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Original Article

Unintended dose to the lower axilla in adjuvant radiotherapy for breast cancer: Differences between tangential beam and VMAT

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ABSTRACT

Background and purpose: To evaluate dosimetric differences in unintended dose to the lower axilla between 3D-standard (3DCRT), tangential beam forward intensity modulated radiotherapy (F-IMRT) and volumetric modulated arc therapy (VMAT). The objective is to evaluate whether results of clinical trials, such as the ACOSOG-Z011 trial, that evaluated omission of axillary clearance can be extrapolated towards more conformal techniques like VMAT.

Materials and methods: Twenty-five consecutive patients treated with whole breast radiotherapy alone (WBRT) using a F-IMRT technique were identified. Three additional plans were created for every patient: one plan using a single 270° arc (VMAT 1x270°), another using two small ≤90° opposing arcs (VMAT 2x < 90°) and thirdly a 3DCRT plan without F-IMRT. Axillary levels I-II were contoured after the treatment plans were made.

Results: The volume of the axilla level I that was covered by the 50% isodose (V50%) was significantly higher for VMAT 2x < 90° (71.3 cm^3, 84% of structure volume, $p < 0.001$) and VMAT 1x270° (68.8 cm^3, 81%, $p < 0.01$) compared to 3DCRT (60.3 cm^3, 71%) and F-IMRT (60.8 cm^3, 72%). The V50% to the axilla level II, however, was low for all techniques: 12.3 cm^3 (12%); 8.9 cm^3 (9%); 4.3 cm^3 (4%); 4.4 cm^3 (4%) for VMAT 2x < 90°, VMAT 1x270°, 3DCRT, F-IMRT, respectively. For the higher doses (V90% and above), no clinically relevant differences were seen between the different modalities.

Conclusion: WBRT treatments with VMAT do not lead to a significant reduction of the unintended axillary dose in comparison with a tangential beam setup. Hence, concerning tumor control, VMAT can be applied to clinical situations similar to the Z0011 trial. The intermediate axillary dose is higher with VMAT, but the clinical consequence of this difference on toxicity is unknown.

 Radiotherapy and Oncology 164 (2021) 282–288

Adjuvant radiation therapy after breast-conserving surgery (BCS) halves the relapse rate and reduces breast cancer death rate by about 8,5% [1]. The majority of clinical trials providing this evidence are based on two-dimensional radiotherapy (RT) techniques or three-dimensional conformal RT (3DCRT) techniques [2–5]. These techniques are based on a tangential technique with two opposed uniform photon beams and the use of wedges to create an homogenous dose distribution in the breast. Intensity modulated radiation therapy (IMRT) allows to improve both dose homogeneity and organ at risk sparing, representing a major shift in the practice of radiation therapy since the 1990s [6,7]. IMRT has taken many forms, such as static beam IMRT (as well forward as reversed planned, with step-and-shoot or sliding window) and volumetric-modulated arc therapy (VMAT). In our study we will focus on Forward IMRT (F-IMRT) and VMAT.

F-IMRT is the simplest form of IMRT using, just like 3DCRT, two opposed tangential fields but instead of wedges there are a few segments (i.e., sub-beams) per field, whose shape and weight are optimized to achieve a more homogenous dose distribution to the target. This tailored technique allows for a more homogeneous dose distribution within the breast than 3DCRT [8].

VMAT was introduced in clinical practice in 2008 [9] and since then VMAT is increasingly used in the adjuvant treatment of breast cancer, in particular when treating the internal mammary nodes [10] or in case of challenging anatomy such as a funnel chest [11]. Dosimetric studies have found that VMAT improves target coverage, lowers the dose to organs at risk and reduces treatment time in comparison to 3DCRT and F-IMRT [10–14].

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Axillary lymph node dissection (ALND) was the only standard treatment for patients with a positive sentinel lymph node but several randomized trials validated the omission of axillary clearance in patients with only one or two positive sentinel lymph nodes after BCS (the ACOSOG trial, the AATRM 48 and IBCSG 23-01 trial) [15–17]. Important is that all patients in these trials received adjuvant whole breast RT (WBRT) in supine position with tangential fields. Hence, the axilla was not intentionally irradiated but axillary levels I and II received unintentional radiation exposure through the tangential fields setup. It has been suggested that this unintended dose to the axilla may have contributed to the low rate of axillary recurrence when omitting axillary lymph node dissection [17–21].

