of patients, and febrile neutropenia was observed in 5.6% of patients. The most common grade 3/4 non-hematologic adverse event was hand-foot syndrome, observed in 11.3% of patients. The median relative dose intensities of FEC, T, and X were 0.982, 0.968, and 0.933, respectively. Patients with HR-negative tumors had significantly higher pCR rate than HR-positive tumors (35.3% vs. 10.5%, p = 0.03). HER2 status was not significantly correlated with pCR rate. Patients with Ki67 expression >20% revealed significantly higher pCR rate than <20% (23.5% vs. 8%, p = 0.02). In HR+negative subgroup, Ki67 expression were significantly correlated with pCR (p = 0.02).

Conclusions: Our data indicate that the sequential combination of XT followed by FEC is a well-tolerated, effective preoperative treatment for stage II/III breast cancer and HR status and Ki67 expression are useful predictive biomarkers.

124 Poster

Estrogen receptor-negative tumour and positive family history for breast cancer highly modify the risk of second contra-lateral breast cancer

E. Rapiti[1], S. Benhamou[2], G. Fioretta[3], H. Verkooijen[4], P. Chappuis[5], I. Neyroud-Caspar[3], M. Castiglione[3], V. Vinh-Hung[6], G. Vlastos[7], C. Bouchardy[3]. *[1]Geneva Cancer Registry, Social and Preventive Medicine Institute University of Geneva, Geneve, Switzerland; [2]CNRS, Gustave-Roussy Institute, Paris, France; [3]Geneva Cancer Registry, Social and Preventive Medicine Institute University of Geneva, Geneva, Switzerland; [4]Department of Epidemiology and Public Health, National University of Singapore, Singapore, Singapore; [5]Department of Genetic Medicine and Laboratory, Geneva University Hospitals, Geneva, Switzerland; [6]Division of Radiation Oncology, Geneva University Hospitals, Geneva, Switzerland; [7]Senology Unit Department of Gynecology and Obstetrics, Geneva University Hospitals, Geneva, Switzerland*

Background: A recent study reported an increased risk of contra-lateral estrogen-negative breast cancer after a first primary estrogen-negative breast cancer. Our study aims to confirm this result and to evaluate how the risk of second breast cancer occurrence is affected by family history of breast cancer and anti-estrogen treatment.

Patients and Methods: We included in the study all 4152 women diagnosed with breast cancer between 1994–2007, using data from the population-based Geneva Cancer Registry. We compared the incidence of second breast cancer among patients according to estrogen receptor (ER) status with that expected in the general population by age-period Standardized Incidence Ratios (SIRs).

Results: Among the cohort, 63 women developed second breast cancer. Patients with ER-positive first tumors had a decreased risk of second breast cancer occurrence (SIR: 0.67, 95% CI: 0.48–0.90), whereas patients with ER-negative primary tumors had an increased risk (SIR: 1.98, 95% CI: 1.19–3.09) limited to ER-negative second tumors (SIR: 7.94, 95% CI: 3.81–14.60). Patients with positive family history had an 8-fold (SIR: 7.67, 95% CI: 2.49–17.90) higher risk of ER-negative second tumor, which increased to nearly 50-fold (SIR: 46.18, 95% CI: 12.58–118.22) when the first tumor was ER-negative. Treatment with anti-estrogen decreased the risk of second ER-positive tumors but not ER-negative tumors.

Conclusions: The risk of second ER-negative breast cancer is very high after a first ER-negative tumor, in particular among women with strong family history. Surveillance and prevention of second cancer occurrence should consider both ER status of the first tumor and family history.

125 Poster

The effect of lymphovascular invasion (LVI) on survival

M. Sundquist, S. Bianchi, A. Douglas-Jones, I. Ellis, A. Lee, S. Pinder, S. Thorstenson, G. Ball, R. Blamey, on behalf of the ONCOPOOL Consortium

The ONCOPOOL database (n = 17,000) is compiled from primary operable (⩽5 cm) breast cancers in women aged ⩽70, from 12 European Breast Units, treated by first line operative treatment and entered in 1990−99 inclusive.

Method: LVI was regularly measured in 4 units (n = 5195) on H & E staining. Scoring was to definite positive or negative. 20% were LVI+.

Results:

- Relation to Nottingham Prognostic Index (NPI). A highly significant rank order from 7% LVI+ lying in Excellent NPI group to 60% and 62% in the Poor and Very Poor groups.
- Overall survival by both LN stage and LVI (Table 1): survival by LN status was moved down one stage by LVI+ positivity.
- LVI positivity lowers survival within all Nottingham Prognostic Index (NPI) groups: Cox Analysis entering NPI and LVI shows both to have p values of <0.000 with hazard ratios of 1: 7 and 1: 6 respectively.

