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Effect of lymphovascular invasion (LVI) on local recurrence after wide local excision (WLE) and after mastectomy (Mx)

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ONCOPOOL is a data set (n = 17,000) compiled from primary operable (⩽5 cm) breast cancers in women aged ⩽50 in 12 European Breast Units, treated by first line operable therapy and entered in 1990−99 inclusive.

Purpose of Investigation: LVI has been frequently quoted as a risk factor for Local Recurrence. This could be because LVI is related to other prognostic factors or because LVI is an independent variable.

Method: LVI was regularly measured by H&E staining in 4 units (n = 4193). 20% were LVI+.

Results:

1997 underwent Wide Local Excision (WLE) + postoperative RT

% LR rates, WLE + postoperative RT			
LVI−		LVI+	
n	% LR @10 yr	n	% LR @10 yr
1610	8±1	387	14±2

Cox Analysis with integrated standard prognostic factors by using Nottingham Prognostic Index (NPI) showed no significance to LVI; the small overall difference was therefore because more LVI+ cases lay in the poorer prognostic groups.

2196 underwent Mastectomy (Mx)

% LR rates, Mastectomy			
LVI−		LVI+	
n	% LR @10 yr	n	% LR @10 yr
1458	8±1	738	11±1

Cox analysis entering LVI and NPI did not show significance to LVI.

Conclusions:

- 'LR' within the breast tissue after WLE is largely made up of residual primary tumour which. LVI cannot influence.
- LR in skin flaps is metastatic, probably through lymphatic channels: LR of this type is rare after RT.
- The overall significances in relation of LR to LVI are explained by the relation of LVI to other prognostic factors.

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An effect of basal-like molecular subtype of breast cancer and BRCA1/2 mutations on patients' survival depending on age

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Background: Basal-like molecular subtype of breast cancer (BLBC) is defined by the absence of estrogen, progesterone and HER2 expression, express basal cytokeratins CK5/14 (CK5/6), have the poor prognosis and the lack of therapeutic options. To clarify clinicopathological similarities and differences between breast carcinomas (BC) depending on age, we compared clinicopathological characteristics between tumors of young and old women. In our study have investigated whether young age at diagnosis is associated with biologically more aggressive cancers and BRCA 1/2 mutations. However, a little studies have demonstrated prognosis of this type BC in young women and with BRCA mutations.

Material and Methods: 573 patients with BC are included in research: 254 − young (till 35 years), 319 − old (over 35 years). ER, PR, Her-2/neu, p53, p63, Ki67, CK5/14, p21, Bag1, Mcl1, pS2, VEGFR, Her-1 were analyzed in all cases by immunohistochemistry and 235 patients (126 − till 35 years and 109 − over 35 years) were tested for the BRCA1 founder mutations 185delAG and 5382insC and the BRCA2 founder mutation 6174delT by flow cytometry. Groups were comparable on TNM classification and morphological variants of BC.

Results: BLBC was detected in 13.6% cases and had a higher prevalence (21.6% versus 7.2%; P < 0.0001) in young patients compared with old. BLBC immunophenotype was characterised by high expression of p53 and Ki67, but Bag1, Mcl1, pS2, VEGFR, Her-1 were negative. Young patients with BLBC have increased Ki67, p53, p63, VEGFR, Her-1 (P < 0.01). BRCA1/2 mutations were detected in 7.2% women, prevalent in young patients than in old (11.1% versus 2.7%, P < 0.05). The higher prevalence of BRCA1/2 mutations was in young patients with BLBC (12.7% versus 4.3%; P < 0.05) than old. The overall 5-year survival rate in young women has made − 73.2%, with BLBC − 65.5% (P = 0.07), in old − 85.3%, with BLBC − 52.2% (P < 0.001).

