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Although higher expression of bcl-2 is associated with better outcome, bcl-2 is not an independent prognosticator of distant disease free survival (DDFS) or overall survival (OS) in breast cancer

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Objectives: It is reported that higher expression of bcl-2 (an antiapoptotic factor) correlates with longer survival. Indeed some studies indicate that bcl-2 is an independent prognostic factor in breast cancer.

The aim of our study was to determine predictive value of bcl-2, hormonal receptor status [estrogen receptors (ER), progesterone receptors(PR)] and histopathological factors [tumor type, grade, mitotic proliferative index (MPI), tumor size, lymphocyte infiltration, lymph node status].

Materials and Methods: A sample of 52 Bosnian women with invasive breast cancer was studied. The mean follow-up was 52 months (range: 4–70 months).

Histopathological evaluation was performed for their formalin fixed and paraffin embedded tumor tissues. For immunohistochemistry bcl-2, ER and PR DAKO monoclonal antibodies were used.

Statistics: Kaplan-Meier and Cox Regression tests.

Results: Higher expression of Bcl-2 was associated with longer DDFS but not OS (p=0.0016, p=0.77,respectively).

According to Cox multivariate analysis tumor size, number of positive lymph nodes, MPI and H-score of progesterone are independent prognosticators of DDFS (p=0.001, p=0.039, p=0.049, p=0.089, respectively). Tumor size and Progesterone and Estrogen H-Score are independent prognosticators of OS (p=0.019, p=0.030, p=0.035, respectively).

Conclusion: Although higher expression of Bcl-2 correlates with longer DDFS, bcl-2 is not independent prognostic factor in breast cancer. Among investigated factors only tumor size and progesteron H-score are proven to be independent prognosticators of both DDFS and OS.

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Prevalence of breast cancer in a symptomatic breast clinic: A simple tool for rapid access

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Background: Within the United Kingdom the introduction of a two-week referral rule (from primary to secondary care) has led to an unprecedented increase in the number of patients with benign disease occupying clinic appointments. This situation could compromise those patients who do have cancer but are not referred within a two-week window. Reasons to account for such referral patterns relate to existing guidelines that fail to benefit those patients with lower risk symptoms. We reviewed prospective audit collated from patients referred to a symptomatic breast unit with the aim of introducing a referral schema based upon symptoms, age and relative risk of cancer.

Method: Demographic details, mode of referral, history and presenting symptoms were collected prospectively from each of the 2064 patients referred to the James Cook University Hospital (JCUH) breast unit from April 2001 to March 2002.

Results: Calculating Odds Ratios from eight dependent variables revealed a 30% improvement in prediction accuracy of breast cancer. From these findings a breast referral schema is presented that is designed to facilitate more expeditious referral from primary care of those patients most at risk.

Conclusions: Utilisation of the schema within primary care could lead to an increase in the number of patients with breast cancer being referred within a two-week window. Evidence as to the efficacy of the schema needs to be determined.

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The prognoses of tumours detected in the UK breast screening programme (NHS BSP) analysed by the Nottingham Prognostic Index (NPI)

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The overall prognosis of the tumours detected at screening is better than for those with symptomatic disease. It has been suggested that all small tumours screen detected do well, regardless of grade. The tumours detected at screening in the NHS BSP in 1992–3, are compared with all cases (symptomatically presenting and screen detected) aged 50 – 64 diagnosed in the Nottingham screening area in 1993 – 1996 inclusive.

Comparison has been made using the Nottingham Prognostic Index (NPI), which combines the time dependent factors of size and LN stage with the biological factor of grade.

NPI Group	NHS BSP (n=10390)		NCH (n=772)	
	% in group	9 year survival	% in group	9 year survival
Excellent	25	94.7	19	96.9
Good	33	93.2	23	94.7
Moderate I	24	84.7	29	80.6
Moderate II	13	66.6	26	63.7
Poor	6	40.1	12	39.9
Overall		88.0		77.6

As expected there are more cases in the best two NPI groups (58 v 42%) in the NHS BSP and more in the worst two in the NCH set (39 v 19%) set, which explains the better overall survival of the screen detected tumours. However once stratified by NPI screen detected tumours have survival rates as expected by NPI in all NPI groups. In particular screen detected tumours of <15 mm, LN negative, grade III (NPI 4.3) have the same survival as MPG I (3.41–4.3) and the same survival as comparable tumours presenting symptomatically.

Conclusion: Both screen detected and small tumours behave according to their combined prognostic factors as predicted by the NPI.

