



Original Article

Evaluation of a Novel Field-placement Algorithm for Locoregional Breast Cancer Radiotherapy Including the Internal Mammary Chain



A. Ranger^{*†}, A. Dunlop^{*†}, P. Shah[‡], K. Amin[‡], D. Henderson[‡], F.R. Bartlett[§], C. Knowles[‡], B. Brigden[‡], C. Lacey[‡], E. Donovan[¶], E. Harris^{*†}, A.M. Kirby^{*†}

^{*}The Institute of Cancer Research, London, UK

[†]The Royal Marsden NHS Foundation Trust, London, UK

[‡]University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

[§]Queen Alexandra Hospital, Portsmouth, UK

[¶]CVSSP, University of Surrey, Guildford, UK

Received 15 April 2018; received in revised form 18 June 2018; accepted 25 June 2018

Abstract

Aims: Irradiation of the internal mammary chain (IMC) is increasing following recently published data, but the need for formal delineation of lymph node volumes is slowing implementation in some healthcare settings. A field-placement algorithm for irradiating locoregional lymph nodes including the IMC could reduce the resource impact of introducing irradiation of the IMC. This study describes the development and evaluation of such an algorithm.

Materials and methods: An algorithm was developed in which six points representing lymph node clinical target volume borders (based on European Society for Radiotherapy and Oncology consensus nodal contouring guidelines) were placed on computed tomography-defined anatomical landmarks and used to place tangential and nodal fields. Single-centre testing in 20 cases assessed the success of the algorithm in covering planning target volumes (PTVs) and adequately sparing organs at risk. Plans derived using the points algorithm were also compared with plans generated following formal delineation of nodal PTVs, using the Wilcoxon signed rank test. Timing data for point placement were collected. Multicentre testing using the same methods was then carried out to establish whether the technique was transferable to other centres.

Results: Single-centre testing showed that 95% of cases met the nodal PTV coverage dose constraints (binomial probability confidence interval 75.1–99.9%) with no statistically significant reduction in mean heart dose or ipsilateral lung V_{17Gy} associated with formal nodal delineation. In multicentre testing, 69% of cases met nodal PTV dose constraints and there was a statistically significant difference in IMC PTV coverage using the points algorithm when compared with formally delineated nodal volumes ($P < 0.01$). However, there was no difference in axillary level 1–4 PTV coverage ($P = 0.11$) with all cases meeting target volume constraints.

Conclusions: The optimal strategy for breast and locoregional lymph node radiotherapy is target volume delineation. However, use of this novel points-based field-placement algorithm results in dosimetrically acceptable plans without the need for formal lymph node contouring in a single-centre setting and for the breast and level 1–4 axilla in a multicentre setting. Further quality assurance measures are needed to enable implementation of the algorithm for irradiation of the IMC in a multicentre setting.

© 2018 Published by Elsevier Ltd on behalf of The Royal College of Radiologists.

Key words: Heart-sparing radiotherapy; internal mammary chain radiotherapy; resource-sparing radiotherapy techniques

Introduction

The indications for locoregional nodal radiotherapy in women with breast cancer are increasing. The Early Breast Cancer Trialists' Collaborative Group's 20 year meta-

analysis of the benefit of radiotherapy for post-mastectomy patients showed a significant reduction in breast cancer mortality associated with locoregional radiotherapy irrespective of the number of lymph nodes involved [1]. The use of postoperative locoregional lymph node radiotherapy is also supported by the results of two large randomised controlled trials that include the internal mammary chain (IMC) in the radiotherapy target volume [2,3]. The benefit specific to IMC radiotherapy has been

Author for correspondence: A. Ranger, The Institute of Cancer Research, London, UK.

E-mail address: alison.ranger@icr.ac.uk (A. Ranger).

further investigated by the Danish Breast Cancer Collaborative Internal Mammary Node trial, which reported a 4.4% overall survival benefit for IMC radiotherapy across the whole trial population and a 7.4% overall survival benefit in those diagnosed with a medially located tumour and/or four or more positive lymph nodes [4]. Following publication of the AMAROS study, irradiation of the axilla is also increasingly used in place of further axillary dissection after sentinel lymph node biopsy [5]. In 2016, the Royal College of Radiologists (UK) published consensus guidelines on post-operative radiotherapy for breast cancer [6]. These guidelines state that IMC radiotherapy should be considered for women at higher risk of locoregional recurrence, that lymph nodes should be defined according European Society for Radiotherapy and Oncology (ESTRO) guidelines [7] and that radiotherapy is a reasonable alternative to further axillary surgery in selected patients with axillary macrometastases. As a result, the frequency and complexity of locoregional breast radiotherapy is increasing in UK practice.

In some healthcare settings, where field-based planning remains the predominant technique for locoregional breast cancer radiotherapy, barriers to the implementation of the above guidance, particularly the use of irradiation of the IMC, include the need to formally outline the lymph node regions. Given that field borders are placed according to the periphery of the formally contoured lymph node target volumes, it may be that placing points on these peripheries could adequately define field borders without the need for formal lymph node delineation.

