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Sequential Volumetric Modulated Arc Therapy (VMAT) Boost in Hybrid Plan With Tangential Beams for Whole Breast Treatment: a Dosimetric Study

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Originînal Research

Abstract

Purpose: Whole breast radiation therapy (WBRT) with a boost to the tumor bed following conservative primary surgery in women with breast cancer (BC) plays a central role in reducing local recurrences and mortality. Volumetric modulated arc therapy (VMAT) technique has been shown to allow better dose conformation with low dose levels to organs at risk (OARs), compared to static fields three-dimensional Conformal Radiotherapy (3D-CRT). The aim of this study was to evaluate the feasibility and dosimetric advantages of sequential boost (SB), administered with VMAT technique in hybrid plans with tangential beams for whole breast treatment.

Material and methods: BC patients undergoing adjuvant RT from June to October 2020 were selected. ESTRO guidelines for the Clinical Target Volume (CTV) delineation were used. Total delivered dose was 60-66 Gy; 50 Gy in 2 Gy daily fractions for whole breast and 10-16 in 2 Gy daily fractions Gy to tumor bed was 10-16 Gy in 2 Gy daily fractions.

Results: The analysis included 31 patients with BC treated with adjuvant RT following conservative surgery. Hybrid treatment plans characterized by a 3D-CRT plan using tangential mediolateral and lateromedial fields for the irradiation of the whole breast Planning Target Volume (PTV) and a sequential VMAT plan with 2 coplanar arches for boost PTV irradiation were generated. Dosimetric analysis resulted in homogeneous target volumes coverage and OARs

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constraints compliance. As regarding to organs at risks (OARs), contralateral breast, ipsi- and contralateral lung and heart constraints values were analysed.

Conclusions: In the frame BC RT, this dosimetric study showed that hybrid plans performed with 3D-CRT and VMAT techniques are feasible in terms of dosimetric outcomes.

Keywords: *Breast Cancer, Radiotherapy, Hybrid plans, VMAT, 3D-CRT*

Introduction

Breast conservative surgery followed by whole breast radiation therapy (WBRT) and a boost to the tumor bed is the treatment of choice for most patients with stages I–II breast cancer (BC) (1–3).

Breast radiotherapy (RT) has been historically performed by two tangential fields for a total dose of about 50 Gy with a conventional fractionation of 1.8-2 Gy (4). More recent evidence have demonstrated the non-inferiority of hypofractionated RT also showing a reduction in acute toxicity (5–9).

Breast conservative approaches have increased significantly in the last decades and techniques have improved with greater awareness of the impact of radiation on the heart (10).

The tumor bed boost can be performed in different modalities, electrons beam radiotherapy, particles RT, photons beam RT or brachytherapy (BT). Electrons beam RT and photons beam RT delivered in sequential boost (SB) have been shown to be the most common modalities (11,12).

Even though particles RT and photons beam RT seem to guarantee better planning solutions, no randomized trials have been designed to identify the best modality to use (13,14).

In recent years, static fields three-dimensional Conformal Radiotherapy (3D-CRT) modality has been replaced by Intensity-Modulated Radiation Therapy (IMRT) modality assuring more conforming doses and volumes. Experience have also showed that IMRT could also provide a minimization of unwanted radiation dose inhomogeneity in the breast leading to late adverse effects reduction (15,16).

Volumetric modulated arc therapy (VMAT) technique is preferred to conventional direct electron in tumor bed boost both for better conformation of the dose and for lung sparing (17).

Electrons should be reserved to very superficially located tumor bed without contact with the thoracic wall (18).

To our knowledge, in literature no studies have analyzed a hybrid treatment with static tangential fields for WBRT and with the use of VMAT technique for the sequential boost.

The aim of this study is to demonstrate the feasibility and dosimetric advantages of SB delivered with VMAT technique in hybrid plans with tangential beams for whole breast treatment.

Material and methods

Patients characteristics

Thirty-one patients from a single institution who received RT following conservative surgery for early BC from June to October 2020 were retrospectively enrolled. Patients enrolled signed a consent for data collection according to the study design requirements and also to department regulation.

Patients had stage I disease according to the 7th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging system (19).

In this study 12 left-sided and 19 right-sided tumors were evaluated.

A heterogeneous patient population was considered for analysis with large or small breast volume and deeply or superficially located tumors.

The boost regions were sixteen in upper outer quadrant (UOQ), two in upper-lower inner quadrants (UIQ – LIQ), two in lower outer quadrant (LOQ), eleven in central quadrant (CQ).

Patients characteristics are reported in table 1.

