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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.

Thursday, 23 March 2006 13:00–14:00

HIGHLIGHTS IN BREAST CANCER

Studies presented in 2005

207 Proffered Paper Oral

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

results in significantly improved DFS with increased cardiotoxicity, and (3) EF decline data suggest that TCH cardiotoxicity may be more reversible than AC-T/AC-TH cardiotoxicity. Longer follow-up is needed in order to determine any differences in efficacy between AC-TH and TCH.

209 Proffered Paper Oral

Post-unbinding analysis of NCIC CTG MA.17 (letrozole vs. placebo to letrozole vs. placebo): Updated results

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Background and Rationale: In MA.17, 5187 postmenopausal women with ER+ and/or PgR+ or receptor-unknown were originally randomized to receive letrozole (LET) or placebo (PLAC) after 5 years of tamoxifen treatment. After a median follow up of 30 months women in the letrozole arm had statistically significant better disease-free survival (DFS) and distant disease free survival (DDFS) than women in the placebo arm (DFS: Hazard ratio = 0.58 [HR], P = 0.00004, DDFS: HR = 0.60, p = 0.002). The trial was unblinded in October 2003 after the first interim analysis due to a significant difference in total events favouring the LET arm. Women randomized to PLAC were offered LET at the time of unblinding. We will present at the meeting an updated comparison of efficacy endpoints in the following three groups: randomized originally to LET (LET), to PLAC but crossed over to LET (PLAC-LET), or stayed on PLAC (PLAC).

Design and Methods: LET and PLAC-LET have been compared to PLAC, based on the hazard ratio and adjusting for baseline patient and disease variables including, among others, tumor size, nodal status and prior adjuvant chemotherapy.

Summary: Information about their follow-up treatment after unblinding was available on 2247 women originally assigned to PLAC and who were free of recurrence and alive at the time of unblinding. Among them, 1601 crossed over from PLAC to LET. Age, nodal status, endocrine symptomatology and being in the USA as compared to Canada were important predictors for switching to LET(Luk C et al., ASCO 2005). The total number of breast cancer events in the three groups since the original randomization is at present 342 with 211 deaths and median follow-up of 49 months. Longer follow up on the adjusted HR of DFS between LET and PLAC as well as PLAC – LET vs PLAC will be presented together with updated analyses of toxicities, new diagnoses of osteoporosis and clinical fractures, and cardiac events.

Conclusion: MA.17 was unblinded at the first preplanned interim analysis because of a strong treatment effect of LET. Among the clinical questions left unanswered is the optimal duration of LET, long term toxicities and whether starting LET after a prolonged period off tamoxifen is of benefit. This updated analysis will address these questions. To further answer the question of duration we have also begun enrolling on MA17R, a re-randomization of all participants completing LET on MA.17 to a further 5 years of treatment.

210 Proffered Paper Oral

Prognostic value of bone marrow micrometastasis on disease outcome in 4703 breast cancer patients: meta- and pooled analysis after 10 years of follow-up

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Background: To assess the prognostic significance of bone marrow micrometastasis (BMM) in breast cancer patients by means of a statistically powerful study and provide the evidence for implementation of BMM in clinical decision making.

Methods: Individual patient data of 9 studies, involving 4703 patients with stage I-III breast cancer, were combined to analyze long-term clinical outcome. Meta-analysis was conducted to summarize the results of included studies. Using the pooled data, piecewise proportional hazards regression models were estimated for the complete set of patients and in subgroup analysis.

