"A New, Semi-Automated Method of Grading Invasive and Non-Invasive Breast Carcinoma Using Image Analysis"

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Breast Cancer grading

Objectives

1. Why Grading is Important? History of grading breast cancer.
2. The current grading system. What is Wrong with the Current Grading Systems?
3. Can we Do Better? A new grading system
“Medical history teaches us where we come from, where we stand in medicine at the present time and in what direction we are marching. It is the campus that guides us into the future”

Henry Sigerist
HISTORY OF BREAST CANCER

- Ancient Civilizations
- Middle Ages
- The Renaissance
- Eighteenth Century
- Nineteenth Century
- Twentieth Century
HISTORY OF BREAST CANCER

• ANCIENT CIVILIZATIONS:
  – Chinese:
    • 2698 BCE  Huang Di - The yellow emperor
      – Wrote the first description of tumors
      – Described 5 forms of therapy: spiritual, diet, pharmacology, acupuncture and treatment of specific diseases.
  – Egyptians:
    • 2650 BCE  Imhotep -
      • physician, architect, astrologer
      – Designed the step pyramid
      – Described first documented case of breast cancer

HISTORY OF BREAST CANCER

• ANCIENT CIVILIZATIONS:
  – Babylonian:

• 1750 BCE first regulation of medical practice
  Description of physicians’ responsibilities and fees.
  “It was stated that “if the patient died or lost an eye
during surgery, the physician’s hands were cut off!!!”

– Classic Greek Period

• 460 BCE – 136 BC Hippocrates – 3 types of diseases
  Those curable by medicine
  Those curable by knife
  Those curable by fire
HISTORY OF BREAST CANCER

• ANCIENT CIVILIZATIONS:
  – **Greco-Roman Period**

• 1st century
  – *Leonides*:
    First operative treatment of breast cancer incision in healthy part of breast with multiple cauterization (stabbing) to kill the diseased part
HISTORY OF BREAST CANCER

• MIDDLE AGES and THE RENAISSANCE
  – Mastectomy procedures:
    • Use of sutures rather than cautery
  – Discovery of swollen glands (lymph nodes)
  – Invention of a device for amputation of breasts - Wilhelm Febry (Father of German Surgery)
HISTORY OF THE THERAPY OF BREAST CANCER

• **EIGHTEENTH CENTURY**
  – Guillotine machine for mastectomy.

• **NINETEENTH CENTURY**
  – Introduction of anesthesia and antiseptic techniques
  – Everard Home (1830) Described cancer cells under the microscope
  – Heinrich von Waldeyer-Hartz (1836): histologic classification of tumors
  – Victor Cornil (1837): Malignant transformation of acinar epithelium in breast
  – David von Hansemann (1896): loss of differentiation (anaplasia)
## HISTORY OF GRADING BREAST CANCER

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>~1900</td>
<td>Von Hansemann</td>
<td>Nuclear morphology and biologic behavior of tumor</td>
</tr>
<tr>
<td>1920’s and 1930’s</td>
<td>Greenhough</td>
<td>Relationship between histologic grade and survival</td>
</tr>
<tr>
<td>1928</td>
<td>Patey and Scarff</td>
<td>Highlighted importance of nuclear size, hyperchromasia and tubule formation</td>
</tr>
<tr>
<td>1950</td>
<td>Bloom</td>
<td>Well, mod, poorly diff Tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Tubule formation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Variations in nuclear size, shape and hyperchromasia (anaplasia)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Mitosis</td>
</tr>
</tbody>
</table>
## HISTORY OF GRADING BREAST CANCER

<table>
<thead>
<tr>
<th>Year</th>
<th>Developer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957</td>
<td>Bloom &amp; Richardson</td>
<td>Numeric scoring system for grading (3-9) Adopted by WHO in 1968</td>
</tr>
<tr>
<td>1975</td>
<td>Black et al</td>
<td>5-tier nuclear grading system Reduced to 3-tier by Fisher et al in 1980</td>
</tr>
<tr>
<td>Early 1990’s</td>
<td>Elston and Ellis</td>
<td>NOTTINGHAM GRADING SYSTEM Modification of the Bloom and Richardson’s system</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adopted by WHO now</td>
</tr>
</tbody>
</table>
Breast Cancer grading

