

Thursday, 21 March 2002

16:30–18:00

PROFFERED PAPERS

Ductal carcinoma in situ (DCIS)

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ORAL

DCIS versus IBC: A cDNA microarray study

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Background: Ductal carcinoma in situ (DCIS) is important because it is very common and gives rise to most invasive breast cancers (IBCs). Additional genetic defects must occur in DCIS to cause its progression to IBC. Knowledge of these defects could be useful clinically as prognostic factors to assess the risk of progression and, more importantly, as therapeutic targets to prevent progression.

Study Design/Methods: Frozen samples of *pure* DCIS and *pure* IBC (n = 15 each) were evaluated using cDNA expression arrays (Clontech Atlas Human Cancer 1.2 Array). The samples were not microdissected to retain potentially important genes from non-tumor cells (e.g. in the stroma) but they were screened to contain a high level of tumor cellularity (>75%).

Results: Wilcoxon analyses identified 114 individual genes expressed at significantly (p < 0.05) different levels in DCIS compared to IBC, many involving processes and pathways which make them reasonable candidates as important "invasion-related" genes (e.g. wnt-signaling, extracellular matrix, stromal proteases, etc.). Cluster analyses identified several groups of genes which also distinguish DCIS from IBC (especially adhesion-related genes), as well as families of highly related DCIS and IBC which may represent important precursor-product pathways. Studies using semi-quantitative RT-PCR are ongoing to confirm the array data. Confirmed differences are being evaluated for their expression profile and prognostic significance using immunohistochemistry and in situ hybridization on tissue arrays of independent samples of DCIS and IBC with known clinical outcome.

Conclusions: A large number of genes have been identified which may be important in the progression of DCIS to IBC.

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Local recurrence (LR) after conservative surgery without (CS) or with radiotherapy (CS + RT) for breast DCIS. Analysis of 208 cases

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Purpose: To evaluate LR histological features, treatment and outcome in women who underwent CS or CS + RT for pure breast DCIS.

Material: From 1985 to 1996, 1215 women with pure DCIS were treated in 11 French Cancer Centers by CS (403) or CS + RT (812). Median age was 53 years and median follow-ups after first surgery and LR diagnosis were 80 and 41 months respectively.

Results: 208 LR occurred (17.1%) with 37- and 53-month median delays in CS and CS + RT groups. 63% and 78% of the women underwent salvage mastectomy in CS and CS + RT groups. Only one woman developed metastases after in situ LR (1.1%), whereas metastasis rates after invasive LR were 9.4% and 16.9% in CS and CS + RT groups.

	CS (403)	CS + RT (812)	TOTAL (1215)
All LR	106 (26%)	103 (12.7%)	208 (17.1%)
In situ LR	52 (13%)	38 (4.7%)	90 (7.4%)
Invasive LR	53 (13%)	65 (8.0%)	118 (9.7%)
Axillary rec.	9 (2.2%)	14 (1.7%)	23 (1.9%)
Metastases	5 (1.2%)	11 (1.4%)	16 (1.3%)

Conclusion: This study confirms the favorable long-term prognosis of DCIS treated conservatively and allows to make a detailed analysis of LR salvage treatments. Moreover, we outline the importance of a close mammographic follow-up to detect LR earliest.

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ORAL

Ductal Carcinoma in situ (DCIS) for women under forty: Predictive factors of relapse in a series of 164 cases

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Purpose: To evaluate the predictive factors of relapse in women under 40 treated for pure DCIS.

Patients and Method: From 1985 to 1995, 164 cases were treated in 12 French Cancer Centres. The median age was 36 years and median follow-up 96 months.

58 (36%) underwent mastectomy (M), 45 (28%) margin-free lumpectomy alone (MFL), 47 (29%) margin-free lumpectomy plus radiotherapy (MFLR) and 12 (7%) margin-invaded lumpectomy plus radiotherapy (MILR).

Results according to treatment:

	M	MFL	MFLR	MILR	Total
Relapses	2 (3%)	5 (11%)	13 (28%)	5 (42%)	25 (15%)
LR (total)	0	4	12	5	21
In situ	0	2	5	2	9 (36%)
Invasive	2	3	8	3	16 (64%)
Nodal R	1	1	1	0	3
Metastasis	1	0	0	0	1

Conclusion: Our study confirms the high LR rate after conservative treatment in young women with DCIS. The LR predictive factors were margin status and comedocarcinoma subtype which were statistically significant. This results could influence the treatment choice in this group of patients in order to reduce LR.

