Definition and Biology of Locally Advanced Breast Cancer (LABC)

Dr Yoon-Sim YAP
Senior Consultant,
Division of Medical Oncology
National Cancer Centre Singapore
Outline of Presentation

• Definition of LABC
  – TNM
  – Inflammatory BC
• Biology

• Conclusion
Definition of LABC

- Stage IIIA to IIIC disease
- Stage IIB disease (T3N0) - ? large operable

<table>
<thead>
<tr>
<th>When T is...</th>
<th>And N is...</th>
<th>And M is...</th>
<th>Then the stage group is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>N1</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>IIB</td>
</tr>
<tr>
<td>T0</td>
<td>N2</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T1</td>
<td>N2</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T2</td>
<td>N2</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T3</td>
<td>N2</td>
<td>M0</td>
<td>IIIA</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4</td>
<td>N1</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4</td>
<td>N2</td>
<td>M0</td>
<td>IIIB</td>
</tr>
<tr>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td>IIIC</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>IV</td>
</tr>
</tbody>
</table>
What is the TNM staging?
Primary Tumor Classification

- T3 – Tumor >50 mm in greatest dimension.
- T4 – Tumor of any size with direct extension to the chest wall and/or the skin (ulceration or macroscopic skin nodules)*.
  - T4a – Extension to 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**.

*Invasion of the dermis alone does not qualify as T4.
Clinical classification of regional lymph nodes

- cNX* – Regional lymph nodes cannot be assessed (e.g., previously removed).
- cN0 – No regional lymph node metastases (neither by imaging nor clinical exam).
- cN1 – Metastasis to movable ipsilateral level I, II axillary lymph nodes(s).
- cN1mi** – Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm).
- cN2 – Metastasis to ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in ipsilateral internal mammary nodes in the absence of clinically evident axillary node metastases.
  - cN2a – Metastasis to ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures.
  - cN2b – Metastasis only in ipsilateral internal mammary nodes, and in the absence of clinically evident axillary node metastases.
- cN3 – Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in 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.
  - cN3a – Metastasis to ipsilateral infraclavicular lymph node(s).
  - cN3b – Metastasis to ipsilateral internal mammary lymph node(s) and axillary lymph nodes.
  - cN3c – Metastasis in ipsilateral supraclavicular lymph node(s).
Summary of changes in the AJCC 8th edition

Incorporates grade, proliferation rate, ER, PR, HER2 and multigene panels (where available) as stage modifiers in prognostic staging group.

eg
T3 N1-2 M0 grade 1-2 becomes stage IB;
T2 N1 M0 grade 3 ER-PR- becomes IIIC;
under new prognostic staging!

Giuliano et al, CA Cancer Journal for Clinicians 2017
Inflammatory Breast Carcinoma (IBC)

- Aggressive form of locally advanced breast cancer.
- Primary IBC is a relatively rare disorder; ~1 to 5 percent of invasive breast cancers, and ~8.5% of LABCs.
- De novo IBC refers to primary disease.
- Typically present with pain and a tender, firm, and enlarged breast. The skin over the breast is reddened, warm, and thickened, with a "peau d'orange" (orange skin) appearance.
- “Secondary IBC’ is used to describe skin changes mimicking primary IBC, such as those resulting from non-inflammatory LABC or breast cancer recurrence in a previously treated breast and/or chest wall.

Tryfonidis et al, Nat Rev Clin Onc 2015
Primary vs Secondary IBC

31yo woman with rapid onset TNBC (BRCA1 carrier)

56yo woman with HR+HER2- breast cancer
Breast lump for >2yrs
Inflammatory Breast Carcinoma (IBC)

- The signs and symptoms of IBC arise rapidly, typically within weeks to 6 months.
- Usually accompanied by pathological findings of tumour emboli in dermal lymphatics, although this finding is not necessary or sufficient (if clinical symptoms are lacking) to confirm the diagnosis of IBC.