The aim of this present study is to evaluate the dosimetric differences in unintentional dose to the lower axilla between 3DCRT, F-IMRT and VMAT. Ultimately, the goal is to estimate whether results of clinical trials omitting axillary clearance while treating patients with tangential fields can safely be extrapolated towards VMAT techniques.

Materials and methods

Simulation

Twenty-five consecutive patients treated with WBRT alone using a F-IMRT technique were identified in 2017. 18 patients (72%) had a left breast cancer and 7 patients (28%) a right breast cancer. Patients having locoregional irradiation as part of the target volume or a simultaneous integrated boost were excluded. 2 patients (8%) were Tis stage, 19 patients (76%) were T1 stage and 4 patients (16%) were T2 stage. A non-contrast enhanced planning CT scan was performed (5 mm axial slice thickness) in free-breathing (right breast cancer) or breath-hold (left breast cancer) using a Toshiba Aquillon LB CT-simulator. The patients were in supine position head first with both arms overhead.

Contouring and planning

The breast was contoured according to the ESTRO contouring guidelines [22]. To generate the planning target volume (PTV) the breast was expanded by 5 mm in all directions, and then 3 mm of skin was cropped from the surface of the body. The organs at risk included the heart, the ipsilateral and contralateral lung, the contralateral breast and the humeral head. The target volumes and the organs at risk were contoured by the same radiation oncologist and according to institutional guidelines.

The prescribed dose to the whole breast was 40 Gy in 15 fractions, 5 days per week, normalized to the D50 (dose received by 50% of the PTV) according to ICRU 83 guidelines [23]. To provide comparable results among patients only the dose to the lymph node levels arising from the whole-breast treatment was analyzed (and thus ignoring the boost plan).

Subsequently, one 3DCRT plan and two VMAT plans were created for every patient: one VMAT plan using a single 270° arc (VMAT 1x270°) and another using two smaller (≤90°) opposing arcs mimicking the tangential fields setup (VMAT 2x < 90°). For VMAT plans, the treatment planning system used was Monaco 5.0 (Elekta AB, Stockholm, Sweden), the dose calculations were performed using a Monte Carlo algorithm and the GRID was 0.3 cm. All plans were made using 6MV photons. The treatment machine was an Elekta Infinity linear accelerator. The deliverability of the VMAT plans was not formally assessed, however standard procedures for creating breast VMAT plans in daily clinic were followed to create the plans.

For the 3DCRT and the F-IMRT plans, the treatment planning system used was Eclipse 10.0 (Varian Medical Systems, Palo Alto, CA, USA), the dose calculations were performed using the anisotropic analytical algorithm (AAA) and the GRID was 0.25 cm. All plans were made using 6MV photons. The treatment machine was a Clinac 2100. Examples of field and arc setups are provided in Fig. 1.

The planning goal was to obtain PTV Breast doses between 95% and 105% of the prescription dose and to respect dose volume constraints for the organs at risk. Ranking of objectives was 1) PTV Breast coverage followed by dose volume constraints for the 2) heart (Dmean < 4 Gy), 3) the ipsilateral lung (V17Gy < 20%), 4) the contralateral lung (Dmean < 4 Gy), 5) the contralateral breast (Dmean < 3.5 Gy) and 6) the humeral head (V30Gy < 2%). A single operator performed the optimization and manual interaction was allowed.

After all treatment plans were completed, the axillary levels I-II were contoured, using the ESTRO contouring guidelines [22]. The person that made the plans subsequently never saw the contours of level I-II and could thus not be influenced by these contours during planning. A mean dose-volume histogram (mean DVH) of all plans was constructed. For axillary levels I and II mean doses, median doses, and dose volumes receiving 20 Gy (V50%, this is the volume receiving 50% of prescription dose) and 36 Gy (V90%), were calculated.

The Radiotherapy Treatment plannINg study Guidelines (RATING) score [24] was 98%, details on the calculation of the RATING score are made available in the supplementary materials.

Statistical analysis

Pairwise comparisons were done using paired student t-tests if normally distributed. If not, non-parametric testing was performed with Wilcoxon rank-sum test. Repeated Measures ANOVA was used to compare 3 or 4 plans, unless when non-normally distributed, the Friedman rank-sum test was used. The R language (version 3.6) was used for all statistical analyses [25]. The mean DVH plots were created using the R package 'RadOnc' (Analytical Tools for Radiation Oncology), version 1.1.5. Confidence intervals and standard estimation of the mean were calculated and plotted using the R package 'plotrix' version 3.7-4.

