Improving Outcomes for Cancer Survivors: Lessons Learned from the Treatment of Breast Cancer

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16th Annual Advances in Oncology 2015
September 25-26, 2015
Sacramento, CA

The Lois O’Grady Lectureship
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Who are the cancer survivors?

• More than 1 in 3 Americans will be diagnosed with cancer in their lifetime.

• More than 14 million Americans have a personal history of cancer; ~4% of US population.

• The number of cancer survivors will increase sharply during the next 25 yrs with aging of the population.
Breast cancer as a model for study of adult cancer survivors

- Most common cancer in women—occurs across the lifespan
- Complex treatments, with high rate of cure
- Treatment affects menopausal status, fertility, and endocrine milieu of the woman
- Potential for substantial impact on physical and emotional health
- Hereditary predisposition genes in 5-10%, with risk of other cancers
- High risk for second breast cancers
Changes in breast cancer treatment across my career

• My 1971 medical school surgery rotation:
  – Woman with breast lump consents for biopsy (frozen section) and possible radical mastectomy or simple mastectomy
  – Awakens from anesthesia, not knowing whether or not she still has a breast!

• NSABP B-04 trial shows that Halsted radical mastectomy is no better than modified radical mastectomy (Cancer, 1977)
Survival Free of Distant Disease (Panel A) and Overall Survival (Panel B) during 25 Years of Follow-up after Surgery

1970s: Breast Cancer Viewed as a Systemic Disease

- Recognition that local treatment of the breast does not affect mortality
- Women still dying from distant disease, especially if tumor involves lymph nodes
- Early trials of adjuvant chemotherapy, first used in women with most advanced local disease
1980s: Increasing consumer involvement in care

- Elimination of the one-step surgical procedure; outpatient biopsy precedes definitive surgery

- Mounting clinical and RCT evidence for efficacy of breast conserving surgery;

  \textit{mastectomy} = \textit{lumpectomy} + \textit{radiation}

- Increasing patient involvement in surgical decision-making
Changes in the Pattern of Use of Screening Mammography among Women 40 to 79 Years of Age (Panel A) and in the Use of Adjuvant Therapy among Women 50 to 69 Years of Age with Node-Positive Stage II or IIIA Breast Cancer (Panel B)

The Growing Number of Breast Cancer Survivors

- There are more than 3 million breast cancer survivors in the US
- 5-year survival exceeds 90% for early stage patients
- Continued improvements in survival expected

Trends in standardized death rates
Breast Cancer Treatment in the 21st Century

• At least 10 years of endocrine therapy for most women!
• Adjuvant trastuzumab (herceptin) becomes a therapeutic option
• Tailoring of treatment based on gene expression profiles
• Breast cancer prevention is a reality for high risk women and BRCA1/2 carriers


**Understanding the Development of Breast Cancer**

- **Normal Ductal Lumen**
- **Benign Proliferative Changes**
- **Atypical Hyperplasia**
- **Ductal Carcinoma in Situ**
- **Invasive Carcinoma**

**Accumulation of genetic and epigenetic changes**

- Abnormal response to growth factors (e.g., estrogen receptor)
- Abnormal oncogene expression (e.g., HER2/neu)
- Loss of tumor-suppressor function (e.g., p53)
- Genetic instability (e.g., loss of heterozygosity)
- Failure to respond to normal signals for apoptosis
- Stromal changes (e.g., angiogenesis)
- Tissue invasion (gain of function by malignant cells vs. loss of function of normal cells)

**Clinical phenotype of tumor determined**

*Figure 1. Pathobiologic Events Associated with Ductal Carcinoma in Situ.*
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sorlie, Charles M. Perou, Robert Tibshirani, Turid Aas, Stephanie Geisler, Hilde Johnsen, Trevor Hastie, Michael B. Eisen, Matt van de Rijn, Stefanie S. Jeffrey, Thor Thorsen, Hanne Quist, John C. Matese, Patrick O. Brown, David Botstein, Per Eystein Lønning, and Anne-Lise Børresen-Dale

Sorlie, PNAS 2001
In the future....

• Therapies will be more tailored
• Chemotherapy will only be given to selected patients
• Targeted and less toxic treatments will be the main form of therapy
• Breast cancer will be prevented through modifying risks (e.g. endogenous hormonal effects, energy balance, reproductive physiology)
But for now, there are still many challenges...

