NEW BREAST CANCER CLASSIFICATION: TRADITIONAL PATHOLOGY AND MOLECULAR SUBTYPES

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Cape Town, South Africa, 13-14 February 2020
ESMO preceptorship on breast cancer
DISCLOSURE OF INTEREST

Consultant:
- Roche
- Roche Diagnostics
- Myriad genetics

Shareholder and Scientific Advisory Board: MYPL
OUTLINE

• Traditional histopathological classification
• Molecular classification
  • Luminal ER+ BC
  • HER2+ BC
  • Triple negative BC
• Conclusion and perspectives
TRADITIONAL HISTOPATHOLOGY

Early breast cancer

Key-points of the pathological report

• Diagnosis of invasive carcinoma: histological type and grade
• Number of tumors, tumor size, nodal status (pTNM, AJCC 8th edition)
• Lymphovascular invasion
• Associated lesions: in situ component, Paget disease…
• Surgical margins
• Prognostic markers
  • Histopathological
  • Molecular
• Predictive biomarkers

After the coffee break!!
HISTOLOGICAL TYPE

Invasive (ductal) of no special type

- 70-80% of BC
- Reproduce ± ductal architecture
- Broad range of morphological pattern...
- ... and a lot of variants!
  - Carcinoma with medullary features
  - Carcinoma with neuroendocrine differentiation
  - Rares variants (sebaceous, oncocytic, clear cells, lipid rich)

- 70-80% ER+
- 10-15% HER2+
- 10-15% Triple negative
Invasive lobular carcinoma

- 10-15 % of BC
- multicentric, bilateral
- dyscohesive cells, E-cadherin loss
- Several variants

**Essential and desirable diagnostic criteria**

**Classic ILC**

*Essential*: an IBC composed of dispersed or linear dyscohesive cells with low- to intermediate-nuclear-grade morphology and a low mitotic count; ER immunoreactivity is high and HER2 is negative/non-amplified.

*Desirable*: coexisting lobular neoplasia; E-cadherin loss may be useful.

**Pleomorphic ILC**

*Essential*: intermediate-high or high nuclear grade/pleomorphism.

- ~90% ER+
- 5% HER2+
- 5% Triple negative
INVASIVE LOBULAR CARCINOMA

INVASIVE LOBULAR CARCINOMA

C. Desmedt et al. JCO 2016
**HISTOLOGICAL TYPE**


### Other special subtypes

- **Tubular**
  - Very good prognosis
  - **ER+ HER2-**

- **Cribriform**
  - **ER+, 5% HER2+**

- **Mucinous**
  - **Triple negative, some HER2+**

- **Mucinous cystadenocarcinoma**

- **Micropapillary**
  - **ER+, 20% HER2+**

- **With apocrine differentiation**
  - **ER-, AR+, HER2+ or -**

- **Metaplastic (several subtypes, some low-grade)**

- **Papillary tumors**

- **Neuroendocrine (pure) tumors**
  - **ER+, HER2- (some HER2+)**

**Very good prognosis**
HISTOLOGICAL TYPE

Rare and salivary gland-type tumours

- Acinic cell carcinoma
- Adenoid cystic carcinoma \(\text{t}(6;9)\) MYB-NFIB, MYBL1, ampl MYB
- Secretory carcinoma \(\text{t}(12;15)\) ETV6-NTRK3
- Mucoepidermoid carcinoma \(\text{MAML2}\)
- Polymorphous carcinoma

**Tall cell carcinoma with reversed polarity** \(\text{IDH2 mutation}\)

- Rare
- Triple negative...
- …but good prognosis!
- hallmark genomic alteration
HISTOLOGICAL GRADE

Elston and Ellis

• Glandular differentiation (tubule formation)
  - >75% : score 1
  - 10-75% : score 2
  - <10% : score 3

• Nuclear atypia (pleomorphism)
  - Small, regular uniform cells: score 1
  - Moderate increase in size and variability: score 2
  - Marked variation: score 3

• Mitotic activity (depending on count/mm²): score 1 to 3
OUTLINE

• Traditional histopathological classification
• Molecular classification
  • Luminal ER+ BC
  • HER2+ BC
  • Triple negative BC
• Conclusion and perspectives
MOLECULAR TAXONOMY OF BREAST CANCER

