Comparison of breast and gastric HER2 immunohistochemistry (IHC) scoring criteria in the assessment of endometrial carcinoma

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Background

- Immunohistochemical (IHC) staining is the primary method of HER2 assessment in solid malignancies at many institutions. Approved algorithms with differing scoring parameters exist for HER2 in breast and gastric carcinomas[1-2].
- Historically, a binary categorization of HER2 status (positive vs. negative) defined the treatment of patients with HER2-expressing tumors based on the activity of trastuzumab[3].
- The development of HER2 antibody-drug conjugates (ADCs) has provided evidence of anti-tumor activity in cancers across a full range of HER2 expression, including equivocal staining[3-4].
- Enrollment in recent clinical trials was based on HER2 diagnostic criteria for gastric carcinoma[4], while breast cancer scoring algorithms are commonly used for HER2 assessment in gynecologic malignancy[5-6].
- Neither breast nor gastric scoring system has been validated in gynecologic neoplasms. Our study seeks to assess the concordance among immunohistochemical (IHC) scoring for HER2 expression in endometrial cancer when gastric versus breast HER2 diagnostic criteria are used.

Methods

- 263 endometrioid adenocarcinoma (EEA) (FIGO grades 1-3), 275 serous endometrial carcinoma (SEC), and 214 uterine carcinosarcoma (UCS) specimens were randomly selected.
- Previously stained HER2 IHC (4B5) slides underwent blinded review by two board-certified pathologists.
- HER2 immunoreactivity was scored utilizing both gastric and breast criteria as follows:
  - Positive [P]: intensity 3+, >10% [breast] or ≥10% [gastric] tumor cell staining
  - Equivocal [E]: 2+, >10% [breast] or ≥10% [gastric]
  - Low/Negative [N]: >1+, ≤10% [breast] or <10% [gastric], or any percentage of 1+
- The results of the two scoring systems were compared.
- Tumors were also analyzed for *ERBB2* copy number amplification by DNA (592-gene or whole exome) sequencing and for *ERBB2* RNA expression (TPM) by RNA (whole transcriptome) sequencing.
- Statistical significance determined using unpaired t-test.

Results

- Overall, 95% of HER2 P cases and 88% of HER2 N cases were concordant between the two scoring algorithms.
- HER2 E tumors showed a lower rate of concordance, with EEAs having the lowest rate of E concordance (50.8%, 30/59).

- **In EEA:** 96.1% (49/51) of HER2 P cases and 85.2% (155/182) of HER2 N cases were concordant between the two scoring algorithms.
- Of discordant EEA E tumors, 26/29 (89.7%) were N by breast, but E by gastric criteria (example case shown in Figure 1).

EEA		Gastric Guidelines		
		P	E	N
Breast Guidelines	P	49	1	0
	E	1	30	1
	N	0	26	155

Table 1: Concordance and discordance of HER2 IHC calls by gastric and breast criteria in EEA

- **In SEC:** 94.2% (81/86) of HER2 P cases , 82.2% (74/90) of HER2 E cases, and 90.4% (104/115) of HER2 N cases were concordant.
- Of discordant SEC E tumors, 68.8% (11/16) cases were negative by breast and equivocal by gastric criteria.

SEC		Gastric Guidelines		
		P	E	N
Breast Guidelines	P	81	0	0
	E	5	74	0
	N	0	11	104

Table 2: Concordance and discordance of HER2 IHC calls by gastric and breast criteria in SEC.

- **In UCS:** 94.6% (35/37) of HER2 P cases, 86.5% (64/74) of HER2 E cases, and 91.2% (104/115) of HER2 N cases were concordant.
- Of discordant UCS E tumor, 81.8% (9/11) were negative by breast and equivocal by gastric criteria.

UCS		Gastric Guidelines		
		P	E	N
Breast Guidelines	P	35	0	0
	E	1	64	0
	N	1	9	104

Table 3: Concordance and discordance of HER2 IHC calls by gastric and breast criteria in UCS.

