**Late effects arising from volumetric modulated arc therapy to the breast:**

**A systematic review**

**Abstract**

**Introduction**

Volumetric modulated arc therapy (VMAT) to the breast offers the potential for excellent dose conformity with the possibility of integrating a simultaneous boost within the treatment plan. This technique, however, also delivers a low dose to a large amount of healthy tissue. This systematic review aimed to determine if VMAT offers a clinically significant difference in late effects compared with conformal radiotherapy techniques for breast radiotherapy.

**Methods**

A systematic review and quality appraisal of primary studies evaluating VMAT to the breast was performed, adopting the PRISMA checklist.

**Results**

A total of 8 studies were included in the review. These demonstrated variation in prescription, outcome measures and cohort characteristics. Findings supported the value of VMAT for reducing organ at risk (OAR) doses but also confirmed the potential secondary cancer risk arising from the low dose bath. Hybrid techniques combining VMAT with tangential intensity modulated or standard radiotherapy showed promise when tangential plans failed to meet objectives.

**Conclusion**

VMAT alone does not offer any significant benefit to late effects over conventional for breast radiotherapy due to the creation of a low dose bath, despite improving OAR doses. More research into hybrid techniques is warranted to identify the most appropriate treatment for different patient subgroups and tumour locations.

**Implications for Practice**

VMAT may not be the optimal technique for breast radiotherapy; hybrid plans combining tangential IMRT with VMAT are recommended.

# **Introduction**

Breast cancer treatments form a major component of the daily radiotherapy department workload1 but present a range of challenges related to the inconsistency in breast shape as well as respiratory and cardiac motion.2 The treatment volume is within close proximity to a variety of organs at risk (OAR)s, such as the heart, lungs and contralateral breast, so planning and treatment requires great care to reduce the incidence of radiation-induced cardiomyopathy, carotid artery stenosis and chronic pericardial disease.3

Volumetric modulated arc therapy (VMAT) is a dynamic form of intensity modulated radiotherapy (IMRT),4 delivered as the gantry rotates through 1 or more arcs. It is capable of creating highly conformal dose distributions, while requiring fewer monitor units and reducing treatment times.5 Understandably there is increasing interest in using VMAT for breast radiotherapy where it offers excellent dose conformity, along with the potential to integrate a boost within the treatment delivery.2 This technique also possesses potential disadvantages; uppermost of these is the low dose bath (LDB), where a large amount of healthy tissue receives very low doses of radiation.Although these doses are too low to cause acute effects, they do increase the incidence of stochastic effects such as secondary cancer induction.2

This review aimed to determine if there is a clinically significant difference in the late effects and secondary cancer induction when using VMAT compared with other techniques for breast cancer treatment.

**Method**

A systematic review was adopted for this study, guided by the Preferred Reporting Items for Systematic Reviews and Meta‐Analyses (PRISMA) checklist6 for design and reporting. This type of review is frequently used to build upon the existing knowledge base to guide the development of healthcare practice.7

A search was performed across the Medline and Scopus databases using the “participants”, “intervention”, “comparison”, “outcome” (PICO) framework8 to define the search terms shown in Table 1. Boolean combinations of search terms were used to ensure all relevant articles were located. Additional hand searches of relevant journals were conducted, and reference lists were scanned for additional evidence.

**Table 1: The PICO framework and keywords utilised**

|  |  |  |  |
| --- | --- | --- | --- |
| **Participants** | **Intervention** | **Comparison** | **Outcomes** |
| Breast cancerBreast neoplasmBreast carcinomaBreast tumourBreast tumor | Volumetric modulated arc therapyVMATRapidArc | Conformal radiotherapy3D-CRT | RiskPTV doseOAR doseLow dose bath |

When the search had been conducted the results required filtering; according to the inclusion and exclusion criteria shown in Table 2. Manual screening of the titles and abstracts eliminated all duplicates and irrelevant papers from the search as seen in Figure 1. Then, full-text articles were read to further filter the search and eliminate inappropriate papers. The screened papers were then subjected to critical appraisal using the well-validated Critical Appraisal Skills Programme (CASP) checklists9 to assess the quality and relevance of the papers. Papers scoring low with the CASP checklists were rejected and not included in the review.

**Table 2: Inclusion and exclusion criteria**

|  |  |
| --- | --- |
| **Inclusion Criteria** | **Exclusion Criteria** |
| All papers must be written in English. | Qualitative studies |
| Primary sources of data | Duplicated papers  |
| Research conducted from 2007 onwards | Editorials / opinion pieces |

**Figure 1: PRISMA flow diagram demonstrating paper selection**

##

**Results**

A total of 8 papers were used within the systematic review; their key characteristics are summarised in Table 3. There was considerable variability in the reported papers in terms of reported outcome measures, tumour laterality and modalities compared. All the papers reported similar outcomes in terms of PTV coverage but considerable variation in OAR doses; these are summarized in Table 4 and form the basis for later discussion. Comparative doses stated in Table 4 show the difference in dose between two modalities (for example “VMAT-FIF” columns show the dose arising from a FIF plan subtracted from that for a VMAT plan).