C Perou & T Sorlie
Significant Prognostic Value of Intrinsic classification
**INTRINSIC MOLECULAR CLASSIFICATION**

**ER+ Tumors**

**Luminal A**
- ≈ 60% of breast cancers
- High expression of ER
- High expression of genes regulated by ER (PR, GATA-3, FOX A1, etc.)
- Low expression of genes linked to proliferation
- Low prevalence of *TP53* mutations: 13%

**Luminal B**
- ≈ 20% of breast cancers
- Lower expression of ER
- Lower expression of genes regulated by ER (PR, GATA-3, FOX A1, etc.)
- High expression of genes linked to proliferation
- High prevalence of *TP53* mutations: 66%
**SURROGATE DEFINITION OF LUMINAL BC BY IHC**

**Luminal A**: ER+ PR+ (>20%) Ki67<14% HER2-

**Luminal B**: ER+ PR≤20% Ki67<14% or ER+ HER2+ Ki67>14%

*Prat A et al. JCO 2013*
LUMINAL A

- grade I or II
- ER + ≥ 1% (10%)
- PR + ≥ 1% (>20%)
- HER2 - (0, 1+, 2+ non-amplified)
- Ki-67 low (< 15-20%)
LUMINAL B

- grade II or III
- ER + ≥ 1% (10%)
- PR + ≤ 20%
- HER2 – (0, 1+, 2+ non-amplified)
- Ki67 high (≥ 15-20%)
LUMINAL B HER2+

- grade II or III
- ER + ≥ 1% (10%)
- PR + ≥ 10% or ≤ 20%
- HER2 + (2+ amplified or 3+)
- whatever the Ki67 level

Thanks to © Gaëtan MacGrogan...
**INTRINSIC MOLECULAR CLASSIFICATION**

<table>
<thead>
<tr>
<th>HER2</th>
<th>Basal</th>
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<tbody>
<tr>
<td>• ≈ 10% of breast cancers</td>
<td>• ≈ 10% of breast cancers</td>
</tr>
<tr>
<td>• No expression of ER</td>
<td>• No expression of ER</td>
</tr>
<tr>
<td>• High expression of genes located in the <strong>ERBB2</strong> amplicon (GRB7, etc..)</td>
<td>• Expression of basal cell genes: high molecular weight cytokeratins (CK5, CK14, CK17), laminin, FAB7, etc.</td>
</tr>
<tr>
<td>• High expression of genes linked to proliferation</td>
<td>• High expression of genes linked to proliferation</td>
</tr>
<tr>
<td>• High prevalence of <strong>TP53</strong> mutations: 71%</td>
<td>• High prevalence of <strong>TP53</strong> mutations: 82%</td>
</tr>
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</table>
MORPHOLOGY OF BASAL LIKE TUMORS

- Histological grade III
- Massive architecture
- High mitotic index

- Pushing borders
- Dense lymphocytic infiltrate
- Necrosis
- Central fibrosis
IHC SURROGATE DEFINITION OF BASAL LIKE

- ER < 1%
- PR < 1%
- HER2 Score 0, 1+, 2+ non amplified
- CK5/6 or CK14+
- Or EGFR+
CLINICAL ASPECTS OF BASAL LIKE TUMORS

- Often young patients
- Grade III tumors
- Preferential metastatic sites: lung, brain
- >95% metastatic relapses before year 6 after diagnosis

Foulkes et al., NEJM 2010
Basal like breast cancers

→ Basal like BC encompasses several histological subtypes with different prognosis

Basal like BC encompasses several histological subtypes with different prognosis.

