Conclusions: In this study, obesity was associated with poorer outcome in node-positive BC patients. The role of CT dosing and/or patient co-morbidities in obese patients is currently being studied. Given the increasing prevalence of obesity worldwide, more research on improving the treatment of obese BC patients is needed.

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Relevance of histological and molecular subtypes in the outcome of primary systemic therapy for operable breast cancer

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Objective: To analyse the relevance of histological subtypes, ductal versus lobular, and molecular subtypes using immunohistochemical profiles: luminal (estrogen-receptor positive and HER2-negative), basal (hormone receptor and HER2 negative) and HER2 positive, in the outcome of primary systemic therapy (PST).

Methods: Retrospective analysis of 254 patients treated with PST between 2000 and 2007 in the Netherlands Cancer Institute. Inoperable patients (T4, N3) were excluded. The majority of patients (70%) were initially treated with doxorubicin and cyclophosphamide and participated in two randomized studies in which antracycline and taxane based regimens were compared. Since 2005 HER2-positive patients received chemotherapy in combination with trastuzumab. The type of surgery feasible prior to neoadjuvant chemotherapy was compared to the actual surgery performed. Pathological complete remission (pCR) was defined as no evidence of invasive cancer in either breast and axilla.

Results: The increase in BCT was 32% (63/195) in patients with ductal carcinoma, and 17% (7/35) in patients with lobular carcinoma. Secondary mastectomy was required because of irradical resection in 2% and 33%, respectively. The pCR rate in ductal and lobular carcinoma was 12% and 2%, respectively. The overall pCR rate was 11%. The pCR rate in luminal, basal and Her2 positive patients treated with trastuzumab was 2%, 28% and 35%, respectively. Multivariate analysis indicated that molecular subtype was the only independent predictor of pCR. (P 0.004).

Conclusion: There is a clear difference in tumor response and surgical downstaging between histological and molecular subtypes. This result provides us another argument to select patients for PST on the basis of these subtypes in future trials.

		N	pCR	P value	Odds Ratio	95% CI
Age	<45 yrs	137	22	0.31	R	
	>45 yrs	114	7		0.42	0.077−2.27
Menopausal status	post	59	3	0.56	R	
	pre/peri	187	26		1.87	0.23−15.3
Histology	lobular	42	1	0.69	R	
	ductal	195	23		1.61	0.16−16.11
Molecular subtype	luminal	138	3	0.004*	R	R
	basal	57	16	0.01*	14.8	2.79−78.4
	Her2+	56	10	0.06	11.9	2.28−63.6
pN category prechemo	N1	169	13	0.10	R	R
	N0	43	13		3.07	0.95−9.94
T category	T1	12	2	0.27	R	R
	T2	151	19	0.76	0.33	0.04−2.76
	T3	88	8	0.11	0.16	0.02−1.62

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Systematic validation of novel breast cancer progression-associated biomarkers via high-throughput antibody generation and application of tissue microarray technology

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Background: There now exist vast quantities of DNA microarray data defining differences in gene expression between different subtypes of breast cancer, including variations in invasiveness and metastatic capabilities. However, this type of genetic assay is of limited prognostic or predictive value in most clinical settings due to general requirements for fresh/frozen tissue. The aim of this project is to translate the genetic data available into a more clinically relevant form – that of immunohistochemistry – identifying from these gene datasets any independent biomarkers that may be potential biomarkers and/or drug targets.

Materials and Methods: Our approach involves the high-throughput validation of the affinity-purified, mono-specific antibodies created by the Swedish Human Proteome Resource (SHPR, www.proteinatlas.com) against candidate breast cancer progression-associated biomarkers selected from publicly available and in-house transcriptomic and proteomic datasets. Initial validation of these antibodies was performed by the SHPR using a variety of normal and cancer tissues. Of the 137 targets selected for production, 32 have begun specificity validation by Western blot analysis. Those that are successful are moved forward to immunohistochemical (IHC) validation using cell pellet arrays derived from different human breast tumour cell lines. Successful IHC validation leads to the use of tissue microarrays (TMAs) of clinical samples to assess the clinical relevance of the putative biomarkers, either individually or as a panel. For efficient validation of the candidate biomarkers a TMA is being used, constructed from a cohort of 512 consecutive breast cancer cases diagnosed between 1988 and 1992.

Results: PDZK1, an estrogen-responsive gene, was previously found to be associated with good prognosis (interval to distant metastasis) at the transcript level in breast tumours. Our TMA IHC results showed PDZK1 protein to be associated with improved breast cancer-specific survival ($p = 0.0247$), ER positivity ($p = 0.041$) and low grade ($p = 0.002$). Another promising putative biomarker undergoing validation according to this schema is PDZ-binding kinase (PBK).

Conclusion: We have developed a comprehensive biomarker pathway that extends from discovery through to validation on TMA and is yielding clinically relevant biomarkers.

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Down regulation of angiogenesis antagonist EFEMP1 is associated with unfavourable prognosis in sporadic breast cancer patients

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Background: EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1) was recently described to be an angiogenesis antagonist and to act as a suppressor of formation and progression of human malignancies.

Materials and Methods: Immunohistochemistry on tissue microarrays of 203 clinically well characterized primary breast carcinomas was used to assess the potential clinical relevance of reduced EFEMP1 protein expression regarding patient outcome. Cox regression for multivariate survival modelling as well as univariate analyses were performed. Next to immune reactivity score for EFEMP1 expression, tumor grade, hormone receptor status, lymph node status, Her-2 status, tumor size, and type of adjuvant systemic therapy were included into analysis.

Results: Multivariate regression analyses in the 186 node-positive cases revealed that next to tumour size and grade EFEMP1 expression remained in the survival model as relevant factor influencing disease-free- and overall survival at borderline significance (DFS: $p = 0.14$; OS: $p = 0.077$). Further analysis of patient subgroups with homogeneous adjuvant systemic therapy revealed a significant correlation of low EFEMP1 expression with poor DFS and OS survival ($p = 0.037$ and $p = 0.032$) only in those node-positive patients who had received adjuvant anthracycline-containing