Table 1

LN group	Stage	LVI	n LN/LVI		10 yr OS (%)	LVI+ .v. Neg
1	LN Neg	Neg	2359	1	86±1	p < 0.000
2	LN Neg	Pos	429	2	78±3	
	LN 1 Pos	Neg	413		80±2	p = 0.025
3	LN 1 Pos	Pos	245	3	73±4	
	LN 2−3 Pos	Neg	307		72±3	p = 0.025
4	LN 2−3 Pos	Pos	266	4	65±4	
	LN 4+ Pos	Neg	574		69±2	p < 0.000
5	LN 4+ Pos	Pos	508	5	44±3	

Conclusion: LVI is an important additional independent variable to NPI for survival.

126 Poster

P-cadherin, Osteopontin and MIB1 as prognostic factors for loco-regional relapse in breast cancer

G. Faria[1], D. Martins[2], H. Bettencourt[3], C. Davila[4], I. Amendoeira[3], F. Schmitt[2], M.J. Cardoso[5]. *[1]Hospital São João, Serviço de Cirurgia Geral, Porto, Portugal; [2]Ipatimup, Ipatimup, Porto, Portugal; [3]Hospital São João, Serviço Anatomia Patológica, Porto, Portugal; [4]Hospital São João, Serviço de Oncologia Médica, Porto, Portugal; [5]Hospital São João, Centro de Mama, Porto, Portugal*

Introduction: Loco-regional relapse in breast cancer is considered to be an independent predictor of subsequent metastization and death. As a consequence, one of the current pathways of research stands on the discovery of new risk factors for local relapse due to the significant discrepancy in prognosis of patients with identical staging and similar pattern of known molecular markers.

Three new molecular markers have been associated in previous studies to worst outcomes in breast cancer patients: P-cadherin has been identified as an independent prognostic factor in breast cancer; Osteopontin in breast cancer stroma has been related with the expression of genes associated with worst prognosis; Proliferation index (MIB1) is also considered to be inversely related with survival. The purpose of this work was to study the value of these three markers as possible determinants factors for loco-regional relapse in breast cancer.

Material and Methods: We retrospectively analyzed the clinical records of 1432 patients treated at our institution between January 1998 and June 2008. The case group consisted of 101 patients (7%) with local relapse as first new related event. The control group, consisted of 92 patients, from the same series with a disease free survival longer than 10 years.

Clinical data and classical pathological factors were retrieved for cases and controls. We performed Tissue MicroArrays and Immunohistochemistry for estrogen and progesterone receptors, HER2, Ck-5, P-cadherin, Osteopontin and MIB1.

Results: The average time to recurrence was 41 months; the mean survival after relapse was 33 months and the 5-year survival was 55%. On multivariate analysis tumour size, nodal status, histological grade and P-cadherin showed independent prognostic value for disease-free survival. None of the studied markers had a significant association with local relapse.

The aberrant expression of P-cadherin was related to higher histological grades and estrogen-receptor negativity; Osteopontin expressing tumours had more advanced disease at diagnosis and the MIB-1 was associated with tumours negative for estrogen receptors.

Conclusion: P-cadherin is a promising marker for loco-regional disease prognosis and a putative novel therapeutic target. Its real biological value is still undetermined and further studies are required.

127 Poster

Cyclin A − an alternative to gene expression profiling for subdividing histological grade 2 breast cancer into groups with different prognosis

C. Strand[1], C. Ahlin[2], M.L. Fjällskog[3], P. Malmström[1], M. Fernö[1]. *[1]Lund University, Oncology, Lund, Sweden; [2]University Hospital Örebro, Gynecological Oncology, Örebro, Sweden; [3]Uppsala University, Oncology Radiology and Clinical Immunology, Uppsala, Sweden*

Background: Ki67 has recently been included in the St Gallen guidelines as a prognostic factor, but the role of other proliferation markers, such as cyclin A, is still under debate. We investigated the prognostic importance of cyclin A, and if this was dependent on estrogen receptor (ER) status. Gene expression profiles, consisting mainly of genes associated to proliferation can subdivide histological grade 2 into two groups, one with a good

prognosis (similar to grade 1) and one with a bad prognosis (similar to grade 3). We therefore also raised the question if a single proliferative factor, i.e. cyclin A, can be used for this purpose.