This article describes an algorithm in which six anatomical points defining the peripheries of the locoregional target volume for breast cancer radiotherapy are identified on a radiotherapy computed tomography planning scan to guide field placement. The ability of this points-based field-placement algorithm to satisfactorily meet target and non-target tissue constraints for locoregional lymph node radiotherapy (including the IMC) was initially tested in a single-centre setting before being tested, in a second phase, by multiple observers from five other radiotherapy centres.

Materials and Methods

Six points were identified as defining the borders of regional lymph node levels according to ESTRO consensus guidelines as described in Table 1. The radius of the points placed reflects the clinical target volume (CTV) to planning target volume (PTV) margin and a margin for the beam penumbra. In order to encompass these margins, fields were placed on the periphery of points, as shown in Figure 1. A written algorithm using these points to place radiotherapy fields capable of satisfying target and non-target tissue dose constraints was devised (Supplementary data).

For single-centre testing, a cohort of 20 patients, treated within the HeartSpare II trial, was randomly selected as a validation group [8]. All patients were using the voluntary

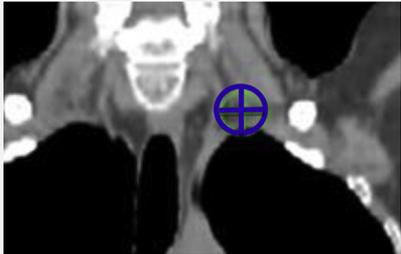
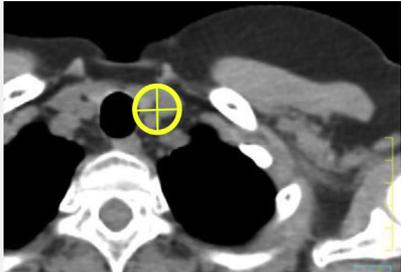
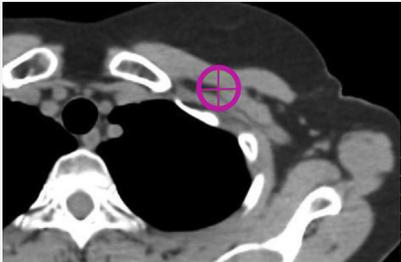
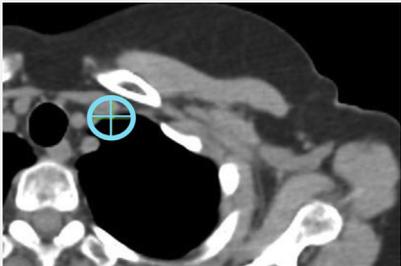
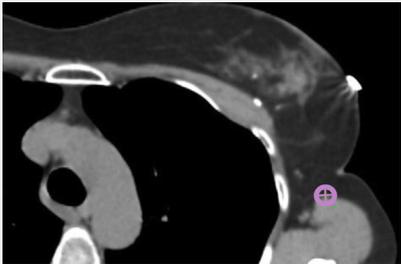
deep inspiration breath-hold technique [9]. A group of four clinical oncologists followed ESTRO consensus guidelines to generate consensus CTVs for the IMC and axillary lymph nodes for all patients [7]. The axillary node CTV included level 1–4 in eight cases, levels 2–4 in three cases and levels 3 and 4 in nine cases (according to clinical need). In each case, the PTV nodes included the relevant axillary lymph node CTVs grown by 5 mm isotropically excluding lung. The PTV IMC was created by growing the IMC CTV by 5 mm, again excluding lung. The two PTVs were evaluated separately to ensure poor IMC coverage was not masked by good coverage of the other nodal levels. Exclusion of lung from the PTV was justified as if either CTV were to move into the area previously occupied by lung, dose would be maintained by virtue of surrounding tissue also moving into this area. Contours were created and PTVs grown in the Pinnacle³ v9.10 (Philips, Fitchburg, WI, USA) treatment planning system (TPS). The heart and lungs were generated using the Smart Probabilistic Image Contouring Engine, which is available within Pinnacle³. The automatically generated contours were assessed and manually edited as necessary.

For the single-centre test phase, nine radiographers and one clinical oncologist (testers) from the same centre, blind to the nodal volumes, followed a written algorithm with figures describing (i) anatomical landmarks for point placement and (ii) placement of field borders and shielding (see Table 1 and Supplementary data). Testers were given a 20 min presentation to ensure they were familiar with the anatomical landmarks for point placement. Once the points and fields had been placed, they were reviewed by a different clinical oncologist (AK or DH) who made amendments if necessary prior to planning. This step emulates local practice where clinicians review digitally reconstructed radiographs created by radiographers to evaluate field placement prior to planning.

