BJR

https://doi.org/10.1259/bjr.20160874

Received: 16 November 2016 | Revised: 13 February 2018 | Accepted: 21 February 2018

Cite this article as:
Lancellotta V, Iacco M, Perrucci E, Falcinelli L, Zucchetti C, de Bari B, et al. Comparing four radiotherapy techniques for treating the chest wall plus levels III–IV draining nodes after breast reconstruction. *Br J Radiol* 2018; **91**: 20160874.

FULL PAPER

Comparing four radiotherapy techniques for treating the chest wall plus levels III–IV draining nodes after breast reconstruction

[1,2]VALENTINA LANCELLOTTA, MD, [1,2]MARTINA IACCO, Phys, [3]ELISABETTA PERRUCCI, MD, [3]LORENZO FALCINELLI, MD, [1,2]CLAUDIO ZUCCHETTI, Phys, [4]BERARDINO DE BARI, MD, [5]SIMONETTA SALDI, MD and [1,2]CYNTHIA ARISTEI, MD

[1]Radiation Oncology Section, Department of Surgical and Biomedical Sciences, University of Perugia and Perugia General Hospital, Perugia, Italy
[2]Medical Physics Unit, Perugia General Hospital, Perugia, Italy
[3]Radiation Oncology Division, Perugia General Hospital, Perugia, Italy
[4]Department of radiation Oncology, University Bourgogne Franche-Comté, CHRU Besançon, INSERM U1098 EFS/BFC, Besançon, France
[5]Radiation Oncology Section, University of Perugia, Perugia, Italy

Address correspondence to: Dr Valentina Lancellotta
E-mail: *valentina.lancellotta@unipg.it*

Objective: To compare the dosimetric outcomes of four radiotherapy (RT) techniques for treating the chest wall plus draining nodes after mastectomy and breast reconstruction.
Methods: Three-dimensional conformal radiotherapy, linac-based intensity modulated RT, helical tomotherapy (HT) and direct tomotherapy treatments were planned for 40 breast cancer patients. Dose prescription was 50 Gy. Plans were compared in terms of doses to the planning target volume, organs at risk and the homogeneity index. The non-parametric Friedman test for paired data and the Conover *post hoc* analysis were used for data analysis.
Results: HT provided the highest D90 and D98% and the lowest HI, V107% and D2%. HT was associated with the lowest D2% and V25 Gy to the heart in left-sided treatments but the mean cardiac dose was highest. HT provided the highest V5 Gy and V20 Gy to the ipsilateral lung, but the V30 Gy was lower. The contralateral breast and lung were more exposed with HT.
Conclusion: The present dosimetric study together with daily use of CT-MV image guided RT have led us to opt for HT after mastectomy and breast reconstruction and to draw up a suitable protocol for treating the chest wall and levels III and IV draining nodes.
Advances in knowledge: HT is a suitable for treating the chest wall and levels III and IV draining nodes.

INTRODUCTION

Breast cancer is the most common type of cancer in females worldwide. After mastectomy, radiotherapy (RT) to the infra- and supraclavicular (levels III–IV) lymph nodes is the standard treatment in patients at high-risk of relapse as it improves locoregional control and overall survival.[1–4] The usual technique for treating the chest wall and lymph nodes was for a long time three dimensional conformal radiotherapy (3DCRT) but, given the complex target shape, it was challenging to achieve a uniform target dose distribution with optimal sparing of adjacent organs at risk (OARs) such as the lungs, heart, spinal cord and contralateral breast. To overcome these difficulties, intensity modulated RT (IMRT) administered with linear accelerators (linac-based IMRT), volumetric modulated arc therapy (VMAT), helical tomotherapy (HT) or direct tomotherapy (DT) were developed.[5–11]

Linac-based IMRT is administered when the linac head reaches the position that was established during treatment planning; leaves are either stationary during delivery (step and shoot) or are continuously modified (sliding windows) to modulate the beam fluence at different gantry angles. Volumetric modulated arc therapy delivers treatment with the gantry rotating in one or more arcs using a dynamic multileaf collimator, variable dose-rates and gantry speeds. In tomotherapy, the couch moves inside the bore and beam intensity is modulated by rapidly moving micromultileaf collimators, so RT is delivered in multiple tiny beamlets. In HT, the linac rotates 360° around the patient while DT uses fixed gantry positions. All these IMRT techniques use inverse planning and optimize non-uniform beam intensities by means of treatment plans that are generated by specific algorithms. The RT dose is calculated according to a convolution–superposition

Table 1. The demographics and clinical details of patients

Median age	47.5 years (range 32–76)
Stage	
IIA	8 patients (20%)
IIIA	19 patients (47.5%)
IIIB	2 patients (5%)
IIIC	10 patients (25%)
Chest wall relapse	1 patient (2.5%)
Histology	
CI NST	37 patients (92.5%)
Lobular carcinoma	2 patients (5%)
Mucinoso	1 patient (2.5%)
Grade	
G1	4 patients (10%)
G2	9 patients (22.5%)
G3	27 patients (67.5%)
Hormonal receptor	
Positive	30 patients (75%)
Negative	10 patients (25%)
HER-2	
Positive	8 patients (20%)
Negative	32 patients (80%)
Hormonal therapy	
Yes	30 patients (75%)
No	10 patients (25%)
Chemotherapy	40 patients (100%)
Trastuzumab	
Yes	8 patients (20%)
No	32 patients (80%)

CI NST, infiltrating carcinoma non special type.

algorithm (C/S), which is based on a collapsed cone convolution approach.[12]

In patients with breast cancer, the present investigation compared the dosimetric results of three IMRT techniques with 3DCRT for treatment of the chest wall plus draining nodes after mastectomy and breast reconstruction.