Fibromatosis-like carcinoma

Secretory carcinoma

Metaplastic carcinomas

Poor prognosis

Poor prognosis

Good prognosis

Triple-negative breast cancer: the importance of molecular and histologic subtyping, and recognition of low-grade variants

Fresia Pareja¹, Felipe C Geyer¹, Caterina Marchiò², Kathleen A Burke¹, Britta Weigelt¹ and Jorge S Reis-Filho¹
MOLECULAR CLASSIFICATION(S) OF TNBC

Lehmann BD et al., PLOS one 2016

- **BL1: Basal Like 1**
  - Cell cycle/proliferation, DNA damage (*BRCA1*)
- **BL2: Basal like 2**
  - Proliferation, growth factors (EGF, MET, IGF1R, Wnt), glycolysis
- **LAR: Luminal Androgen Receptor**
  - Steroid metabolism, AR, FOXA1, *PIK3CA*mut
- **M: Mesenchymal like**
  - Cell motility, EMT, *PIK3CA*mut
- **MSL: Mesenchymal Stem like**
  - EMT, growth factors (EGFR, PDGF), low proliferation, stem cells, claudinlow, *PIK3CA*mut, metaplastic
- **IM: immunomodulatory**
MOLECULAR CLASSIFICATION(S) OF TNBC
Burstein MD et al., Clin Cancer Res 2015

- **BLIA: Basal Like Immune Activated**
  Upregulation of immune/cytokine genes, activated STAT pathway, \( CDK1^{\text{ampl}} \)

- **BLIS: Basal like Immune Supressed**
  Downregulation of immune/cytokine, expression of SOX transcription factors, \( FGFR2^{\text{ampl}} \)

- **LAR: Luminal Androgen Receptor**
  AR, ESR1, ERBB4, FOXA1, \( CCND1^{\text{ampl}} \)

- **MES: Mesenchymal like**
  Low cell cycle, DNA damage, hereditary BC, IGF1, PDGFR, claudin\text{low}, \( EGFR^{\text{ampl}} \)
IN SUMMARY...
Towards an integrative BC classification

→ Combine histopathology and molecular classifications in order to better understand BC heterogeneity and better personalize treatment!

• « traditional » pathology is the cornerstone of BC management
  - histological type and grade
  - pTNM (AJCC)
  - margin assessment
  - prognostic and predictive markers

• Molecular tools
  - better stratify patients with regards to outcome
  - identify new therapeutic targets
**TAKE-HOME MESSAGES**

<table>
<thead>
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<th>Intrinsic subtype</th>
<th>Clinicopathological surrogate definition</th>
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<tr>
<td>Luminal A</td>
<td>'Luminal A-like’&lt;br&gt;ER-positive&lt;br&gt;HER2-negative&lt;br&gt;Ki67 low&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;PgR high&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Low-risk molecular signature (if available)</td>
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<tr>
<td>Luminal B</td>
<td>'Luminal B-like (HER2-negative)'&lt;br&gt;ER-positive&lt;br&gt;HER2-negative&lt;br&gt;and either&lt;br&gt;Ki67 high or&lt;br&gt;PgR low&lt;br&gt;High-risk molecular signature (if available)</td>
</tr>
<tr>
<td>Luminal B</td>
<td>'Luminal B-like (HER2-positive)'&lt;br&gt;ER-positive&lt;br&gt;HER2-positive&lt;br&gt;Any Ki67&lt;br&gt;Any PgR</td>
</tr>
<tr>
<td>HER2</td>
<td>'HER2-positive (non-luminal)'&lt;br&gt;HER2-positive&lt;br&gt;ER and PgR absent</td>
</tr>
<tr>
<td>'Basal-like'</td>
<td>'Triple-negative'&lt;br&gt;ER and PgR absent&lt;sup&gt;c&lt;/sup&gt;&lt;br&gt;HER2-negative&lt;sup&gt;c&lt;/sup&gt;</td>
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**SPECIAL ARTICLE**

**Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†**

F. Cardoso<sup>1</sup>, S. Kyriakides<sup>2</sup>, S. Ohno<sup>3</sup>, F. Penault-Llorca<sup>4,5</sup>, P. Poortmans<sup>6,7</sup>, I. T. Rubio<sup>8</sup>, S. Zackrisson<sup>2</sup> & E. Senkus<sup>9</sup>, on behalf of the ESMO Guidelines Committee<sup>2</sup>

For the purpose of prognostication and treatment decision making, tumours should be grouped into surrogate intrinsic subtypes, defined by routine histology and IHC data [III, A]
THANKS!

Classification challenge…
…it’s all about the lonely, mismatched salad!