Unfavourable factors in older women with clinically favourable breast cancer
A clinical prediction model for recurrence

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SIOG
Breast cancer in the elderly

- Treatment recommendations are largely based on trials performed in younger patients
  - Selective inclusion
  - Limited generalizability

- Observational studies

Biganzoli et al. Lancet Oncology 2012; van de Water et al. JNCI 2014
Overtreatment vs. Under-treatment

Treatment efficacy

Treatment tolerability
- Treatment toxicity
- General life expectancy
- Quality of Life
- Patient preferences
• However: Adjuvant! Online does not adequately predict overall survival and recurrence in older breast cancer patients

De Glas et al., Lancet Oncology 2014
Probability of cancer specific death: Competing risks

- Older early breast cancer patients are at higher risk of non-cancer mortality than breast cancer mortality
  → risk on non-cancer mortality increases with age

Objective

- To identify predictive factors for recurrence in older women with clinically favourable breast cancer

→ To create a tool to help select patients with a relatively good and worse prognosis, to base individual treatment recommendations on
Methods

• Netherlands Cancer Registry:
  • All consecutive breast cancer patients diagnosed between 2003-2006
  • Age 65 years and older
  • Clinically negative axillary lymph nodes
    • Clinical examination and/or ultrasound
  • Max. tumour size 5 cm
  • Breast surgery
Primary endpoint

• Recurrence
  • Local recurrence (in-breast)
  • Regional recurrence (axillary or supraclavicular lymph nodes)
  • Distant metastases
Statistics

- Fine and Gray regression analysis
  - Takes into account competing risk of mortality
  - Deceased patients are not at risk for recurrence any more
  - To prevent overestimation of the effect in prediction
Model building

- Candidate predictors:
  - pT
  - Grade
  - Morphology (ductal/lobular/mixed/other)
  - Multifocality
  - Estrogen Receptor (ER)
  - Progesterone Receptor (PR)
  - Human Epidermal growth factor-2 (HER2)

- Backward elimination at p-level <0.05
Validation

- Discrimination: ROC curve
  - Area Under the Curve (AUC)

- Internal validation
  - Bootstrapping (1000x)

- External validation
  - FOCUS cohort:
    - All consecutive older breast cancer patients in the Leiden region, diagnosed between 1997-2002
    - Same inclusion criteria
Results

• Development cohort: 9,183 patients

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>5,655</td>
<td>61.6%</td>
</tr>
<tr>
<td>75 or older</td>
<td>3,528</td>
<td>38.4%</td>
</tr>
<tr>
<td><strong>pT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>5,816</td>
<td>63.3%</td>
</tr>
<tr>
<td>T2</td>
<td>3,367</td>
<td>36.7%</td>
</tr>
<tr>
<td><strong>pN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>6,646</td>
<td>72.4%</td>
</tr>
<tr>
<td>N1</td>
<td>1,819</td>
<td>19.8%</td>
</tr>
<tr>
<td>N2</td>
<td>294</td>
<td>3.2%</td>
</tr>
<tr>
<td>N3</td>
<td>127</td>
<td>1.4%</td>
</tr>
<tr>
<td>Missing</td>
<td>297</td>
<td>3.2%</td>
</tr>
</tbody>
</table>
## Treatment

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCS</td>
<td>4,564</td>
<td>49.7%</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>4,619</td>
<td>50.3%</td>
</tr>
<tr>
<td>None</td>
<td>274</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Axillary surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sentinel node</td>
<td>4,704</td>
<td>51.2%</td>
</tr>
<tr>
<td>ALND</td>
<td>4,136</td>
<td>45.0%</td>
</tr>
<tr>
<td>unknown</td>
<td>69</td>
<td>0.8%</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>327</td>
<td>3.6%</td>
</tr>
<tr>
<td><strong>Endocrine therapy for ER+</strong></td>
<td>2700</td>
<td>43.6%</td>
</tr>
</tbody>
</table>

BCS: breast conserving surgery
ALND: axillary lymph node dissection
## Final model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/10</td>
<td>1.12 (1.01-1.24)</td>
</tr>
<tr>
<td>T1</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>T2</td>
<td>1.90 (1.64-2.20)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1.83 (1.46-2.30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2.52 (1.97-3.24)</td>
</tr>
<tr>
<td>Multifocality</td>
<td>1.24 (1.01-1.54)</td>
</tr>
<tr>
<td>ER negative</td>
<td>1.39 (1.11-1.72)</td>
</tr>
<tr>
<td>PR negative</td>
<td>1.56 (1.27-1.92)</td>
</tr>
</tbody>
</table>

**Hazard Ratio**
Internal validation

Discrimination

AUC: 0.691

AUC: 0.691 (95% CI 0.686-0.696)
External validation
Discrimination

AUC: 0.680
Internal validation

Calibration

Observed cumulative incidence at 5 years

Predicted cumulative incidence at 5 years
Internal validation
Calibration

Observed cumulative incidence at 5 years vs. Predicted cumulative incidence at 5 years.
External validation

Calibration

Observed cumulative incidence at 5 years vs. Predicted cumulative incidence at 5 years.
Conclusion

• With this model including
  • Age
  • Tumour size (T stage)
  • Histological grade
  • Multifocality
  • ER
  • PR

... we can adequately predict breast cancer recurrence in older, clinically node negative, breast cancer patients, *without* information from axillary surgery
Discussion

Interpretation

• First step in prediction of recurrence in older breast cancer patients

• In this model, no additive predictive value of HER2 or morphology
  • Further research
Discussion

Limitations

• Most patients did receive axillary surgery (51% SNLB, 45% ALND)

• \( pT \) in model
  • all patients had breast surgery
    → future: incorporate clinical stage (risk prediction prior to breast surgery)

• No clinical geriatric parameters in model
  • Impact on competing risk of mortality

• Discrimination vs. Calibration
  • Underestimation of the absolute risk in external validation set
Discussion

Future

• Development of model including patient characteristics and molecular tumour characteristics

• To predict who will die from the tumour and who will die with the tumour
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