METHODS AND MATERIALS

3DCRT, linac-based step and shoot IMRT, HT and DT treatments were planned for 40 breast cancer patients (20 right-sided, 20 left) after mastectomy with immediate breast reconstruction. Table 1 reports the demographics and clinical details of patients. All patients received RT to the chest wall and to the infra-and supraclavicular lymph nodes (levels III–IV lymph nodes). The RT dose was calculated according to a convolution–superposition algorithm (C/S), which is based on a collapsed cone convolution approach.[12]

Computed tomography simulation and volume definition

Free breathing CT scans without contrast medium were acquired in the treatment position. Each patient lay supine with both arms raised above her head, and was supported by a breast board that was inclined in 11 patients and flat in 29. Radiopaque landmarks identified chest wall margins. CT data were acquired from the mandible to the diaphragm with 5 mm slice thickness in the first 9 patients and 2.5 mm slice thickness in the last 31, in accordance with policy in our unit.[2] All CT scans were sent to the Pinnacle[3] treatment planning system V9.8 (Philips Radiation Oncology Systems, Fitchburg, WI). One radiation oncologist contoured the clinical target volume (CTV), *i.e.* chest wall and levels III and IV lymph nodes and OARs, following the Italian guideline atlas,[2,13] reproducibility of which were assessed in an Italian national multicentre study.[14] Contoured OARs were the lungs, heart, contralateral breast, spinal cord, larynx, mandible, thyroid, esophagus and humeral head.

The planning target volume (PTV) chest wall coincided with the CTV chest wall as it was not expanded. For PTV lymph nodes, expansion was 0.5 cm in all directions. To create PTVevals, all PTVs were restricted to 2 mm skin depth. To surround the PTVs, two rings with 10 mm expansion were created inside the body (chest wall and lymph node rings). To restrict high doses to the PTVs, a healthy tissue structure was created from the whole body minus PTVs, ring structures and 2 mm skin depth. To obtain the spinal cord planning risk volume), the spinal cord was expanded by 5 mm.

Dose prescription was 50 Gy to the PTVevals in 25 fractions. The maximum (D2%) and the minimum (D98%) doses were planned in accordance with the ICRU 83 recommended range.[13] Dose constraints followed the QUANTEC recommendations,[15–18] supplemented by an internal dose constraint protocol (Table 2).

3DCRT planning

For each patient, the 3DCRT plan was based on a monoisocentric technique. Two tangential, opposed, wedged quarter-beams treated the chest wall. Gantry angles were selected using the beam's eye view of the Pinnacle[3] treatment planning system, avoiding direct exposure of the contralateral breast. Three oblique, wedged halfbeams treated the lymph nodes. Two were anterior, with a mean gantry angle of ±39°, while the third was posterior, with a gantry angle chosen to avoid direct exposure of the spinal cord. Wedge angles and beam weights were selected during optimization to avoid hot spots and cover underdosed areas. Beam energy was 6 MV. To achieve better dose distribution in large breasts or when the chest separation was >21–22 cm, 15 MV were used. Usually a field-in-field technique was adopted to further reduce hot spots. When dose constraints were not satisfied, leaves shielded the ipsilateral lung or the heart in the left-sided treatments.

IMRT planning

In linac-based IMRT plans, six beams were equally spaced throughout the 180° sector angle in the axial plane. The beam energy was 6 MV for all beams. The optimization algorithm was

Table 2. Dose constrains and optimization objectives

Structure	Dose Constraints	IMRT linac-based planning aims (weight)	HT and DT planning aims (weight)
PTV breast\chest wall eval, PTV LN evals		Min dose = 45 Gy (5)	Min dose = 47.5 Gy (5)
		Min dVH 50% = 50 Gy (5)	V50 Gy = 50%
		Min DVH 95% = 47.5 Gy (5)	V49 Gy = 95%
		Uniform dose = 50 Gy (5)	V51 Gy = 5%
		Max dose=52 Gy (10)	Max dose = 52.5 Gy (10)
PTV breast\chest wall, PTV LN		Min dose = 45 Gy (1)	
Ipsilateral lung	V5 Gy < 75%	V5 Gy = 75% (5)	V5 Gy = 75% (5)
	V20 Gy < 30%	V20 Gy = 30% (5)	V20 Gy = 30% (5)
	V30 Gy < 20%	V30 Gy = 20% (5)	V30 Gy = 20% (5)
			Max dose = 47.5 Gy (1)
Contralateral lung	V5 Gy < 26%	V5 Gy = 26% (5)	V5 Gy = 26% (5)
	V15 Gy < 10%	V15 Gy = 5% (5)	V15 Gy = 5% (5)
			Max dose = 25 Gy (1)
Total lung	V5 Gy < 45%	V5 Gy = 42% (5)	V5 Gy = 42% (1)
	V15 Gy < 30%	V15 Gy = 25% (5)	V15 Gy = 25% (1)
			Max dose = 47.5 Gy (1)
Heart	Left-sided treatment:	Left-sided treatment:	Left-sided treatment:
	V25 Gy < 10%	V25 Gy = 10% (5)	V25 Gy =10% (5)
			Max dose = 40 Gy (1)
	Right-side treatment:	Right-sided treatment:	Right-sided treatment:
	V15 Gy < 5%	V15 Gy = 5% (5)	V5 Gy = 50% (1)
		V5 Gy = 50% (1)	V15 Gy = 5% (5)
			Max dose = 30 Gy (1)
PRV SC	D2% < 20 Gy	Max dose = 20 Gy (1)	V10 Gy = 50%
			V18 Gy = 1%
			Max dose =20 Gy (1)
Contralateral breast	D2% < 10 Gy	D50% = 5 Gy (5)	D50% = 5 Gy (5)
	Dmean < 5 Gy	Max dose = 10 Gy (5)	Max dose = 10 Gy (5)
Ipsilateral humeral head	D2% < 30 Gy	Max dose = 30 Gy (1)	D50% = 20 Gy (5)
			D1% = 29 Gy (5)
			Max dose = 30 Gy (1)
Mandible		Max dose = 10 Gy (5)	D50% = 2 Gy (5)
			Max dose = 10 Gy (1)
Thyroid		Dmean < 35 Gy (1)	D50% = 25 Gy (1)
		Max dose = 50 Gy (5)	Max dose = 50 Gy (5)
Larynx		Max dose = 45 Gy (1)	D50% = 20 Gy (1)
			Max dose = 45Gy (1)
Ring breast/chest wall		Max dose = 47.5 Gy (1)	D50% = 45 Gy (1)
			Max dose = 47.5 Gy (1)

