group was represented by 96 healthy women (aged 32–64 average 49.3). The body posture was analised by a computer using three-dimensional photometry (CQ Electronics System) consisting in three-dimensional reproduction of shapes and positions based on the photos of examined surface. The examination was conducted in Photogrametry Studio of Rehabilitation Centre "Akwawit" in Leszno in similar, repetitive conditions, five times every six months. The statistical analysis was carried out with the use of Mann-Whitney's and Friedman's nonparametric tests.

Results: The comparative analysis of variables defining body posture in frontal and sagital plane showed essential difference between measurements in group of women after mastectomy in comparison with group of healthy women. A greater intensification of changes in position of symmetrical osseous points (shoulder-blades, shoulders, pelvis) was noted in a group of women after mastectomy.

Table 1. A comparison of women after mastectomy and healthy women

Item	Abbr.	p value
1. Difference in distances of lower angles of shoulder-blades from spinal column	OL	0.04
2. Difference in height of lower angles of shoulder blades (inclination)	UL	0.01
3. Inclination of shoulder line to the level	KLB	0.04
4. Difference in height of shoulder position	LBW	0.02
5. Difference in height of waist triangle	TT	0.01
6. Max. deviation in the spinous processes from the vertical position	UK	0.01
No essential differences in both examined groups of women in the range of:		
1. Trunk inclination	KNT	0.1
2. Pelvis inclination	KNM	0.46

Conclusions:

1. The photogrametry estimation of the body posture shows essential disorders at women after mastectomyin comparison with a group of healthy women.
2. The noninvasive photogrametry method of body posture analysis is useful in the estimation of the quality of the postsurgical rehabilitation.

387 POSTER

Questionable successful pregnancy after chemotherapy and TRAM flap surgery? Case Report

J. Jankau, J. Jaskiewicz. *Medical University of Gdansk, Poland, Plastic Surgery and Burns, Gdansk, Poland*

The authors would like to present a case of a 30 year old woman with family history of breast cancer who were diagnosed in the age of 27, pending annual medical check-up, with breast cancer (USG guided punch biopsy – cellular carcinomatosis). Before the surgical removal of the cancer patient went two courses of chemotherapy (CMF Bonadonna trial – 5FU 1000 mg, MTX 70 mg). After this two courses of chemotherapy patient underwent mastectomy (Ca mammae dx ductale invasivum/T2N1aMx, no axillary's lymph nodes involved) with simultaneous ipsi-lateral-TRAM flap reconstruction. In the post op follow-up patient did not present any complication due to surgery and no hernia were present. After the reconstruction patient underwent additional four courses of chemotherapy (CMF Bonadonna trial – 5FU 1000 mg, MTX 70 mg). At that time the council advise her not to get pregnant, despite this warning after eight month patient made her own decision to be pregnant and she did. The council with oncologists, gynecologists and breast surgeons decide that in that case there is no reason to terminate as long as patient is self-conscious of possible complications. In 32nd week of pregnancy patient underwent caesarean section and deliver baby-girl with Down Syndrome with no additional abnormalities. The post-op period was without any complication like abdominal wall laxity and abdominal hernia or any infections; no abdominal revisions were required after delivery. In two years of follow-up due to controls mother and child has no major complications, abdominal contour is acceptable and there are no signs of cancerous disease in both mother and child.

The author would like to arise a question whether it was a successful pregnancy?, no complication before and after surgery, and what should council advice to a woman who had a history of breast cancer and underwent TRAM flap reconstruction with pre and post chemotherapy whether to have or not to have a child? Upon the presented case and literature we can state that TRAM flap reconstruction (if properly executed) is not a contraindication to pregnancy, rather chemo or radiotherapy may be.

388 POSTER

Arm lymphedema reduction in breast reconstruction with transverse abdominal island (TRAM) flaps

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Background: Tissue expander/implant breast reconstruction in patients after radical mastectomy and adjuvant radiotherapy is relatively contraindicated in cases of lymphedema of the arm. In such a clinical situation the use of autogenous tissue for breast reconstruction may have more advantages.

The aim of the study is determine why an autogenous well vascularised TRAM flap used for breast reconstruction may reduce symptoms of lymphedema.

The authors present material of 15 non-consecutive pts from three different dept. (Gdańsk, Warszawa, Grodno) with breast reconstruction with free and pedicle TRAM flaps where the tendency to reduce lymphedema of the upper extremity lymphatic edema as well as improvement in movements in the shoulder joint at the operated side were observed. Check measurements of swollen upper extremities were carried out in the pre-, early and late postoperative periods. The observation period is 3 years. The mentioned positive effects after autogenic tissues breast reconstruction is sustained successfully by wearing elastic compressive garment and physiotherapy exercises. Late results of the operation demonstrate a long term reduction in an upper extremity lymphatic edema. The authors presents possible explanations of this results on the basis of understanding of the lymphoedemas pathophysiology and classification. Thus, in the the basis ofpresence of an upper extremity lymphatic edema of post-mastectomy genesis, breast reconstruction with vascularized flaps is the method of choice because of a high level of rehabilitation and improvement in quality of patients life. Postmastectomy pts who are obese, have had previous chest wall radiation and slight symptoms of lymphedema, are not good candidates for tissue expander reconstruction. The reconstruction with autogenous tissue has a number of distinct advantages.