Dose distributions were calculated in Pinnacle³ for six of the 20 cases and the remaining 14 cases were created in the Eclipse[™] v13.7 (Varian Medical Systems, Palo Alto, CA, USA) TPS. Opposing wide tangential step-and-shoot photon beams with a non-divergent posterior field edge modified to cover the breast or chest wall, IMC and the inferior part of lymph node levels 1–3 were used [2]. A matched anterior field (matched at the level of the inferior aspect of the medial head of the clavicle) was used to cover lymph node level 4 and the superior part of levels 1–3. Lymph node levels were defined according to the points algorithm. Heart and lung shielding was achieved using multileaf collimation according to points 4 and 6 (Figure 1). 6 MV photon beams were used for most patients. 10 MV beams were used for the anterior field to achieve coverage of nodal volumes at greater depth.

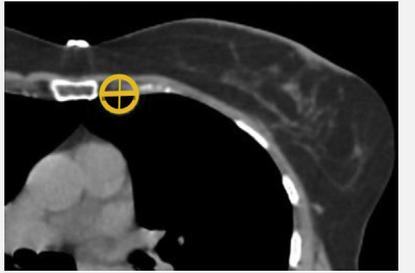
In order to meet the ipsilateral lung dose constraint ($V_{17\text{ Gy}} \leq 35\%$), cranial displacement of the match line was used in cases where the lung dose exceeded the constraint (Figure 1). This involved moving the match line to the computed tomography slice below the inferior aspect of the head of the humerus. In these cases, anatomical point 4 was re-positioned at the level of the new match line to ensure

Table 1
Point position and corresponding field borders

	Field border	Point position	
1	Superior border of anterior field	Superior aspect of subclavian artery	
2	Medial border of anterior field	Medial aspect of internal jugular vein	
3	Lateral border of anterior field	Dependent on nodal level requiring treatment, e.g. level 3 – medial border of pectoralis minor muscle	
4	Posterior border of wide tangents	Most superior part of internal mammary vessels in wide tangential field	
5	Lateral border of wide tangents	Mid-point of anterior surface of latissimus dorsi muscle at the level of the fourth rib	

(continued on next page)

Table 1 (continued)

	Field border	Point position	
6	Heart and lung multileaf collimator shielding	Internal mammary vein at the insertion of fourth rib to sternum	

The point number, field border it dictates and the anatomical position of the point (illustrated using axial computed tomography slices). The centre of the point is placed on the anatomical landmark described. The radius of the point reflects the clinical target volume to planning target volume distance plus a margin for the field penumbra.

Examples of field placement and shielding following the points algorithm.