(Continued)

Table 2. (Continued)

Structure	Dose Constraints	IMRT linac-based planning aims (weight)	HT and DT planning aims (weight)
Ring LN		Max Dose=47.5 Gy (1)	D50%=45 Gy (1)
			Max Dose 47.5 Gy (1)
Healthy tissue		Max dose=45 Gy (1)	D30% = 5 Gy (1)
			D20% = 10 Gy (5)
			D2% = 30 Gy (5)
			Max dose = 45 Gy (1)

DT, direct tomotherapy; HT, helical tomotherapy; LN, lymph node; PRV, planning risk volume; PTV breast/chest wall eval, planning target volume breast/chest wall evaluation; PTV LN eval, planning target volume LN evaluation; SC, spinal cord.

the direct machine parameter optimization with the following parameters: maximum 50 segments, minimum 5 Monitor Units for each segment, a minimum segment area of 8 cm^2. The calculation grid was 2.0 mm. Optimization objectives are listed in Table 2.

Helical and direct tomotherapy planning

After contouring, CT and volumes were transferred via DICOM-RT to the tomotherapy planning system. HT treatment plans were generated and optimized using Tomotherapy HD treatment planning station v. 5.0.4 (Accuray, Sunnyvale, CA). HT plan parameters were: 5.02 cm field width (FW), 0.287 pitch, and 2.7–3 modulation factor (MF). The planning risk volume spinal cord, mandible, contralateral breast and lung, were spared by directional blocks. To prevent posterior and contralateral beamlets from entering the chest wall/breast area another L-shaped directional block was used, excluding lymph node areas.

DT planned for seven beams to the chest wall/breast PTVeval and from 4 to 7 beams to lymph node PTVevals. Four or five flash beams compensated for intrafraction motion. The FW and the pitch were set at respectively, 5.02 cm and 0.287. In three cases, a pitch of 0.430 was used. Modulation factor ranged from 1.8 to 3. The OAR sparing directional blocks were the same as for HT, while the L-shaped directional block was not used.

Table 2 shows DVH starting points and penalties for HT and DT.

Plan comparisons and statistical analyses

Plans were compared in terms of doses to the PTVs, homogeneity index (HI) and doses to OARs.

Parameters for minimum PTV doses were D98, D90, D95%. Parameters for maximum PTV doses were D2% and V107%. Dose indicators were D50% and Dmean. HI for each technique was calculated using the formula HI = (D2–D98%)/D50%. The lower the HI, the more homogeneous dose distribution across the PTV.[15,18]

OAR parameters, *i.e.* volume indices, Dmean and D2%, varied with the OAR.

V100% of healthy tissue assessed high doses outside the PTV.

The Shapiro–Whilk test showed variable distribution was asymmetric. The non-parametric Friedman test for paired data and the Conover *post hoc* analysis were used to compare the four irradiation techniques. All statistical analyses were performed using IBM-SPSS® v. 22.0 (IBM Corp., Armonk, NY, 2011). A two-sided p-value < 0.05 was considered significant.

RESULTS

HT emerged as best for target coverage. Compared with 3DCRT, linac-based IMRT and DT, D90 and D98% were significantly higher. For example, the median HT D98% was: +13 Gy *vs* 3DCRT, +2.7 Gy *vs* linac-based IMRT and +0.5 Gy *vs* DT. HI, V107% and D2% were significantly lower than with the other techniques.

D95, D50% and Dmean were almost the same for HT and DT. In particular, median HT D95% was 1 Gy more than linac-based IMRT and 5 Gy more than 3DCRT. Compared with 3DCRT, median Dmean was significantly increased by 1.5 Gy for linac-based IMRT, 1.9 for HT and DT (Table 3).

Significantly different OAR doses are summarized below and reported in full in Table 4.

Ipsilateral lung

3DCRT provided the lowest V5 and V20 Gy. Compared with 3DCRT, the median linac-based IMRT V5 Gy was +34.6 Gy, HT was +31.2 Gy and DT was +30.63 Gy and the median linac-based IMRT V20 Gy was +4.72 Gy, HT was +3.25 Gy and DT was +3.7 Gy. HT was associated with the lowest V30 Gy (median value −5.5 Gy *vs* 3DCRT). In 14 cases, linac-based IMRT did not satisfy the normal tissue constraint guidelines of V5 Gy <75% (9 cases), V20 Gy <30% (3 cases) and V30 Gy <20% (2 cases). In eight cases, 3DCRT did not satisfy the normal tissue constraint guidelines for V20 Gy (four cases) and V30 Gy (four cases). In four cases, HT failed V5 Gy dose constraints (two cases) and V20 Gy constraints (two cases). In two cases, DT failed V5 Gy dose constraints (one case) and V20 Gy (one case).