Table 1 - *Patients characteristics*

Patient	Side	Quadrant	Gy/fraction Whole breast	Total dose Whole breast	Gy/fraction Tumoral bed	Total dose Tumoral bed
1	R	UOQ	2	50	2	10
2	R	LOQ	2	50	2	10
3	L	UOQ	2	50	2	10
4	R	CQ	2	50	2	10
5	R	LOQ	2	50	2	10
6	R	UOQ	2	50	2	16
7	L	CQ	2	50	2	10
8	L	CQ	2	50	2	16
9	R	CQ	2	50	2	10
10	L	UOQ	2	50	2	10
11	R	CQ	2	50	2	10
12	R	UIQ-LIQ	2	50	2	10
13	L	CQ	2	50	2	10
14	R	UOQ	2	50	2	16
15	L	UOQ	2	50	2	10
16	R	UOQ	2	50	2	10
17	R	UOQ	2	50	2	10
18	R	UIQ-LIQ	2	50	2	10
19	R	UOQ	2	50	2	10
20	R	UOQ	2	50	2	10
21	R	UOQ	2	50	2	10
22	L	UOQ	2	50	2	10
23	L	QC	2	50	2	10
24	L	UOQ	2	50	2	10
25	L	UOQ	2	50	2	10
26	R	UOQ	2	50	2	10
27	R	UOQ	2	50	2	10
28	R	CQ	2	50	2	10
29	L	CQ	2	50	2	10
30	R	CQ	2	50	2	10
31	L	CQ	2	50	2	10

R: right; L: left; UOQ: upper outer quadrant; LOQ: lower outer quadrant. UIQ: upper inner quadrant; LIQ: lower inner quadrant; CQ: central quadrant;

Contouring

The patients underwent a 2.5-mm slice thickness, free-breathing computed tomography (CT) scan in supine position on breast board (C-qual) with both arms raised above the head.

The clinical target volume of whole breast (CTV_{breast}) was contoured according to European Society for Radiotherapy and Oncology (ESTRO) guidelines (20).

The CTV_{boost} was defined as the tumor bed identified through the study of pre-operative mammography and/or MRI images and the visualization of the surgical alteration, with the help of a metal marker on the scar; any seromas near the tumor bed were included.

The PTV_{breast} and PTV_{boost} were created by adding an isotropic 5 mm margin expansion to CTV_{breast} and CTV_{boost} respectively.

The PTVs were cropped to 5 mm from the body as Italian guideline recommendation (1).

The organs at risk (heart, ipsilateral lung, contralateral lung and lungs) were delineated according to National guidelines (1).

Planning

31 hybrid treatment plans were generated characterized by a 3D-CRT plan using tangential mediolateral and lateromedial fields for the irradiation of the PTV_{breast} and a sequential VMAT plan with 2 coplanar arches for PTV_{boost} irradiation with an amplitude of 120° (240°-40° for right breast, 320°- 120° for left breast).

All treatment plans were calculated using the Pinnacle3 vers.16.02 from Philips, collapsed cone algorithm and 3x3x2.5 mm calculation grid and were optimized for Elekta Synergy® linear accelerator equipped with an 80-leafs multi-lamellar collimator.

The dose prescribed to the whole breast was 50 Gy in 2 Gy daily fractions according to internal department regulamentation. The dose to the tumor bed was 10-16 Gy in 2 Gy daily fractions, higher boost dose was prescribed for patients with close margins status at pathological examination. The total delivered dose was 60-66 Gy.

The target volume and prescription dose were defined according Report 50, 62 and 83 recommendations of the International Commission on Radiation Units and Measurements (ICRU) (21–23).

Both plans aimed to PTV V95% and CTV 98% higher than 95% of the prescribed dose, and also to PTV V107% inferior to 5% and PTV Dmax not exceeding 110%.

The conformity index ($CI_{95\%}$) was calculated as

$$CI = \frac{TV_{RI}}{TV} \cdot \frac{TV_{RI}}{V_{RI}}$$

where TV_{RI} represents the target volume covered by the reference isodose (95% of the prescription dose); TV is the target volume, V_{RI} is the volume of the reference isodose. The value of CI ranges from 0-1, with a value closer to 1 indicating better conformity of the dose to the PTV (24).

The dose constraints considered for Organs at risk (OARs) were:

- Heart V10Gy < 10%, V40Gy < 4% and Dmean < 3 Gy
- Ipsilateral lung Dmean < 18 Gy and V20Gy < 25%
- Contralateral lung Dmax < 5 Gy
- Bilateral lungs V5Gy < 60%
- Contralateral breast Dmax < 5 Gy and V10 Gy < 5%. (25–27)

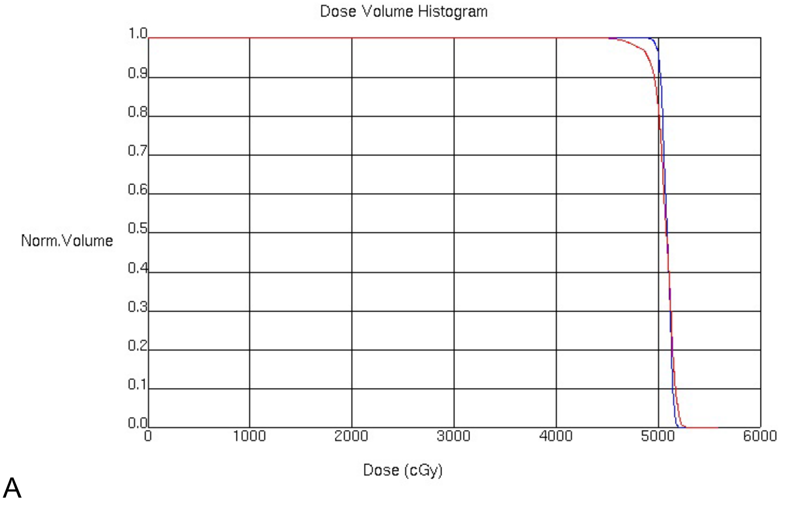
Plan evaluation

The dosimetric data of the individual and the sum plans considered were:

