Prognostic factors in breast cancer: Which patients should receive adjuvant systemic therapy?

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Clinical problems in breast cancer treatment

• Which patients should receive adjuvant systemic treatment
• What is optimal locoregional treatment for individual patients (example: breast conserving therapy vs mastectomy)
• Can the sensitivity of tumors to specific drugs be predicted?
• Which carcinomas in situ are “dangerous”; which are not

Genetic alterations in breast cancer

• Are starting to show us how breast cancer develops

however

• Not many clinically useful prognostic and predictive factors have been identified yet.

Tumor cell behavior is determined by the activity of many genes

• The activity of one or a few genes cannot predict tumor cell behavior in a reliable way.

• Gene expression profiling (if anything) is expected to provide new prognostic and predictive profiles

Decisions on adjuvant systemic treatment for breast cancer patients

• Who should be treated
• What treatment should be given

From: Polychemotherapy for early breast cancer: an overview of the randomised trials
Early Breast Cancer Trialists' Collaborative Group; Lancet, 1998
2008: Clinicopathological factors used to guide adjuvant systemic treatment:

- Age
- Lymph node status
- Tumor size (>1 cm: most patients in the USA receive adjuvant systemic treatment)
- ER status (USA: most ER+ patients receive adjuvant hormonal therapy)

Gene expression profiling: Frozen tumor material is needed

- Surgical excision
- Fine Needle Aspirate
- Core Needle Biopsy

Spots of microarray

One spot = Many copies of one gene

Determining gene activity with microarrays

Analysis of gene expression in breast cancer

Scanned image of a flexjet 25,000 gene human microarray

Hybridized with mixture of 'red'-labeled cRNA of a tumor sample and 'green'-labeled reference cRNA
Analysis of gene expression data

- Unsupervised classification
  - 2D Hierarchical cluster analysis
- Supervised classification
  - “gene by gene”
- Applying gene expression signatures
  - i.e. “proliferation signature”, etc

Cohort of 295 consecutively treated breast cancer patients

- Stage I and II breast cancer
- 151 lymph node negative; 144 lymph node positive patients
- Age <53 years

Perou et al., Nature 2000
Supervised Classification for Prognosis

- 78 breast tumors
  - patients < 55 years
  - tumor size < 5 cm
  - lymphnode negative (LN0)

Prognosis Reporter Genes

- distant metastasis < 5 years (n=34)
- no distant metastasis > 5 years (n=44)

Validation series; n=295 (stage I and II)

Metastasis-free probability and overall survival for the whole cohort

Wound Response Signature

- In vitro Wound Model – 516 genes
- Prognostic Significance in
  - Breast
  - Lung
  - Gastric cancer

* Iyer et al. Science 1999 83-7
Chang et al. PLoS Biology 2004 Feb 2 2 1-9
Chang/Nuyten et al. PNAS 2005 March 8 102 10 3738 - 3743

Three Breast Cancer Studies Used To Select 21 Gene Panel
16 Cancer and 5 Reference Genes

- Best RT-PCR performance and most robust predictions
Current Status of Micro-Array Prognosis Prediction in Breast Cancer

- 70-genes (Mammaprint®)
- 76-genes (Rotterdam)
- 21-genes (Oncotype DX®)
- Intrinsic Genes (Perou, Sorlie)
- Wound Signature (Chang, Nuyten)

High Concordance in Signatures

RASTER study

MicroarRAy prognoSTication in breast cancER

- Technology introduction program for 70 gene prognosis profile
- T1/2 N0 patients <60 years
- 16 participating hospitals

Standardizing methods to obtain tumor for gene expression profiling

RNA later
RASTER study

Patient inclusion: 2004-2006

- Patients included: 812 (100%) [mean age 48 yrs (range 27-60)]
- 70-gene expression profiles: 427 (53%)
  - Poor profile: 208 (49%)
  - Good profile: 219 (51%)
- Exclusion: 385 (47%)

Clinical profile (CBO) vs. 70-gene profile

Discordant risk profiles: 30%

<table>
<thead>
<tr>
<th></th>
<th>70-gene signature</th>
<th>Clinical CBO high risk</th>
<th>Clinical CBO low risk</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>167 (39%)</td>
<td>76 (18%)</td>
<td>243 (57%)</td>
<td></td>
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<tr>
<td>High risk</td>
<td>219 (51%)</td>
<td>132 (31%)</td>
<td>184 (43%)</td>
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</tr>
<tr>
<td>Total</td>
<td>386 (100%)</td>
<td>208 (49%)</td>
<td>427 (100%)</td>
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EORTC-BIG MINDACT TRIAL DESIGN
6,000 Node negative women

 Evaluate Clinical-Pathological risk and 70-gene signature risk

- 55%  32%  13%

Gene expression profiling in “basal type” tumors

- Breast tumors selected based on IHC:
  - ER-, PR-, HER2-
- 99 patients
- Gene expression profiling
- IHC
  - p53, KRT5/6, c-KIT, EGFR
- For 70 patients with >5 year FU: survival analysis

Kaplan Meier curve (n=70)

- Almost all ER-negative tumors have a 70 gene poor prognosis profile
- Patients with ER-negative tumors have ~60-70 survival
- Additional prognostic factors are needed in ER-negative breast cancer
Clustering filtered gene set expression compared to group mean

Conclusions

- Gene expression profiling and other genetic techniques are helping to discover novel predictive tests
- These tests will help in guiding adjuvant systemic treatment

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