THE BIOLOGY OF LOCALLY ADVANCED BREAST CANCER:

Inflammatory and non-inflammatory

Frédérique Penault-Llorca

Preceptorship in breast cancer 2019
DISCLOSURE OF INTEREST

Frédérique Penault-Llorca

- **Personal financial interests:** Abbvie, Astrazeneca, Bayer, BMS, Genomic Health, Lilly, MERCK lifa, MSD, Myriad, Nanostring, Novartis, Pfizer, Pierre-Fabre, Roche, Tesaro

- **Institutional financial interests:** Astrazeneca, Bayer, BMS, Genomic Health, MSD, Myriad, Nanostring, Roche

- **Congress invitations:** Abbvie, Astrazeneca, BMS, MSD, Novartis, Roche
Outlines

• Definition
• Diagnosis
• Biology
  – LABC
  – IBC
• Neoadjuvant evaluation
LOCALLY ADVANCED BREAST CANCER
LABC: TNM

• LABC corresponds either to
  – T4a extension to the **chest wall**,  
  – T4B ulceration, ipsilateral satellite **skin** nodules or skin oedema (including peau d’orange)  
  – or both (T4c)
Clarifications of the 7th AJCC

- Skin involvement
  - Satellite skin foci must be macroscopically identified and separate from the primary tumor (not contiguous).
  - Direct extension into skin and skin involvement only identified microscopically are NOT categorized as pT4b. Such tumors are categorized based on tumor size.
  - In the **absence of clinical findings of inflammatory carcinoma** (erythema and edema involving 1/3 of breast skin), **dermal lymphatic tumor emboli are NOT categorized as pT4d**.
We therefore propose a simple stratification for the prognostic grouping of patients with stage IV disease based on the presence of inflammatory criteria characteristic of IBC at diagnosis (Stage IVIBC).”

“In preparing the next edition of the AJCC staging system, consideration should be given to incorporating an IBC as a prognostic factor within stage IV disease. This modification will allow the UICC/AJCC staging system to more accurately reflect the heterogeneous nature of metastatic breast cancer.”
BIOLOGY OF LABC
Characteristics of LABC

Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Theresa Sætiræ, Charles M. Perouæ, Robert Tibshiraniæ, Turid Aasæ, Stephanie Golubø, Kjell Johannsonæ, Trevor Hastieæ, Michael B. Eisenb, Matt van de Rijbæ, Stefanie S. Jeffreyæ, Thor Thorsenæ, Hanne Quistæ, John C. Matesæ, Patrick O. Brownæ, David Botsteinæ, Per Eystein Lenningæ, and Anne-Ulla Borresen-Daleæ

Departments of æGenetics and Surgery, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway; æDepartment of Genetics and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC 27599; Departments of æHealth Research and Policy and Statistics, æGenetics, Pathology, Surgery, and æBiochemistry and Howard Hughes Medical Institute, Stanford University School of Medicine, Stanford, CA 94305. Departments of æMedicine (Section of Oncology), Surgery, and æBiochemical Endocrinology, Haukeland University Hospital, N-5021 Bergen, Norway; and æLife Science Division, Lawrence Berkeley National Laboratories, and Department of Molecular and Cellular Biology, University of California, Berkeley, CA 94720

Contributed by David Botstein, July 17, 2001

...cells. Fifty-one of the patients were part of a prospective study on locally advanced breast cancer (T_3/T_4 and/or N_2 tumors) treated with doxorubicin monotherapy before surgery followed...
INFLAMMATORY BREAST CANCER
A RARE AND AGGRESSIVE VARIANT OF LABC
WHAT BREAST CANCER CAN LOOK & FEEL LIKE

- thick mass
- indentation
- skin erosion
- redness or heat
- new fluid
- dimpling
- bump
- growing vein
- retracted nipple
- new shape/size
- orange peel skin

"A cancerous lump is often hard and immovable, like a lemon seed."
IBC: clinical presentation

Redness

Oedema

Skin dimpling

Tenderness

Morrow RJ et al Mediators of Inflammation 2017, doi.org/10.1155/2017/4754827
Inflammatory breast cancer

- T4d
- Erythema, “peau d’orange” aspect
- Swelling
- Rare (<5%) and aggressive
IBC: differential diagnosis

- This swollen and inflammatory aspect is also present in **inflammatory lesions** of the breast
  - Abcess
  - Mastitis
  - Galactophoritis

- **Metastatic carcinoma to the breast** may produce clinical signs mimicking IBC (metastatic from ovarian origin, gastric carcinoma, rarely from squamous cell carcinoma of the tonsil, and lung and pancreatic adenocarcinoma)
Primary versus secondary IBC

• “Primary IBC” = *de novo* development of IBC in a previously normal breast.