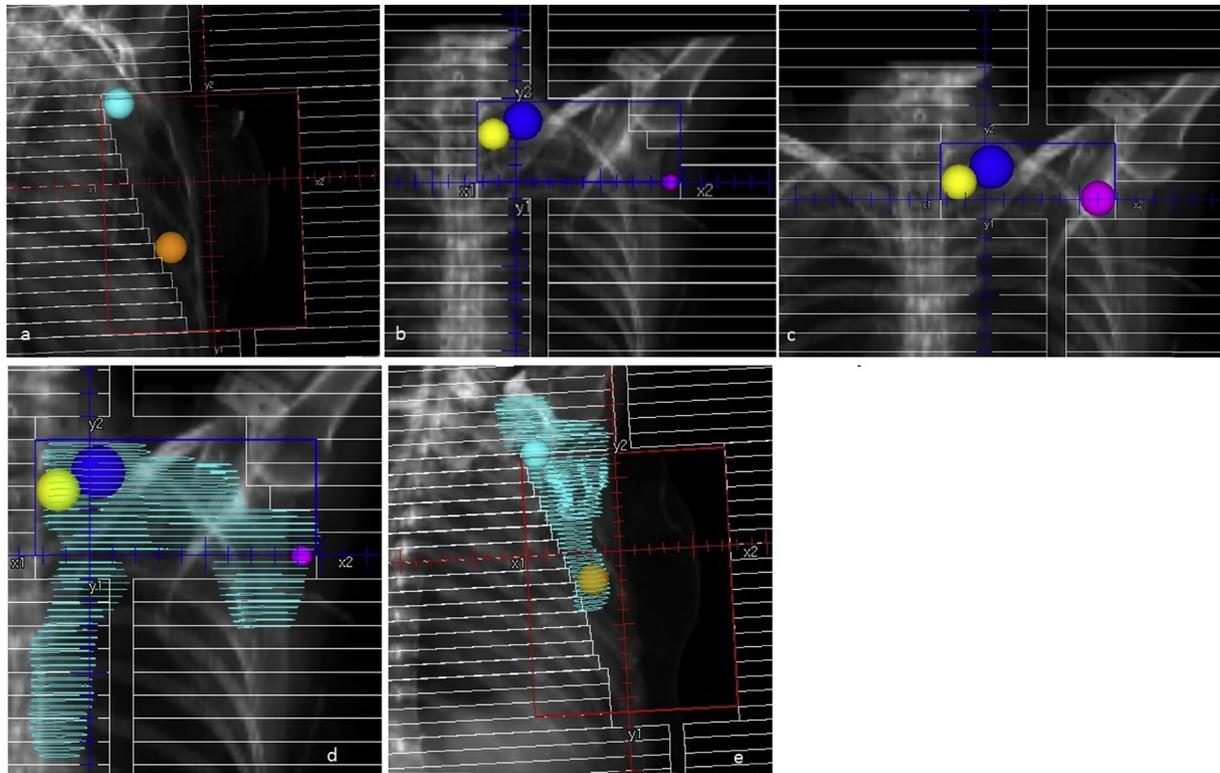


Fig 1. (a) Digitally reconstructed radiograph of the left posterior oblique field with multileaf collimation shielding of the heart and lungs placed according to points 4 and 6 (sky blue and orange); (b) anterior field with normal match line (at the inferior aspect of the head of the clavicle) with field borders placed according to points 1, 2 and 3 (blue, yellow, purple); (c) Anterior field with cranial displacement of the match line with field borders placed according to points 1, 2 and 3 (blue, yellow, purple); (d) anterior and (e) tangential fields with fields placed according to points 1–6 conforming closely to the planning target volume (blue).

the superior (often more posterior and medial) part of the IMC was included in the wide tangential fields. Cranial displacement of the match line was only possible in cases where the resulting anterior field was greater than $3\text{ cm} \times 3\text{ cm}$ in size (to allow for accurate dosimetry and verification on treatment) and did not encompass any of the patient's arm.

The primary end point of the single-centre study was the pass rate (proportion) of cases meeting the nodal PTV

coverage objective of $\geq 90\%$ coverage with 80% of the prescribed dose ($V_{32\text{Gy}}$). To pass, this objective had to be met for both the PTV nodes and PTV IMC. Secondary end points were: (i) the percentage difference in target volume coverage resulting from plans created using fully delineated nodal volumes (planned as previously described) compared with those created using the points algorithm (analysed using the Wilcoxon signed rank test), (ii) the proportion of cases meeting non-target tissue dose constraints (mean

heart dose [MHD] ≤ 4 Gy for left-sided cases and ipsilateral lung $V_{17\text{Gy}} \leq 35\%$ for all cases) and (iii) the time taken to place points.

A multicentre evaluation was then carried out where five pairs of clinicians and radiographers were invited to test the algorithm on up to three cases with a total sample size of 13 tests. The primary and secondary end points were the same as for single-centre testing. Multicentre testers were given the same 20 min teaching presentation before testing (as used in the single-centre test phase). Dose distributions were calculated in Pinnacle³ TPS for all 13 tests using the same technique as for single-centre testing. The sample size for multicentre testing aimed to exclude a mean difference of 5% (standard deviation of 5%, 90% power) between plans derived from following the points algorithm and those derived using fully delineated nodal volumes. Organ at risk (OAR) dose statistics were also compared.

Results

Dose statistics for single-centre testing (presented in Table 2) showed that 95% (19/20) of cases planned using the points algorithm met the target volume dose constraints for the PTV IMC and the PTV nodes (95% binomial probability confidence interval 75.1–99.9%). In cases where the target volume dose constraint was met, use of the points algorithm resulted in fields and multileaf collimation shielding, which conformed closely to the PTVs (Figure 1d, e). Comparison of dose distributions derived from plans created based on fields shaped according to formally delineated nodal volumes versus those derived from plans based on fields placed according to the points algorithm during single-centre testing (also presented in Table 2) showed that there was no statistically significant difference in coverage of the PTV IMC ($P = 0.09$). There was a statistically significant difference between coverage of the PTV nodes between the two techniques ($P = 0.04$). However, this is clinically insignificant as all plans using both techniques passed target volume coverage constraints.

In the case where the target volume (PTV IMC) was inadequately covered ($V_{32\text{Gy}} = 88\%$, as opposed to 90%), the superior IMC point (point 4) had not been placed at the level of the match line, i.e. the top of the tangential fields. This was not recognised by the checking oncologist and resulted in the posterior field edge of the tangential fields being too

shallow to adequately encompass the most superior part of the IMC (Figure 2a).

In the single-centre study, four of 20 cases failed OAR dose volume constraints using the points algorithm compared with two cases planned following formal delineation of nodal volumes. One case failed due to a MHD of 4.2 Gy (i.e. only just in excess of the constraint of 4.0 Gy). Given that, in this case, the MHD achieved following formal delineation of the IMC was 4.6 Gy, it is likely that this represented unfavourable patient anatomy rather than a failure of the points algorithm itself. Three cases failed to meet the ipsilateral lung dose constraint with a $V_{17\text{Gy}}$ of 44%, 37% and 36%, respectively. In the first case the inferior IMC point had been placed in the fourth rather than the third intercostal space, resulting in a considerable increase in lung dose, which was not identified by clinician review before planning. When planned with the point in the correct position all constraints were met. In the second case (ipsilateral lung $V_{17\text{Gy}}$ 37%), it was not possible to perform cranial displacement of the match line due to the patient's arm position. However, an ipsilateral lung $V_{17\text{Gy}}$ of 35% was achieved with a plan created following formal delineation of lymph node levels. Similarly, in the third case, the ipsilateral lung $V_{17\text{Gy}}$ was reduced from 36 to 34% when plans were created using formally delineated lymph node volumes, suggesting a small reduction in lung dose may be achieved by formal nodal delineation. However, there was no statistically significant difference between the lung doses for the two groups overall ($P = 0.47$). Point placement for radiographers took an average of 13.3 min.

