Surgical Management of Locally Advanced Breast Cancer in a Resource-poor Setting

Mr Peter Bird FRACS, AIC Kijabe Hospital
Locally Advanced Breast Cancer

NCCN Guidelines

- Any tumour Stage III

<table>
<thead>
<tr>
<th>Stage</th>
<th>T0</th>
<th>N2</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
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<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
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<tr>
<td>IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
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<td></td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
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<td>N2</td>
<td>M0</td>
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<td>Any T</td>
<td>N3</td>
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<td>IIIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
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<tr>
<td></td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
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</tbody>
</table>
Locally Advanced Breast Cancer

EUSOMA website – European Society of Breast Cancer Specialists

• Tumour >5 cm measured clinically, by ultrasound or mammography
• Proven skin involvement (not dermis alone)
• Chest wall muscle or chest wall skeletal involvement
• Fixed axillary lymph nodes
• Tumour-positive apical (infraclavicular) node
Locally Advanced Breast Cancer

**Primary Tumor (T)**

<table>
<thead>
<tr>
<th>T</th>
<th>Description</th>
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<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Tis (DCIS)</td>
<td>Ductal carcinoma in situ</td>
</tr>
<tr>
<td>Tis (LCIS)</td>
<td>Lobular carcinoma in situ</td>
</tr>
<tr>
<td>Tis (Paget’s)</td>
<td>Paget’s disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget’s disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget’s disease should still be noted</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 20 mm in greatest dimension</td>
</tr>
<tr>
<td>T1mi</td>
<td>Tumor ≤ 1 mm in greatest dimension</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor &gt; 1 mm but ≤ 5 mm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 5 mm but ≤ 10 mm in greatest dimension</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor &gt; 10 mm but ≤ 20 mm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 20 mm but ≤ 50 mm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 50 mm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)</td>
</tr>
</tbody>
</table>

**Note:** Invasion of the dermis alone does not qualify as T4

| T4a | Extension to the chest wall, not including only pectoralis muscle adherence/invasion |
| T4b | Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma |
| T4c | Both T4a and T4b |
| T4d | Inflammatory carcinoma (see “Rules for Classification”) |
Locally Advanced Breast Cancer

Regional Lymph Nodes (N)

**CLINICAL**

NX  Regional lymph nodes cannot be assessed (for example, previously removed)
N0  No regional lymph node metastases
N1  Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2  Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
N2a Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3  Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a Metastases in ipsilateral infraclavicular lymph node(s)
N3b Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c Metastases in ipsilateral supraclavicular lymph node(s)
Locally Advanced Breast Cancer

• Some historical French terms...

Peau d’orange
Cancer-en-cuirasse
First described by French surgeon Alfred Velpeau in 1838
Kijabe Breast Cancer Study
2001-2007

- 125 female, 4 male between 2001 and 2007
- Excluded non-Africans, non-IDC tumours
- Median age 47 (range 26-76)
- Mean parity 4.1
- Mean size of tumour (clinical) 6.8cm
- Average length of history – 12 months
- LABC 59%

Kijabe Breast Cancer Cases
2011-12

- 59 cases Jan 11 to Feb 12
- 48 IDC (NOS); 11 special types
- Median age 45
- 62.5% under 50yo
- LABC 48%
Kijabe Breast Cancer Cases

2015

- 92 cases Jan to Dec
- 83 IDC (NOS); 6 special types
- 3 DCIS
- Median age 50.9 (range 22-92)
- 54.9% under 50yo
- LABC 51%
Workup & Staging LABC

- History and examination
- CBC, LFTs
- Mammography +/- targeted US
- Liver US, CXR, CT scans (chest, abdo, pelvis, brain)
- Pathology (CBx), including ER/PR/HER2
- Breast MRI, PET scan, bone scan
Workup & Staging LABC

- History and examination
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- Liver US, CXR, CT scans (chest, abdo, pelvis, brain)
- Pathology (CBx), including ER/PR/HER2
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## Recent IHC Data from Sub-Saharan Africa

