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Intrinsic subtypes in a cohort of early breast cancer patients

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Background

As the most common cancer worldwide breast cancer (BC) is a heterogeneous disease with regard to diagnosis, therapy and survival. The diversity of respect to molecular alterations, cellular composition and clinical outcome creates a challenge in developing tumour classifications that are clinically useful to prognosis or prediction. Complementary to the traditional histopathological classifications of the tumours, molecular biological tests specify individualised therapy recommendations (1,2).

Table 1: Classification of intrinsic subtypes (3)

	Luminal A	Luminal B	HER2-enriched	Basal-like
Estrogen receptor positive	90%	98%	38%	8%
Progesterone receptor positive	89%	82%	20%	7%
HER2 positive	14%	24%	72%	7%

Aim of the Study

Our aim was to classify tumours into intrinsic subtypes and to analyse the association of these subtypes with disease progression.

Patients and Methods

- Prospective, multicenter cohort of 1,270 breast cancer patients (PiA, Prognostic Assessment in Routine application, NCT 01592825)
- RNA expression evaluation by: nCounter® (NanoString), GenChip™ HG U133 Plus 2.0 (Affymetrix) or BioMark™ (Fluidigm)
- Intrinsic subtyping by PAM50 Bioclassifier (4)

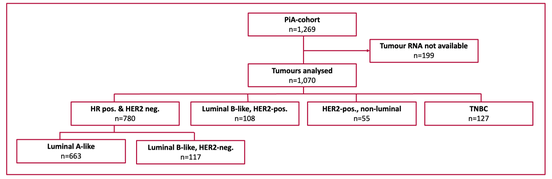

Figure 1: Enrollment of the PiA-cohort (n=1,269) and classification into histopathological subgroups

Table 2: Classification of intrinsic subtypes and histopathological subgroups (5)

Intrinsic subtypes	Luminal A	Luminal B		HER2-enriched	Basal-like
Histopathological subgroups	**Luminal A-like**	**Luminal B-like, HER2-negative**	**Luminal B-like, HER2-positive**	**HER2-positive, non-luminal**	**TNBC**
	ER+ PgR+/- HER2- G1, G2	ER+ PgR+/- HER2- G3	ER+ PgR+/- HER2+ G1, G2, G3	ER- PgR- (<10%) HER2+ G1, G2, G3	ER- PgR- (<10%) HER2- G1, G2, G3
Therapy	**Endocrine**	**Endocrine & Chemo**	**Endocrine, Chemo & Anti-HER2**	**Chemo & Anti-HER2**	**Chemo**

Abbreviations: ER= estrogenreceptor, PgR= progesteronreceptor, G= grading, HER2= human epithelial growth factor receptor 2

ER or PgR positive: ≥ 1%; HER2 positive: DAKO 2+ and ISH+, DAKO 3+

Primary Objectives

- Distribution of intrinsic subtypes
- Associations of intrinsic subtypes with clinical and histopathological parameters, including histopathological subgroups

Secondary Objectives

- Association of intrinsic subtypes and histopathologic subgroups with recurrence-free interval (RFI) and overall survival (OS)
  RFI: local recurrence, distant metastases, death from breast cancer
  OS: any death
  - univariate and multivariate Cox regression analysis
  - median follow-up time: 62 months (6-126)

Results

A significant correlation was observed between intrinsic subtypes and each selected parameter shown in table 2.

Table 2: Distribution of intrinsic subtypes

Parameters	All		Luminal A		Luminal B		HER2-enriched		Basal-like	
	n=1.070	(100.00%)	n=480	(44.86%)	n=256	(23.93%)	n=154	(14.39%)	n=180	(16.82%)
Age at time of diagnosis										
< 50	275	(25.70%)	108	(22.50%)	52	(20.31%)	51	(33.12%)	64	(35.56%)
≥ 50	795	(74.30%)	372	(77.50%)	204	(79.69%)	103	(66.88%)	116	(64.44%)
Nodal status										
negative	661	(61.78%)	331	**(68.96%)**	145	(56.64%)	81	(52.60%)	104	(57.78%)
positive	409	(38.22%)	149	(31.04%)	111	(43.36%)	73	(47.40%)	76	(42.22%)
Histological types										
NST	869	(81.21%)	365	(76.04%)	217	(84.77%)	134	(87.01%)	153	(85.00%)
non-NST	201	(18.79%)	115	(23.96%)	39	(15.23%)	20	(12.99%)	27	(15.00%)
Tumour size										
< 2cm	544	(50.84%)	309	**(64.38%)**	97	(37.89%)	65	(42.21%)	73	(40.56%)
≥ 2cm	526	(49.16%)	171	(35.63%)	159	(62.11%)	89	(57.79%)	107	(59.44%)
Tumour differentiation										
G1 and G2	813	(75.98%)	453	**(94.38%)**	191	(74.61%)	90	(58.44%)	79	(43.89%)
G3	257	(24.02%)	27	(5.63%)	65	(25.39%)	64	(41.56%)	101	(56.11%)
Histopathological subgroups										
Luminal A-like	663	(61.96%)	424	**(88.33%)**	178	(69.53%)	34	(22.08%)	27	(15.00%)
Luminal B-like, HER2-neg.	117	(10.93%)	24	(5.00%)	55	(21.48%)	19	(12.34%)	19	(10.56%)
Luminal B-like, HER2-pos.	108	(10.09%)	27	(5.63%)	22	(8.59%)	51	(33.12%)	8	(4.44%)
HER2-pos., non-luminal	55	(5.14%)	1	(0.21%)	-	-	38	(24.68%)	16	(8.89%)
TNBC	127	(11.87%)	4	(0.83%)	1	(0.39%)	12	(7.79%)	110	**(61.11%)**

