Treatment Options for Early Breast Cancer

OB/Gyn Grand Rounds
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University of Vermont
Title of Program: Obstetrics, Gynecology & Reproductive Sciences Grand Rounds
Title of Talk: Treatment options for early breast cancer
Speaker/Moderator: Marie Wood, M.D.
Planning Committee Members: Drs. George Till, Elise Everett, Marjorie Meyer, Cheung Wong & Mary Clairmont RN
Date: Tuesday, February 2, 2016
Workshop #: 16-117-23

Learning Objectives
1. To understand options for treatment of early breast cancer
2. To understand how decisions are made regarding systemic treatment
3. To understand the importance of considering hereditary factors and risk of second primary cancers for women with early breast cancer
4. To understand importance of fertility preservation for young women with early breast cancer

DISCLOSURE:
Is there anything to disclose? No
Please list the Potential Conflict of Interest (if applicable): NONE

All Potential Conflicts of Interest have been resolved prior to the start of this program.
YES (If no, credit will not be awarded for this activity.)

All recommendations involving clinical medicine made during this talk were based on evidence that is accepted within the profession of medicine as adequate justification for their indications and contraindications in the care of patients. YES

COMMERCIAL SUPPORT ORGANIZATIONS (if applicable): NONE

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• In order to receive CME credit participants must fill out an evaluation form.

This slide was presented at the start of the program.
Topics to be covered

• Treatment options for early breast cancer
  – Surgical
  – Radiation therapy
  – **Systemic Therapy**
    • Chemotherapy, hormonal therapy, biologic therapy
    • Bisphosphonates

• How decisions are made

• Important considerations
  – Risk of second primary cancers
  – Fertility preservation
Surgical Options for Early Breast Cancer
Surgical Treatment Issues to Consider

• Lumpectomy

• Lumpectomy and radiation

• Mastectomy

• Bilateral mastectomy
Surgical Treatment Issues to Consider

- Lumpectomy
- **Lumpectomy and radiation**
  - Standard of Care
- Mastectomy
- Bilateral mastectomy
Survival after breast cancer surgery

- Two large studies have compared breast conserving surgery to mastectomy
- Veronesi et al:
  - 701 women with tumors <2cm were randomized between 1973 – 1980 to lumpectomy with radiation or mastectomy
  - 20 year follow-up
    - Local recurrence higher in breast conserving group (p<0.001)
    - Overall and breast cancer survival similar
- Fisher et al:
  - 2163 women with tumors <4 cm randomized between 1976- 1984 to lumpectomy v lumpectomy and radiation v mastectomy
  - 20 year follow-up
    - Local recurrence higher with lumpectomy +/- radiation (39.2 v 14.3% p<0.001)
Survival after breast cancer surgery

Lumpectomy and Radiation is Standard of Care

Fisher NEJM 2002
Do all women need radiation?

- Older women with small receptor positive tumors have good prognosis and competing risk factors for mortality.

- US trial studied women older than 70 with <2cm and receptor positive breast cancer
- Randomized to tamoxifen +/- radiation
- Enrolled 636 women between 1994 - 1999
Radiation is optional for elderly women

Table 1. Clinical Outcome: Recurrence and Death

<table>
<thead>
<tr>
<th>Treated Patients</th>
<th>TamRT Arm</th>
<th>Tam Arm</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>317</td>
<td>319</td>
<td>636</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>42</td>
<td>65</td>
</tr>
<tr>
<td>Local or regional ± distant</td>
<td>6</td>
<td>32</td>
<td>38</td>
</tr>
<tr>
<td>IBTR alone</td>
<td>2</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Axilla alone</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>IBTR with axilla</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IBTR with distant</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Distant alone</td>
<td>17</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause</td>
<td>166</td>
<td>168</td>
<td>334</td>
</tr>
<tr>
<td>Breast cancer specific</td>
<td>13</td>
<td>8</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviations: IBTR, ipsilateral breast recurrence; Tam, tamoxifen alone; TamRT, tamoxifen plus radiation therapy.

