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Partial breast irradiation: an emerging standard? A critical review of current experience

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At least three-quarters of ipsilateral breast tumour relapses occurring in women with early unifocal cancer present in the vicinity of the primary tumour during the first 10 years of follow up after tumour excision and whole breast radiotherapy. The relapses tend to have pathological features resembling that of the primary tumour, and are assumed to arise from residual foci of the primary neoplasm. Ipsilateral breast relapses presenting beyond the index quadrant tend to develop later (5–15 years), may have distinct pathologically features, and occur at a rate similar to that of contralateral primary breast cancers. This pattern underpins the hypothesis that a high proportion of ipsilateral relapsed developing outside the index quadrant represent new primary tumours rather than true recurrences. On this basis, and given that radiotherapy has a very limited role in cancer prophylaxis, it is logical to test the effects of radiotherapy restricted to the vicinity of the primary tumour. This is being done in subgroups of women with small unifocal invasive ductal carcinomas of the breast after complete microscopic excision. The predictions are that therapeutic ratio will be much enhanced. Ipsilateral tumour relapse rate is expected to be comparable to that following whole breast radiotherapy and late adverse effects will be much reduced, due to the exclusion of large volumes of non-target tissues. A number of techniques are being used, including a single fraction of intra-operative radiotherapy and conformal external beam radiotherapy delivered by accelerated hypofractionation. A number of randomised clinical trials are underway that test the clinical benefits of partial breast radiotherapy, each defining the target volume, dosimetry and dose regimen differently. A major problem for radiation oncology is that centres in North America, and increasingly in Europe, are offering partial breast radiotherapy outside the context of a well designed randomised trial, contrary to the principles and practice of evidence based medicine. Reasons why partial breast radiotherapy may not work are not difficult to identify. For example, first ipsilateral tumour relapse may occur close the primary site because the greatest density of tumour cells is found there, not because the nature of the disease is different to that in other parts of the breast, generating a lead-time bias that obscures the significance of more distant relapse (patients are treated by mastectomy at first relapse or otherwise censored). Second, it is not certain that the rate of ipsilateral relapse outside the index quadrant is comparable to that of contralateral tumours. Recent data suggest that it is lower, consistent with a therapeutic effect of whole breast radiotherapy. Third, target volumes and radiotherapeutic parameters vary greatly between clinical trials, raising doubts whether the concept has been sufficiently thought through. Despite these concerns, the design, size and conduct of ongoing trials are adequate to address most concerns. It is worth bearing in mind, though, that reliable outcome data will not be available for at least 10 years.

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HIGHLIGHTS IN BREAST CANCER

Studies presented in 2005

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Breast-conserving treatment with or without radiotherapy for ductal carcinoma in situ (DCIS): ten-year results of European Organisation for Research and Treatment of Cancer (EORTC) randomized phase III trial 10853

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Background: Since the introduction of population based mammographic screening in the Western world, ductal carcinoma in situ (DCIS) has changed from being a rare disease to a lesion detected in up to 20–30% of all breast cancers in screening programmes. Controversy regarding the most optimal local therapy for women diagnosed with these non-invasive lesions still exists. This report presents the 10-year results of the EORTC 10853 study investigating breast-conserving treatment with or without radiotherapy for DCIS.

Patients and Methods: After complete excision of the lesion, women with DCIS were randomly assigned to receive either no further treatment or radiotherapy, to a total dose of 50 Gray in five weeks to the whole breast. Between 1986 and 1996, 1010 women with clinically or mammographically (71%) detected DCIS, measuring ⩽ 5 cm were entered in the trial. The median duration of follow-up was 10.5 years.

