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CLINICAL INVESTIGATION

TOMOTHERAPY AND MULTIFIELD INTENSITY-MODULATED RADIOTHERAPY PLANNING REDUCE CARDIAC DOSES IN LEFT-SIDED BREAST CANCER PATIENTS WITH UNFAVORABLE CARDIAC ANATOMY

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Purpose: For patients with left-sided breast cancers, radiation treatment to the intact breast results in high doses to significant volumes of the heart, increasing the risk of cardiac morbidity, particularly in women with unfavorable cardiac anatomy. We compare helical tomotherapy (TOMO) and inverse planned intensity modulated radiation therapy (IMRT) with three-dimensional conformal radiotherapy using opposed tangents (3D-CRT) for reductions in cardiac volumes receiving high doses.

Methods and Materials: Fifteen patients with left-sided breast cancers and unfavorable cardiac anatomy, determined by a maximum heart depth (MHD) of ≥1.0 cm within the tangent fields, were planned for TOMO and IMRT with five to seven beam angles, in addition to 3D-CRT. The volumes of heart and left ventricle receiving ≥35 Gy (V35) were compared for the plans, as were the mean doses to the contralateral breast and the volume receiving ≥20 Gy (V20) for the ipsilateral lung.

Results: The mean MHD was 1.7 cm, and a significant correlation was observed between MHD and both heart and left ventricle V35. The V35s for IMRT (0.7%) and TOMO (0.5%) were significantly lower than for 3D-CRT (3.6%). The V20 for IMRT (22%) was significantly higher than for 3D-CRT (15%) or TOMO (18%), but the contralateral breast mean dose for TOMO (2.48 Gy) was significantly higher than for 3D-CRT (0.93 Gy) or IMRT (1.38 Gy).

Conclusions: Both TOMO and IMRT can significantly reduce cardiac doses, with modest increases in dose to other tissues in left-sided breast cancer patients with unfavorable cardiac anatomy. © 2009 Elsevier Inc.

Breast cancer, Radiation, Cardiotoxicity, IMRT, Tomotherapy.

INTRODUCTION

Breast-conserving therapy has become the standard treatment for patients with early-stage breast cancer and typically includes whole-breast external-beam radiotherapy after lumpectomy. This is conventionally achieved with tangential fields, which also include portions of the anterior thoracic cavity. For left-sided breast cancers, this often results in radiation doses to the heart that may increase the risk of cardiac morbidity (1–4). The late effects of cardiac radiation can result in chronic pericardial disease, coronary artery disease, cardiomyopathy, valvular disease, or conduction system abnormalities that occur many years after completion of radiation treatment. Women with pre-existing cardiac risk factors or disease are at particularly increased risk of death secondary to myocardial infarction, congestive heart failure, or coronary artery disease (2, 3).

Although several factors contribute, the most significant determinants of this risk are radiation dose and cardiac volume (1, 4, 5). A dose–response relationship has been demonstrated between the risk of coronary heart disease and radiation doses to small cardiac volumes (1, 6–9). The anterior heart, including the left anterior descending (LAD) artery, is typically exposed to the highest doses in radiotherapy for breast cancer (10). Recently, myocardial single photon emission computed tomography studies have shown the left ventricle irradiated volume to be an important determinant of perfusion changes in the distribution of the LAD coronary artery after radiation treatment (11).

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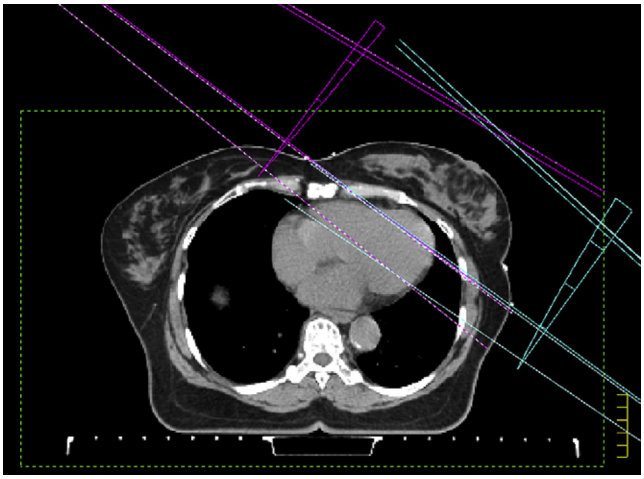

Fig. 1. Typical three-dimensional conformal radiotherapy beams.

