The Role of the Oncotype DX® Breast Cancer Assay in the Neoadjuvant Setting
Neoadjuvant Therapy and Oncotype DX®

Case Study: Neoadjuvant Therapy

Neoadjuvant Therapy in Breast Cancer

Role of Oncotype DX in Clinical Decision Making

Can Oncotype DX Be Performed with Core Biopsies?

Case Study Resolution: Neoadjuvant Therapy
Case Study: Could this Patient Benefit from Neoadjuvant Therapy?

Patient WN (62 years old)

Medical history
- Lobular carcinoma in the right breast

Findings
- Vague, poorly demarcated abnormality MRI (5.5 cm)
- Tumor is ER+/PR+/HER2- (needle core biopsy)

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<td>Tumor size</td>
<td>5.5 cm</td>
</tr>
<tr>
<td>Tumor grade</td>
<td>N/A</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>No palpable adenopathy</td>
</tr>
<tr>
<td>ER/PR status</td>
<td>ER+/PR+</td>
</tr>
<tr>
<td>HER2 status</td>
<td>Negative</td>
</tr>
<tr>
<td>Oncotype DX® Recurrence Score®</td>
<td>10</td>
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• Patient WN expressed a desire for breast conservation, but her tumor is of large size.
• Could this patient benefit from neoadjuvant therapy, thus making breast-conserving surgery a possibility?
• What information can the Oncotype DX Recurrence Score provide to guide neoadjuvant treatment decisions?
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Comparison Between Neoadjuvant and Adjuvant Therapies: Risks and Benefits

- Disease-free survival (DFS) and overall survival (OS) are equivalent in patients treated with the same adjuvant or neoadjuvant chemotherapy regimen.¹

- Neoadjuvant therapy has the following clinical advantages:²
  - Improves surgical options
  - Response to neoadjuvant therapy is a predictor of long-term outcome
    - Pathologic CR correlates with improved DFS and OS
  - Neoadjuvant therapy can be offered to candidates for adjuvant therapy, regardless of tumor size

- Neoadjuvant therapy is also associated with significantly increased risk of loco-regional disease recurrence, especially when radiotherapy without surgery was used.¹

Appropriately Selected Neoadjuvant Therapies Can Improve Surgical Outcomes

• For postmenopausal women with hormone receptor-positive disease, neoadjuvant therapy with anastrozole or letrozole provided objective response and superior rates of breast conserving surgery\(^1,2\)

• For women with operable breast cancer, pre-operative anthracycline-based neoadjuvant chemotherapy allowed significantly higher rates of breast-conserving surgery, compared with post-operative chemotherapy (68% vs. 60%, \(P=0.002\))\(^3\)

• Women with HER2-positive tumors who added trastuzumab to neoadjuvant chemotherapy had an increase in pCR rate (65% vs. 26%; \(p=0.016\))\(^4\)

NCCN Guidelines Recommend that Neoadjuvant Therapy Be Considered to Improve Surgical Options in Candidates for Adjuvant Therapy

• Neoadjuvant therapy may improve resection options in patients with locally advanced breast cancer
  – To allow for breast conserving surgery or to make inoperable tumors resectable

• Recommended adjuvant regimens are appropriate to consider in the neoadjuvant setting
  – (e.g., endocrine therapy, trastuzumab, chemotherapy)

Pathologic Complete Response to Neoadjuvant Chemotherapy Is Correlated with Improved Disease-free and Overall Survival (NSABP B-27)

- There was no significant difference in overall survival (OS) between the treatment arms (data not shown).
- Pathologic CR (pCR) was a significant predictor of OS, regardless of treatment.
- How can we identify the patients most likely to have pCR to neoadjuvant chemotherapy?
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Gianni Neoadjuvant Study

Istituto Nazionale Tumori (Milan, Italy)

N=89 women with locally advanced breast cancer

- Core biopsy
  - For RT-PCR analysis

- Primary chemotherapy
  - doxorubicin/paclitaxel x 3 → paclitaxel x 12

- Surgery
  - For pathology determination of pCR

- Adjuvant chemotherapy
  - IV CMF q 4 weeks x 4

- RT +/- hormonal therapy

Patients with a Low Recurrence Score® Are Less Likely to Respond to Neoadjuvant Anthracycline-Taxane Treatment

N=89

P=0.005

Chang Neoadjuvant Study

Baylor College of Medicine (Houston, TX)

- N=97 women with locally advanced breast cancer enrolled in 3 phase II studies of neoadjuvant docetaxel
  - Core biopsies (10 µm sections x 3) were obtained before neoadjuvant treatment with single agent docetaxel (100 mg/m2 q3wks) for 4 cycles

- 81 patients had adequate tumor tissue (≥5% tumor)
  - 80 had adequate RNA and expression signal
    - 72 had response data (RECIST)

Patients with Low Recurrence Scores® Are Less Likely to Experience a Clinical Complete Response to Chemotherapy

<table>
<thead>
<tr>
<th>Recurrence Category</th>
<th>Clinical Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Low risk (RS &lt; 18)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intermediate risk (RS 18-30)</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>High risk (RS ≥ 31)</td>
<td>9 (21.4%)</td>
</tr>
</tbody>
</table>

Patients with a Low Recurrence Score® Are Less Likely to Respond to Neoadjuvant Docetaxel

