were assessed by univariate analysis (Log Rank test) and multivariate analysis (Cox model). Median follow-up was 150(147–152) months.

Results: By univariate analysis, age[(≤40 vs >40 yrs) p = 1.6 10−7], tumour size [(≤20 vs >20 mm) p = 1.1 10−15], modified SBR grade [p = 4.5 10−10], peritumoral vascular emboli [p = 8.9 10−13], N status [p = 4.6 10−13], ER [(<10%vs ≥10%) p = 0.01], PR [(<10% vs ≥10%) p = 0.003], Her2neu [(0+ vs 2+ and 3+) p = 0.0003] and Mib1 [(<20% vs ≥20%) p = 7.5 10−8] were significantly associated with probability of metastasis.

By Cox analysis, the final model showed as independent factors, tumour size [OR = 2.16(1.63–2.86) p < 10−3], vascular emboli [OR = 1.8(1.38–2.42) p < 10−3], N status [OR = 1.8(1.35–2.45) p < 10−3], age [OR = 1.8(1.24–2.67) p = 0.002], Her2neu [OR = 1.58(1.09–2.29) p = 0.015] and grade [OR = 1.7(1.04–2.75) p = 0.03]. Mib1 was selected in this model but was not statistically significant [OR = 1.31(0.96–1.79) p = 0.08].

Conclusion: Mib1 may represent an alternative to grade for prognostication in breast cancer however it did not surpass this factor in this series.

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B3 or B4 core breast biopsies: Are they indeterminate?

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Introduction: Histological diagnosis is essential in definitive management of breast lesions. However, a small proportion of core biopsies are reported in the uncertain categories (B3 & B4), which can lead to therapeutic dilemmas for the clinician. Our study aims to evaluate the predictive value of these indeterminate biopsies.

Methods: A prospectively maintained BASO database was used to identify patients with B3 or B4 breast core biopsies between Jun-02 and May-05. The retrieved data was analysed using MS Excel®.

Results: Thirty-three patients (21 B3 and 12 B4) were identified during this 3-year study period. The median age was 60 years and in 30 patients, a breast lump was the primary symptom at presentation.

Excision biopsy was performed in 22 patients. Seventeen patients (6 B3 & 11 B4) were identified to have invasive breast cancer or DCIS on subsequent assessment, yielding a positive predictive value of 29% (B3) and 92% (B4).

Patients with age > 70 years seemed to have an increased incidence of invasive cancer. Malignancy was more likely when associated with a high clinical and radiological (P4/5; R4/5) score. It was also evident that FNAC complemented the diagnostic accuracy of core biopsies.

Conclusion: The positive predictive value for diagnosing malignancy is high following a B4 core biopsy and in patients over 70 years. Also, diagnostic accuracy is superior in the presence of a high clinical, radiological and/or cytological score. Further biopsies or advanced imaging may be essential prior to definitive management in these indeterminate lesions.

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The histopathological profile of gestational breast cancer

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Few studies have reported on the pathology of gestational breast cancer (GBC) and most have been limited to a basic description. The only reported case-control study was very small (n = 27). It has been reported that GBC is more aggressive, with low expression of hormone receptors.

The aim of this study to establish whether there were any pathological characteristics identified that are unique to gestational breast cancer and which can be related to the disease outcome.

A comparison was made between the pathology from women diagnosed with GBC and women age and date of diagnosis matched diagnosed with non-GBC. GBC cases were identified from the Western Australian Gestational Breast Cancer Project and the non-GBC cases were identified from the PathWest archives. The pathology specimens were retrieved, re-reviewed and where necessary re-staining for hormone receptors was undertaken.

One hundred and twenty (120) GBC cases and 240 non-GBC cases were identified. Tumour size for the GBC cases ranged from 1 to 120 mm (median 20 mm) and lymph node positive status was similar for GBC cases (55%) and non-GBC cases (53%). Proportionally more GBC cases (69%) were histological grade III than non-GBC cases (57%). Analysis of the data continues and will be reported at the conference.

Our preliminary results conclude that women with GBC do have a more aggressive phenotype.

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Expression of estrogen receptors alpha and beta (ERa and ERb) and progesterone receptor (PgR) in male breast cancer

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Background: Male breast cancer (MBC) is a rare disease, accounting for only 1% of all breast cancers. Therefore, carcinoma of male breast has not been studied as extensively as carcinoma of the female breast (FBC). Steroid hormone receptors are more frequently positive in MBC than in FBC. The identification of the second human estrogen receptor, ERβ, raised a question of its role in male breast cancer.

The aim of this work was to determine the extent of ERβ expression in male breast cancer and to determine if ERβ expression is correlated with some clinical parameters and biological markers.

Material and Methods: Formalin-fixed, paraffin embedded breast cancer tissues from 28 male patients were used in this study. Immunostaining for ERa, ERβ and PgR (progesterone receptor) was performed using monoclonal antibodies against ERa, PgR (DakoCytomation), and against ERβ (CHEMICON). The EnVision detection system was applied. The study population comprised a control group of 120 women with breast cancer who had been operated in our clinic. The data were analyzed using a nonparametric Fisher-Freeman-Halton test; the statistical significance was considered when $p < 0.05$.