Primarily as a result of the proximity of the heart to the higher-dose regions, women treated with whole-breast radiation for left-sided cancers are at much higher risk for cardiac morbidity (4, 5) than those treated for right-sided breast cancers and, in some studies, at higher risk for cardiac mortality as well (6, 11, 12). The prevalence of stress test abnormalities in patients with left-sided cancers is higher than with right-sided cancers, with the majority of these abnormalities in the distribution of the LAD artery (12). The risk for fatal myocardial infarction after postlumpectomy radiation treatment for left-sided breast cancer has been observed to be more than double that for right-sided breast cancer (3). Anatomic variation of heart and left ventricle location within the tangent fields places some women at even higher risk for cardiac morbidity as a result of higher cardiac doses (13), and maximum heart depth (MHD) in left-sided tangent fields may serve as a reliable predictor of women with unfavorable cardiac anatomy for conventional radiation techniques (14).

Despite the potential for accelerated partial-breast irradiation (APBI) as a means to reduce this risk (15), the long-term efficacy of APBI has yet to be demonstrated; moreover, women with unfavorable cardiac anatomy are not always candidates for APBI. Intensity-modulated radiotherapy (IMRT) has been widely used for many treatment sites, allowing both improved sparing of normal tissues and more conformal dose distributions. IMRT techniques have also been adopted for whole-breast radiation in cases for which anatomic considerations render dose distributions from tangent fields unacceptable, and can be used to reduce acute skin toxicity rates to less than those seen with standard techniques (16, 17). IMRT techniques for breast cancer radiotherapy have been studied both for standard linear accelerator applications (18–24) as well as helical tomotherapy (TOMO) (25, 26).

The goal of this study was to compare linear accelerator–based multifield IMRT and TOMO planning methods with opposed tangents planned conventionally (three-dimensional conformal radiotherapy [3D-CRT]), for reductions in cardiac and left ventricle doses in women with left-sided breast cancers and unfavorable cardiac anatomy.

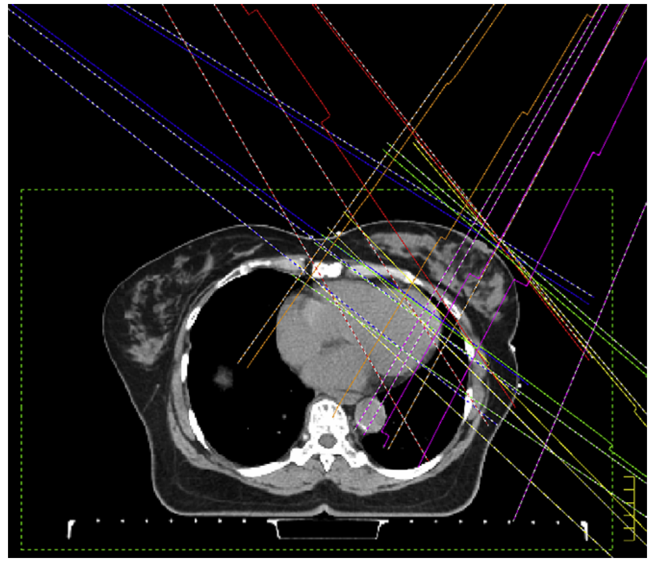

Fig. 2. Typical intensity-modulated radiotherapy beams.

METHODS AND MATERIALS

The study population comprised 15 patients with left-sided breast cancers who were previously planned with 3D-CRT. All patients in the study were determined to have unfavorable cardiac anatomy by having a MHD, measured as the maximum distance the heart extended perpendicularly beyond the block edge using a beams-eye view of the medial and lateral beams, ≥1.0 cm.

Patients had a noncontrast CT simulation in the supine position on a breast board with the ipsilateral arm up and head turned to the contralateral side. Radio-opaque wires were used to mark the lumpectomy scar, palpable breast tissue, and clinical boundaries: cephalad at the inferior edge of the medial head of the clavicle, caudal at 1 to 2 cm inferior to inframammary fold, medial at patient midline, and lateral at the midaxillary line. A CT scan was performed using 3-mm slice thickness. The medial and tangential angles and isocenter were set using CT simulation software (Phillips Medical Systems, Bothell, WA) and transferred to the treatment planning system (Pinnacle v7.6c; Philips Medical Systems).