Haematoxylin and eosin stain of infiltrative inflammatory breast cancer (A). High-magnification image of inflammatory breast cancer tumour cells (B).
Woodward et al, Lancet Oncol 2017
Inflammatory Breast Carcinoma (IBC)

- On presentation, almost all women with IBC have lymph node involvement.
- Approximately one-third have distant metastases.
- IBC tends to have a higher preponderance of visceral metastases compared with other forms of breast cancer due to earlier and more aggressive hematogenous spread.
- An exclusion criteria in certain clinical trials, due to typically aggressive nature and worse prognosis.

Matro et al, Clin Breast Ca 2015
Biology of LABCs

- Probably similar “biology” to early breast cancers for most, especially if neglected, but some may be more aggressive intrinsically.
- Overall slightly higher percentage of HER2+ and triple negative subtypes.
- <5-10% of patients in EU, US present with LABC, vs ~60% in developing countries.
- IBC has distinct biological features.
- ‘Favourable’ histologies, such as tubular carcinomas, less likely to present at an advanced stage unless they have neglected for a long time.

Tryfonidis et al, Nat Rev Clin Onc 2015
Biology of LABCs

• Neoadjuvant trials often include a mixture of operable tumours and inoperable LABCs - different biology.
• Higher risk of relapse compared to early stage tumours due to tumour burden and possibility of micrometastatic disease at diagnosis.
• Patients who attain pathological complete response (pCR) defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival.
• The prognostic value is greatest in aggressive tumour subtypes.
• pCR is rare with neoadjuvant endocrine therapy; reduction in Ki67 and PEPI (Preoperative Endocrine Prognostic Index) are often used as surrogate of response.
Neoadjuvant setting - pCR rates lowest for lobular, grade 1, HR+HER2- in metaanalysis

Cortazar, Lancet 2014
**pCR rates in the real world**
(5 public hospitals in Singapore and Malaysia)

**Table 4.** pCR rates of breast cancer patients who underwent neoadjuvant chemotherapy stratified by ER, PR, and HER2 status.

<table>
<thead>
<tr>
<th>pCR (ypT0/is) (N = 510)</th>
<th>Adjusted odds ratio(^1) and 95% confidence interval</th>
<th>pCR (ypT0/is ypN0) (N = 560)</th>
<th>Adjusted odds ratio(^1) and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ER+ PR+ and HER2-</td>
<td></td>
<td>12</td>
<td>210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.4%</td>
<td>94.6%</td>
</tr>
<tr>
<td>ER+ PR+ and HER2+</td>
<td></td>
<td>8</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.8%</td>
<td>88.2%</td>
</tr>
<tr>
<td>ER- PR- and HER2+</td>
<td></td>
<td>30</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.3%</td>
<td>69.7%</td>
</tr>
<tr>
<td>ER- PR- and HER2-</td>
<td></td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20.7%</td>
<td>79.3%</td>
</tr>
</tbody>
</table>

ER, estrogen receptor.
Statistically significant values are formatted in bold.
\(^1\)adjusted for ethnicity, age, period of diagnosis, preneoadjuvant chemotherapy clinical T stage, grade, and neoadjuvant chemotherapy regimen.

Lim et al, Cancer Medicine 2016
Association between pCR and event-free survival, by breast cancer subtype

Cortazar et al, Lancet Oncol 2014
Characterisation of Residual Disease after neoadjuvant chemotherapy

Elements not always routinely included in the adjuvant setting but recommended in the pathology report of the post-NAST specimen.

Report the elements as for any other type of specimen, plus the following:

<table>
<thead>
<tr>
<th>Element</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>In the opinion of the working group, the largest dimension in (A) (longest blue arrow), together with tumor cellularity, is likely a better indicator of response than measurement (B) [19, 24]. The report should clearly state how the size was determined and which dimension was used for staging, especially in cases with scattered residual disease, where there is possible interobserver variability due to differences in guidelines regarding how size should be measured. (A) is needed to calculate the Residual Cancer Burden (RCB) score.</td>
</tr>
<tr>
<td>Cellularity</td>
<td>Assessment of average cancer cellularity across the largest cross section of the residual tumor bed (that contains residual cancer) is needed to calculate the Residual Cancer Burden (RCB) score.</td>
</tr>
<tr>
<td>Tumor bed</td>
<td>The largest distance between tumor cell foci including intervening areas of fibrosis. Size of largest metastasis is needed to calculate the Residual Cancer Burden (RCB) score.</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>Treatment effect</td>
<td></td>
</tr>
</tbody>
</table>