Objectives

1. Why Grading is Important?
2. What is Wrong with the Current Grading Systems?
3. Can we Do Better?
BREAST CANCER - PROGNOSIS

**Depends on**

- Tumor size - <2 cm favorable
- Lymph node involvement
  - Negative: 80% 5 yr survival
  - 1-3 +: 50% “ “
  - >4 +: 21% “ “

- Histologic type and grade
- ER and PR status
  - ER +: 70% regress w anti estrogen therapy
  - ER -: 5% respond
- Other biomarkers (MIB-1, p53, Bcl-2, Her2, p21, p27, EGFR, etc.)
- Skin involvement: poor prognosis
- Distant metastasis: “ “
Targeted CHEMOTHERAPY
Breast Cancer grading

Objectives

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3. Can we Do Better?
Tumor Grading in Breast Ca

- Elston and Ellis modification of the Bloom & Richardson method (NOTTINGHAM GRADING SYSTEM “SBR”)
- 3 features examined:
  - tubule formation
  - nuclear pleomorphism
  - mitotic rate
- scored:
  - 3 – 5 points = Grade 1 / well differentiated
  - 6 – 7 points = Grade 2 / moderately differentiated
  - 8 – 9 points = Grade 3 / poorly differentiated
TUMOR GRADING

Well Differentiated

Moderately Differentiated

Poorly Differentiated
Cancer Research Campaign Trial: correlation b/t histological grade & prognosis. P-value for trend is < 0.001. Kings/Cambridge. 1982.
Histologic Grading of Breast Carcinomas

- Provides clinically prognostic information

- However, despite recommendations by College of Am Pathologists. The latest Breast Task Force of the American Joint Committee on Cancer did not include histologic grading in its staging criteria

- Reason:
  - **INSURMOUNTABLE INCONSISTENCIES BETWEEN INSTITUTIONS!!!!!**
Problems with THE NOTTINGHAM GRADING SYSTEM

- Lack of precision in assessing all three parameters, specifically mitotic frequency leading to an element of subjectivity
- Difficulty in the reproducibility of the findings
- Nuclear>mitosis>tubular component of the SBR were shown to be not predictive of disease free or metastasis-free survival
- 35% – 75% agreement between pathologists utilizing the SBR grading system and a low predictive value of prognosis for individual patients.
Problems with THE NOTTINGHAM GRADING SYSTEM (Cont.)

• The system is not ideal for grading lobular, metaplastic, mucinous, squamous or medullary carcinomas

• The system is not ideal for grading carcinomas in cytologic specimens

• The system is not ideal for grading carcinomas following adjuvant chemotherapy or radiation

• Its use is of limited value in small specimens such as core biopsies
Interobserver Variability in Grading Breast carcinomas

- Accuracy range is only 35% - 75%
- Less than one half of all breast cancers are assigned histologic grade 1 or 3 status
- 60-80% of cases classified as grade 2
  - Issues with clinical decision
  - Issues with disease outcome
  - Issues with prospective studies
Breast Cancer grading

Objectives

1. Why Grading is Important?

2. What is Wrong with the Current Grading Systems?

3. Can we Do Better?
The Newly Proposed KU Grading System!!!!

- Modification of the SBR
- Elimination of the tubular component
- Elimination of Mitosis and its replacement by automated MIB-1 count - WHY???
The Newly Proposed System

Human Eye - Strengths & Weaknesses

The human eye is unsurpassed at pattern recognition.
The Newly Proposed KU Grading System!!!!

- **Automated MIB-1 count**
  - Accurate
  - Automated
  - Reproducible
  - More reliable
  - Can be used with more reproducibility on core biopsies and limited specimens
The human eye is less adept at discriminating subtle differences in hue and intensity of color.