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Assessment and validation of van nuys prognostic index in a series of patients with ductal carcinoma in situ

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Introduction: The Van Nuys Prognostic Index (VNPI) is a numerical algorithm based on tumour features and recurrence data from a large series of DCIS patients. It permits qualification of easily measured prognostic factors in a reproducible fashion separating DCIS patients into three clearly defined risk groups. Radiotherapy significantly reduces recurrence rates in DCIS patients treated with breast-conserving therapy (BCT) though studies lack subset analysis. A low score (3 or 4) is associated with low recurrence rates and no significant difference in recurrence rates in patients treated with either BCT alone or BCT with radiotherapy (DXT). VNPI was designed to be used in conjunction with, not instead of, clinical experience and prospective randomised data and requires independent validation.

Methods: 700 DCIS patients were identified from a prospective audit. Clinical and pathological data were assessed.

Results: 423 patients underwent BCT. 179 (42.4%) received adjuvant DXT. In the BCT alone group, 80 patients had a score of 3 or 4 with 8 recurrences (10%). 42 patients received DXT with 1 recurrence (3%). Where a score of 4 is considered alone, recurrence rates were 14% (BCT alone) and 3% (BCT/DXT). In the group with scores 5, 6, or 7, 115 patients underwent BCT alone with 49 recurrences (42%). 76 patients underwent BCT/DXT with 9 recurrences (9%). In the group with a score of 8 or 9, there were 8 patients and 4 recurrences (50%). Patients with a high score usually underwent mastectomy and are not considered here.

Conclusions: The VNPI remains useful in predicting recurrence and guiding therapies. However, in contrast to other studies, BCT patients with a low VNPI (3 or 4) score appeared to derive significant benefit in terms of reduced recurrence rates when DXT is used.

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The significance of cytokeratin positive cells in lymph nodes at the time of mastectomy

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Aim: To assess the significance of cytokeratin positive cells in lymph nodes at the time of mastectomy for the management of ductal carcinoma in situ (DCIS)

Method: 66 low axillary lymph nodes found in 15 patients who had mastectomies for the management of DCIS during the period of 1991 to 1998 were assessed by two independent pathologists. The median clinical follow up was 5 years and all the patients are alive without recurrence or metastasis at the time of the study. All patients had had either a core or open biopsy performed at least 12 days prior to the time of mastectomy. The histology of the original slides was reviewed to confirm the original pathological diagnosis. 10 levels of each of the lymph nodes were assessed with haematoxylin and eosin (H & E) stain. Immunohistochemistry for cytokeratin marker (AE1/AE3) was performed at levels 3 and 7 on each node. The slides were then assessed for the presence or absence of epithelial cells.

As a control group, low axillary lymph nodes found in seven prophylactic mastectomies were also assessed. None of these had had previous biopsy performed.

Results: Lymph nodes from all patients demonstrated no obvious epithelial cells on H&E stain. Peripheral sinuses of lymph nodes from 3 patients, who had mastectomies for DCIS, contained a few cytokeratin positive cells on immunohistochemistry. Of these 2 had had open biopsies previously and 1 had had a 14-gauge core biopsy. Of the 16 lymph nodes examined from the control group, none demonstrated cytokeratin positive cells.

Conclusions: This study shows that epithelial cells may be present in the lymph nodes draining a site of recent breast biopsy in the absence of invasive carcinoma. This phenomenon has relevance in the interpretation of sentinel lymph nodes biopsies studied by cytokeratin immunohistochemistry.

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Reproducibility and prognostic value of three histologic classifications for intraductal carcinomas of the breast

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The aim of the study was to assess the reproducibility interobserver of three intra ductal carcinoma (DCIS) histologic classifications and their prognostic value. This retrospective study has taken into account seventy-six cases treated by conservative surgery and radiotherapy with a median follow up of 5 to 15 years.

Five pathologists evaluated 76 cases of DCIS according to 3 histologic classifications: European classification (EC), Van Nuys (VN) and A.F.I.P (AF). Final DCIS consensual grade was obtained and compared to clinical evolution.

Results:

	EC	VN	AF
Grade 1	15	18	10
Grade 2	44	18	32
Grade 3	13	40	34
Non gradable	4	0	0
Reproducibility (Kappa test)	0.698	0.665	0.716

Fourteen patients developed a local recurrence, resulting in a five-year actuarial local recurrence rate of 8.3%. Reproducibility is considered at a good quality level using AFIP classification. Local recurrence was observed in all grades of each classification, not any sub group had a prognostic value.

