7 & 53 Gy for _/_ = 1 and 20 & 120 Gy for _/_ = 1.5. In our pilot study of 26 patients (age 30–80 years, T = 0.42–4.0 cm), we replaced the routine post-operative tumour bed boost with targeted intra-operative radiotherapy. There have been no major complications and no patient has developed local recurrence, although the median follow-up time is short at 29 months. The cosmetic outcome is satisfying to both the patient and the clinician. Having established the feasibility, acceptability and safety in the pilot study, we started in March 2000, a randomised trial that compares *Targit* with conventional post-operative radiotherapy for infiltrating duct carcinomas, with local recurrence and cosmesis as the main outcome measures. Patient accrual in this trial has been excellent and it has attracted several international collaborative groups. If proven effective, *Targit* could eliminate the need for post-operative radiotherapy potentially saving time, money and breasts.

192 INVITED

Intraoperative electron irradiation (IOERT) in breast cancer: Methodological description of a 7 years instutional experience

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Purpose: To analyze retrospectively the outcome and cosmetic results of breast cancer patients in which IOERT was used as a component of treatment.

Patients and Methods: From October 1993 to October 2000, 21 breast cancer patients recieved IOERT. Age ranged from 35 to 75 years (median 53 years). Conservative surgery was perfomed in 14 (66%). Tumor stages were: 3 I (14%); 12 IIA (T_1N_1–T_2N_0); 3 advanced (1 T_2N_2; 2 inflamatory); 3 loco-regional recurrences. Histological subtypes were: 12 invasive ductal (57%), 3 lobulillar, 3 intraductal, 2 inflamatory carcinoma and 1 phylloides sarcoma. Postoperative treatments included external radiotherapy (76%), chemotherapy and hormonotherapy. IOERT target was the surgical tumor bed (negative-close margin 95%), with applicator size range from 5 to 10 cm Ø, electron energies from 4 to 12 MeV, single doses from 8 to 15 Gy and multiple field employed in 3 procedures.

Results: Median follow-up time is 36 months (range 8 to 91 months). 81% of patients are alive (76% NED). No local recurrence has been detected: 3 patients developed distant metastasis (bone and lung). In breast preserved patients cosmetic results are categorized as excellent. No acute or late toxicities have been exclusively related to the IOERT component of treatment.

Conclusion: In the context of an expert IOERT institution this radiation boosting technique used as a component of treatment is feasible to introduce in the multimodal management of localized breast cancer. Cosmetic and local control results are attractive, in particular for breast conserving approaches. Information is limited regarding its potential value in recurrent disease and locally advanced post-mastectomy patients.

193 INVITED

The Milan trial

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Local recurrences after breast conserving surgery occur mostly in the quadrant harbouring primary carcinoma. The main objective of postoperative radiotherapy should be the sterilization of residual cancer cells in the operative area while irradiation of the whole breast may be avoided. We have developed a new technique of intraoperative radiotherapy of a breast quadrant after the removal of the primary carcinoma. A mobile linear accelerator with a robotic arm is utilized delivering electron beams with four energies from 3 to 9 MeV. Through a perspex applicator (available with different diameters - from 4 to 10 cm and angles) the radiation is delivered directly to the reconstructed portion of mammary gland around the tumor bed, stretching out the skin from the radiation field. In the first phase, since February 1999 to November 2000, different dose-levels were tested from 10 to 21 Gy on 101 patients without important acute side effects. According the radiobiological models, can be estimated that a single fraction of 21 Gy is equivalent to 60 Gy delivered at 2 Gy daily. All patients underwent quadrantectomy and axillary dissection and/or sentinel node biopsy. Seventeen patients received a dose of IORT of 10 to 15 Gy as an anticipated boost while 86 patients received a dose of 17-19-21 Gy intraoperatively as a complete treatment. No major late effects have been observed with a follow-up of 12-24 months. The cosmetic outcome was very good. A phase III randomized study comparing IORT at the dose of 21 Gy (prescribed at yhe 90% isodose) and a conventional course of external irradiation (60 Gy/30 fractions) is oingoing since November 2000 and is expected to finish in 3 years. During the first 12 months more than 180 patients fullfilling the inclusion criteria (age more than 48 years, histologically confirmed unifocal infiltrating carcinoma of the breast, maximum diameter of the tumor 2.5 cm) have been enrolled.

