Breast Imaging to Monitor the Response to Treatment

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OVERVIEW

- Conventional imaging methods for evaluating response (mammography and ultrasound)
- Emerging role of MRI for monitoring treatment response
- Functional imaging methods as in-vivo biomarkers (DCE-MRI, PET)
Conventional imaging: agreement with pathological residual disease size

- No large prospective studies evaluating conventional imaging

- Small studies have shown variable results for agreement between imaging and pathology

- Retrospective analysis of conventional imaging and physical exam in MD Anderson neoadjuvant chemotherapy trials *(Chagpar et al, Ann Surg, 2006)*
  - Included a comparison of published studies
Conventional imaging for measuring treatment response
MD Anderson study

- 189 patients participating in 1 of 2 NACT trials

- Single direction tumor diameter measured by physical exam (PE), ultrasound (US) and/or mammography

- Residual disease size by imaging and physical exam compared to residual pathologic tumor size

Correlation of Tumor Measurements

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Preneoadjuvant Chemotherapy</th>
<th>Postneoadjuvant Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE vs. US</td>
<td>0.45</td>
<td>0.28</td>
</tr>
<tr>
<td>PE vs. M</td>
<td>0.40</td>
<td>0.26</td>
</tr>
<tr>
<td>US vs. M</td>
<td>0.58</td>
<td>0.35</td>
</tr>
<tr>
<td>PE vs. pathology</td>
<td>--</td>
<td>0.42</td>
</tr>
<tr>
<td>US vs. pathology</td>
<td>--</td>
<td>0.42</td>
</tr>
<tr>
<td>M vs. pathology</td>
<td>--</td>
<td>0.41</td>
</tr>
</tbody>
</table>

*Correlation Between Measurements*

* Spearman rank correlation coefficients.

PE indicates physical examination; US, ultrasonography; M, mammography

Only moderate correlation of imaging with pathologic residual disease, similar among imaging methods. Correlations between imaging measurements decreased from pre- to post-treatment.

Agreement with pathology by size category:
(0, 0.1-1.0, 1.1-2.0, > 2.0 cm)

<table>
<thead>
<tr>
<th>Clinical measurement</th>
<th>Weighted Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>0.24</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>0.30</td>
</tr>
<tr>
<td>Mammography</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Poor agreement between clinical measurements and pathologic measurements

*Chagpar et al, Ann Surg, 2006*
### False negatives and false positives rates

<table>
<thead>
<tr>
<th>Clinical measurement</th>
<th>False Positive Rate (%)</th>
<th>False Negative Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>20% (5/40)</td>
<td>57% (73/127)</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>65% (26/40)</td>
<td>10% (14/137)</td>
</tr>
<tr>
<td>Mammography</td>
<td>46% (16/35)</td>
<td>20% (24/119)</td>
</tr>
</tbody>
</table>

Ultrasound had highest rate of false positives; physical exam had highest rate of false negatives.

*Chagpar et al, Ann Surg, 2006*
Correlation with pathologic tumor size among other published studies

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Physical Exam</th>
<th>Ultrasound</th>
<th>Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fourouhi et al (1994)</td>
<td>35</td>
<td>0.88</td>
<td>0.96</td>
<td>0.94</td>
</tr>
<tr>
<td>Gawne-Caine et al (1995)</td>
<td>16</td>
<td>0.74</td>
<td>0.85</td>
<td>0.61</td>
</tr>
<tr>
<td>Herrada et al (1997)</td>
<td>100</td>
<td>0.73</td>
<td>0.60</td>
<td>0.65</td>
</tr>
<tr>
<td>Akashi-Tanaka et al (2001)</td>
<td>57</td>
<td>0.57</td>
<td>0.56</td>
<td>0.55</td>
</tr>
<tr>
<td>Fiorentino et al (2001)</td>
<td>141</td>
<td>0.68</td>
<td>0.29</td>
<td>0.33</td>
</tr>
<tr>
<td>Chagpar et al (2006)</td>
<td>189</td>
<td>0.42</td>
<td>0.42</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Correlation is highly variable among studies; close correspondence within studies.

