One important set of candidates for predictive factors is formed by the genes are found to be functionally altered by mutations in tumors. To date, mainly amplification of approximately 10 different chromosomal regions and inactivation of a limited number of tumour suppressor genes have been found. The presence of frequent loss of heterozygosity for many chromosomal regions indicates that more tumour suppressor genes are likely to be present and will be identified in the coming years. There is a small number of studies trying to identify genetic alterations associated with local recurrence, but these have not resulted in good risk factors for local recurrence.

DNA microarrays use gene chip technology to simultaneously measure the mRNA expression of several thousand genes in biological specimens. Using this approach, prognostic subgroups of breast carcinomas have been identified. Using supervised classification, an expression profile of 70 genes has been identified that can predict distant metastasis-free probability in node-negative breast cancer patients younger than 53 years of age. More recently, a gene expression profile consisting of 76 genes was identified by a similar approach that led to the identification of the 70 gene profile. Other investigators have also identified subgroups of tumours characterized by specific gene expression profiles, which are associated with outcome. These are recent results and at present there is not yet a gene expression pattern that integrates all of these studies. Prospective studies are now underway to validate the findings of these retrospective gene expression-profiling studies.

The use of DNA microarray technology to identify a prognostic gene expression signature is but one of its many potential applications in breast cancer management. There is also evidence that the technology may be able to define a multigene predictor of complete pathological response to a particular primary systemic chemotherapy regimen; and also predict responsiveness to hormonal therapy.

We have recently performed a study illustrating this approach fo predicting local recurrence after breast conserving therapy.

Gene expression profiles were obtained from 50 patients who underwent BCT and were younger than 51 years at the time of diagnosis for a primary invasive breast carcinoma. Of these 50 patients 19 developed a local recurrence in the treated breast and 31 controls were free of local recurrence at least 11 years after treatment. From 9 patients the primary tumor and its recurrence were profiled. Gene expression profiling was performed using an 18K cDNA glass slide microarray. Unsupervised and supervised methods of classification were used to separate patients in groups corresponding to disease outcome and to study the overall gene expression of primary tumors and their recurrences.

Hierarchical clustering of patients did not show any grouping reflecting local recurrence status. Supervised analysis revealed a possible classifier, but was prone to be biased by the estrogen receptor status of the primary tumor. After correcting for this possible bias no significant set of genes was able to distinguish recurring tumors from non-recurring tumors. Paired-data analysis of primary tumors and local recurrences showed no set of genes consistently different in expression between primary tumors and recurrences.

From this small study we conclude that there are no great differences in gene expression between primary breast cancer tumors in young women with or without local recurrence after breast conserving therapy. Furthermore, analysis of primary tumors and local recurrences in a paired model shows a preservation of the overall gene expression pattern in the local recurrence, even after radiotherapy.

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Neo-adjuvant vs adjuvant treatment – evidence from clinical trials

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We aimed to evaluate whether the cumulative randomized data suggest that there are any differences in clinical endpoints when breast cancer patients are given systemic therapy preoperatively (neoadjuvant treatment) vs. the same regimen postoperatively (adjuvant treatment). the meta-analysis included data with updated follow-up from 9 randomized studies (3946 patients) comparing neoadjuvant versus adjuvant systemic therapy. Primary outcomes were death, disease progression, distant recurrence and loco-regional recurrence. Fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird) methods were used to combine data. Secondary outcomes were local response and conservative local treatment. We found that there was no significant difference between neoadjuvant and adjuvant treatment regarding death, disease progression and distant recurrence and the 95% confidence intervals (CI) excluded the presence of any clinically meaningful difference (summary risk ratios, 1.00 [95% CI, 0.90–1.12], 0.99 [95% CI, 0.91–1.07], and 0.94 [95% CI, 0.83–1.06], respectively). Conversely, the risk of loco-regional recurrences increased significantly by 1.22-fold (95% CI, 1.04–1.43) with neoadjuvant treatment. This excess risk was most obvious in trials with excess adoption of radiotherapy without surgery in the neoadjuvant arms (1.53-fold [95% 1.11–2.10]). Treatment effects for the main clinical outcomes did not show any significant between-study heterogeneity. Conversely, there was statistically significant heterogeneity across studies ($p < 0.001$) in the rates of complete clinical response, while rates of pathological response were typically low, with some variability across studies (range, 4–29%). Rates of adoption of conservative local treatment also differed significantly across trials (range 28–89% in neoadjuvant arms, heterogeneity $p < 0.001$). In the face of this evidence, neoadjuvant treatment seems equivalent to adjuvant treatment in terms of survival and overall disease progression. With neoadjuvant treatment there is a significant increase in the risk of loco-regional recurrence, especially when radiotherapy without surgery is adopted. The results will have to be interpreted also in the context of ongoing and recently accumulated evidence in the field using different systemic regimens with potentially different response and clinical outcome profiles.

