

in a primary breast carcinoma is highly preserved in its distant metastasis. These findings suggest that metastatic capability in breast cancer is an inherent feature, and is not based on clonal selections. The results further imply that neo-adjuvant treatment given to patients based on (yet to be established) response expression profiles of their primary breast tumor might indeed prevent the outgrowth of micrometastases.

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INVITED

#### Pharmacogenetics and genomics – prognostication and prediction: where is the future?

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Development of analytical methods as cDNA micro arrays and proteomics provides new opportunities with respect to studying cancer biology and development, early detection as well as prognostication and prediction of treatment sensitivity. Interesting findings are emerging from studies applying cDNA micro arrays to different tumour forms. Despite a substantial heterogeneity in gene expression between individual tumours [1], differences between tumours forms have been revealed [2]. Studies on breast cancer [1] and other tumours have shown that within each cancer form, individual tumours may be grouped into classes based on their gene expression profile. The identification of a subgroup of tumours expressing "basal-cell"-like characteristics, in contrast to the more common "luminal-cell" profile, has suggested a different cellular origin for tumours of the different classes [1]. Moreover, classifications based on gene expression profiles have been shown to be of prognostic value in a diversity of cancer forms [3–8]. Further, micro-array techniques have been successfully applied to in vitro experiments, exploring multiple gene activation in relation to events like restoration of p53 function [9], but also exploring mechanisms of drug resistance [10]. Contrary, only a few studies have so far evaluated use of micro arrays as tools exploring chemoresistance in vivo. These studies have involved a limited number of patients only [11,12]. While correlations between gene expression profiling and therapy response has been found, clearly the predictive value of these gene profiles need to be confirmed in larger studies. Further, these preliminary data do not suggest a predictive accurateness sufficient for therapeutic use. While the studies so far have applied different forms of global gene expression analysis, future studies may incorporate biological hypotheses, analysing expression of groups of genes known to be involved in a functional pathway.

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#### Combining proteomics and genomics for cancer analysis

J. Hoheisel. Deutsches Krebsforschungszentrum, Functional Genome Analysis, Heidelberg, Germany

In the Division of Functional Genome Analysis, we are developing technologies for the identification, description and evaluation of cellular functions and their regulation by producing and processing biological information on a genomic scale. One emphasis in our efforts is work on DNA-, protein- and peptide-microarrays. Many chemical and biophysical issues are being addressed as part of this work in an attempt to understand the underlying procedural aspects, thereby eventually establishing superior analysis procedures. Based on the technical advances, the resulting methods are immediately put to the test in relevant, biologically driven studies on various organisms.

Concerning the analysis of human material, systems are being developed toward early diagnosis, prognosis and evaluation of the success of disease treatment with accentuation on cancer. Beside other applications, analyses are performed on the detection and use of disease-relevant polymorphisms in the area of molecular epidemiology. Also, comparative studies on epigenetic variations, transcript levels and actual protein expression by means of complex DNA- and antibody microarrays are under way. Early diagnosis from blood samples is being worked at that is based on the

binding of serum components to peptide microarrays. Combining this data with clinical information permits the definition of sub-groups within an analysed cohort and eventually a means for diagnosis and prognosis as well as the identification of highly relevant targets.  
(www.dkfz.de/funct\_genome)

Friday, 19 March 2004

14:15–15:45

#### SYMPOSIUM

### Late sequelae of breast cancer treatment, are they preventable?

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INVITED

#### Cognitive functions after chemotherapy

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Currently, the interest in cognitive functioning following chemotherapy is rapidly expanding, as is reflected in a growing number of published articles on this topic. Although most studies are indicative of cognitive deficits after chemotherapy in at least a subset of patients, little is known about the pattern of cognitive deficits, the course of the deficits over time and the impact of deficits on daily-life situations. Moreover, a number of important confounding factors still exists and potential mechanisms by which chemotherapy can adversely affect the brain are insufficiently understood.

In 1998, a large prospective longitudinal neuropsychological study was started in the Netherlands Cancer Institute/Antoni van Leeuwenhoek hospital. In this study, several groups of breast cancer patients adjuvantly treated with cytotoxic agents (including high-dose CTC chemotherapy and standard dose FEC and CMF chemotherapy) were tested neuropsychologically at three points in time: at baseline (i.e. after surgery and prior to the start of chemotherapy) at 6 months and at 12 months after completion of treatment. Patients treated with chemotherapy were compared with stage I breast cancer patients not treated with chemotherapy and with healthy controls, tested at similar points in time. At each assessment point patients and controls were additionally interviewed with regard to cognitive problems experienced in daily life, psychological distress and fatigue. In co-operation with 15 hospitals in the Netherlands, approximately 400 breast cancer patients were tested.

