for tailoring adjuvant treatments to the individual cancer patient. In the meantime, adjuvant locoregional radiotherapy with appropriate radiotherapy techniques should be considered for patients having adverse risk factors.

31 INVITED

Partial breast irradiation

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Background: Breast conserving therapy (BCT) is the gold standard for patients presenting with early stage breast cancer. Post-operative radiotherapy nevertheless implies both a long overall treatment time, which can exceed 6 weeks – with all direct and indirect costs it imposes in terms of health economics – and, in some cases, a risk of post-radiotherapeutic complications or reduced cosmesis at the level of the whole breast.

Rationale for breast partial irradiation: The concept of partial breast irradiation was promoted by both surgeons and radiation oncologists, at first in patients aged 60+ and presenting with small T1 tumors. This subgroup of patients should indeed benefit the delivery of irradiation doses to a limited portion of the breast. It is assumed that the low risk of recurrence in other quadrants is likely to avoid any deleterious effect of partial irradiation on local control, with the advantage of sparing the rest of the gland, reducing the risk of late complications and increasing the quality of life.

Material and Methods: A first approach consists of an *intra-operative delivery* of irradiation using electron beams. Several approaches have been recently developed by various companies for intra-operative treatments: ELIOT, NOVAC-7, TARGIT, INTRABEAM and the treatment feasibility is now well documented. Mid-term results in terms of efficacy should be available within the next 12 months. In *post-operative setting* partial breast irradiation can be based on brachytherapy with doses reaching 32–34 Gy, when tumor presentation is compatible with a partial irradiation of the breast. In a very recent past, a new applicator (MammoSite®) has been developed to address these drawbacks of conventional brachytherapy techniques, allowing a more simple and reproducible radiation delivery to the target tissue area. This radionuclide delivery system is ideally inserted at the time of the surgical procedures, in order the balloon-shaped applicator fills up the cavity created by the tumor removal. With this system the overall treatment time is reduced from 6 weeks down to only 5 days, with all the advantages it implies in terms of logistics and direct/indirect costs for the patients. The role of intensity modulated radiation therapy in the field of partial breast irradiation is still investigational but this high conformality approach offers powerful tools that should allows an increase in total dose and a better sparing of normal tissues including lung, myocardium, and mammary gland tissue outside the target volume.

Results and Discussion: Preliminary results will be presented regarding treatment safety and efficacy will be presented for partial breast irradiation, in both peri- and post-operative settings. The discussion will be articulated around the advantages and limitations of this approach, as well as strategies aiming at an ultra-selection of patients according to their risk factors, disease pattern and treatment optimization tools.

32 INVITED

Altered fractionation schemes

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Radiotherapy regimens for women with early breast cancer based on 2.0 Gy fractions represent safe and effective approaches to patient management. They may, however, not be optimal. The results of a prospective randomised trial undertaken in Canada suggest that 16 fractions of 2.65 Gy are as safe and effective as 25 fractions of 2.0 Gy fractions in terms of local tumour control and late adverse effects [1]. Differences in overall treatment time between randomised groups make it difficult to take account of tumour cell repopulation in estimating the influence of fraction size on outcome. However, limited clinical data suggest that adenocarcinoma of the breast is significantly more sensitive to fraction size than squamous cell carcinoma of the head and neck, cervix uteri and lung, and may be as sensitive as the dose-limiting normal tissues of the breast. In a prospective randomised trial involving 1420 patients that compared two dose levels of a 13-fraction regimen (testing 3.0 Gy and 3.3 Gy fractions) delivered over 5 weeks against a control regimen of 50 Gy in 25 fractions in 5 weeks, the α/β value for late adverse effects (primary endpoint) was 3.6 Gy (95% CI 1.8–5.4) [2]. The point estimate of α/β for tumour control (secondary endpoint) was 4 Gy (no CI) [3]. The latter estimate is imprecise, but greater statistical power will be gained from 4450 women entered into the UK Standardisation of Radiotherapy (START) trial between 1998 and 2002 testing two 13-fraction schedules (testing 3.0 Gy and 3.2 Gy fractions) and 40 Gy in 15 daily fractions, against 50 Gy in 25 fractions. If the fractionation sensitivity of breast cancer is confirmed to be comparable to dose-limiting normal tissues of the breast and chest wall, there are potential benefits to be considered from hypofractionation with respect to tumour repopulation, scheduling with cytotoxic therapy, patient convenience and health services resource usage.

References

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33 INVITED

Timing of radiotherapy and chemotherapy

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Combined treatment modalities with radiotherapy and chemotherapy result in lower locoregional and distant recurrences in patients at risk. Following conservative surgery or mastectomy, the relative risk reduction with radiotherapy averages 66%, whether patients receive adjuvant systemic treatment or not. This reduction in local recurrences result in a significant improvement in disease-specific survival.

Few data are available regarding the effects of timing or sequencing of chemotherapy and radiotherapy on the outcome of patients treated with primary surgery. Conclusions from retrospective studies are conflicting, but these studies suggest an increase rate of recurrence if this interval between surgery and radiotherapy is greater than 8 weeks when no chemotherapy is given, or greater than 6 months in patients who receive chemotherapy. Other studies suggest an increase rate of recurrence with increasing radiotherapy interval in subgroups at risk (i.e: with involved margins after breast-conserving surgery, or with involved axillary nodes). One randomised trial has compared two sequences, chemotherapy (4 cycles) followed by radiotherapy vs. radiotherapy followed by surgery, and show no differences in local or distant recurrence rates.

Recent trials have evaluate the effects of concurrent radiotherapy and chemotherapy and suggest some benefit in groups at risk.

In conclusion, few data are available on the effects of delaying radiotherapy or chemotherapy on outcome after surgery for breast cancer. An evaluation of the most effective sequencing of both treatment modalities must be considered in the design of upcoming trials.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Specific issues in early breast cancer related to very young women

34 INVITED

Genetics in very young patients

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Epidemiologic characteristics and risk factors are slightly different in young breast cancer patients as compared to their older counterparts. Classical hormonal risk factors appear either to see their impact decrease with a decreasing age or to be inverted, while family history appear to have a relatively higher effect on risk. Despite these observations, germline deleterious mutations of genes predisposing to breast cancer in an autosomal dominant manner remain rare among young or very young breast cancer patients. In population-based series published, the prevalence of BRCA1 and BRCA2 deleterious mutations among patients diagnosed with breast cancer at ages less than 36 to 40 years is respectively around 4–6% and 2–3%. These numbers, however, increase dramatically with either the presence of an Ashkenazi descent (16–25% BRCA1- and 8% BRCA2-positive), of a family history of breast or ovarian cancer (linear increase with the number of first/2nd degree relatives affected), or, as recently shown, with the bilateralism or even multifocality of breast cancer. Except a recent series describing four germline mutations in the p53 gene among patients diagnosed with breast cancer before 30, the search for mutations in other predisposing genes have not been helpful yet.