Material and Methods: In 219 consecutive premenopausal node negative patients, cyclin A was determined with immunohistochemistry on tissue microarray. High cyclin A was defined as the 7th decile of positive cells. Only 13% of the patients received adjuvant systemic therapy. Cox proportional hazards regression was used to model the impact of the prognostic factors on distant disease-free survival (DDFS). Due to non-proportional hazards, the analysis was restricted to the first five years after diagnosis, a time period during which 34 patients developed distant recurrences.

Results: Cyclin A was associated to DDFS in univariate analysis (hazard ratio (HR) 3.6, 95% confidence interval (CI): 1.8−7.1, $p < 0.001$). Corresponding HR:s were 2.7 for Ki67 (95% CI: 1.3−5.5, $p = 0.005$) and 2.7 for grade 3 *vs* 1+2 (95% CI: 1.3−5.2, $p = 0.004$). HER2, age, ER and progesterone receptor were also significant factors, whereas tumor size was not. Cyclin A could divide histological grade 2 into two groups with significantly different DDFS (HR: 15, 95% CI: 4.3−52, $p < 0.001$). In the grade 1 and 3 subgroups, cyclin A was not a prognostic factor. When subdividing according to ER status, cyclin A was a prognostic factor in the ER positive subgroup, but not in the ER negative (HR: 5.8, 95% CI: 2.2−16, $p < 0.001$) *vs*. 1.5 (95% CI: 0.6−3.9, $p = 0.44$). In multivariate analysis, cyclin A was an independent prognostic factor for DDFS (HR: 2.9, 95% CI: 1.2−7.0, $p = 0.018$), together with HER2 and age. Due to colinearity, histological grade and Ki67 were not included in the same model.

Conclusion: In this study cyclin A was an independent prognostic factor for premenopausal patients with node-negative breast cancer, but only in the ER positive subgroup. Similar to gene expression analyses, cyclin A can subdivide histological grade 2 breast cancer into two groups with different prognosis. Taken together, cyclin A may be an alternative or a complement to histological grade and Ki67 for prognostic considerations.

128 Poster

Locoregional recurrences in triple-negative, node-negative early stage breast cancer treated with breast-conserving treatment

T. Hijal[1], N. Gault[2], X. Sastre[3], A. Savignoni[2], M.A. Bollet[1], F. Reyal[4], A. Fourquet[1]. *[1]Institut Curie, Dept. of Radiation Oncology, Paris, France; [2]Institut Curie, Dept. of Biostatistics, Paris, France; [3]Institut Curie, Dept. of Pathology, Paris, France; [4]Institut Curie, Dept. of Surgery, Paris, France*

Background: Breast conserving-surgery followed by whole breast radiotherapy is standard of care in patients (pts.) with early-stage breast cancer. It is unclear if loco-regional control after breast-conserving therapy is affected by the tumor's phenotype. The aim of this study was to assess whether triple negative phenotype (TN: ER-ve and PR-ve and Her2-ve) was associated with locoregional recurrences (LRR) in node-negative patients.

Materials and Methods: We studied a consecutive series of 754 patients with node-negative breast cancer treated with breast-conserving treatment at the Institut Curie between 1995 and 1998. All pts. underwent breast-conserving surgery and axillary lymph node dissection, followed by whole breast irradiation. 22% of patients received a tumor bed boost while 50% received regional lymph node irradiation. Adjuvant systemic treatment was delivered to 18%. ER and PR status were determined by immunohistochemistry (IHC). HER2/neu status was determined by IHC, and confirmed by FISH in uncertain cases. Cumulative locoregional recurrence and survival rates of TN tumors were compared to other tumors using a log-rank test. Multivariate Cox proportional hazard model was used to determine independent predictors of loco-regional recurrence.

Results: Among the 754 pts., 81 (10.7%) were TN. Compared to other tumors, TN phenotype was more likely associated with non-ductal/non-lobular subtypes, and less often with lobular cancers; it was significantly associated with pT2 tumors, grade III, lympho-vascular invasion, and high mitotic index. With a median follow-up of 11.7 years, the 10-year cumulative rates of LRR were 19.2% in TN tumors and 13.9% in other tumors, ($p = 0.11$). TN tumors tended to occur earlier than other tumors. On multivariate analysis, only age and grade were significant, independent predictors of LRR. Ten-year survival rates were 70.5% in TN tumors and 88.7% in others, respectively ($p < 0.0001$).

Conclusion: This retrospective study with long follow-up confirms that, in pts. with node-negative breast cancer of whom only 18% had receivd adjuvant systemic treatment, TN phenotype was associated with a worse survival than other tumors. However, this study did not find a significant increase in loccoregional recurrences in TN tumors, whereas age and grade were significant predictors of LRR. It suggests that breast-conserving treatment can be carried out in pts. with TN tumors.

