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Pattern of distant relapse according to intrinsic molecular subtype in patients with early HER2-positive breast cancer: a combined analysis of ShortHER, CherLOB and two Institutional cohorts.

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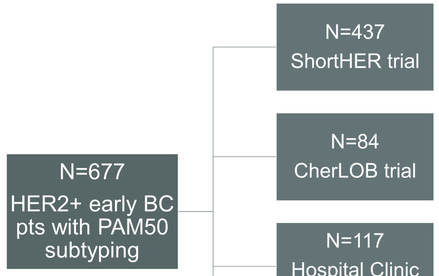
Background and aim

All intrinsic molecular subtypes are represented among HER2-positive breast cancer, with implications on clinical outcome and treatment sensitivity. The impact of molecular subtypes on the pattern and site of relapse is largely unexplored.

Methods

Patients with HER2-positive early breast cancer treated with chemotherapy and anti-HER2 with available PAM50 subtyping were included.



We analyzed the **incidence of distant relapse (at any site and at specific sites) as the first event.**

Cumulative incidence was estimated according to **competing risk analysis** (Fine and Gray's method). Competing risk regression was used to calculate the subdistribution Hazard Ratios (subHR) and their 95% Confidence Interval (CI).

Results

Figure 1. Distribution of intrinsic subtypes (n tot=677).

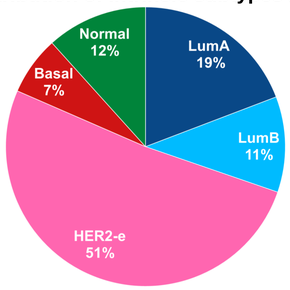


Table 1. Cumulative incidence rates of distant relapse as first event (any and specific sites) by intrinsic molecular subtype.

		Dist relapse (any)	Brain	Brain only	Lung	Bone	Bone only	Liver
LumA	5-yr	3.1%	0.0%	0.0%	0.8%	3.1%	2.3%	0.0%
	10-yr	7.9%	0.0%	0.0%	1.9%	8.7%	5.3%	2.7%
LumB	5-yr	10.7%	0.0%	0.0%	1.4%	6.7%	2.7%	5.4%
	10-yr	14.8%	0.0%	0.0%	3.3%	8.9%	4.8%	5.4%
HER2-e	5-yr	10.5%	3.8%	2.3%	2.6%	3.8%	1.2%	4.1%
	10-yr	14.7%	3.8%	2.3%	3.3%	4.4%	1.5%	6.6%
Basal	5-yr	10.9%	0.0%	0.0%	8.7%	4.3%	0.0%	2.2%
	10-yr	15.5%	0.0%	0.0%	11.1%	6.6%	0.0%	4.4%
Normal	5-yr	6.3%	2.5%	0.0%	0.0%	2.5%	1.3%	2.5%
	10-yr	10.4%	2.5%	0.0%	0.0%	6.6%	5.4%	2.5%
Gray's p		***0.179***	***0.049***	***0.102***	***0.010***	***0.679***	***0.187***	***0.383***

- Distant relapses (any site):
  - less frequent in LumA tumors (HER2-e vs LumA subHR=2.21, 95%CI 1.05-4.64, p=0.037), with similar rates for LumB, HER2-e and Basal.
- Brain metastases:
  - HER2-e tumors were more prone vs other subtypes to develop brain metastases.
  - Brain-only metastases occurred only in case of HER2-e tumors.
  - All brain metastases occurred within 5 years from diagnosis.
- Lung metastases:
  - Basal tumors were more prone vs other subtypes to develop lung metastases.

Figure 2. Representative cumulative incidence curves of distant metastasis as first event by intrinsic subtype.

