Since the technologist checks the image quality within a few seconds, a new exposure can immediately be done if necessary without loss of time.

During printing on a high-resolution laser film printer, the patient is accompanied to an examination room.

The radiologist, reads the films and CAD on the reading console, compares the pictures with the old films on a view box. He then examines the patient, does a breast ultrasound exam followed by cytology or micro biopsy when needed. The results and films are given to the patient and the report is sent to the referring physician.

Such a powerful tool as the FFD 2000 easily takes 7-8 diagnostic mammography /hour. Because of possible time limitations, the physical exam should not be done in the same room and we believe that interventional procedures should not be done on such a system even if technically feasible.

The CAD is known to detect around 20% more breast cancers than the radiologist alone. This great tool represents a progress as long as it is used before the physical exam. According to the CAD result, the diagnosis can then be improved by a tailored magnification view or an ultrasound exam.

32 INVITED

Application of mri to diagnosis and treatment of breast cancer

K.G.A. Gilhuijs[1], E.E. Deurloo[1], S.H. Muller[1], W.F.A. Klein Zeggelink[1], M. van Vliet[1], J.L. Peterse[2], M. van de Vijver[2], E.J.T. Rutgers[3], L.J. Schultze Kool[1], H. Bartelink[4]. *[1] The Netherlands Cancer Institute, Department of Radiology, Amsterdam, The Netherlands; [2] The Netherlands Cancer Institute, Department of Pathology, Amsterdam, The Netherlands; [3] The Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands; [4] The Netherlands Cancer Institute, Department of Radiotherapy, Amsterdam, The Netherlands*

MRI became clinically valuable for the detection and characterization of breast cancer after the introduction of Gd-DTPA contrast agent. Currently, contrast-enhanced (CE) MRI is capable of detecting mammographically occult cancers, even in dense breast tissue. It shows tumor extent in 3-D, employing magnetism rather than ionizing radiation. Nonetheless, CE MRI has two major drawbacks: its high cost and limited, varying specificity. As a consequence, application of CE MRI is often restricted to selected indications, e.g., suspicion of multifocal/multicentric disease, and detection of the unknown primary in patients with positive lymph nodes.

New applications of CE MRI in diagnosis and treatment of breast cancer are currently investigated. Worldwide multi-institutional trials assess the efficacy of MR screening in women at high lifetime risk of breast cancer. Preliminary results from our institute show high sensitivity but lower specificity for this population, resulting in frequent biopsies on benign lesions. A clinical workstation has been developed to offer objective and reproducible guidelines for the interpretation of MR screening images. In agreement with findings from other groups, combination of computer-rated washout of contrast, smoothness of uptake, mean and variation of margin sharpness yielded significant contribution to the characterization into benign and malignant lesions: estimated NPV exceeds 98% at 50% PPV. These results indicate capability of the system to reduce the number of biopsies on benign lesions in screening without compromising the ability to exclude malignant disease.

Application of CE MRI is currently also investigated for pre-operative estimation of tumor extent aimed at staging and treatment selection, as well as for guidance to breast-conserving surgery and post-operative boost irradiation. For this purpose, the geometrical reproducibility of the mammary gland structure between diagnostic imaging and treatment was estimated by quantification of tissue shifts in the breasts of healthy volunteers using repeat MR setups in supine orientation. Fiducial points in the mammary gland structure were identified and automatically registered with their counter locations in the repeat MRI scans. Margins (5 mm) were derived to take this geometrical uncertainty into account.

Future developments in MRI technology and contrast agents will provide new insights and advances in the diagnosis and treatment of breast cancer.

34 INVITED

Ultrasound: high-frequency, 3D and contrast agents

G. Rizzatto. *Vittorio Emanuele III Hospital, Department of Diagnostic Imaging, Gorizia, Italy*

The diagnostic role of breast ultrasound (US) has been expanded along with the improvement of high frequency transducers and digital technology. Vascular assessment has progressed enough to depict normal vascular anatomy of the breast and the lymph nodes. Pathologic vessels are seen in almost all the tumors, thus improving US sensitivity for nonpalpable carcinomas. New contrast agents will recirculate enough to search for vascular foci during a thorough investigation of both breasts and nodal stations.

