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.

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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.

Beside explaining the occurrence of unexpected breast cancer among very young patients, one would have thought genetics may highlight certain specific phenotypic, biologic and behavioural characteristics of breast cancer among the youngest. Indeed, BRCA1-linked breast cancer shares certain specific characteristics with that of young women, such as a high grade, high proliferation rates and the frequent absence of hormone receptors. As well, recent descriptions of gene expression profiles appear similar and might plead for a common stem cell progenitor. However, although this remains controversial, genetics do not appear to account for the high prevalence of local recurrence of breast cancer in the populations of young women. We showed that among breast cancer patients with a strong family history and treated with conservative surgery, young age remained the only risk factor of local relapse, whereas the presence of a BRCA1/2 mutation was not.

We will discuss on the bases of recently acquired knowledge, the specific care of young carriers of BRCA1 or BRCA2 mutations, as well as the care of very young women affected with breast cancer, whether genetically-determined or not.

35 INVITED

Early breast cancer in very young women: the interphase between endocrine and chemotherapy treatment

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One in forty women with breast cancer is very young (<35 yrs). Outcomes in this age group have unique aspects. St Gallen Guidelines on Early Breast Cancer exclude women <35 from minimal risk category because of higher relapse risk.

IBCSG found women <35 yrs had higher risk of relapse after adjuvant CMF with 10 yr DFS of 35% which was significantly worse than 47% in older premenopausal women [1]. The relapse rate in women <35 yrs was particularly high in ER+ve group, who had a worse outcome than women <35 yrs with ER−ve tumors (10 yr DFS in <35 yrs: ER+ve = 25%, ER−ve = 47%). When US groups studied trial outcomes, a similar pattern was seen [2]. For ER−ve tumors, the outcome in women <35 yrs was similar to the older premenopausal women.

In premenopausal women with ER+ve cancer who receive chemotherapy, the outcome is better if amenorrhea occurs. The poor outcome for very young with ER+ve tumors treated with chemotherapy alone, maybe due to failure to achieve endocrine benefit of amenorrhea in this age group.

Adjuvant ovarian ablation is effective in women <50, but if chemotherapy is also given, ovarian ablation is of uncertain benefit [3]. The data are mainly from women aged 40–50 yrs who become menopausal from chemotherapy. This may underestimate benefit for very young.

US Intergroup randomized premenopausal receptor positive women to CAF, CAF + goserelin, or CAF + goserelin + tamoxifen. There was no significant benefit overall with addition of goserelin [4]. Retrospectively the subgroup <40 yrs appeared to benefit from goserelin. IBCSG randomized premenopausal women to CMF, or goserelin, or CMF then goserelin [5]. Goserelin after CMF resulted in a non-significant benefit. In an unplanned analysis, it appeared the ER+ve subgroup <40 yrs derived benefit from goserelin after CMF.

US groups assessed outcomes of very young ER+ve women compared with their older premenopausal counterparts, from trials with chemotherapy followed by tamoxifen. The results suggest an increased relative risk for those <35 yrs [2].

Very young women with receptor positive cancer deserve attention because of their poor outcome. Optimal chemo-endocrine strategies will be tested in a suite of 3 trials (**SOFT**, **TEXT** and **PERCHE**) led by IBCSG and joined by Breast International Group (BIG) and North American Breast Intergroup.

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36 INVITED

Mastectomy: the preferred treatment in young women?

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Nowadays, breast-conserving therapy is a generally accepted and widely embraced treatment modality for the majority of patients with early-stage breast cancer. Trials comparing breast-conserving therapy versus mastectomy revealed comparable results with respect to overall survival. However, several studies demonstrated the influence of young age as an independent risk factor of poor disease outcome. Patients with breast cancer diagnosed at younger age present more frequently with factors associated with a poor prognosis, such as larger tumours, vascular invasion, high-grade tumours, lymph node involvement, negative hormone receptors, and tumours with high S-phase fractions and overexpression of p53. In addition, young age has also been shown to be an independent risk factor. So the question arises whether breast-conserving surgery is justified as a treatment option in the management of early-staged, young breast cancer patients.

Randomised-controlled trials that studied mastectomy versus breast-conserving surgery without radiotherapy indeed showed a difference in overall survival in favour of more aggressive surgery. It is assumed that local recurrence after breast-conserving therapy arises from tumour cells that are left in the breast after local excision. Apart from the emotionally devastating events of any recurrence for the patient, distant metastasis may develop as a result of local recurrence. Furthermore, tumour bed re-excisions are performed more frequently in the younger age group, although no differences are observed in the final negative margin status among the other age groups. This might indicate the difficulties encountered when trying to achieve negative resection margins in younger patients and suggesting the presence of an extensive intraductal component or multifocal disease in younger women. Remarkably, no trials exist whom specifically compare breast conservative surgery versus mastectomy in women diagnosed at young age. A meta-analysis of three randomised EORTC-trials 10801, 10854, and 10902 revealed that patients of 35 years and younger diagnosed with breast cancer not only have almost three times higher local recurrence rates, but also a lower survival rate. However, adjuvant radiotherapy demonstrated very similar survival patterns when compared to mastectomy alone and seems to reduce the risk of local recurrence. Especially in women with early-onset breast cancer, perioperative chemotherapy demonstrated also a reduction of local recurrence rate. To date, no clinically useful risk factors for local recurrence have been identified within the population of young breast cancer patients. This is an important area of breast cancer research; especially gene expression profiling using microarray analysis is a promising method tho investigate this problem.

But should adjuvant treatment compensate for possibly inadequate surgery? After all, adjuvant radiotherapy trials have also demonstrated a beneficial effect for radiotherapy on overall survival after mastectomy in early breast cancer patients. Patients with limited nodal involvement benefited more from adjuvant radiotherapy than patients with extensive nodal disease. Although excessive radiation and chemotherapeutic regimes are obsolete, the long-term effects on in particular cardiovascular disease have to be taken into account when planning an optimal strategy in young breast cancer patients.

Finally, women with early-onset breast cancer are more likely to harbour one of the breast-cancer susceptibility genes, BRCA1 or BRCA2, or to have another genetic predisposition. Overall, the prognosis of breast cancer in carriers of a BRCA1- or BRCA2-mutation seems to be similar to that in age-matched patients with so-called sporadic breast cancer. In addition, since normal BRCA1/2 function may be associated with DNA repair, the possibility of an increased rate of radiation-induced malignant disease in carriers of BRCA1/2 mutations has been raised. An international collaboration study found no significantly increased rates in local recurrence after 10 years when comparing breast-conserving therapy in women with germline BRCA1/2 mutations to matched sporadic controls. However, it is noteworthy that significantly higher rates of contralateral events are observed in the genetic predisposed group. Bilateral mastectomy has demonstrated a substantially reduction of subsequent breast cancers in this group of patients. Although no evidence exists that overall or disease-specific survival is impaired by opting for conservative treatment, careful monitoring will be necessary for early detection.

The management of young women with newly diagnosed breast cancer still remains a challenging problem with complicated medical, psychological, and social implications. Although eventually breast-conserving therapy is regarded as the prime option, mastectomy and subsequent