A dosimetric study to improve the quality of nodal radiotherapy in breast cancer

INTRODUCTION
Radiotherapy (RT) for early-stage breast cancer reduces the recurrence risk and improves overall survival. In patients with a positive sentinel node biopsy (SNB), the Early Breast Cancer Trials Collaborative Group reported a significant reduction in mortality with adjuvant loco-regional RT, regardless of the number of positive lymph nodes (LNs) or systemic treatments. The AMAROS trial compared axillary LN dissection (ALND) to regional nodal irradiation (RNI) in post-menopausal, SNB-positive patients. They concluded RNI was equivalent to ALND in efficacy and resulted in less lymph-oedema but increased rates of shoulder stiffness. The trial mandated contouring of LNs and 3D planned RT to include LNs – neither of which is currently employed by all UK departments.

Traditional field-based techniques: anterior field, PAB and anterior- and posterior axillary boost employed bony landmarks to position fields and were widely used. However, previous studies have demonstrated marked variation in the depth and position of LNs, due to the range of body habitus, depth of subcutaneous adipose tissue, and arm position. The variation in LN positions suggested these techniques to be suboptimal and subsequently, they were replaced with 3D conformal RT (3DCRT) techniques. 3DCRT was the standard until the introduction of IMRT, improving nodal target volume coverage and reducing high-dose areas. Despite the increased cost of IMRT, compared to non-IMRT techniques, both IMRT techniques are suitable for supraclavicular and axillary nodal RT.

Advances in knowledge: Forward-planned IMRT already resulted in significant dose reduction to organs at risk and improved planning target volume coverage. This new, simplified forward-planned IMRT technique has not been published in this context and is easy to implement in routine clinical practice.

OBJECTIVES: Field-based planning for regional nodal breast radiotherapy (RT) used to be standard practice. This study evaluated a field-based posterior axillary boost (PAB) and two forward-planned intensity-modulated RT (IMRT) techniques, aiming to replace the first.

METHODS: Supraclavicular and axillary nodes, humeral head, brachial plexus, thyroid, and oesophagus were retrospectively delineated on 12 CT scans. Three plans, prescribed to 40.05 Gy, were produced for each patient. Breast plans consisted of field-in-field IMRT tangential fields in all three techniques. Nodal plans consisted of a field-based PAB (anterior and posterior boost beam), and 2 forward-planned techniques: simple IMRT 1 (anterior and posterior beam with limited segments), and a more advanced IMRT 2 technique (anterior and fully modulated posterior beam).

RESULTS: The nodal V90% was similar between IMRT 1: mean 99.5% (SD 1.0) and IMRT 2: 99.4% (SD 0.5). Both demonstrated significantly improved results (p = 0.0001 and 0.005, respectively) compared to the field-based PAB technique. IMRT 2 lung V12Gy and humeral head V45Gy were significantly lower (p = 0.002, 0.0001, respectively) than the field-based PAB technique. IMRT 1 exhibited significantly lower brachial plexus Dmax and humeral head V5, 10, and 15Gy doses (p = 0.007, 0.013, 0.007 and 0.007, respectively) compared to the field-based PAB technique. The oesophagus and thyroid dose difference between methods was insignificant.

CONCLUSIONS: Both IMRT techniques achieved the dose coverage requirements and reduced normal tissue exposure, decreasing the risk of radiation side effects. Despite the increased cost of IMRT, compared to non-IMRT techniques, both IMRT techniques are suitable for supraclavicular and axillary nodal RT.

ADVANCES IN KNOWLEDGE: Forward-planned IMRT already resulted in significant dose reduction to organs at risk and improved planning target volume coverage. This new, simplified forward-planned IMRT technique has not been published in this context and is easy to implement in routine clinical practice.

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This study compared LN planning target volume (PTV) dose conformity, homogeneity and OAR exposure of a field-based posterior axillary boost (PAB) and two forward-planned IMRT techniques, intending to replace the current field-based PAB method.

**METHODS AND MATERIALS**

**Patient selection, positioning, and CT scanning**
CT scans of 12 consecutive patients referred for adjuvant breast/chest wall irradiation were selected for the study. Patients were scanned in a supine position on a breast board with arms raised and head straight. 3 mm slices from mid-neck to 50 mm inferior to the breast were performed on a wide bore Philips AcQSim CT Scanner (Philips Medical Systems, Guildford, UK). Retrospective field-based PAB and two forward-planned IMRT plans were generated, and evaluation based on ICRU 62 requirements.10 The study received local information governance and institutional audit committee approval.

