.5	48.5	49.5	49.5	48.5
	D98 (Gy)	≥45.0	45.8	47.5	48.1	47.8	47.7
	D2 (Gy)	≤53.5	54.8	53.7	53.3	52.4	53.0
	Dmean (cGy)	50.0	51.3	50.8	51.4	50.5	50.8
	HI	Minimize	18	12.4	10.4	9.2	10.6
PTV SCL	D95 (Gy)	≥47.5	47.8	47.5	49.5	49.6	49.6
	D98 (Gy)	≥45.0	46.5	46.2	48.5	49.0	49.2
	D2 (Gy)	≤53.5	53.3	52.8	53.3	52.9	53.1
	Dmean (cGy)	50	50.5	50.2	51.6	51.1	51.2
	HI	Minimize	13.6	13.2	9.6	7.8	7.8
PTV IMN	D95 (Gy)	≥47.5					48.5
	D98 (Gy)	≥45.0					49.2
	D2 (Gy)	≤53.5					52.8
	Dmean (cGy)	50					51.0
	HI	Minimize					7.2
Conformity	CN	1.0	0.57	0.64	0.68	0.76	0.71
Heart	Dmean (Gy)	<4	5.9	6.1	6.2	4.0	4.7
	V5 (%)		15.1	18.3	34.8	14.1	20.9
	V10 (%)		10.5	14.7	15.5	6.9	8.4
	V20 (%)	≤10	7.4	11.8	9.2	3.6	4.5
	V30 (%)	≤5	6.1	9.2	4.5	2.2	2.6
	$NTCP_{per}$	Minimize	0	0	0	0	0
	$NTCP_{long}$	Minimize	0	0	0	0	0
Left lung	Dmean (Gy)		16.3	16.2	14.4	12.5	156
	V5 (%)	<50	54.5	55.2	87.1	55.4	71.0
	V10 (%)	<35	42.1	44.1	44.2	36.1	44.1
	V20 (%)	<20	31.2	35.2	24.4	21.3	27.6
	V30 (%)		26.1	28.8	16.2	15.5	19.8
	$NTCP_{pneu}$	Minimize	5.1	4.8	2.6	0.8	3.0
Right lung	Dmean (Gy)		0.7	0.6	2.4	2.4	3.9
Contralateral breast	Dmean (Gy)	<2	1.1	1.1	1.4	1.3	1.9
	D1cc (Gy)	<5	4.1	4	4.4	4.3	4.8
Healthy tissues	ID ($Gy \times cm^3 \times 10^{-6}$)	Minimize	1.023	1.044	1.055	0.981	1.089

Abbreviations: AP-MAT = automated planning volumetric arc therapy; CN = conformity index; HI = homogeneity index; HMRT = hybrid intensity modulated radiation therapy; HVMAT = hybrid volumetric arc therapy; ID = integral dose; IMN = internal mammary node; MP-MAT = manual planning volumetric arc therapy; $NTCP_{long}$ = long-term mortality normal-tissue complication probability; $NTCP_{pneu}$ = pneumonitis normal-tissue complication probability; $NTCP_{per}$ = pericarditis normal-tissue complication probability; PTV CW = planning target volume, chest wall; PTV SCL = planning target volume, supraclavicular nodes.

* This plan was considered a feasibility exercise; the patient was not treated by this plan.

represented a further measure aimed at preserving healthy organs. To date, a recent study showed that AlignRT coupled with deep inspiration breath-hold prevented radiation-induced abnormalities in blood flow to the heart, thus preventing early cardiac perfusion defects.[19]

As far as radiation therapy technique is concerned, this case was, to our knowledge, one of the first clinical experiences involving AP-VMAT for this type of tumor and clinical stage. Notwithstanding several articles that have described the use of IMRT in patients with breast cancer,[20-23] some conflicting experiences have been reported about the use of VMAT in the same clinical setting.[24-26]

