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Breast Surgical Oncology

INFLAMMATORY BREAST CANCER: AN UNDERAPPRECIATED ENTITY
Disclosures

I do not have anything to disclose
Objectives

1. Define the disease
2. Explore the current treatment recommendations
3. State the limitations of what we know
**Historical Context**

1814: Sir Thomas Bell
- “purple color . . on the skin over the tumor accompanied by shooting pains”

1887: Thomas Bryant
- Dermal lymphatic invasion

1875: Volkmann
- Mastitis carcinomatosa

1924: Lee and Tannenbaum
- “Inflammatory carcinoma of the breast”
Definition Over Time

• Evolution over time
• Current definition-AJCC 7th edition
  – Erythema and warmth encompassing at least one third of the skin of the breast
  – Demonstration of tumor in the dermal lymphatics not required for diagnosis
Epidemiology-United States

• Comprises 2.5% of all breast cancers
  – 6,231 people will be diagnosed this year
  – Incidence is increasing (1.23%/year)
• Comprises 7% of all breast cancer related deaths
  – Estimated 2,862 will die from the disease
  – Mortality has decreased in recent decades
    • DFS increased from 62% to 76% between 1990 and 2010
  – Median survival 4 years
  – 5 year survival rate 30%
Epidemiology-United States

- Mean age at diagnosis-58.8
  - 66.5- men
  - 57- women

Epidemiology-World Wide

- 2.9% Spain
- 5% Turkey
- 5.4% France
- 12% Pakistan
- 55% Tunisia
- 6.2% Tunisia
- 11.1% Egypt
- 17% Nigeria
Epidemiology-Race Matters

- More common in African American and Hispanic American/Latina women

![Bar chart showing median survival months by race/ethnicity]
Epidemiology

- Risk factors
  - Obesity
  - Early age at menarche
  - Early age at first full-term pregnancy
- Predictors of poor prognosis
  - Higher stage at diagnosis
  - Grade 3 tumor
  - Premenopausal status
  - Obesity
Diagnosis-Clinical Presentation

- Clinical Presentation
  - Erythema and edema occupying at least 1/3 of the skin
  - Abrupt onset of symptoms (less than 3 months)
  - Mass often not identified
  - Classified as T4d

- Differential Diagnosis
  - Mastitis
  - Radiation change
  - Locally advanced breast cancer
  - Primary breast lymphoma
Diagnosis-Clinical Presentation
Diagnosis-Clinical Presentation
Diagnosis-Clinical Presentation
Diagnosis-Clinical Presentation
Diagnosis-Mammography

- Thickening of the skin (84%)
- Trabecular thickening (81%)
- Asymmetric focal density (61%)
- Microcalcifications (56%)
- Nipple retraction
- Axillary lymphadenopathy
- Breast mass (16%)

*Least sensitive mode of detection*
Diagnosis-Mammography
Diagnosis-Ultrasonography

- Skin thickening
- Mass
  - Irregular, hypoechoic, poorly defined margins
- Lymphadenopathy
Diagnosis-Magnetic Resonance Imaging

• Skin thickening
• Underlying mass
• Skin enhancement
• Axillary lymphadenopathy

• Limitations
  – Cost
  – Patient positioning
MRI
Diagnosis-Tissue

- Biopsy proven carcinoma is necessary for the diagnosis
- Core needle biopsy
- Skin punch biopsy
  - Not necessary for biopsy of inflammatory cancer to be made
Diagnosis-Tissue

- Majority of IBC cases are estrogen receptor negative
- Estrogen positivity linked to higher survival rates
- Her 2 positivity in 36-50% of IBC cases
- Tumor suppressor gene P53 mutations common
  - Associated with worse overall survival
- 96% have a genomic alteration
  - TP53 most common (62%)
Treatment

Inflammatory Breast Cancer

CLINICAL PRESENTATION

Clinical pathologic diagnosis of inflammatory breast cancer (IBC)
Stage T4d, N0-N3, M0