Thus, reproducibility was better with AFIP classification and by them self those classifications seem not good enough to assess local recurrence.

References

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POSTER

Distance from the nipple is a factor predicting for local recurrence in patients with DCIS treated by wide local excision

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Introduction: Patient selection for wide local excision(WLE)is difficult in DCIS. Distance from the nipple has been shown to predict for recurrence in invasive breast cancer.

Aims: To assess factors associated with recurrence in patients with DCIS treated by WLE alone over an 11 year period at one breast unit.

Methods: Pathology specimens and mammograms for patients treated between January 1986 and January 1997 were reviewed. Type and grade of DCIS,lesion size and distance from the nipple were assessed. Factors predicting recurrence were analysed by univariate and multivariate analysis.

Results: 153 patients had WLE alone over this period (70% of the total number treated for DCIS). 22 patients had radiotherapy, 54 had tamoxifen, 21 had both treatments. Follow up time ranged from 3 to 10 years. 20(13%) patients developed local recurrence in the breast of which 7(35%) were invasive. Mean time to recurrence was 28 months(range 4-54 months). The only factors predicting for recurrence were nipple to lesion distance of <40mm and intermediate/high grade DCIS.

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POSTER

Survival after ductal carcinoma in situ (DCIS)

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From January 1973 to December 1998, a total of 331 consecutive cases of DCIS were diagnosed. Age range was 24-74 (median 55). 175 patients (62.8%) presented symptomatically and 120 patients were screen detected. In all cases no invasive carcinoma was found in the primary specimen.

Dates Protocol	n	Local Recurrence (LR)	Total breast cancer deaths	Deaths after LR
WLE ± RT	111	21	2	2
Mastectomy	220	11	2	0

Death from metastases without prior local recurrence, occurred in 1%. 3 of the deaths occurred in the 33 women suffering LR, a 10% mortality, again emphasising the importance of local control.

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POSTER

Examination of the prognostic characteristics, treatment and outcome of women with breast ductal carcinoma in situ diagnosed in the West Midlands region by the UK NHS breast screening programme

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Objective: The number of cases of ductal carcinoma in situ (DCIS) has risen dramatically in the West Midlands since the introduction of the NHS Breast Screening Programme (NHSBSP). There is wide variation in the management of women diagnosed with DCIS and therefore this study aims to examine the prognostic characteristics, methods of treatment and outcome for women diagnosed with DCIS through the NHS screening programme and construct guidelines for the management of screen-detected DCIS.

Method: The study population has been obtained using the computer systems at each of the ten breast screening units in the West Midlands.

Treatment and follow up data are collected using a specialist data collection proforma from the original hospital case notes and information held on the West Midlands Cancer Intelligence Unit (WMCIU) database. A pathological slide review has been undertaken by a consultant pathologist to obtain consistent information on diagnostic characteristics throughout the study period. The slides included in the slide review have undergone an extensive double blinding exercise to ensure that confidentiality can be maintained while still being able to compare original and review pathology results.

Results: To date, 840 cases are included in the study which were recorded as screen detected DCIS without invasive disease between 1st March 1988 and 31st March 1999. Interim results demonstrate that low grade DCIS is infrequent forming only 11% of the cases undergoing histological review. Calcification is present in 81% of cases reviewed and 80% of cases underwent a localisation procedure. The mastectomy rate in those cases reviewed so far is 21%.

Conclusions: This study when complete will provide valuable data on the significant factors which affect the likely outcome for women diagnosed with DCIS through the breast screening programme and will help to ensure that the prognosis of these women is good with minimal risk of recurrence.

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Epidemiology and prevention

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POSTER

The prevention of breast cancer induction by plant extracts and the postradiation alterations of DNA structure

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The goal of the present study was to reveal relationship between relatively early alterations of DNA structure in blood leukocytes and frequency of breast cancer (BC) in rats induced by radiation in case of some nutrition addition administrations.

The 755 female rats with initial mass 140–160 g were used in the experiment. The animals were irradiated totally with 4 Gy single dose at the "IGUR-1" unit (^{137}Cs). In 11 days after irradiation rats received with drinking water cyclically (administration during 3 weeks, then interval during 1 week) difluoromethylornithine (DFMO) - as a standard anticarcinogen in dose 2 g/l, and extracts of medicinal plants (1–2% solutions): *Plantago major* (L), *Eleuterococcus senticosus* (Rupr. et Maxim), *Rhaponticum carthamoides* (Willd. Iljin), bioginseng (BGS) biotechnological drug from root biomass of *Panax Ginseng* (C.A.Mey). A hot herbal extract of *Filipendula* (EF) - *Filipendula ulmaria* (L) was administered to rats with drinking water without interruption. The alteration of DNA structure in blood leukocyte was determined by means of two-parameters fluorescent analysis including ethidium bromide and 4',6-diamidino-2-phenylindole, as described earlier [Ivanov SD et al., 1999].