Opposed tangent geometry was based on field borders defined during the CT simulation. The 3D-CRT technique used opposed tangential photon beams with lung blocks defined in the beam's-eye view for each field, and dynamic wedges. The IMRT technique used five to seven beams equally spaced, with a hinge angle of approximately 200° between the most medial and lateral beams. The medial-most beam angle was typically 5°–15° shallower than the conventional medial beam gantry angle but did not enter through the contralateral breast. Example beam arrangements are shown in Figs. 1 and 2. The TOMO technique was based on the Tomotherapy Hi-ART II (Madison, WI) device, with a nominal jaw width of 2.5 cm, pitch of 0.4, and a modulation factor of 4.

Cardiac contact distances in the axial planes (CCDax) and parasagittal planes (CCDps) were measured in accordance with the definitions given by Hiatt *et al*. (15). The CCDax was the shortest linear distance from the medial point of contact of the cardiac silhouette with the chest wall to the lateral point of contact with the chest wall

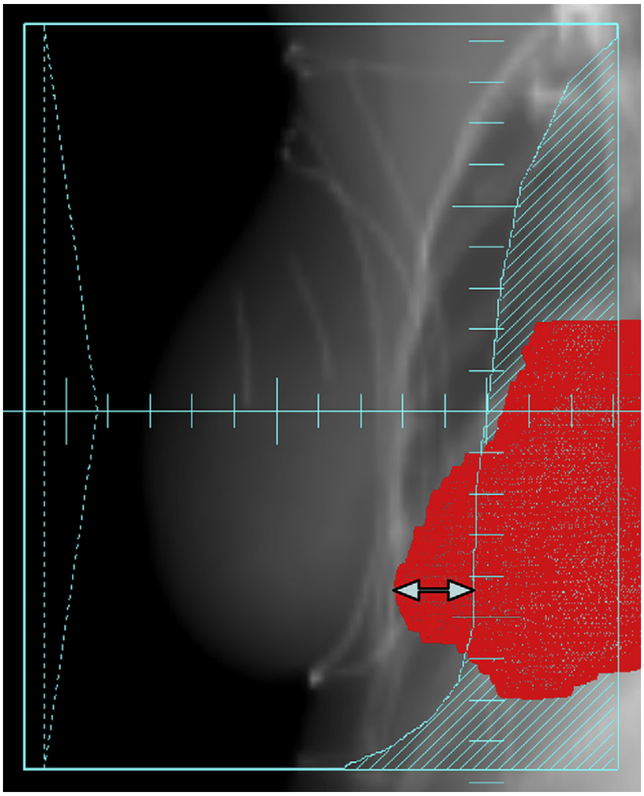

Fig. 3. Maximum heart depth measured in beam's-eye view.

at the level of the right hemidiaphragm. The CCDps was the linear distance of direct contact of the heart with the chest wall, measured at the midpoint of the left hemithorax. Correlations between measures of unfavorable cardiac anatomy (MHD, axial cardiac contact distance, parasagittal cardiac contact distance) and cardiac doses (volume of heart and left ventricle receiving ≥35 Gy [V35]) were determined by Spearman's rank correlation coefficient. All statistical analyses were executed in SPSS v14.0 for Windows (SPSS, Chicago, IL).

Target volume and critical structure definition

The borders for the tangent fields were set so that they included the entire breast volume plus a 1- to 2-cm margin. The boundaries were defined clinically using digitally reconstructed radiographs. The isocenter was set for a half-beam technique, with conformal blocks to accommodate patient variability in chest wall contour. The MHD was measured by using digitally reconstructed radiographs to determine the maximum distance in the beam's-eye view from the block edge to the heart (measured along the normal to the block edge; see Fig. 3). The whole-breast irradiation (WBI) plans used dynamic wedges. The planning target volume for the WBI included the breast parenchyma within the opposed tangent fields, excluding the tissue within 0.5 cm of the skin. No additional regional lymph nodes were included, and heart and lung were excluded. On the basis of the WBI plan, a planning target volume (PTV) was autocontoured according to the 95% isodose line. This PTV was used for the IMRT and TOMO plans. The mean PTV volume was 1062 cm^3 (range, 417–2905 cm^3). The contralateral breast, ipsilateral and contralateral lung, heart, and left ventricle were contoured.