- CTV boost bed V95% and V107%
- PTV boost bed V95%, V107% and $CI_{95\%}$
- Ipsilateral lung mean dose and V20Gy
- Contralateral lung max dose and mean dose
- Bilateral lungs V5Gy
- Heart V20Gy, V40Gy and mean dose
- Contralateral breast max dose and V10Gy

3. Results

Plan evaluation resulted in homogeneous dosimetric values for target coverage as Mean PTV boost V95% resulted in 98,2% ± 1,8 DS with a mean PTV boost CI 95% result of 1,0 ± 0,0 DS. Coverage of both PTV_{breast} and PTV_{boost} are shown in Figure 1 and 2.



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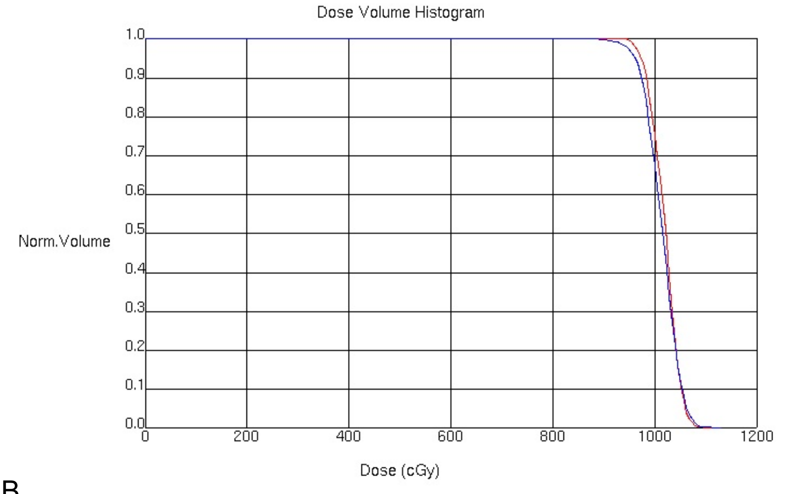

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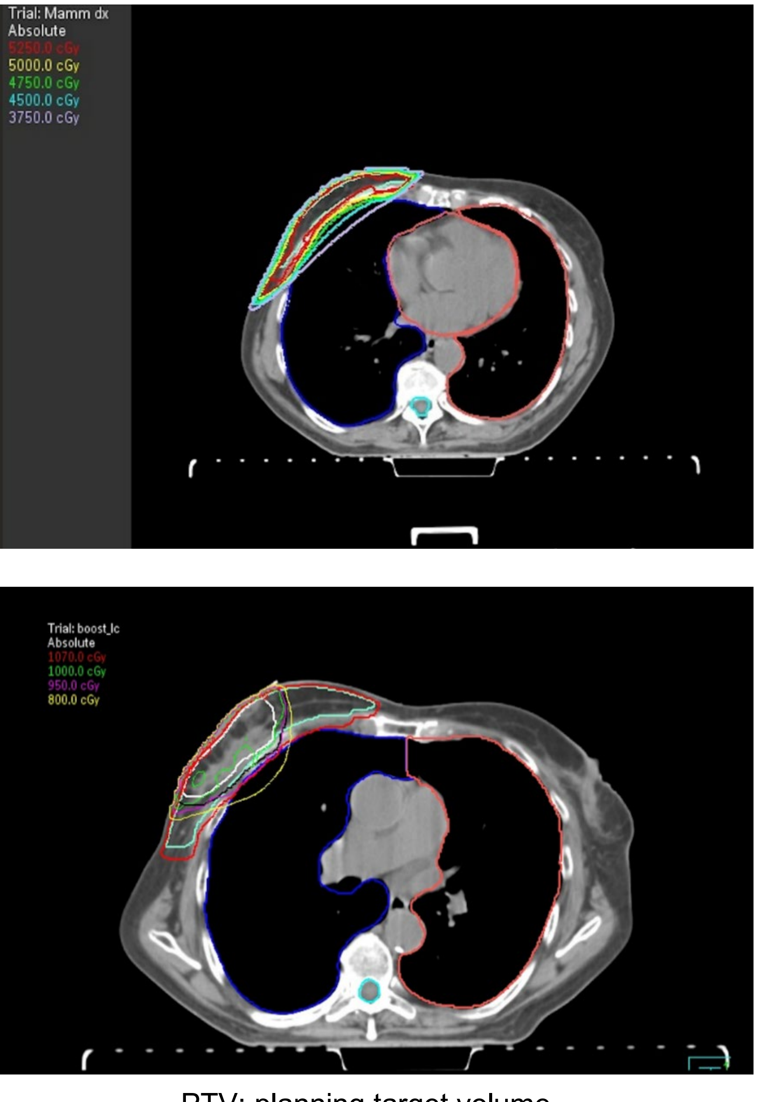
PTV: planning target volume

Figure 1 – Dose Volumes Histograms for PTV_{breast} (A) and PTV_{boost} (B)



A

B

PTV: planning target volume

Figure 2 – Dose coverage for PTVbreast (A) and PTVboost (B)

Heart constraints were respected as mean heart V20 Gy resulted in 1,4 Gy ± 2,5 DS and 1,5 Gy ± 2,7 DS in WBRT plans and boost plans sum. Also constraints for the other OARs were respected.

