Prognostic value of ER, PR, and HER2 breast cancer biomarkers and AJCC’s TNM staging system on overall survival of Caucasian females with breast cancer – an institution’s 10 year experience

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Introduction

**ANATOMIC STAGE • PROGNOSTIC GROUPS**

<table>
<thead>
<tr>
<th>GROUP</th>
<th>T</th>
<th>CLINICAL</th>
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<th>M</th>
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<td>N1**</td>
<td>M0</td>
<td></td>
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<tr>
<td>IB</td>
<td>T0</td>
<td>N1**</td>
<td>M0</td>
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<td>M0</td>
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<tr>
<td>III</td>
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<td>N1</td>
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<tr>
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<td>Stage IIIC</td>
<td>T4</td>
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<td>M0</td>
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</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N</td>
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* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IA and are classified Stage IB.

<table>
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<td>Stage IV</td>
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<td>M1</td>
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Introduction

- Measuring the Estrogen Receptor (ER), Progesterone Receptor (PR) and Epidermal Growth Factor Receptor 2 (HER2) is standard of care for breast cancer management\(^1\)

- **Recent Proposals:** Inclusion of biomarkers into the TNM system (bTNM) improves the TNM accuracy for staging, prognosis, and treatment\(^2-4\)

Introduction

• Our initial study\(^5\) on 595 Caucasian patients with invasive breast carcinoma (2000-2004):
  • TNM status and age were significant predictors of overall survival
  • ER/PR/HER2 expressions were not predictive when using the St. Gallen five-group ER/PR/HER2 subtype classification\(^6\).

Introduction

• Our recent study: What is the relevance of the tumor biomarkers in the recently proposed bTNM classification system in which the inclusion of triple negative ER/PR/HER2 phenotype (TNP) could improve the prognostic accuracy of TNM?

• One of our ongoing studies: Can classification system that uses only ER biomarker status, but also incorporates grade into the TNM stage improve prognostic accuracy of TNM?

Methods (TNP vs nonTNP)

- From 791 Caucasian women diagnosed with primary invasive ductal carcinoma from 1/1998-7/2008 (10 year period) 782 patients had complete data on TNM stage

- Patients were categorized according to their TNM stage and TNP vs. non-TNP phenotype

- The Overall Survival (OS) was measured comparing these categories using Kaplan Meier curves and Cox regression analysis
Biomarkers and TNM Stage

Stage IV

Stage III

Stage II

Stage I

782 F with IDC

NonTNP
306 (81.6%)

TNP
69 (18.4%)

NonTNP
239 (79.6%)

TNP
61 (20.3%)

NonTNP
62 (73%)

TNP
23 (27%)

NonTNP
19 (86.3%)

TNP
3 (13.6%)
Clinico-pathologic characteristics of patients with IDC when divided by the TNM stage and TNP and Non-TNP ER/PR/HER2 phenotype

<table>
<thead>
<tr>
<th>Stage</th>
<th>Phenotype</th>
<th>Age*</th>
<th>Grade**</th>
<th>Nottingham Score**</th>
<th>Size (mm)*</th>
<th>Survival months*</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Non-TNP</td>
<td>60.8</td>
<td>1</td>
<td>6</td>
<td>11.9</td>
<td>96.4</td>
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<tr>
<td>Stage I</td>
<td>TNP</td>
<td>56.4</td>
<td>3</td>
<td>8</td>
<td>12.1</td>
<td>98.4</td>
</tr>
<tr>
<td>Stage II</td>
<td>Non-TNP</td>
<td>57.8</td>
<td>2</td>
<td>7</td>
<td>26.1</td>
<td>96.0</td>
</tr>
<tr>
<td>Stage II</td>
<td>TNP</td>
<td>52.5</td>
<td>3</td>
<td>8</td>
<td>28.7</td>
<td>93.3</td>
</tr>
<tr>
<td>Stage III</td>
<td>Non-TNP</td>
<td>56.7</td>
<td>3</td>
<td>8</td>
<td>36.9</td>
<td>78.9</td>
</tr>
<tr>
<td>Stage III</td>
<td>TNP</td>
<td>54.8</td>
<td>3</td>
<td>8</td>
<td>39.6</td>
<td>64.1</td>
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<tr>
<td>Stage IV</td>
<td>Non-TNP</td>
<td>61.4</td>
<td>2</td>
<td>7</td>
<td>28.3</td>
<td>27.7</td>
</tr>
<tr>
<td>Stage IV</td>
<td>TNP</td>
<td>47.6</td>
<td>3</td>
<td>8</td>
<td>16.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

**Table legend:** * = mean value; ** = most frequent
Kaplan Meier Survival Curves

Note: + = Censored
Cox Regression Analyses

TNM

bTNM
Summary of Results

• TNM stage and age are predictive of OS
  Stage II = HR 1.41, 95%CI 1.01-1.97
  Stage III = HR 3.96, 95%CI 2.68-5.88
  Stage IV = HR 27.25, 95%CI 16.84-44.08

  Age = HR 1.05, 95%CI 1.04-1.06

• Adding TNP to TNM staging is predictive of OS only for higher TNM stages
  Stage III=HR 3.08, 95%CI 1.88-5.04
  Stage IV=HR 24.36, 95%CI 13.81-42.99

• No significant effect on TNM Stages I and II
Biomarkers with St. Gallen’s Groups

782 F with IDC
St. Gallen’s grouping

Group 1
Luminal A-like
ER or PR+, HER2- Ki-67<14%
205 (26.2%)

Group 2
Luminal B/HER2- like
ER or PR+, HER2- Ki-67≥14%
240 (30%)