*Chagpar et al, Ann Surg, 2006*
Accuracy of conventional imaging for estimating residual disease:

• Imaging correlation with pathology only fair \( (r^2 = .41-.42) \)

• No strong evidence that mammography or US perform significantly better than physical exam for measuring estimating residual disease after chemotherapy
  
  - Large prospective trials (NSABP B18, B27) have not incorporated imaging for measuring response, but have relied on physical exam
Breast MRI for assessing residual disease and response to treatment
Breast MRI for staging extent of disease pre-treatment

- MRI prior to chemotherapy has shown greater accuracy than mammography and ultrasound for estimating disease extent, particularly when multi-focal disease or DCIS is present
Example: patient with a palpable mass; dense breast; mammography shows a spiculated mass and area of suspicious calcifications
Hypo-echoic, spiculated mass on ultrasound
Multiple enhancing masses on MRI
Extensive multi-focal and multi-centric disease
Breast MRI for staging residual disease post-treatment

• MRI following chemotherapy is less effective, but still performs with greater accuracy than conventional imaging or clinical exam
MRI versus conventional imaging for estimating residual disease

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>MRI</th>
<th>Physical Exam</th>
<th>Mammo</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weatherall et al (2001)*</td>
<td>20</td>
<td>0.93</td>
<td>0.72</td>
<td>0.63</td>
<td>--</td>
</tr>
<tr>
<td>Rosen et al (2003)*</td>
<td>21</td>
<td>0.75</td>
<td>0.61</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Akazawa et al (2006)*</td>
<td>38</td>
<td>0.89</td>
<td>--</td>
<td>--</td>
<td>0.48</td>
</tr>
<tr>
<td>Montemurro et al (2005)*</td>
<td>21</td>
<td>0.82</td>
<td>--</td>
<td>--</td>
<td>0.71</td>
</tr>
<tr>
<td>Balu-Maestro et al (2002)†</td>
<td>51</td>
<td>63%</td>
<td>52%</td>
<td>38%</td>
<td>43%</td>
</tr>
<tr>
<td>Yeh et al (2005)†</td>
<td>31</td>
<td>71%</td>
<td>19%</td>
<td>26%</td>
<td>35%</td>
</tr>
</tbody>
</table>

*Comparison given by correlation coefficient.
†Comparison by concurrence criteria.

Consistent finding showing greater agreement of MRI with pathology compared to PE and conventional imaging.
• MRI is effective for measuring the degree of tumor response, but can miss residual disease, particularly for good responders
  

• Complete response on post-chemotherapy MRI cannot be used to rule out surgery
Disease extent after chemotherapy by MRI

Pre-chemo

Post-chemo
Dynamic contrast-enhanced (DCE) MRI

- T1-weighted imaging performed with injection of gadolinium-based contrast agent
- Time course of contrast enhancement analyzed to estimate pharmacokinetic parameters related to tumor permeability and blood volume ($k_{\text{trans}}$, $v_e$)
DCE-MRI combines anatomic staging with functional assessment

- **Pre-contrast $S_0$**
- **Early post-contrast**
- **Late post-contrast**

Permeability:
- **High**
- **Moderate**
- **Low**
MRI for Monitoring Response to Pre-operative Treatment

• MRI staging accuracy has led to increased interest in using MRI to assess response to treatment
  ⇒ Conventional imaging has not been fully explored in this role

• Functional information can be obtained as part of the clinical exam
  ⇒ No extra exams required
Tracking tumor change during treatment

Assess tumor size:

MRI before chemotherapy

MRI after 1 cycle of chemotherapy

MRI after full course of chemotherapy

Assess tumor vascularity:
Tumor response by MRI

- **Complete response** (Volume change = 100%)
- **Partial response** (Volume change = 69%)
- **Progressive disease** (Volume change = -178%)

Can greater accuracy in capturing size change lead to better survival stratification?
Measurements other than longest diameter may also be informative

- Tumor volume
- Tumor morphology
- Vascular heterogeneity
**Volumetric Size Assessment**