Table 2 and 3 resume data of target coverage and OARs doses in both WBRT and boost plans sum.

Table 2 - Target coverage values

	CTV boost V95%	**CTV boost V107%**	**PTV boost V95%**	**PTV boost V107%**	**PTV boost V110%**	**PTV boost Dmax**	**PTV CI 95%**
MEAN	99.8	1.3	98.2	1.4	0.0	10.4	1.0
ST. DEV	*0.3*	*1.5*	*1.8*	*1.6*	*0.1*	*2.7*	*0.0*

CTV: Clinical Target Volume; PTV: Planning Target Volume; CI: Conformity Index; ST. DEV: Standard Deviation

Table 3 - OARs dose constraints values

	Heart V20Gy Boost	**Heart V20Gy WBRT**	**Heart V20Gy Plan Sum**	**Heart V40Gy Boost**	**Heart V40Gy WBRT**	**Heart V40Gy Plan Sum**	**Heart Dmean Boost**	**Heart Dmean WBRT**	**Heart Dmean Plan Sum**
MEAN	0.0	1.4	1.5	0.0	0.6	0.7	1.0	1.7	2.7
ST. DEV	*0.0*	*2.5*	*2.7*	*0.0*	*1.1*	*1.3*	*0.7*	*1.4*	*1.6*

	Contralateral Breast Dmax Boost	**Contralateral Breast Dmax WBRT**	**Contralateral Breast Dmax Plan Sum**	**Contralateral Breast V10Gy Boost**	**Contralateral Breast V10Gy WBRT**	**Contralateral Breast V10Gy Plan Sum**
MEAN	1.2	2.8	3.8	0.0	0.2	0.3
ST. DEV	*0.5*	*1.0*	*1.0*	*0.0*	*0.6*	*0.8*

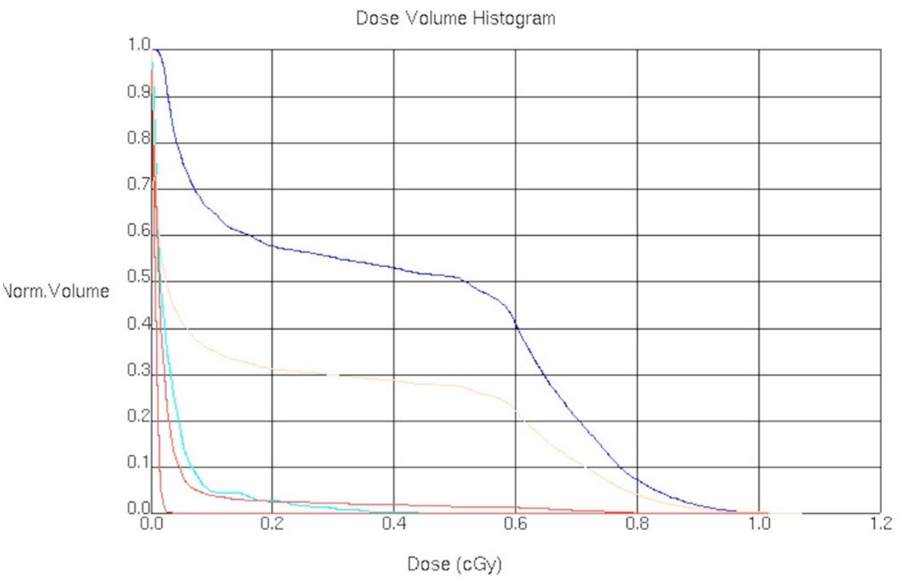
	Ipsilateral Lung Dmean Boost	***Ipsilateral Lung Dmean WBRT***	***Ipsilateral Lung Dmean Plan Sum***	***Ipsilateral lung V20Gy Boost***	***Ipsilateral Lung V20Gy WBRT***	***Ipsilateral Lung V20Gy Plan Sum***
MEAN	*1.3*	*8.1*	*9.4*	*0.0*	*13.7*	*14.8*
ST. DEV	*0.6*	*3.3*	*3.2*	*0.0*	*5.0*	*5.3*

	Contralateral Lung Dmean Boost	Contralateral Lung Dmean WBRT	Contralateral Lung Dmean Plan Sum	Contralateral Lung Dmax Boost	Contralateral Lung Dmax WBRT	Contralateral Lung Dmax Plan Sum
MEAN	*0.4*	*0.3*	*0.7*	*1.9*	*2.4*	*3.7*
ST. DEV	*0.1*	*0.3*	*0.3*	*0.7*	*0.9*	*1.1*

	Lungs V5Gy Boost	Lungs V5Gy WBRT	Lungs V5Gy Plan Sum
MEAN	2.4	13.7	17.8
ST. DEV	*2.1*	*5.0*	*6.2*

ST. DEV: Standard Deviation; WBRT: Whole Breast Radiotherapy

No statistically significant differences in Heart Dmean of PTV boost (p=0,14) were shown. Dose volume histograms for OARs ais shown Figure 3.