The study was approved by the ethical committee of the Jules Bordet Institute. Patients have access to their clinical data on written request.

Results

The median age of the patients was 52 years (range: 24–70 years). 21 Patients (84%) have an invasive ductal carcinoma, 2 patients (8%) have a ductal carcinoma in situ and 2 patients (8%) have a mucinous carcinoma. Clinical and pathological characteristics of patients are shown in Table 1. The dose received by 50% of the PTV breast (D50%) is similar in the four treatment techniques: 40.1 Gy. There is no significant difference in the dose received by 90% of the PTV breast (D90%): 39.2 Gy (±0.03), 39.1 Gy (±0.03), 38.6 Gy (±0.1) and 38.7 Gy (±0.1) for VMAT 2x < 90°, VMAT 1x270°, 3DCRT and F-IMRT, respectively.

For axillary level I, the V20Gy was significantly higher for VMAT 2x < 90°: 71.3 cm^3; 84.1% of structure volume ($p < 0.001$) and VMAT 1x270°: 68.8 cm^3; 81.1% ($p < 0.01$) in comparison with F-IMRT: 60.8 cm^3; 71.7% and 3DCRT: 60.3 cm^3; 71.1%. There is a small but significant difference between the two VMAT techniques ($p < 0.05$) with a higher V20Gy for VMAT 2x < 90°. No significant difference between F-IMRT and 3DCRT was found. Conversely, the V36Gy was significantly ($p < 0.001$) higher for F-IMRT: 47.9 cm^3; 56.5% and 3DCRT: 46.6 cm^3; 55% than for VMAT 1x270°: 35.2 cm^3; 41.5%; without a significant difference between the tangential field techniques and VMAT 2x < 90°. When

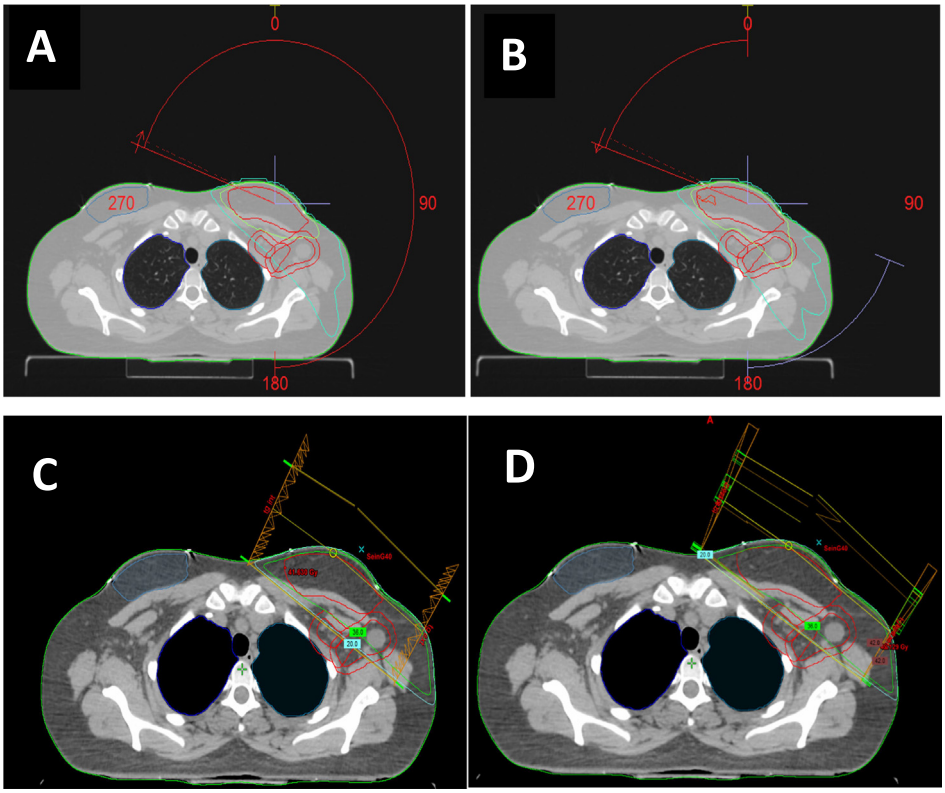

Fig. 1. Field and arc setup in the different treatment techniques: (A) VMAT 1x270°, (B) VMAT 2x < 90°, (C) Tangential field setup for F-IMRT, (D) 3DCRT. PTV Breast, Level I, level II are indicated by the red area. Isodose lines are represented: the green line indicates the 36 Gy isodose and the cyan line indicates the 20 Gy isodose. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article).

