Breast Cancer

Introduction

Breast cancer is the commonest cancer in women in the UK and most patients are being diagnosed at an early stage due to the success of the NHS Breast Screening Program. Radiotherapy has long been established as an important treatment modality in the adjuvant and palliative setting in breast cancer. Recent technological advances and results of pivotal trials have led to significant changes in practice in the UK in the last few years.

Adjuvant Radiotherapy to the breast and chest wall

1. Radiotherapy has a key role in the conservation management of primary breast cancer, where it increases both local control and overall survival [1]. It performs the same role in selected patients after mastectomy [2]. It also reduces ipsilateral breast tumour recurrence following breast conservation in patients with a diagnosis of ductal carcinoma in situ (DCIS) [3,4]

2. Although radiotherapy reduces the risk of recurrence for both DCIS and invasive disease for all patients groups, given the small benefits of adjuvant radiotherapy following breast conserving radiotherapy in low risk patient groups, it is reasonable to consider omission of radiotherapy in patients with oestrogen receptor positive, node negative tumours which are less than 3 cm in maximum diameter and who are aged over 70 years [5,6].

3. The previous standard breast fractionation was a regimen of 50 Gy in 25 fractions over 5 weeks as reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) breast cancer trials [7]. Currently the most widely used UK regimen is the hypofractionated regimen of 40 Gy in 15 fractions over 3 weeks as used in the UK START Study B [8]. Mature data from the START and a Canadian study [9] support the equivalence of this hypofractionated regimen to the previous standard of 2 Gy daily fractionation (Level 1++)

4. There are no trials addressing 40Gy in 15 fractions vs 50 Gy in 25 fractions following breast reconstruction, but there is no radiobiological reason to recommend that 50Gy in 25 fractions in this situation; in fact results of START B trial suggest that 40Gy in 15 fractions leads to fewer late effects [8].

Recommendations:

For adjuvant radiotherapy of breast or chest wall

40 Gy in 15 daily fractions over 3 weeks (Level A)

42.5 Gy in 16 daily fractions over 3.5 weeks (Level A)
5. Further hypofractionation for breast radiotherapy is currently under investigation. The FAST Forward trial is investigating 40Gy in 15F vs 27 or 28Gy in 5F over 1 week. Main trial closed 2014, earliest results for local control will be available in 2019. FAST Forward nodal study opening 2015 with normal tissue endpoints. [10]

6. It is recognised that whole breast radiation can cause unacceptable toxicity in patients with large breasts. Partial breast radiation can improve this outcome. Currently the role of partial breast radiation in low-risk breast cancer is unclear; the UK IMPORT LOW Trial investigating 2 schedules of partial breast radiation v whole breast 40 Gy in 15 fractions has closed to accrual and will report in 2016.

7. 2 trials of IORT have reported: ELIOT [11] did not report breast cancer recurrence as a primary end point and the TARGIT A [12] has insufficient median follow up to draw firm conclusions.

Breast Boost

8. Delivery of a boost the to the tumour bed following whole breast radiotherapy reduces the risk of ipsilateral breast cancer recurrence (Level 1++) [13]. However, there is no impact on overall survival.

9. The relative benefit is similar across all age groups but the absolute benefit falls with increasing age and hence the biggest absolute benefit is in women under 50 years of age.

10. Incomplete resection margin, where further surgery is not possible should be an indication for breast boost regardless of age.

11. A boost dose of 16 Gy in 8 fractions [13] or 10 Gy in 5 fractions is most commonly prescribed. The lower dose has not been tested against the higher one in a RCT, however indirect evidence [Level 1+]from an EORTC trial [14] shows it is equivalent to a higher boost dose of 26 Gy in patients with an ‘incomplete’ resection margin with lower rates of fibrosis (3.3%) at 10 years.