• “Secondary IBC” = development of inflammatory skin changes that mimic primary IBC either in a breast that already had cancer or on the chest wall after a mastectomy for non-IBC.
Figure 3: Proposed role of primed breast parenchyma in clinical presentations of breast cancer involving the skin
T4d inflammatory breast cancer could occur when an inflammatory breast cancer-inducing mutation occurs in a primed inflammatory breast cancer breast (A). T4b could occur when an inflammatory breast cancer-inducing mutation occurs in an unprimed breast (B). Inflammatory recurrence after a non-inflammatory breast cancer could occur when a non-inflammatory breast cancer-inducing mutation occurs in a primed inflammatory breast cancer breast and then recurs as an inflammatory breast cancer mutation in this primed breast later (C). Reproduced by permission of the University of Texas MD Anderson Cancer Center.
Secondary IBC
Chest wall disease

An other biology, probably linked to inflammation, in particular to IL-6 pathways

Courtesy Dr Curigliano
IBC DIAGNOSIS
International expert panel on inflammatory breast cancer: consensus statement for standardized diagnosis and treatment

S. Dawood¹, S. D. Merajver², P. Viens³, P. B. Vermeulen⁴, S. M. Swain⁵, T. A. Buchholz⁶, L. Y. Dirix⁷, P. H. Levine⁸, A. Lucci⁹, S. Krishnamurthy¹⁰, F. M. Robertson¹¹, W. A. Woodward¹², W. T. Yang¹², N. T. Ueno¹³ & M. Cristofanilli¹⁴⁺
• Vanishing of subcutaneous transparency
• Skin thickness
• Breast hyper density
Cutaneous biopsy

• By punch or scalpel (at least 2)
• Aiming to identify dermal embolis
Histopathology

- Presence of numerous dermal tumor emboli in the papillary and reticular dermis of the skin overlying the breast
- But
  - Absent in 25% of IBC (the diagnosis is clinical)
  - In the absence of a clinical presentation of inflammatory carcinoma (i.e. erythema and oedema invading 1/3 of breast skin), dermal tumor emboli ARE NOT CLASSIFIED as pT4d
BIOLOGY OF IBC
NORMAL BREAST PARENCHYMA AS A COMPLICIT PARTNER OR AN INNOCENT BYSTANDER?
Inflammatory breast cancer: unique biological and therapeutic considerations

**Lancet Oncol** 2015; 16: e568–76

**Pattern of broad involvement throughout the breast, but not beyond, despite absence of a clear anatomical barrier**

- Molecular signature of IBC are also present in a subset of non IBC (poorer prognosis)

- The unique presentation of IBC might require **specific, identifiable changes in the breast parenchyma that occur before the tumour-initiating event** (increased breast density, no breast feeding or interrupted BF, no involution...?) ➔ production of CD44+CD49f+CD133+ **stem cells** that are found in 100% of IBC with a unique distribution (IBC-promoting tissue) “**Primed parenchyma**”?

- Difference between a **local skin limitation** and the **highly metastatic predisposition**
IBC PATHOLOGY: SPECIFIC PROFILES?
**Lobular** histology only in 4.5%.

- **Histology has no significant effect on survival outcomes in IBC patients**, unlike in patients with non-inflammatory breast cancer (n-IBC), indicating the distinct biological behavior of the IBC phenotype.
IBC INTRINSIC CLASSIFICATION
Outcomes of patients with inflammatory breast cancer by hormone receptor- and HER2-defined molecular subtypes: A population-based study from the SEER program

Juanjuan Li1,*, Yue Xia2,*, Qi Wu1, Shan Zhu1, Chuang Chen1, Wen Yang1, Wen Wei1 and Shengrong Sun1

- 403 pts extracted from 2010-2013
- HR+/HER2-: 36.5% - BCSM 16.3% - higher prob of bone mets
- HR+/HER2+: 20.5% - BCSM 9.8%
- HR-/HER2+: 17% - BCSM 21.7%
- TN: 26% - BCSM 30.5% - higher prob of lung mets

