Guidelines for the treatment of Breast cancer with radiotherapy
v.1.0
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Contents – needs editing

1. Introduction ................................................................................................................. 3
2. Indications and dosing schedules ............................................................................... 3
  2.1. Ductal carcinoma in situ (DCIS) ........................................................................... 3
  2.2. Invasive breast cancer after breast-conserving surgery ........................................ 5
  2.3. Invasive breast cancer after primary mastectomy ± reconstruction .................... 7
  2.4. Invasive breast cancer after neoadjuvant chemotherapy or hormone therapy then mastectomy .................................................................................................................. 8
  2.5. Supraclavicular fossa irradiation ............................................................................. 9
  2.6. Axillary nodal irradiation ..................................................................................... 10
  2.7. Internal mammary chain irradiation ..................................................................... 11
  2.8. Patients of Poor Performance Status ................................................................... 11
  2.9. Partial Breast Radiotherapy ................................................................................ 12
  2.10. Safe Omission of Radiotherapy ......................................................................... 12
3. Radiotherapy trials ...................................................................................................... 13
4. Timing of radiotherapy ............................................................................................... 13
5. Investigations .............................................................................................................. 13
6. Patient preparation ...................................................................................................... 13
7. Planning considerations ............................................................................................... 14
  7.1. Positioning ............................................................................................................. 14
  7.2. Scanning ................................................................................................................ 14
  7.3. Beam arrangements ............................................................................................. 14
  7.4. Whole breast radiotherapy fields ........................................................................ 14
  7.5. Chest wall radiotherapy fields ............................................................................. 15
  7.6. Tumour bed boost radiotherapy fields .................................................................. 15
  7.7. Supraclavicular fossa radiotherapy fields .......................................................... 15
  7.8. Axillary radiotherapy fields ................................................................................ 15
  7.9. Organs at risk ....................................................................................................... 16
  7.10. Cardiac sparing ................................................................................................... 16
8. Toxicities ..................................................................................................................... 16
1. Introduction

These guidelines are intended to direct the treatment of patients with ductal carcinoma in situ (DCIS) and invasive carcinoma of the breast with radiotherapy. They have been developed from guidelines already in existence at Barts Health NHS Trust, Homerton University Hospital, the Whittington Hospital, University College London Hospitals NHS Foundation Trust, Royal Free London NHS Foundation Trust, Princess Alexander Hospital, North Middlesex Hospital, Barnet and Chase Farm Hospitals and Barking, Havering and Redbridge University Hospitals NHS Trust. They should be read and used in conjunction with other guidelines covering the investigation and surgical and chemotherapeutic management of breast cancer. They also do not remove the need to follow the Local Rules and Work Instructions that have been developed at individual radiotherapy departments.

2. Indications and dosing schedules

2.1. Ductal carcinoma in situ (DCIS)

2.1.1. Indication

The need for radiotherapy in patients with DCIS can be guided by use of the Van Nuys Prognostic Index (VNPI) score. However it should be noted that the score was developed from a small study of patients treated in a very strict fashion, with unusually complex histological scrutiny of tumours. The need for informed decisions made at multi-disciplinary meetings is vital. A tumour bed boost should be considered.

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mm)</td>
<td>&lt;15</td>
<td>16-40</td>
<td>≥41</td>
</tr>
<tr>
<td>Margin width (mm)</td>
<td>≥10</td>
<td>1-9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pathologic classification</td>
<td>Non-high grade without necrosis</td>
<td>Non-high grade with necrosis</td>
<td>High grade with or without necrosis</td>
</tr>
<tr>
<td>Age (yr.)</td>
<td>&gt; 60</td>
<td>40-60</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>

One to three points are awarded for each of four different predictors of local breast recurrence (size, margin width, pathologic classification and age). Scores for each of the predictors are totalled to yield a Van Nuys Prognostic Index score ranging from a low of 4 to a high of 12.