US role in screening might be now revised. Many factors are now in favour of targeted US screening in dense and complex breasts, and in high risk patients. Screening sensitivity is significantly increased; most of these US detected tumors are small enough to be curable. Mammography and sonography together are an unique problem solving, and cost effective tool. They can easily guide fine aspirations or larger biopsies reducing the cost of unnecessary surgical procedures.

Accurate US investigations facilitate the surgical approach to a very conservative and cosmetic operation. High-resolution sonography can demonstrate the intraductal spread of tumors and their multiple foci more easily than mammography; but US diagnosis is less sensitive than magnetic resonance mammography in the evaluation of the real tumoral extent. Ductal branching has a complex pattern; therefore intraductal spread and multifocal nodes are better demonstrated by multiplanar analysis of 3D ultrasound data volumes. Sonography can easily explorate the different nodal chains. Metastatic disease is indicated by an enlarged and round shape and the absence of the echogenic hilum. Irregularities in the cortex are a very useful sign in metastatic nodes without total replacement of lymphoid tissue by neoplastic cells. These signs are very specific. A time consuming, radiation emitting and costly sentinel biopsy may be avoided in one every five clinically node-negative patients. But preoperative US assessment is also important as sonography is very sensitive in patients with extensive nodal involvement that might result negative at the sentinel node procedure. New technologies and contrast agents allow perfusional studies that enhance the contrast resolution and will increase the sensitivity of US for small nodal metastases.

Wednesday, 20 March 2002 14:45–16:45

SYMPOSIUM

Pathology: the interface molecular – histopathology

35 INVITED

Molecular changes in normal breast epithelial cells and 'borderline' epithelial proliferations - implications for classification of breast disease

S.R. Lakhani. *Institute of Cancer Research, The Breakthrough Toby Robins Breast Cancer Researc, London, United Kingdom*

Breast cancer is thought to arise in a multistep fashion. A transition from normal epithelium to invasive carcinoma via non-atypical and atypical hyperplasia and in situ carcinoma has been proposed. The introduction of mammographic screening has led to the increased detection of 'borderline lesions' and this has highlighted deficiencies in our understanding and classification of breast disease. Atypical Ductal Hyperplasia (ADH) is a controversial lesion, which shares features with DCIS and non-atypical hyperplasia. Despite clear diagnostic criteria agreement even amongst experienced breast pathologists has been low. Molecular analysis using LOH and CGH has demonstrated genetic changes with similar frequency to that seen in DCIS and invasive cancer. This indicates that ADH is a clonal (neoplastic) proliferation and raises questions about the validity of separating ADH from DCIS as a separate entity.

Retrospective studies indicate that Hyperplasia of Usual Type (HUT) has a relative risk of 2 for the subsequent development of invasive carcinoma. LOH at many different loci have been identified in HUT with frequencies ranging from 0-15%. These frequencies are lower than in DCIS and ADH (range 25-55%). At least a proportion of non-atypical hyperplasia is therefore also clonal, neoplastic proliferation and is likely to be non-obligate precursor. Should the proliferative lesions be classified using -intraepithelial neoplasia- classification similar to CIN in the cervix?

Apocrine papillary hyperplasia is considered to be a benign lesion despite a similar architecture to low grade DCIS. Our laboratory has investigated genetic alterations in benign apocrine hyperplasia and compared these to apocrine ductal carcinoma in-situ (DCIS) and invasive apocrine carcinomas of the breast using CGH. All lesions exhibited DNA copy number changes. The average number of alterations in apocrine hyperplasia was 4.1 compared to 10.2 in apocrine DCIS and 14.8 in invasive carcinoma. The changes show considerable overlap with those identified in in-

situ and invasive apocrine carcinoma. The data suggest that apocrine hyperplasia may not be entirely benign and may be a precursor of apocrine carcinoma.

LOH identified in invasive carcinoma is also present in morphological normal lobules. We have demonstrated that LOH in normal breast is seen independently in luminal and myoepithelial cells. The frequency and significance of such alterations remains unknown at the present time.