Table 3. Comparison of PTV tot eval dosimetry for three-dimensional conformal radiotherapy, intensity modulated radiotherapy, helical tomotherapy, and direct tomotherapy

	3DCRT (range)	IMRT (range)	HT (range)	DT (range)	*p*
D90%	44.99 Gy (39.50–47.50)	46.71 Gy (42.10–48.37)	47.97 Gy (46.91–49.10)	47.87 Gy (46.15–48.73)	3DCRT *vs* IMRT: $p < \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p < \mathbf{0.0001}$; HT *vs* DT: $p = \mathbf{0.0064}$.
D95%	41.65 Gy (25–45.60)	45.33 Gy (43.70–47.26)	46.46 Gy (45.08–48.69)	46.66 Gy (42.74–47.92)	3DCRT *vs* IMRT: $p < \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p < \mathbf{0.0001}$; HT *vs* DT: $p = 0.74$.
D98%	31.80 Gy (6.00–43.00)	43.54 Gy (40.40–45.88)	44.75 Gy (42.22–47.86)	44.24 Gy (38.69–46.55)	3DCRT *vs* IMRT: $p < \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p = \mathbf{0.0115}$; HT *vs* DT: $p = \mathbf{0.03}$.
V107%	0.21% (0.00–5.05)	0.61% (0.00–3.31)	0.12% (0.00–1.56)	0.44% (0.01–2.65)	3DCRT *vs* IMRT: $p = 0.167$; 3DCRT *vs* HT: $p = \mathbf{0.05}$; 3DCRT *vs* DT: $p = 0.538$; IMRT *vs* HT: $p = 0.607$; IMRT *vs* DT: $p = 0.441$; HT *vs* DT: $p = 0.2007$.
D2%	52.79 Gy (49.00–54.40)	52.79 Gy (51.20–53.90)	52.44 Gy (51.92–53.256)	52.71 Gy (51.87–53.69)	3DCRT *vs* IMRT: $p = 0.008$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p = \mathbf{0.001}$; IMRT *vs* HT: $p = \mathbf{0.004}$; IMRT *vs* DT: $p = 0.595$; HT *vs* DT: $p = \mathbf{0.019}$.
D50%	49.60 Gy (48.30–50.50)	49.75 Gy (46.15–50.20)	50.14 Gy (49.49–50.56)	50.95 Gy (49.90–50.59)	3DCRT *vs* IMRT: $p = 0.643$; 3DCRT *vs* HT: $p = \mathbf{0.004}$; 3DCRT *vs* DT: $p = \mathbf{0.019}$; IMRT *vs* HT: $p = \mathbf{0.001}$; IMRT *vs* DT: $p = \mathbf{0.005}$; HT *vs* DT: $p = 0.579$.
Dmean	47.96 Gy (44.03–49.67)	49.44 Gy (48.23–49.96)	49.89 Gy (49.27–50.31)	49.84 Gy (49.27–50.33)	3DCRT *vs* IMRT: $p = \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p < \mathbf{0.0001}$; HT *vs* DT: $p = 0.81$.
HI	0.43 (0.19–0.91)	0.19 (0.11–0.24)	0.15 (0.09–0.20)	0.17 (0.11–0.29)	3DCRT *vs* IMRT: $p < \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p = 0.0366$; HT *vs* DT: $p = \mathbf{0.050}$.

3DCRT, three dimensional conformal radiotherapy; DT, direct tomotherapy; HI, homogeneity index; HT, helical tomotherapy; IMRT, intensity modulated radiotherapy; PTV, planning target volume.

Contralateral lung

DT provided the lowest V15 Gy while HT was associated with the highest. 3DCRT provided the lowest V5 Gy. Linac-based IMRT, HT and DT did not satisfy normal tissue constraint of V5 Gy < 26% in nine, seven and two cases respectively.

Heart (left-sided treatment)

HT was associated with the lowest D2% and V25 Gy. 3DCRT had the lowest Dmean and highest D2%. Compared with 3DCRT, median Dmean was +3 Gy for linac-based IMRT, DT, and HT. Median D2% value was −9.6 Gy for linac-based IMRT, 4.48 Gy for DT, dropping to −20 Gy for HT.

Heart (right-sided treatment)

3DCRT provided the lowest Dmean, D2% and V15 Gy. DT was associated with a lower Dmean, than HT and linac-based IMRT and lower D2% than linac-based IMRT.