We will present the first data of this study, and results will be related to the above-mentioned gaps in current knowledge.

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INVITED

#### Surgery

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Since Halsted time, the surgical treatment of breast cancer has dramatically changed. The extent of demolitive operations has progressively reduced with a positive impact on the rate of complications and on the quality of patients life. Conservative surgery has allowed to achieve good cosmetic results with the same survival and without increase in local recurrence. Unfortunately a percentage of sequelae after surgery for breast cancer is still present. The most severe complication is lymphoedema of the operated arm. This is secondary to axillary dissection and normally causes functional impairment and psychological morbidity. The risk to develop lymphoedema is approximately 25% with a great range in literature; the rate can raise if radiotherapy is associated. Once that lymphoedema is occurred, its treatment is very difficult with poor results and improvements. Manual lymphatic drainage is helpful for the initial phase and is pleasant for patients but requires specialized staff and high costs. Elastic bandage produces differentiated pressures on the arm decreasing from wrist towards shoulder. They have to be weared during activities or at rest. No importance was seen for treatment with drugs like anti-inflammatory, antihistamines and diuretics. 60–70% of patients with lymphoedema are overweight and maybe diet can play a role in the etiology of this complication. Neural "Stupor" of the brachial plexus is present in about 1% of cases and is due to an incorrect position during the operation. The patient has difficulty to move the arm in

abduction and in bending the forearm with paraesthesiae and disaesthesiae. Section of the thoracic long nerve is a lesion that happens in 20% of the operated women. It is more frequent in conservative operations as it is complicate to separate. It causes the "scapula alata" with hard movements of the arm over the head especially with extended elbow. Section of intercosto-brachial nerve causes anaesthesia, paraesthesia, pain of the axillary region, of the 2/3 of posterior-medial area of the arm. These symptoms last for some months and normally improvement is obtained without therapy. Nowadays, preservation of the intercosto-brachial is performed by the majority of surgeons but there is no consensus about the importance of this technique to reduce discomfort of the arm. The lesion of the anterior thoracic nerve leads to an atrophy of the pectoralis muscle. This damage can nullify a reconstruction with tissue expander. Lesion of the thoraco-dorsal nerve involves the adduction and the internal rotation of the arm produced by the alteration of the contraction of the latissimus dorsi muscle. Pericarditis and osteitis of the breast bone, acromial bursitis, sclerosis of the major pectoralis muscle and scars are also described.

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INVITED

#### **Late sequelae of breast cancer treatment, are they preventable? Radiotherapy**

*J. Jassem. Medical University of Gdansk, Radiotherapy and Oncology, Gdansk, Poland*

Breast cancer is the most common woman malignancy in Europe. Radiotherapy after mastectomy or breast conserving surgery decreases the risk of locoregional failure and improves overall survival.

Traditionally, postoperative radiotherapy of the breast has been delivered with wide rectangular tangential photon fields. Many patients have also been irradiated with photon beams to the regional nodal areas. These techniques, however, not always provide satisfactory dose homogeneity within the irradiated volume and may imply the risk of late cardiac and pulmonary toxicity. Indeed, in early trials of post mastectomy radiotherapy, reduced risk of death from breast cancer was offset by increased cardiovascular mortality, particularly in patients with left-sided tumors.

Recently, several techniques have been developed to improve the therapeutic ratio. Heart injury following postmastectomy radiotherapy may be decreased by the use of electron rather than photon beam irradiation of the chest wall and parasternal lymph nodes. Important improvement has come from immobilization of the patients using a support cushion and arm handle, or a hard foam cradle. Precision of radiotherapy delivery has been improved by virtue of meticulous portal verification systems. In patients managed with breast conserving surgery better dose conformation to the target volume can be achieved with the use of 3-dimensional (3D) CT planning, and particularly with intensity modulated radiotherapy (IMRT). In these patients, customized 3D compensators allow for better dose distribution than a standard wedge. Probably the most effective protection of critical organs outside of target volume may be achieved by the use of proton irradiation, yet this technique is relatively expensive and not commonly available. Most recently, breathing-adaptation techniques have been shown to reduce cardio-pulmonary radiation doses. These innovative methods turn the radiation beam on only during a pre-specified phase of the respiratory cycle, thus modifying organ movement and position in the field.