Overall Survival (proportion)

Time Since Study Entry (years)

No. at risk
TamRT: 317, 264, 168, 7
Tam: 319, 262, 167, 4

HR, 0.95; 95% CI, 0.77 to 1.18
P = .64

Hughes JCO 2013
New trend in bilateral mastectomies

Mahmood AnnSurgOnc 2013
Contralateral Mastectomy

- Meta-analysis performed in 2010
- Included 39 studies and 7384 women
- Contralateral Mastectomy
  - Decreased incidence of contralateral breast cancer
  - Inconsistent regarding improvements in disease free survival and overall survival
  - Psychological satisfaction was higher and cancer worry was lower for women choosing bilateral mastectomies but not satisfaction with cosmetic results
  - Adverse events include unanticipated re-operation (4 – 49%)
Contralateral mastectomy may benefit young women or women with strong family history.

Bedrosian 2010
Boughey 2010
Surgical Treatment Issues to Consider

- **Lumpectomy**
  - Can be considered for women >70 with small/Er+ tumors

- **Lumpectomy and radiation**
  - Is the standard of care

- **Bilateral mastectomy**
  - May be an option for young women or women with strong family histories
Systemic Options for Early Breast Cancer
Systemic Options

- Chemotherapy
- Hormonal therapy
- Biologic therapy
- Bisphosphonates
Goal of Adjuvant Therapy

- Reduce the risk of recurrence
  - **Radiation Therapy** - largely reduces the risk of local recurrence
  
  - **Adjuvant Therapy** – can decrease risk of systemic recurrence and increase overall survival
Options for Systemic Adjuvant Therapy

Chemotherapy

Lower risk options:
- Cyclophosphamide/Methotrexate/5Florouricil
  - Older regimen, lower toxicity, still active
- Adriamycin/Cyclophosphamide
  - Standard, more active than CMF, consider cardiotoxicity
- Taxotere/Cyclophosphamide
  - Improved survival over 4AC given every 3 week

Higher risk options:
- Adriamycin/Cyclophosphamide followed by Taxane
  - Standard for LN+ and higher risk
  - Taxane (Taxol/Taxotere, weekly or every 2 or 3 weeks)

Choice depends on risk of recurrence, age, comorbidities
Options for Systemic Adjuvant Therapy
Endocrine Therapy

- Targets only ER or PR+ tumors
- Premenopausal women:
  - Tamoxifen for 5 years, sometimes 10 years
  - LHRH/BSO and Aromatase Inhibitors
- Postmenopausal women:
  - Aromatase Inhibitor
  - Sequential therapy (Tamoxifen $\rightarrow$ AI, for today of 5 years)
  - Extended therapy (Tamoxifen for 5 followed by AI for 5 years)
- Length of therapy is under investigation
Options for Systemic Adjuvant Therapy

Other therapies

• Biologic Therapy
  – Targeting Her2 amplification
    • Trastuzumab, pertuzumab
  – Other biologics in trials
    • Everolimus

• Bisphosphonates
  – Used for prevention of osteoporosis
  – May prevent bone metastasis
How choices are made

• Tumor related factors
  – Lymph node status
  – Tumor size, receptors, grade
  – Mathematical Models (Adjuvant online)
  – Oncotype Dx testing (for Er/Pr+ tumors only)

• Additional evaluation
  – Family History/Genetic Testing
Long-Term Risk of Recurrence:
<1cm vs. 1-2cm

Joensuu, Cancer 1999
### Effect of Nuclear Grade on Recurrence

<table>
<thead>
<tr>
<th>Tumor Size</th>
<th>.0 -1.0 cm</th>
<th>1.1-2.0 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Grade</td>
<td>5 year RFS</td>
<td>10 year RFS</td>
</tr>
<tr>
<td>Grade I</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>Grade II</td>
<td>89</td>
<td>84</td>
</tr>
<tr>
<td>Grade III</td>
<td>86</td>
<td>74</td>
</tr>
</tbody>
</table>

Chia, JCO 2004
Long-Term Risk of Recurrence: Estrogen Receptor +/-

Saphner, JCO 1996
Breast Cancer Survival After Tamoxifen

- **Recurrences**
  - 15% at 5 years
  - 17% at 10 years
  - 68% at 15 years
- **Breast Cancer Deaths**
  - 9% at 5 years
  - 18% at 10 years
  - 73% at 15 years