**Delineation**
Two experienced breast specialists retrospectively delineated supraclavicular and axillary nodes, humeral head, brachial plexus (BP), thyroid and oesophagus. Delineation of nodal clinical target volumes (CTVs) conformed to the European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines.11

**Planning**
Tangential fields were planned first with a field-in-field, forward-planned IMRT technique. The posterior tangential field edges were non-divergent to minimise in-field lung and heart. For each tangential field, 80–85% of the dose was delivered by an open field, and the rest of the dose, typically by 3–5 segments per field. After that, nodal fields were matched to the tangential fields utilising a mono-isocentric beam arrangement. Three nodal plans: a field-based PAB, simple forward-planned IMRT 1, and a more advanced forward-planned IMRT 2 technique were produced for each patient.

In all three plans, the LN CTV was expanded by 5 mm to create a PTV and modified medially, excluding the trachea.12 Previous studies have shown that recurrences occur within the field, and larger volumes could cause increased toxicity13; therefore, every effort was made to ensure the treatment field encompassing the PTV was not more extensive than traditional nodal fields.

In the field-based PAB technique, the single anterior oblique field border was defined laterally by the humeral head, superiorly by the fourth and fifth cervical vertebral space, and medially by the trachea. A PAB field encompassed the lateral half of the anterior field. The humeral head was shielded with multi-leaf collimation (MLC) on both anterior and posterior fields. In both forward-planned IMRT techniques, MLC conformed to the PTV + 0.5 cm (Figures 1 and 2).

Treatment plans were generated with commercial software (Nucletron, OTP v.4.1). Type B (collapsed cone) dose calculations took lung density into account. A combination of dynamic wedges (opposing fields), field-in-field modulation (IMRT plans), and six or 10 MV photon energies (depending on hot spots and nodal volume depth) were applied to create homogeneous dose distributions. A minimum of five monitor units was delivered per segment. In both forward-planned IMRT methods, nodal fields weighted approximately 80:20, anterior: posterior (Figures 3–5).

A dose of 40.05 Gy in 15 fractions over three weeks was prescribed to the ICRU recommended reference point.10 Dose-volume histograms (DVH) calculated and assessed the dosimetry of composite breast/chest wall and nodal fields. The nodal prescribed dose in the field-based PAB technique was modified to ensure the BP tolerance dose was not exceeded.

The following planning and dose objectives were applied:
- LN PTV: V90% ≥ 90% (LN PTV volume receiving 90% of the dose is greater than 90%).
- Breast/chest wall: V95% ≥ 95% (volume receiving 95% of the dose is greater than 95%).
- V107% ≤ 1 cc
- LN and breast PTV maximum dose: ≤ 110% prescribed dose.
- LN PTV DVH: V107% ≤ 2%
- BP maximum point: ≤ 110% of the prescribed dose.
- Ipsilateral lung: V12Gy ≤ 25% (similar to the V30% < 17%, POSNOC trial.14

**Figure 1.** Digitally reconstructed radiographs displaying the anterior fields and shielding for the field-based posterior axillary boost and IMRT techniques
For the nodal IMRT plans, anterior and posterior beams were angled to encompass the LN PTV (supraclavicular and axillary nodes) with a margin for beam penumbra. The posterior beam in the simple IMRT 1 technique comprised of 1–2 segments. In the more advanced IMRT 2 technique, LN PTV under dosed areas were iteratively defined as pseudo targets to guide segment design. The modulation of the posterior field was optimised to compensate accordingly. The resultant 4–7 segments were merged into a single step-and-shoot IMRT field for delivery, preventing an increase in treatment delivery time (Figures 3–5). To demonstrate the dosimetric implications of the junction between tangential and nodal fields, we have created a "junction structure" (6 mm slice of junction PTV) and recorded minimum and maximum doses.

Analysis
Plan evaluation parameters were calculated for each structure, and 26 DVHs were generated.

