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Progression of precursor and pre-invasive lesions to invasive cancer

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In order to better understand the transition of normal breast epithelial cells through hyperplasia, DCIS and to invasive cancer we have analyzed a series of breast tissues, normal and malignant, sampled from healthy women and women with breast cancer at various stages of the disease at DNA and RNA level using various microarrays. Expression analyses revealed a distinct pattern of gene expression in normal vs malignant breast tissue. Focusing on genes involved in synthesis, degradation and binding of N-linked and O-linked glycans, Lewis antigens, glycosaminoglycans and glycosphingolipids demonstrated a unique glycan gene expression signature indicating that synthesis, degradation and adhesion mediated by glycans are altered drastically in mammary carcinomas. These genes are involved in regulation of growth factors/growth factor receptors, cell-cell adhesion and motility as well as immune system modulation, demonstrating that altered glycan structures are of importance in malignant transformation, and that a more comprehensive understanding of the glycobiology are of importance to elucidate the whole carcinogenic process.

Expression analyses also revealed heterogeneity within the different premalignant/malignant subgroups, identifying the five main intrinsic subtypes in all cohorts. Within the DCIS group a distinct subgroup with gene expression characteristics more similar to advanced tumours were identified, reflecting activated processes related to re-organisation of the microenvironment. This raises interesting possibilities for identification of DCIS lesions both with and without invasive characteristics.

DNA from the various tissue cohorts were submitted to quantitative DNA methylation analysis of 12 *selected genes* by pyrosequencing. Aberrant hypermethylation was observed in all malignant diagnosis groups for *ABCB1, FOXC1*, *GSTP1*, *MGMT, MLH1*, *PPP2R2B*, *PTEN* and *RASSF1A*. For most of these genes, methylation was already present in DCIS with the same frequency as within IDCs. The average DNA methylation levels were significantly higher in the pure IDCs and IDCs with DCIS compared to pure DCIS ($p = 0.007$ and $p = 0.001$, respectively). For *FOXC1* significant differences in methylation levels were observed between normal breast tissue and invasive tumours ($p < 0.001$). Low *FOXC1* gene expression in both methylated and unmethylated DCIS and IDCs indicates that the loss of its expression is an early event during breast cancer progression.

References

Potapenko et al. Mol Onc, in press 2010.
Muggerud et al. BCR in press, 2010.

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Should all pre-invasive lesions be excised and irradiated?

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In situ malignant lesions cover a wide spectrum of cell proliferations with different potential evolutions to invasive tumours. We focused our analysis on ductal carcinoma in situ (DCIS), sometimes also called ductal intra-neoplasia (DIN) [4], and lobular carcinoma in situ (LCIS), also called lobular intra-epithelial neoplasia (LIN).

Both lesions can be graded in there categories: DIN 1, 2 and 3, and LIN 1, 2 and 3. With the wide use of mammographic screening, these lesions reach 15−20% of all breast cancers.

1. Ductal Carcinoma In Situ (DCIS): DCIS represents 85−90% of all in situ lesions. DCIS treatments are mastectomy, breast conserving surgery alone (BCS) and BCS with whole breast irradiation (BCS + RT). There is a risk of progression to invasive carcinoma, with a 15% long-term risk of metastasis occurrence.

1.1. Mastectomy: Mastectomy provides approximately 98% of local control rate.

1.2. Breast Conserving Surgery (BCS): BCS, both in retrospective studies and randomized trials, leads to a 20−25% local recurrence (LR) rate at 7 years, including 40−45% invasive. Young age and small margins increase LR rates. In a recent very much selected study (only 6 mm median size lesions) by ECOG including 565 low-intermediate grade DCIS and 105 high-grade DCIS, the 7-year LR rates were 10% (53% invasive) and 18% (35% invasive).