Conclusions: Young patients had a higher prevalence BLBC with lower indicators of survival rate than old (P < 0.05). There was detected an interrelation between BLBC and BRCA1/2 mutations (P = 0.007), however the authentic data about influence of BRCA1/2 mutations on survival rate has not been received in the multifactorial analysis. BRCA mutations lead to decrease of survival rate (P = 0.002), but in young patients with BLBC this influence is not marked (P > 0.05).

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Three different antibodies for estrogen receptor analysis in breast cancer − implications for positive frequency, reproducibility and clinical outcome

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Background: Estrogen receptor is a predictive factor in breast cancer patients. Assessment with different antibodies might produce different results.

Material and Methods: 564 premenopausal women with stage two breast cancer were randomised to tamoxifen for two years vs no tamoxifen independent of estrogen and progesterone receptor status. Recurrence-free survival (RFS) was chosen as the primary outcome.

A tissue microarray was prepared from 500/564 primary tumors. Immunohistochemical staining (IHC) with three different antibodies for estrogen receptor were evaluated (ER1D5 (DAKO, Denmark), ERSP1 (Neomarker, CA, USA), 352 evaluable cases and DAKO kit (DAKO, Denmark), 347 evaluable cases) twice by a pathologist using a semiquantitative score of positive cells. Scores were grouped in order to evaluate numbers of positive and negative cases and reproducibility at the 10% cut off. Categorization into three groups, totally negative, <50% positive cells and ⩾50% positive cells, was also evaluated.

Results: With a 10% cut off, the number of positive cases in the first reading was 223 (63%), 252 (72%), and 211 (64%) with ER1D5, ERSP1 and DAKO kit, respectively. The overall agreement between evaluation one and two was 97%, 100% and 98%. When classifying cases as totally negative, <50% positive and ⩾50% positive cells, the frequencies in the first reading were for ER1D5 104 (30%), 54 (15%), 194 (55%), for ERSP1, 69 (20%), 52 (15%), and 231 (66%), and for the DAKO kit 105 (30%), 103 (30%), and 139 (40%), respectively. Overall agreement between evaluation one and two was 93%, 95% and 91%.

Combining the first readings of ER1D5 and ERSP1, with cut off 10%, a total of 222 cases were positive with both antibodies and 100 cases were negative with both. All the remaining 29 cases were positive with ERSP1 and negative with ER1D5. With a follow-up period of 5 years, the recurrence-free survival of the discordant group resembles that of the double negative group, logrank P = 0.77 compared to P = 0.06 when comparing it to the double positive group. However, for recurrence-free survival the first two years after diagnosis, a reverse pattern was observed.

Conclusion: The evaluated cut offs are fairly well reproducible with all three antibodies. Choice of antibody is important for recurrence free survival of estrogen receptor positive and negative patients.

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Positive HER2 status − Is it a discriminating factor for disease outcome in steroid receptor-positive early breast cancer patients treated with adjuvant endocrine therapy only?

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Background: Since HER2-positive status has been repeatedly reported as negative predictive factor for response to endocrine therapy, we investigated the influence of HER2 status on disease outcome in ER+ and/or PgR+ early breast cancer (BC) patients treated with adjuvant endocrine therapy only.

Patients and Methods: We analyzed 263 (148 premenopausal and 115 postmenopausal) stage 1/2 SR+ BC patients who underwent a radical

surgery from 1986 to 1995. Premenopausal women were treated with adjuvant ovarian ablation by irradiation and postmenopausal women with adjuvant Tamoxifen for 5 years. Steroid receptors contents were determined prospectively by the classical biochemical DCC method, while HER2 gene amplification was determined retrospectively by CISH in 134 women whose archival paraffin tissue samples were retrieved.