• Breast cancer treatment is....
  – Complex
  – Multi-modal
  – Multi-disciplinary
  – Toxic
  – Expensive
  – And often poorly coordinated

• Women with breast cancer pay a high upfront cost for prolongation of survival!
For many individuals, cancer is now a chronic disease.....
What are the physical costs of survivorship?
Changes in Physical Functioning

• Cardiorespiratory symptoms – CHF, radiation fibrosis
• Fatigue – multi-factorial
• Cognitive dysfunction - ?late effect of chemotherapy
• Sexual and urinary problems – local effects of treatment; secondary to chemotherapy or hormonal changes
SWOG 8897 Schema: Adjuvant RX of Early Breast CA

Stratification Factors

1. Hormone receptors
2. Timing of surgery
3. Menopausal status

- CMF x 6 cycles + Tamoxifen
- CMF x 6 cycles
- CAF* x 6 cycles
- CAF* x 6 cycles + Tamoxifen

* Total dose of doxorubicin = 360 mg/m²
## MUGA Scan Results at 5-8 yrs

<table>
<thead>
<tr>
<th></th>
<th>CMF Arm</th>
<th>CAF Arm</th>
<th>P-value</th>
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<tbody>
<tr>
<td>LV Ejection Fraction</td>
<td>7%</td>
<td>5%</td>
<td>NS</td>
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<tr>
<td>&lt; 50%</td>
<td></td>
<td></td>
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<tr>
<td>Mean LV Ejection</td>
<td>64.9%</td>
<td>61.2%</td>
<td>0.006</td>
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<tr>
<td>Fraction</td>
<td>(44-89 range)</td>
<td>(47-79 range)</td>
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Resting LV Ejection Fraction (%) by Treatment

Ganz, JCO 2008
Correlates of fatigue

**Biological factors**
- Anemia
- Immune changes

**Comorbid medical conditions**
- Cardiovascular disease

**Comorbid symptoms**
- Pain
- Sleep disturbance
- Menopausal symptoms

**Psychosocial factors**
- Catastrophizing coping style
- Depression
- Anxiety

**Demographic factors**
- Age
- Income
- Marital status
Vulnerability factors:
- Depression
- HPA axis dysregulation
- Cytokine gene polymorphisms?

Immune and neuroendocrine changes:
- Alterations in cellular immune system
- Alterations in HPA axis function

Bower Model—Brain, Behavior and Immunity, 2007
Other Medical Late Effects

• Lymphedema – critical need for prevention and intervention strategies
• Premature menopause
• Infertility
• Osteoporosis/fractures – need for preventive strategies
• Chronic pain; scars; body changes
Risk of Amenorrhea with Adjuvant Therapy in Younger Breast Cancer Patients

# Multivariate Analysis of Weight Change

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<thead>
<tr>
<th>Parameter</th>
<th>Parameter Est</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Intercept</td>
<td>1.574</td>
<td>.0003</td>
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<tr>
<td>BMI at Diagnosis</td>
<td>-0.037</td>
<td>.02</td>
</tr>
<tr>
<td>Adj Rx-horm only v no rx</td>
<td>0.310</td>
<td>.12</td>
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<tr>
<td>Adj Rx-any chemo v no rx</td>
<td>0.428</td>
<td>.03</td>
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<tr>
<td>Still premeno v change</td>
<td>-0.478</td>
<td>.03</td>
</tr>
<tr>
<td>Still postmeno v change</td>
<td>-0.425</td>
<td>.05</td>
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Goodwin, et al., 1999
Understanding the Mechanisms & Consequences of Weight Gain after Chemotherapy in Breast Cancer Survivors

- Premature menopause leads to decreased metabolic rate
- Increased fatigue after primary treatment leads to decreased physical activity and subsequent weight gain
- *Late medical consequences*: diabetes, cardiac disease, and increased risk of breast cancer recurrence

*(Dignam JNCI 2003)*
Research questions we have explored…

• What is the impact of breast cancer and its treatment on QOL?

• Is QOL better for women with breast conserving treatment?

• Why does sexual functioning get worse after breast cancer treatment?

• How can we do a better job managing menopausal symptoms in breast cancer survivors?

• What can be done to decrease the physical & emotional effects of breast cancer treatments?

• What are their mechanisms?
Impact of Different Adjuvant Therapy Strategies on Quality of Life in Breast Cancer Survivors

Ganz et al., Rec Res Can Res, 1998
Medical Characteristics of Study Sample  
(N=1,096)  
Post-Treatment 1-5 Years

• Type of surgery  
  – Lumpectomy = 61.8%  
  – Mastectomy alone = 22.3%  
  – Mastectomy & recon = 16%

• Adjuvant therapy  
  – None = 24.2%  
  – Chem = 16.4%  
  – Tam = 32.5%  
  – Tam + Chem = 26.9%
Breast Cancer Survivors
Symptoms in Past 4 Wks

- Hot Flashes*
- Night Sweats*
- Vag Discharge*

- No RX
- Tam
- Chem
- Chem + Tam

%
Breast Cancer Survivors
Symptoms in Past 4 Wks

Vag Dryness*  Dyspareunia*  Wt. Gain

No RX  Tam  Chem  Chem + Tam

%
Breast Cancer Survivors

CARES Body Image & Sex Functioning

Body Image

- No Rx
- TAM
- Chemo
- Chemo + TAM

Sex Function*

- No Rx
- TAM
- Chemo
- Chemo + TAM
Breast Cancer Survivors

SF-36 Subscale Scores

No RX
Tam
Chem
Chem + Tam
Breast Cancer Survivors
SF-36 Component Summary Scales
Early Conclusions

• Physical and sexual functioning are poorer in survivors who received adjuvant therapy
• Vasomotor and vaginal symptoms are more frequent after adjuvant therapy
• Physical and emotional functioning of survivors is similar to healthy women
And 5 years later...