A prescription dose of 5040 cGy in 28 fractions to the whole breast was used for the 3D-CRT, IMRT, and TOMO plans. The treatment plans delivered 5040 cGy to the PTV. For the IMRT and TOMO plans, the ipsilateral lung V20 (volume of lung that

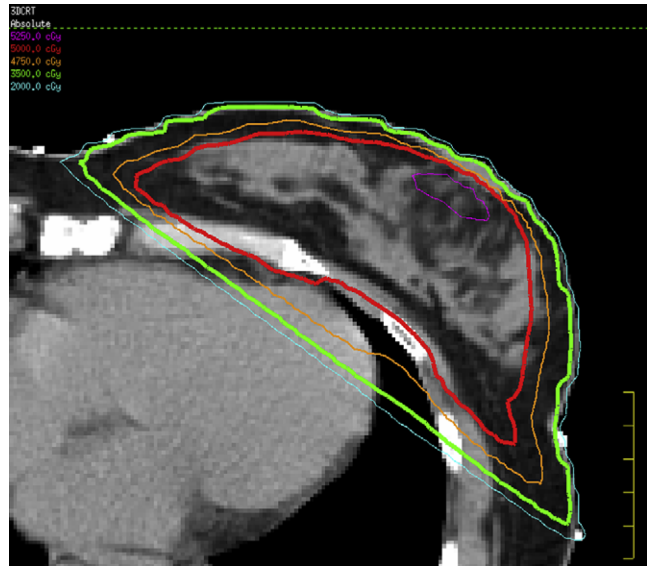

Fig. 4. Dose distribution for a three-dimensional conformal radiotherapy plan.

received ≥20 Gy) was limited to 30%. Typical dose distributions are shown in Figs. 4–6. The heart and left ventricle V35 (volumes receiving ≥35 Gy) were then compared in each patient for the 3D-CRT, IMRT, and TOMO plans.

Dosimetric endpoints

The V35 of the heart and left ventricle were averaged over all 15 patients and reported as the mean V35 for heart and left ventricle for each of the 3D-CRT, IMRT, and TOMO plans. The means over all patients for V20 of the ipsilateral and contralateral lungs were similarly determined, as was the mean contralateral breast mean dose. Statistically significant differences in endpoints were determined using a Student's *t* test (two-sided, assuming different variances) or Wilcoxon signed ranks, whenever appropriate.

RESULTS

MHD, CCDax, and CCDps

The correlation of MHD with dose was statistically significant for both heart and left ventricle V35 using opposed tangents, with Spearman's $\rho = 0.704$ ($p = 0.003$) and 0.745 ($p = 0.001$), respectively. Similarly, MHD correlated well with IMRT-planned V35 for heart and left ventricle, with Spearman's $\rho = 0.714$ ($p = 0.003$) and 0.757 ($p = 0.001$), respectively. The mean MHD was 1.7 cm. Neither cardiac contact distance in the axial or parasagittal planes showed a significant correlation with heart or left ventricle V35 using opposed tangents. Likewise, no significant correlation was observed between CCDax or CCDps and V35 for heart or left ventricle in plans devised using IMRT.

Heart and left ventricle

The mean dose–volume histograms (averaged over all 15 patients) for heart and left ventricle for 3D-CRT, IMRT, and TOMO techniques are shown in Figs. 7 and 8.

Intensity-modulated radiotherapy and TOMO consistently lowered the heart V35 for all patients, with the exception of

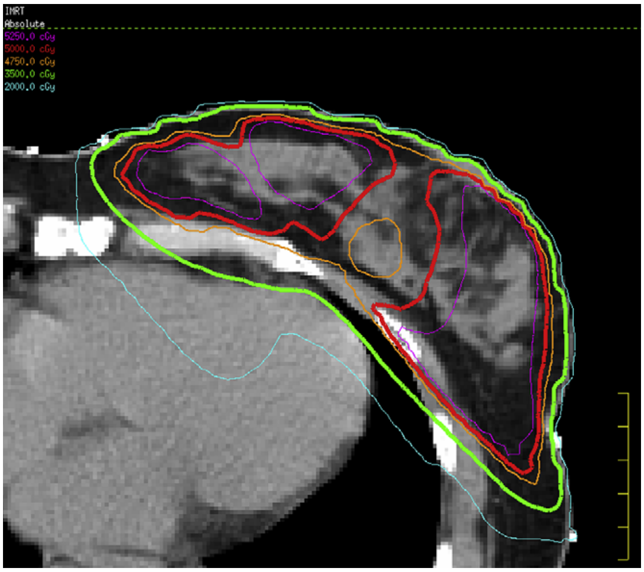

Fig. 5. Dose distribution for an intensity-modulated radiotherapy plan.