Results: One hundred and thirty four patients whose HER2 status was determined (66 premenopausal and 68 postmenopausal) of median age of 51 years (range 35−76), were followed for median 11.8 years (range 0.9−19). Eleven (8.21%) patients were node negative with grade 3 BC and 125 (93.28%) had 1−3 positive nodes irrespective of tumor grade. Median disease free interval was 12.3 years (95% CI 10–17.8); median BC specific survival (BCSS) was 16.2 years (95% CI 13-Inf) and overall survival (OS) was 15.2 years (95% CI 12.1-Inf). HER2 gene amplification (CISH+) were noted in 21 (15.67%), while 113 (84.33%) had no HER2 gene amplification (CISH−). There was no significant difference in the risk for disease relapse [HR 1.25 (95% CI 0.678–2.29), p = 0.489], death from BC [HR 1.21 (95% CI (0.608–2.42), p = 0.591], and death from any cause [1.19 (0.637–2.23), p = 0.590] between CISH+ and CISH− subgroup. Cox regression analysis showed that only ER-/PgR+ status was an independent favorable risk factor for BCSS [HR 8.29 (95% CI 1.14–60.24, Wald test p = 0.028)] and OS [HR 7.51 (95% CI 1.31–68.97, Wald test p = 0.0009)]. Comparison between premenopausal and postmenopausal subgroups with CISH+ BC showed a trend toward longer OS in premenopausal women (Log rank test χ^2_1= 3.302, p = 0.069), while the OS difference in CISH− group reached statistical significance in premenopausal women (Log rank test χ^2_1= 4.849, p = 0.028). However, there was no difference in BCSS between premenopausal and postmenopausal subgroups regardless of HER2 status.

Conclusion: Our results did not show that positive HER2 status had a significant influence on disease outcome in early SR-positive breast cancer patients treated with adjuvant endocrine therapy only.

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Clinicopathological implications of cyclin B1, cdc2, p16 and p53 expression in breast cancer

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Backgound: Cell cycle prgression is governed by cooperation of specific cyclin and cyclin-dependent kinase (Cdk) at G1-S and G2-M checkpoint and the cell cycle deregulation plays a major role in carcinogenesis of human cancers. Therefore, the evaluation of cell cycle proteins is important. The molecular mechanism responsible for initiation and progression of breast cancers are largely unknown. The aim of this study was to analyze the cyclin B1, cdc2, p16 and p53 tumor suppressor gene in breast cancers.

Materials and Methods: Tumor samples were obtained from 98 patients with breast carcinomas. To investigate the role of cyclin B1, cdc2, p16 and p53 in the pathogenesis and prgression of breast carcinomas, 98 cases of breast cancers were examined for the expression of cyclin B1, cdc2, p16 and p53 by immunohistochemical method. The correlation of cyclin B1, cdc2, p16 and p53 expression with various clinicopathological findings was also analyzed.

Results: Cyclin B1, cdc2, p16 and p53 were diffusely expressed in 55 cases (56.1%), 52 cases (53.1%), 57 cases (58.2%) and 68 cases (69.4%) out of 98 cases studied, respectively. In normal breast tissues, cyclin B1, cdc2, and p16 were weakly expressed and p53 was not expressed. The overexpression of cyclin B1, cdc2, p16 and p53 in breast cacner were noted. The correlation between the loss of expression of cyclin B1, cdc2 and distant metastasis was noted (p < 0.05). The correlation between the expression of cdc2 and infiltrative tumor border pattern was noted (p < 0.05). In addition, the overexpression of cdc2 and p53 were correlated with histologic high grade carcinomas (p < 0.05).

Conclusions: Cyclin B1 and cdc2 appeared to be involved in the genesis or progression of breast cancers. In addition, overexpression of cdc2 and p53 may play important roles in progression into high grade group in patient of breast carcinomas. Deranged overexpression of cyclin B1, Cdk, p16 and p53 may play an important role in human breast carcinogenesis.

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Changes in nutrition parameters among women with early breast cancer

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Material and Methods: 127 blood samples from women with diagnosed breast cancer were collected. Received results were compared to control group (n = 35) of healthy women with the similar age (middle age 55 years old) and from the similar region. Further data (weight, height, other diseases) were received from the hospital documentation (patients with breast cancer) and directly from other patients. Received data were calculated statistically by using tests t-Student and U Mann-Whitney.