<table>
<thead>
<tr>
<th>Country</th>
<th>Year Published</th>
<th>Pts</th>
<th>ER/PR % +ve</th>
<th>HER2 % +ve</th>
<th>TNBC %</th>
<th>Journal</th>
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<tbody>
<tr>
<td>Kenya</td>
<td>2006</td>
<td>158</td>
<td>37/49</td>
<td>13</td>
<td>28</td>
<td>Ann Quant Cytol Histol</td>
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<tr>
<td>Nigeria</td>
<td>2008</td>
<td>192</td>
<td>71/64</td>
<td>6</td>
<td></td>
<td>Breast Cancer Res Treat</td>
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<tr>
<td>Kenya</td>
<td>2008</td>
<td>129</td>
<td>24/34</td>
<td>26</td>
<td>44</td>
<td>Ann Surg Oncol</td>
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<tr>
<td>Kenya</td>
<td>2010</td>
<td>101</td>
<td>46/42</td>
<td>23</td>
<td></td>
<td>Annal Afr Surg</td>
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<tr>
<td>Ghana</td>
<td>2010</td>
<td>75</td>
<td>25/33</td>
<td>4</td>
<td>75</td>
<td>Cancer</td>
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<tr>
<td>Ghana</td>
<td>2012</td>
<td>330</td>
<td>47/13</td>
<td>20</td>
<td>43</td>
<td>Ghana Med J</td>
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<tr>
<td>South Africa</td>
<td>2013</td>
<td>1092</td>
<td>64/52</td>
<td>26</td>
<td>20</td>
<td>Brit Cancer Res</td>
</tr>
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</table>
What could account for the highly variable ER/PR/HER2 results?

• Specimen handling
  – Degradation of receptors if poorly fixed
    • incorrect concentration of formalin
    • tumour not cut before being placed in fixative
    • ratio of specimen tissue to formalin ideally 1:10
    • Long warm ischaemia time (>60 min)

• Methodology
  – Auto vs manual IHC
  – Antibody retrieval, antibody type
  – Cut off has changed over the years (Current ASCO/CAP guidelines <1%, J Clin Oncol 2010)
  – Double reporting in studies not uniform
Is breast cancer from Sub Saharan Africa truly receptor poor? Prevalence of ER/PR/HER2 in breast cancer from Kenya


- 301 consecutive IDC cases
- ASCO/CAP Guidelines followed for test accuracy and reporting of results
- Rigorous specimen handling protocols
  - 10% neutral buffered formalin, rapid immersion, large specimens bivalve, times recorded etc
- Automated platforms for IHC determination
- ER/PR reporting by Allred system
  - 1% staining or more deemed positive (ASCO/CAP Guidelines 2010)
- HER2 2+ subjected to FISH analysis
- Double reporting by pathologists
Is breast cancer from Sub Saharan Africa truly receptor poor? Prevalence of ER/PR/HER2 in breast cancer from Kenya


RESULTS:

• 301 cases of invasive BC (84% IDC)
• Median age 47.5
• ER positive 73%
• PR positive 65%
• HER2 18.5%
• TNBC 20.2 %
Principles in Breast Cancer Management (1)

Management of the breast cancer patient involves treating two separate entities: the locoregional disease and the systemic disease
Principles in Breast Cancer Management (2)

• In most cases with LABC, systemic treatment (PSTx) is given first:
  – able to downsize tumours for clear surgical margins (sometimes BCS), can measure treatment response and alter if necessary, better prognostication etc.

• PSTx is followed by surgery then RT then HT

• However, survival not affected by sequence of treatment
Principles in Breast Cancer Management (3)

The management of a woman with breast cancer involves a MULTIDISCIPLINARY TEAM APPROACH

Her (his) treatment needs to be individualized
Treatment Options for Locally Advanced Breast Cancer

- **SURGERY**
  - Breast conserving (after PSTx), mastectomy +/- chest wall reconstruction, axillary dissection
- **CHEMOTHERAPY**
  - Usually before surgery. Anthracycline-based +/- taxanes
- **HORMONAL THERAPY**
  - SERMs, AIs, LHRH analogues, oophorectomy
- **TARGETED BIOLOGICAL THERAPY**
  - Trastuzumab and other new monoclonal AB therapies
- **RADIOTHERAPY**
  - Teletherapy, brachytherapy
Treatment Options and Costs in Kijabe and Kenya

Mastectomy USD 600
(At Kijabe)

Radiotherapy USD 1200
(In private facilities. Done at KNH for USD200?)

Chemotherapy USD 1200
(Done in Nairobi. Done at KNH for USD200?)

Biological Rx
(Not affordable!)

