trials of local treatments in early breast cancer beginning before 1995. Information was available for 78 randomized trials involving 42,000 women (23,500 in trials of radiotherapy (RT) vs. no RT; 9,300 in trials of more vs. less surgery; and 9,300 women in 17 trials of more surgery vs. RT).
Major findings from the update were: (1) breast cancer mortality was reduced with RT following breast-conserving surgery [hazard ratio 0.83, 95% CI 0.75−0.91 (p = 0.0002)]. This effect was seen for node-negative and node-positive disease and paralleled the substantial reduction in local recurrence seen at 5 years; (2) a reduction in breast cancer mortality was also seen post-mastectomy in node positive patients (p = 0.002). No effect was seen for node-negative disease; (3) an important relationship between local control and the impact on breast cancer mortality was observed. In most trials of RT, the impact on local recurrence was seen rapidly and substantially by 5 years. Little effect in breast cancer mortality was observed in the first 2−3 years, but a definite effect was seen at 10 years and was maximally at 15 years. Among the 25,000 women in whom there was a reduction in local recurrence at 5 years of >10%, there was an absolute reduction in breast cancer mortality at 15 years of approximately 5%; and (4) the use of radiotherapy was associated with an increased incidence of contralateral breast cancer (rate ratio (RR) = 1.18, p = 0.002), lung cancer (RR = 1.61, p = 0.0007), leukemia and soft tissue sarcoma. There was an associated increase in non-breast cancer deaths mainly involving heart disease (RR = 1.25, p = 0.00003).
Since this update the 2005/06 cycle of the EBCTCG has commenced including additional trials started in 1995–2000 with extended follow-up up to 2005. A preview of these findings and implications for clinical practice and research will be presented.

189 INVITED

Does everyone need breast radiotherapy?

J. Yarnold. *The Institute of Cancer Research, Academic Unit of Radiotherapy, Sutton, United Kingdom*

The risk of local tumour relapse has fallen to such low levels for most patients after breast conservation surgery, systemic therapies and radiotherapy for early breast cancer that it prompts reassessment of guidelines that recommend breast radiotherapy in all cases. Trials randomising to radiotherapy versus no radiotherapy primarily test treatment effect, but they also offer valuable prospective data on the consequences of observation (no radiotherapy) in well-characterised populations. These typically include women aged over 50 years with completely excised oestrogen receptor (ER) positive, node negative tumours less than 20 mm in microscopic diameter. Recent results have been interpreted as evidence that radiotherapy can be safely withheld in defined subgroups, but these judgements seem premature based, as they are, on trials with less than 5−10 years follow up. Nevertheless, several factors are likely to be driving local relapse risk down independent of radiotherapy, including patient selection for breast conservation and more careful attention to surgical excision margins. In addition, advances in adjuvant systemic therapy are having a significant impact. The 2005 update of adjuvant systemic therapy by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) confirms that 5 years tamoxifen or several months of polychemotherapy reduce the annual hazards of local relapse to a similar extent as distant metastases. This amounts to a 50% reduction in local relapse risk after 5 years tamoxifen in ER positive tumours. After cytotoxic therapy, the magnitude of local effect depends on drug regimen and ER status, but is substantial in ER negative tumours. Preliminary data from trials testing adjuvant aromatase inhibitors report a reduction in local relapse risk of around 30% compared to tamoxifen alone. The combined effects of tamoxifen and aromatase inhibitor are, therefore, comparable to the benefits of radiation (hazard ratio = 0.3). The effects of trastuzumab in patients over-expressing the HER2 protein are also impressive, reducing local relapse risk by around 50%. In conclusion, while it is not currently possible to confidently identify subgroups with <10% risk of local relapse at 10 years after surgery and appropriate systemic therapies alone, it is likely that selective avoidance of breast radiotherapy in defined subgroups will be possible in the next 5 years or so. The selection process is likely to take account of encouraging evidence that biological markers help to reliably define low risk subgroups.

190 INVITED

Partial breast irradiation – a valid option?