WORKUP

• History and physical exam by multidisciplinary team
• CBC
• Liver function tests
• Pathology review
• Determination of tumor ER/PR status and HER2 status
• Bilateral diagnostic mammogram, ultrasound as necessary
• Breast MRI (optional)
• Fertility counseling if premenopausal
• Bone scan or sodium fluoride PET/CT (category 2B)
• Chest/abdominal/pelvic diagnostic CT (category 2B)
• Chest diagnostic CT (if pulmonary symptoms are present)
• Genetic counseling if patient is at high risk for hereditary breast cancer
• FDG PET/CT scan (category 2B)

Response

Preoperative systemic therapy, anthracycline + taxane (preferred). If tumor HER2 positive, HER2-targeted therapy

No response

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment

Inflammatory Breast Cancer

TREATMENT^1

Response → Total mastectomy + level VII axillary dissection + radiation therapy to chest wall and supraclavicular area (plus internal mammary nodes if involved, consider internal mammary nodes if not clinically involved [category 3]) ± delayed breast reconstruction → Complete planned chemotherapy regimen course if not completed preoperatively plus endocrine treatment if ER-positive and/or PR-positive (sequential chemotherapy followed by endocrine therapy). Complete up to one year of HER2-targeted therapy if HER2 positive (category 1). May be administered concurrently with radiation therapy and with endocrine therapy if indicated.

No response → Consider additional systemic chemotherapy and/or preoperative radiation → Response → See above pathway → No response → Individualized treatment

^1Patients with stage IV or recurrent IBC should be treated according to the guideline for recurrence/stage IV disease (BINV-17 to BINV-22).
^2See Principles of Breast Reconstruction Following Surgery (BINV-H).
^3See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).
^4See Principles of Radiation Therapy (BINV-I).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Treatment-Neoadjuvant chemotherapy

- Standard treatment for IBC
- Prognosis linked to pathologic complete response rate
- Optimal NAC regimen has transformed over time
  - Anthracycline based regimens
    - Increased medial survival from 18 months to 30 months
  - Use of taxanes
    - Addition of paclitaxel improved overall survival from 41 weeks to 52 weeks
- Current standard for Her 2 negative tumors: anthracycline and taxane based regimen

Treatment-Neoadjuvant chemotherapy

- Limited data on benefit in IBC alone
- Trastuzumab
  - Increased pCR rate from 13% to 48%
  - Linked to decrease metastatic rate
- Lapatinib
  - Inferior to trastuzumab in achieving pCR (30.3% vs 22.7%)
- Pertuzumab
  - Improved pCR rate when added to trastuzumab
Treatment-Surgery

• Surgery alone results in poor overall survival
  – “when no cures can be expected, and no definite evidence of prolongation of life can be shown, it seems entirely unreasonable to treat these patients by radical mastectomy”

• Surgery improves locoregional control, disease-free survival and overall survival

• Should be considered in patients who respond to neoadjuvant chemotherapy with subsiding of inflammatory characteristics
<table>
<thead>
<tr>
<th>Author</th>
<th>LRC%</th>
<th>DFS%</th>
<th>OS%</th>
<th>Author</th>
<th>LRC%</th>
<th>DFS%</th>
<th>OS%</th>
</tr>
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<tr>
<td>Buzdar 1981</td>
<td>75</td>
<td>32</td>
<td>34</td>
<td>Maloisel 1990</td>
<td>NA</td>
<td>48</td>
<td>75</td>
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<tr>
<td>Lamb 1991</td>
<td>51</td>
<td>NA</td>
<td>30</td>
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<td>NA</td>
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<td>29</td>
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<td>NA</td>
<td>De Boer 2000</td>
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<tr>
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<td>NA</td>
<td>NA</td>
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<td>38</td>
<td>Bristol 2008</td>
<td>84</td>
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<td>51</td>
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<tr>
<td>Bourgier 2012</td>
<td>75</td>
<td>39</td>
<td>39</td>
<td>Damast 2010</td>
<td>87</td>
<td>40</td>
<td>61</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>62.5</strong></td>
<td><strong>24</strong></td>
<td><strong>34</strong></td>
<td><strong>Overmoyer Diseases of the Breast 2014</strong></td>
<td><strong>82</strong></td>
<td><strong>37</strong></td>
<td><strong>49</strong></td>
</tr>
</tbody>
</table>
Treatment-Surgery