Table 1
Patients characteristics.

		Number (n = 25)	Percent (%)
Age (years)	Median	52	
	Range	24–70	
T stage	T1	19	76
	T2	4	16
	Tis	2	8
Laterality	Right	7	28
	Left	18	72
Pathology	Invasive Ductal carcinoma	21	84
	Mucinous carcinoma	2	8
	Ductal carcinoma in situ	2	8
ER/PR/HER2 status	ER/PR positive	22	88
	ER/PR negative	3	12
	HER2 positive	8	32
	HER2 negative	17	68

comparing VMAT 1x270° and VMAT 2x < 90°, the difference was also significant (p < 0.001) with a higher V36Gy for VMAT 2x 90°: 42.6 cm^3; 50.3%.

There is no significant difference in the D50% (dose received by 50% of the volume) between the four different techniques (p = 0.85): 36.6 Gy (91.5%), 34.9 Gy (87.3%),37.2 Gy (93%), 37.6 Gy (94%) for VMAT 2x < 90°, VMAT 1x270°, 3DCRT and F-IMRT, respectively.

For axillary level II, the V20Gy was significantly (p < 0.01) higher for VMAT 2x < 90°: 12.3 cm^3; 12.3% than for F-IMRT: 4.4 cm^3; 4.4% and 3DCRT: 4.3 cm^3; 4.3%. The V20Gy of VMAT 1x270° was 8.9 cm^3 (8.9%).The V36Gy was 0.1 cm^3 (0.1%), 0 cm^3 (0%), 0.2 cm^3 (0.2%) and 0.8 cm^3 (0.8%) for VMAT 2x < 90°, VMAT 1x270°, 3DCRT and F-IMRT, respectively.

All mean DVHs are depicted in Fig. 2. Numerical and statistical values can be found in Fig. 3 and Table 2.

Discussion

Several trials justified the omission of ALND in patients with one or two positive SN after BCS. The Z0011 trial demonstrated the axillary recurrence rate after sentinel lymph node dissection (SLND) to be less than 1% with a median follow-up of 9.3 years, lower than the previously estimated 10% [26]. At ten years, the cumulative incidence of nodal recurrences was 1.5% in the SLND arm and 0.5% in the ALND arm. Ten-year cumulative locoregional recurrence was 5.3% with SLND and 6.2% with ALND [27].

Several factors can affect local control rates of sentinel-positive breast cancer in case of omission of ALND. Adjuvant systemic treatment, hormonal treatment and RT can play a role in explaining these results. To provide an explanation for the role of RT, it has been suggested that unintentional coverage of axillary levels I and II by tangential fields might play a key role in preventing axillary relapse in case of omission of ALND [17]. The Z0011 protocol [17] required all patients to receive WBRT in supine position using standard tangential fields, this setup will always cause unintended dose to the lower axilla. The use of a third field (nodal treatment) was also prohibited. Jagsi et al. [28] performed a revision of the RT fields used in the Z0011 trial and demonstrated that 15 percent of the patients were treated with a third field, contrary to protocol requirements. Eleven percent of the patients did not receive RT at all. In addition, half of patients treated in both arms, received high tangents (defined as the superior border of the tangential field being within 2 cm of the humeral head), leading to a greater volume of incidental axillary irradiation. Reznik et al. suggested the proportion of level I receiving 95% of the prescribed dose (V95%)