The IORT treatment was very well accepted by all patients, either due to the rapidity of the radiation course in case of IORT as a whole treatment or to the shortening of the subsequent external radiotherapy in case of IORT as an anticipated boost. We believe that single dose intraoperative radiotherapy after breast resection for small mammary carcinomas may be an excellent alternative to the traditional postoperative radiotherapy, which deserves a clinical evaluation through a large-scale randomized controlled trial.

Thursday, 21 March 2002 14:45–16:15

SYMPOSIUM

Molecular biology

194 INVITED

Growth factor regulation of angiogenesis, lymphangiogenesis and metastasis

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Angiogenesis and permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors VEGFR-1 and VEGFR-2. The VEGFR-3 receptor tyrosine kinase is related to the VEGF receptors, but does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. We have found that homozygous VEGFR-3 targeted mice die around day 10 of embryonic development due to failure of cardiovascular development and that heterozygous missense mutations of VEGFR-3 inactivating the tyrosine kinase activity are associated with human hereditary lymphedema. We have also purified and cloned the VEGFR-3 ligand, VEGF-C. Transgenic mice expressing VEGF-C developed a hyperplastic lymphatic vessel network and show evidence of lymphangiogenesis. However, proteolytically processed VEGF-C was also capable of stimulating VEGFR-2 and was weakly angiogenic. VEGF-C induced vascular permeability, but its point mutant, which retained lymphangiogenic properties and activated only VEGFR-3 did not.. VEGF-D is closely related to VEGF-C, similarly processed and binds to the same receptors. Thus, VEGF-C and VEGF-D appear to be both angiogenic and lymphangiogenic growth factors. VEGF-C induced the growth of peritumoral lymphatic vessels and was associated with lymphatic metastasis in transgenic mice. VEGF-C overexpression also led to lymphangiogenesis, intralymphatic tumor growth and lymph node metastasis in an orthotopic model of human breast carcinoma in immunoincompetent mice. Furthermore, soluble VEGFR-3, which blocks embryonic lymphangiogenesis, blocked these changes. However, VEGFR-3 is also induced in blood vessels of various types of human cancer. Ongoing experiments address the role of the VEGFR-3 signaling pathway in embryonic and tumor angiogenesis and the mechanisms of lymphatic metastasis.

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195 INVITED

Cell cycle regulation by cyclin-dependent kinases and their inhibitors

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Most human tumors carry mutations that deregulate the G1/S transition of the cell cycle, the process by which quiescent cells initiate their replication. This transition is primarily regulated by the sequential phosphorylation of the Rb family of proteins. Rb phosphorylation is mediated by two classes of cyclin-dependent kinases: Cdk4 and Cdk6, which are regulated by D-type cyclins and Cdk2, which is sequentially regulated by E- and A-type cyclins. In addition, these kinases can be negatively regulated by two families of inhibitory proteins. The INK4 family, which inhibits Cdk4 and Cdk6 by preventing binding of the D-type cyclins, consists of four highly related proteins designated as P16INK4a, P15INK4b, P18INK4c and P19INK4d.. The Cip/Kip family, P21Cip1, P27Kip1 and P57Kip2, blocks Cdk2 by binding to Cdk2-cyclin E/A complexes. Cip/Kip inhibitors also bind to Cdk4/6-cyclin D complexes but do not inhibit their kinase activity. These G1/S regulators are often absent (pRb, P16INK4a, P15INK4b), over-expressed (cyclin D1, cyclin E1, Cdk6) or mutated (Cdk4) in a variety of human tumors such as SCLC (pRb), melanomas (p16INK4a, Cdk4), lymphomas (Cdk6) and breast carcinomas (cyclin D1, cyclin E1). Our laboratory is engaged in studying the role that these proteins play in vivo as well as the mechanism(s) by which they contribute to neoplastic transformation. To this end, we are in the process of generating strains of genetically engineered mice carrying germ line as well as conditional mutations in the genes encoding each of the four cell cycle Cdk's. Here, I will present our results obtained with mice that either lack Cdk4 or express a mutant form (Cdk4R24C) present in human familial melanoma that cannot bind INK4 inhibitors. Cdk4 null mice have a dramatic defect in postnatal proliferation of pancreatic beta cells and testicular Leydig cells. Moreover, these mice are small due to reduced numbers of cells in most organs. Cdk4 (R24C) knock-in mice are slightly larger than their wild type littermates and develop a variety of tumors including those of endocrine origin such as insulinomas, testicular and pituitary tumors. Moreover, these mice are highly susceptible to melanoma development, since most of them develop invasive melanomas upon carcinogenic exposure.