OARs: Organs at risk

Figure 3 – Dose Volumes Histograms for OARs

4. Discussion

This study analyzes the dosimetric data of adjuvant radiation treatment plans in patients with early stage BC, using hybrid plans delivered through a 3D-CRT plan for WBRT and a sequential VMAT plan for tumor bed boost.

The use of hybrid plans could allow us to improve the dose homogeneity without exceeding the low doses rates typical of WBRTs performed entirely with the IMRT / VMAT technique.

In addition, the delivery of the single boost with the VMAT technique proved to be really simple and fast, with excellent visualization and reproducibility of the target through daily cone beam computed tomography (CBCT).

A recent experience showed that whole breast IMRT and Hypofractionated VMAT RT are feasible and well tolerated in elderly patients affected by early-stage BC, also showing lower risks of acute and late RT-related side effects (28).

Several experiences have been published regarding RT treatments with IMRT-VMAT technique with simultaneous integrated boost (SIB) and Accelerated Partial Breast Irradiation (APBI) (28–31; 47). Further studies also compared sequential boost with simultaneous boost.

A significant reduction in the severity of acute radiation dermatitis in IMRT-SIB RT compared to 3D-CRT-SB was shown (32).

Preliminary data from the prospective IMRT-MC2 trial, reported a non-inferiority of IMRT-SIB versus 3D-CRT sequential boost with respect to cosmesis and LC at 2 years of follow up (33).

IMRT planning also has been shown to provide higher dose conformity and to assure shorter treatment duration, even though with a slightly higher planning maximum and increased lung doses (34).

Other experiences showed a significantly reduced surface dose with IMRT compared to 3D-CRT, in the adjuvant treatment of BC (35).

However, many authors have shown tangential fields RT approach delivered with modern techniques such as IMRT and tomotherapy could be an optimal modality especially for minimizing organs at risk (OAR) low-doses. Nissen et al have demonstrated as deep inspiration breath hold (DIBH) in conjunction with tangential-field, forward-planned IMRT treatment plans can lead to a significant reduction in heart and lung dose while optimizing PTV coverage (36). Other experience showed as tangential fields tomotherapy could result in better dose coverage and OARs constraints compliance compared to other RT modalities (37,38).

A recent experience from Joseph et al, recently showed that IMRT SIB does not seem to have any dosimetric advantage compared to field-in-field 3D-CRT (39). Significantly higher doses to contralateral lung and heart and radiation exposure in terms of Monitor Units were also shown in IMRT SIB treatments (39).

Limited benefits of IMRT have been shown in specific patients subsets, mainly in treatments with large boost planning tumor volume (PTV) and an overlap between heart and breast PTV (40).

Several authors have proposed hybrid plans with SIB to take advantages of both 3D technique and IMRT(41,42). Onal et al demonstrated that the D2, D98, and V107 values for PTV_{breast} and PTV_{boost}, and Homogeneity Index of PTV_{breast} with VMAT technology were higher with SB technique compared to the SIB technique (43).

In the frame of dosimetric analysis, an excellent target coverage and dose homogeneity is shown with mean values of PTV boost CI 95% 1.0 and media of CTV boost V95% 99.8%. Mean PTV boost V107% is always less than 5% except in 1 case where it is 5.1%.PTV boost V110% is always less than 1% and almost always is 0%. This high homogeneity of dose distribution is typical of IMRT / VMAT techniques.

As regarding to OARs, the dosimetric data show that the dose contribution of the boost plan is minimal and does not lead to large variations in the costraints used in clinical practice for treatment plan approvement.

In particular the difference of the heart V20 values between WBRT performed by 3D-CRT technique alone and the plan sum, is always less than 0.5% exception a case that is 1.4%; in most cases the difference is 0%.

Given the latest evidence in the article by Killander et al (26), where no correlation was found between cardiac toxicity and Dmean value inferior to 4 Gy, we have verified that the VMAT boost low doses did not go to affect the increase of this constraint.

We performed a subset analysis of patients with left BC and found no statistically significant differences between right and left side. The mean value of Heart Dmean was 1.0 Gy ± 0.7 SD and allowed not to exceed 3-4 Gy in the plan sum. Authors are aware of the limitations of this study such as the small simple size and the limited number of patients with internal quadrants for whom hearth doses could be increased.

In literature there are no studies investigating the use of hybrid plans with 3D-CRT plan with tangential fields for WBRT and with VMAT / IMRT plan for boosting the tumor bed. Balaji et al demonstated the feasibility of flattening filter-free (FFF) photon beams in hybrid volumetric modulated arc therapy (23). (41).