Table 4. Comparison of OARs dosimetry for three-dimensional conformal radiotherapy, intensity modulated radiotherapy, helical tomotherapy, and direct tomotherapy

	3DCRT (range)	IMRT (range)	HT (range)	DT (range)	*p*
Ipsilateral lung					
V5 Gy	38.46% (23.93–48.45)	73.62% (61.67–82.05)	71.54% (64.66–77.22)	70.65% (51.54–75.10)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p < 0.0001$; HT *vs* DT: $p = 0.748$.
V20 Gy	22.05% (11.25–35.21)	29.15% (17.43–33.64)	27.64% (24.79–31.61)	27.40% (25.27–30.87)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p = 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.007$; IMRT *vs* DT: $p = 0.026$; HT *vs* DT: $p < 0.639$.
V30 Gy	17.81% (7.99–26–63)	17.84% (10.18–20.45)	14.20% (11.27–16.81)	15.43% (8.81–20.40)	3DCRT *vs* IMRT: $p = 0.010$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p = 0.005$; HT *vs* DT: $p < 0.0001$.
Contralateral lung					
V5 Gy	5.75% (0.00–6.98)	21.99% (6.48–56.06)	24.21% (17.87–38.63)	21.75% (7.90–26.22)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p = 0.568$; HT *vs* DT: $p < 0.0001$.
V15 Gy	0.00% (0.098–5.537)	0.09% (0.00–6.98)	2.26% (0.10–5.54)	0.37% (0.00–2.05)	3DCRT *vs* IMRT: $p = 0.25$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p = 0.604$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p = 0.096$; HT *vs* DT: $p < 0.0001$.
Heart (right-sided treatment)					
Dmean	0.80 Gy (0.62–1.90)	7.42 Gy (5.53–10.29)	7.54 Gy (5.81–9.07)	6.76 Gy (4.46–7.84)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.033$; IMRT *vs* DT: $p = 0.843$; HT *vs* DT: $p = 0.052$.
D2%	2.61 Gy (1.90–11.44)	18.90 Gy (13.27–24.30)	18.49 Gy (14.00–22.23)	16.84 Gy (11.68–20.31)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.294$; IMRT *vs* DT: $p = 0.923$; HT *vs* DT: $p = 0.340$.
V15 Gy	0.00% (0.00–5.32)	6.50% (0.01–30.40)	4.50% (0.39–7.04)	4.31% (0.05–7.22)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.285$; IMRT *vs* DT: $p = 0.868$; HT *vs* DT: $p = 0.218$.
Heart (left-sided treatment)					

(Continued)

Table 4. (Continued)

	3DCRT (range)	IMRT (range)	HT (range)	DT (range)	*p*
Dmean	5.58 Gy (2.09–8.62)	8.60 Gy (6.22–13.31)	11.70 Gy (8.42–14.67)	9.06 Gy (6.63–12.58)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.201$; IMRT *vs* DT: $p = 0.007$; TH *vs* DT: $p = 0.148$.
D2%	42.65 Gy (28.25–48.24)	34.69 Gy (19.80–38.60)	29.00 Gy (23.74–33.74)	34.90 Gy (21.91–42.14)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p < 0.0001$; HT *vs* DT: $p < 0.0001$.
V25 Gy	7.28% (0.62–14.19)	6.71% (4.00–15.49)	4.31% (0.00–6.59)	6.71% (1.23–8.32)	3DCRT *vs* IMRT: $p = 0.036$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p = 0.001$; HT *vs* DT: $p = 0.001$.
Contralateral breast					
Dmean	0.58 Gy (0.38–3.49)	3.36 Gy (1.95–5.27)	4.78 Gy (3.34–5.90)	3.76 Gy (2.18–4.87)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p < 0.0001$; IMRT *vs* DT: $p = 0.024$; HT *vs* DT: $p < 0.0001$.
D2%	2.10 Gy (1.38–16)	8.84 Gy (5.80–13.60)	9.52 Gy (7.77–11.22)	8.81 Gy (3.07–12.49)	3DCRT *vs* IMRT: $p < 0.0001$; 3DCRT *vs* HT: $p < 0.0001$; 3DCRT *vs* DT: $p < 0.0001$; IMRT *vs* HT: $p = 0.308$; IMRT *vs* DT: $p = 0.0008$; HT *vs* DT: $p = 0.016$.
Healthy tissue					
V100%	0.1900% (0.0009–1.85)	0.0013% (0.000–0.49)	0.0000% (0.0000–0.30)	0.0045% (0.0000–0.05)	3DCRT *vs* IMRT: $p < \mathbf{0.0001}$; 3DCRT *vs* HT: $p < \mathbf{0.0001}$; 3DCRT *vs* DT: $p < \mathbf{0.0001}$; IMRT *vs* HT: $p < \mathbf{0.0001}$; IMRT *vs* DT: $p = 0.2814$; HT *vs* DT: $p < \mathbf{0.0001}$.

3DCRT, three dimensional conformal radiotherapy; DT, direct tomotherapy; HT, helical tomotherapy; IMRT, intensity modulated radiotherapy.

Contralateral breast

3DCRT provided the lowest Dmean and D2%. HT was associated with the highest Dmean. Compared with 3DCRT median Dmean was +3 Gy for linac-based IMRT and DT, rising to +4 Gy for HT; the median D2% was +7 Gy for all IMRT techniques.

Other OARs

3DCRT provided the lowest Dmean for the spinal cord, esophagus, humeral head, larynx and the lowest D2% for the humeral head and larynx. HT provided the lowest D2% for the spinal cord. Linac-based IMRT provided the lowest D2% for the esophagus and thyroid. 3DCRT and linac-based IMRT provided the lowest Dmean and D2% for the mandible. 3DCRT irradiated healthy tissue the most and HT the least (V100% = 0.19 *vs* 0.00%; $p < 0.001$).