Group 3
Luminal B/HER2+ like
ER or PR+, HER2+ Any Ki-67
96 (12.2%)

Group 4
HER2+ /nonluminal-like
ER-/PR-, HER2+ Any Ki-67
84 (10.7%)

Group 5
Triple negative
ER-/PR-, HER2- Any Ki-67
156 (19.9%)
Kaplan-Meier curve

St. Gallen’s Groupings
Cox Regression Analysis

St. Gallen’s Groupings
Summary of Results
St. Gallen ER/PR/HER2 grouping

- The St. Gallen ER/PR/HER2 grouping had no significant impact on survival regardless of TNM stage or age
ER, Grade and TNM stage

Incorporation of grade and ER status to pathologic TNM stage

ER, Grade and TNM stage

Incorporation of grade and ER status to pathologic TNM stage\(^8\)

Final score = ER + Grade + Stage -> 0-4

- **ER**
  - ER+ = 0
  - ER- = 1

- **Grade**
  - Grade 1 & 2 = 0
  - Grade 3 = 1

- **Stage**
  - Stage I = 0
  - Stage IIA & IIB = 1
  - Stage IIIA = 2

Patients characteristics for Final Score
ER + Grade + Stage

<table>
<thead>
<tr>
<th>Final score</th>
<th>Total (N)</th>
<th>Dead (N)</th>
<th>Alive (N)</th>
<th>% Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>387</td>
<td>58</td>
<td>329</td>
<td>85%</td>
</tr>
<tr>
<td>1</td>
<td>326</td>
<td>64</td>
<td>262</td>
<td>80.4%</td>
</tr>
<tr>
<td>2</td>
<td>233</td>
<td>48</td>
<td>185</td>
<td>79.4%</td>
</tr>
<tr>
<td>3</td>
<td>136</td>
<td>31</td>
<td>105</td>
<td>77.2%</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>14</td>
<td>12</td>
<td>46.2%</td>
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<tr>
<td>Overall</td>
<td>1108</td>
<td>215</td>
<td>893</td>
<td>80.6%</td>
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</table>
Kaplan Meier curve, OS
ER+Grade+Stage Scoring system
<table>
<thead>
<tr>
<th></th>
<th>Total (N)</th>
<th>Dead (N)</th>
<th>Alive (N)</th>
<th>% Survival</th>
</tr>
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<tr>
<td><strong>ER</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>936</td>
<td>216</td>
<td>720</td>
<td>76.9%</td>
</tr>
<tr>
<td>1</td>
<td>284</td>
<td>69</td>
<td>215</td>
<td>75.7%</td>
</tr>
<tr>
<td><strong>Grade</strong></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>775</td>
<td>164</td>
<td>611</td>
<td>78.8%</td>
</tr>
<tr>
<td>1</td>
<td>470</td>
<td>127</td>
<td>343</td>
<td>73%</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>584</td>
<td>90</td>
<td>494</td>
<td>84.6%</td>
</tr>
<tr>
<td>1</td>
<td>452</td>
<td>96</td>
<td>356</td>
<td>78.8%</td>
</tr>
<tr>
<td>2</td>
<td>101</td>
<td>38</td>
<td>63</td>
<td>62.4%</td>
</tr>
</tbody>
</table>
Final score

p = 0.63

ER

p < 0.001

Stage

p = 0.008

Grade
Summary for ER + Grade + Stage

- Final score (p=0.014)
  - Patients with the highest score (score 4) are 8.53x more likely to die than score 0 (95% CI 1.54-47.26)

- Cox regression: ER, Grade and Stage: only stage predicts for survival
  - Stage score 1 – HR 1.39 (95% CI 1.03 – 1.87)
  - Stage score 2 – HR 3.06 (95% CI 2.07 – 4.52)
Summary of Results

- TNM stage and age are predictive of OS
- Adding TNP to TNM staging is predictive of OS only for higher TNM stages (stage III and IV) but had no significant effect on TNM stages I and II
- The St. Gallen ER/PR/HER2 grouping had no significant impact on survival regardless of TNM stage or age
- ER alone and in combination with grade have no significant impact on survival; Stage is the only predictor of survival in this model
Conclusions

• Our data support the traditional, current TNM staging as a continued relevant predictive tool for breast cancer outcomes.

• Our results also suggest that biomarkers are relevant predictors of outcomes, but they primarily improve the accuracy of TNM staging in more advanced stages of breast cancer.

• In early stage breast cancer (Stage I and Stage II) the ER/PR/HER2 status had no significant impact on survival outcomes.
Conclusions

We propose that systematic analysis addressing issues such as:

1) Classification system(s) used for determining the ER/PR/HER2 subtypes

2) Characteristics of populations studied (Caucasians, minorities, etc.)

3) Consistency in choosing the time periods in which studies are conducted should be performed perhaps both nationally and internationally before biomarkers are fully incorporated into the TNM staging system (bTNM).
Collaborators

- **Surgical Oncology**
  - John Bell, MD, Professor of Surgery, Director of UTMCK Cancer Institute
  - James McLoughlin, MD, Associate Professor of Surgery

- **Oncology**
  - Timothy Panella, MD, Associate Professor of Oncology

- **Graduate School of Medicine**
  - Robert E Heidel, PhD, Statistician

- **Pathology**
  - Jason Chen, MD, Pathology Resident

- **Pathology – Outside Learners Program**
  - Avanti Rangnekar and Prathmesh Desai, Farragut High School and Dept. of Pathology Collaborative Science-Research Program
  - Christina Geddam MD, Research Volunteer
  - Megan McNeil, Parks Scholar, North Carolina State University
References


Thank you 😊