We analysed the mean $V_{95\%}$ (volume receiving 95% of the dose) for ipsilateral breast PTV dose coverage, $V_{40\,\text{Gy}}$ (volume receiving 40.05 Gy), and $D_{\text{mean}}$.

For dose coverage of the LN PTV above the junction and the total LN PTV, mean $V_{90\%}$ (volume receiving 90% of the dose) was analysed.

Hotspots were represented by breast $D_{2\,\text{cc\,max}}$ (absolute volume in cc), $V_{107\%}$ within and outside the LN PTVs, and LN $D_{\text{max}}$ to determine dose uniformity.

OAR data included: BP $D_{\text{max}}$, ipsilateral lung $V_{5, 10, 12, 20, 30 \,\text{Gy}}$ (volume receiving 5, 10, 12, 20, and 30 Gy, respectively), oesophagus $D_{\text{mean}}$, and thyroid $V_{30\,\text{Gy}}, D_{\text{mean}}, D_{\text{max}}$ and $D_{2\,\text{cc\,max}}$. Humeral head $V_{5\,\text{Gy}}, V_{10\,\text{Gy}}$ and $V_{15\,\text{Gy}}$ were selected for plan evaluation in the absence of published dose constraints.
Statistical analysis was performed with IBM SPSS statistics software, v.27. Means, standard deviations (SD) and 95% confidence limits (95% CI) were calculated for all parameters. The three techniques’ dose parameter means were compared with the Friedman’s test, a non-parametric alternative to the ANOVA test, to determine the statistical significance of differences. In the event of null hypothesis rejection ($p ≤ 0.05$), pairwise comparisons were performed to determine the location of significant differences between techniques. The significance level was set at a $p$-value of <0.05 and adjusted by the Bonferroni correction to avoid type I errors when making multiple statistical tests.

**RESULTS**

**Breast/thoracic wall PTV**

Overall, V$_{95\%}$ was achieved. $D_{\text{mean}}$ for the field-based PAB technique was mean 40.3 Gy (SD ±0.4, CI: 40.1–40.6), IMRT 1: 40.4 Gy (SD ±0.4, CI: 40.1–40.6) and IMRT 2: 40.2 Gy (SD ±0.4, CI: 40–40.5). $D_{2cc}$ were below the maximum dose constraint of 110% (44.05Gy), indicating a homogeneous dose distribution. (Table 1)

**Lymph node PTV**

Figures 3–5 demonstrate the isodose distributions for the three techniques. When comparing $V_{90\%}$ (above the junction) between field-based PAB: mean 56.7% (SD ±24.7, CI: 41.0–72.4) and IMRT 1: mean 99.5% (SD ±1.0, CI: 98.8–100.1), and field-based PAB and IMRT 2: mean 99.4% (SD ±0.5, CI: 99.1–99.6), the difference was statistically significant, $p = 0.0001$ and $p = 0.005$, respectively, demonstrating improved dose conformity in both IMRT techniques. $V_{90\%}$, field-based PAB technique, was particularly low in patients 1, 5, 6 and 11: 13.5%, 23.1%, 29.6 and 36.4%, respectively. (Figure 6) $V_{80\%}$, field-based PAB technique was 65.4, 77.7, 82.9 and 80.5%, respectively. $V_{107\%} \leq 1$ cc was achieved in both IMRT techniques with no significant differences between the three techniques. (Table 1)

The mean $V_{107\%}$ outside the PTVs were <1 cc in all three techniques.