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Breast conservation – why still a challenge?

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Standard therapy for early stage breast cancer is based on conservation of the involved breast. There has been sufficient progress in technique that most women with breast cancer will survive free of recurrent disease and have minimal sequelae of either the disease or its treatment. Although this outcome can be had for most, there exist a great number of women for whom this outcome is not achieved.

What are the challenges to breast conservation that remain, and how can they best be addressed?

- Large tumors still present and pose a challenge to breast conservation. Neoadjuvant therapy will allow many of these tumors to be downstaged to a degree that breast conserving therapy [BCT] is possible. Improved imaging with MRI and ultrasound, when the extent of tumor is not clear from mammography and physical examination, allows pre-operative planning to be more precise and localization to be provided to the surgeon as required. The neoadjuvant therapy can be tailored to the biology of the tumor for optimal reduction in size.
- Premalignant lesions can be present throughout the breast, e.g. ALH, ADH, DCIS, and pose the risk for new invasive carcinoma arising in the years following initial treatment. These must be encompassed in the original treatment plan to make BCT worthwile.
- Technique is essential to obtaining the best cosmetic outcome. This involves initial needle biopsy for diagnosis, placement of the incision for tumor resection, limited margins in small breasts with orientation of each surface to allow re-excision of a margin if too close, rather than wider reexcision of the cavity, oncoplastic revision if required, and marking of the tumor bed for tailoring of the irradiation dose.
- Defined genetic risk, e.g. BRCA1 and BRCA2, pose additional concerns and BCT must be approached in light of a comprehensive plan for management of the ovaries, and prophylactic agents to lower breast cancer risk.
- The late risks of radiation therapy include increased cardiovascular deaths and increased risk of contralateral breast cancer and lung cancer. These must be considered in light of fewer breast cancer deaths for a net of no additional deaths overall.
- Superb reconstructions with skin sparing techniques permit a superb cosmetic outcome for women who desire or require mastectomy. For women who are unhappy with the appearance of their breasts, this may cause mastectomy and reconstruction to be a more appealing choice than BCT. Recent studies suggest that some women may accept BCT because of the enthusiasm of the medical team rather than their own desire for breast conservation.
- Prior breast augmentation offers special challenges that make BCT more complex, but do not prevent it.

Breast cancer arises from differing mechanisms. Increasing knowledge of the genomic perterbations of a specific tumor allow systemic treatment to be tailored to the biologic specifics of the tumor. Even tumors with aggressive genotypes appear to be eliminated [98–99% free of distant disease at ten years] if found by screening, when still very small. Hormonal therapy alone appears to be as effective as cytotoxic chemotherapy for at least half of the women with node negative cancers that express hormone receptors and have appropriate genotype [Oncotype and other assays]. In an analagous fashion the specific desires and philosophy of a carefully informed patient must trump the general philosophy or any treatment algorithm of her breast center team and the treatment tailored to her choices.