Overview of Presentation

- Where have we been? OR What do we know?
- Where are we now? OR At least survival research is on the table for discussion.
- Where should we be going? OR Personal thoughts about future research efforts.
General Considerations

- Risk of late effects depends on the tissue and age of patient at time of treatment
- Late effects are dose and modality specific (e.g., surgery, radiation, chemotherapy)
- Combined modality therapy can have additive risks
Tissues at Risk for Late Toxicity

- Bone/soft tissues
- Cardiovascular
- Dental
- Endocrine
- Gastrointestinal
- Hepatic
- Hematological
- Immune system
- Nervous system
- Neuropsychologic
- Ophthalmologic
- Pulmonary
- Renal
- Reproductive
Case Examples

- 20 y.o. male who received combined modality therapy for Wilms tumor at age 5, including radiotherapy given to chest for lung metastases
  - cc: hemiatrophy of right chest wall musculature, scoliosis, decreased lung volumes
Case Examples

- 53 y.o. female with a history of breast cancer diagnosed at age 40 treated with surgery and adjuvant chemotherapy → premature menopause
- cc: multiple atraumatic fractures, marked reduction in bone mineral density
35 y.o. male with history of Wilms tumor left kidney treated with surgery and radiation therapy at age 7 years; basal cell carcinoma left abdominal wall at age 28

cc: needs health insurance coverage; has change in bowel habits and needs some tests
Case Examples

- 28 y.o. female with history of treatment with mantle irradiation for stage II Hodgkin’s disease at age 18
- cc: lump in right breast which is biopsied and shows breast cancer
Case Examples

- 75 y.o. male with history of high grade lymphoma treated with CHOP chemotherapy 2 years ago
  - While traveling in Japan with his daughter, he becomes exhausted and short of breath with exertion
  - He returns home and is found to have a cardiac ejection fraction of 35%; his symptoms improve after treatment for congestive heart failure
What can we learn from these case examples?

- Late effects can occur shortly after treatment or many years later.
- Patients of all ages can be affected.
- Degree of risk to individual patients cannot be predicted.
- Second cancers are the most life-threatening late effect, but other disabling conditions occur.
Understanding the potential toxicities of each treatment modality is critical if we are to develop preventive strategies!!
Late Effects of Surgery

- **Limb Amputation**: functional changes, cosmetic deformity
- **Abdominal surgery**: intestinal obstruction from adhesions, short bowel syndrome
- **Lymphadenectomy**: lymphedema
- **Splenectomy**: immune dysfunction, sepsis
- **Pelvic surgery**: impotence, incontinence
## Late Effects of Chemotherapy

<table>
<thead>
<tr>
<th>Renal</th>
<th>Cisplatin, Methotrexate, Nitrosourea</th>
<th>Renal Failure, Mg++, wasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary</td>
<td>Cyclophosphamide</td>
<td>Hemorrhagic Cystitis, Bladder fibrosis</td>
</tr>
</tbody>
</table>
# Late Effects of Chemotherapy

<table>
<thead>
<tr>
<th>System</th>
<th>Drugs</th>
<th>Late Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Steroids</td>
<td>Avascular necrosis</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Anthracyclines, Cyclophosphamide, Methotrexate, BCNU</td>
<td>Cardiomyopathy CHF</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Bleomycin, Methotrexate, BCNU</td>
<td>Pulmonary fibrosis, Intersitial pneumonitis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Steroids</td>
<td>Cataracts</td>
</tr>
</tbody>
</table>
### Late Effects of Chemotherapy

<table>
<thead>
<tr>
<th>CNS</th>
<th>Methotrexate</th>
<th>Structural changes, Hemiplegia, Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Nervous System</td>
<td>Cisplatin Vinca Alkaloids Paclitaxel</td>
<td>Peripheral neuropathies, Hearing loss</td>
</tr>
</tbody>
</table>
## Late Effects of Chemotherapy

<table>
<thead>
<tr>
<th>Hematological</th>
<th>Alkylation agents</th>
<th>Myelodysplasia, AML</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Topo II inhibitors</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Methotrexate</td>
<td>LFT abnormalities, Hepatic fibrosis or cirrhosis</td>
</tr>
<tr>
<td></td>
<td>BCNU</td>
<td></td>
</tr>
<tr>
<td>Gonadal</td>
<td>Alkylation agents</td>
<td>Sterility</td>
</tr>
<tr>
<td></td>
<td>Procarbazine</td>
<td>Early menopause</td>
</tr>
</tbody>
</table>
## Late Effects of Radiotherapy