In conclusion, modern techniques of postoperative breast irradiation allow better protection of critical organs, without jeopardizing tumor control. However, in some patients some damage of heart or lung cannot be completely avoided. Future studies weighing individual risk of locoregional failure versus benefits of irradiation are therefore warranted.

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INVITED

#### **Quality of life – the psycho-social aspects**

*A. Fernandez-Marcos. Asociación Española Contra el Cáncer, Madrid, Spain*

Overall, studies comparing disease-free breast cancer survivors and healthy women show no major differences in their quality of life. Poorer outcomes in long-term quality of life in breast cancer survivors are clearly related to comorbidity. Fatigue, arm problems and difficulties in sexual functioning are key elements explaining most of the problems found in the different dimensions of quality of life studied.

Although data can be controversial depending on the study reviewed and the variables assessed, common findings from a broad review on long-term quality of life in disease-free breast cancer survivors reveals several factors that may predict the long-term outcomes after completion of treatment. Those factors are: *Age at diagnosis* – women younger than 45 years at diagnosis show worse outcomes in the social dimension while women diagnosed at an older age (>65 years) report more problems in the physical domain; *Disease stage at diagnosis* – patients with advanced disease report worse long-term quality of life; *Having received systemic adjuvant treatment* – side effects of this type of therapy correlate with a negative impact on sexual functioning which persists over time; and, *Having undergone axillary dissection* which is related to an increased risk of arm problems.

Some recent studies on the psychological aspects of long-term quality of life in breast cancer survivors report higher rates of Post-traumatic Stress Disorder and emotional distress in breast cancer survivors compared to controls (healthy women).

As the number of disease-free years has extended for breast cancer patients, more attention should be paid to prevent long-term sequelae. In the decision-making process on the best procedure or treatment regimen for a given patient, long-term sequelae of each treatment and the life stage of the patient at diagnosis should be taken into account as variables that may affect long-term quality of life.

Breast cancer patients should be informed about possible long-term side-effects of treatments, ie) fatigue/lymphoedema, in order to allow them to choose the best possible option and in order to facilitate the adjustment to illness and treatments, not just thinking on the short term, but also, in the years to come.

A careful planning of treatment and follow-ups should include the monitoring of acute and delayed (long-term) side-effects, and the establishment of a community-based early referral protocol for breast cancer survivors, in order to prevent, detect early, and treat long-term sequelae.

More research is needed to find out and prove new treatment procedures that minimise late side effects, ie) lymphoedema, taking into account that breast cancer survival rates are improving and long-term quality of life is becoming a major issue for breast cancer patients.

Friday, 19 March 2004

16:00–17:30

#### **SYMPOSIUM**

### **The use of complementary medicine (CAM) in breast cancer**

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INVITED

#### **CAM: what is it, which breast cancer patients use it and why?**

*G.A. Bendelow. University of Sussex, Department of Sociology, Brighton, UK*

This presentation will begin by describing the enormous range and diversity of therapies under the umbrella of CAM (complementary and alternative medicines) which have particular relevance for women with breast cancer. Factors such as the philosophical aims behind different therapies, as well as the practical and therapeutic interventions will be elaborated in order to develop typologies and identify differences, but also similarities between biomedicine and other orientations such as Ayurvedic or Chinese healing systems.

Central to this process is the need to understand the perceived limits of biomedicine, and why women choose to either supplement or even to reject conventional medical interventions. Data from qualitative empirical research studies will be used to illustrate these choices.

The available statistical evidence of women using these therapies will be examined in the UK, and as far as possible, in the rest of Europe, but problems and limitations of collecting data of this nature will also be highlighted.

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INVITED

#### **The menopause: does CAM provide an answer?**

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A holistic medical approach, which is so important in CAM, means that the subject of the therapy is considered as a whole, not as a puzzle of symptoms or parts. Therefore, talking of menopause and CAM, we have to stress that the gold standard of each evaluation of efficacy of the therapies is not the menopausal syndrome, but the quality of life (QoL), as evaluated by the patient herself. In fact, as regards the menopausal syndrome, we do not have consistent scientific reports of the benefits of CAM; and, besides that, we are not sure of the safety of some of the commonly proposed therapies, such as phytoestrogens.

In the experience of CSPO, we evaluated the QoL of 60 patients who asked an alternative approach. We chose the SF-36 questionnaire, which was administered at the first visit and after two months. The CAM intervention consisted basically in Bach Flowers remedies, and, occasionally, by the teaching of relaxing techniques. Each of the 8 domains of the questionnaire (physical activity, role limitations due to physical and emotional status, physical pain, perception of general health status, vitality,