DISCUSSION

Our RT Centre designed the present study comparing the dosimetric parameters of 3DCRT, linac-based IMRT, HT and DT in order to select the best technique for post-operative RT delivery to the chest wall plus levels III–IV draining nodes after mastectomy with breast reconstruction. To our knowledge, a similar assessment has not been performed elsewhere. Other research groups focused on tomotherapy in different clinical situations, *e.g.* left breast cancer after conserving surgery and adjuvant RT only to the breast,[19–22] mastectomy or conserving surgery and adjuvant RT to chest wall/breast and different lymph node stations (levels I–IV ± internal mammary chain).[8–10] Consequently, comparing our results with others is arduous but one common finding was that tomotherapy provided optimal target coverage, dose conformity and homogeneity, sparing OARs from high radiation doses.[8,10]

In fact, in the present study 3DCRT provided the poorest target coverage. Factors accounting for this result include target shape complexity and underdosage of the junction of two contiguous fields between the chest wall and lymph nodes. Moreover, 3DCRT was associated with the highest HI, supporting previous evidence that IMRT techniques provided more homogeneity and fewer hotspots.[19,20] When IMRT techniques were analyzed, linac-based IMRT provided the poorest values. HT was associated with the best target coverage and lowest HI, so it delivered the most homogeneous dose inside the PTV. It provided significantly lower maximum doses (D2%) and hotspots (V107%) than the other two IMRT techniques, proving it had a higher modulation potential which may impact on choice of RT delivery.

In assessing the dose to the OARs, dose constraints and low dose volumes need to be considered. It is worth noting that lung constraints derive from lung cancer patients who received chemo-RT and very few data are available for breast cancer patients. To ensure a low risk of pneumonitis in breast cancer patients Quantec constraints for the ipsilateral lung recommend V20 Gy < 30%[16] which was medianly achieved with all four techniques. Although Quantec did not make any recommendations for V30 Gy, it is usually kept <20%[23,24] and, in fact, in the present study, the median value was always <20%, but HT was significantly lower than the other techniques. V5 Gy was accepted as another significant dose constraint in the development of pneumonitis.[25,26] In accordance with Goddu et al[8] the present study established, and medianly achieved, V5 Gy as 75% for the ipsilateral lung and 26% for the contralateral with linac-based IMRT, HT and DT. V5 Gy was lowest with 3DCRT because field angles were set to avoid direct exposure of both lungs.

Dose spillage was an issue with all IMRT techniques. Due to the HT rotational delivery, multiple beams transverse through normal tissue that would otherwise be unexposed to radiation with the fixed angles of 3DCRT, thus accounting for HT's larger low-dose volumes (V5 Gy) in both lungs. Despite their fixed angles, linac-based IMRT and DT were similar to HT because once multiple beams leave the target some pass through adjacent OARs, resulting in a low dose exposure, as occurs with rotation techniques.

Although cardiac toxicity, a major issue in patients undergoing RT for breast cancer, may be linked to systemic adjuvant treatments such as hormone therapy, antracycline or trastuzumab,[27] limiting the RT cardiac dose is crucial. Indeed, improvements in treatment planning and RT delivery have significantly reduced the incidence of cardiac toxicity.[28,29] Quantec reported that V25 Gy <10%, which was achieved in the present study for left breast treatment planning with all techniques, was associated with a < 1% mortality at 15 years after RT.[17] HT delivered the lowest V25 Gy and the lowest maximum cardiac dose, confirming its heart-sparing property. For the right breast, V15 Gy <5% was accepted as constraint and results were best with 3DCRT. Furthermore, the mean cardiac dose is emerging as a parameter to be considered in treatment planning since Darby et al[28] (28) reported a mean dose of 4.9 Gy overall (6.6 Gy for left breast cancer patients and 2.9 Gy for right breast cancer) and stated that a 1 Gy increase was associated with a 7.4% relative increase in cardiac events.[28] Our mean doses were lowest with 3DCRT and highest with HT for both left and right breast irradiation. Although the mean threshold dose has not yet been established, our new IMRT protocols now require the mean heart dose to be 5 Gy or below for the left breast and 4 Gy or below for the right in accordance with our latest dosimetric results.[30]

Dose constraints were recently suggested for the left anterior descending artery, which has emerged as another OAR for cardiac toxicity.[31,32] In the present study, dose to the left anterior descending was not evaluated as it was not contoured due to difficulties in its delineation[33,34] even on a contrast medium CT scan.[35]

The risk of contralateral breast cancer needs to be considered with IMRT techniques, particularly with HT because it delivers the highest dose to the contralateral breast. As its absolute risk, though low overall, is greatest in females < 40–45 years old[36] the benefits and side effects of HT, *e.g.* target dose homogeneity *vs* OAR exposure to low doses, need to be carefully weighed up in these young patients.

Technically speaking, 3DCRT and IMRT each has its own pitfalls but common to all is the risk of lower than prescribed dose to the target surface, due to the patient breath motion. To counterbalance this interference, strategies vary with the technique: 3DCRT uses an anterior margin in the chest wall/breast beams; DT copes by means of its built-in flash beam in the planning software. With linac-based IMRT, the PTV is expanded outside the body, to try and force beam opening on to the target surface. No options are suggested for HT as the surface dose is higher than a fixed beam technique.[37] Another problem with HT and DT is dose fall-off caudally and cranially which becomes more marked as the field widens.[38] Consequently, the present study considered the mandible as an OAR and applied a directional block. One option for counteracting dose fall-off is to narrow FW, which however, is associated with lengthened treatment times.

CONCLUSION

We are confident that present data will be useful to other RT centres that use tomotherapy to treat breast cancer patients. IMRT techniques, particularly HT, were associated with best HI and target dose coverage but at the cost of a greater OAR exposure to low doses and to higher mean doses. 3DCRT provided the poorest target coverage and was associated with the highest HI, probably on account of target shape complexity and underdosage of the junction of two contiguous fields between the chest wall and lymph nodes.