N=72

Akashi Neoadjuvant Study

National Cancer Center Hospital (Tokyo, Japan)

- N=87 postmenopausal women with operable ER and PR positive breast tumors >3 cm who received neoadjuvant endocrine therapy (anastrozole or tamoxifen x 4 months)
  - Recurrence Score® determined from pre-treatment core biopsy specimens (10 3-µm sections and 2 hematoxylin and eosin sections from each core needle biopsy)

- Primary tumors were clinically assessed by measuring their size in 2 dimensions with calipers (WHO response criteria)

- Relapse-free survival was defined as time from the initiation of treatment to local, regional, or distant treatment failure

The Recurrence Score® Predicts Response to Neoadjuvant Endocrine Treatment

Clinical Response Rate by Recurrence Score (RS)

<table>
<thead>
<tr>
<th>Neoadjuvant treatment</th>
<th>RS &lt;18</th>
<th>RS 18-30</th>
<th>RS ≥31</th>
<th>N</th>
<th>P value trend</th>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>2 (67%)</td>
<td>2 (33%)</td>
<td>2 (40%)</td>
<td>14</td>
<td>0.53</td>
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<tr>
<td>Anastrozole</td>
<td>5 (63%)</td>
<td>3 (30%)</td>
<td>3 (27%)</td>
<td>29</td>
<td>0.13</td>
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<tr>
<td>All</td>
<td>7 (64%)</td>
<td>5 (31%)</td>
<td>5 (31%)</td>
<td>43</td>
<td>0.11</td>
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</tbody>
</table>

- Low RS tended to have better clinical response than intermediate and high RS
- RS tended to predict response both in tamoxifen and anastrozole groups
- Low RS tended to have better relapse-free survival than intermediate and high RS (5-year RFS: 100% vs. 84% and 73% respectively)

Exploratory Neoadjuvant Studies Are Consistent with Adjuvant Studies

The lower the Recurrence Score:
• The lower the benefit of chemotherapy
• The greater the benefit of endocrine therapy

The higher the Recurrence Score:
• The greater the benefit of chemotherapy
• The lower the benefit of endocrine therapy
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Case Study Resolution: Neoadjuvant Chemotherapy
Can Oncotype DX® Be Performed in Tumor Tissue from Core Needle Biopsies?

Tumor blocks from 8 patients

Core samples (0.6 mm) taken:
- Day 1: Core 0
- Later day: Cores 1, 2, and 3

Whole sections (5 mm) taken:
- Later day: Whole sections 1 and 2

RT-PCR analysis

### Strong Correlation Between the Recurrence Score® From Cores and Whole Sections*

<table>
<thead>
<tr>
<th>Patient ID No.</th>
<th>Recurrence Score</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Core 0</td>
<td>Core 1</td>
<td>Core 2</td>
<td>Core 3</td>
<td>Section 1</td>
<td>Section 2</td>
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<tr>
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<td>22</td>
<td>36†</td>
<td>27†</td>
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*In appropriately sampled tumors; †Cores 2 and 3 of Patient 104 were not taken in areas of enriched tumor

- The Recurrence Score results measured in core biopsies were consistent with results in whole sections.
- In all cases, intra-patient Recurrence Score results were similar in the two whole sections.
- In most cases, intra-patient core Recurrence Score results were similar to each other and to whole section Recurrence Score results.

Core Biopsy Experience at Genomic Health

>97% of Core Biopsies Generate Successful Reports

- From July 15, 2005 through May 31, 2009, there were 103,863 submissions to the clinical laboratory
  - 11,757 core biopsies (11.3%)
- Initial submission success rate
  - Surgical resections: 95.7% (4.3% failure rate)
  - Core biopsies: 91.6% (8.4% failure rate)
  - Most common reason for initial failure was insufficient tumor or no tumor found
- High resubmission rate for failures > 80%
- Success rate on resubmitted samples was > 80% for core biopsies and surgical resections
- Overall success rate was >97% for core biopsies and surgical resections

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Patient Case submitted by Dr. Pat Whitworth, Director Nashville Breast Center, Nashville, Tennessee.
Case Study: Recurrence Score® of 10 is in the Low-risk Range

**RESULTS**

Recurrence Score = 10

**CLINICAL EXPERIENCE**

Patients with a Recurrence Score of 10 in clinical validation study had an Average Rate of Distance Recurrence at 10 years of 6.9% (95% CI: 4.4%, 9.3%)
Case Study: The Recurrence Score® Helps this Patient Choose a Treatment Plan

• Patient WN has a strong preference for breast-conserving surgery.

• Her Recurrence Score of 10 indicates that she is more likely to respond to neoadjuvant endocrine therapy and less likely to respond to neoadjuvant chemotherapy than would a patient with a high score.

• Based on this, patient WN chooses neoadjuvant endocrine therapy.
Oncotype DX® Can Play an Important Role When Determining Neoadjuvant Therapy

• Neoadjuvant therapy has an increasingly important role in treatment of ER+ breast cancer

• Oncotype DX Recurrence Score® has predictive value that can help in selecting the most appropriate neoadjuvant therapy
  – Benefit of neoadjuvant chemotherapy in high Recurrence Score group
  – Benefit of neoadjuvant endocrine therapy in low Recurrence Score group

• Oncotype DX may help physicians and patients assess the benefit of neoadjuvant therapy options