However, we have found studies that support the use of the VMAT technique for the boost (17,18). Most of the recent literature regarding BC tumor bed boost focuses on SIB studies in full IMRT/VMAT plans. (30,32,33,40,43–46). But some studies suggest that the low doses given by many fractions in IMRT / VMAT may not justify the use of this technique for the entire treatment (34,39).

5. Conclusion

This study aimed to demonstrate the very low impact of boost with VMAT technique on constraints and low doses, to suggest the use of hybrid plans that can avoid the low doses of many fractions with IMRT / VMAT technique but exploit their potential in few fractions of the boost.

Comparative dosimetric studies on this hybrid technique applied in different modalities of treatment and large-scale studies to evaluate clinical outcomes should be designed to address the potential benefit of hybrid treatments.

Abbreviations:
WBRT - whole breast radiation therapy
BC - breast cancer
VMAT - volumetric modulated arc therapy
OARs - organs at risk
3D-CRT - three-dimensional Conformal Radiotherapy
SB - sequential boost
CTV - clinical target volume
PTV - planning tumor volume
RT – radiotherapy
BT – brachytherapy
IMRT - intensity-modulated radiation therapy
AJCC - American Joint Committee on Cancer
UICC - Union for International Cancer Control
UOQ - upper outer quadrant
UIQ – LIQ - lower inner quadrants
CQ - central quadrant
CT - computed tomography
ESTRO - European Society for Radiotherapy and Oncology
ICRU - International Commission on Radiation Units and Measurements
CI - conformity index
CBCT - cone beam computed tomography
SIB - simultaneous integrated boost
APBI - accelerated partial breast irradiation
DIBH - deep inspiration breath hold

Statements:

Authors' contribution - AP: Conceptualization, Writing - Review & Editing; LB: Conceptualization, Supervision; A D'A: Writing - Original Draft, Writing - Review & Editing; AS: Investigation, Data Curation; SM: Investigation, Data Curation; MM: Writing - Review & Editing Supervisio; MS: Writing - Review & Editing; GP: Writing - Review & Editing; TA: Writing - Review & Editing; AD: Supervision.

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Ethics approval - The study was conducted according to the guidelines of the declaration of Helsinki. Patients enrolled signed a consent for data collection according to the study design requirements and also to department regulation.
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References

1. Gregucci F, Fozza A, Falivene S, Smaniotto D, Morra A, Daidone A, et al. Present clinical practice of breast cancer radiotherapy in Italy: a nationwide survey by the Italian Society of Radiotherapy and Clinical Oncology (AIRO) Breast Group. Radiol Med (Torino) 2020;125:674–82. https://doi.org/10.1007/s11547-020-01147-5.

2. Sedlmayer F, Sautter-Bihl M-L, Budach W, Dunst J, Fastner G, Feyer P, et al. DEGRO practical guidelines: radiotherapy of breast cancer I: radiotherapy following breast conserving therapy for invasive breast cancer. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2013;189:825–33. https://doi.org/10.1007/s00066-013-0437-8.

3. Smith BD, Bellon JR, Blitzblau R, Freedman G, Haffty B, Hahn C, et al. Radiation therapy for the whole breast: Executive summary of an American Society for Radiation Oncology (ASTRO) evidence-based guideline. Pract Radiat Oncol 2018;8:145–52. https://doi.org/10.1016/j.prro.2018.01.012.

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. 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 Lond Engl 2011;378:1707–16. https://doi.org/10.1016/S0140-6736(11)61629-2.

5. Valle LF, Agarwal S, Bickel KE, Herchek HA, Nalepinski DC, Kapadia NS. Hypofractionated whole breast radiotherapy in breast conservation for early-stage breast cancer: a systematic review and meta-analysis of randomized trials. Breast Cancer Res Treat 2017;162:409–17. https://doi.org/10.1007/s10549-017-4118-7.

6. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94. https://doi.org/10.1016/S1470-2045(13)70386-3.

7. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Lond Engl 2008;371:1098–107. https://doi.org/10.1016/S0140-6736(08)60348-7.

8. Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20. https://doi.org/10.1056/NEJMoa0906260.

9. Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial. J Clin Oncol Off J Am Soc Clin Oncol 2020;38:3615–25. https://doi.org/10.1200/JCO.20.01363.

10. Boyages J, Baker L. Evolution of radiotherapy techniques in breast conservation treatment. Gland Surg 2018;7:576–95. https://doi.org/10.21037/gs.2018.11.10.

11. Jalali R, Singh S, Budrukkar A. Techniques of tumour bed boost irradiation in breast conserving therapy: current evidence and suggested guidelines. Acta Oncol Stockh Swed 2007;46:879–92. https://doi.org/10.1080/02841860701441798.

12. Kindts I, Verhoeven K, Laenen A, Christiaens M, Janssen H, Van der Vorst A, et al. A comparison of a brachytherapy and an external beam radiotherapy boost in breast-conserving therapy for breast cancer: local and any recurrences. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2019;195:310–7. https://doi.org/10.1007/s00066-018-1413-0.

13. Toscas JI, Linero D, Rubio I, Hidalgo A, Arnalte R, Escudé L, et al. Boosting the tumor bed from deep-seated tumors in early-stage breast cancer: a planning study between electron, photon, and proton beams. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;96:192–8. https://doi.org/10.1016/j.radonc.2010.05.007.