Present dosimetric results have led us to opt for HT after modifying some approaches so as to design the new protocol, which is currently in use in our centre. The cardiac dose is now

established, expansion around the CTV breast and lymph nodes is limited to 0.5 cm which consequently lowers doses to OARs, and dose fall-off to the mandible, so the block is no longer needed.

REFERENCES

1. NCC (National Comprehensive Cancer Network). Clinical Practice Guidelines in Oncology™. NCCN guidelines for treatment of cancer by site. Breast cancer. Version 1. 2016. Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf [Accessed October 02 2016].
2. Associazione Italiana di Radioterapia Oncologica (AIRO), Gruppo di lavoro per la patologia mammaria. La Radioterapia dei Tumori della Mammella Indicazioni e Criteri Guida. 2013. Available from: http://www.radioterapiaitalia.it [Accessed October 02 2016].
3. Sautter-Bihl ML, Sedlmayer F, Budach W, Dunst J, Feyer P, Fietkau R, et al. DEGRO practical guidelines: radiotherapy of breast cancer III-radiotherapy of the lymphatic pathways. *Strahlenther Onkol* 2014; **190**: 342–51. doi: https://doi.org/10.1007/s00066-013-0543-7
4. EBCTCG (Early Breast Cancer Trialists' Collaborative Group), McGale P, Taylor C, Correa C, Cutter D, Duane F, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 2014; **383**: 2127–35. doi: https://doi.org/10.1016/S0140-6736(14)60488-8
5. Krueger EA, Fraass BA, McShan DL, Marsh R, Pierce LJ. Potential gains for irradiation of chest wall and regional nodes with intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2003; **56**: 1023–37. doi: https://doi.org/10.1016/S0360-3016(03)00183-4
6. Dogan N, Cuttino L, Lloyd R, Bump EA, Arthur DW. Optimized dose coverage of regional lymph nodes in breast cancer: the role of intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; **68**: 1238–50. doi: https://doi.org/10.1016/j.ijrobp.2007.03.059
7. Popescu CC, Olivotto IA, Beckham WA, Ansbacher W, Zavgorodni S, Shaffer R, et al. Volumetric modulated arc therapy improves dosimetry and reduces treatment time compared to conventional intensity-modulated radiotherapy for locoregional radiotherapy of left-sided breast cancer and internal mammary nodes. *Int J Radiat Oncol Biol Phys* 2010; **76**: 287–95. doi: https://doi.org/10.1016/j.ijrobp.2009.05.038
8. Goddu SM, Chaudhari S, Mamalui-Hunter M, Pechenaya OL, Pratt D, Mutic S, et al. Helical tomotherapy planning for left-sided breast cancer patients with positive lymph nodes: comparison to conventional multiport breast technique. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1243–51. doi: https://doi.org/10.1016/j.ijrobp.2008.11.004
9. Jones R, Yang W, Read P, Sheng K. Radiation therapy of post-mastectomy patients with positive nodes using fixed beam tomotherapy. *Radiother Oncol* 2011; **100**: 247–52. doi: https://doi.org/10.1016/j.radonc.2011.05.004
10. Lauche O, Kirova YM, Fenoglietto P, Costa E, Lemanski C, Bourgier C, et al. Helical tomotherapy and volumetric modulated arc therapy: new therapeutic arms in the breast cancer radiotherapy. *World J Radiol* 2016; **8**: 735–42. doi: https://doi.org/10.4329/wjr.v8.i8.735
11. Tyran M, Mailleux H, Tallet A, Fau P, Gonzague L, Minsat M, et al. Volumetric-modulated arc therapy for left-sided breast cancer and all regional nodes improves target volumes coverage and reduces treatment time and doses to the heart and left coronary artery, compared with a field-in-field technique. *J Radiat Res* 2015; **56**: 927–37. doi: https://doi.org/10.1093/jrr/rrv052
12. Liu HH, Mackie TR, McCullough EC. Correcting kernel tilting and hardening in convolution/superposition dose calculations for clinical divergent and polychromatic photon beams. *Med Phys* 1997; **3424**: 2070–6. doi: https://doi.org/10.1118/1.597960
13. Cucciarelli F, Kirova YM, Palumbo I, Aristei C. Supraclavicular and infraclavicular lymph node delineation in breast cancer patients: a proposal deriving from a comparative study. *Tumori* 2015; **101**: 478–86. doi: https://doi.org/10.5301/tj.5000330
14. Ciardo D, Argenone A, Boboc GI, Cucciarelli F, De Rose F, De Santis MC, et al. Variability in axillary lymph node delineation for breast cancer radiotherapy in presence of guidelines on a multi-institutional platform. *Acta Oncol* 2017; **56**: 1081–8. doi: https://doi.org/10.1080/0284186X.2017.1325004
15. 3. Special considerations regarding absorbed-dose and dose-volume prescribing and reporting in IMRT. *J Icru* 2010; **10**: 27–40. doi: https://doi.org/10.1093/jicru/ndq008
16. Marks LB, Bentzen SM, Deasy JO, Kong FM, Bradley JD, Vogelius IS, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S70–S76. doi: https://doi.org/10.1016/j.ijrobp.2009.06.091
17. Gagliardi G, Constine LS, Moiseenko V, Correa C, Pierce LJ, Allen AM, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010; **76**(3 Suppl): S77–S85. doi: https://doi.org/10.1016/j.ijrobp.2009.04.093
18. ICRU. "International commission on radiation units and measurements". Report No: ICRU Report 50. Bethesda, Md, USA. 1993.
19. Schubert LK, Gondi V, Sengbusch E, Westerly DC, Soisson ET, Paliwal BR, et al. Dosimetric comparison of left-sided whole breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and topotherapy. *Radiother Oncol* 2011; **100**: 241–6. doi: https://doi.org/10.1016/j.radonc.2011.01.004
20. Haciislamoglu E, Colak F, Canyilmaz E, Dirican B, Gurdalli S, Yilmaz AH, et al. Dosimetric comparison of left-sided whole-breast irradiation with 3DCRT, forward-planned IMRT, inverse-planned IMRT, helical tomotherapy, and volumetric arc therapy. *Phys Med* 2015; **31**: 360–7. doi: https://doi.org/10.1016/j.ejmp.2015.02.005
21. 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. doi: https://doi.org/10.1016/j.meddos.2013.12.003
22. Sas-Korczyńska B, Sladowska A, Rozwadowska-Bogusz B, Dyczek S, Lesiak J, Kokoszka A, et al. Comparison between intensity modulated radiotherapy (IMRT) and 3D tangential beams technique used in patients with early-stage breast cancer who received breast-conserving therapy. *Rep Pract Oncol Radiother* 2010; **15**: 79–86. doi: https://doi.org/10.1016/j.rpor.2010.06.002
23. Ramella S, Trodella L, Mineo TC, Pompeo E, Stimato G, Gaudino D,