Quantitative Immunohistochemistry: The need for Standardization!!!
ChromaVision ACIS

Nuclear Applications (ER, PR, Ki-67, p53)
Example of High MIB-1 count

Example of Low MIB-1 count
Breast Cancer grading

Objectives

1. Why Grading is Important?
2. What is Wrong with the Current Grading Systems?
3. Can we Do Better?
So!!!
What did we do?????

Collected 788 breast cancer cases over a 13 year duration
## Tumor SBR Grades

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDC</td>
<td>137</td>
<td>246</td>
<td>266</td>
</tr>
<tr>
<td>IDC/ILC</td>
<td>7</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>ILC</td>
<td>26</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Mucinous</td>
<td>17</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Tubular</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cribriform</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Medullary</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Pap/SCCa</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>196 (25%)</td>
<td>307 (39%)</td>
<td>285 (36%)</td>
</tr>
</tbody>
</table>
## Grading Criteria of the KU System

<table>
<thead>
<tr>
<th>Feature</th>
<th>Score</th>
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<tbody>
<tr>
<td><strong>Nuclear pleomorphism</strong></td>
<td></td>
</tr>
<tr>
<td>Small regular uniform nuclei</td>
<td>1</td>
</tr>
<tr>
<td>Moderate nuclear variation in size and shape</td>
<td>2</td>
</tr>
<tr>
<td>Marked variation in size and shape</td>
<td>3</td>
</tr>
<tr>
<td><strong>Automated MIB-1 count</strong></td>
<td></td>
</tr>
<tr>
<td>Equal to or less than 9 %</td>
<td>1</td>
</tr>
<tr>
<td>10-25%</td>
<td>2</td>
</tr>
<tr>
<td>More than 25%</td>
<td>3</td>
</tr>
</tbody>
</table>

**Final histologic grade:**
- Grade 1: N grade 1 or 2 and MIB-1 score 1 or 2
- Grade 2: N grade 3 and MIB-1 score 1 or 2 **OR** MIB-1 score 3 and n grade 1 or 2
- Grade 3: N grade 3 and MIB-1 score 3
### Comparison of the SBR to the KU grading systems

<table>
<thead>
<tr>
<th>KU Grading System</th>
<th>SBR Grading System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>I</td>
<td>178 (22%)</td>
</tr>
<tr>
<td>II</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>III</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>196</td>
</tr>
</tbody>
</table>

62% no change in grade  
33% down grade  
5% upgrade
Validation of the KU system

• Comparison of the SBR and KU systems:
  
  – **Histologic Parameters:**
    • Tumor Size
    • Angiolymphatic invasion
    • LN status
  
  – **Prognostic Biomarkers:**
    • ER
    • PR
    • Her-2
    • Bcl-2
    • EGFR
    • p53
Proposed grading system

Tumor Size in cm

Histologic Grade

Negative vascular invasion

Negative lymph node mets

Histologic Grade

Tumor Size in cm

Proposed grading system

SBR
The KU grading system is at least as good as the SBR system
Step 2

Re-graded all cases into Low and Intermediate Grades based on the Proposed “KU grading system” and correlated histopathology with biomarker studies.
**Current SBR Grade I cases**

Re-grading into Low and Intermediate Grades based on the Proposed “**KU grading system**” and correlation with histopathologic and biomarker studies

<table>
<thead>
<tr>
<th>KU System Grade</th>
<th>ER</th>
<th>PR</th>
<th>p53</th>
<th>EFGR</th>
<th>Bcl-2</th>
<th>Her-2/neu</th>
<th>Vas Inv</th>
<th>LN +</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92</td>
<td>72</td>
<td>10</td>
<td>0.8</td>
<td>66</td>
<td>8</td>
<td>10</td>
<td>14</td>
<td>125</td>
</tr>
<tr>
<td>II</td>
<td>90</td>
<td>80</td>
<td>10</td>
<td>3</td>
<td>53</td>
<td>10</td>
<td>10</td>
<td>17</td>
<td>30</td>
</tr>
<tr>
<td>III</td>
<td>70</td>
<td>60</td>
<td>30</td>
<td>0</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>All</td>
<td>90</td>
<td>73</td>
<td>12</td>
<td>1</td>
<td>50</td>
<td>9</td>
<td>10</td>
<td>14</td>
<td>165</td>
</tr>
</tbody>
</table>
Current SBR Grade II cases
Re-grading into Low, Intermediate and High Grades based on the
Proposed “KU grading system”
and correlation with histopathologic and biomarker studies.