196 INVITED

Microarray expression profiling in breast cancer tailors optimal treatment

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Microarray gene expression profiling combined with advanced bioinformatics is beginning to show its power in delineating disease entities that are otherwise indistinguishable. This refinement in tumor classification allows a more accurate prediction of outcome of disease for patients that present with the same stage of disease based on conventional clinical and histopathological criteria. Gene activities determining the biological behaviour of the tumour may indeed be more likely to reflect the aggressiveness of the tumor than general parameters like tumor size, age of the patient, or even tumor grade. Therefore, the immediate clinical consequences are that treatment schemes can be tailored based on the gene activity patterns of the primary tumor.

We used gene expression profiling with DNA microarrays harboring 25,000 genes on 97 primary breast cancers of young lymph node negative patients to establish and validate a signature, predictive for a short interval to distant metastases. This 'poor prognosis' signature consists of genes involved in cell cycle, invasion and angiogenesis. The prognosis signature is superior to currently available clinical and histo-pathological prognostic factors in predicting outcome of disease (OR = 18 (95% CI 3.3–94), $p < 0.001$, multivariate analysis).

At present, consensus guidelines in the management of breast cancer select up to 90% of lymph node negative young breast cancer patients for adjuvant systemic therapy (e.g., St Gallen). As 70–80% of these patients would have remained disease-free without this adjuvant treatment, these patients are 'overtreated'. Our 'poor prognosis' signature provides a novel strategy to accurately select patients who would benefit from adjuvant systemic therapy and can greatly reduce the number of patients that receive unnecessary treatment.

197 INVITED

How does the clinician integrate rapid advances in molecular biology into patient management

Abstract not received.

Thursday, 21 March 2002 14:45–16:15

EUROPA DONNA SYMPOSIUM

Communication – influences on the doctor/patient relationship

198 INVITED

Can training in communication make doctors' interactions more patient-centred?

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Purpose: To measure the effect of a training course in communication skills on psychosocial attitudes and beliefs and subsequent communication behaviours with patients in consultations.

Subjects and Methods: As part of a large RCT conducted in the UK, 93 clinicians completed a 32-item Physician Psychosocial Belief (PPSB) questionnaire at baseline. They were then randomised to attendance at a 3-day residential communication skills course (N=48) or to a control group (N=45). Three months later both groups completed a further PPSB together with a self-assessment questionnaire recording perceived changes in communication with patients. At both time-points doctors' consultations with 2 consenting clinic patients were videotaped. Communication behaviours were assessed by independent raters using the Medical Interaction Processing System.

Results: Doctors who attended the course showed significantly more positive attitudes and beliefs towards psychosocial issues compared with controls (p=0.002). This improvement was reflected in the analysis of the video-taped recordings of their communication behaviour with patients which was significantly more patient-centred. The course group exhibited more empathy (p=0.042), used fewer leading questions (p=0.024) made more appropriate responses to patient cues (p=0.01) and did more psychosocial probing (p=0.041) than those who did not attend a course. These objective findings concurred with the doctors' self-report of perceived changes in communication style with patients.

Conclusion: The results show that communication skills training interventions that employ behavioural, cognitive and affective components not only increase potentially beneficial and more effective interviewing styles, but can also alter attitudes and beliefs thus increasing the likelihood that patient-centred skills will be employed in clinics.

199 INVITED

The influence of specialist nurses as patient advocates on the doctor/patient relationship

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Specialist breast cancer nurse roles have been developed in the UK since the 1980's. These roles originated in the work of Maguire et al and Watson et al, who investigated the value of specially trained nurses in counselling women following a diagnosis of breast cancer, and in identifying those at high risk of developing psychopathology who might benefit from psychiatric help. Specialist breast care nurses are now seen as integral members of the cancer treatment team, and their role in providing information and support for women undergoing diagnostic investigations and treatment for breast cancer is seen as a core part of breast cancer services. Virtually all breast cancer services in the UK now have specialist breast cancer nurses.

The existence of a significant body of specialist nurses for the last 20 years who have been active in establishing professional interest groups and patient support and lobbying groups, mean that nurses have had a key influence on health care policy in relation to breast cancer services. Nurses have argued strongly for priority to be given to full disclosure of information about diagnosis, treatment and the long-term consequences of cancer treatment, the need for emotional support and active involvement of women in decisions about their treatment, and issues such as breast recon-