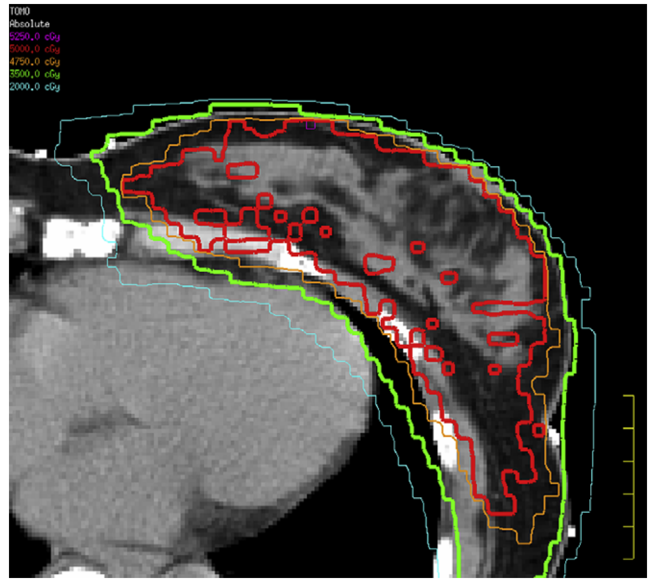

Fig. 6. Dose distribution for a helical tomotherapy plan.

one patient for whom the V35 was 0 for all three methods (notably, this was the only patient with MHD at the 1.0 cm minimum for our definition of unfavorable cardiac anatomy). The mean heart V35 was greater for 3D-CRT at 3.6% relative to IMRT at 0.7% ($p = 0.006$) and TOMO at 0.5% ($p = 0.003$), a relative decrease of 81% and 86% for those two methods, respectively. The difference between the mean heart V35 for IMRT and TOMO was not statistically significant.

As with the heart V35, the left ventricle V35 was lower for each patient using IMRT and TOMO compared with 3D-CRT (again, with the exception of the single patient for whom the left ventricle V35 was 0 for all methods). The mean V35 value for the left ventricle was smaller for IMRT at 1.2% ($p = 0.003$) and TOMO at 0.7% ($p = 0.001$) relative to 3D-CRT at 6.4%, a relative decrease of 81% and 89%, respectively, with no statistically significant difference seen between the IMRT and TOMO means.

Ipsilateral lung, contralateral lung, and contralateral breast

The mean V20 for the left lung in these left-sided breast patients was greater for IMRT at 22% than for 3D-CRT at 15% ($p = 0.002$) or TOMO at 18% ($p = 0.037$). The difference between the mean left lung V20 for 3D-CRT and TOMO was not statistically significant. For the contralateral lung, no statistically significant differences between the mean V20s for 3D-CRT, IMRT, or TOMO were observed. However, for the mean dose to the contralateral breast, the average over all patients for TOMO was 2.48 Gy, which was significantly higher than for IMRT at 1.38 Gy ($p = 0.044$) and 3D-CRT at 0.93 Gy ($p = 0.004$). Average dose–volume histograms for the 15 patients for the contralateral breast are shown in Fig. 9. The difference between the IMRT and 3D-CRT contralateral breast mean doses was not statistically significant.

DISCUSSION

This study compared conventional 3D-CRT with multi-field IMRT (inverse planned without manual selection of segments) and TOMO planning for the utility of these approaches in reducing heart and left ventricle volumes receiving high doses in patients with left-sided breast cancers in the particularly problematic setting of unfavorable cardiac anatomy. Both IMRT and TOMO techniques provided significant reductions of >80%, on average, in V35s compared with 3D-CRT. These reductions seem to come at the cost of modest increases in doses to normal tissues, with significant differences in the affected tissues between the IMRT and TOMO plans.