Table 1: Calculation of the VNPI score

- Patients with a VNPI score of 4-6 should be observed only after tumour excision (grade B evidence)
- Radiotherapy should be considered for patients with a VNPI score of 7-9 (grade A)
- Patients with a VNPI score of 10-12 should be considered for mastectomy (grade B)
2.1.2. Dosing schedule

A dosing schedule of:
40.05Gy in 15 fractions over three weeks
Dose of boost: see section 2.2.2

2.1.3. References


2.2. Invasive breast cancer after breast-conserving surgery

2.2.1. Indication

Whole breast radiotherapy is recommended in all patients with invasive breast cancer treated with breast-conserving surgery where complete microscopic excision has been achieved (grade A), unless life expectancy is less than three years due to co-morbidities (grade C).

A tumour bed boost is recommended in patients with either:

- age less than 50 years (grade B), or
- disease at the resection margins, and the patient is either unable or unwilling to have further surgery (grade B)
- for those over 50 years with high pathological features (especially Grade3 and/or extensive intraductal component (EIC), consider the benefit of boost in context of both local recurrence and normal tissue toxicity risks).

Surgical clips should be deployed intraoperatively to facilitate localisation of boost radiotherapy. Note that oncoplastic techniques may introduce inaccuracy in clip placement.

A conformal photon boost with appropriate technique specific margins and image-guided radiotherapy (IGRT) should be standard of care. Electrons and mini-tangents are acceptable alternatives if photon boost is not clinically appropriate.

2.2.2. Dosing schedule

The recommended whole breast dosing schedule is:

- 40.05Gy in 15 fractions over three weeks.

The tumour bed boost should be administered as:

- 10Gy in 5 fractions over one week
- 16Gy in 8 fractions over one week, or radiobiologically equivalent dose such as 12Gy in 4 fractions

2.2.3. References


2.3. **Invasive breast cancer after primary mastectomy ± reconstruction**

2.3.1. **Indication**
Radiotherapy to the chest wall in patients with invasive breast cancer who have had a primary mastectomy is recommended where any of the following is present:
- T3 or T4 disease (grade A), or
- axillary node positivity (absolute indication if ≥4 nodes involved-ASCO guidelines Oct 2016 support RT in if 1-3 LN positive)
  Although controversial, for patients with a deep positive margin if under 50 or with adverse pathological features, RT should be considered.

2.3.2. **Dosing schedule**
The recommended chest wall dosing schedule is:
- 40.05Gy in 15 fractions over three weeks (grade A)
  with bolus applied as indicated by dosimetric plan to deliver adequate skin dose).

  Alternatively 50Gy in 25 fractions may be indicated in some cases following immediate reconstruction although evidence for superior cosmesis is not available.

2.3.3. **References**
2.4. Invasive breast cancer after neoadjuvant chemotherapy or hormone therapy then mastectomy

2.4.1. Indication

Chest wall radiotherapy is recommended in patients who have received neoadjuvant chemotherapy or hormone therapy then a mastectomy and have either of the following:

- Pathologically positive axillary nodes after neoadjuvant treatment (i.e. status ypN+) (grade B)
- Large primary tumour or triple-negative disease plus cytologically positive axillary nodes and/or clinically suspicious enlargement at presentation, even when axillary nodes are pathologically negative after neoadjuvant treatment (i.e. status ypN-) (grade C)

2.4.2. Dosing schedule

The recommended dosing schedule in these patients remains as:

- 40.05Gy in 15 fractions over three weeks

2.4.3. References


2.5. **Supraclavicular fossa irradiation**

2.5.1. **Indication**

Radiotherapy to the supraclavicular fossa is recommended in patients who have had primary surgical treatment and are found to have ≥4 metastatic axillary lymph nodes at pathological staging (grade B).

With one to three positive lymph nodes in addition to other poor prognostic factors e.g. T3 and/or histological grade 3 tumours, radiotherapy can be offered in patients with good performance (as per NICE guidance).

In patients who have had neo-adjuvant chemotherapy or hormone therapy:
- If axillary nodes are negative at presentation, and the nodal status is ypN- after neo-adjuvant treatment, supraclavicular fossa radiotherapy is not recommended (grade C).
- If axillary nodes are cytologically positive and/or clinically or radiologically suspiciously enlarged at presentation, and if the nodal status is ypN- after neo-adjuvant treatment, supraclavicular fossa radiotherapy should be considered.
- If the nodal status is ypN+ after neo-adjuvant treatment, supraclavicular fossa radiotherapy is recommended (grade B).