Tamoxifen effect varies with ER expression

Patients receiving any endocrine therapy (n = 777)

Best Cutpoint: IHC score >2 (p<0.0001)

IHC Score (% patients)
- 8 (5.8%)
- 7 (19.8%)
- 5 (17.4%)
- 6 (23.4%)
- 4 (11.7%)
- 3 (5.1%)
- 2 (2.1%)
- 0 (14.7%)

ER positive

ER negative

Harvey, JCO 1999
Estimation of Risk and Benefit of Treatment

- Decisions for adjuvant therapy need to consider
  - Absolute benefits of treatment
    - LN status, size, grade, receptor status
  - Risks of treatment
    - Short and long term
    - Co-morbidity

- Mathematical Model – Adjuvant!
  - Developed to assess risk based on tumor related factors and comorbidities
Validation of Adjuvant! Model

- 10 year risk based on model vs actual outcomes in a population 5600 women in BC
  - (A) overall, (B) breast cancer–specific, and (C) event-free survival.
- Underestimates risk for 20-35 y/o
- Overestimates risk for older women

- Recent updates account for
  - Poorer prognosis of young women
  - Incorporates lymphovascular invasion and Her2 status

Olivetti JCO 2005
Case 1

- 41 year old woman
  - 1.0 cm tumor poorly differentiated ductal carcinoma
  - Er 60%, Pr 40%
  - Node negative
Case 2

- 60 year old woman
  - 2.5 cm well differentiated ductal carcinoma
  - Er 90%, Pr 90%
  - Node Negative
Can molecular characteristics of breast cancer better define risk of recurrence?

- Models do not incorporate other than clinical/pathologic features
- Recent advances in molecular characterization in breast cancer
- Study of genetic changes in tumor tissue and prognosis
- Tumor blocks from 2 large trials were used to identify a set of genes which correlate with risk of recurrence.

Paik, NEJM 2004
Can molecular characteristics of breast cancer better define risk of recurrence?

Paik, NEJM 2004
Estimates of the Rate of Distant Recurrence at 10 years

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Percentage of Patients</th>
<th>Rate of Distant Recurrence at 10 Yr (95% CI)†</th>
<th>P&lt;.0001 low vs high</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>51</td>
<td>6.8 (4.0–9.6)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>22</td>
<td>14.3 (8.3–20.3)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>27</td>
<td>30.5 (23.6–37.4)</td>
<td></td>
</tr>
</tbody>
</table>

Paik, NEJM 2004
TAILORx Trial

Node Negative ER+

OncotypeDX™ Assay

RS < 11
Hormone Therapy
Risk < 6%

RS 11-25
Randomize
Hormone Rx
vs.
Chemotherapy
Risk 6-17%

RS > 25
Chemotherapy +
Hormone Rx
Risk 18+%
Low Recurrence Score Associated with Excellent Survival

Sparano NEJM 2015
Case 1

- 41 year old woman
  - 1.0 cm PD IDCA, Er+, Pr+, LN-

- Oncotype Dx
  - Recurrence score 31
    - Greater than 30% risk of recurrence over 10 years after 5 years of tamoxifen

- Treatment
  - Add chemotherapy to endocrine therapy
Case 2

• 60 year old woman
  – 2.5 cm WD IDCA, Er+, Pr+, LN-

• Oncotype Dx
  – Recurrence score 0
    • Less than 10% risk of recurrence over 10 years after 5 years of tamoxifen

• Treatment
  – Tamoxifen → AI or AI alone
Can Bisphosphonates Prevent Bone Metastasis?
Bisphosphonates and Breast Cancer

• Both bisphosphonates and rank ligand inhibitors have been shown to:
  – Prevent fracture in patient with bone metastasis
  – Prevent aromatase inhibitor associated bone loss
  – Prevent menopause related bone loss in women who have chemotherapy induced menopause

Hadji AnnOnc 2011
Shapiro EuJCan 2011
Ability of bisphosphonates to inhibit cancer cell growth