**Dimensions of largest cross section of entire area involved by scattered residual tumor foci**

1. **Size**
   - (A) Two dimensions of largest cross section of entire area involved by scattered residual tumor foci (e.g., largest distance between invasive tumor cell foci)
   - (B) Extent of largest contiguous focus of invasive carcinoma as recommended by AJCC 7th edition [23]

---

**Bossuyt et al, Ann Onc 2015**
Residual Cancer Burden

*Values must be entered into all fields for the calculation results to be accurate.

1. **Primary Tumor Bed**
   - Primary Tumor Bed Area: (mm) \(\times\) (mm)
   - Overall Cancer Cellularity (as percentage of area): (%)
   - Percentage of Cancer That Is \textit{in situ} Disease: (%)

2. **Lymph Nodes**
   - Number of Positive Lymph Nodes: 
   - Diameter of Largest Metastasis: (mm)

Residual Cancer Burden:
Residual Cancer Burden Class:

The following parameters are required from pathologic examination in order to calculate Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mm) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")
   - If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross-sectional area of primary tumor bed were submitted in cassettes A5 - A9")
3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:
   - 0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%
   - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
   - When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
   - Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.
   - e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

---

Triple negative

HR+ HER2-

All HER2+

Symmans et al, JCO 2017

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3
Molecular characterization of patients with pCR or early failure after neoadjuvant chemotherapy for LABC using NGS and nCounter assay

Frequent mutations: TP53 (65.8%), APC (43.4%), RB1 (32.9%), SMAD4 (27.6%), KIT (26.3%), MET (26.3%), PIK3CA (26.3%), ALK (21.1%), EGFR (19.7%), GNAQ (18.4%), MLH1 (18.4%), PTEN (18.4%), CDKN2A (17.1%), RET (15.8%), and VHL (15.8%).

The incidence of missense mutations in KRAS was much higher in patients with EF than in other groups ($p < 0.01$).

Park et al, Oncotarget 2015
Selected Biomarkers from Neoadjuvant Trials (mixture of operable BCs and LABCs)

- HER2+
  - PI3K pathway activation: PI3K mutations, low PTEN associated with resistance to trastuzumab, lapatinib (Rimawi, BCRT 2017; Shi, Ann Onc 2017; Bianchini, BrCaRes 2017)
  - HER2-enriched subtype, high levels of ERBB2/HER2 and low levels of ESR1 better response to trastuzumab, lapatinib (Llombart-Cussac, Lancet Onc 2017; Carey, JCO 2016; Fumagalli, JAMA Onc 2017)
  - TILs predictive of pCR and prognostic (IngoldHeppner, CCR 2016; Salgado, JAMA Onc 2015; Solinas Ca Trt Rev 2017)
Selected Biomarkers from Neoadjuvant/Presurgical Trials (mixture of operable BCs and LABCs)

- **Triple Negative**
  - PARPi-7, *BRCA1*ness and MP1/2 signatures associated with improved response to veliparib carboplatin (Severson, BrCaRes 2017; Wolf, npj BrCa 2017).
  - *BRCA1/2* germline mutation higher pCR overall (Hahnen, JAMA Onc 2017)
  - TILs predictive of pCR (Denkert, JCO 2015; Wimberly, Ca Immunol Res 2015)
- **HR+HER2-**
  - Oncotype RS low risk better clinical response and breast conservation rate than high risk (Ueno, Int J Oncol 2014)
  - TP53 mutations resistant to aromatase inhibition (Ellis, Nature 2012; Gellert, Nat Comm 2016)
  - Non-luminal subtypes resistant to palbociclib (Ma, CCR 2017)
Most “promising” biomarkers assessed on post-NAT residual tissue