2.5.2. **Dosing schedule**

The recommended dose to the supraclavicular fossa is:
40.05Gy in 15 fractions over three weeks

2.5.3. **References**

2.6. Axillary nodal irradiation

2.6.1. Indication

Following the summary statement made by Association of Breast Surgery in Jan 2015, the following recommendations are made:

- No further axillary treatment is required after breast conservation surgery or mastectomy if sentinel node (SN) shows isolated tumour cells or micrometastases
- If the SN(s) shows macrometastases, further axillary treatment is no longer mandatory for breast conservation patients receiving whole breast radiotherapy for T1, Grade 1 or 2, ER+, HER2 negative and post-menopausal. These patients could be entered into POSNOC or equivalent
- If the SN(s) shows macrometastases, further axillary treatment should be recommended for patients undergoing mastectomy or with tumours with one of the following features: T3, Grade 3, ER- or HER2 positive. These patients could be entered into POSNOC or equivalent trial
- For SN positive patients with macrometastases (AMAROS eligible), axillary radiotherapy is a reasonable alternative to further axillary surgery
- Radiotherapy can offered to patients where there is macroscopic disease extending to the margins of axillary resection (grade C)
- Axillary radiotherapy may also be considered in addition to surgery where there are multiple positive nodes with extracapsular spread, or where there has been sharp dissection of large nodes
- Radiotherapy to the axilla is not recommended in patients in whom a complete microscopic clearance of the axillary nodes has been achieved. This is due to the increased risk of treatment-associated morbidity with radiotherapy over that seen with surgery (grade B).

In all patients receiving axillary radiotherapy, the increased risk of lymphoedema and brachial plexopathy must be explained.

2.6.2. Dosing schedule

The recommended dose to the axilla is:

- 40Gy in 15 fractions over 3 weeks using a CT-planned approach with disease localised using clips and/or MRI imaging (grade C).

2.6.3. References

Mignano JE et al. Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. Cancer 1999; 1258-62


Grills IS et al. Risk factors for regional nodal failure after breast-conserving therapy: regional nodal irradiation reduces rate of axillary failure in patients with four or more positive lymph nodes. Int J Radiat Oncol Biol Phys 2003; 56:658-70


2.7. Internal mammary chain irradiation

Following analysis of EBCTCG meta-analysis of outcomes in women treated with/without post-mastectomy loco regional radiotherapy including the supraclavicular fossa, axilla and IMC (8% reduction on breast cancer mortality at 20 years in patients with 1-3 positive lymph nodes), MA20 and EORTC internal mammary- medial supraclavicular trials (305) disease free survival benefit) and a Danish internal mammary node study (3.7% overall survival benefit with increased benefit in N2 disease, and N1 disease with central/medial tumour location the following recommendations are made:

- Internal mammary chain nodal radiotherapy should be given in patients at high risk of locoregional recurrence (i.e. T4 and/or 4 or more axillary lymph node macrometastases)
- In patients with 1-3 axillary macrometastases, who have been recommended locoregional irradiation, based on risk factors, inclusion of IMC in the target volume should be considered if tumour location is central/medial

It is recommended that lymph nodes are defined according to the ESTRO guidelines

It is recommended that the UK should adopt consistent technical approaches to treating the IMC that minimizes dose to organs at risk (particularly heart, lung and contralateral breast) but do not overwhelm current capacity. Centres treating IMC should have breath- hold techniques. Wide tangents in breath-hold or rotational therapies are capable of meeting constraints in the majority of patients

2.8. Patients of Poor Performance Status
Less intense radiotherapy dosing schedules may be considered for such patients, including:

- 27Gy in 6 fractions, three times weekly over two weeks, or
- 28.5Gy in 5 fractions, weekly over five weeks, or
- 30Gy in 6 fractions, twice weekly over three weeks, or
- 36Gy in 6 fractions, weekly over six weeks

2.9. Partial Breast Radiotherapy

Partial Breast Radiotherapy techniques can be considered for patients 50 years of over, Grade 1-2, less than 3cms, ER+, HER2 neg, N0 using either using (i) external beam radiotherapy with 40Gy in 15 fractions over 3 weeks or (ii) multicatheter brachytherapy using fractionation within GEC-ESTRO trial. Margins should be carefully considered if adopting this technique and 2mm margin is recommended.