Results: MBC: 67% of tumors were ERa positive, 78.6% were PgR positive and 64.3% were ERβ positive; FBC: 57.5% of tumors were ERa positive, 64% were PgR positive and 55% were ERβ positive. As many as 14% of both MBC and FBC of ERβ positive tumors showed no expression of ERa. In male breast cancer correlations between tumor size, lymph nodes status, grade of malignance, p53, Ki-67 and expression of ERβ were not significant.

Conclusions: The expression of ERβ, like this of ERa, was more frequently positive in MBC than in FBC. In male breast cancer the expression of ERβ was also present in a noticeable proportion of ERa negative tumors. It may eventually result in new strategies in the hormonal treatment of male breast cancer.

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Metastatic models in different histologic types of breast lobular carcinoma

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There are several histological types of invasive lobular carcinoma (ILC): classical, alveolar, solid, pleomorphic, and tubulo-lobular. To determine whether the metastatic pattern was related to histologic subtype, we retrospectively analyzed a series of 72 cases of metastatic ILC. Tumors were classified in classical or variants forms. Estrogen receptor (ER), progesterone receptor (PR), E-cadherin, and ERB-B2 were assessed in 50 cases. The patterns of metastatic sites were analyzed in the different groups. 68% of cases corresponded to the classical type of ILC. The histologic variants included 23% pleomorphic carcinomas, 4% tubulo-lobular carcinomas, 3% alveolar carcinomas and 2% solid carcinomas. The metastatic sites were axillary lymph nodes (85% of cases), non axillary lymph nodes (8.06% of cases) and ovary (6.99% of cases). No significant corespondence was found between metastatic patterns and histology or E-cadherin expression. No relationship between histologic subtypes and specific patterns of dissemination was observed in this series of metastatic ILC. A high rate of pleomorphic type was found as compared with that observed among ILCs at diagnosis. A high rate of E-cadherin loss was found in metastatic ILCs, which corresponds to complete loss of E-cadherin expression in over 80% of ILCs documented in the literature. The lack of E-cadherin expression found also in metastases emphasized the adverse outcome of the disease.

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Intraoperative imprint cytology for evaluation of sentinel lymph node in breast cancer

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Introduction: Sentinel lymph node (SLN) biopsy in patients with breast cancer has emerged as a conservative and promissing procedure. One of the most important issue is the evaluation intraoperative of the SLN with a high degree of accuracy. Frozen section and/or imprint cytology can be

used for this purpose. The objective of this study was to test the ability of intraoperative touch imprint cytology (IC) to predict metastatic disease on SLN.

Design: SLN were received fresh and examined grossly, when less than 0.5 cm in size were bisected and when more than 0.5 cm in size were serially sectioned at 2 mm intervals along the long axis. Each surface of the sections were touched on the glass slide, stained by H&E. Results of IC were compared with results of section permanents, wich were analyzed with 10 serial levels stained with H&E and one level stained with cytokeratin AE1/AE3. Sensitivity (Se), specificity (Sp), positive and negative predictive value (PPV & NPV) and accuracy were calculated for all metastases (macro & micrometastases), micrometastases, macrometastases. False negatives were rescreened.

Results: We analyzed 179 SLN from 110 patients. The comparison between IC and definitive results of the SLN (including macro & micrometastases) showed 139 (77.65%) true negative imprints, 28 (15.64%) true positive imprints. There were not false positive imprints, there were 12 (6.70%) false negative imprints. False negative imprints were 6 macrometastases (mean size metastases 5 mm, range 3–7 mm), 3 micrometastases (mean size metastases 1.6 mm, range 2–1.5 mm) and 3 isolated tumour cells. Rescreening of the false negative imprints showed 10 negative imprints, one imprint with two diagnostic groups of cells and one imprint with multiple diagnostic groups of cells. Se, Sp, PPV, NPV, Acc for all metastases, micrometastases, macrometastases are shown in the table.

	Se	NPV	Sp	PPV	Acc
All metastases	70%	92.05%	100%	100%	93.29%
Micrometastases	73.60%	93.37%	100%	100%	94.41%
Macrometastases	82.35%	96.02%	100%	100%	96.64%

Conclusions: The majority of macrometastases can be detected by IC however IC fails to detect most micrometastases. False negative imprints for macrometastases are mainly due to sampling error. The high Sp, PPV and preservation of the arquitecture of the lymph node for histopathologic examination are the major advantages of IC for intraoperative evaluation of SLN.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Tumour biology and immunology

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Bex2 identifies a novel subtype of breast cancer associated with estrogen-response and NGF/NF-KB pathway

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Background: Heterogeneity of breast cancer is a significant challenge in diagnosis and therapy of the disease. Despite advancements in the molecular profiling of breast cancer, there are still only three known molecular subtypes which can be used as classifiers; ER+, ER−, and ERBB2+. Better molecular classification of breast cancer can improve our understanding of the disease and potentially lead to the discovery of novel therapies.