We acknowledge that manual planning for complex cases is a challenging task; enhancing the therapeutic ratio requires the management of many competing parameters and is a time-consuming trial-and-error process. Full implementation of an automated planning system into a clinical routine for breast or chest wall treatments could potentially reduce operator variability and ameliorate the quality of plans. Moreover, a significant reduction in the range of doses to the lung and heart, including the low-dose region, was obtained by the AP-VMAT plan. In fact, the integral dose was lower by approximately 4% to 7% compared with manual plans. Owing to increased survival among patients with

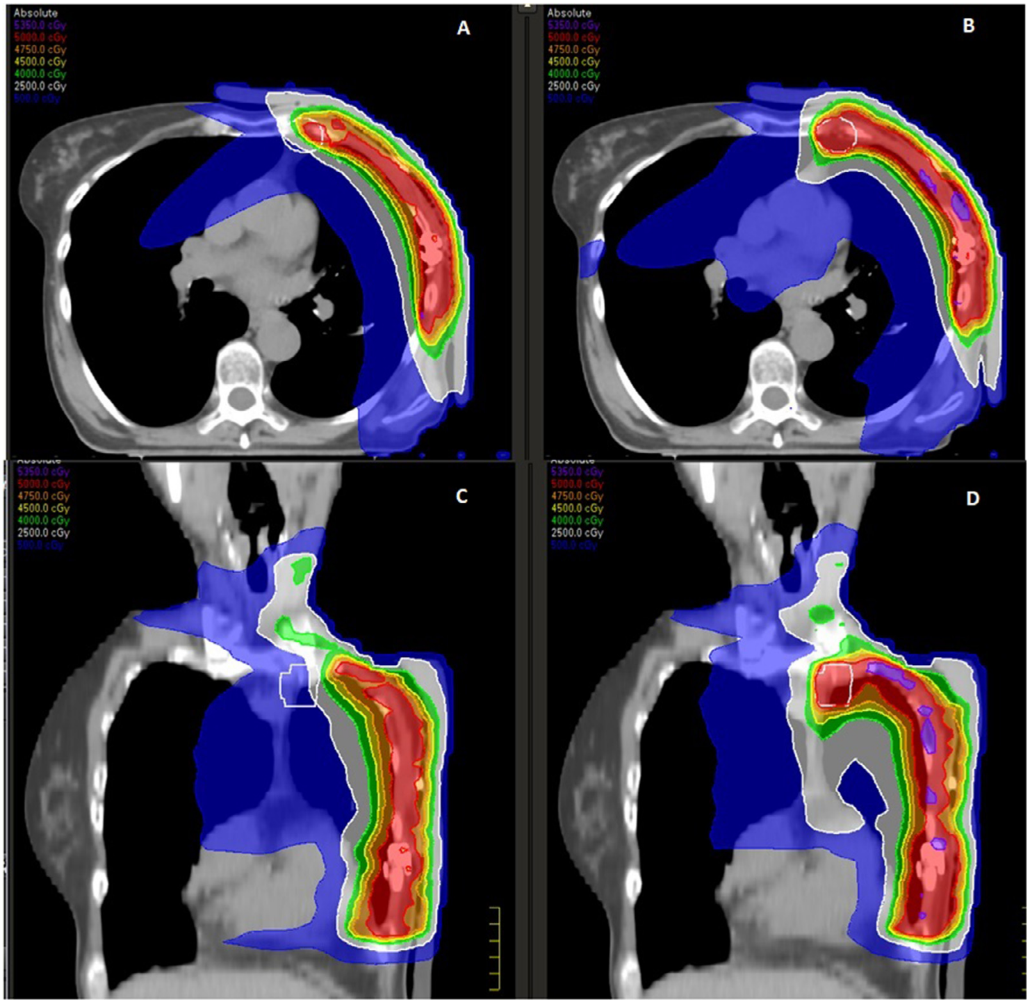

Fig. 2 Dosimetric comparison between automated plans with (B, D) or without (A, C) irradiation of internal mammary nodes.

advanced breast cancer, the problem of radiation-induced secondary cancers and the need to reduce as much as possible the irradiation dose in normal tissues becomes cogent.[27] In the present case, a careful cardiologic and oncologic follow-up is ongoing to register any late toxicity or recurrence of cancer.