IMPORT LOW trial is yet to be published at time of writing. Abstract data was favourable in terms of non-inferiority and some centres are likely to change practice ahead of the publication of full manuscript.

Intraoperative Radiotherapy should be used within the context of a clinical trial.

2.10. Safe Omission of Radiotherapy

Avoidance of radiotherapy should be considered in patients deemed to be at very low risk of local recurrence, for example with T1N0 ER+, PR+, HER2-, Grade1-2 tumours AND are willing to take endocrine therapy for a minimum of five years AND with be followed up mammographically for ten years. These criteria are best fulfilled with the UK PRIME TIME biomarker-directed study and participation is recommended.

If the breast multidisciplinary team considers omitting radiotherapy after breast conserving surgery, a radiotherapy consultation is required to discuss risks and benefits with the patient.
3. **Radiotherapy trials**

All patients should be offered entry into a clinical trial if they meet the eligibility criteria. Information regarding relevant radiotherapy trials currently open to recruitment is available on London Cancer Website.

4. **Timing of radiotherapy**

Radiotherapy should be started between 3-4 weeks following any adjuvant chemotherapy, although planning may commence before this.

Treatment breaks should be avoided wherever possible. Where a break is unavoidable, dose compensation is not necessary.

5. **Investigations**

The following investigations should have been performed and the results available before radiotherapy planning commences:

- Clinical history
- Baseline clinical examination
- Clinical examination post-surgery
- Original mammography/MRI/ultrasound imaging (specifically to localise tumour position within breast)
- Biopsy and tumour excision/mastectomy results, including tumour grade, hormone receptor status and HER-2 status
- Results of staging investigations, if appropriate

6. **Patient preparation**

All patients must have given written informed consent before radiotherapy planning commences. Consent should be taken by a practitioner who is familiar with breast radiotherapy planning and administration. Patients should be given an appropriate patient information leaflet about breast radiotherapy, and have access to a breast care nurse or other specialist practitioner.
7. Planning considerations

7.1. Positioning
Patients should be planned and treated in the supine position on a breast board, with both arms raised. A breast shell may be required for patients with large pendulous breasts.

7.2. Scanning
It is recommended that breast radiotherapy is 3D-planned using data from a CT planning scan. The patient should be scanned in the treatment position (see above). It is recommended that the scan boundaries are:

- For breast fields only – lung apices to bottom of the lung
- For breast and nodal fields – mastoid to bottom of lungs

7.3. Beam arrangements
For whole breast and chest wall radiotherapy, it is recommended that a two-field tangentially-opposed photon beam arrangement is used. Boost segments may be added to improve dose homogeneity. Appropriate beam energy should be selected dependent on local availability.

For tumour bed boost dosing, it is recommended that a mini-tangential-opposed photon beam approach is an acceptable alternative. Localisation can be performed either by using surgical clips to conformally delineate or failing this, a clinical mark-up technique. As an alternative, an applied electron beam may be used. Appropriate beam energy should be selected using estimation of the tumour bed depth measured from the planning CT scan.

For nodal dosing, it is recommended that an anterior field is used with a posterior field used to encompass CTV when needed. This is then matched to the associated tangential breast/chest wall fields. Isocentric techniques are recommended.

7.4. Whole breast radiotherapy fields
The clinical target volume (CTV) should include all remaining ipsilateral breast tissue, including the deep fascia but not underlying muscle or skin.

The planning target volume (PTV) should be set using the following anatomical landmarks and taking into account locally derived CTV to PTV margins:

- Superior – coverage of breast with a 1.0cm margin
- Inferior – 1.0cm inferior to the position of the contralateral breast tissue
- Medial – the midline
- Lateral – 1.0cm lateral to the position of the ipsilateral breast tissue

The medial and lateral borders may be adjusted to reduce heart and lung volume in the field.
7.5. **Chest wall radiotherapy fields**

The CTV should include the deep fascia, subcutaneous tissue and any remaining breast tissue.