129 Poster

Down regulation of Heat Shock Protein 70 (HSP70) predicts responsiveness to neoadjuvant aromatase inhibitors in post-menopausal hormonal receptors expressing breast cancer

C.C.P. Yiu[1], H. Sasano[1], N. Chanplakorn[1], M.S.M. Chan[2], L.W.C. Chow[3]. *[1]Tohoku University School of Medicine, Pathology, Miyagi Prefecture, Japan; [2]UNIMED Medical Institute, Comprehensive Centre for Breast Diseases, Hong Kong, Hong Kong; [3]The University of Hong Kong, Li Ka Shing Faculty of Medicine, Hong Kong, Hong Kong*

Introduction: Aromatase inhibitor is an effective endocrine therapy in breast cancer patients expressing endocrine receptors. Our group has demonstrated changes in protein expression profile using proteomic approach before, ten proteins were found to have potential impact as predictors for AI responsiveness or resistance. In the present study, we test the change in expression profile of heat shock protein70 (HSP70), carbonic anhydrase 1 (CA1) and GDI in larger cohort of patients using immunohistochemical (IHC) staining.

Methods: Eligible post-menopausal breast cancer patients were recruited. Pre- and post-treatment tumour tissues were obtained and IHC staining was performed for targeted proteins. The changes of expression profile were compared to clinical response to determine the correlations.

Results: Total 32 patients, with both pre- and post-treatment carcinoma samples available, were recruited. Majority of patients responded to treatment (16 patients with PR, 14 with SD and 2 with PD). Increment in tumour size was observed in 4 patients (2 PD and 2 SD patients). Down-regulation of HSP70 was significantly associated with clinical responsiveness of AI treatment, $p = 0.014$; and change of proliferative index, Ki67, $p = 0.042$. Patients with pre-treatment high HSP level and proliferative index using Ki67 assay, were associated significantly with downregulation of HSP after treatment.

Conclusions: With the use of AI as neoadjuvant treatment, downregulation of HSP is associated with observed clinical response. Pre-treatment high HSP and Ki67 levels predict treatment response via their significant correlation with HSP downregulation. Therefore, pre-treatment HSP and Ki67 can be potential surrogate markers for AI treatment.

130 Poster

Small breast tumours with adverse prognosis

M. Sundquist[1], G. Tejler[2], L. Gustavsson-Wallander[1], S. Thorstensson[3], L. Brudin[4]. *[1]County Hospital, Surgery, Kalmar, Sweden; [2]Hospital, Surgery, Västervik, Sweden; [3]County Hospital, Pathology, Kalmar, Sweden; [4]County Hospital, Physiology, Kalmar, Sweden*

Background: Tumours less than 10 millimetres are often node negative, of grade 1 and have an excellent prognosis. However, even a tumour of a few millimetres would sometimes be mortal. We wanted to assess risk factors for dissemination of very small breast cancers.

Materials and Methods: The patient registry and pathology database were used to identify all patients with breast tumours less than 10 millimetres that were diagnosed 1985 to 2008 in the Kalmar county and their outcome. Multivariate analyses were carried out.

Results: 220 pts with tumours less than 10 mm were identified. 118 were grade 1, 73 grade 2 and 32 grade 3. HER2 was amplified and/or IHC 3+ in 36 cases. One or more lymph nodes were positive in 10 pts. Lymphovascular invasion (LVI) occurred in 13 cases. DCIS grade 3 of an extension of 15 mm or more accompanied 65 of the tumours.

During a median observation period of 9 years 20 pts, 9%, had distant metastasis. In the multivariate analysis HER2 positivity and the coexistence of extensive DCIS grade 3 were the only significant parametres, $p < 0.001$ and <0.006 resp.

Conclusion: Tumours less than 10 millimetres with extensive DCIS grade 3 and HER2 positivity have an increased risk of dissemination.

131 Poster

A straightforward but not piecewise relationship between age and lymph node status in Chinese breast cancer patients

K.D. Yu[1], Z.M. Shao[1]. *[1]Cancer Hospital, Breast Surgery, Shanghai, China*

Purpose: To investigate the relationship between age and axillary lymph node (LN) involvement in Chinese breast cancer patients, and to replicate a recently identified piecewise relationship between age and LN involvement.

Patients and Methods: A dataset, consisting of 3,715 patients (with complete information on study variables) with operable breast cancer consecutively surgically treated between 1996 and 2006, was derived from the database of Shanghai Cancer Hospital. Univariate and multivariate logistic regression were employed to analyze the relationship between age and LN. We subsequently performed a similar analysis on another dataset