Dose statistics for multicentre testing of the algorithm are presented in Table 3. PTV IMC coverage was statistically significantly less using the points algorithm than fully delineated nodal volumes ($P < 0.01$), with only 69% of plans passing the PTV IMC target volume constraint. However, all cases met the PTV nodes constraint and there was no statistically significant difference between coverage of the PTV nodes when plans derived from the points algorithm were compared with those planned from fully delineated lymph node volumes ($P = 0.11$). Median MHDs were 2.1 Gy for the fully outlined plans and 2.2 Gy for the points plans ($P = 0.03$). Twelve of 13 cases (92%) met MHD constraints using the points algorithm. Median ipsilateral lung $V_{17\text{Gy}}$ was 29.9% for fully contoured plans and 32.9% for points plans. Plans derived from the points algorithm resulted in

Table 2

Comparison of dose parameters and pass rates for plans derived from fully contoured lymph node volumes with plans derived following the points algorithm during single-centre testing

Target volume coverage/organ at risk dose	Median (range)		Pass rate (%)	
	Contoured plans	Points plans	Contoured plans	Points plans
PTV IMC $V_{32\text{Gy}}$	97.0% (93.0–100%)	96.0% (88.0–100%)	100	95
PTV nodes $V_{32\text{Gy}}$	97.0% (94.0–100%)	95.0% (91.0–100%)	100	100
Mean heart dose*	1.5 Gy (1.3–4.6 Gy)	1.8 Gy (1.4–4.2 Gy)	80	90
Ipsilateral lung $V_{17\text{Gy}}$	28.5% (17.0–35.0%)	26.5% (15.0–44.0%)	100	85

PTV, planning target volume; IMC, internal mammary chain.

* Left-sided cases only.

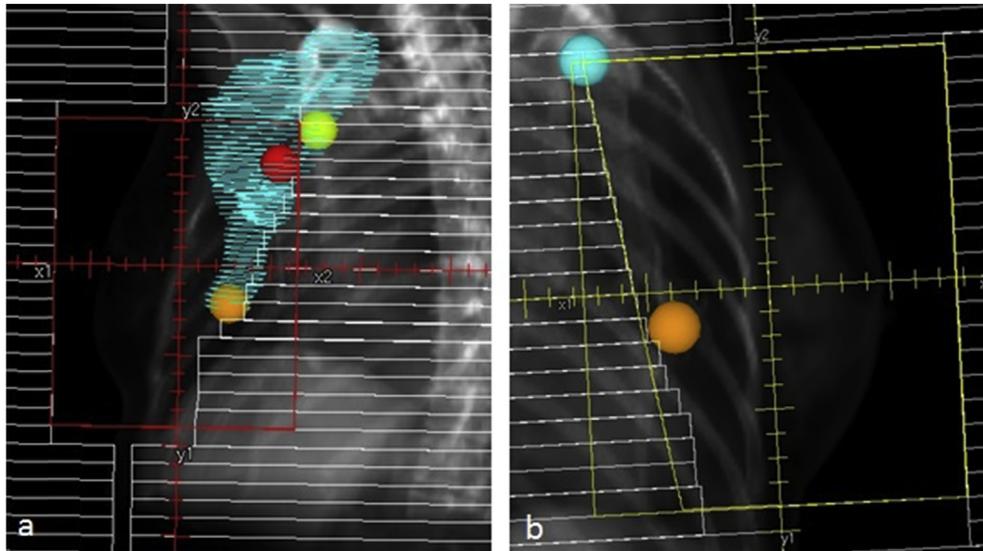


Fig 2. (a) Single-centre case where the algorithm failed to provide adequate coverage of the planning target volume (PTV) internal mammary chain (IMC); point 4 (red) was placed incorrectly by the tester. If the point had been placed correctly (lime green) the posterior border of the tangential field would have encompassed the PTV IMC. (b) Multicentre test where the algorithm failed to provide adequate coverage of the PTV IMC; fields were placed incorrectly in relation to points, resulting in under-dosing of the PTV IMC.