<table>
<thead>
<tr>
<th>KU System Grade</th>
<th>ER</th>
<th>PR</th>
<th>p53</th>
<th>EFGR</th>
<th>Bcl-2</th>
<th>Her-2/neu</th>
<th>Vas Inv</th>
<th>LN +</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>89</td>
<td>66</td>
<td>19</td>
<td>9</td>
<td>72</td>
<td>17</td>
<td>19</td>
<td>13</td>
<td>53</td>
</tr>
<tr>
<td>II</td>
<td>76</td>
<td>65</td>
<td>20</td>
<td>5</td>
<td>34</td>
<td>22</td>
<td>41</td>
<td>24</td>
<td>59</td>
</tr>
<tr>
<td>III</td>
<td>66</td>
<td>54</td>
<td>30</td>
<td>10</td>
<td>38</td>
<td>26</td>
<td>40</td>
<td>14</td>
<td>80</td>
</tr>
<tr>
<td>All</td>
<td>76</td>
<td>58</td>
<td>24</td>
<td>8</td>
<td>46</td>
<td>22</td>
<td>34</td>
<td>17</td>
<td>192</td>
</tr>
</tbody>
</table>
Current SBR Grade III cases
Re-grading into Intermediate and High Grades based on the Proposed “KU grading system” and correlation with histopathologic and biomarker studies

<table>
<thead>
<tr>
<th>KU System Grade</th>
<th>ER</th>
<th>PR</th>
<th>p53</th>
<th>EFGR</th>
<th>Bcl-2</th>
<th>Her-2/neu</th>
<th>Vasc Inv</th>
<th>LN +</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>53</td>
<td>37</td>
<td>26</td>
<td>37</td>
<td>42</td>
<td>21</td>
<td>74</td>
<td>58</td>
<td>19</td>
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<tr>
<td>III</td>
<td>30</td>
<td>23</td>
<td>55</td>
<td>27</td>
<td>29</td>
<td>29</td>
<td>48</td>
<td>28</td>
<td>192</td>
</tr>
<tr>
<td>All</td>
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<td>24</td>
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<td>28</td>
<td>30</td>
<td>28</td>
<td>51</td>
<td>31</td>
<td>211</td>
</tr>
</tbody>
</table>

CONCLUSION - 2

The KU grading system is potentially better than the SBR system.

It provides accurate information that correlate better with tumor biology.
Step 3

Correlation of both grading system with patients survival
Survival Data

Comparison between the KU and the SBR grading system
The KU grading system correlates better with patients overall survival than the SBR system.
KU grading System of DCIS

- Identical to the Van Nuys System
- Correlates with
  - ER, PR
  - EGFR, Her-2, Bcl-2
  - p53, p27, p21

Relationships Between Grade (Van Nuys vs. KU) of DCIS Tumors and ER, PR, EGFR and Her-2 Status

Relationships Between Grade (Van Nuys vs. KU) of DCIS Tumors and Bcl-2, p27, p21 and p53 Status
The newly proposed grading system appears to be superior to the SBR grading system:

* It is user friendly, easy to implement, semi-automated, and more reproducible.

* It provides more accurate information about the biology of the tumor, allowing clinicians to better customize treatment for their patients.

* It is applicable to all types of epithelial tumors.

* It is applicable to specimens with limited tumor material such as cytologic specimens, core bx’s and Trs previously treated with adjuvant chemo or radiation cases.