Molecular classification of breast carcinoma; how useful?

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What happened in the field of breast cancer in 25 years?
Breast cancer mortality rates in women aged 35-69 in the United Kingdom.
Why?

1. **Early Diagnosis**
   - Breast screening

2. **More effective treatment**
   - Tamoxifen, Chemotherapy, Radiotherapy, Herceptin, etc...

3. **Based on more comprehensive pre-operative and post-operative diagnosis and classification of tumours**
Classification of Breast Carcinoma

1. **Traditional microscopic classification**

2. **Immunohistochemical classification**
   - ER
   - HER2

3. **Molecular classification**
Molecular Classification of Breast Carcinoma
CK5/6

Basal/Myoepithelial

Luminal
Molecular Classification of Breast Carcinoma*

- This was carried out using ‘microarray-based expression profiling’

- A microarray is a solid surface (a Chip) containing spots (shallow holes), arranged in an orderly fashion

- Each individual spot contains a high concentration of unique DNA fragments that map to specific genes (e.g. ER, HER2 etc),

- representing a target for the hybridization of test cDNA derived (by reverse transcription of mRNA) extracted from tissue samples

Chip

spot

ER

PgR

HER2

CK5

DNA from tumour

ER

PgR

HER2

CK5

ER

PgR

HER2

CK5

Luminal Type

Basal Like type

+ +

- -

+ +

- -

+ +

- -
Molecular classification of breast carcinoma

Molecular Classification of Breast Carcinoma

Five main molecular sub-groups were identified which differ in their ‘intrinsic gene list’*

3 ER positive:

- **Luminal A** (ER+ (high levels), Ki 67 low levels, low grade; excellent prognosis)

- **Luminal B** (ER+, HER2 +, high Ki67 expression, high grade; poor prognosis)**(but, there may be a continuous spectrum; A-B))

- **Normal-like** (ER+, good prognosis), but poorly characterised, may be the result of sample contamination with normal tissue)

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** Cheang MCU et al. J Natl Cancer Inst 2009; 101:736-750
Molecular Classification of Breast Carcinoma

2 ER negative

4. **HER2 positive** (ER-, bad prognosis)

5. **Basal-like** (ER-, bad prognosis, good response to chemotherapy)
Molecular Classification of Breast Carcinoma

- There may be 3 more, recently described, ER negative types:

1. **Apocrine group**
2. **Interferon group** (high expression of STAT 1)
3. **Claudin-low group** (with features suggestive of a ‘cancer stem cell-like’ phenotype)
After 14 years of the introduction of molecular classification, 
Do we ever use it in our routine clinical practice?

NO
Why?
Because:
1. you do not treat a patient on the basis of whether her tumour is Luminal A, B or Basal-like
You treat her on the basis of:
1. Tumour size
2. histological type
3. grade
4. ER
5. HER2 &
6. lymph node status
2. The molecular ‘type’ can be misleading
For example: the 2 Common Luminal types:

Invasive Ductal

Invasive Lobular
Are genetically different from each other and are managed differently:

- Lobular cancers are E-Cadherin negative,
- invade diffusely
- can be multi-focal or bilateral more commonly;
- Hence need MRI
Where is this in the molecular classification?
2. HER2 positive group
HER2 positive tumours have been placed in their own group as well as in Luminal B (if they are ER+)
Clinically, a patient with HER2 positive tumour will have anti-HER2 treatment whatever the molecular sub-group is
3. Basal like Type Breast Carcinoma

- ER, PgR and HER2 negative

- & Express: CK 5/6 and/or CK 14 and/or EGFR positive
  (Not all triple negative tumours are basal-like)

Basal like Type Breast Carcinoma

- Around 12% of all invasive breast carcinomas
- Most are clinically aggressive
- Most disseminates via blood stream more than via lymphatics

Not all basal like breast carcinomas are the same,

and there are several subtypes
Basal Like Type Breast Carcinoma

- *Currently includes:*
  - Triple negative Grade 3 invasive ductal Carcinoma
  - Metaplastic (spindle cell) carcinoma
  - Lympho-epithelioma-like Carcinoma
  - Medullary and medullary-like Carcinoma
  - Secretory carcinoma
  - Adenoid cystic carcinoma
Following is a series of basal-like breast cancers with nothing histologically or clinically in common.
Pleomorphic invasive ductal carcinoma

From a patient with Huntington’s disease
Grade 3 IDC with Comedo necrosis
Medullary Carcinomas

Probably from a patient with BRCA mutation
Secretory Carcinoma
F27, 22mm mass, Rt breast

Very good prognosis
Eosinophilic secretion
Adenoid cystic carcinoma
F 45y, Lt breast lump

Very good prognosis
Conclusions

- The molecular classification, so far, has not played any significant role in the management of breast carcinoma.

- Histopathology, including immunohistology, remains the main tool used for classifying breast carcinomas into categories that guide the management of the disease.

- Adding the ‘molecular type’ to your report does not serve any purpose.

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