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>Biomarker</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR+</td>
<td>Ki67 index</td>
<td>Prognosis&lt;sup&gt;58,59,63&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>PEPI score</td>
<td>Prognosis&lt;sup&gt;60&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Loss of ER positivity&lt;sup&gt;70,73,79&lt;/sup&gt;</td>
<td>Prognosis/Treatment adaptation</td>
</tr>
<tr>
<td>HER2+</td>
<td>Loss of HER2 positivity&lt;sup&gt;72,74&lt;/sup&gt;</td>
<td>Treatment adaptation</td>
</tr>
<tr>
<td></td>
<td>Gain of ER positivity&lt;sup&gt;78&lt;/sup&gt;</td>
<td>Treatment adaptation</td>
</tr>
<tr>
<td></td>
<td>TIL quantity/profile</td>
<td>Prognosis&lt;sup&gt;108&lt;/sup&gt;</td>
</tr>
<tr>
<td>TNBC</td>
<td>Gene mutations</td>
<td>Treatment adaptation&lt;sup&gt;11&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>TIL quantity/profile</td>
<td>Prognosis&lt;sup&gt;120&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; HER2+, HER2-positive; HR+, hormone receptor-positive; NAT, neoadjuvant therapy; PEPI, preoperative endocrine prognostic index; TIL, tumour-infiltrating lymphocytes; TNBC, triple negative breast cancer.

Biology of IBCs

• IBC is more frequently ER, PR negative compared with non-IBC.
  – Eg MDA series of IBC patients treated with neoadjuvant chemotherapy
  – TNBC 26.4%, HR-HER2+ 23.1%, HR+HER2- 35.7%, HR+HER2+ 14.8%
    (Masuda et al, Ann Onc 2014)

• Hormone receptor and HER2 molecular subtypes
  – limited predictive and prognostic power in MDACC serien of 527 patients
  – But better prognosis than triple negative in 403 stage 4 and 4 IBCs captured
    on SEER 2010-2013. BC specific mortality was 16.3% for the HR+/HER2-
    group, 9.8% for the HR+/HER2+ group, 21.7% for the HR-/HER2- group,
    and 30.5% for the TN group. (Li et al, Oncotarget 2017)
  
  ? Likely related to improved efficacy of anti-HER2 and endocrine therapies.

• Often high ki67, E-cadherin and p-Cadherin positive, high angiogenic index
  (Bertucci et al, Breast 2014).
Unique Biology of IBC?

- Few microscopic differences between IBC and non-IBC.
- While there may be genes that are significantly overexpressed in IBC compared with non-IBC, and gene signatures that are enriched in IBC, none have been sufficiently sensitive or specific for use as a molecular diagnostic tool.
- An alternative possibility is that IBC tumour cells are an aggressive subset of non-IBC tumour cells, prompted to function differently by the environment into which they are initiated; interaction with skin parenchyma?
- Potential role for mammary stem cells in pathogenesis.

Woodward et al, Lancet Oncol 2017
Profilng studies of non-microdissected pretreatment IBC clinical samples.