Results: The 10-year local relapse-free rate was 74% in the group treated with local excision alone compared with 85% in the women treated by local excision plus radiotherapy (logrank $p < 0.0001$, HR = 0.53 (95%CI 0.40–0.70)). The risk of DCIS was reduced with 48% and that of invasive local recurrence with 42% ($p = 0.0011$ and $p = 0.0065$, respectively). There was no difference in the development of distant metastases and death between the treatment groups. At multivariate analysis, factors significantly associated with an increased risk of local recurrence were, young age (⩽ 40 years, HR = 1.89 (95%CI 1.21–3.19)), symptomatic detection (HR = 1.55 (95%CI 1.11–2.16)), intermediately or poorly-differentiated DCIS (as opposed to well-differentiated DCIS, HR = 1.85 (95%CI 1.18–2.90) and HR = 1.61 (95%CI 0.93–2.79) respectively), solid or cribriform growth pattern (as opposed to clinging/micropapillary subtypes, HR = 2.25 (95%CI 1.21–4.18) and HR = 2.39 (95%CI 1.41–4.03) respectively), doubtful margins (HR = 1.84 (95%CI 1.32–2.56)), and treatment by local excision alone (HR = 1.82 (95%CI 1.33–2.49)). Some groups were at high risk of recurrence: women of 40 years of age or younger and treated with excision plus radiotherapy had a 26% local recurrence rate. When excision margins were doubtful, 25% of the patients developed a local recurrence after treatment with radiotherapy. DCIS with a clinging or micropapillary growth pattern had the lowest recurrence rate of 6% after radiotherapy.

Conclusions: With long-term follow-up, radiotherapy after local excision for DCIS continued to reduce the number of ipsilateral breast tumour recurrences, with a 47% reduction at 10 years. Treatment with radiotherapy reduced the risk of local recurrence in all clinical and pathological subgroups of patients. Women who appear at high risk for local recurrence are those of 40 years of age or younger, and those with lesions that cannot be excised with tumour-free margins.

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Docetaxel, carboplatin and trastuzumab (TCH) and doxorubicin/cyclophosphamide followed by docetaxel/trastuzumab (AC-TH) produce superior disease-free survival (DFS) compared to AC-T in patients (pts) with HER-2 positive early breast cancer (EBC), with increased cardiac toxicity confined to AC-TH: BCIRG 006 study

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Background: We compared standard AC-T chemotherapy to the same regimen with H, and to a novel translationally-derived regimen consisting of H in combination with Carboplatin and Docetaxel, drugs which synergise with H, as post-operative adjuvant (adj) therapy for pts with HER-2+ BC.

Methods: Pts with HER-2 + EBC (central FISH testing) which was axillary lymph node positive, or high risk node-negative (age<35, grade II-III, >2.0 cm, or hormone receptor-HR negative) were randomized to AC (60/600 mg/m^2 q3wk x4) followed by T (100 mg/m^2 q3wk x 4) or two H-containing regimens; AC-T with H x 1 year (q1wk during T, then q3 wk) or TC (75 mg/m^2/AUC6 q3wk x 6) with H x 1 year. Patients with HR+ tumors received adj hormonal therapy for 5 yrs. The primary endpoint was DFS with 80% power (0.05 significance) to detect an absolute difference of 7%. Secondary endpoints included survival, safety and cardiotoxicity (symptomatic events: Congestive Heart Failure, gr3/4 ischemia/infarction, gr3/4 arrhythmia; and asymptomatic ejection fraction (EF) decline. We report the results of the first protocol-mandated interim analysis after 322 events (relapse, new primary cancer or death).

Results: A total of 3222 pts were recruited between Apr 2001 and Mar 2004. At median follow-up of 23 months, the hazard ratios for DFS for AC-TH and TCH versus AC-T were 0.49 (p-value = 0.00000048) and 0.61 (p-value = 0.00015) respectively. There was no significant difference between the two H-containing arms in this analysis. Protocol-defined, clinically significant cardiotoxicity was significantly more common with AC-TH: (2.3%) vs AC-T: (1.2%), p-value = 0.046; but not for TCH (1.2%) vs AC-T, p-value = 1.00. Absolute EF decline >15% and below lower limit of normal occurred in 0.6% pts in AC-T, 2.4% in AC-TH and 0.4% in TCH arms respectively (AC-T vs AC-TH $p = 0.001$; AC-T vs TCH $p = 0.54$). Using a mixed model analysis to analyse EF decline over time, the slope of the decline was significant for AC-T and for AC-TH, but not for TCH.

Conclusions: In the treatment of HER2+ EBC, (1) TCH, a non-anthracycline containing regimen produces significantly improved DFS and equivalent cardiotoxicity compared to AC-T; (2) the addition of H to AC-T