Hormonal Rx USD 650
(5 years of tamoxifen)

TOTAL USD 3650
Annual GNI per Capita 2014 (213 countries)

<table>
<thead>
<tr>
<th>Country</th>
<th>GNI per Capita</th>
<th>Rank</th>
</tr>
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<tbody>
<tr>
<td>Nigeria</td>
<td>$2950</td>
<td>151</td>
</tr>
<tr>
<td>Ghana</td>
<td>$1620</td>
<td>168</td>
</tr>
<tr>
<td>Cote d’Ivoire</td>
<td>$1550</td>
<td>172</td>
</tr>
<tr>
<td>Kenya</td>
<td>$1290</td>
<td>177</td>
</tr>
<tr>
<td>S Sudan</td>
<td>$960</td>
<td>186</td>
</tr>
<tr>
<td>Tanzania</td>
<td>$930</td>
<td>187</td>
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<tr>
<td>Uganda</td>
<td>$660</td>
<td>197</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>$550</td>
<td>203</td>
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<tr>
<td>Somalia</td>
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<tr>
<td>Bermuda</td>
<td>$106,140</td>
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<tr>
<td>Australia</td>
<td>$64,680</td>
<td>10</td>
</tr>
<tr>
<td>USA</td>
<td>$55,200</td>
<td>15</td>
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</table>
Management of LABC in Kijabe, Kenya

- Patients of highly variable economic status – determines possibility of pre-op systemic Rx, extent of surgery & adjuvant Rx
- Preop systemic Rx, MRM & adjuvant therapies offered to wealthier patients
  (NCCN Optimal Level available in Kenya)
- Poor patients get mastectomy & AD +/- LD flap coverage only if the tumour can be macroscopically excised, followed by Hormonal Rx if appropriate
Surgical Options in LABC

- Only attempt surgery if all macroscopic tumour can be removed!
- Modified radical (Patey) mastectomy – breast and axillary nodes removed
- AD to Level II unless palpable disease in Level III
- “Partial radical” mastectomy if tumour invasion into muscles?
- Lat dorsi flap or STSG for large defects
- Little role for radical mastectomy, except when no adjuvant or neoadjuvant treatment is available – very deforming; but excellent local control possible (Halsted, 1894)
Halsted’s Radical Mastectomy Series

*Ann Surg* 1894

- 50 cases of radical mastectomy (not consecutive?)
- Average age 51
- All 50 with nodal disease, so Stage II or III
- LABC 33/48 (68%)
- 27 of 50 (54%) prognosis regarded as “hopeless or unfavourable” after surgery & path assessment
- 6% local recurrence rate (“Return of the disease in the field of operation”)

Halsted WS. The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894. *Ann Surg* 1894 Vol 20: 497-555
Halsted’s Radical Mastectomy

- Removal of skin, breast, axillary nodes to level III, pectoralis muscles
- IM nodes not removed
- Chest wall defect skin grafted after granulating
Sixty-Three Latissimus Dorsi Myocutaneous Flaps at Kijabe Hospital
P Bird, 2000-2016

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of cases</th>
<th>Pathology</th>
<th>Complications</th>
<th>Local recurrence</th>
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<tbody>
<tr>
<td>Coverage of anterior chest wall defect</td>
<td>46</td>
<td>Breast malignancy, soft tissue sarcoma</td>
<td>3 minor flap-skin dehiscences</td>
<td>2</td>
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<tr>
<td>Augmentation after partial mastectomy</td>
<td>6</td>
<td>Breast cancer</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Delayed BR</td>
<td>3</td>
<td>Breast cancer</td>
<td>Implant Migration</td>
<td>N/A</td>
</tr>
<tr>
<td>Coverage of posterior chest wall defect</td>
<td>2</td>
<td>Recurrent soft tissue sarcoma</td>
<td>Partial flap necrosis x1</td>
<td>0</td>
</tr>
<tr>
<td>Neck contracture, Thoracoplasty</td>
<td>3</td>
<td>Burn, chronic empyema</td>
<td>1 minor flap-skin dehiscence</td>
<td>N/A</td>
</tr>
<tr>
<td>Immediate BR</td>
<td>3</td>
<td>Breast cancer</td>
<td>None</td>
<td>0</td>
</tr>
</tbody>
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Biological Therapies

- Oncogene HER-2-neu receptor over-expressed in 15-20% of BCs (higher in Africans?)
- Targeted monoclonal antibody therapies work against this receptor
- Trastuzumab (Herceptin) monthly for 12 months
- 2015 NCCN Guidelines recommends neoadjuvant dual MAB therapy for HER2 +ve pts with Stage II disease
  - Trastuzumab/pertuzumab/docetaxel
- Prohibitive expense ($2500 per dose for 55kg pt)
- Trastuzumab on WHO Essential Medicines List 2015!
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Radiotherapy Resources in Africa 2010

Kenya and Neighbours  8

Kenya  2 (Private 7)
Ethiopia  2
South Sudan  0
Somalia  0
Uganda  1
Tanzania  3

Population: 243 million

Australia (public)  33
Australia (private)  26

Population: 23 million

Abdel-Wahab et al, Status of radiotherapy resources in Africa: an IAEA analysis Lancet Oncol 2013
Radiotherapy Resources in Africa 2010