14. Aghili M, Barzegartahamtan M, Alikhassi A, Mohammadpour R. Investigation of electron boost radiotherapy in patients with breast cancer: Is a direct electron field optimal? Cancer Radiother J Soc Francaise Radiother Oncol 2018;22:52–6. https://doi.org/10.1016/j.canrad.2017.08.109.

15. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol J Eur Soc Ther Radiol Oncol 2007;82:254–64. https://doi.org/10.1016/j.radonc.2006.12.008.

16. Haussmann J, Corradini S, Nestle-Kraemling C, Bölke E, Njanang FJD, Tamaskovics B, et al. Recent advances in radiotherapy of breast cancer. Radiat Oncol Lond Engl 2020;15. https://doi.org/10.1186/s13014-020-01501-x.

17. Alexander A, Soisson E, Hijal T, Sarfehnia A, Seuntjens J. Comparison of modulated electron radiotherapy to conventional electron boost irradiation and volumetric modulated photon arc therapy for treatment of tumour bed boost in breast cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2011;100:253–8. https://doi.org/10.1016/j.radonc.2011.05.081.

18. an Parijs H, Reynders T, Heuninckx K, Verellen D, Storme G, De Ridder M. Breast conserving treatment for breast cancer: dosimetric comparison of different non-invasive techniques for additional boost delivery. Radiat Oncol Lond Engl 2014;9:36. https://doi.org/10.1186/1748-717X-9-36.

19. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4. https://doi.org/10.1245/s10434-010-0985-4.

20. Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol J Eur Soc Ther Radiol Oncol 2015;114:3–10. https://doi.org/10.1016/j.radonc.2014.11.030.

21. ICRU Report 50, Prescribing, Recording, and Reporting Photon Beam Therapy – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-50/ (accessed June 10, 2022).

22. ICRU Report 62, Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU 50) – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-62/ (accessed June 10, 2022).

23. CRU Report 83, Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT) – ICRU n.d. https://www.icru.org/report/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrticru-report-83/ (accessed June 10, 2022).

24. Feuvret L, Noël G, Mazeron J-J, Bey P. Conformity index: a review. Int J Radiat Oncol Biol Phys 2006;64:333–42. https://doi.org/10.1016/j.ijrobp.2005.09.028.

25. Nielsen MH, Berg M, Pedersen AN, Andersen K, Glavicic V, Jakobsen EH, et al. Delineation of target volumes and organs at risk in adjuvant radiotherapy of early breast cancer: national guidelines and contouring atlas by the Danish Breast Cancer Cooperative Group. Acta Oncol Stockh Swed 2013;52:703–10. https://doi.org/10.3109/0284186X.2013.765064.

26. Killander F, Wieslander E, Karlsson P, Holmberg E, Lundstedt D, Holmberg L, et al. No Increased Cardiac Mortality or Morbidity of Radiation Therapy in Breast Cancer Patients After Breast-Conserving Surgery: 20-Year Follow-up of the Randomized SweBCGRT Trial. Int J Radiat Oncol Biol Phys 2020;107:701–9. https://doi.org/10.1016/j.ijrobp.2020.04.003.

27. Stovall M, Smith SA, Langholz BM, Boice JD, Shore RE, Andersson M, et al. Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study. Int J Radiat Oncol Biol Phys 2008;72:1021–30. https://doi.org/10.1016/j.ijrobp.2008.02.040.

28. Fiorentino A, Gregucci F, Mazzola R, Figlia V, Ricchetti F, Sicignano G, et al. Intensity-modulated radiotherapy and hypofractionated volumetric modulated arc therapy for elderly patients with breast cancer: comparison of acute and late toxicities. Radiol Med (Torino) 2019;124:309–14. https://doi.org/10.1007/s11547-018-0976-2.

29. sang Y, Ciurlionis L, Kirby AM, Locke I, Venables K, Yarnold JR, et al. Clinical impact of IMPORT HIGH trial (CRUK/06/003) on breast radiotherapy practices in the United Kingdom. Br J Radiol 2015;88. https://doi.org/10.1259/bjr.20150453.

30. Meng J, Huang W, Mei X, Yu X, Pan Z, Ma J, et al. Adjuvant breast inversely planned intensity-modulated radiotherapy with simultaneous integrated boost for early stage breast cancer : Results from a phase II trial. Strahlenther Onkol Organ Dtsch Rontgengesellschaft Al 2020. https://doi.org/10.1007/s00066-020-01611-1.

31. Cozzi L, Lohr F, Fogliata A, Franceschini D, De Rose F, Filippi AR, et al. Critical appraisal of the role of volumetric modulated arc therapy in the radiation therapy management of breast cancer. Radiat Oncol Lond Engl 2017;12. https://doi.org/10.1186/s13014-017-0935-4.

32. Lee H-H, Hou M-F, Chuang H-Y, Huang M-Y, Tsuei L-P, Chen F-M, et al. Intensity modulated radiotherapy with simultaneous integrated boost vs. conventional radiotherapy with sequential boost for breast cancer - A preliminary result. Breast Edinb Scotl 2015;24:656–60. https://doi.org/10.1016/j.breast.2015.08.002.