We acknowledge that some practitioners would recommend the treatment of IMNs in similar cases; however, IMN irradiation is really a dosimetric challenge when faced with severe cardiopulmonary comorbidities. According to a national consensus for the irradiation of mammary lymph nodes, the irradiation of IMNs is indicated in the case of involvement.[28] In the case of clinically negative IMNs, there is currently no unanimous opinion on the indication for precautionary radiation therapy on these lymph node stations. Therefore, in the current case, burdened by cardiopulmonary risk factors, we treated only the levels I to IV. However, to further stress the value of automated Treatment Planning System, together with all other technique and devices, we simulated a plan including IMNs and reported results that are almost comparable with the AP-VMAT plan without IMNs, as shown in Table 1 and Figure 2. This comparison allowed us to highlight the still little-known power of automated planning even in an extremely challenging case.

In conclusion, this case highlights the PMRT techniques used in treating a patient with breast cancer who had a resected lung and an enlarged heart. Advanced radiation therapy approaches gave the possibility to perform a curative treatment considered unthinkable until a few years ago, allowing us to considerably reduce the heart and lung exposure to ionizing radiation without underdosage of the chest wall and lymph-nodal areas. The sharing of knowledge allows us to prevent the risk of missing important therapeutic options based on new technologies or cutting-edge updates generally known only by health care professionals and trained individuals.