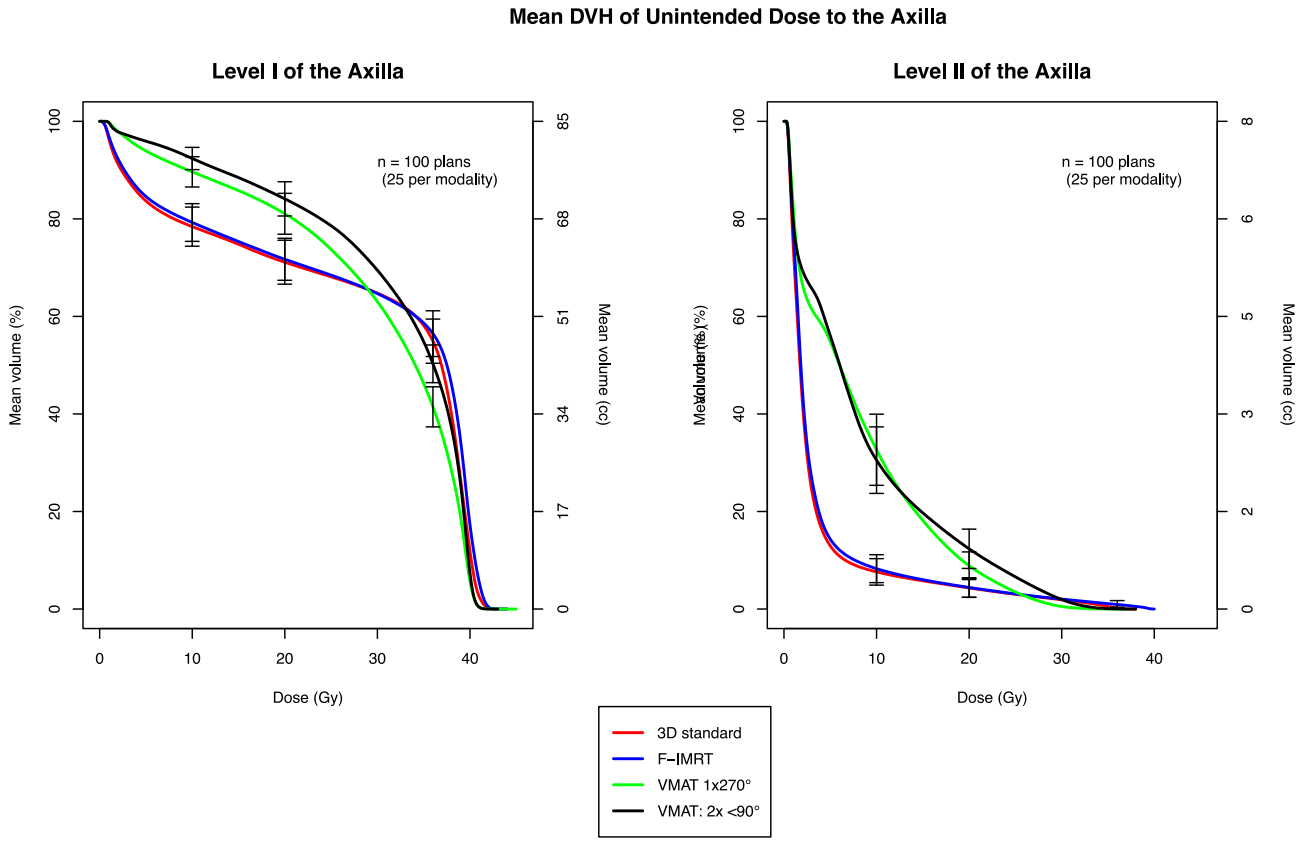

Fig. 2. Mean DVH of Unintended dose to the Axilla. Abbreviations: F-IMRT, Forward IMRT; VMAT, Volumetric arc therapy. VMAT 1x270° is a treatment plan with a single 270° arc whereas VMAT 2x < 90° is a treatment plan with two small opposing arcs. Brackets indicate the standard deviation of the mean.

Table 2
Comparison of V20Gy, V36Gy, D50%, Dmean and Dmedian in Axilla level I and II. *Abbreviations*: 3DCRT, 3D-standard; F-IMRT, Forward IMRT; VMAT, Volumetric arc therapy; V20Gy: volume receiving 20 Gy; V36Gy: volume receiving 36 Gy; D50%: dose received by 50% of the volume; Dmedian: median dose; Dmean: mean dose.

	3DCRT		F-IMRT		VMAT 2x90°		VMAT 1x270°	
	Axilla I	Axilla II	Axilla I	Axilla II	Axilla I	Axilla II	Axilla I	Axilla II
V20Gy, in cm^3	60.3 cm^3	4.3 cm^3	60.8 cm^3	4.4 cm^3	71.3 cm^3	12.3 cm^3	68.8 cm^3	8.9 cm^3
(% of volume)	(71.1%)	(4.3%)	(71.7%)	(4.4%)	(84.1%)	(12.3%)	(81.1%)	(8.9%)
V36Gy, in cm^3	46.6 cm^3	0.2 cm^3	47.9 cm^3	0.8 cm^3	42.6 cm^3	0.1 cm^3	35.2 cm^3	0 cm^3
(% of volume)	(55%)	(0.2%)	(56.5%)	(0.8%)	(50.3%)	(0.1%)	(41.5%)	(0%)
Dmean, in Gy	31.1Gy	2.1Gy	29.2Gy	2.4Gy	34Gy	7.6Gy	31.8Gy	6.6Gy
(% of prescription dose)	(77.8%)	(5.3%)	(73%)	(6%)	(85%)	(19%)	(79.5%)	(16.5%)
Dmedian, in Gy	37.2Gy	1.7Gy	37.6Gy	1.7Gy	36.6Gy	6.2Gy	34.9Gy	5.9Gy
(% of prescription dose)	(93%)	(4.3%)	(94%)	(4.3%)	(91.5%)	(15.5%)	(87.3%)	(14.8%)