Bertucci et al, Breast 2014

<table>
<thead>
<tr>
<th>Molecular level</th>
<th>Ref.</th>
<th>Technology</th>
<th>N° of IBC</th>
<th>N° of non-IBC</th>
<th>Main results</th>
</tr>
</thead>
</table>
| mRNA expression | 22   | Affymetrix U133 series | 137       | 252           | * Molecular heterogeneity of IBC, frequency of aggressive molecular subtypes  
|                 |      |                     |           |               | * Many differences between IBC and non-IBC are molecular subtype-dependent  
|                 |      |                     |           |               | * Supervised analysis (BCxnon-IBC stratified upon molecular subtypes: 79-gene signature robust (independent validation set) with prognostic value for DFS in non-IBC  
|                 |      |                     |           |               | * Repression of TGFβ signaling pathway in IBC  
|                 |      |                     |           |               | * Supervised analysis between pCR and no pCR: 107-gene signature robust (independent validation set) with predictive value for pCR in non-IBC  
|                 |      |                     |           |               | * Signature enriched in adaptive and innate immunity genes (pCR)  
|                 |      |                     |           |               | * No robust signature identified for MFS in T0G IBC  
|                 |      |                     |           |               | * Similar molecular heterogeneity in TN IBC and TN non-IBC similar 7 Lehman's subgroups and similar proportions in IBC and non-IBC  
|                 |      |                     |           |               | * Molecular heterogeneity of IBC  
|                 |      |                     |           |               | * More frequent “complex” genomic patterns and higher % of genes with CNAs per sample in IBC vs non-IBC: IBC genome is more unstable  
|                 |      |                     |           |               | * Integrated analysis (array-CGH and mRNA expression profiles) identified 24 potential IBC-specific candidate genes mainly located in 6q and 17p regions (supervised analysis not stratified upon molecular subtypes) and robust (independent validation)  
| DNA copy number alterations | 43   | Agilent 244K (Affymetrix U133 + 2.0) | 49        | 124           | * No comparison between IBC and non-IBC  
|                 |      |                     |           |               | * Mutation rates in 47 pooled samples: 66% TP53, 20% PIK3CA, 17% RB1 and BRCA1/2 8% ROTECH  
|                 |      |                     |           |               | * Amplification rates in 47 pooled samples: 29% MYC, 20% CDK12, 14% ERBB2  
| DNA mutations | 46   | Targeted NGS: Foundation Medicine (exons 182 genes) | 43 (PT and/or M) from 31 patients | 4 (M)           | * Molecular heterogeneity of IBC  
|                 |      |                     |           |               | * Clustering of samples into high and low methylation groups: high methylation group enriched for IBCs  
|                 |      |                     |           |               | * Comparison IBC/non-IBC identified only 4 differentially methylated genes; supervised analysis not stratified upon molecular subtypes and no independent validation  
|                 |      |                     |           |               | * Aberrant DNA methylation is not the main force driving the biology of IBC  
| DNA methylation | 47   | Illumina Infinium Methylation Assay (CpG sites in CpG islands) | 19        | 43            | * Molecular heterogeneity of IBC  
|                 |      |                     |           |               | * Clustering of samples into high and low methylation groups: high methylation group enriched for IBCs  
|                 |      |                     |           |               | * Comparison IBC/non-IBC identified only 4 differentially methylated genes; supervised analysis not stratified upon molecular subtypes and no independent validation  
| mRNAs expression | 48   | quantitative PCR (384 mRNAs) | 20        | 50            | * Molecular heterogeneity of IBC  
|                 |      |                     |           |               | * 13 mRNAs of which expression levels correctly predicted the IBC/non-IBC phenotype (supervised analysis not stratified upon molecular subtypes and no independent validation)  
|                 |      |                     |           |               | * Molecular heterogeneity of IBC  
|                 |      |                     |           |               | * 13 mRNAs differentially expressed (IBC vs. non-IBC: supervised analysis not stratified upon molecular subtypes), including 13 validated in an independent set (85 IBCs, 95 non-IBCs)  
|                 |      |                     |           |               | * 5-mRNA signature predictive for IBC phenotype (80% accuracy) and independent predictive value for MFS in non-IBC  

pCR, pathological complete response; MFS, metastasis-free survival; TN, triple-negative; CNAs, copy number alteration; NGS, next-generation sequencing; PT, primary tumor; M, metastasis.
Genomic profiling of 53 IBCs

Ross et al, BCRT 2015

Fig. 1  Distribution of genomic alterations in 53 cases of inflammatory breast cancer

Fig. 2  Genomic alterations in 53 cases of inflammatory breast cancer grouped by biology pathways
Genomic and Immunological Tumor Profiling of 19 IBCs

- Recurrent genomic alterations in core biologic pathways, including activating and targetable variants in HER/PI3K/mTOR signaling.
- High rates of activating HER3 point mutations.
- Immunologic analysis revealed a subset of IBC tumors associated with high CD8+/PD-L1+ lymphocyte infiltration.
- DNA mismatch repair alterations, which may contribute to higher iScores, occurred at greater frequency in tumors with higher immune infiltration.

Hamm et al, Molecular Cancer Therapeutics 2016
Take Home Messages

• LABC – anatomical definition Stage IIIA to IIIC +/- Stage IIB (T3N0)
• Biology – intrinsically more aggressive tumours versus neglected tumours?
• IBC definitely more aggressive overall.
• Characterisation of pre-treatment tissue and post-treatment residual disease may help with elucidating predictive biomarkers, understanding mechanisms of resistance and development of new targets.