36 INVITED

Cell biological and molecular changes in benign and malignant breast disease- implications for future classification

W. Boecker. *Muenster, Germany*

A spectrum of intraductal epithelial proliferations, namely benign usual ductal hyperplasia, atypical ductal hyperplasia and ductal carcinoma *in situ*, are thought to represent individual steps along a linear sequence in the development of breast cancer.

In order to investigate this hypothesis more thoroughly we applied the comparative genomic hybridisation and double immunofluorescence labelling techniques for simultaneous analysis of different antigens in the same cell. We analysed approx. two hundred cases of breast cancer and sixty of benign proliferative breast disease lesions. The results obtained for the lesions located at the different stages of the above-mentioned progression cascade will be reported here. Usual ductal hyperplasia appears to be a Ck5-positive committed stem (progenitor) cell lesion with the same differentiation potential as seen in the normal breast. This is in sharp contrast to atypical ductal hyperplasia/ductal carcinoma in situ, which display the differentiated glandular immunophenotype (Ck8/18-positive, but Ck5-negative). A comparision of cases of UDH and DCIS at the macrogenetic level reveals that nearly all DCIS cases have genetic alterations, albeit with qualitative and quantitative differences in the different subgroups, whereas DH does not show such macrogenetic alterations in our test system. This data require abandoning the idea of an obligate biologic continuum of intraductal proliferations from benign to malignant. The implications of these results for future classifications will be discussed.

37 INVITED

Overview of HER2 and Type I growth factor receptor influences in breast cancer development and biology

Y. Yarden[1]. [1] *Weizmann Institute of Science, Department of Biological Regulation, Rehovot, Israel*

Growth factors and their transmembrane receptor tyrosine kinases play important roles in the control of cell proliferation, migration, and differentiation. One group of growth factors, comprising epidermal growth factor- (EGF-) like proteins and neuregulins (NRGs), stimulates cells to divide by activating a group of highly homologous receptors of the ErbB/HER family. Oncogenic animal viruses frequently activate ErbB proteins. Moreover, sustained activation of ErbBs by secreted growth factors (autocrine loops) occurs in several types of human cancer. Amplification and rearrangements of the erbB-1 gene occur in a significant fraction of glioblastoma and correlate with reduced patient survival. Similarly, amplification of the erbB-2 gene correlates with shorter time of relapse of breast cancer, shorter overall patient survival and resistance to hormonal therapy and chemotherapy.

Consistent with their pivotal role in inductive signaling to cell proliferation, blocking ErbB function results in retarded tumor growth. Examples include the clinically approved anti-ErbB-2 monoclonal antibody (Herceptin), similar antagonists of ErbB-1, and low molecular weight inhibitors of tyrosine kinases. Comprehensive understanding of ErbB signaling may provide more opportunities for drug development. Our studies imply the existence of a richly interactive, layered signaling network, which involves ErbB-2, a ligandless co-receptor, and its major partner, the kinase-defective ErbB-3. The network will be discussed in terms of robustness, diversification of signal transduction, added control and complex machineries of signal termination.

38 INVITED

Use of molecular technology in routine breast disease diagnosis and classification – Current status and future perspectives

J. Costa. *Yale University School of Medicine and Yale Comprehensive Cancer Center, USA*

Advances in the descriptive molecular pathology of breast cancer and in the understanding of its pathophysiology at the cellular level have progressed vigorously in the recent years. Yet, with a few exceptions, the use of tumor markers in the management of patients with breast cancer has not significantly changed during the last decade. Once a tissue diagnosis is obtained, most therapeutic decisions are made based on estrogen and progesterone receptor status, proliferative index and Her2neu status.

In practice, most molecular markers are used as single parameters to provide prognostic and/or predictive information. Because of technological and fundamental progress, we are at the cusp of a paradigm change. Constellations of molecular markers (e.g. complex patterns of gene expression) will delineate new nosological entities. Tumors will not be only classified by their histological appearance, but subsets of tumors with practically identical phenotype will be further subdivided based on their structural or functional genetic alterations. These markers will have both prognostic significance and may well predict the response to therapeutic agents. Rather than by blind mining of large data sets the truly useful tumor profiles (molecular signatures) are likely to emerge when the analysis of large data sets is guided by biological insight and an understanding of the development and physiology of the mammary gland.

