Breast Cancer

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Delaware CCOP

CALGB CRA Orientation, October 2005

CALGB BREAST CANCER TRIALS

Topics

Early breast cancer- primary Rx (goal= least invasive/complicated Rx that→
highest possible freedom-from-recurrence)

Early breast cancer- adjuvant studies (goal= using systemic therapy, prevent
relapse in patients who are at high risk for relapse)

Advanced/metastatic cancer (goal= cancer shrinkage and prolongation of life,
with the best possible quality of life)

Special populations (e.g., elderly, premature menopause, patients experiencing
nausea, etc.)
2005 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>33%</td>
<td>710,040</td>
<td>662,870</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>17%</td>
<td></td>
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</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2005.

2005 Estimated US Cancer Deaths*

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Percentage</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>31%</td>
<td>295,280</td>
<td>275,000</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver and intrahepatic bile duct</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
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</tbody>
</table>

*ONS=Other nervous system.
Source: American Cancer Society, 2005.

*Age-adjusted to the 2000 US standard population.

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AVG. ANNUAL BREAST CANCER INCIDENCE

INCIDENCE / 100,000

AGE
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85+

MINIMUM ADDITIONAL RISK NECESSARY FOR INCLUSION IN PROTOCOL
SEER DATA (1983-"87)
Breast Anatomy

- A ducts
- B lobules
- C dilated duct for milk
- D nipple
- E fat
- F pectoralis muscle
- G chest wall/rib
- A normal duct cells
- B basement membrane
- C lumen

Axillary Lymph Nodes

- A Pectoralis major
- B Level I axillary nodes
- C Level II axillary nodes
- D Level III axillary nodes
- E Supraclavicular nodes
- F Internal mammary
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Diagnostic Studies

Physical examination- measure nodules, assess tenderness, weight↓, performance status

Ultrasound- measure & quantify nodules, solid v. fluid-filled

Scans/X-rays- mammogram, bone scan, CXR, CT

Biopsy/definitive surgery- histologic sub-type, staging, margins of resection

Immunohistochemistry- ER/PR, HER2/neu oncogene over expression, others

Others- MRI & PET scans, laboratory values

Metastases
Breast CA PET Scan

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Prognostic Factors

(What the CRA will have to identify in primary records and enter onto on-study forms)

- Type of surgery
- Tumor size & nodal status (positive v. negative, sentinel lymph node, # of involved lymph nodes)
- IHC (hormone receptors, HER2 oncogene status, others)
- Margins of resection (primary tumor)
- Pathologic sub-type & differentiation (grade)
- Sites and number of sites of metastases
- Number of prior chemoRx and hormones for metastatic disease
- Others
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Prognostic Factors

“We can foresee a future full of opportunities for designing proper trials that will offer a wide range of treatment options tailored to each major prognostic subset. On the basis of prognostic factors, patients and physicians will be able to choose from the simple tamoxifen to ... intensive drug treatments... as well as between adjuvant and neoadjuvant therapy, or the application of both modalities.”

Bonadonna & Valagussa
JNCI 82:543, 1990

Role of HER2 in Breast Cancer

- HER2 proto-oncogene involved in regulation of normal cell growth
- Gene amplification or HER2 overexpression produces activated HER2 receptors and stimulates cell growth
- Gene amplification or HER2 overexpression occurs in 25-30% of breast cancers
- HER2-positive tumors are associated with poor prognosis and shortened disease-free survival
Panel of 21 Genes and the Recurrence-Score Algorithm

- **Proliferation**
  - G67
  - STK15
  - Survivin
  - CCNB1 (cycin B1)
  - MYC

- **HER2**
  - GRB7
  - HER2

- **Estrogen**
  - ER
  - PGR
  - BCL2
  - SCUBE2

- **Invasion**
  - MMP11 (stromelysin 3)
  - CTS12 (cathepsin L2)

- **Reference**
  - ACTB (β-actin)
  - GAPDH
  - RPLPO
  - GUS
  - TFRC

Likelihood of Distant Recurrence, According to Recurrence-Score Categories

Rate of Distant Recurrence as a Continuous Function of the Recurrence Score
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Therapy-Local/Regional

Surgery
• Core needle biopsy v. incisional or excisional biopsy
• Mastectomy (simple, total, modified radical, radical) v. lumpectomy
• Axillary dissection v. sentinel LN biopsy (+ “completion” axillary dissection)
• Reconstruction (immediate v. delayed)

Radiation therapy
• Breast conservation XRT v. post-mastectomy chest wall XRT
• External beam v. Brachytherapy

Needle Biopsy

Needle biopsy:
A needle is used to draw sample fluid and tissue from a lump to be studied