Results: The prevalence of BMM was 30.6%, and was significantly associated with larger tumor size, higher grade, lymph node metastasis and endocrine non-responsiveness (each P < 0.001). Meta-analytic hazard ratios indicated a more than 2-fold increased risk of either dying or relapse for overall (OS), cancer-specific (CCS), disease-free (DFS) and distant disease-free survival (DDFS). Assessment of statistical heterogeneity revealed significant inter-study variation of hazards ratio estimates (Q-test, P = 0.007 for OS; P < 0.001 for DFS). According to sensitivity analysis this did not bias the pooled survival estimates. Residual heterogeneity was removed by stratifying by center. Multivariable regression including established prognostic factors demonstrated that BMM was an independent prognostic variable for all investigated endpoints. This effect was strongest during the first years following primary breast cancer diagnosis: adjusted hazards ratios were 1.81 (95% CI, 1.51–2.16) for OS, 1.93 (1.58–2.36) for CCS, 1.85 (1.59–2.14) for DFS, and 2.03 (1.72–2.39) for DDFS. On univariate analysis, survival of patients with BMM in subgroups with either endocrine therapy or chemotherapy alone was significantly reduced (each P < 0.001). Among patients with pT1N0 disease, who received no systemic adjuvant treatment, those with BMM had significantly reduced OS (P = 0.001), CSS (P < 0.001), DDFS (P = 0.007), and DFS (P = 0.01). Specifically to the sites of first relapse, bone metastases were more frequent in patients with BMM than in those without BMM (IRR 1.37, CI 1.09–1.73). Among patients with BMM, distant metastases occurred more frequently at multiple sites than at a single site (IRR 1.85, CI 1.21–2.06).

Conclusions: This pooled analysis provides conclusive evidence that presence of bone marrow micrometastasis is a significant indicator of poor prognosis in breast cancer patients.

Thursday, 23 March 2006 13:00–14:00

SPECIAL SESSION

Breast cancer in the elderly

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Statistical issues for cancer clinical trials in the elderly

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For a long time, elderly patients were excluded from clinical trials. The main reason for excluding the elderly was the fear of increased toxicity and reduced efficacy due to comorbidities and competing risks, resulting in a less favourable risk/benefit ratio in this group of patients. Today, the need for age-based exclusion criteria is questioned, and trials specifically aimed at elderly populations are being conducted. This talk will illustrate the impact of competing risks on different endpoints. Statistical methods that allow for competing risks will be introduced, and their difficulties underlined. The usefulness of stratifying by age and testing for interactions will be discussed.

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Systemic treatment for elderly women with breast cancer: tradeoffs between duration and quality of survival

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For an elderly woman with breast cancer, the 10-year risk of relapse and death due to cancer can be estimated from disease-related factors such as nodal involvement, tumour size and grade. Relative benefits of adjuvant systemic therapy may be similar to those of a younger woman, but the absolute benefit is smaller due to competing risks of death. Clinical trials suggest that many older women tolerate chemotherapy as well as younger women, but there is bias since trials accrue a lower proportion of eligible elderly women. Also, clinical trials record side-effects such as nausea, vomiting, neutropenia and GI upset; side-effects such as fatigue and cognitive dysfunction may be more important for older people because they add to tiredness and cognitive decline that occur with aging, and increase the likelihood of dependence. Thus, toxic effects of treatment will be greater in older women, and the risk-benefit ratio increases with age. Changes in the risk-benefit ratio may be accompanied by changes in patient preference for quality versus quantity of life. Many younger women accept toxic treatments for a very small gain in the probability of cure, but cure has a different context for a woman whose life expectancy is naturally limited by the aging process. There are certainly older women for whom adjuvant therapy is appropriate, since few events decrease quality of life more than recurrence of disease. The above factors must be discussed with an elderly woman when considering adjuvant therapy; they will be illustrated by comparing decisions about adjuvant therapy for a woman of 75 and a woman of 55 who present with breast cancer with similar clinical characteristics.

Decisions about systemic treatment must also be modified for an elderly woman with symptoms due to metastatic breast cancer. Hormonal therapy is preferred in women with ER+ disease. For women with hormone-resistant disease, chemotherapy is likely to have at most small effects to prolong life, so that symptom control and quality of life are paramount. Treatment with single drugs that have relatively few side effects is preferred in the elderly, even if the response rate is lower than that of other regimens. This will be illustrated by the case history of a 96 year old woman with symptomatic ER-negative recurrent breast cancer.