**PTV $D_{\text{max}}$ in IMRT 2:** mean 106.9% (SD ±1.4, CI: 106.1–107.8) was statistically significantly lower ($p = 0.002$) than simple IMRT 1: 111.9% (SD ±4.4, CI: 109.2–114.7) and lower than field-based PAB: 111.6% (SD ±6.0, CI: 107.8–115.3), indicating a more homogeneous dose distribution in IMRT 2 (Table 1).
Table 1. Dose parameters for planning techniques: Field-based posterior axillary boost, IMRT one and IMRT 2. (n = 12)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Field-based PAB</th>
<th>Simple IMRT 1</th>
<th>IMRT 2</th>
<th>Field-based PAB compared to IMRT 1</th>
<th>IMRT two compared to field-based PAB</th>
<th>IMRT two compared to IMRT 1</th>
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<tr>
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<td>Mean (SD)</td>
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<td>Ipsilateral breast PTV</td>
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| V40.05Gy                   | 62.4 (14.5)     | 62.9 (14.8)  | 58.6 (14.3)
|                            |                 |              |         | 0.002                             | 0.003                               |                               |
| V 95%                      | 95.6 (4.1)      | 95.4 (3.9)   | 95.1 (4.4)
|                            |                 |              |         | 0.043                             |                                     |                               |
| Dmean                      | 40.3 (0.4)      | 40.4 (0.4)   | 40.2 (0.4)
|                            |                 |              |         | 0.013                             | 0.009                               |                               |
| D2cc max (Gy)              | 41.9 (0.3)      | 41.9 (0.4)   | 41.8 (0.5)
|                            |                 |              |         | 0.043                             |                                     |                               |
| Lymph node PTV (SCF and axilla) |         |              |         |                                   |                                      |                               |
| V90% (above junction)      | 56.7 (24.7)a    | 99.5 (1.0)   | 99.4 (0.5)
|                            |                 |              |         | 0.0001                            | 0.005                               |                               |
| V90% Total LN PTV (≥90%)   | 67.0 (15.7)a    | 94.5 (5.3)   | 94.4 (4.6)
|                            |                 |              |         | 0.0001                            | 0.013                               |                               |
| V107% (≤1 cc)              | 1.2 (3.0)       | 0.6 (0.9)    | 0.0 (0)                                    | 0.0001                              |                                     |                               |
| Brachial Plexus            |                 |              |         |                                   |                                      |                               |
| Dmax (≤110% PS dose)       | 0.1 (0.2)       | 0.0 (0.1)    | 0 (0.1)                                   |                                      | 0.002                              |                               |
| Ipsilateral lung (V12Gy ≤ 25%) |        |              |         |                                   |                                      |                               |
| V5Gy                      | 44.7 (5.9)      | 42.2 (5.9)a  | 41.5 (5.7)
|                            |                 |              |         | 0.001                             | 0.043                               |                               |
| V10Gy                     | 55.3 (19.0)     | 31.1 (5.7)a  | 30.7 (5.7)
|                            |                 |              |         | 0.005                             | 0.001                               |                               |
| V12Gy                     | 31.9 (6.3)      | 29.0 (6.2)   | 28.4 (6.0)
|                            |                 |              |         | 0.002                             |                                     |                               |
| V20Gy                     | 26.4 (5.5)      | 23.6 (5.2)   | 22.8 (5.2)
|                            |                 |              |         | 0.001                             |                                     |                               |
| V30Gy                     | 12.0 (47)a      | 16.4 (5.0)   | 14.4 (4.6)
|                            |                 |              |         | 0.0001                            | 0.024                               |                               |
| Humeral head               |                 |              |         |                                   |                                      |                               |
| V5Gy                      | 74.0 (15.2)     | 27.1 (10.8)a | 22.4 (10.1)
|                            |                 |              |         | 0.013                             | 0.001                               |                               |
| V10Gy                     | 55.3 (19.0)     | 14.4 (8.7)a  | 10.7 (7.9)
|                            |                 |              |         | 0.007                             | 0.001                               |                               |
| V15Gy                     | 37.7 (7.9)      | 10.0 (7.5)a  | 7.6 (6.9)
|                            |                 |              |         | 0.007                             | 0.001                               |                               |
| Oesophagus                 |                 |              |         |                                   |                                      |                               |
| Dmean                     | 1.2 (0.3)       | 2.0 (2.0)    | 1.0 (0.4)                                   |                                      |                                     |                               |

(Continued)
Dose in the junction between the nodal and tangential fields

For the field-based PAB technique, D_{max}: mean 41.9 Gy (SD ±2.4, CI: 40.4–43.4) was significantly lower (p = 0.043) compared to IMRT 1: 42.6 Gy (SD ±1.3, CI: 41.6–43.5). D_{max} in IMRT 2: mean 40.8 Gy (SD ±1.3, CI: 40.0–41.6) was significantly lower (p = 0.007) compared to IMRT 1.