In order for these novel markers to become the standard of practice, it is likely that they will be refined and reduced to the minimal set of parameters that is capable of resolving a diagnostic or therapeutic question. Even for a single tumor many decision forks will be driven by chips that will provide an answer to a question such as "is this particular tumor going to respond to estrogen deprivation." Thus, from the large data sets and the correlations derived from large studies, there is likely to emerge a diverse menu of highly specific tests. The second-generation tests are as likely to be based on proteomics as on genomics. Besides the intrinsic features of the tumor cells, future markers will interrogate the functional characteristics of the tumor milieu and the constitutional characteristics of the host. Tumor vascular networks may be monitored and imaged and the pharmacogenomics of the host may reveal the need for specific drug dosage schedules. Ideally the markers of the near future will provide a series of specific molecular therapeutic targets that will indicate patient-specific drug regimens. We will then inaugurate personalized cancer medicine based on molecular markers.

39 INVITED

Will there be a happy marriage between traditional histological evaluation of breast disease and molecular analysis?

I. Ellis. *City Hospital NHS Trust, Department of Histopathology, Nottingham, United Kingdom*

In the past the importance of the Pathology Laboratory in the field of tumour pathology has been under-estimated and under-utilised, the clinician wanting (and receiving) only a one line report stating the diagnosis. It has, however, now become widely accepted that more information can be gleaned from the histopathological appearance of a tumour and that this may be used to predict the biological behaviour and clinical outcome in many malignancies, including breast cancer. At the present time the most valuable prognostic factors in breast cancer appear to be those which can be assessed in routine histological sections: histological grade, lymph node stage, tumour size, vascular invasion and tumour type. Using a combination of these histological features it is possible at this time to predict reliably an individual patients likelihood of survival. In addition, the use of other techniques, such as immunohistochemistry and molecular examination, are being expanded in the search for features of the tumour which can predict reliably not only the prognosis of the patient but also the potential for response to a given treatment. For example immunohistological assessment of tissue sections for ER & PR is the method of choice to identify those patients who are likely to receive benefit from hormone therapies. The evolution of testing strategies for ER & PR provides a useful example of how tissue evaluation methods require a combination of laboratory technique development and expertise in morphological assessment of tissues. Future routine testing for such predictive variables will require translation of methodology to allow routine lab evaluation. More complex methodology will require close cooperation between skilled morphological and molecular scientists at least to ensure appropriate tissue or cells are examined and to interpret any re-

sult in context with other tumour characteristics. Any successful long term marriage requires hard work by both sides and has many ups and downs. Success will benefit both parties and most importantly the patient.

Wednesday, 20 March 2002 14:45–16:15

EUROPA DONNA SYMPOSIUM

Building a multidisciplinary team

40 INVITED

EUSOMA guidelines – the framework

L. Holmberg. *University Hospital, Regional Oncologic Center, Uppsala, Sweden*

The EUSOMA guidelines are a result of a broad professional and consumer collaboration to set standards for management of women with breast cancer. Differences in clinical management matter. There are regional differences in survival and mortality (also when we correct for the underlying incidence) in breast cancer and there are clinically relevant differences in results between institutions. We have rational arguments to believe that a substantial part of these differences are due to how breast cancer is diagnosed and treated. The course of the psychosocial rehabilitation after a breast cancer diagnosis is influenced by how the professional team communicate and interact with the breast cancer patient. Behind the guidelines is also a common value ground of creating equal opportunities for all women with breast cancer in Europe.

The guidelines rest on a set of basic principles of which to me the following are the most essential. First is the recommendation that a multidisciplinary and multiprofessional team in an integrated manner leads the management of women at high risk for breast cancer, the diagnostic work-up, the psychosocial support, the treatment, follow-up and the research. Further, the guidelines acknowledge that a team approach is necessary to offer women with breast cancer up to date diagnosis and treatment. A subspecialisation is needed in the core professions dealing with breast cancer. The subspecialisation in turn calls for training within each discipline especially targeted for breast cancer management. The team must have an accountable leadership and a goal for the future is an accreditation mechanism for teams. Finally, there is a demand to measure the outcome.