Large, long-term studies of breast cancer patients treated with conventional radiation, including meta-analyses of randomized trials, have shown a substantially elevated risk of cardiac morbidity and mortality for these patients relative to women who did not receive radiation treatment, and for patients who received radiation treatments to the left side relative to those treated on the right (27–31). Although recent studies indicate that the overall risk of cardiac mortality after breast irradiation may have decreased in recent years with improved radiation techniques (7, 8, 30, 32–34), this risk has not been completely eliminated and may still be substantial for certain subsets of patients, including those with unfavorable cardiac anatomy and/or those receiving additional cardiotoxic systemic and biologic therapies, and those with additional risk factors (*e.g.*, hypertension, diabetes, and smoking). Furthermore, long-term follow-up (up to 20 years or more) for patients treated with more modern techniques may still be needed to fully assess cardiac risks for these women in general (35).

Recent attempts to model the risk of cardiac morbidity using a relative seriality model (36, 37) have shown that aperture-based intensity modulation reduces estimated

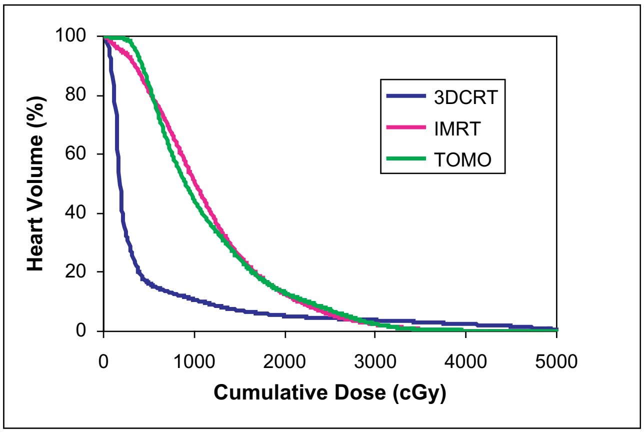

Fig. 7. Mean dose–volume histograms for the heart. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TOMO = helical tomotherapy.

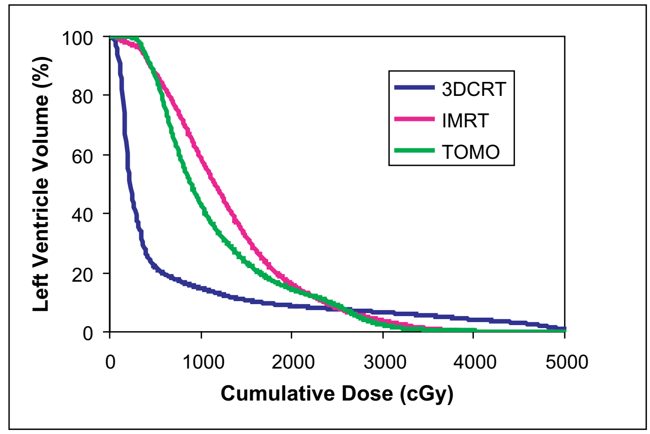

Fig. 8. Mean dose–volume histograms for the left ventricle. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TOMO = helical tomotherapy.

excess cardiac risk from approximately 6% to <1% (38), in line with previous applications of this model in breast radiation (39). This model does not necessarily reflect the differential sensitivity of myocardium across the region at risk, and validation of this approach by outcomes data is limited by the dearth of 3D dosimetric data for women treated sufficiently long ago for those outcomes to be measurable. Additional clinical results for which detailed dosimetric data are available with ample follow-up periods will be needed to assess this approach and develop refinements that better quantify long-term cardiac risk as a function of cardiac dose distributions.

Radiation doses to the myocardium >35 Gy increase the risk of cardiac injury in children and adults, including accelerated coronary atherogenesis and ischemia (40–42). Large volumes of the left ventricle may be exposed to the highest radiation doses when conventional tangent fields are used. Heart blocks can be used with tangent fields to reduce cardiac dose. In effect, conformal blocks in 3D-CRT plans serve as partial heart blocks (see Fig. 3). Although this provides reductions in cardiac volumes receiving high doses compared with rectangular fields, the benefit diminishes as MHD increases (43). Completely blocking the heart could provide even greater reductions but typically yields unacceptably poor PTV coverage, particularly with increasing MHD.