Multivariate analysis ➔ ER and HER2 positivity associated with better survival ➔ TN subtype: poorer OS and BCSM (p< 0.05).
• 75% of IBCs belonged to aggressive subtypes (basal-like, ErbB2e, claudin-low and luminal B), vs 53% of non-IBCs.
• Luminal A subtype: 19% of IBCs vs 42% of non-IBCs
• Differences in gene expression between IBC and non-IBC are dominated by the molecular subtype related differences.
IBC ACTIVATED PATHWAYS
Classical activated pathways

- Angiogenesis ➔ no benefit of bevacizumab, deceptive results with pazopanib (HER2+)
- HER2 ➔ better survival of HER2+ IBC, HER3 potential target
- EGFR ➔ potential target (7/16 IBC TNBC with pCR)
- mTOR/AKT ➔ potential target
- JAK/STAT (activation of transcription) ➔ potential target
- RHOC GTPASE (motility) ➔ potential target
- Cell cycle/MYC ➔ CD4/6 inhibitors?
- PD-L1 activation ➔ immunotherapy
CONCLUSION
Conclusion

• LABC reflect all the subtypes
• IBC is a rare and aggressive form of breast cancer that remains poorly understood (role of normal breast ? Specific genes ?).
• Under-representation of lobular cancer
• More aggressive phenotypes (TNBC 26%, HER2+ 37,5%, 43% HR-)
• Standard tt is neoadjuvant approach and clinical trials when available
Conclusion ..

- Discriminator genes (IBC vs non IBC) are associated with cell motility, adhesion and angiogenesis
- Activated pathways in IBC tumor tissues can provide potential therapeutic targets in HER2/PI3K/mTOR signaling
- Neoadjuvant treatment is the standard/ radiation therapy is important
- Potential candidate for immunotherapy
PREDICTION OF RESPONSE TO NEOADJUVANT TREATMENT
Neoadjuvant treatment

Initial concept
- Early introduction of a systemic treatment
  - Locally advanced BC
  - Survival benefit?
  - Conservative surgery
- Meta-analysis NACT vs adjuvant CT
  - No difference in OS/DFS
  - Augmentation of breast conservation rate

Evolution of the concept
- Clinical situation allowing in vivo analysis of tumor response
- Prognosis of pCR in HER2 and TNBC
- Dynamic evaluation
- Treatment adjustment
Different Goals

Before
Prediction of response to NACT

After
Prognosis
Prediction of response to different drugs

During
Treatment adaption
Prediction of response to NAT

Before

Prediction of response to NACT

Histologic subtype
Tumor grade
HR status
HER2 status
SBR grade, proliferation
Intrinsic classification
High TILs
Clinical implications of the intrinsic molecular subtypes of breast cancer

Table 4 Association of the intrinsic subtypes with chemotherapy response across the various pathology-based groups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All patients</th>
<th>Luminal A</th>
<th>Luminal B</th>
<th>HER2-enriched</th>
<th>Basal-like</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
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<td>All subgroups</td>
<td>838</td>
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<td>HER2+</td>
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<td>292</td>
<td>37%</td>
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*Likelihood ratio tests: adjusting clinical features: age, clinical stage, clinical nodal status and study cohort. Hormone receptors status and HER2 status were also included in "all subgroups"
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TILs as Predictive factors of response of NACT

Table 2
Neoadjuvant trials in which TILs have been assessed and their prognostic values. Adapted from Savas et al. [114].