Table 3

Comparison of dose parameters and pass rates for plans derived from fully contoured lymph node volumes with plans derived following the points algorithm during multicentre testing

Target volume/organ at risk	Median (range)		Pass rate	
	Contoured plans	Points plans	Contoured plans	Points plans
PTV IMC	97.3% (92.2–98.3%)	91.0% (78.9–96.8%)	100%	69%
PTV nodes	95.5% (94.0–99.7%)	96.2% (90.8–97.7%)	100%	100%
Mean heart dose	2.1 Gy (1.5–2.6 Gy)	2.2 Gy (1.8–4.3 Gy)	100%	92%
Ipsilateral lung $V_{17\text{Gy}}$	29.9% (25.2–33.9%)	32.9% (22.3–41%)	100%	77%

PTV, planning target volume; IMC, internal mammary chain.

significantly higher ipsilateral lung $V_{17\text{Gy}}$ doses (3/13 plans failed to meet the dose constraint).

Discussion

The single-centre phase of this study showed that a points-based algorithm is capable of meeting target volume dose constraints and OAR constraints in most cases tested, thus presenting an alternative to formal nodal delineation. In just one of 20 cases, incorrect positioning of the point led to algorithm failure by covering only 88% of the PTV IMC with 32 Gy (80% isodose) rather than 90%. It should be borne in mind, however, that considerable interobserver variability exists even when formally delineating structures for breast radiotherapy [10–15]. In the context of locoregional breast radiotherapy, this can result in nodal PTVs, which vary by up to 15% [16], such that the reduced coverage observed with the points-based algorithm in 1/20 cases would seem at least comparable with the discrepancies in target volume coverage resulting from interobserver variation in target volume delineation.

Sixteen of the 20 cases met OAR dose constraints during single-centre testing. MHD results in this study compare

favourably with published planning studies in which the IMC is included in the target volume [17–23]. Three cases exceeded the dose constraint for the ipsilateral lung. In one case, where the inferior IMC point was placed in the wrong intercostal space, the dose was well above tolerance. In clinical practice, this error would have been identified and corrected during the planning of the patient's treatment and review of the DVH. For the other two cases, comparison with plans generated from fully delineated volumes does suggest a small advantage in reduction of ipsilateral lung $V_{17\text{Gy}}$ associated with formal nodal delineation. This limitation of the algorithm is the result of the diagonal line of multileaf collimator shielding between point 4 and 6 described, as opposed to multileaf collimator shaping, which closely conforms to the PTV IMC. However, an additional step can be taken when using the points algorithm to improve conformality (shown in Figure 3).

Comparison of dose statistics between plans derived from the points algorithm and those derived from formally delineated nodal volumes in the single-centre phase of testing show that good agreement can be achieved. The median difference between PTV IMC coverage in the two groups was 1.5%. For the PTV nodes (axillary levels 1–4) the

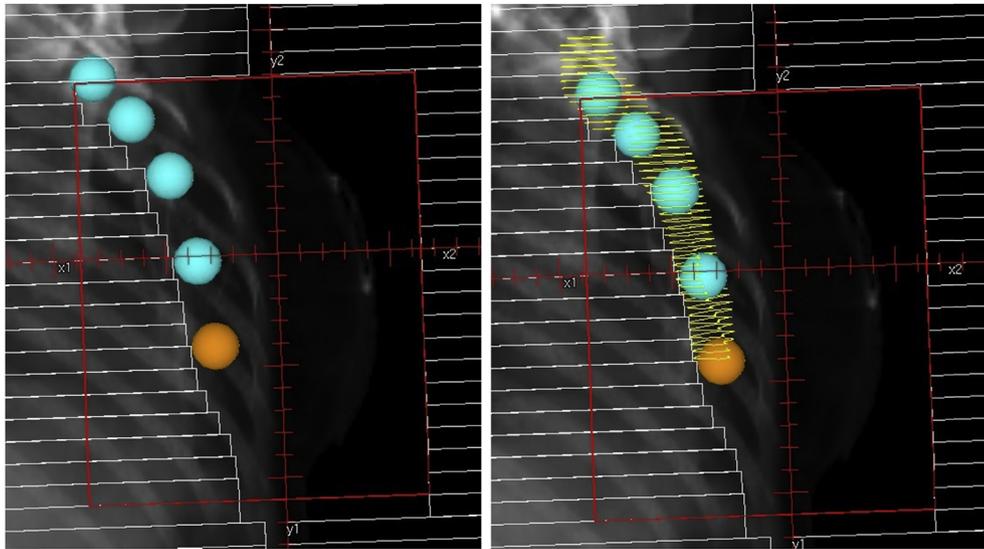


Fig 3. Multiple points positioned along the internal mammary chain creating a virtual planning target volume to which multileaf collimation can be conformed, this reflects the shape of the planning target volume internal mammary chain (yellow).

median difference was 1%. Although the difference in PTV nodes coverage was statistically significant between the two groups, this is unlikely to be clinically significant and suggests there is little advantage in formally delineating locoregional target volumes. There was no statistically significant difference in OAR doses between the two techniques, again suggesting no advantage in formal lymph node delineation for organ-sparing purposes.