• Mastectomy or lumpectomy?
• Sentinel lymph node biopsy or axillary dissection?
• Reconstruction or no reconstruction?
Treatment-Mastectomy vs lumpectomy

- Standard of care: Mastectomy
- Margin status
  - Positive margins associated with 0% overall survival
  - Reliable prognostic indicator
    - Curcio et al- 3 year OS, DFS, LRC
      - 47%, 38%, 60% with negative margins
      - 0%, 17%, 32% with positive margins
- Higher recurrence rates linked with breast conservation
  - Mixed results from previous series
Treatment-Sentinel node or axillary dissection

- Standard of care: Axillary dissection
- Rationale: Dermal lymphatics block migration of the tracer
  - SLN identification 80%
  - False negative rate 18.2%-40%
  - No way to improve rates

Treatment-Reconstruction yes or no

- Standard of care: Delayed reconstruction
- Similar locoregional recurrence rates despite presence of reconstruction
- Skin sparing mastectomy compromises margin status
- Radiation treatment increases complication rate with reconstruction
- No difference in survival between immediate and delayed reconstruction

Treatment-Radiation therapy

- Should include chest wall (including mastectomy scar), supraclavicular nodes, infraclavicular nodes, internal mammary nodes +/- axillary nodes
- Goal: brisk erythema of the skin
- Hyperfractionation resulted in higher locoregional control rates
  - No prospective randomized trials
  - Total 66 Gy given twice daily
  - Benefit seen in patients with partial response and those with suspicious margin status
  - Associated with higher lymphedema rate
Treatment-Radiation therapy

I.J. Bristol and T.A. Buchholz / Inflammatory Breast Cancer: Current Concepts in Local Management

Table 1
Locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) in patients treated before 1986 (n = 61) versus after 1986 (n = 54) at MD Anderson Cancer Center. Modified from Liao et al. [4].

<table>
<thead>
<tr>
<th></th>
<th>Before 1986</th>
<th>After 1986</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LRC</td>
<td>58</td>
<td>84</td>
<td>73</td>
</tr>
<tr>
<td>% DFS</td>
<td>26</td>
<td>39</td>
<td>32</td>
</tr>
<tr>
<td>% OS</td>
<td>35</td>
<td>46</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 2
Locoregional control (LRC), disease-free survival (DFS), and overall survival (OS) in patients treated before 1986 (n = 61; 10 CR, 27 PR, 24 NR) and after 1986 (n = 54; 7 CR, 34 PR, 13 NR) according to clinical response to chemotherapy at MD Anderson Cancer Center. Modified from Liao et al. [4].

<table>
<thead>
<tr>
<th></th>
<th>Before 1986</th>
<th>After 1986</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>LRC (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>88</td>
<td>100</td>
<td>94</td>
</tr>
<tr>
<td>PR</td>
<td>79</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td>NR</td>
<td>32</td>
<td>39</td>
<td>38</td>
</tr>
<tr>
<td>DFS (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>56</td>
<td>71</td>
<td>63</td>
</tr>
<tr>
<td>PR</td>
<td>39</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>NR</td>
<td>0</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>OS (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CR</td>
<td>56</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>PR</td>
<td>45</td>
<td>54</td>
<td>47</td>
</tr>
<tr>
<td>NR</td>
<td>11</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete response; PR = partial response; NR = no response; N/A = data not available.
Treatment-Radiation Disparities

- Medicare insurance, lower income, failure to receive adjuvant therapy, treatment at low-volume centers, treatment in South or West associated with underutilization of radiation therapy in IBC
Treatment-New Directions