Ziebart 2013
## Clinical Trials Using Bisphosphonates

<table>
<thead>
<tr>
<th>Study year</th>
<th>Intervention</th>
<th>Duration of treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCSG-12 (2011)</td>
<td>Zoledronic acid/Observation</td>
<td>3 years</td>
<td>62 months</td>
</tr>
<tr>
<td>AZURE (2011)</td>
<td>Zoledronic acid/Observation</td>
<td>5 years</td>
<td>59 months</td>
</tr>
<tr>
<td>E-ZO-FAST (2009)</td>
<td>Upfront or delayed zolendronic acid</td>
<td>5 years</td>
<td>36 months</td>
</tr>
<tr>
<td>Z-FAST (2012)</td>
<td>Upfront or delayed zolendronic acid</td>
<td>5 years</td>
<td>61 months</td>
</tr>
<tr>
<td>ZO-FAST (2013)</td>
<td>Upfront or delayed zolendronic acid</td>
<td>5 years</td>
<td>60 months</td>
</tr>
<tr>
<td>Talahashi et al., (2013)</td>
<td>Upfront or delayed zolendronic acid</td>
<td>1 year</td>
<td>36 months</td>
</tr>
<tr>
<td>Leal et al., (2010)</td>
<td>Zoledronic acid/Observation</td>
<td>1 year</td>
<td>96 months</td>
</tr>
<tr>
<td>Aft et al., (2012)</td>
<td>Zoledronic acid/Observation</td>
<td></td>
<td>61.9 months</td>
</tr>
</tbody>
</table>
### Meta-analyses of randomized trials

<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Postmenopausal women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>0.94 (0.87–1.01) p=0.08</td>
<td>0.82 (0.74–0.92) p=0.0003</td>
</tr>
<tr>
<td>Bone Recurrence</td>
<td>0.83 (0.73–0.94) p=0.004</td>
<td>0.72 (0.60–0.86) p=0.0002</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.91 (0.83–0.99) p=0.04</td>
<td>0.82 (0.73–0.93) p=0.002</td>
</tr>
</tbody>
</table>

- 18,766 women in trials of 2–5 years of bisphosphonate with median follow-up 5-6 woman-years
- 3453 first recurrences, and 2106 subsequent deaths
Second Primary Cancers
Case 1

- 41 year old woman
  - 1.0 cm poorly differentiated ductal carcinoma
  - Er 60%, Pr 40%, Her 2 -
  - Node negative
  - T1N0M0 (Stage I)

- Family history
  - Paternal aunt with early breast cancer
  - Paternal aunt with ovarian cancer
Case 2

- 60 year old woman
  - 2.5 cm well differentiated ductal carcinoma
  - Er 90%, Pr 90%
  - Node negative
  - T2N0M0 (Stage II)

- Family history
  - Mother breast cancer at 70
  - Paternal grand mother breast cancer 65
# Effect of Family History on Second Primary Breast Cancers

<table>
<thead>
<tr>
<th>Family History</th>
<th>Positive FHx</th>
<th>Negative FHx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vlastos 2002</td>
<td>9.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Brekelmans 1999</td>
<td>10.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Eccles 2001</td>
<td>35.9</td>
<td>16</td>
</tr>
<tr>
<td>Anderson 1985</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Chabner 1998</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Pierce 2000</td>
<td>22</td>
<td>2</td>
</tr>
</tbody>
</table>

**Risk of 2\textsuperscript{nd} primary**
- Negative FHx: 5-10% over 10-20 years
- Positive FHx: 15-35% over 10-20 years
Options for Genetic Testing

- Panel testing has changed the way cancer genetic testing is offered due to
  - Next generation sequencing
  - Myriad lawsuit resolution June 2013
  - Advancement in cancer predisposition research

- Panel testing for Hereditary Breast Cancer
  - BRCA1 and BRCA2
  - 6 gene panel: BRCA1, BRCA2, CDH1, PTEN, TP53 and STK11
  - Multigene panel: 18 - 40 gene panels
High-penetrance, rare cancer predisposition genes (Relative risk \( \geq 5 \))

Moderate risk alleles (Relative risk \( \geq 1.5 \) and < 5.0)

Low penetrance, high frequency risk alleles* (Relative risk < 1.5)

Very Rare

Common

Population Frequency

Genome-wide Association Studies

Stadler JCO 2010
Multiplex panel testing for analysis of germline cancer susceptibility