to increase from 51% with standard tangents to 79% with high tangents, and the level II V95% increases from 26% to 51% [29].

Borm et al. estimated the dose distribution to the lymph nodes in different trials (MA.20, EORTC trial 10981-22023, AMAROS and Z0011) according to CTV volumes contoured following the ESTRO guidelines) [30]. The estimation was done by reproducing in silico the treatment techniques used for each trial on three template patients (standard, obese and slender patients). The Z0011 and the EORTC 10981-22023 treatment plans did not intentionally include the axillary levels I and II as target volumes. Correspondingly the axillary doses were lower compared to the AMAROS and MA.20 trial which included all the axillary levels and the internal mammary nodes. The authors conclude that the extent of incidental irradiation depended on the upper field border (high tangents vs. standard tangents) as well as patient body shape. For the high tangents a similar dose distribution compared to the AMAROS treatment plan was found in axillary level I and II, hence supporting earlier assumptions that radiation therapy may have accounted for the favorable results after SLND alone in the Z0011 trial.

In our study, constraints or targets to the axilla were intentionally not imposed to be able to measure the unbiased unintended dose. The axilla was hence not a target volume nor an organ at risk and was thus not taken into account during creation of the treatment plan. The main reason for this choice is that we wished to replicate the same conditions as used in the Z0011 study with 3D-CRT, in which the axilla was also not a clearly defined target nor an organ at risk. If we had imposed a constraint to the axilla to create the VMAT plans, the axillary dose would probably be less than the axillary dose of 3D-CRT and F-IMRT because of the more conformal nature of VMAT. However, this might come at the expense of a higher lung dose and a reduction of the incidental axillary irradiation may have a negative impact on axillary recurrence because it has been suggested that unintended axilla dose

from tangential fields may play a role in controlling axillary occult disease. On the other hand, if an axillary target dose was used when creating the VMAT plans, the axilla would be well covered in comparison to 3D-CRT and F-IMRT. However, the dose to the axilla might have been too high, as suggested by the study of Borm et al. that argue that treating the complete axilla using extensive target volumes is probably not necessary for all patients to reproduce the clinical benefit shown in randomized trials such as the Z0011 study [30].

Our study found no significant difference between 3DCRT and F-IMRT for the unintended dose to the axilla (level I and II), which can be explained by the fact that 3DCRT and F-IMRT use the same gantry angles and a tangential field setup. For level I of the axilla, VMAT yielded higher intermediate doses than 3DCRT and F-IMRT whereas the high dose is comparable between all techniques. Strictly statistically speaking we did find a high dose (V36Gy) that was significantly higher for F-IMRT and 3DCRT than for VMAT 1x270°. When comparing VMAT 1x270° and VMAT 2x < 90°, the difference was significant ($p < 0.001$) with a higher V36Gy for VMAT 2x 90°. However, these results are difficult to interpret because when comparing dose volume histogram (DVHs), one should also consider the uncertainty on the dose, especially when comparing volumes on a steep portion of a DVH (Fig. 2). This uncertainty on the dose causes a DVH shifting that will have a great impact on the V36Gy. This effect leads to more important differences between the different techniques than a calculated difference in DVH dose point such as the V36Gy. Therefore, the differences measured at a precise point (36 Gy) are not interpretable. This can be quantified by comparing the D50% (dose received by 50% of the volume): there is no significant difference in the D50% between the four different techniques.