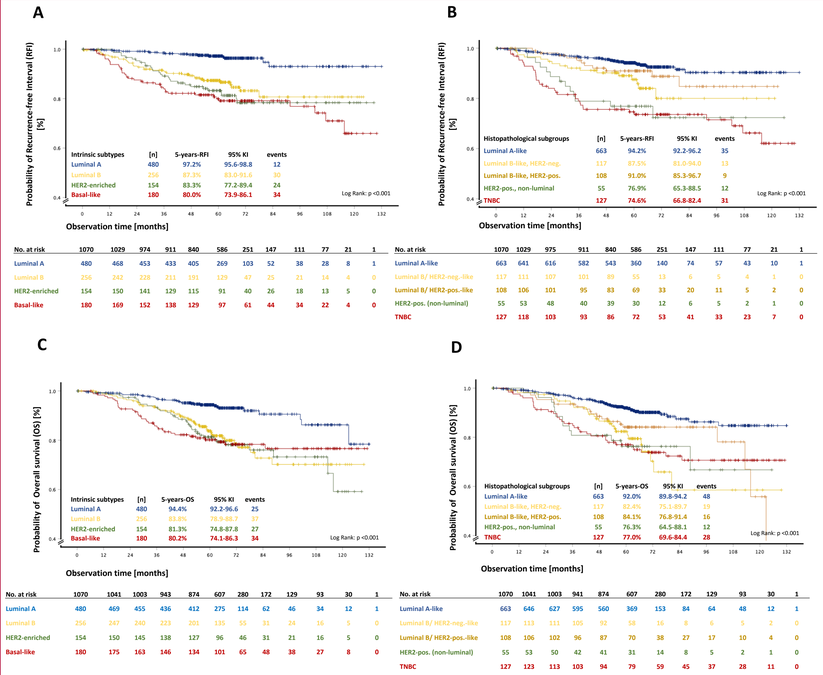

Figure 2: Survival analyses of intrinsic subtypes (A, C) and histopathological subgroups (B, D) with regard to recurrence-free interval and overall survival

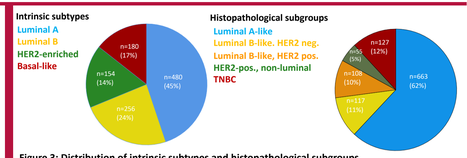

Figure 3: Distribution of intrinsic subtypes and histopathological subgroups

- The distribution of intrinsic subtypes was feasible
- Patients with a Luminal A tumour (Fig. 2A) had less disease-related events (2.8%) than patients with a Luminal A-like tumour (5.8%) (Fig. 2B).
- Only 5.6% of the patients with a Luminal A tumour (Fig. 2C) died compared to 8% of the patients with a Luminal A-like tumour (Fig. 2D).

Table 3: Multivariate Cox regression analysis of intrinsic subtypes

		Recurrence-free Interval (RFI), 5 years		
		Multivariate analysis		
Parameters	**sample size n=1,070**	**events n=101**	**Hazard Ratio**	**95% KI**
Intrinsic subtypes				
Luminal A	480	12	1	
Luminal B	256	30	**3.88**	1.959-7.691
HER2-enriched	154	24	**4.71**	2.306-9.628
Basal-like	180	35	**6.74**	3.358-13.532
Histopathological subgroups				
Luminal A-like	663	35	1	
Luminal B-like, HER2-neg.	117	13	1.79	0.947-3.392
Luminal B-like, HER2-pos.	108	9	1.29	0.619-2.706
HER2-pos., non-luminal	55	12	**3.62**	1.875-7.018
TNBC	127	32	**4.02**	2.469-6.562

*adjusted for age, nodal status, tumour size, grading, **adjusted for age, nodal status, tumour size,
bold = statistically significant (p=<0.05)

Conclusion

- Classification into intrinsic subtypes is a useful tool to identify more precise low risk BC-patients (Luminal A).
- Classification by histopathological parameters assigns more patients to the low risk group, however, at the cost of more recurrences.
- Prognostic assessment either by PAM50 or by IHC is still valid according to guideline-based adjuvant therapy recommendation; nevertheless requesting better treatments for each group.

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This presentation is the intellectual property of the authors. The presenting author has nothing to declare.
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