<table>
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<tr>
<th>Trial</th>
<th>Treatments</th>
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<td>Doxorubicin, Cytoteaxel, Cyclophosphamid</td>
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<td>&gt;60% sTILs: pCR 41.7%</td>
<td>OR 1.38 of pCR per 10% sTILs (95% CI 1.08–1.78, P = 0.012)</td>
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<td>Doxorubicin, Cytoteaxel, Cyclophosphamid, Vinorelbine, Capecitabine</td>
<td>All</td>
<td>840</td>
<td>&gt;60% sTILs: pCR 40%</td>
<td>OR 1.21 of pCR per 10% sTILs (95% CI 1.08–1.35, P = 0.001)</td>
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<td>GeparQuattro [70]</td>
<td>Epirubicin, Cyclophosphamid, Doxorubicin, Capecitabine, Trastuzumab</td>
<td>HER2+</td>
<td>156</td>
<td>&gt;50% sTILs: pCR 47.4%</td>
<td>OR 1.16 of pCR per 10% sTILs (95% CI 1.01–1.32, P = 0.038)</td>
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<td>GeparQuinto [67]</td>
<td>Epirubicin, Cyclophosphamid, Taxane, Everolimus</td>
<td>ER+ and TNBC</td>
<td>313</td>
<td>&gt;60% sTILs: pCR 36.6%</td>
<td>OR 1.2 of pCR per 10% sTILs (95% CI 1.0–1.3, P = 0.01)</td>
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<tr>
<td>GeparSixto [66]</td>
<td>Paclitaxel, Liposomal Doxorubicin, Carboplatin, Bevacizumab, Trastuzumab</td>
<td>HER2+ and TNBC</td>
<td>580</td>
<td>&gt;60% sTILs: pCR 59.9%</td>
<td>OR 1.2 of pCR per 10% sTILs increase (95% CI 1.11–1.29, P &lt; 0.001)</td>
</tr>
<tr>
<td>EORTC 10994 and BIG 00–01 [68]</td>
<td>FEC, Docetaxel, Trastuzumab, Paclitaxel, FEC</td>
<td>ER–</td>
<td>111</td>
<td>High gTILs: pCR 74.2%</td>
<td>OR 2.66 of pCR for &gt;60% sTILs (95% CI 1.76–4.02, P &lt; 0.001)</td>
</tr>
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<td>CHER-LOB [69]</td>
<td>FEC, Docetaxel, Trastuzumab, Paclitaxel, FEC</td>
<td>HER2+</td>
<td>105</td>
<td>Low gTILs: pCR 31.3%</td>
<td>OR 6.42 of pCR for high versus low gTILs (95% CI 2.08–19.83, P = 0.001)</td>
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ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; gTIL, gene-expression surrogate TIL; H&E, haematoxylin and eosin; iTIL, intratumoural TIL; OR, odds ratio; pCR, pathological complete response; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte.
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<td>OR 1.46 of pCR per 10% iTILs (95% CI 1.08–1.95, P = 0.010)</td>
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<td>&gt;50% sTILs: pCR 36.6%; &lt;50% sTILs: pCR 14.3%</td>
<td>OR 1.2 of pCR per 10% sTILs (95% CI 1.01–1.32, P = 0.038)</td>
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|               |                     |                          |    |                                    | Not reported                              |

ER, estrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; gTIL, gene-expression surrogate TIL; H&E, haematoxylin and eosin; iTIL, intratumoural TIL; OR, odds ratio; pCR, pathological complete response; sTIL, stromal TIL; TIL, tumour-infiltrating lymphocyte.

High TILs is a reliable biomarker of pathological complete response across ALL BC subtypes.
Emerging: prediction of response to platininium salts....and PARPi?

Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer


Table 1. HR deficiency status and association with response to platinum-containing therapy

<table>
<thead>
<tr>
<th>Responder</th>
<th>Deficient number (%) response</th>
<th>Nondeficient number (%) response</th>
<th>OR (95% CI) Reference = nondeficient</th>
<th>Logistic P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCB I/II = No</td>
<td>16 (30%)</td>
<td>14</td>
<td>4.96 (1.61-15.3)</td>
<td>0.0036</td>
</tr>
<tr>
<td>RCB I/II = Yes</td>
<td>34 (68%)</td>
<td>6 (30%)</td>
<td>4.96 (1.61-15.3)</td>
<td>0.0036</td>
</tr>
<tr>
<td>pCR = No</td>
<td>29</td>
<td>18</td>
<td>6.52 (1.36-31.2)</td>
<td>0.0058</td>
</tr>
<tr>
<td>pCR = Yes</td>
<td>21 (42%)</td>
<td>2 (10%)</td>
<td>6.52 (1.36-31.2)</td>
<td>0.0058</td>
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Cisplatin Trials Cohort (N = 50)