The single-centre phase of this study is limited by the small number of cases tested, resulting in a large binomial confidence interval for the predicted proportion of cases meeting target volume constraints. Furthermore, if there is a clinical need to know absolute values for target volume coverage, target volumes will clearly need to be formally delineated.

The multicentre phase tested whether or not the results described above could be replicated when the algorithm was used by staff from other centres. PTV IMC coverage was statistically significantly lower following use of the points algorithm when compared with formal lymph node delineation, resulting in only 69% of cases passing the target volume constraint in the multicentre phase. However, the median difference between PTV IMC coverage in the two groups was only 4.1%, a difference that again might be considered relatively small in the context of inter-observer variation for formal nodal delineation. In two cases, PTV IMC coverage differed significantly from plans based on formally delineated volumes. Both of these cases were performed by a clinical oncologist without a radiographer partner (due to a lack of radiographer availability from that centre) and the large differences resulted from incorrect positioning of field borders in relation to points (Figure 2b). It would be highly unusual in UK clinical practice for fields to be placed by a clinician rather than a radiographer such that it is unlikely that this error would occur in standard departmental practice. For the remaining two cases, where

PTV IMC coverage did not meet the 90% objective, coverage was 87% and 89%, respectively, which may be deemed clinically acceptable. Nonetheless, this algorithm failure highlights the need for a process of quality assurance when implementing use of the points algorithm. Two possible options include a set up phase, where new centres formally delineate nodal volumes and also follow the points algorithm in an initial test cohort to ensure fields placed using the algorithm adequately cover nodal volumes. Alternatively, an established algorithm user could quality assure point placement for a new user for an initial training period.

Coverage of the axillary nodal PTV excluding the IMC using the points algorithm was highly consistent with coverage achieved by plans derived from fully delineated nodal volumes (median difference 0.7%, $P = 0.11$) and all cases met the target volume dose constraint. This suggests that use of the points algorithm could be successfully adopted by other centres to define the anterior field for locoregional breast radiotherapy without the need for any additional steps.

MHD results from the multi-observer part of the study were consistent with those in the first part of the study and compare favourably with published literature. Again, there was an increase in ipsilateral lung V_{17Gy} associated with use of the points algorithm. However, in 10 of 13 tests the dose constraint was met. As discussed above, cranial displacement of the match line or the additional step described in Figure 3 could be used to decrease lung V_{17Gy} .

In summary, single-centre testing shows that the points algorithm is capable of covering target volumes and sparing OARs for locoregional breast radiotherapy without the need for formal lymph node contouring. Multicentre testing suggests the technique is transferable outside our centre, but appropriate quality assurance measures need to be taken prior to implementation in order to ensure adequate coverage of the IMC.

Conclusion

The optimal strategy for breast and locoregional lymph node radiotherapy planning is target volume delineation. However, use of this novel points-based field-placement algorithm results in dosimetrically acceptable plans without the need for formal lymph node contouring in a single-centre setting and, for the breast and level 1–4 axilla, in a multicentre setting. Further quality assurance measures are needed to enable implementation of the algorithm for IMC radiotherapy in a multicentre setting.

Acknowledgements

With thanks to colleagues who tested the algorithm: Jane Francis, Emer Henegan, Tasneem Kabir, Karen Carr, Heidi Greenstreet, Sadia Choudhury, Mark Davies, Richard Keane, Cathy King, Neil Johns, David Bloomfield, Jackie Sham, Jotsna Varsani, Charlotte Westbury, Elinor Sawyer, Roshni Chauhan, Suzy Cleator, Imogen Locke, Navita Somaiah. This research is funded by The Royal Marsden National Institute of Health Research Biomedical Research Centre grant 'A079 - HeartSpare-Plus: Optimising radiotherapy planning & delivery for pan-regional lymph node radiotherapy in patients with breast cancer'. This research is supported by The Royal Marsden CRUK program grant C33589/A19727.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.clon.2018.06.014>.