12. The UK IMPORT-HIGH trial will close in 2015 and is investigating sequential vs simultaneous integrated boost (IMRT and IGRT) including dose escalation [15]

13. There is currently insufficient evidence to recommend IORT for boost; the TARGIT B trial is currently recruiting (Clinical Trials Group, UCL, UKCRN ID 14208) and randomising to convention boost vs IORT boost in high risk disease.
Recommendations:

For boost after whole breast RT, in women with a higher risk of local recurrence:

<table>
<thead>
<tr>
<th>Fractional Dose</th>
<th>Grade</th>
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<tr>
<td>16 Gy in 8 daily fractions</td>
<td>A</td>
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<tr>
<td>10 Gy in 5 fractions</td>
<td>B</td>
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Regional Nodal Irradiation

14. Axillary Sentinel Lymph Node Biopsy (SLNB) is now the BASO (British Association of Surgical Oncologists) recommended standard procedure for axillary staging in early breast cancer with clinically negative lymph nodes.

15. For clinically positive nodes; a level III Axillary Lymph Node Dissection (ALND) remains the standard procedure.

16. Nodal irradiation is not recommended following a negative SLNB.

17. Following a positive SLNB, the AMAROS trial demonstrated an axillary recurrence rate of 0.43% for ALND vs 1.19% for axillary radiotherapy after a median follow-up of 6.1 years. The trial was underpowered for the planned non-inferiority test due to the low number of events. Axillary RT produced lower long term toxicity compared to ALND [Level 1+] [16]

18. The ACOS-OG Z0011 trial demonstrated a low axillary recurrence rate of 0.9% vs 0.5% for SLNB + standard breast RT compared to SLNB followed by ALND + standard breast RT in a RCT comparing ALND vs no axillary treatment in women with T1/T2 N0 breast cancer undergoing BCT. Most patients were over 50 years of age and had grade 1 or 2, T1, oestrogen receptor positive, ductal cancer with no LVI. [17]

19. Radiotherapy to the ipsilateral SCF is recommended for N2 or N3 disease following ALND. Axillary radiotherapy following ALND produces significant toxicity and should only be recommended in women with very high risk of recurrence (high proportion of involved nodes, extensive extra-nodal disease or biologically aggressive cancer)

20. Prospective studies of the benefit of nodal irradiation, the North American MA20 trial and the European EORTC 22922 trial are yet to report and will help inform future practice [18-19] however emerging evidence provides a strong case for considering regional irradiation in node-positive breast cancer [20]

21. Data for hypofractionated nodal irradiation is limited to small subsets of patients from RCTs (14% in START A, 7% in START B) but it is promising
and shows no increase in toxicity compared to standard fractionation nodal irradiation (Level 1-) [21]

<table>
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<th>Recommendations</th>
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<tr>
<td>Where indicated, for Regional Nodal Irradiation:</td>
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<tr>
<td>40 Gy in 15 daily fractions (Grade B)</td>
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<td>50 Gy in 25 daily fractions (Grade B)</td>
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Radiotherapy planning and delivery

22. Simple, forward-planned, field-in-field IMRT reduces the late toxicity and improves cosmetic outcome following adjuvant whole breast radiotherapy (Level 1+) [22].

23. 2-Dimensional CT-Based planning is no longer recommended for adjuvant radiotherapy to the breast or chest wall.

24. There is evidence of increased late cardiac toxicity following left sided breast or chest wall radiotherapy [23]. Planning and delivery techniques for left-sided treatment should include methods to reduce the delivered cardiac dose. These include MLC cardiac shielding and voluntary breath holding in larger-breasted women (Level 1+) [24].

Palliative treatment

25. There are no good quality head-to-head trials evaluating the optimum schedules for palliative radiotherapy to the breast, chest wall or regional nodes. The commonest doses range from 20 Gy to 40 Gy over 5 to 15 fractions (Grade D).
References


[24.] R Bartlett et al. The UK HeartSpare Study (Stage IB): Randomised comparison of a voluntary breath-hold technique and prone radiotherapy after breast conserving surgery Radiother Oncol 2015; 114: 66-72