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<tr>
<td>RCB I/II = No</td>
<td>14</td>
<td>19</td>
<td>10.18 (2.00-51.89)</td>
<td>0.0011</td>
</tr>
<tr>
<td>RCB I/II = Yes</td>
<td>15 (51.7%)</td>
<td>2 (9.5%)</td>
<td>10.18 (2.00-51.89)</td>
<td>0.0011</td>
</tr>
<tr>
<td>pCR = No</td>
<td>21</td>
<td>21</td>
<td>10.18 (2.00-51.89)</td>
<td>0.0011</td>
</tr>
<tr>
<td>pCR = Yes</td>
<td>8 (27.5%)</td>
<td>0 (0%)</td>
<td>17.00 (1.91-2249)</td>
<td>0.0066</td>
</tr>
</tbody>
</table>

*Based on Firth’s penalized profile likelihood.
Post treatment specimen

→ a standardized procedure of gross handling will be provided to the local pathologist (sampling will depend on the presence or not of a lesion and on the size of the specimen)

→ a standardized histologic report will be provided to the pathologists (presence or not of tumor cells)

→ inking of the tumors’ margins is mandatory
Different patterns of pathological response

- No change resistance
- Complete pathological response
- Concentric shrinking, same cellularity
- Heterogeneity
- Decrease in cellularity
- Tumor fragmentation
- Heterogeneity
Outcomes of neoadjuvant therapy: Pathological complete response (pCR) or residual disease


Neoadjuvant therapy

Surgery

No invasive cancer cells in breast or axillary nodes

Micrometastatic disease may be present

pCR

Residual disease

Evidence of invasive disease remaining in breast or axilla

Micrometastatic disease may be present

Adjuvant treatment can be optimised based on neoadjuvant response
Neoadjuvant treatment response can be assessed using pCR

### pCR is defined as the absence of residual disease¹,²

Total pCR (tpCR)

| Total pCR (tpCR) | ypT0/is ypN0 | Absence of invasive cancer in breast and axillary nodes (irrespective of ductal carcinoma in situ) |

tpCR is the most commonly used definition of pCR

---

pCR, pathological complete response; RCB, residual cancer burden; tpCR, total pathological complete response.

When we don’t have a ypT0/is ypN0

Before

Very good response

Partial response

Absence of response

After
Residual breast cancer burden

The pathological variables included bidimensional diameters of the primary tumour bed (d1, d2), the proportion of primary tumour area containing invasive carcinoma (f_{inv}), the number of positive lymph nodes (LN), and the diameter of the largest nodal metastasis.

Residual breast cancer burden (RCB):

\[
RCB = 1.4 \left( f_{inv} d_{prim} \right)^{0.17} + \left[ 4 \left( 1 - 0.75^{LN} \right) d_{met} \right]^{0.17}
\]


http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3
Survival according to the Residual Cancer Burden
BIOMARKERS AFTER (PROGNOSTIC AND PREDICTIVE)
Summary

**Table 6 | Most promising biomarkers assessed on post-NAT residual tissue**

<table>
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<tr>
<th>Molecular subtype</th>
<th>Biomarker</th>
<th>Purpose</th>
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<tbody>
<tr>
<td>HR+</td>
<td>Ki67 index</td>
<td>Prognosis&lt;sup&gt;58,59,63&lt;/sup&gt;</td>
</tr>
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<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.

New for HER2+  
Katherine trial ➔ non pCR ➔ benefit from post neoadj TDM-1
Outcome Prediction for Estrogen Receptor–Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics


Table 4. The preoperative endocrine prognostic index*

<table>
<thead>
<tr>
<th>Pathology, biomarker status</th>
<th>RFS</th>
<th>BCSS</th>
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<tbody>
<tr>
<td>Pathological tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>2.8</td>
<td>4.4</td>
</tr>
<tr>
<td>T3/4</td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>Node status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Positive</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ki67 level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%–2.7% (0–1†)</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>&gt;2.7%–7.3% (1–2†)</td>
<td>1.7</td>
<td>2</td>
</tr>
<tr>
<td>&gt;7.3%–19.7% (2–3†)</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>&gt;19.7%–53.1% (3–4†)</td>
<td>2.9</td>
<td>3.8</td>
</tr>
<tr>
<td>&gt;53.1% (&gt;4†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER status, Allred score</td>
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<td></td>
</tr>
<tr>
<td>0–2</td>
<td>2.8</td>
<td>7.0</td>
</tr>
<tr>
<td>3–8</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>
The residual tumor can give us a lot of informations!
THANK YOU FOR YOUR ATTENTION