- Significantly poorer physical function for those who received any adjuvant therapy
- Past chemotherapy treatment predicts poorer quality of life
SF-36 Scores in LTS According to Adjuvant Treatment

* Ps < .05 favoring no RX
Long Term Survivors

SF-36 Component Summary Scales

No RX
Tam
Chem
Chem + Tam

P=.001
Other findings....

- Chemotherapy is significantly associated with sexual dysfunction
- About one-third of survivors report fatigue
- Fatigue (> 5 years) is more strongly associated with combined modality therapy
- Persistent fatigue is associated with increase in pro-inflammatory cytokines and decreased cortisol
Moving Beyond Cancer (MBC): QOL at the end of primary breast cancer treatment

NCI R01 63028

The MBC Psychosocial Intervention Trial

Ganz et al., JNCI 2004; Stanton et al., JCO, 2005;
Mandelblatt et al., JCO 2008
Concerns voiced by women at the end of treatment....

• How will I know if my treatments worked?
• When will I get my energy back?
• What is the follow-up plan now that my treatments are over?
• Does this new ache mean that the cancer is coming back?
• Why does my family think that everything is okay now when I know it isn’t?
Subject Recruitment

• From offices of surgeons and medical oncologists
• Identified shortly after diagnosis, registered, and then tracked until treatment completed
• Geographic diversity: Los Angeles, Kansas, and Washington DC
Characteristics of sample (N=558) at baseline (end of treatment)

- Mean age 56.9
- Mean days since surgery 173.8
- 86% white
- 70% married
- 57% working
- LA = 50%
- DC = 29%
- Kansas = 21%
- 63% college graduate or higher
SF-36 Subscale Scores at Baseline (end of treatment)

* Ps < .05

Ganz, JNCI 2004
SF-36 Component Summary Scales

Ganz, JNCI 2004
Other Findings at the End of Primary Treatment

• Greater sexual problems and impact on sex life for women who received chemotherapy

• >50% of women report being unhappy with appearance, hot flashes, aches & pains, forgetfulness, breast sensitivity, joint pains, muscle stiffness

• These symptoms contribute significantly to decreased physical and mental health

Ganz, JNCI 2004
What is the impact of chemotherapy treatment on recovery after breast cancer?
Pattern of Recovery after Treatment: Physical Function

MBC - Physical Functioning

- No Chemo
- Chemo

adjusted for age, marital status, current tamoxifene use and immediate reconstruction
Pattern of Recovery after Treatment: Emotional Well-Being

MBC - Emotional Well-being

adjusted means

adjusted for age, marital status, current tamoxifen use and immediate reconstruction
Pattern of Recovery after Treatment: Vitality (Energy)

MBC - Energy

adjusted means

months since surgery

adjusted for age, marital status, current tamoxifen use and immediate reconstruction
Propensity adjusted mixed models comparing chemotherapy vs. no chemotherapy in 558 women in the year following the completion of treatment. No significant difference in recovery of PCS or MCS in the year after treatment ends.
Propensity Adjusted Mixed Models

Several symptoms are worse and persistent in chemotherapy treated patients!

BCPT Symptom Scales

JCO 2011
NSABP B-30 Clinical Trial

• 3-armed RCT comparing of >5000 women
  • 4 cycles vs. 6 cycles of chemo
  • one of the 4 cycles regimens excludes cytoxan, with predicted lower rate amenorrhea
Overall and Disease-Free Survival Slightly Favor 6 cycles of Treatment
QOL, Symptoms and Amenorrhea

- Persistent amenorrhea is less frequent with AT (no cytoxan)
- QOL returns to pretreatment level
- More than 50% increase in sx post treatment
Data from these two studies are consistent and find that while QOL returns to pre-treatment levels after adjuvant chemotherapy, breast cancer survivors have persistent symptoms and these must be addressed as part of survivorship care!
Conclusions

• Breast cancer survivors experience considerable acute toxicity from surgery, radiation therapy, and adjuvant chemotherapy.

• The acute impact on QOL resolves after treatment ends and stabilizes at about 1 year.

• Persistent problems beyond that time are symptom-focused and relate to:
  - Premature menopause
  - Endocrine treatment-associated vasomotor symptoms
  - Sexual difficulties
  - Musculoskeletal complaints
  - Fatigue and cognitive complaints

• Post-treatment symptoms are often worse for younger women.
Diagnosis and Staging

Treatment With Intent to Cure

Cancer-Free Survival

Medical Outcomes and Quality of Life

Recurrence/Second Cancer

Risk assessment and intervention at diagnosis

Safer therapies

Survivor health care delivery: Palliation, Prevention and Health Promotion

Start Here
With attention to survivorship needs, there can still be a good life after cancer!