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Complementary medicine use among Iranian breast cancer patients

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A cross-sectional study was conducted to evaluate the use of complementary medicine by cancer patients in two comprehensive clinics, in Tehran, Iran. This paper reports the results for breast cancer patients. A specially designed questionnaire was completed for 177 breast cancer patients after informed consent was obtained. The Mean age of the participants was 47.1 years (SD=10.9) ranging from 25 to 80 years. Most were married (78%) and housewife (91%). In all 57 patients (32%) had used complementary medicines. Users and non-users did not differ significantly in educational level. Among users 50 patients (88%) indicated the use of complementary medicine after cancer diagnosis. The most commonly used complementary medicines were spiritual healing (n=45, 79%), bio-energy (12%) and homeopathy and herbal medicine (9%). The main sources of information on complementary medicines were personal believes (77%), previous information (9%), and information obtained from relatives or friends (19%). Only 7% of the users received information from their physicians. The majority of the users were satisfied with alternative therapies (37% fully satisfied and 60% relatively satisfied). Two-Thirds of the users indicated that they would like to receive complementary medicine prescriptions by medical doctors. The study findings suggest that the breast cancer patients frequently use complementary medicine after diagnosis. It seems that medical doctors should ask patients about their use of complementary medicine when they obtain medical history and they need to know more about complementary medicine to offer a better consultation to breast cancer patients.

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Prognostic significance of urokinase plasminogen activator (uPA) and its inhibitor (PAI-1) in breast cancer

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Urokinase plasminogen activator (uPA) and its inhibitor (PAI-1) have an important role in tumor growth and metastasing. It seems that determining of uPA and PAI-1 could be of significant value in evaluation of disease prognosis.

The aim of our research was to determine whether increased values of uPA and PAI-1 in our group of patients imposed worse prognosis.

Values of uPA and PAI-1 were determined using ELISA method in breast cancer citosol of 150 patients. Data on axilar lymph nodes, tumor size, hystologic grade and tumor type were collected. Data on disease exitus of 113 patients were obtained from Cancer Register of Republic of Croatia. Median of disease surveilance was 44 months. There were 31 deaths and 82 patients survived.

Diagnostic accuracy of laboratory tests was assessed by ROC analysis (Receiver Operating Characteristic Analysis). Surface under ROC curve

for uPA is 0.709 (95% C.I. 0.616–0.791), and for PAI-1 is 0.731 (95% C.I. 0.639–0.81) which shows good discriminatory efficacy. Limit values obtained by ROC analysis were 0.92 for uPA, and for PAI-1 1.44 ng/mg protein.

Curves of survival were obtained by Kaplan-Meier analysis. Survival curves of 72 patients with uPA<=0.92 and 41 patients with uPA>0.92 ng/mg proteins showed statistically significant difference (P<0.001). Statistical probability of difference in curves of 62 patients with PAI-1<=1.44 and 51 patients with PAI-1>1.44 ng/mg protein (P<0.001) is the same. Corelation coeficient of uPA and PAI-1 is 0.714 (P<0.0001).

Our research confirmed prognostic significance of both parameters.

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Associated changes of lipid peroxidation and transglutaminase activity in the evolution of breast tissue to cancer

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Background: Lipid peroxidation and tissue transglutaminase (tTG) have been indipendently implicated in tissue damage associated with several disease including breast cancer. We have investigated lipid peroxidation products, such as malondialdehyde (MDA) and 4-hydroxy-nonenal (HNE)-protein adducts, and tTG activity in tissues from breast surgical specimens to study the evolution from the normal to the cancerous tissue.

Methods: We have collected breast tissues from surgical specimens affected by primary invasive ductal breast carcinomas (C), fibroadenoma (F) and atypical ductal hyperplasia (H). The samples were obtained during surgical resection, directly frozen in liquid nitrogen and stored at −80°C until use. The tissue was suspended in hypotonic buffer Tris-HCl 10mM, EDTA 0.1mM and MgCl$_2$ 5mM, PMSF 90µM, 2-β mercaptoethanol 0.1mM (pH 7.5). The suspensions were homogenized by a Ultradurax T25 basic, then they were centrifuged at 13,000 rpm for 10 min. Biorad protein assay, spettrofluorimetric analyses of HNE-proteins adducts and tTG activity were conducted on the supernatants. The quantitation of the fluorescence intensity at 360 nm excitation/430 nm emission was taken as an indirect measure of the HNE-protein adduct (AFU/mg protein) The pellets were added of 500 µl urea 6M, SDS 8.1% buffer. After mixing the samples were centrifuged at 15,000 rpm for 15 min and 100 µl of supernatants were used for the TBA test in buffer TCA 15%, TBA 0.3%, HCl 0.12 N.