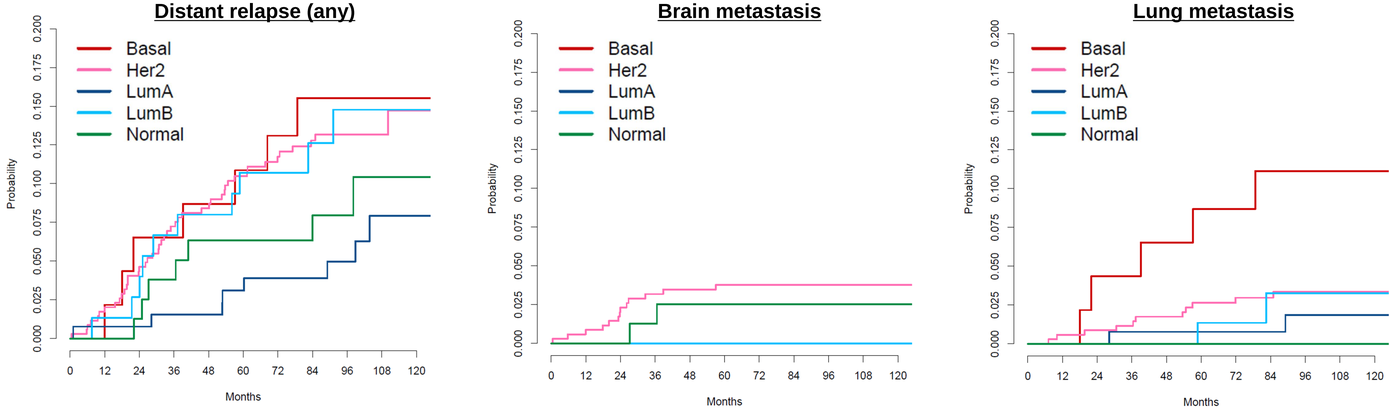
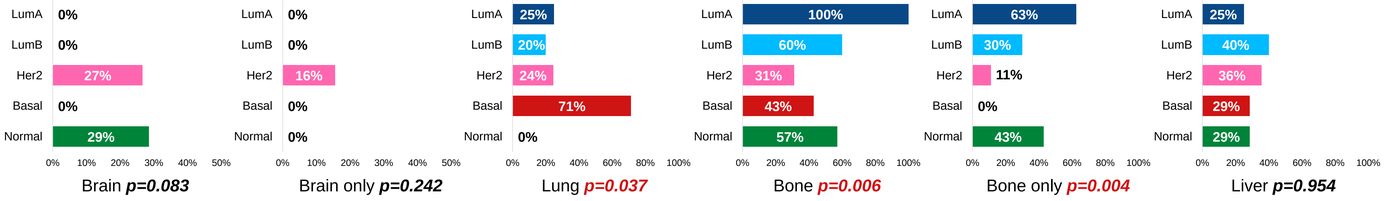


Figure 3. Frequency of site-specific metastasis among patients who developed distant disease by intrinsic subtypes (n tot=77)

Distribution of intrinsic subtypes: LumA n=8 (10%), LumB n=10 (13%), HER2-e n=45 (58%), Basal n=7 (9%), Normal n=7 (9%).
Distribution of metastatic sites: Brain n=14 (18%), Brain only n=7 (9%), Lung n=20 (26%), Bone n=35 (45%), Bone only n=16 (21%), Liver (n=26 (34%).



Conclusions

- Patients with HER2-positive, LumA tumors develop less frequently distant metastases as first event as compared to other intrinsic subtypes.
- Although the cumulative incidence of distant metastasis as first event is similar for LumB, HER2-e and Basal subtypes, the pattern of relapse is different (brain metastases more frequent in HER2-e, lung metastases more frequent in Basal).
- Among patients who developed metastatic disease as first event, the pattern of metastatic spread differed by intrinsic subtype (brain-only metastases more frequent in HER2-e, lung metastases more frequent in Basal, bone and bone-only metastases more frequent in LumA).

Molecular subtypes influence the metastatic behavior of clinically HER2-positive breast cancer.
These results, if further validated, may have implication in planning personalized monitoring strategies.