<table>
<thead>
<tr>
<th>Category</th>
<th>Gene</th>
<th>Ambry CancerNext</th>
<th>Myriad myRisk</th>
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</thead>
<tbody>
<tr>
<td>High risk breast cancer genes</td>
<td>BRCA1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDH1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>STK11</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Moderate risk breast and ovarian cancer genes</td>
<td>ATM</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BARD1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BRIP1</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CHEK2</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>MRE11A</td>
<td>X</td>
<td></td>
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<td></td>
<td>NBN</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>PALB2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>RAD50</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RAD51C</td>
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<td></td>
<td>RAD51D</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Colon or other cancer genes</td>
<td>APC</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>BMP2</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>MSH2</td>
<td>X</td>
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<td></td>
<td>MSH6</td>
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<td>X</td>
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<tr>
<td></td>
<td>MUTYH</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>PMS2</td>
<td>X</td>
<td></td>
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<tr>
<td></td>
<td>SMAD4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDK4</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>CDKN2A</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

NCCN guidelines exist for testing and intensive clinical management of breast and other associated cancer risks

- Breast cancer risks variably defined (or controversial)
- No guidelines for testing or management of carriers
- Unclear associated cancer risks

- Established risks and guidelines for other cancers
- Breast cancer risk unclear or controversial

BROCA: Above + 21 more genes; Fulgent: Above + 83 more genes

Presented By Kara Maxwell at 2014 ASCO Annual Meeting
## Risk of Second Primary Breast Cancer for BRCA Carriers

<table>
<thead>
<tr>
<th></th>
<th>5 year</th>
<th>10 year</th>
<th>15 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Mutation</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>BRCA 1</td>
<td>15%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>(9.5-20%)</td>
<td>(21-33%)</td>
<td>(28-38%)</td>
</tr>
<tr>
<td>BRCA 2</td>
<td>9%</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>(5-14%)</td>
<td>(15-23%)</td>
<td>(16-29%)</td>
</tr>
</tbody>
</table>

Risks is higher for women diagnosed at younger ages.

Molina-Montes The Breast 2014
Case 1

- 41 year old woman
  - 1.0 cm PD IDCA, Er+, Pr+, LN-
- Family history
  - Paternal aunt with early breast cancer
    - BRCA1+
    - Paternal aunt with ovarian cancer
- BRCA1+: 33% or greater risk for 2nd cancer
  - Consider bilateral mastectomies and BSO
- BRCA1-: 3-5% risk of 2nd primary
  - No change in management
Case 2

- 60 year old woman
  - 2.5 cm well differentiated ductal carcinoma
  - Er 90%, Pr 90%
  - Node Negative

- Family history
  - Mother breast cancer at 70
  - Paternal grand mother breast cancer 65

- Risk of 2nd primary may be 15% at 10-20 years
  - No change in management
Fertility Preservation

- Fertility after breast cancer is an important consideration
- Pregnancy is safe after a breast cancer diagnosis
- Options to consider for fertility preservation
  - Oocyte or embryo cryopreservation
    • Safe but takes time…
  - LHRH agonist during chemotherapy
    • Randomized controlled trial of chemotherapy +/- LHRH agonist in Er- breast cancer
    • Examined ovarian failure at 2 years
      - 22 v 8% ovarian failure (OR 0.30 p=0.02)
      - 12 vs 22 achieved pregnancy (OR 2.45 p=0.03)
      - 78 vs 89% 4 year estimated survival (p=0.04)

Lambertini BMCMed 2016
Moore NEJM 2015
Case 1

• 41 year old woman
  – 1.0 cm PD IDCA, Er+, Pr+, LN-
  – Oncotype Dx testing revealed Recurrence score 31
  – BRCA 1 mutation

• Desires fertility preservation
  – Chemotherapy has about 50% chance of inducing menopause
  – Options include
    • Harvest with AI stimulation
    • LHRH agonist starting 2 weeks before chemotherapy if able
Conclusions

• Treatment options
  – Surgical
  – Systemic Therapy
    • Chemotherapy, biologic therapy, hormonal therapy
    • Bisphosphonates

• How decisions regarding best treatment for any specific patient are made

• Important considerations
  – Familial and hereditary factors and risk of additional primary cancers
  – Fertility preservation
Sunset at the North Pole