References

1. Clarke M, Collins R, Darby S, et al. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of

differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of randomised trials. *Lancet*. 2005;366:2087–2106.
2. Remouchamps VM, Letts N, Yan D, et al. Three-dimensional evaluation of intra- and interfraction immobilization of lung and chest wall using active breathing control: A reproducibility study with breast cancer patients. *Int J Radiat Oncol Biol Phys*. 2003;57:968–978.
3. Barry A, Rock K, Sole C, et al. The impact of active breathing control on internal mammary lymph node coverage and normal tissue exposure in breast cancer patients planned for left-sided postmastectomy radiation therapy. *Pract Radiat Oncol*. 2017;7(4):228–233.
4. Massaccesi M, Caravatta L, Cilla S, et al. Active Breathing Coordinator in adjuvant three-dimensional conformal radiotherapy of early stage breast cancer: A feasibility study. *Tumori*. 2010;96(3):417–423.
5. Nobnop W, Phakoetsuk P, Chitapanarux I, et al. Dosimetric comparison of TomoDirect, helical tomotherapy, and volumetric modulated arc therapy for postmastectomy treatment. *J Appl Clin Med Phys*. 2020:155–162.
6. Nichols GP, Fontenot JD, Gibbons JP, et al. Evaluation of volumetric modulated arc therapy for postmastectomy treatment. *Radiat Oncol*. 2014;9:66.
7. Hazell I, Bzdusek K, Kumar P, et al. Automatic planning of head and neck treatment plans. *J Appl Clin Med Phys*. 2016;17(1):272–282.
8. Breast Cancer Atlas. Available at: https://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx. Accessed September 16, 2021.
9. *National Surgical Adjuvant Breast and Bowel Project (NSABP). Protocol B-51: A randomized phase III clinical trial evaluating post-mastectomy chestwall and regional nodal XRT and post-lumpectomy regional nodal XRT in patients with positive axillary nodes before neoadjuvant chemotherapy who convert to pathologically negative axillary nodes after neoadjuvant chemotherapy*. NSABP; 2013. v2016, February 24. Available at: https://med.uc.edu/docs/default-source/cancercenter/all-protocols/breast/nsabp_b51_randomized-phase-iii-clinical-trial-evaluating-post-mastectomy-chestwall.pdf. Accessed June 28, 2020.
10. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys*. 2010;76(3):77–85.
11. Hu J, Han G, Lei Y, et al. Dosimetric comparison of three radiotherapy techniques in irradiation of left-sided breast cancer patients after radical mastectomy. *Biomed Res Int*. 2020 7131590.
12. Lee BM, Chang JS, Kim SY, et al. Hypofractionated radiotherapy dose scheme and application of new techniques are associated to a lower incidence of radiation pneumonitis in breast cancer patients. *Front Oncol*. 2020;10:124.
13. Lyman JT. Complication probability as assessed from dose-volume histograms. *Radiat Res Suppl*. 1985;8:S13–S19.
14. US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE), version 5.0*. Washington, DC: US Department of Health and Human Services; November 27, 2017.
15. Taylor CW, Wang Z, Macaulay E, et al. Exposure of the heart in breast cancer radiation therapy: A systematic review of heart doses published during 2003 to 2013. *Int J Radiat Oncol Biol Phys*. 2015;93:845–853.
16. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998.
17. Wong JW, Sharpe MB, Jaffray DA, et al. The use of active breathing control (ABC) to reduce margin for breathing motion. *Int J Radiat Oncol Biol Phys*. 1999;44:911–919.
18. Kunheri B, Kotne S, Nair SS, Makuny D. A dosimetric analysis of cardiac dose with or without active breath coordinator moderate deep inspiratory breath hold in left sided breast cancer radiotherapy. *J Cancer Res Ther*. 2017;13:56–61.
19. Zagar TM, Kaidar-Person O, Tang X, et al. Utility of deep inspiration breath-hold for left sided breast radiation therapy in preventing early cardiac perfusion defects: A prospective study. *Int J Radiat Oncol Biol Phys*. 2017;97(5):903–909.
20. Yang B, Wei X, Zhao Y, et al. Dosimetric evaluation of integrated IMRT treatment of the chest wall and supraclavicular region for breast cancer after modified radical mastectomy. *Med Dos*. 2014;39:185–189.
21. Xie Y, Bourgeois D, Guo B, et al. Postmastectomy radiotherapy for left-sided breast cancer patients: Comparison of advanced techniques. *Med Dos*. 2020;45:34–40.
22. Ma JL, Li JY, Xie J, et al. Post mastectomy linac IMRT irradiation of chest wall and regional nodes: Dosimetry data and acute toxicities. *Radiat Oncol*. 2013;8:81.
23. Morganti AG, Cilla S, De Gaetano A, et al. Forward planned intensity modulated radiotherapy (IMRT) for whole breast postoperative radiotherapy. Is it useful? When? *J Appl Clin Med Phys*. 2011;12(2):213–222.
24. Badakhshi H, Kaul D, Nadobny J, et al. Image-guided volumetric modulated arc therapy for breast cancer: A feasibility study and plan comparison with three-dimensional conformal and intensity-modulated radiotherapy. *Br J Radiol*. 2013;86: 20130515.
25. Jin G, Chen L, Deng X, et al. A comparative dosimetric study for treating left-sided breast cancer for small breast size using five different radiotherapy techniques: Conventional tangential field, filed-in-filed, tangential-IMRT, multi-beam IMRT and VMAT. *Radiat Oncol*. 2013;8:89.
26. Osman SO, Hol S, Poortmans PM, et al. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiother Oncol*. 2014;112:17–22.
27. Corradini S, Ballhausen H, Weingandt H, et al. Left-sided breast cancer and risks of secondary lung cancer and ischemic heart disease: Effects of modern radiotherapy techniques. *Strahlenther Onkol*. 2018;194(3):196–205.
28. Consensus per l'irradiazione delle stazioni linfonodali mammary. Associazione Italiana Radioterapia Oncologica (AIRO). Position paper V.01. 2016.