Irradiation of rats resulted in significant life span shortening (LSS) and increase of tumor frequency (from 22% to 77%). The frequency of BC increased in the most degree - almost 16-fold, while for other tumors - approximately 3-fold. The administered preparations did not influence on the LSS dynamics. The administration of DFMO, BGS and EF reduced the amount rats with tumors (1.5–1.6 fold), and a number of BC per animal (1.6–2.0 fold). These preparations (in contrary to others) did not changed the amount of blood leukocytes, but it resulted in alterations of their DNA structure. The correlation ($R = -0.683$) was revealed between a number of BC per rat after administration of all preparations and an index of DNA structure alterations in blood leukocytes, measured in 30 days after irradiation.

So, the DFMO, BGS and EF reduced the frequency of BC on the given experimental model, and the DNA structure alterations may be used as an early prognostic index for the acceleration of the anticarcinogenic preparation screening.

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POSTER

Persistent adrenal gland activity observed in postmenopausal women (PMW) with breast cancer(BC); Preliminary results

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Purpose: adrenal gland synthesis of various sex hormone precursors have been reported to decrease by 60% or more in PM. High plasma testosterone and estrogen levels have often been associated with an increased risk of BC in PMW. DHEA and testosterone are considered beneficial to PMW to alleviate major complications of the menopause. Conflicting reports regarding this matter have been published. Despite the fact that the mortality of BC has decreased significantly in the past years, it is still a major health problem associated with a high morbidity in many of the more developed countries. We have yet to find a reliable marker to predict breast cancer occurrence.

Methods: In a case-control study in Montreal, a total of 70 newly diagnosed PMW with BC and 70 population-based controls, matched for age (within 5 years age groups), selected by random digit dialing telephone directory method or hospital admission offices. We measured fasting blood levels of cortisol, C-peptide, insulin, free testosterone (FT), total testosterone (TT), DHEAS, androstenedione, SHBG, estrone, estradiol as well as IGF-1 and IGFBG-3 from both cases and controls.

Results: No difference was observed on key demographics variables between groups. Among cases, the mean blood levels of DHEAS, TT, androstenedione were twice of that observed in the controls. Receiver Operating Characteristic (ROC) curves were performed for all laboratory variables and significant ($p < 0.001$) discriminatory accuracy (expected to observed ratio) of 0.82 (95%CI 0.74-0.90) is noted for TT as well as for FT (0.77;0.69-0.84), androstenedione (0.74;0.66-0.82), estradiol (0.72;0.63-0.80), DHEAS (0.68;0.59-0.76) and estrone (0.66;0.58-0.75). Fasting insulin, C-peptide, cortisol, IGF-1, and IGFBP-3 curves revealed a weak association if present.

Conclusions: Our results so far suggest that PMW with BC have increased/persistent adrenal gland activity contrary to the controls. TT has a significant discriminatory index for identifying PMW with BC. The adrenal gland activity should be further explored in PMW. supported by the Jean H. Picard foundation.

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POSTER

Pedigree analysis of women attending a breast family history clinic

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The Nottingham Breast Family History Clinic, set up 10 years ago, serves a population of 1 million. Over 600 asymptomatic women per year are referred for assessment of their family history; 50% of these are considered low risk and are not further followed. 1800 women are being followed up regularly. This represents approximately 40% of all women eligible for screening within our catchment area. 5% per year are lost to follow up.

Retrospective review of family pedigrees showed that 31% were classified as high risk and 69% as moderate risk by standard risk assessment. Only 11% of women presented with a history of cancer in their father's side of the family, this reflecting a public under-estimation of the importance of the paternal family history in hereditary breast cancer. Overall, 8% of women had ovarian cancer family history. A history of colon cancer was more common in the high risk group than in the moderate risk group (13.4% vs. 5.5%, $p < 0.05$).

The running of a Breast Family History Clinic has significant service implications. Important and useful information to service provision and resources organisation can be obtained by audit. Adequate funding for data collection and data analysis is essential. Additional funding of genetic services for mutation analysis of high risk women, and funding for ovarian screening research, is required.