- Concordant HER2 P tumors had the highest median ERBB2 copy number and TPM across subtypes with EEA having the highest.
- Discordant HER2 N tumors by breast, but E by gastric criteria were compared to concordant HER2 N and E tumors:
  - ***In EEA:*** *CNA*: 1.39-fc (1.8 vs 1.9; 1.8 vs 2.5 copies), p=0.0485, p<0.02. *RNA:* 1.27-fc (45 vs 19.6; 45 vs 35.4 TPM), p=0.99, p=0.96.
  - ***In SEC:*** *CNA*: 0.84-fc (2.41 vs 1.70; 2.41 vs 2.87 copies), p=0.178, p=0.411. *RNA*: 1.22-fc (60.5 vs 28.9; 60.5 vs 49.5 TPM), p=0.009, p=0.776.
  - ***In UCS:*** *CNA*: (9 vs 1.98; 9 vs 2.76 copies), p=0.005, p=0.072. *RNA:* 1.12-fc (48.6 vs 27; 48.6 vs 43.3 TPM), p=0.035, p=0.662.

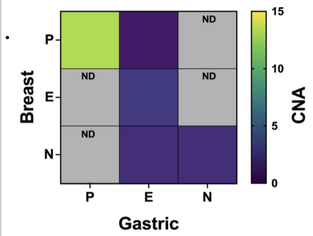


Figure 2: Copy number alterations (CNA) of *ERBB2* stratified by HER2 IHC staining in EEAs

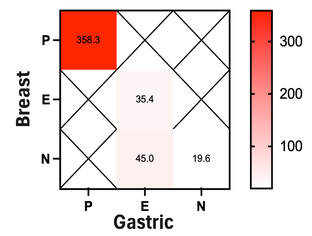


Figure 3: *ERBB2* RNA expression (TPM) stratified by HER2 IHC staining in EEA

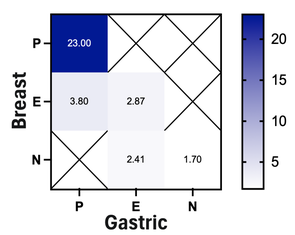


Figure 4: Copy number alterations (CNA) of *ERBB2* stratified by HER2 IHC staining in SEC.

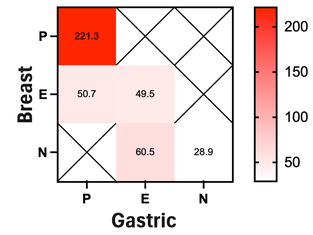


Figure 5: *ERBB2* RNA expression (TPM) stratified by HER2 IHC staining in SEC.

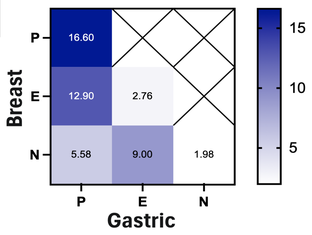
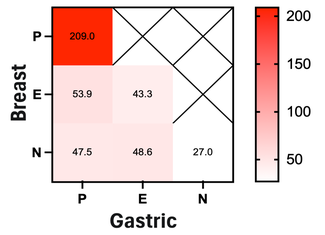


Figure 4: Copy number alterations (CNA) of *ERBB2* stratified by HER2 IHC staining in UCS.



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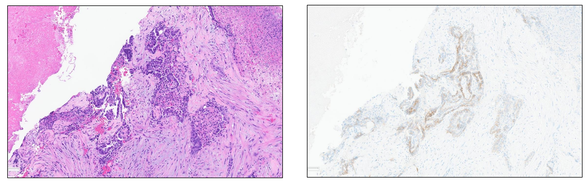

Figure 1: Example of discordant staining. Hematoxylin and eosin staining (left), 20x magnification, and companion HER2 IHC (clone 4B5) staining (right), 20x magnification), demonstrating EEA with 2+ staining intensity in 5% of neoplastic cells by breast IHC criteria, but 15% of neoplastic cells by gastric IHC criteria

Conclusions

- There is a high level of concordance between gastric and breast criteria for HER2 IHC staining in identifying endometrial carcinomas positive for HER2 overexpression.
- Equivocal staining was more often documented with gastric scoring criteria (negative by breast scoring criteria) across all three subgroups of endometrial cancer.
- This greater frequency of equivocal results may suggest a preference for gastric criteria in the assessment of endometrial cancer, matching trial inclusion criteria where clinical benefit of HER2 ADCs has been established in patients with HER2 equivocal tumors.
- **Further work is focused on exploring survival by cancer type amongst the different HER2-expressing cohorts.**

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