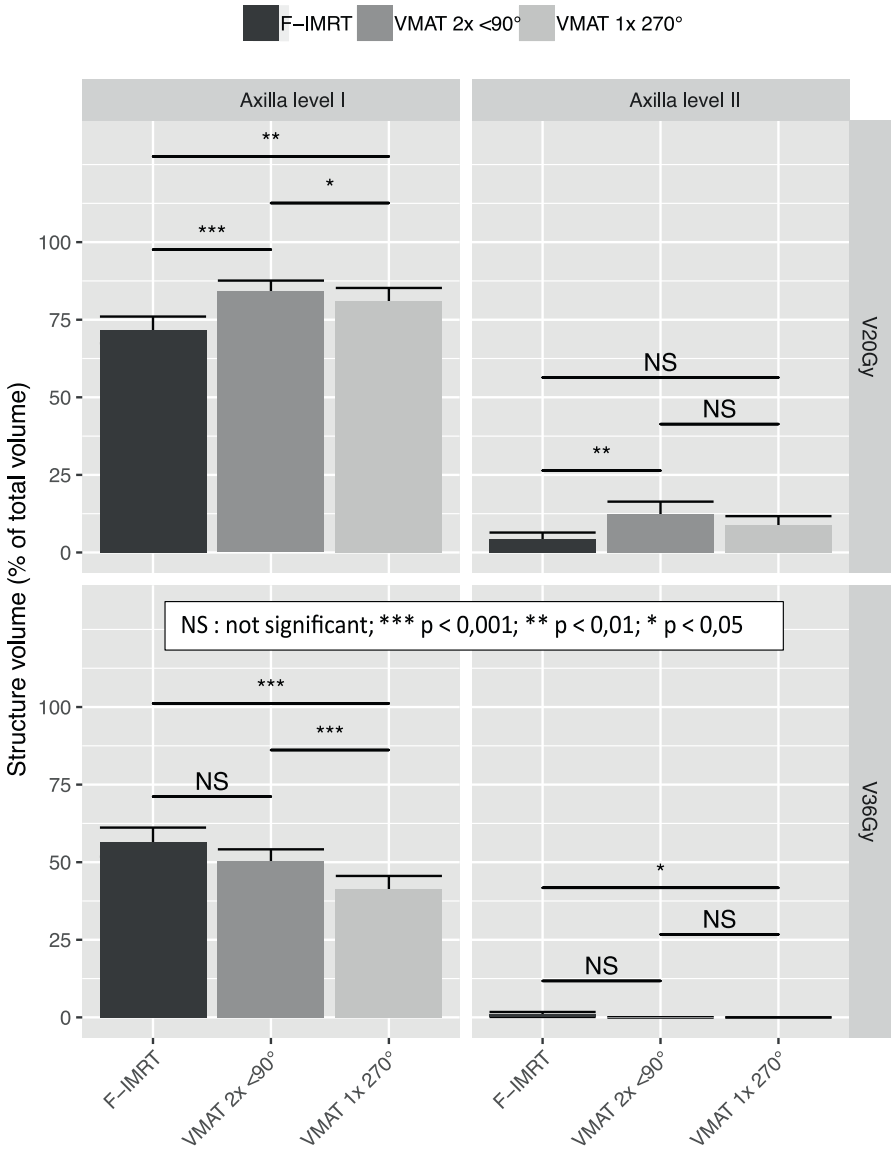

Fig. 3. Comparison of unintended axillary dose V20Gy and V36Gy to the axilla level 1 and 2 between the 3 different treatment techniques. VMAT 1x270° is a treatment plan with a single 270° arc whereas VMAT 2x < 90° is a treatment plan with two small opposing arcs. *Abbreviations*: F-IMRT, Forward IMRT; VMAT, Volumetric arc therapy; V20Gy: volume receiving 20 Gy; V36Gy: volume receiving 36 Gy. Statistical tests used: Paired Student T test when normally distributed; if not normally distributed: Wilcoxon rank-sum test. Note: 3D-standard is not mentioned in this figure because the results are comparable to Forward IMRT.

Our intermediate dose volume on level I is significantly higher with VMAT than with tangential fields. This finding might have clinical implications on tumor control, toxicity, and secondary cancers. The radiation dose necessary to eliminate subclinical disease remains subject of debate [31,32]. The prevailing consensus states that the dose necessary for radiation therapy to eradicate microscopic disease is approximately 45–50 Gy in 2 Gy per fraction [32]. However, it is unclear whether the low to intermediate dose (0–20 Gy) to the axilla influences local control rates given the limited evidence for a dose–response relationship for these doses. Lymphoedema after breast cancer treatment has a negative impact on quality of life and is the most reported complication. Axillary surgery increases the risk for lymphedema, with the highest risk (greater than 25% at 5 years) occurring in those receiving a combination of ALND with nodal radiation and/or chemotherapy. The introduction of the SN procedure and the frequent omitting of the ALND decreased the risk of lymphedema [33]. Warren et al. demonstrated that lymph nodes irradiation significantly increased the risk of lymphoedema compared to breast/chest wall radiation alone [34]. But it remains to be seen whether this higher intermediate dose with VMAT will lead to significant increasing risk of lymphoedema.