The planning target volume (PTV) should be set using the following anatomical landmarks and taking into account locally derived CTV to PTV margins:

- Superior – 1.0cm superior to the position of the contralateral breast
- Inferior – 1.0cm below the inframammary fold of the contralateral breast
- Medial – the midline
- Lateral – 1.0cm lateral to the position of the contralateral breast

7.6. **Tumour bed boost radiotherapy fields**

The CTV should encompass the entire tumour bed (as defined by clinical mark-up or the use of surgical clips) plus 5-10mm dependent on surgical margins.

The PTV should encompass the CTV with a 5-10mm margin, dependent on local guidance for CTV expansion.

7.7. **Supraclavicular fossa radiotherapy fields**

The CTV should encompass the entire supraclavicular fossa. Consideration should be given to axillary level 3 in addition if surgery has not been performed there.

The planning target volume (PTV) should be set using the following anatomical landmarks and taking into account locally derived CTV to PTV margins:

- Superior – covering the supraclavicular fossa but leaving a small corridor of skin
- Inferior – matched to tangentially-opposed fields
- Medial – 0.5cm from spinal cord
- Lateral – mid-coracoid process or junction between medial 2/3 and lateral 1/3 of clavicle; but consider extending to the medial border of the humeral head to include level 3 axillary nodes

7.8. **Axillary radiotherapy fields**

The CTV should encompass the level 1, 2 and 3 axillary nodes, plus the supraclavicular fossa.

The planning target volume (PTV) should be set using the following anatomical landmarks and taking into account locally derived CTV to PTV margins:

- Superior – covering the supraclavicular fossa but leaving a small corridor of skin
- Inferior – matched to tangentially-opposed fields
- Medial – 0.5cm from spinal cord
- Lateral – lateral border of humeral head
Shielding to the humeral head and to lung below the clavicle should be considered.

CT planning is recommended for more complex 4 field treatment and also for some clinical trials.

7.9. Organs at risk

Organ at risk dose constraints are recommended for a standard 40.05Gy in 15 fraction plan as follows. Consideration should be given to outlining the organs to allow accurate calculation of dose-volume histograms (DVHs).

- Ipsilateral lung: maximum lung depth (MLD) below the chest wall for tangentially-opposed fields should be ≤2.5 cm for all patients, and ≤2.0cm for most patients; V18 ≤15% for two-field plans, ≤30% for three-field plans
- Contralateral lung: avoid irradiation wherever possible; V2.5 ≤15%; mean dose ≤2Gy
- Heart: minimise irradiation wherever possible; V13 ≤10%
- Brachial plexus: maximum dose <50Gy in 2Gy fractions, <40Gy in 2.67Gy fractions
- Spinal cord: maximum dose <44Gy in 2Gy fractions, <37Gy in 2.67Gy fractions

7.10. Cardiac sparing

The heart should be routinely excluded from the radiotherapy field. It is recommended that all UK departments should have a breath hold techniques to facilitate this. In left breast affected patients undergoing radiotherapy (not including IMC) >90% of patients should be treated to a mean heart dose of <2Gy.

8. Toxicities

All toxicities should be explained to the patient at the time of consent being taken. Standardised consent forms are recommended to reduce variation in consent process.

Common early toxicities associated with breast radiotherapy include:
- Skin reaction – usually erythema, occasional moist desquamation; follow local skin care guidelines
- Skin pigmentation
- Lethargy
- Reduced range of ipsilateral arm movement

Late toxicities may include:
- Subcutaneous oedema of the breast
- Subcutaneous fibrosis of the breast
- Telangiectasiae
- Chest wall pain
- Radiation pneumonitis and lung fibrosis
- Radiation-induced brachial plexopathy, in patients who have received supraclavicular and/or axillary irradiation
- Increased risk of rib fracture
- Lymphoedema of the arm, in patients who have received axillary irradiation

References