1.3. Breast Conserving Surgery With Radiotherapy (BCS+RT): In several large series, the 7-year LR rate was approximately 10%, but with large heterogeneities due to selection criteria, extent of surgery and RT modalities. Four randomized trials (NSABP B-17, EORTC 10583, UK-DCIS and SweDCIS) confirmed a significant benefit with whole breast RT (50 Gy/25 fractions or equivalent), with a 50−60% LR reduction (both in situ and invasive). The results are shown in table 1. Both in NSABP and EORTC trials, RT efficiency was observed in all clinical or histopathological subgroups. Young age (under 40) and incomplete/doubtful excision remain the most important LR risk factors. Therefore, BCS+RT is considered the standard treatment with a 1% annual risk of LR and 98% 15-year specific survival. In a recent meta-analysis, a 2 mm (minimal) margin excision was required to optimize the long-term results of BCS+RT. Despite these results, RT usefulness was questioned by some authors.

Table 1: Results of trials comparing breast conserving surgery alone (BCS) or with radiotherapy (BCS+RT): local recurrence rates in %.

	NSABP B-17		EORTC 10583		UK-AZ DCIS		SWE DCIS	
	BCS (403)	BCS+RT (410)	BCS (500)	BCS+RT (502)	BCS (502)	BCS+RT (522)	BCS (520)	BCS+RT (526)
LR	31.7	15	26.4	14.9	20.7	7.7	27.1	12.2
In situ LR	14.1	7	13.4	7.2	10.4	4	14.8	4.9
Invasive LR	16.6	8	13	7.7	10.3	3.7	12.3	7.3
Follow-up	129 mo		120 mo		152 mo		101 mo	

2. Lobular Carcinoma In Situ (LCIS): Lobular carcinoma in situ (LCIS) represents 1−2% of all breast cancers and the exact significance remains uncertain, ranging from subsequent carcinoma marker to real precancerous lesion. LCIS is now revealed by several radiological features, especially microcalcifications.

The literature data on LCIS treatment are rare, but there are the same DCIS options, although BCS+RT was only reported in details in one study. Mastectomy gives an almost 100% cure rate. BCS alone gives an average 15% of subsequent invasive LR at 10−15 years. In a recent French retrospective study including 255 cases treated by BCS (with a 9.4-year median follow-up), 49 LR occurred (21 in situ and 28 invasive), corresponding to 12% and 23% of LR rates at 5 and 10 years respectively. Moreover, among 37 women treated by BCS+RT, only two LR (5.4%) were observed. LCIS is not always an “indolent” disease and, in several cases, it looks like DCIS, but with a longer relapse length. Several aggressive subtypes (i.e. pleiomorphic and some other LIN-3 patterns)) are now defined by pathologists. Both mastectomy and CS+RT could be seen as possible options instead of simple lumpectomy. In the NSABP P-1 chemoprevention trial, Tamoxifen reduces the subsequent risk of invasive BC by 56%.

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CLINICAL SCIENCE SYMPOSIUM

Gene profiling and treatment of disease

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Why Adjuvant! Online remains a useful tool in the era of multigene expression signatures

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Adjuvant! is a tool that was developed to present numerical estimates of outcome to breast cancer patients as part of shared decision making with a patient. As part of this effort in the 1990’s we studied the numerical knowledge that patients and their doctors had about prognosis without adjuvant therapy and the relative efficacy in terms of proportional risk reductions of adjuvant therapy. We found that there was a wide variation in these estimates and that many of them were very unrealistic. Guidelines were of no help in this regard as they were amount always non-numerically based prescriptive recommendations.

Adjuvant! draws from information from large registries to make estimates of patient outcome. These registries such as the United States SEER registry have classical information about patient outcome. The current version uses information about tumor size, nodal status, estrogen receptor status, and histologic grade to make estimates of outcome at 10 years of follow-up. Efficacy estimates for different classes of the hormone and chemotherapy are drawn directly or indirectly from the Early Breast Cancer Clinical Trialist’s meta-analyses. Estimates of completing mortality come from United States mortality tables.

The goal of the output of this tool is to provide to the patient and physician good general estimates of patient outcome with the strongest endpoint being survival and the program providing estimates of survival at 10 years, death due to breast cancer at 10 years (with or without adjuvant therapy), and an estimates of death due to competing mortality. The overall accuracy of this tool has been validated in Canadian and Dutch registries. Some much sought after estimates such as how adjuvant trastuzumab affects 10 year outcomes cannot be made because of the short follow-up of the trials assessing prognostic estimates.

Can such a tool be improved upon? When new technologies become available is it still relevant?