**BASELINE (pre-chemo):**
- Longest diameter = 1.9 cm
- Volume = 7.4 cc

**Change after 1 cycle AC:**
- Longest diameter = 2.0 cm
- Volume = 6.5 cc

**Change after 4 cycles AC:**
- Longest diameter = 1.4 cm
- Volume = 3.9 cc
Tumor Morphology

- **Baseline Imaging Patterns (IP)**

1 - 5:

% complete responders by IP

Breast conservation rates by IP

P<0.01
Heterogeneity of the microvasculature
ACRIN 6657
Prospective Imaging Trial as part of the I-SPY Collaboration

• The “I-SPY” trial combines serial imaging and tissue-based molecular markers for assessing response to pre-operative treatment

• ACRIN 6657 is testing MRI for measuring response to treatment
  – Compare to clinical response and path residual disease as a predictor of disease-free survival
  – Size is primary measurement; functional information about tumor vascularity also being explored
I-SPY Trial Design

- Patients enroll on both CALGB 150007 (tissue markers) and ACRIN 6657 (imaging)
- Tissue acquisition and imaging performed at comparable times during treatment
  - Pre-treatment, post 1 cycle anthracycline, between anthracycline and taxane regimens, and post-chemo
Functional imaging methods as in-vivo biomarkers (DCE-MRI, PET)
Functional MRI as an Imaging Biomarker

- Functional measurements by MRI (DCE-MRI, diffusion-weighted MRI, MR spectroscopy) can be used to make quantitative measurements of tumor biology (microvascular permeability, water diffusion, choline concentration)
DCE-MRI in Phase I trials

- A number of recent Phase I clinical trials have added DCE-MRI to measure effects of anti-angiogenic agents (Wedam et al, JCO 2006; O’Donnell et al, Br J Cancer 2005; Morgan et al, JCO 2003; Liu et al, JCO 2005)
  - Most found correlations of $k_{\text{trans}}$, $v_e$ with treatment response endpoints
  - Some mixed results; several evaluated MRI in multiple metastatic solid tumors; correlative studies - not powered to answer imaging question
  - Suggest potential for DCI-MRI as a biomarker of anti-tumor treatment
FDG PET to Monitor Response to Neo-Adjuvant Chemotherapy

<table>
<thead>
<tr>
<th>Time</th>
<th>SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Rx</td>
<td>5.7</td>
</tr>
<tr>
<td>2 months Rx</td>
<td>4.1</td>
</tr>
<tr>
<td>4 months Rx</td>
<td>3.3</td>
</tr>
</tbody>
</table>

*breast lesion*

*axillary node*
FDG PET to Monitor Breast Cancer Response to Therapy

(Wahl, J Clin Oncol 11:2101, 1993)
## Summary of Mid-Therapy Response Evaluation by PET

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Rx</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahl, 1993</td>
<td>11</td>
<td>AC</td>
<td>R: -48% SUV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR: -19% SUV</td>
</tr>
<tr>
<td>Bassa, 1996</td>
<td>15</td>
<td>FAC</td>
<td>All: -51% SUV</td>
</tr>
<tr>
<td>Schelling, 2000</td>
<td>24</td>
<td>EC or ET</td>
<td>mCR: -46% SUV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>not mCR: -8% SUV</td>
</tr>
<tr>
<td>Smith, 2000</td>
<td>30</td>
<td>CVAP</td>
<td>mCR: -86% SUV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>not mCR: -40% SUV</td>
</tr>
<tr>
<td>Mankoff, 2003</td>
<td>35</td>
<td>FAC or AC (weekly)</td>
<td>mCR: -65% MRFDG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR: -49% MRFDG</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR: -40% MRFDG</td>
</tr>
</tbody>
</table>
In Summary

• Conventional imaging has shown only fair accuracy for assessing response
  – Has not proven of greater accuracy than physical exam

• MRI establishing itself as a superior anatomic staging method, compared to mammography and ultrasound, for extent of primary tumor
  – Better agreement with pathology for residual disease assessment
  – Complete response by MRI cannot obviate surgery

• Functional imaging techniques (DCE-MRI, MRS, PET, Optical imaging) hold promise for in vivo assessment of tumor biology - but are still investigational