#ADAM
Excisional Biopsy

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Staging

Why stage breast cancer?
- Prognosis is inversely related— the higher the stage, the lower the cure rate.
- Treatment is conditional on stage
- Clinical Trials outcomes are comparable

How to stage breast cancer?
- Tumor size
- Nodal status
- Metastases
Tumor Size
Early Stage Breast CA Therapy

- Local Therapy to the Breast (Primary):
  - Surgery: Lumpectomy, Mastectomy, Nodes
  - Radiation
- Systemic Therapy (Adjuvant):
  - Hormonal Therapy
  - Chemotherapy
  - Targeted Molecules
Lumpectomy

• A dark area indicates tumor
• B Light pink is extent of tissue removed
Margins of Resection

- A  cancer cells
- B  normal tissue
- C  inked margin

Overview of Breast Lymphatics
Sentinel Lymph Node

Nodal Basin Mapping
Three Reasons to Perform

#1 Identification of Total Hot Nodes
Surgeon can obtain count of total hot nodes prior to surgery, decreasing likelihood of missed sentinel node

#2 Precise Localization of Each Hot Node
Surgeon can precisely locate radioactive node(s) prior to surgery marking best entry point to ensure small, tactical incision

#3 Detection of Nonaxillary Drainage
Surgeon can observe drainage to internal mammary, supradivicular nodes, enabling identification of patients without axillary drainage
Sentinel Node Biopsy

- **A** blue dye in lumpectomy site
- **B** Level I nodes
- **C** Level II nodes
- **D** Level III nodes

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Sentinel Node Biopsy

- **E** large lymphatic channels
- **F** small lymphatic channels
- **G** sentinel lymph nodes with dye
Sentinel Lymph Node Biopsy

• A  pink indicates tissue removed
• B  Level I nodes
• C  Level II nodes
• D  Level III nodes

Modified Radical Mastectomy

• A  pink indicates tissue removed
• B  Level I nodes
• C  Level II nodes
• D  Level III nodes
Modified Radical Mastectomy

- A pink indicates tissue removed
- B Level I nodes
- C Level II nodes
- D Level III nodes
- E Supraclavicular nodes
- F Internal mammary nodes

Radical Mastectomy
Breast Radiation

OPERABLE BREAST CANCER HYPOTHESES

- Halstedian
  - Local/Regional Disease
- Alternative
  - Systemic Disease
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Adjuvant systemic therapy

‘‘... the tumor in the breast is only a local manifestation of a blood affliction.’’

George T. Beatson

Lancet 2:104, 1896
Early Stage Systemic Therapy

- Adjuvant Chemotherapy
  - Adjunct to local therapy
  - Treat micrometastatic disease
  - Improve relapse free survival
- Neoadjuvant Chemotherapy
  - Before or in place of local therapy
  - Tumor is biological marker of efficacy
  - Organs spared of radical surgery

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Systemic Therapy- Standard & Investigational

Targeted therapies
  » Hormonal therapy
    » Tamoxifen
    » Aromatase Inhibitor
  » Targeted molecules
    » Herceptin
    » Avastin

“Broadly active” therapies
  » Chemotherapy
HORMONAL STIMULATION OF TUMOR GROWTH

Hormone-Dependent Tumor

Hormone-Independent Tumor

Estrogen

Activated Complex

Enters Nucleus

DNA Synthesis

BLOCKADE OF HORMONE CASCADE BY AN ANTIESTROGEN

Estrogen

Antiestrogen

Antiestrogen Monopolizes Estrogen Receptors

Protein Synthesis Blocked
Mechanism of Action of Aromatase Inhibitors and Tamoxifen

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Follow-up/End-points

Relapse- local, regional, distant, combination

Survival- from diagnosis to death, from on-study to death

Toxicity- judged by the physician and the CRA, Use CTCAE Version 3.0

Quality of life- judged by the patient

Special end-points- change in bone density, SRE, cosmetic outcome, lymphedema, etc.
Active CALGB Trials

- 40101: Adjuvant Chemo, Node Negative
- 40401: LHRH Analogue + Chemo, Premenopausal Adjuvant
- 49801: DCIS, Surgery w/wo RT
- 49907: Adjuvant Chemo, 65 + years old
- 150106: Correlative Science 40401

Relative Survival* (%) during Three Time Periods by Cancer Site

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<tr>
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<tbody>
<tr>
<td>All sites</td>
<td>50</td>
<td>52</td>
<td>62</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>75</td>
<td>78</td>
<td>86</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>50</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>12</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Melanoma</td>
<td>80</td>
<td>85</td>
<td>89</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>47</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Ovary</td>
<td>37</td>
<td>41</td>
<td>53</td>
</tr>
<tr>
<td>Pancreas</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Prostate</td>
<td>67</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>73</td>
<td>78</td>
<td>82</td>
</tr>
</tbody>
</table>