et al. Adding ipsilateral V_{20} and V_{30} to conventional dosimetric constraints predicts radiation pneumonitis in stage IIIA-B NSCLC treated with combined-modality therapy. *Int J Radiat Oncol Biol Phys* 2010; **76**: 110–5. doi: https://doi.org/10.1016/j.ijrobp.2009.01.036

24. Hernando ML, Marks LB, Bentel GC, Zhou SM, Hollis D, Das SK, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. *Int J Radiat Oncol Biol Phys* 2001; **51**: 650–9. doi: https://doi.org/10.1016/S0360-3016(01)01685-6
25. Song CH, Pyo H, Moon SH, Kim TH, Kim DW, Cho KH, et al. Treatment-related pneumonitis and acute esophagitis in non-small-cell lung cancer patients treated with chemotherapy and helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2010; **78**: 651–8. doi: https://doi.org/10.1016/j.ijrobp.2009.08.068
26. Wang S, Liao Z, Wei X, Liu HH, Tucker SL, Hu C-su, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non–small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). *Int J Radiat Oncol Biol Phys* 2006; **66**: 1399–407. doi: https://doi.org/10.1016/j.ijrobp.2006.07.1337
27. Aristei C, Palumbo I, Perrucci E, et al. The association of chemotherapy and radiotherapy: breast cancer. *Curr Drug ther* 2010; **5**: 192–201. doi: https://doi.org/10.2174/157488510791561011
28. Darby SC, McGale P, Taylor CW, Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 2005; **6**: 557–65. doi: https://doi.org/10.1016/S1470-2045(05)70251-5
29. Taylor CW, McGale P, Povall JM, Thomas E, Kumar S, Dodwell D, et al. Estimating cardiac exposure from breast cancer radiotherapy in clinical practice. *Int J Radiat Oncol Biol Phys* 2009; **73**: 1061–8. doi: https://doi.org/10.1016/j.ijrobp.2008.05.066
30. Palumbo I, Palumbo B, Fravolini ML, Marcantonini M, Perrucci E, Latini ME, et al. Brain natriuretic peptide as a cardiac marker of transient radiotherapy-related damage in left-sided breast cancer patients: a prospective study. *Breast* 2016; **25**: 45–50. doi: https://doi.org/10.1016/j.breast.2015.10.004
31. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368**: 987–98. doi: https://doi.org/10.1056/NEJMoa1209825
32. Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the heart in breast cancer radiation therapy: a systematic review of heart doses published during 2003 to 2013. *Int J Radiat Oncol Biol Phys* 2015; **93**: 845–53. doi: https://doi.org/10.1016/j.ijrobp.2015.07.2292
33. 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* 2013; **52**: 703–10. doi: https://doi.org/10.3109/0284186X.2013.765064
34. Offersen B, Højris I, Overgaard M. Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer - is it still an issue? *Radiother Oncol* 2011; **100**: 157–9. doi: https://doi.org/10.1016/j.radonc.2011.08.007
35. Lorenzen EL, Taylor CW, Maraldo M, Nielsen MH, Offersen BV, Andersen MR, et al. Inter-observer variation in delineation of the heart and left anterior descending coronary artery in radiotherapy for breast cancer: a multi-centre study from Denmark and the UK. *Radiother Oncol* 2013; **108**: 254–8. doi: https://doi.org/10.1016/j.radonc.2013.06.025
36. Abo-Madyan Y, Aziz MH, Aly MM, Schneider F, Sperk E, Clausen S, et al. Second cancer risk after 3D-CRT, IMRT and VMAT for breast cancer. *Radiother Oncol* 2014; **110**: 471–6. doi: https://doi.org/10.1016/j.radonc.2013.12.002
37. Roland TF, Stathakis S, Ramer R, Papanikolaou N. Measurement and comparison of skin dose for prostate and head-and-neck patients treated on various IMRT delivery systems. *Appl Radiat Isot* 2008; **66**: 1844–9. doi: https://doi.org/10.1016/j.apradiso.2008.05.003
38. Sugie C, Manabe Y, Hayashi A, Murai T, Takaoka T, Hattori Y, et al. Efficacy of the dynamic jaw mode in helical tomotherapy with static ports for breast cancer. *Technol Cancer Res Treat* 2015; **14**: 459–65. doi: https://doi.org/10.1177/1533034614558746