HER2 expression in a molecularly characterized cohort of endometrial cancer (EC) patients: SPECTRUM study

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Background

- Human epidermal growth factor receptor 2 (HER2)-low is a new category defined by HER2 1+ or 2+ by immunohistochemistry (IHC) and lack of HER2 amplification by in situ hybridization (ISH)[1].
- Trastuzumab deruxtecan has demonstrated antitumor activity in HER2-expressing gynecologic tumors[2].
- Little is known about HER2-low frequency in EC subtypes, the heterogeneity of the expression, the best scoring criteria or the prognostic value.

Methods

- This is a single center, retrospective study including patients diagnosed with EC amenable to curative treatment from 2003 to 2019.
- Two tissue cores of each sample were selected for the creation of 5 tissue microarrays (TMA).
- Molecular subrogated (MS) classification (WHO 5ed) was performed: polymerase epsilon mutated (POLEmut), mismatch repair deficiency (dMMR), TP53 abnormal (p53abn) or non-specific molecular profile (NSMP)[3].
- HER2 was assessed by IHC (4B5) and ISH on TMAs.
- HER2 scoring was performed according to ASCO/CAP guidelines for breast and the proposed endometrial criteria[4].
- HER2 heterogeneity was defined as a difference in HER2 IHC ≥2+ or discrepancy in HER2 ISH between cores.

Primary objective was to describe the frequency of HER2-low according to MS.

Secondary objectives included to assess the heterogeneity of the expression, the concordance between breast and endometrial criteria, the prognostic impact of HER2-low and the evolution of the expression.

Conclusions

- **This is the first study showing the spectrum of HER2 expression in a cohort of EC molecularly characterized.**
- **HER2-low status is more frequent in POLEmut and p53abn subtypes.**
- **Breast and endometrial scoring criteria showed high concordance.**
- **HER2-low status showed no prognostic significance.**

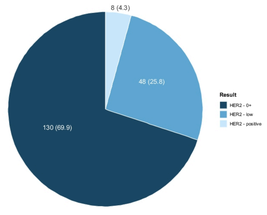
Table 1. Demographic characteristics. All results are shown as n (%), unless otherwise stated.

	All N = 193
Age, mean (SD)	66.4 (11.8)
Min. – max.	31 – 90
Stage at diagnosis	
I	138 (71.5)
II	27 (14.0)
III	30 (10.4)
IV	8 (4.1)
Histological subtype	
Endometrioid G1 – 2	111 (57.5)
Endometrioid G3	23 (11.9)
Serous	27 (14.0)
Clear cells	10 (5.2)
Mixed	13 (6.7)
Undifferentiated	2 (1.0)
Carcinosarcoma	5 (2.6)
Mesonephric-like	1 (0.5)
Neuroendocrine	1 (0.5)
Molecular subtype	
TP53	54 (28.0)
Ultramutated (POLE)	6 (3.1)
Hypermutated (MMRd)	49 (25.4)
Non-specific	79 (40.9)
Unclassifiable	5 (2.6)

Results

- 193 patients were included in the analysis. Patients' characteristics are described in **Table 1.**
- Considering the entire cohort, 69.9% were HER2-negative (0+), 25.8% HER2-low and 4.3% HER2-positive (3+ or ISH+)* (**Figure 1).**
- The frequency of HER2-low was highest for POLEmut (66.7%)** followed by p53abn (42.6%) **(Figure 2).**
- Low heterogeneity in HER2 expression was demonstrated, with an agreement between cores in 84.5% of cases.
- Breast and endometrial criteria showed concordance in 85.5% of patients, kappa 0,624 ($p < 0,05$) **(Table 2).**
- HER2-low status had no impact on recurrence free (p 0.686) and overall survival (p 0.964)***.
- HER2 0+ expression was stable between localized and metastatic lesions ^ **(Figure 3).**

Figure 1. HER2 status - endometrial cohort



* According to proposed endometrial criteria.
** 6 cases.
*** Only analyzed in high grade cases.
^ 7 cases

Figure 2. HER2 status according to molecular subtype

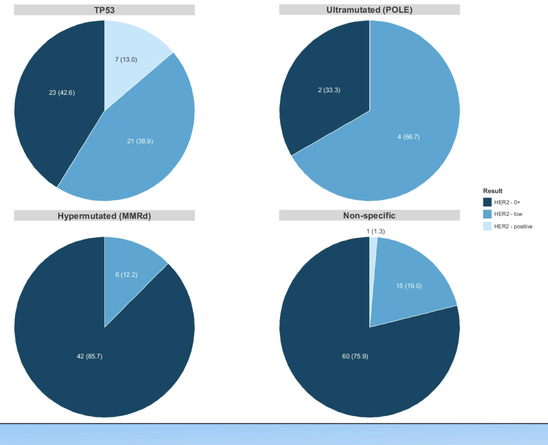
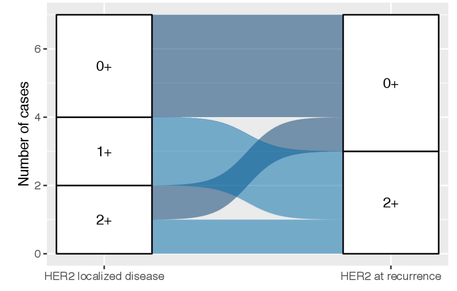


Table 2. HER2 expression (results according to breast criteria and endometrial criteria). All results are shown as n (%), unless otherwise stated.

	All N = 193	
	Breast	Endometrial
Molecular subtype		
TP53 (N)	51	51
0+	29 (53.7)	21 (38.9)
1+	11 (20.4)	7 (13.0)
2+	9 (16.7)	21 (38.9)
3+	2 (3.7)	2 (3.7)
Ultramutated (POLE) (N)	6	6
0+	5 (83.3)	2 (33.3)
1+	1 (16.7)	3 (50.0)
2+	0 (0.0)	1 (16.7)
3+	0 (0.0)	0 (0.0)
Hypermutated (MMRd) (N)	48	48
0+	45 (91.8)	42 (85.7)
1+	3 (6.1)	3 (6.1)
2+	0 (0.0)	3 (6.1)
3+	0 (0.0)	0 (0.0)
Non-specific (N)	76	76
0+	69 (87.3)	60 (76.0)
1+	5 (6.3)	5 (6.3)
2+	2 (2.5)	11 (13.9)
3+	0 (0.0)	0 (0.0)
Unclassifiable (N)	5	5
0+	5 (100.0)	5 (100.0)
1+	0 (0.0)	0 (0.0)
2+	0 (0.0)	0 (0.0)
3+	0 (0.0)	0 (0.0)

Figure 3. Evolution of HER2 expression



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