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Guidelines for the treatment of breast cancer with radiotherapy

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Contents

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.

Score	**1**	**2**	**3**
Size (mm)	≤15	16-40	≥41
Margin width (mm)	≥10	1-9	<1
Pathologic classification	Non-high grade without necrosis	Non-high grade with necrosis	High grade with or without necrosis
Age (yr)	> 60	40-60	< 40
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

2.1.3. References

Julien JP *et al*. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 2000; 355:528-33

Fisher ER *et al*. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) eight-year update of Protocol B-17: intraductal carcinoma. Cancer 1999; 86:429-38

Bartelink H *et al*. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med 2001; 345:1378-87

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)

A boost may also be considered in patients aged over 50 with ≥T2 (size ≥2cm) or grade 3 tumours.

Surgical clips should be deployed intraoperatively to facilitate localisation of boost radiotherapy.

2.2.2. Dosing schedule

The recommended whole breast dosing schedule is:

- 40.05Gy in 15 fractions over three weeks.

An alternative schedule of:

- 50Gy in 25 fractions over five weeks- if there is a clinical indication for smaller fraction size

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

2.2.3. References

U-OBCSG. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst 1990; 82:277-82

Liljegren G *et al*. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. J Natl Cancer Inst 1994; 86:717-22

Smith BD *et al*. Effectiveness of radiation therapy for older women with early breast cancer. J Natl Cancer Inst 2006; 98:681-90

Clarke M *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366:2087-2106

Yarnold J *et al*. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol 2005; 75:9-17

Whelan T *et al*. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst 2002; 94:1143-50

START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008; 9:331-41

START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008; 371:1098-1107

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)

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).

An alternative schedule of:

- 50Gy in 25 fractions over five weeks
  can be considered in patients who have had an immediate reconstruction. No bolus is required in such patients, unless there is concern regarding close superficial margins.

2.3.3. References

Recht A *et al*. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19:1539-69

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

Wallgren A *et al*. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 2003; 21:1205-13

EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365:1687-1717

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 or
- 50Gy in 25 fractions over five weeks

2.5.3. References

Recht A *et al*. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19:1539-69

2.6. Axillary nodal irradiation

2.6.1. Indication

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).

Radiotherapy to the axilla is recommended:

- in patients where there is macroscopic disease extending to the margins of axillary resection (grade C)
- in patients who do not have axillary surgery due to patient choice or poor fitness, unless surgery was withheld due to a very low risk of involvement (grade A)

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.

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:

- 50Gy in 25 fractions over five weeks

using a CT-planned approach with disease localised using clips and/or MRI imaging (grade C).

2.6.3. References

Strom EA *et al*. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys 2005; 63:1508-13

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

Fisher BJ *et al.* Extracapsular axillary node extension in patients receiving adjuvant systemic therapy: an indication for radiotherapy? Int J Radiat Oncol Biol Phys 1997; 38:551-9

Hetelekidis S *et al*. The significance of extracapsular extension of axillary lymph node metastases in early-stage breast cancer. Int J Radiat Oncol Biol Phys 2000; 46:31-4

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

Handley RS. Carcinoma of the breast. Ann R Coll Surg Engl 1975; 57:59-66

Recht A *et al*. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001; 19:1539-69

2.7. Internal mammary chain irradiation

Radiotherapy to the internal mammary chain is not recommended for any patient group (grade B).

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 including intra operative radiotherapy should be offered only in the context of a clinical Trial

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 an applied electron beam is used. Appropriate beam energy should be selected using estimation of the tumour bed depth measured from the planning CT scan. 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

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. Respiratory gating

This should be considered for left-sided lesions particularly in young patients with unsatisfactory heart DVH.

8. Toxicities

All toxicities should be explained to the patient at the time of consent being taken.

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