Results: The average level of TC in analyzed patients with breast cancer was 228.03 mg/dl with variability factor (v) 20%, which was significantly more than in control group (204.7 mg/dl, v=19%), p < 0.01. Over 76% of women with breast cancer had the level of TC in serum higher than 200 mg/dl and 8% of them had the level of TC higher than 300 mg/dl. The average level of HDL in blood serum of women with breast cancer was 58.66 mg/dl (v=27.75%), and in general population of women with similar age it equaled 63 mg/dl (v=16%), p < 0.05. The average level of LDL in blood serum among women with breast cancer was 142.35 mg/dl (v=29.05%) vs. 117.4 mg/dl (v=32%), p < 0.01 among women from control group. The average level of TGC in blood serum of women with breast cancer was 134.94 mg/dl (v > 35%) and the average level of TGC in general population of women was 119.2 mg/dl, p > 0.05 (statistically not significant). The BMI of women with breast cancer was similar to the general population of women with the same age group and from the same region. It was respectively 27.52 kg/m^2 and 27.31 kg/m^2 (v < 35%, p > 0.05).

The women were also divided into groups dependently of malignancy of the cancer (G). However, there were no statistic significance when comparing BMI, TC, HDL, LDL in women with breast cancer of G1, G2, and G3 malignancy, the average values of some studied parameters tended to change. The average level of TGC in blood serum in women with grade G3 breast cancer was 131.09 mg/dl vs. 143.06 mg/dl in women with breast cancer in grade G2. The average BMI of women with G3 breast cancer was 27.06 kg/m^2 vs. 27.26 kg/m^2 in women with G2 breast cancer. Unfortunately, the group of women with G1 breast cancer was too small to compare it to other groups.

Conclusions: The nutrition parameters like TC, HDL and LDL could the possible risk factors in breast cancer.

The level of TGC in blood serum and BMI could be helpful in the risk of malignancy of breast cancer.

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Relationship between hormone receptors, MIB-1 index and serum tumour markers CEA and CA 15−3 in patients with pT1−2 breast cancer

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Background: CEA and CA 15−3 are the best investigated serum tumor markers in breast cancer (BC) patients. The aim of this study was to find relationship between serum CEA and CA 15−3 and prognostic markers, such estrogen receptor (ER), progesterone receptor (PGR), and tumor proliferation rate index measured by MIB-1 index, in women with pT1−2 breast cancer.

Patients and Methods: Preoperative measurement of serum CEA and CA 15−3 was obtained from 301 women (median age 61.2 years, range 28−85 years) with confirmed BC, who underwent curative surgery. The removed tumor tissue was routinely processed for ER and PGR using a quantitative standard immunoenzymatic method, while the immunostaining of Ki-67 antigen was performed using the monoclonal antibody MIB-1.

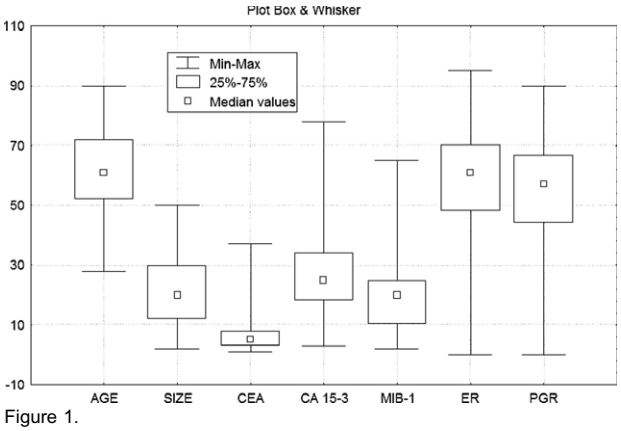

Figure 1.

Results: The results (age of the patients [61.2±12.9 years], size of the tumor [20.7±10.2 mm], CEA [6.3±5.0 ng/mL], CA 15−3 [26.1±12.4 U/mL],