References

- [1] McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, 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;383:2127–2135. [https://doi.org/10.1016/S0140-6736\(14\)60488-8](https://doi.org/10.1016/S0140-6736(14)60488-8).
- [2] Whelan TJ, Olivetto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:307–316. <https://doi.org/10.1056/NEJMoa1415340>.
- [3] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast Cancer. *N Engl J Med* 2015;373:317–327. <https://doi.org/10.1056/NEJMoa1415369>.
- [4] Thorsen LBJ, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016;34:314–320. <https://doi.org/10.1200/JCO.2015.63.6456>.
- [5] Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. *Lancet Oncol* 2014;15:1303–1310. [https://doi.org/10.1016/S1470-2045\(14\)70460-7](https://doi.org/10.1016/S1470-2045(14)70460-7).
- [6] *Postoperative radiotherapy for breast cancer: UK consensus statements 2016*.
- [7] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Bieta Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015;114:3–10. <https://doi.org/10.1016/j.radonc.2014.11.030>.
- [8] Bartlett FR, Donovan EM, McNair HA, Corsini LA, Colgan RM, Evans PM, et al. The UK HeartSpare Study (Stage II): multi-centre evaluation of a voluntary breath-hold technique in patients receiving breast radiotherapy. *Clin Oncol* 2017;29:e51–e56. <https://doi.org/10.1016/j.clon.2016.11.005>.
- [9] Bartlett FR, Colgan RM, Carr K, Donovan EM, McNair HA, Locke I, et al. The UK HeartSpare Study: randomised evaluation of voluntary deep-inspiratory breath-hold in women undergoing breast radiotherapy. *Radiother Oncol* 2013;108:242–247. <https://doi.org/10.1016/j.radonc.2013.04.021>.
- [10] Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. *Int J Radiat Oncol Biol Phys* 2007;67:1299–1308. <https://doi.org/10.1016/j.ijrobp.2006.11.026>.
- [11] Petersen RP, Truong PT, Kader HA, Berthelet E, Lee JC, Hilts ML, et al. Target volume delineation for partial breast radiotherapy planning: clinical characteristics associated with low inter-observer concordance. *Int J Radiat Oncol Biol Phys* 2007;69:41–48. <https://doi.org/10.1016/j.ijrobp.2007.01.070>.
- [12] Gwynne S, Spezi E, Sebag-Montefiore D, Mukherjee S, Miles E, Conibear J, et al. Improving radiotherapy quality assurance in clinical trials: assessment of target volume delineation of the pre-accrual benchmark case. *Br J Radiol* 2013;86:1–11. <https://doi.org/10.1259/bjr.20120398>.
- [13] Yang J, Woodward WA, Reed VK, Strom EA, Perkins GH, Tereffe W, et al. Statistical modeling approach to quantitative analysis of interobserver variability in breast contouring. *Int J Radiat Oncol Biol Phys* 2014;89:214–221. <https://doi.org/10.1016/j.ijrobp.2014.01.010>.
- [14] Struikmans H, Rodenhuis C, Stam T, Stapper G, Tersteeg RJHA, Bol GH, et al. Interobserver variability of clinical target volume delineation of glandular breast tissue and of boost volume in tangential breast irradiation. *Radiother Oncol* 2005;76:293–299. <https://doi.org/10.1016/j.radonc.2005.03.029>.
- [15] Eriksen JG, Salembier C, Rivera S, De Bari B, Berger D, Mantello G, et al. Four years with FALCON – an ESTRO educational project: achievements and perspectives. *Radiother Oncol* 2014;112:145–149. <https://doi.org/10.1016/j.radonc.2014.06.017>.
- [16] Li XA, Tai A, Arthur DW, Buchholz TA, Macdonald S, Marks LB, et al. Variability of target and normal structure delineation for breast cancer radiotherapy: an RTOG multi-institutional and multiobserver study. *Int J Radiat Oncol Biol Phys* 2009;73:944–951. <https://doi.org/10.1016/j.ijrobp.2008.10.034>.
- [17] Lomax AJ, Cella L, Weber D, Kurtz JM, Miralbell R. Potential role of intensity-modulated photons and protons in the treatment of the breast and regional nodes. *Int J Radiat Oncol Biol Phys* 2003;55:785–792. [https://doi.org/10.1016/S0360-3016\(02\)04210-4](https://doi.org/10.1016/S0360-3016(02)04210-4).
- [18] Johansen S, Cozzi L, Olsen DR. A planning comparison of dose patterns in organs at risk and predicted risk for radiation induced malignancy in the contralateral breast following radiation therapy of primary breast using conventional, IMRT and volumetric modulated arc treatment technique. *Acta Oncol* 2009;48:495–503. <https://doi.org/10.1080/02841860802657227>.
- [19] Popescu CC, Olivetto 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: 287–295. <https://doi.org/10.1016/j.ijrobp.2009.05.038>.
- [20] Osman SOS, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. *Radiother Oncol* 2014;112:17–22. <https://doi.org/10.1016/j.radonc.2014.04.004>.
- [21] Sakumi A, Shiraishi K, Onoe T, Yamamoto K, Haga A, Yoda K, et al. Single-arc volumetric modulated arc therapy planning for left breast cancer and regional nodes. *J Radiat Res* 2012;53: 151–153. <https://doi.org/10.1269/jrr.11159>.
- [22] Ares C, Khan S, MacArtain AM, Heuberger J, Goitein G, Gruber G, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 2010;76: 685–697. <https://doi.org/10.1016/j.ijrobp.2009.02.062>.
- [23] Ashenafi M, Boyd RA, Lee TK, Lo KK, Gibbons JP, Rosen II, et al. Feasibility of postmastectomy treatment with helical tomotherapy. *Int J Radiat Oncol Biol Phys* 2010;77:836–842. <https://doi.org/10.1016/j.ijrobp.2009.06.027>.