<table>
<thead>
<tr>
<th>All tissues</th>
<th>Second malignancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone &amp; Soft Tissues</td>
<td>Abnormal growth, short stature; atrophy, deformity, fibrosis, osteonecrosis</td>
</tr>
<tr>
<td>Dental/Oral Health</td>
<td>Poor enamel &amp; root formation; dry mouth</td>
</tr>
</tbody>
</table>
### Late Effects of Radiotherapy

<table>
<thead>
<tr>
<th>System</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Neuropsychological deficits; structural changes; hemorrhage</td>
</tr>
<tr>
<td>Hematological</td>
<td>Cytopenias</td>
</tr>
<tr>
<td></td>
<td>Myelodysplasia</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Bladder fibrosis, strictures</td>
</tr>
</tbody>
</table>
## Late Effects of Radiotherapy

<table>
<thead>
<tr>
<th>Ophthalmologic</th>
<th>Cataracts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retinopathy</td>
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<tr>
<td></td>
<td>Keratoconjunctivitis</td>
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<tr>
<td>Cardiovascular</td>
<td>Pericardial effusion</td>
</tr>
<tr>
<td></td>
<td>Constrictive pericarditis</td>
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<tr>
<td></td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis</td>
</tr>
<tr>
<td></td>
<td>Decreased lung volumes</td>
</tr>
</tbody>
</table>
## Late Effects of Radiotherapy

<table>
<thead>
<tr>
<th>System</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Malabsorption, Intestinal stricture, Abnormal LFTs</td>
</tr>
<tr>
<td>Endocrine</td>
<td>GH &amp; other deficiencies, Hypothyroidism, nodules, Sterility, Leydig cell dysfunction, ovarian failure, premature menopause</td>
</tr>
<tr>
<td>Pituitary</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
</tr>
<tr>
<td>Gonadal</td>
<td></td>
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</tbody>
</table>
Appreciation to Pediatric Oncology Researchers...

- You have taught us much about the late effects of cancer treatment---you lead the way
- Your high survival rates and commitment to clinical trials are a model and a resource for survivorship research!
Some late effects in adults may be less life-threatening, but more troubling....
Estrogen Deficiency: Short Term Effects

- Vasomotor symptoms, vaginal dryness, mood changes, sleep disturbance
- Musculoskeletal complaints, joint pains, skin changes
- Urinary incontinence (women)
- Sexual changes, dyspareunia (women)
Oncology Treatments that Exacerbate this Problem

- SERMS
- Anti-estrogens, ER degradation agents
- Aromatase Inhibitors
- GnRH analogs (in both men and women)
- Oophorectomy
- Orchiectomy
“It has been several months since I started taking Femara. Although I do want to continue taking it and not take any chances with a cancer recurrence, I have encountered some problems. I am experiencing constant pain in my muscles, joints etc., as if my body was continuously sore from strenuous exercise. The hardest times are in the morning and in the late afternoon, and I am usually very tired in the afternoon as well. I feel much better after exercise, but often I do not have enough energy or willpower after work to go to the gym. Instead I go to my bedroom and sleep. All together, this is not me and I want to do something to change it.”
Estrogen Deficiency: Late Effects

- Osteoporosis and fracture (men and women)
- Infertility (women)
- Lipid changes...? Cardiac risks
And where are we now?

- A decade of RFA supported research funded by the NCI
- An NCI Office of Cancer Survivorship
- Several NCI sponsored conferences such as this
- A developing body of descriptive research
- Multi-dimensional health-related QOL as a short & long-term outcome
QOL in Long-term, Disease-Free, Breast Cancer Survivors: A Follow-up Study
Longitudinal Cohort Study

- 763 early stage breast cancer patients assessed at two times
  - Baseline: between 1 and 5 years after dx
  - Follow-up: between 5.0 and 9.5 years after dx
- Use of standardized measures of QOL, depression, mood, sexual functioning