33. Hörner-Rieber J, Forster T, Hommertgen A, Haefner MF, Arians N, König L, et al. Intensity-modulated radiotherapy (IMRT) with simultaneously integrated boost shortens treatment time and is non-inferior to conventional radiotherapy 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 2020. https://doi.org/10.1016/j.ijrobp.2020.12.005.

34. Small K, Kelly C, Beldham-Collins R, Gebski V. Whole breast and excision cavity radiotherapy plan comparison: Conformal radiotherapy with sequential boost versus intensity-modulated radiation therapy with a simultaneously integrated boost. J Med Radiat Sci 2013;60:16–24. https://doi.org/10.1002/jmrs.4.

35. Rudat V, Nour A, Alaradi AA, Mohamed A, Altuwaijri S. In vivo surface dose measurement using GafChromic film dosimetry in breast cancer radiotherapy: comparison of 7-field IMRT, tangential IMRT and tangential 3D-CRT. Radiat Oncol Lond Engl 2014;9:156. https://doi.org/10.1186/1748-717X-9-156.

36. Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. Radiother Oncol 2013;106:28–32. https://doi.org/10.1016/j.radonc.2012.10.016.

37. Michalski A, Atyeo J, Cox J, Rinks M, Morgia M, Lamoury G. A dosimetric comparison of 3D-CRT, IMRT, and static tomotherapy with an SIB for large and small breast volumes. Med Dosim 2014;39:163–8. https://doi.org/10.1016/j.meddos.2013.12.003.

38. Meyer P, Niederst C, Scius M, Jarnet D, Dehaynin N, Gantier M, et al. Is the lack of respiratory gating prejudicial for left breast TomoDirect treatments? Phys Med 2016;32:644–50. https://doi.org/10.1016/j.ejmp.2016.04.001.

39. Joseph B, Farooq N, Kumar S, Vijay CR, Puthur KJ, Ramesh C, et al. Breast-conserving radiotherapy with simultaneous integrated boost; field-in-field three-dimensional conformal radiotherapy versus inverse intensity-modulated radiotherapy - A dosimetric comparison: Do we need intensity-modulated radiotherapy? South Asian J Cancer 2018;7:163–6. https://doi.org/10.4103/sajc.sajc_82_18.

40. van der Laan HP, Dolsma WV, Schilstra C, Korevaar EW, de Bock GH, Maduro JH, et al. Limited benefit of inversely optimised intensity modulation in breast conserving radiotherapy with simultaneously integrated boost. Radiother Oncol J Eur Soc Ther Radiol Oncol 2010;94:307–12. https://doi.org/10.1016/j.radonc.2010.01.024.

41. Balaji K, Balaji Subramanian S, Sathiya K, Thirunavukarasu M, Anu Radha C, Ramasubramanian V. Hybrid planning techniques for hypofractionated whole-breast irradiation using flattening filter-free beams. Strahlenther Onkol 2020;196:376–85. https://doi.org/10.1007/s00066-019-01555-1.

42. Lin J-F, Yeh D-C, Yeh H-L, Chang C-F, Lin J-C. Dosimetric comparison of hybrid volumetric-modulated arc therapy, volumetric-modulated arc therapy, and intensity-modulated radiation therapy for left-sided early breast cancer. Med Dosim Off J Am Assoc Med Dosim 2015;40:262–7. https://doi.org/10.1016/j.meddos.2015.05.003.

43. ONAL C, EFE E, GULER OC, YILDIRIM BA. Dosimetric Comparison of Sequential Versus Simultaneous-integrated Boost in Early-stage Breast Cancer Patients Treated With Breast-conserving Surgery. In Vivo 2019;33:2181–9. https://doi.org/10.21873/invivo.11720.

44. Aly MMOM, Abo-Madyan Y, Jahnke L, Wenz F, Glatting G. Comparison of breast sequential and simultaneous integrated boost using the biologically effective dose volume histogram (BEDVH). Radiat Oncol Lond Engl 2016;11:16. https://doi.org/10.1186/s13014-016-0590-1.

45. Van Parijs H, Reynders T, Heuninckx K, Verellen D, Storme G, De Ridder M. Breast conserving treatment for breast cancer: dosimetric comparison of sequential versus simultaneous integrated photon boost. BioMed Res Int 2014;2014:827475. https://doi.org/10.1155/2014/827475.

46. Xi D, Ding Y, Hu R, Gu W, Mu J-M, Li Q-L. Advantages of a technique using two 50 degree arcs in simultaneous integrated boost radiotherapy for left-sidebreast cancer. Sci Rep 2017. https://doi.org/10.1038/s41598-017-15307-7.

47. Piras A, Menna S, D'Aviero A, Marazzi F, Mazzini A, Cusumano D, Massaccesi M, Mattiucci GC, Daidone A, Valentini V, Boldrini L. New fractionations in breast cancer: a dosimetric study of 3D-CRT versus VMAT. https://doi.org/10.1002/jmrs.530