The EUSOMA guidelines create a strong framework to foster better clinical management of breast cancer. They are a good weapon in the hands of consumers and health professionals to demand reasonable support for the infrastructure of breast cancer prevention and care. Interesting challenges and questions remain. Which elements in the organisation of care do really matter for long term results? Which are the key outcome variables to follow? How can we better support clinical studies and translational research within this framework? When our studies of outcome reveal substandard practise, are we prepared to act?

41 INVITED

The role of the family doctor

D. Lister. *Abbey Medical Centre, London, United Kingdom*

The role of the family doctor is changing. The traditional GP has been involved in the care of the patient and family "from cradle to grave".I will mention some of the changes later.

The GP's Role
Diagnosis
Referral
Acting as advocate for the patient
Support during treatment
Follow up
Support following treatment
Education
Palliative care
Support for the patient's family
Screening
Referral of at risk relatives for screening

The above list details the present role of the family doctor in the care of the breast cancer patient.

However there are changes taking place in how GP's deliver care.

Change and the future

Walk in centres and NHS direct (increasing importance of the nurse's contribution)

Continuity of care in the new NHS ?Patient held records

The role of genetic testing

Internet-help or hindrance?

42 INVITED

The nurse - an integral member of the multidisciplinary team

P. Hargadon. *ARC Cancer Support Centre, Breast Cancer Nurse Counsellor, Dublin, Ireland*

Evidence exists that referral to a specialist breast clinic where there is a multidisciplinary approach to treatment results in improved survival outcomes for women with breast cancer. The EUSOMA guidelines state that the Breast Care Nurse Specialist (BCNS)- with specialist training in breast cancer- is a core member of the multidisciplinary team. It is well documented that the BCNS provides psychosocial support, education and information to women with breast cancer and this helps them to meet their health care needs.

This presentation will define the role of the BCNS in a multidisciplinary team context. Particular emphasis will be placed on the core concepts of education and training, clinical focus, skills, patient advocacy, audit and research. Effective multidisciplinary teamwork models, that demonstrate the positive outcomes for women where the BCNS is an integral part of the breast cancer treatment team, will be examined. Deterrents to the successful integration of the BCNS into the team are also discussed. The presentation will conclude with a case study on the recent integration of the BCNS into a multidisciplinary team at a specialist breast clinic in Dublin, Ireland.

43 INVITED

Building a multidisciplinary team – Europa Donna's role and contribution

M. Buchanan. *Europa Donna, Meapham Kent DA130, UK*

Europa Donna (ED), The European Breast Cancer Coalition's Mission is to promote best practice in all aspects of breast cancer for the women of Europe. This Mission Statement is built on the ten goals of the organisation. The goals promote breast awareness, dissemination and exchange of factual up-to-date information about breast cancer; they emphasise the need for appropriate screening and early detection and they address optimum treatment, appropriate training for health professionals, regular quality assessment of equipment, the advancement of research and that women fully understand the vital importance of clinical trials.

These goals underpin our commitment to the establishment of specialist breast units. The framework for establishing these has been set by the EUSOMA Guidelines and we have already heard that the basis of such a unit is the multi-disciplinary team. ED subscribes fully to this concept, supports the EUSOMA Guidelines and is already advocating at European Parliamentary level for their implementation. To enhance this, we would press for accreditation across Europe of these specialist breast units and ultimately, of breast specialists.

In the Guidelines, associated services and non-core personnel are listed. These include dedicated psychological support and an identified physiotherapist trained in the treatment of lymphoedema. ED strongly recommends the inclusion of these professionals if the care of the patient is to be fully comprehensive. We also believe there is a place for an appropriate, well trained and well informed volunteer.

The paper discusses the way in which Europa Donna sees its position in the pursuit of specialist breast units based on their multi-disciplinary teams and how, as the leading breast cancer advocacy group in Europe, it is training it's members in advocacy skills to promote the vital importance of these units. Information and education are the other key elements in this process and our programmes are directed towards ensuring that our members are well informed and fully able "to take their seat at the table" so that the woman's voice is heard and welcomed there. All "sides" are recognising this as the way forward in the fight against breast cancer.