Friday, 19 March 2004 16:00–17:15

PROFFERED PAPERS

Pathology/Predictive and prognostic factors

389 ORAL

DNA damage control genes that predispose for radiation-induced breast cancer

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Background: The most important risk factor for breast cancer development is a family history of the disease. Genes implicated in family history of breast cancer include the high penetrance genes BRCA1 and BRCA2. 5–10% of all breast cancer can be explained by germline mutations in these high-risk genes. A larger part, ~10–30%, might be explained by mutations in low penetrance genes, for which candidates are ATM and CHEK2. The contribution of these genes might be explained by the role they play in the DNA damage control pathway. Radiation has been shown to be a strong risk factor for breast cancer and thus genetically predisposed individuals, especially women with inherited mutations in genes involved in DNA-damage repair and cell cycle control, may have an increased sensitivity to environmental exposures such as radiation. To evaluate the significance of germline mutations in ATM, CHEK-2 and BRCA1/2 to the risk of (radiation-induced) contralateral breast cancer (clbc), we assessed its mutation frequency in women who developed a clbc, with and without radiation treatment (RT) for the first breast tumor.

Methods: Clbc patients will be included if their first bc is diagnosed before age 50, and the interval between 1st and 2nd bc is at least 1 year. So far we collected 169 patients who did and 64 who did not receive RT for their primary bc. For each patient we obtained the full medical records for data collection. DNA was isolated from peripheral blood or paraffin tissue and currently screened for all ATM germline mutations, for one particular

CHEK2*1100delC mutation and for 48 BRCA1 and 2 founder or recurrent mutations.

Results: So far we determined 15 CHEK2 1100delC mutations among 233 (6.4%) clbc patients, 13 among 169 (7.7%) patients who did and 2 among 64 (3%) who did not receive RT. We identified 30 BRCA1/2 mutations among 188 (16%) clbc patients, 23 among 128 (18%) patients who did and 7 among 60 (11.7%) who did not receive RT. ATM truncating germline mutations were determined among 4 out of 188 clbc patients (2.1%), all were detected among those who received RT. The ATM missense mutations spectrum is under analysis.

Conclusion: In the subset of 188 clbc patients with complete mutation data, 26% carries a germline mutation in one of the tested genes. Thirty percent of the women who received RT carried a germline mutation versus 15% among those who did not receive RT, OR=2 (95% CI 1.045–3.888, p=0.03). Our results suggest that ionizing radiation treatment might be a risk factor for breast cancer development in these mutation carriers. The excess risk for heterozygotes to develop radiation induced contralateral breast cancer provides a scientific basis for mutation analysis and subsequently an intensified follow-up protocol for mutation carriers.

390 ORAL

Changes in gene expression profiling due to primary chemotherapy in patients with locally advanced breast cancer

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Background: Patients with locally advanced breast (LABC) cancer often undergo neoadjuvant chemotherapy treatment. At present, commonly used regimens of neoadjuvant chemotherapy include the combination of adriamycine and cyclophosphamide (AC). Good responses have also been observed with adriamycine and docetaxel (AD).

It is currently not possible to predict sensitivity or resistance of tumors to specific drugs. Some patients may therefore undergo the toxicity of these drugs, but do not benefit from the therapy. This study was designed to identify gene expression patterns that can predict which tumors will respond to a combination of AC and which tumors to a combination of AD.

Material and Methods: We started a prospective phase III trial for patients diagnosed with locally advanced breast cancer, randomizing between six courses of adriamycine (60 mg/m^2) and cyclophosphamide (600 mg/m^2) or adriamycine (50 mg/m^2) and docetaxel (75 mg/m^2) respectively. Chemotherapy was administered every three weeks.

Total RNA was isolated from a frozen 14 G core needle biopsy obtained from the tumor before treatment. All patients underwent surgery after completing chemotherapy. If there was residual tumor after completion of chemotherapy, RNA was isolated from frozen tissue sections. Amplified mRNA was hybridized on human 18k cDNA microarrays obtained from the NKI microarray facility. Supervised and unsupervised classification have been used to analyze differences between gene expression before and after treatment and to correlate gene expression profiles to patient's response to the chemotherapy administered.