**Table 3: Summary of included papers**

|  |  |  |
| --- | --- | --- |
| **Paper** | **Design** | **Cohort** |
| Fogliata 201810 | Single centre prospective planning study comparing excess absolute risk between “Field-in-field “(FIF) and VMAT | 20 left sided at deep inspiration breath-hold (DIBH) |
| Xu et al 201611 | Single centre prospective planning study comparing dosimetry of FIF and VMAT plans | 22 left sided chest wall node positive |
| Pasler 201312 | Single centre prospective planning study comparing dosimetry of VMAT with IMRT | 10 large breast volumes |
| Jin 201313 | Single centre prospective planning study comparing dosimetry of VMAT, Hybrid, conformal radiotherapy (CRT) and IMRT | 20 left sided small breast volumes |
| Corradini 201714 | Single centre retrospective dosimetric comparison of CRT and VMAT  | 10 left sided early-stage  |
| Abo-Madyan 201415 | Single centre retrospective dosimetric comparison of CRT, tangential IMRT and VMAT | 10 (5 left and 5 right) |
| Dumane 201816 | Single centre retrospective dosimetric comparison of hybrid VMAT + CRT with VMAT alone | 10 (6 VMAT and 4 hybrid) |
| Jöst 201517 | Single centre retrospective dosimetric comparison of FIF vs Hybrid (IMRT tangential + VMAT) | 20 (10 left and 10 right)No nodal involvement |

# **Table 4: Comparative Organ at Risk (O) Doses**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **OAR** | **Outcome** | **VMAT –FIF10** | **VMAT – FIF11** | **VMAT – IMRT12** | **VMAT – IMRT13** | **VMAT – CRT14** | **VMAT – CRT15** | **VMAT-HY16** | **HY-CRT17** |
| Heart | Dmean | 0.3Gy |  | 0.3Gy | 2.4Gy | 0.96Gy |  | 1Gy | -0.7Gy |
|  | D2% |  |  | -3.6Gy |  |  |  |  |  |
|  | V5Gy |  | 13% | 3.8% | 19.8% |  |  | -1.2% | -6.5% |
|  | V10Gy |  |  |  | 3.4% |  |  |  | -1.2% |
|  | V20Gy |  |  | 3.9% | 0.5% |  |  |  |  |
|  | V25Gy |  |  |  |  |  |  | 0.1% | -0.9% |
|  | V30Gy |  |  | -1.5% | -0.1% |  |  |  |  |
|  | V40Gy |  |  |  | -0.2% |  |  |  |  |
| LADCA | Dmean | -2.3Gy |  |  | 2.1Gy |  |  |  |  |
| L (IP) | Dmean | -1Gy |  | 0 | 3.3Gy |  | 2.5Gy | -1.1Gy | -1.4Gy |
|  | D2% |  |  | -3.6Gy |  |  |  |  |  |
|  | V5Gy |  | 32.1% |  | 26.9% |  |  | -0.6% | -5.5% |
|  | V10Gy |  |  |  | 12.2% |  |  | -2.3% | -3.5% |
|  | V20Gy |  | -12.3% | 2.9% | 3.5% |  |  | -3.1% | -2.4% |
|  | V30Gy |  |  | -1.5% | 0.7% |  |  |  |  |
|  | V40Gy |  |  |  | -1.2% |  |  |  |  |
| L (CN) | Dmean | 0.03Gy |  | -0.3Gy |  |  | 1.6Gy | 0.4Gy | 0 |
|  | D2% |  |  | 1.6Gy |  |  |  |  | -1Gy |
|  | V5Gy |  | 15.8% | 2.8% |  |  |  | 8.5% |  |
|  | V10Gy |  |  | -1.4% |  |  |  | 2.1% |  |
| B (CN) | Dmean | 0.2Gy |  | 0 | 1.5Gy |  | 1.3Gy | 0.1Gy |  |
|  | D2% |  |  | -0.2Gy |  |  |  |  |  |
|  | V5Gy |  | 12.1% |  | 4% |  |  |  |  |
| NT | Dmean |  |  |  |  |  |  |  | -0.3Gy |
|  | D2% |  |  |  |  |  |  |  | -5.1Gy |
|  | V5Gy |  |  |  |  |  |  |  | -1.4% |
|  | V10Gy |  |  |  |  |  |  |  | -0.8% |
| Skin | Dmean | -3.1Gy |  |  |  |  |  |  |  |