D_{mean} in IMRT 2: mean 36.8 Gy (SD ±1.8, CI: 35.7–37.9) compared to IMRT 1: 38.4 Gy (SD ±2.4, CI: 36.9–39.9) was significantly lower (p = 0.003). (Table 1)

Critical structures

**Brachial plexus**

D_{max} was < 110% in all three techniques. This, however, was achieved in the field-based PAB technique by prioritising BP sparing over LN PTV dose coverage, reducing the nodal prescribed dose. Pairwise comparisons of D_{max} between IMRT 2: mean 98.8% (SD ±1.90, CI: 97.6–100.0) and IMRT 1: 103.0% (SD ±1.9, CI: 101.8–104.2) was significantly lower (p = 0.007) for IMRT 2. (Table 1)

**Ipsilateral lung**

In the field-based PAB technique V_{20Gy}: mean 26.4 Gy (SD ±5.5, CI: 22.9–29.8), V_{12}: 31.9 Gy (SD ±6.3, CI: 27.4–36.4), V_{10Gy}: 55.3 Gy (SD ±19, CI: 43.2–67.3) and V_{5Gy}: 44.7 Gy (SD ±5.9, CI: 41.0–48.5) were significantly higher (p = 0.0001, 0.002, 0.0001 and 0.001, respectively) when compared to IMRT 2: V_{20Gy}: mean 22.8 Gy (SD ±5.2, CI: 19.5–26.1), V_{12Gy}: 28.4 Gy (SD ±6.0, CI: 24.1–32.7), V_{10Gy}: 30.7 Gy (SD ±5.7, CI: 27.0–34.3) and V_{5Gy}: 41.5 Gy (SD ±5.7, CI: 37.9–45.1).

V_{30Gy}, IMRT 2: mean 14.4 Gy (SD ±4.6, CI: 11.5–17.3) compared to V_{30Gy}, IMRT 1: 16.4 Gy (SD ±5.0, CI: 13.2–19.5) was significantly lower (p = 0.024) in IMRT 1. V_{30Gy} field-based PAB: mean 12.0 Gy (SD ±4.7, CI: 9.0–14.9), compared to V_{30Gy}, IMRT 1: 16.4 Gy (SD ±5.0, CI: 13.2–19.5) was significantly lower (p = 0.0001) in the field-based PAB technique. (Table 1)
Humeral head
IMRT 2, V_{50Gy}: mean 22.4 Gy (SD ±10.1, CI: 16.0–28.8), V_{100Gy}: 10.7 Gy (SD ±7.9, CI: 5.7–15.7) and V_{150Gy}: 7.6 Gy (SD ±6.9, CI: 3.2–12.0) compared to field-based PAB: V_{50Gy}: 74.0 Gy (SD ±15.2, CI: 64.3–83.6), V_{100Gy}: 55.3 Gy (SD ±19.0, CI: 43.2–67.3) and V_{150Gy}: 37.7 Gy (SD ±15.9, CI: 32.7–42.7), confirmed significantly lower doses in IMRT 2 (V_{50Gy}, V_{100Gy} and V_{150Gy} p = 0.0001). IMRT 1, V_{50Gy}: 27.1 Gy (SD ±10.8, CI: 20.3–34.0), V_{100Gy}: 14.4 Gy (SD ±8.7, CI: 8.9–19.9) and V_{150Gy}: 10.0 Gy (SD ±7.5, CI: 5.2–14.7) also confirmed significantly lower doses (p = 0.013, 0.007 and 0.007, respectively) when compared to the field-based PAB technique. (Table 1)

Oesophagus
D_{mean} was ≤ 2 Gy and similar for all three techniques. The difference in D_{max} between field-based PAB: mean 10.1 Gy (SD ±10.8, CI: 3.2–16.9), IMRT 1: 16.2 Gy (SD ±15.2, CI: 6.6–25.9) and IMRT 2: 11.4 Gy (SD ±11.4, CI: 4.1–18.6), was not significant.