Zhang et al. compared multibeam IMRT (five to seven beams) with F-IMRT (two opposite beams with the fields-in-fields techniques) and found that unintended dose to axilla (Dmean, V40Gy, V45Gy) was lower for IMRT than F-IMRT [35]. In our study we did not examine multibeam IMRT, however it is expected that the axillary dose is reduced if less dose is given in a tangential way. Jo et al. compared the incidental axillary dose (level I-III) between 3DCRT and VMAT [36]. The mean dose and the V40Gy were significantly reduced at all axillary levels with VMAT. Jo et al., however, utilized a different VMAT technique than our study: two arcs, clockwise and counterclockwise, from 290 to 145° and they did not use the ESTRO guidelines to contour the axilla. The different technique, contouring and the use of different optimization parameter could explain the difference in unintended axillary dose.

The irradiated volumes of level II were lower in our study than in the published literature and were so small that differences between techniques became clinically insignificant. Aguiar et al. [37] evaluated axillary dose coverage according to breast volume and shape. They observed inadequate dose coverage to all axillary levels even after applying a sub analysis accounting for different breast volumes and shapes. Their mean doses were 43.9 Gy in level I, and 38.6 Gy in level II (prescribed dose of 50 Gy), compared to our study with mean doses of 31.1 Gy in level I and 2.1 Gy in level II (3DCRT technique). Krasin et al. [38] demonstrated WBRT using standard tangential fields not to fully cover the axilla. Mean doses were 32 Gy in level I and 26.5 Gy in level II. These differences of axillary level II coverage during tangential breast RT might be related to variations of level I-II contouring. In our study, we used the ESTRO guidelines [22] whereas Kraisin et al. used the ICRU 50 recommendations, Aguiar et al. the Radiation Therapy Oncology Group guidelines. Another hypothesis might be a difference in tangents height as already discussed earlier. The use of CTV or PTV to evaluate the dose might be another explanation, we evaluated the dose on the CTV.

A possible drawback of the VMAT technique is the "low dose bath" which may increase the risk of secondary carcinoma [39]. The exact mechanism of radiation-induced second cancer is unknown. Therefore, the role of the low dose bath in the carcinogenesis is unclear. RT contributes to only about 5% of the total treatment related second malignancies however more than 50% of all cancer-patients need RT at some point of the time [40].The recent study of Quanbin et al. [41] estimates the radiation-related secondary cancer risks in organs during the treatment of breast cancer with different radiotherapy techniques, such as 3DCRT, IMRT and VMAT. Secondary cancer risks were the highest for VMAT. In a meta-analysis by Grantzau et al. [42], RT for breast cancer significantly increased the risk of second non breast cancers with a RR of 1.22 (95% CI, 1.06–1.41). VMAT regroups different techniques to minimize the low dose bath: VMAT 2x90° mimic tangential fields setup thereby possibly reducing ipsilateral organs at risk and contralateral structures [43,44]. Hybrid-VMAT is a combination of traditional conformal tangential RT and VMAT [45]. Several dosimetric studies compared the use of hybrid VMAT and VMAT 2x90° for left-sided breast cancer. It appears that hybrid VMAT provides better dose homogeneity and conformity and delivers less dose to the ipsilateral lung and heart than VMAT 2x90° [45].

A limitation of our study is that we did not investigate the axillary dose contribution of the boost. This choice was made to avoid bias by the variation of the localization of the boost across patients. Hence, only the dose to the lymph node levels arising from the whole-breast treatment was taking into consideration. A VMAT boost, by its more conformal nature, might deliver a lower unintended axillary dose than a boost given by using tangential fields.

In conclusion, the high dose unintended coverage of the axilla is comparable between VMAT and tangential fields whereas the intermediate dose coverage is higher with VMAT. Given these findings, VMAT is probably a safe alternative to tangential fields concerning tumor control by unintended axillary dose and VMAT could thus be applied to clinical situations similar to patients included in the Z0011 trail. However, further research on the impact of this difference regarding toxicity and secondary cancers is warranted.

Conflicts of interest

None.

Acknowledgment

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.10.005.

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