<table>
<thead>
<tr>
<th></th>
<th>Population (thousands)</th>
<th>GNI per head* (US$)</th>
<th>New cancer cases in 2008† (x10³)</th>
<th>Patients who need radiotherapy‡ (x10³)</th>
<th>Machine needed§</th>
<th>Existing machines</th>
<th>Teletherapy per million people</th>
<th>Additional machines needed</th>
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<tbody>
<tr>
<td><strong>East Africa</strong></td>
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<td></td>
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<td>Burundi</td>
<td>8074</td>
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<td>Somalia‡</td>
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<td>0.03</td>
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Radiotherapy Resources in Africa 2010

<table>
<thead>
<tr>
<th>West Africa</th>
<th>Population (thousands)</th>
<th>GNI per head* (US$)</th>
<th>New cancer cases in 2008 † (×10³)</th>
<th>Patients who need radiotherapy‡ (×10³)</th>
<th>Machine needed§</th>
<th>Existing machines</th>
<th>Teledtherapy per million people</th>
<th>Additional machines needed</th>
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<td>Benin</td>
<td>8 662</td>
<td>700</td>
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<td>3·382</td>
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<tr>
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Abdel-Wahab et al, Status of radiotherapy resources in Africa: an IAEA analysis Lancet Oncol 2013
Conclusions

• Most BCs in Africa present locally advanced and multidisciplinary treatment is unaffordable/unavailable

• BC management in LMICs must be tailored to best fit the economic circumstances

• Surgery is the mainstay of treatment of LABC in LMICs and surgeons need to be taught techniques to meet this challenge
Kijabe, Kenya
Principles in Breast Cancer Management (2)

• Improvements in survival in the last 70 years have been made in treating the systemic disease

• 7-11% absolute improvement in 10-year survival for women <50

Principles in Breast Cancer Management (3)

- The ONLY reason to perform breast-conserving surgery (BCS) is **cosmesis**.

- Oncologically, BCS is a second best option for local control (because of increased local recurrence requiring further treatment and the need for RT, but no difference in survival).

- BCS is a compromise between cosmesis and local control.
Principles in Breast Cancer Management (4)

- In most cases of BCS, adequate local control can only be achieved with clear margins (“No ink on margins”) and the addition of RT
  16% absolute improvement (19% vs 35%) in BC recurrence risk

- Adjuvant RT also prolongs BC-specific survival in BCS
  Reduces the overall death rate at 15 years by 3.8%: from 25.2% to 21.4%

Margins in Stage I & II Breast Conserving Surgery (“No ink on tumour”)

Clinical Investigation: Breast Cancer

Society of Surgical Oncology—American Society for Radiation Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Stages I and II Invasive Breast Cancer

Meena S. Moran, MD, * Stuart J. Schnitt, MD, † Armando E. Giuliano, MD, ‡ Jay R. Harris, MD, § Seema A. Khan, MD, ‖ Janet Horton, MD, ¶ Suzanne Klimberg, MD, # Mariana Chavez-MacGregor, MD, ** Gary Freedman, MD, †† Nehmat Houssami, MD, PhD, ‡‡ Peggy L. Johnson, §§ and Monica Morrow, MD}
Hormonal Therapy

• Aromatase inhibitors provide superior DFS compare to tamoxifen in post-menopausal ER positive pts, but no survival advantage shown yet
  ATAC Trial, Lancet Oncol 2010, 10 yr follow up

• Ovarian suppression plus SERMs in premenopausal ER positive pts
  • SOFT Trial: women 35 years and younger, the 5-year breast-cancer-free rate:
    • 67.7% in those on tamoxifen alone
    • 78.9% in those on tamoxifen plus ovarian suppression
    • 83.4% in those on exemestane plus ovarian suppression
    • Most marked improvement in those who received CT and remained premenopausal

SOFT & TEXT trials, NEJM 2014
Radiotherapy

- 50-60Gy given in 25 fractionated doses over 5-6 weeks
- RT is critical in achieving acceptable LR rates and improving survival in BCS
- Irradiating an axilla that has had an axillary dissection will result in a higher incidence of lymphoedema
- Tissue can only be safely irradiated once at these doses
- Survival advantage irradiating the chest wall and regional nodes after mastectomy for node positive disease, even 1-3 nodes (EBCTCG Lancet 2014)
- RT will cause skin/tissue fibrosis, telangiectasia and deformity in some cases; therefore, adjuvant RT is a relative contraindication to immediate breast reconstruction
- Rarely, can cause radiation-induced sarcoma (RIS)