Results: The MDA levels and HNE-protein adducts of normal tissues obtained from specimens affected by breast cancer were compared with benign breast disease. In the breast cancer the values were respectively 60±5 nmol/g and 2.2 AFU/mg protein while in the normal tissue belonging to specimens with atypical ductal hyperplasia the values were 30±2.5 nmol/g and 79±4.5 AFU/mg protein. In the control group represented by fibroadenoma affected one the values were 12.4±1.6 nmol/g and 11.5 AFU/mg protein. The tTG activity increased only in normal tissues obtained from specimens affected by breast cancer.

Conclusion: Oxidative stress can damage many biological molecules; indeed, proteins and DNA are more significant targets than are lipids, and lipid peroxidation often occurs late in the injury process. In fact HNE-protein adducts increased in precancerous tissue, while higher MDA values are shown in cancer tissue damage. We speculated that these biochemical parameters together with the tTG activity may be a diagnostic index for cancer research.

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Prediction of axillary lymph node status in breast cancer patients by the presence of cancer emboli in the primary tumor's vessels

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Objective: To identify the presence of vascular emboli of breast cancer histologic specimens and validate its significance for the axillary lymph node (LN) involvement.

Methods: Two hundred and twenty-four patients with invasive breast cancer, who underwent modified radical mastectomy or breast-conserving surgery and standard axillary dissection (level I and II) at the Metaxa Memorial Anticancer Hospital the last 3 years, were assessed for the presence of cancer emboli in at least one vascular structure, irrelevantly of the size of the vessel. Then we applied chi-square test and logistic regression analysis (univariate and multivariate analysis) for the evaluation of the statistical association between the vascular invasion and the number of the metastatic infiltrated LN. In the present study the 224 patients, which participated, had a tumor size until 3 cm. We excluded patients with larger tumors owing to their likelihood of positive LN (74%).

Results: Vascular 'invasion (VI) was seen in 29.9% of 127 and 54.6% of 97 patients with ⩽2 cm and >2 cm tumors respectively. 81.5% of the patients with VI and tumors ⩽2 cm had axillary lymph node metastases, compared with 35.9% of patients without VI. Also for tumors >2 cm 77.3% of patients with VI had at least one positive LN, compared with 52.2% of patients without VI.

Conclusions: By multivariate analysis axillary lymph node metastases are significantly related to VI (p-value: <0.001 for tumors ⩽2 cm and p-value <0.05 for tumors >2 cm). The absence of VI can be considered as a favourable prognostic factor for the axillary status.

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PAI-1 and PAI-2 as predictive factors in breast cancer

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Introduction: The prognostic value of PAI-1 and PAI-2 in breast cancer has already been confirmed. However, the factors that predict the response to therapy are even more important. The latest observations made in the patients with operable breast cancer have shown that PAI-1 may have predictive value in breast cancer.

Aim: To evaluate the correlation between PAI-1 and PAI-2 measured in primary tumor and the efficacy of systemic therapy with cytostatics and hormonal therapy in advanced breast cancer.

Patients and methods: The patients treated for advanced disease with chemotherapy (ChT) (CMF, vepeside, taxane or platinum-based) or hormonal therapy (HT) (tamoxifen or aromathase inhibitors) were included in the study. PAI-1 and PAI-2 values were determined in the primary tumor using ELISAs (American Diagnostica Inc.; CT). High and low levels of PAI-1 as well as PAI-2 were dichotomized using median value for PAI-1 and optimal cut-off level for PAI-2. Those who achieved complete or partial response by RECIST were considered responders, whereas in patients treated by HT, stable disease for more than six months (mo) was also regarded as response. Differences in response were calculated using chi-square test, time to progression (TTP) was presented by Kaplan-Maier curves and differences in TTP calculated by log rank test.

Results: In 45 patients treated by HT, a higher response rate, though statistically not significant, was observed in the patients with high PAI-1 levels compared to the patients with low PAI-1 levels (60% vs. 50%). In these, prognostically unfavourable group of patients, the median TTP was even longer compared to the group of patients with low PAI-1 levels (6.7 vs. 4.1 mo; p=NS). A slightly better response to treatment was observed in the patients with low PAI-2 levels (56% vs. 44.4; p=NS). However, no difference in TTP was observed. The correlation between the PAI-1 and PAI-2 levels and the efficacy of ChT was estimated in 144 patients. The patients with low PAI-1 levels responded better to ChT compared to the patients with high levels of PAI-1 (52.8% vs. 46.2%; p=NS). However, no difference in TTP was observed. A better response to chemotherapy was observed in the patients with low PAI-2 levels (49.1% vs. 38.9%; p=NS). In these, prognostically unfavourable group of patients, also a longer median TTP was observed (6.3 vs. 5.7 mo), this difference was just over the limit of statistical significance (p=0.095).