Thyroid
Field-based PAB, V_{30Gy}: mean 17.6 Gy (SD ±14.3, CI: 8.6–26.7) and D_{mean}: 10.3 Gy (SD ±6.8, CI: 6.0–14.6) was higher but not significant compared to the IMRT techniques. IMRT 1, V_{30Gy} was: mean 14.3 Gy (SD ±11.3, CI: 8.6–26.7) and D_{mean}: 8.4 Gy (SD ±4.7, CI: 5.4–11.3) whereas IMRT 2, V_{30Gy} was: mean 13.3 Gy (SD ±12.2, CI: 5.6–21.1) and D_{mean}: 7.9 Gy (SD ±4.8, CI: 4.9–10.9). The difference in D_{2cc max} between field-based PAB: mean 33.5 Gy (SD ±3.5, CI: 31.2–35.7), IMRT 1: 35.2 Gy (±6, CI: 31.4–39.1) and IMRT 2: 31.8 Gy (±10.9, CI: 24.8–36.7), were insignificant. D_{max} was significantly higher (p = 0.024) in IMRT 1: 34.8 (±10.0, CI: 28.4–41.2) compared to field-based PAB: mean 33.7 Gy (±20.6, CI: 20.6–46.7). However, D_{max}, compared to the other techniques was the highest in IMRT 2: mean 35.7 Gy (SD ±7.6, CI: 30.9–40.6), but not significant.

DISCUSSION
We explored a satisfactory compromise of two forward-planned IMRT techniques to improve dose conformance, homogeneity and OAR dose, compared to a field-based PAB method. The forward-planned IMRT modulations were relatively simple, averaging 1–2 segments in IMRT 1 and 4–7 segments in IMRT 2, making them more robust for treatment delivery and virtually invisible at the treatment end. The integral dose in forward-planned IMRT, unlike inverse planned IMRT, remains low and is also invisible at the treatment end. The common cause of poor dose conformance in these four patients.

At the time of this study, no published thyroid, oesophagus, and humeral head dose constraints were available. When evaluating OAR doses, the brachial plexus D_{max}, ipsilateral lung V_{5} and V_{30Gy} were the only dose parameters that were statistically significantly lower in IMRT 2 compared to IMRT 1. The lower doses were achieved by reducing medial hotspots with lateral segments to the posterior field.

High-dose irradiation is associated with hypothyroidism and Graves’ disease, but no studies have reported a significant increase in hypothyroidism due to moderate-to low-dose irradiation.17 Our results confirmed a lower D_{mean} for both nodal IMRT techniques, 7.9 Gy (±4.8) and 8.4 Gy (±4.7). Higher thyroid D_{mean} doses (13.6 Gy ± 2.9) have been reported when combining VMAT breast plans with 3D nodal techniques.18 The lower D_{mean} can also be attributed to the difference in RTOG and ESTRO contouring guidelines. With the ESTRO guidelines, the distance between the thyroid and nodal CTV is larger, and consequently, thyroid exposure will be lower. Considering the development of volumetric techniques, thyroid dose constraints are an area of future research that may impact RT planning for individual patients. There is insufficient clinical data regarding doses to thyroid, oesophagus and humeral head, so the best practice would be to achieve the lowest possible doses for these OAR.

When comparing simple IMRT 1 to IMRT 2, there were no significant differences in the LN PTV coverage; however, IMRT 1 compares slightly better to the field-based PAB technique than IMRT 2. Despite a higher BP dose in IMRT 1, most dose constraints have been achieved. The mean D_{max} for IMRT 1 was 111.9%, exceeding 110% by less than 1 Gy. The only significant difference between the two techniques was V_{5Gy} and V_{30Gy}, which are not routinely used in the clinic. Outcomes from both IMRT techniques demonstrate target volume dose conformity, homogeneity and OAR dose benefits, supporting the replacement of...
the field-based PAB technique. IMRT 1 is a simplified technique consisting of fewer segments and reduced planning time. Based on dose information from this small sample size of 12 cases, IMRT 1 is a suitable choice for treating the breast, SC and AX nodes in a busy RT department.

CONCLUSION
Both forward-planned IMRT techniques were an improvement on the field-based PAB technique as they enabled the delivery of the prescribed dose to a designated PTV volume. This study confirmed the feasibility of a simplified IMRT 1 technique compared to a more advanced IMRT 2 technique. Although IMRT planning is more costly,\(^1\) enhanced dose homogeneity and reduced lung, humeral head, and brachial plexus doses make it the RNI technique of choice. Inverse and rotational IMRT techniques, with resultant increased low dose areas, should be reserved for internal mammary nodal irradiation or anatomically challenging cases. Ultimately, technique choices depend on equipment and skill mix.

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