A. Fourquet. *Institut Curie, Dept. de Radiothérapie, Paris, France*

Partial breast irradiation (PBI) is a new modality of radiotherapy, delivering radiation solely to the surgical area of excision in the setting of breast conservation of small breast cancer.
PBI was originally designed to allow breast conservation to patients with small tumors, who, because whole-breast radiotherapy (WBR) over several weeks could not be carried out in some areas due to distance to radiotherapy centers, costs, or long waiting lists, were treated with mastectomy. The first reports of PBI were of series of highly selected patients treated with conventional low-dose rate brachytherapy using Iridium 192, implanted through plastic catheters in the surgical site area, treating a wide volume, with doses around 50 Gy over 5 to 6 days. Reports from these experiences suggested that 5-year local control rates were similar to those obtained with WBR.
More recently, new techniques were introduced and are still under evaluation, aiming at targetting smaller treatment volumes, and at reducing the treatment time with accelerated irradiation (APBI). These techniques include: high dose rate brachytherapy, delivered through ambulatory care, or external beam photon radiotherapy. In both instances, a 50 Gy or more "biologically equivalent" dose is usually delivered in 10 or more fractions, twice daily with at least 6 hours interval, over 5 days. Another technique uses intraoperative radiotherapy with low-energy photons or electrons, delivering a single dose of radiation in the surgical bed immediately follwing excision. Results from these various techniques are reported with short follow-up in selected patients. Several prospective phase III randomised trials are ongoing in North America and Europe.
Obvious advantages of these techniques are practical: the reduction of overall treatment time makes it possible for patients to undergo treatments which otherwise they would be able to afford daily over several weeks, because of physical incapacity, distance to radiotherapy centers, professionnal constraints, or in some countries, cost of treatment. Treating the site of excision only with a predetermined margin would limit irradiation of organs at risk, such as the heart, lungs, or contralateral breast. Finally, the short overall treatment time would allow an earlier delivery of irradiation in patients who receive adjuvant chemotherapy.
However, this new technique raises many issues that need to be solved before it can be recommended for routine practice. Among them are the following:

- What will be the consequences of not treating the whole-breast, as achieved by mastectomy or WBR, as has always been the basis of the locoregional treatment of breast cancer? The rationale of this new paradigm relied on the observation that the majority of breast recurreces occurred within the area of the primary tumor location in the breast, which led to the postulate that only these recurrences shoud be prevented, wheras recurrences elsewhere in the breast would represent new primaries. However, some data suggest that, in the long term, WBR can prevent the occurrence of such elsewhere recurrences, the exact nature of which remain to be precisely determined by biological characterization.
- The planned treatment volume defined in most PBI techniques, usually encompasses the vague definition of the surgical cavity with arbitrary margins aimed at treating the microscopic residual disease and taking into account set-up variations and patient's respiratory movement. These definitions vary from one technique to another and are often mostly determined by the constraints of the technique itself. Therefore, the definition of margin in these techniques is highly imprecise.
- Hypofractionation has not been validated in the long term, using these particular regimen. Single doses, or high doses per fraction, with a short repair interval, may lead to increase long-term sequelae in the treated area; models of biological equivalence are not fully reliable, and need to be validated in breast cancer. Recent results from large, randomised multicentric studies of hypofractionated WBR suggest that regimen using 13 to 16 fractions can be safely applied, which are not much different from the 10 or more fractions used in the APBI regimen.

Finally, the technical delivery of whole-breast radiotherapy has dramatically improved in the recent years, allowing in most instances to safely prevent the unnecessary irradiation of organs at risk.
In conclusion, the concept of partial breast irradiation represents a significant shift in the current paradigm of breast-conserving treatment. It raises many unsolved issues that need to be validated in prospective trials, and its effects will have to be measured in the long term. It is much too early yet to determine whether it would be a becomme a valid alternative to whole-breast irradiation in selected groups of patients.

191 INVITED

The effects and interaction by multimodal therapies, radiation, cytostatics and trastuzumab, on cardiac toxicity

J. Bergh. *Karolinska University Hospital Solna, Department of Oncology, Stockholm, Sweden*

Background: Postoperative radiotherapy reduces the risk for local recurrence with around 2/3. Adjuvant tamoxifen, cytostatics, and combinations with trastuzumab improve overall survival. For many patients, the use of systemic adjuvant therapies have presently to be combined with postoperative radiotherapy in order to obtain the most optimal results, trading of benefits versus increased side-effects.