• Radiation sensitizers
  – Phase II Capecitabine + radiotherapy converted 82% of inoperable cases to operable
  – 5-FU/ Capecitabine, vinorelbine + radiotherapy converted 100% of inoperable cases to operable
Recurrence/ Metastatic Disease

Sites of first relapse among stage III patients who recurred (N=203), and of metastatic disease among patients with stage IV disease at diagnosis (N=195).³

<table>
<thead>
<tr>
<th>Site</th>
<th>Stage III with recurrence</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Bone/Bone marrow</td>
<td>57</td>
<td>28</td>
</tr>
<tr>
<td>Brain/CNS/Meninges</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>Lung/Pleural Effusion</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>Liver</td>
<td>42</td>
<td>21</td>
</tr>
<tr>
<td>Chest Wall</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Regional Lymph Nodes²</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Contralateral locoregional Lymph Nodes³</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Ipsilateral Breast</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

³Totals may be greater than 100% as patients may have had more than one site of first recurrence.
²Includes ipsilateral axillary and supraclavicular lymph nodes
³Includes contralateral breast, contralateral supraclavicular lymph nodes
⁴Includes intraabdominal, other distant lymph nodes, other distant visceral, other distant non-visceral, and other.
## Recurrence/ Metastatic Disease

Sites of first recurrence (stage III) and of metastatic disease at diagnosis (stage IV), by tumor subtype.

<table>
<thead>
<tr>
<th>Site</th>
<th>Stage III with recurrence</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triple Negative N=72</td>
<td>HER2 + N=60</td>
</tr>
<tr>
<td></td>
<td>N (%) N (%) N (%) N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Bone/Bone marrow</td>
<td>17 (24) 10 (17) 25 (49)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Brain/CNS/Meninges</td>
<td>12 (17) 22 (37) 5 (10)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Lung/pleural effusion</td>
<td>18 (25) 9 (13) 11 (22)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>Liver</td>
<td>17 (24) 13 (22) 11 (22)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Chest Wall</td>
<td>15 (21) 8 (13) 5 (10)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Regional Lymph Nodes b</td>
<td>10 (14) 3 (5) 3 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Contralateral locoregional Lymph Nodes c</td>
<td>5 (7) 4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Skin</td>
<td>4 (6) 2 (3) 2 (4)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Ipsilateral breast</td>
<td>1 (1) 6 (10) 0</td>
<td>0</td>
</tr>
<tr>
<td>Other d</td>
<td>18 (25) 10 (17) 10 (20)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

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*Totals may be greater than 100% as patients may have had more than one site of first recurrence.

*bIncludes ipsilateral axillary and supraclavicular lymph nodes

*cIncludes contralateral breast, contralateral supraclavicular lymph nodes

*dIncludes intraabdominal, other distant lymph nodes, other distant visceral, other distant non-visceral, and other.
Other Considerations

- Genetics?
  - Currently no specific guidelines for IBC (based on same criteria as non-IBC)

- Fertility management?
  - Recommended by NCCN for younger patients
    - Same as recommendations for non-IBC
Conclusion

• Diagnosis is a clinical one with major therapeutic and prognostic implications
• Multimodality treatment is the current standard of care for IBC
• More research is needed to identify molecular targets for improved diagnosis and survival
MOC Questions

1. Which of the following is required for the diagnosis of inflammatory breast cancer?
   A. Tumor present in dermal lymphatics on histology
   B. Edema and erythema of at least 1/3 of the breast
   C. Mass present within the breast

2. All of the following are poor prognostic indicators in inflammatory breast cancer except:
   A. Estrogen receptor negative status
   B. High nuclear grade
   C. Premenopausal status
   D. Presence of an associated mass

3. True or False: In inflammatory breast cancer, complete axillary lymph node dissection is always the recommended surgical management of the axilla.

4. In the treatment of inflammatory breast cancer, NCCN Category 2A recommendations state that post-mastectomy radiation should be given to:
   A. Chest wall only
   B. Chest wall and axillary region only
   C. Chest wall, axillary and supraclavicular regions
Thank you!

QUESTIONS