Results and Discussion: Thus far 62 patients with LABC have been randomized in the study. Good quality RNA from tissue with more than 50% tumor cells was obtained from 46 biopsies and 18 tumors. In total, data from 49 patients (three tumors without biopsy) could be included into the analysis. From these patients 25 were treated in the AC arm, 24 in the AD arm of the study.

Preliminary analysis indicates that there are significant differences in gene expression in the tumor before and after chemotherapy treatment. There does not appear to be a major difference in gene expression between tumors from patients with a complete pathological remission compared to all other patients. There are subtle differences in gene expression between these two groups, but the identification of a reliable "response signature" probably requires a higher number of patients for analysis.

391 ORAL

Gompertzian effect of tumor size on mortality in early breast cancer

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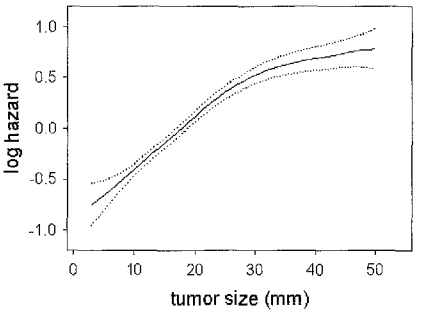
Purpose: To determine the type of relationship between tumor size and mortality in T1-T2 breast carcinoma.

Methods: Data on 83,686 women from the Surveillance, Epidemiology and End Results (SEER), diagnosed 1988–1997, no metastases, in whom axillary node dissection was performed: 58,070 node-negative (N0), 25,616 node-positive (N+). Endpoint is death from any cause. Tumor size in millimeters is modeled as a continuous variable by proportional hazards (PH), using a Generalized additive models procedure.

Results: Functionally, the same Gompertzian expression **exp(−exp(−(*size* − 15)/10))** provided a good fit to the effect of tumor size on mortality, irrespective of nodal status, and irrespective of the number of nodes involved (npos).

Quantitatively, for tumor size from 5 mm to 50 mm, the crude death rate increase was (figures rounded) from 10% to 25% in N0, 15% to 35% with npos=1, 29% to 40% with npos=2, 15% to 30% with npos=3, 30% to 50% with npos>3.

Conclusion: The effect of tumor size is functionally and quantitatively independent of nodal involvement. This is in contradiction with the Halstedian concept of a sequential involvement of nodes.



392 ORAL

Tissue inhibitor of metalloproteinases-1 (TIMP-1) and prognosis in primary breast cancer: an EORTC–RBG collaborative validation study including 2984 patients

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Introduction: Previous studies have indicated that TIMP-1 levels in primary breast tumours may be related to patient prognosis. To validate this, in the present EORTC–Receptor and Biomarker Group (RBG) collaborative study we investigated the association between total tumour tissue levels of TIMP-1 and prognosis in 2984 patients with primary breast cancer. We also analysed whether TIMP-1 may be useful as a prognostic marker in combination with urokinase plasminogen activator (uPA) and plasminogen activator inhibitor type-1 (PAI-1).

Experimental Design: In cytosolic extracts of 2984 primary breast tumours, total levels of TIMP-1 were determined using an established, validated TIMP-1 ELISA and the results were analysed statistically. TIMP-1 was analysed as a continuous, log-transformed variable and as a dichotomised one. Dichotomisation of data was done using a statistically identified cut-point. Median follow-up time was 98 months. 51% of the patients were lymph node-negative and 48% lymph node-positive; median age of the patients was 57 years. Levels of uPA and PAI-1 have previously been determined in the extracts.

Results: The cut-point identified and used in the analyses was 11.71 ng/mg of total protein. In univariate survival analysis, high levels of tumour tissue TIMP-1 were associated with a poor prognosis [recurrence-free survival (RFS), overall survival (OS), P<0.001], both when including TIMP-1 as a continuous and as a dichotomised variable. Also in subgroups of lymph node-negative and lymph node-positive patients, high TIMP-1 levels were associated with a significantly shorter RFS (dichotomised variable, both groups P<0.05). In a multivariate model including established prognostic parameters (lymph node status, age and menopausal status, tumour size, grade of malignancy, hormone receptor status), high tumour tissue levels of TIMP-1 (dichotomised variable) were associated with a significantly shorter RFS (P<0.001) and OS (P=0.003). When adding uPA and PAI-1 to the multivariate model, TIMP-1 still added significantly to the model for RFS (P=0.002).

Conclusion: This study supports previous findings, namely that high levels of tumour tissue TIMP-1 are associated with poor prognosis in patients with primary breast cancer. It also shows that TIMP-1 may be useful as a prognostic marker in combination with components of the urokinase-plasminogen activation system (uPA and PAI-1), which have been established as strong prognostic markers in breast cancer.