Ganz et al., JNCI, January 2, 2002
SF-36 Health Profile Scores

Baseline vs Follow-up

- Physical functioning: Baseline 81.9 vs Follow-up 79.4 (p = 0.0001)
- Role function-physical: Baseline 77.2 vs Follow-up 73.9 (p = 0.014)
- Mental Health: Baseline 76.5 vs Follow-up 78.0 (p = 0.005)
- Role function-emotional: Baseline 79.2 vs Follow-up 81.2 (p = 0.139)
- Social functioning: Baseline 87.3 vs Follow-up 87.9 (p = 0.417)
- Bodily pain: Baseline 79.0 vs Follow-up 76.6 (p = 0.001)
- Vitality: Baseline 61.4 vs Follow-up 60.9 (p = 0.461)
- General Health: Baseline 74.2 vs Follow-up 71.9 (p = 0.0001)
SF-36 Scores According to Adjuvant Treatment
Long Term Survivors
MOS-SF-36 Component Scales

- No RX
- Tam
- Chem
- Chem + Tam

P = .001
Late Cardiac Effects of Adjuvant CMF vs. CAF in Women with Node Negative Breast Cancer Treated on SWOG 8897: Initial Results from SWOG 9342

P. A. Ganz, S. J. Green, L. Hutchins, S. Martino, J. Gralow, R. Livingston, K. Albain for the Southwest Oncology Group

San Antonio Breast CA meeting, 2002
1. Hormone receptors
2. Timing of surgery
3. Menopausal status

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

![Graph showing resting LV ejection fraction by treatment with CMF and CAF arms compared. The x-axis represents the resting LV ejection fraction (%) ranging from 40-45 to 86-90, and the y-axis represents the number of patients. Bars are color-coded: blue for CMF arms and red for CAF arms.]
And persistent **FATIGUE**...

- Another common complaint in survivors
- Is it from the disease or the treatment?
Predictors of Vitality (Energy/Fatigue) in Early Stage Hodgkin’s Disease: Results from SWOG 9133

P.A. Ganz, C.M. Moinpour, S. McCoy, D.K. Pauler, O.W. Press, R.I. Fisher

ASCO, 2004
Relationship Between Vitality at Baseline & 1 Year

- Correlation = .41
- Classified patients
  - *Improved, No Change, Worsened*
- Clinically significant change = ≥ 10 points
  - 10% change on 0 to 100 scale (scale range)
  - Reflective of a moderate effect size (Cohen, 1988; Sloan et al., 1998)
- *No change* boundaries + or - <10 points
  - *Improved* above boundary area
  - *Worsened* below boundary area
Vitality

Improved = 23%

Worsened = 32%
Conclusions

- In early stage HD, disease and treatment factors are not related to decreased vitality *initially* or in *follow-up*.
- It is possible that elevated levels of pro-inflammatory cytokines, as part of the underlying disease, may play a role.
- Further research is necessary to understand the mechanisms of fatigue in HD patients.
Where should we be going?

- Need to understand the mechanisms of more common late effects
- Must reduce or prevent the late serious toxicities of treatments
- Need for multidisciplinary, prospectively designed studies with long-term follow-up
Conceptual Model of Fatigue in Cancer

- Psychological distress
- Infection
- Fatigue
- Physical symptoms
- Cancer Therapies
- Tissue Trauma
- Pro-inflammatory Cytokines

Bower & Ganz, 2004
Fatigue and Immune Markers in Breast Ca Survivors

Cortisol

<table>
<thead>
<tr>
<th></th>
<th>Non-fatigued</th>
<th>Fatigued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (µg/dl)</td>
<td>14.0 (3.2)</td>
<td>11.9 (3.7)*</td>
</tr>
</tbody>
</table>

- Cortisol *negatively* correlated with immune activation markers in non-fatigued group
- Cortisol *positively* correlated with immune activation markers in fatigued group
Cortisol Response to Experimental Stress According to Fatigue Status

Cortisol Response to Experimental Stress
According to Fatigue Status

- Non-fatigued
- Fatigued

P < .05
Fatigue and Sickness Behaviors

- Somnolence
- Decreased activity
- Less social interest
- Forgetfulness
- Distractibility

All ps ≤ .05
Distribution of leukocytes in fatigued & non-fatigued Breast Cancer Survivors

Bower, et al., JNCI 2003
Relationships between soluble inflammatory markers & leukocyte distributions in breast cancer survivors

Bower, et al., JNCI 2003
How to go forward?

- Develop centers of excellence to study late effects from a multidisciplinary perspective
- Validate observations from individual laboratories in the cooperative group setting, specifically in controlled trials
- Test preventive interventions along with treatments in the cooperative group setting
Treatment decisions must weigh the benefits against the harms.....
In spite of the uncertainties, there can still be a good life after cancer.....