Key: HY = Hybrid VMAT and Tangential IMRT; CRT = Conformal Radiotherapy; FIF = Field in Field IMRT; LADCA = Left Anterior Descending Coronary Artery; L (IP) = Ipsilateral lung; L (CN) = Contralateral lung; B (CN) = Contralateral breast; NT – Normal Tissue

**Discussion**

In general VMAT produced higher OAR doses than FIF, IMRT and CRT techniques. This was more dramatic for the low dose constraints than the higher ones where VMAT tended to outperform other techniques by limiting volumes receiving high doses. The V5Gy contralateral lung dose exhibited the greatest impact of this with VMAT producing over 25% more dose than the other techniques. The influence of the planner and choice of optimisation constraints and weighting must be acknowledged, but the high volumes receiving low doses associated with VMAT are associated with the unavoidable low dose bath (LDB). The authors of two studies agreed that VMAT plans should be used as an alternative treatment technique when CRT is unable to meet planning constraints.10,11

Conversely, the two studies16,17 investigating hybrid techniques found that they were capable of outperforming both CRT and VMAT, especially for contralateral OARs. There were slightly higher doses associated with ipsilateral lung compared to VMAT but overall hybrid techniques outperformed both CRT and VMAT alone treatments across a range of outcome measures. These combination techniques generally reduce OAR doses, suggesting that these more complex solutions be reserved for situations where CRT or VMAT alone failed to meet constraints.

## While the evidence presents a complex picture of varying performance across a range of dosimetric constraints, this must be related to the impact on patient toxicity. This was specifically addressed in several of the reviewed studies. Fogliata’s study10 determined that VMAT’s dose sculpting abilities decreased the potential for radiation pneumonitis/fibrosis when compared with conventional plans, due to the decreased dose deposition. These findings were confirmed by Xu11 as a higher distribution of V20Gy within the lungs is believed to be the causal factor of this late effect.

The risk of radiation induced oesophagitis was explored in a couple of studies12,16 as VMAT planning was found to increase oesophageal dose. Inclusion of the internal mammary chain in the treatment volume increased dose deposition and the toxicity of treatment. There was variation between studies regarding oesophageal dose; Pasler12 found that the oesophageal doses remained within tolerance making late effects unlikely. This contrasts with Dumane’s16 findings, which linked VMAT technique for chest wall and IMN with the development of grade 2 oesophagitis within 2-3 weeks of treatment commencing. Dumane’s study did, however, investigate regional nodal irradiation for potential metastatic lymph nodes in the internal mammary chain where higher oesophageal doses would be expected. This issue, nonetheless, was cited as strong rationale for developing hybrid plans to reduce both LDB and the dose delivered to the oesophagus. Across the range of OARs, there is a suggestion that both acute and late toxicities can be reduced with VMAT compared to FIF or standard IMRT; further work is needed to confirm this.

The relative risk of secondary cancer induction arising from a LDB compared to CRT is increased by use of VMAT.10,15 This poses an issue for breast cancer patients, with their potential for good prognosis post-treatment.18 Abo-Madyan15 identified a 96-280% increase in risk when using VMAT compared to CRT. The resulting cost-benefit analysis concluded that CRT and FIF techniques carry a reduced risk of secondary cancer induction; especially for younger patients. However, these papers concluded that VMAT should remain a viable treatment option, especially in situations where standard techniques cannot achieve the required dosimetric constraints. Although not specifically measured, there was an indication of reduced LDB associated with a hybrid technique combining CRT and VMAT.16 The reduced V5Gy dose evident in Table 4 is associated with reduced risk of secondary cancer induction.

Several limitations of this review must be acknowledged. Firstly the relatively small size of the evidence base was a limitation to the validity of the findings and was further compounded by the variations between the studies. Cohort populations and tumour sites varied between papers and internal validity for the studies was hard to judge. The prescription variation (ranging from 40.05Gy in 15# to 50Gy in 25#) and the range of OAR outcome measures presented also thwarted comparisons between the papers assessed within this study. Population size was also a limiting factor of this study, as the largest sample included only 22 patients.11 More research, drawn from larger cohorts and with more consistently used outcome measures would have improved the reliability and validity of the findings.

**Conclusion**

Overall, the evidence supported the value of VMAT in reducing high doses to OARs and thus reducing potential late toxicities. This dose reduction, however, is offset by the spread of low dose around the patient and increased risk of secondary cancer induction. Emerging hybrid techniques, combining the benefits of VMAT with the reduced low dose bath of conventional treatment may offer improved levels of toxicity. More work is recommended to confirm the role of hybrid techniques and clarify indications for use. Findings from this review support further evaluation of the hybrid 3D-CRT and VMAT technique as a means of improving dose conformity and OAR protection. Future studies will need to overcome the current limitations within the evidence base arising from small sample sizes to identify which patients would benefit most from the technique.

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