Radiation doses to the heart with opposed tangents are strongly correlated with the MHD. Mean heart doses (and to a lesser extent, LAD artery mean doses and biologically equivalent doses) have been recently shown to be strongly predicted by the MHD (14), whereas assessment of a single CT slice (midplane) failed to provide an accurate prediction of cardiac dose. Similarly, we were unable to show a statistically significant correlation between the heart V35 and left ventricle V35 and the cardiac contact distances assessed in single axial and parasagittal CT slices, as defined previously (15). On the other hand, statistically significant correlations between MHD and both the heart V35 and left ventricle V35 were demonstrated in our population of women with MHD >1 cm. A retrospective study of cardiovascular disease in 1601 women treated with opposed tangential radiation after lumpectomy (44) failed to show a statistically significant trend in cardiovascular morbidity with increasing MHD among left-sided breast cancer patients; however, with only 139 total events and a median follow-up of 16 years for these patients, the study may have been underpowered and/or had insufficiently long follow-up to detect an effect that may not be evident for 2 decades or more.

Although doses to the ipsilateral lung increased significantly for the IMRT plans we investigated, the ipsilateral lung V20 was always well below the target upper bound of 30% and was not an active constraint in the optimal plan for any patient. Clinical or radiologic evidence of pulmonary complications in radiation treatment for breast cancer are rare when the ipsilateral lung V20 is held below 30% (45). Furthermore, there was no statistically significant increase in contralateral breast dose for our IMRT plans. Conversely, the slight increase in the V20 for the TOMO plans was not statistically significant, but the increase in the contralateral breast dose was.

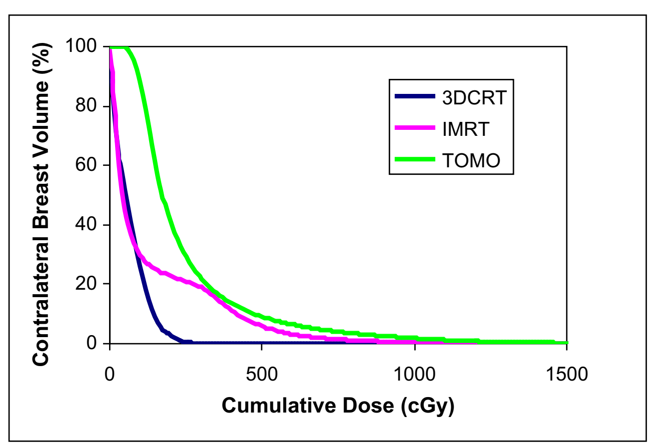

Fig. 9. Mean dose–volume histograms for the contralateral breast. 3DCRT = three-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy; TOMO = helical tomotherapy.

Increased contralateral breast doses may expose patients to increased risk of developing a secondary malignancy (46–51). Statistically significant increases in contralateral breast mean doses with IMRT compared with conventionally planned left breast radiation treatments have been reported for plans including the internal mammary nodes, with an average increase of 4.3 Gy from 2.9 Gy for a prescription dose of 50 Gy (23). Using an aperture-based intensity modulation method with postlumpectomy left-sided breast cancer patients treated to 50 Gy, similar increases in mean contralateral breast doses relative to conventional 3D planning have been reported (5.4 Gy vs. 1.15 Gy) (38). Increases in contralateral breast mean dose have also been reported when TOMO-based planning is compared with an electronic tissue compensation method (fluence distribution selected to match desired isodose surface with multileaf collimator) (26). In our population of women with unfavorable cardiac anatomy, the 0.45-Gy increase in contralateral breast mean dose for IMRT plans over 3D-CRT was not statistically significant, in contrast to the 1.55 Gy increase for TOMO plans.

In principle, restriction of the tomotherapy beam angles and the addition of avoidance structures could be used to reduce the contralateral breast dose, but likely at the cost of an increased lung dose and/or a cardiac dose. It is, perhaps, more practical to view this as a comparison between two intensity-modulation techniques, one with which the beam angles are limited in number and degrees, and the other without those beam angle constraints. Thus, the latter method could be expected to deliver more dose through angles that include contralateral breast when doing so results in adequate target coverage with reduced cardiac dose. Patient-specific clinical considerations will be needed to assess the advisability of this trade-off. For instance, in addition to ipsilateral lung V20, increasing age and reduced preradiation lung function have also been shown to be associated with risk of pulmonary complications in breast cancer radiation patients (45). Therefore, older women with unfavorable cardiac anatomy, as well as those with pre-existing pulmonary function deficits, may be better candidates for cardiac dose reduction using TOMO. Conversely, given the modestly increased risk of contralateral breast cancers with increasing contralateral breast dose in women under the age of 45 years (46, 47), multifield IMRT planning should be considered to reduce cardiac doses for younger patients with unfavorable cardiac anatomy in the absence of any pre-existing pulmonary dysfunction.

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