Methods: In this study we performed microarray expression analysis of 135 breast tumors to identify novel classifiers in breast cancer. In addition, we evaluated clinical and biological relevance of our findings.

Results: We identified Bex1 and 2 genes as novel classifiers of breast cancer. Overexpression of these genes was present in 15% of samples and was associated with estrogen-response and apoptotic function. We showed Bex2 expression is necessary and sufficient for NGF anti-apoptotic activity. Moreover, Bex2 induction is mediated through p75NTR and located upstream of NF-κB. Furthermore, estrogen induces Bex2 in a time and dose dependent fashion and Bex2 is necessary for estrogen mediated anti-apoptotic activity. We also found cases with Bex2 overexpression responded better to tamoxifen therapy and proved the interaction between Bex2 and tamoxifen activity in breast cancer cells.

Conclusion: Although the importance of NGF/Bex3/NF-κB pathway is well known in neural tissues, NGF has recently been implicated in pathogenesis of breast cancer as well. Importantly, the function of Bex1 and 2 remains virtually unknown to date. Here, we show Bex1 and 2 classify a novel subtype of ER positive breast tumors which respond better to tamoxifen therapy. We demonstrate Bex2 is part of estrogen response and NGF/NF-κB pathways with anti-apoptotic function in breast cancer. NF-κB activity has recently gained much attention in the development of hormone refractory breast cancer and Bex2 can potentially be applied as an activity marker or therapeutic target within this pathway. The findings reported here show Bex1 and 2 are novel breast cancer-related genes and significantly advance our understanding of NGF/NF-κB pathway with potential clinical implications.

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The prognostic significance of inflammation in invasive carcinoma of the breast

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The prognostic significance of inflammation in invasive carcinoma of the breast is controversial with previous studies producing conflicting results. The predominant pattern of inflammation is a diffuse infiltrate of T cells and macrophages in the stroma between carcinoma cells. Perivascular and perilobular clusters of B and T cells are less prominent. The cells necessary for a cell-mediated immune response are often present, but there is evidence that their function is impaired. Inflammatory cells may also stimulate tumour growth by release of proleolytic enzymes or angiogenic factors. 1599 patients aged less than 71 years with operable invasive carcinomas, diagnosed from 1974 to 1988, with median follow up 9.4 years were studied. No patient received adjuvant systemic treatment. An overall assessment of the intensity of lympho-histiocytic inflammation was made on haematoxylin and eosin sections by one observer. Inflammation was associated with higher grade, ductal and medullary histological types, tumour size and inversely with patient age. On univariate analysis patients with tumours with marked or moderate inflammation had a better survival than patients with tumours with absent or mild inflammation ($P = 0.04$). On multivariate analysis survival was associated with inflammation (relative risk 0.61 (95% confidence intervals 0.47 to 0.79), $P = 0.0002$) in addition to lymph node stage, histological grade, tumour size, vascular invasion and tumour type; survival was not related to patient age or oestrogen receptor status. This study suggests that the anti-tumour effects of inflammation predominate over the pro-tumour effects. Critical review of previous large studies with assessment of histological grade and multivariate analysis shows that the majority find prominent inflammation is associated with a better prognosis, consistent with the present study. These results support further studies trying to harness the immune response in the treatment of breast cancer.

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Identification of cell-of-origin subtypes and a wound healing response signature in inflammatory breast cancer

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Introduction: Recently, gene expression studies demonstrated the significance of different biological breast cancer subtypes with regard to prognosis and treatment. In this study we tested to what extent these subtypes contribute to the specific inflammatory breast cancer phenotype (IBC).

Materials and Methods: The presence of different cell-of-origin subtypes (Perou et al.) and of a wound healing signature (Chang et al.) was analyzed in gene expression data sets from 16 IBC and 18 nIBC specimens. A set was compiled of genes being part of respectively the intrinsic gene set (Perou et al.) and the wound healing response signature (Chang et al.) which were also present on the cDNA microarrays used to compare IBC and nIBC specimens (Van Laere et al). 144 and 98 genes were selected from both gene lists. These gene lists were then tested for performance in the original data sets. Next, centroids for each cell-of-origin subtype and for the quiescent and activated fibroblast signature were calculated. These centroids were than used to classify our specimens. For the cell-of-origin subtype classification, the robustness of the taxonomy was confirmed using an alternative data set of 141 genes related to the cell-of-origin subtypes. Contribution of each of the cell-of-origin subtypes to the IBC phenotype was tested by principle component analysis (PCA).

Results: The performance of the selected data sets was 84% and 100%, respectively. 8/16 IBC specimens belonged to the combined Basal-like and ErbB2-overexpressing cluster, compared to only 3/18 nIBC specimens