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

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Abstract

Background: The DESTINY-PanTumor02 trial demonstrated efficacy of HER2-directed antibody drug conjugates (ADCs) in the treatment of gynecologic malignancies, including endometrial endometrioid adenocarcinoma (EEA). Trial eligibility was determined utilizing HER2 IHC gastric criteria, but many institutions historically use breast criteria for IHC interpretations. As neither scoring system has been validated in gynecologic neoplasms, our study seeks to compare them in EEA.

Methods: Blinded pathology review of HER2 IHC (4B5) from 263 randomly selected EEAs was performed by two board-certified pathologists utilizing gastric and breast criteria. Results of the two scoring systems were compared (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+). Tumors were analyzed for *ERBB2* copy number amplification by DNA (592-gene or whole exome) sequencing and statistical significance determined using unpaired T-test.

Results: Of HER2 P cases, 96% (49/51) were concordant between breast/gastric criteria, median of 13.0 copies of *ERBB2*. HER2 E tumors showed a lower rate of concordance with 51% (30/59) concordant cases, median of 2.5 copies of *ERBB2*. Of discordant HER2 E tumors, 44% (26/59) of E cases were N by breast/E by gastric (1.8 median copies, $p < 0.02$ vs concordant cases). HER2 N cases were 86% (155/182) concordant (1.9 median copies, $p = 0.96$ vs N by breast/E by gastric cases).

Conclusion:While gastric and breast criteria demonstrated 96% concordance in identifying EEAs positive for HER2 overexpression, equivocal staining was more often documented with gastric scoring. This greater frequency of equivocal results may suggest a preference for gastric criteria in the assessment of EEA, matching trial inclusion criteria where clinical benefit of HER2 ADCs has been established in patients with HER2 equivocal tumors.

Background

- Immunohistochemical (IHC) staining is the primary method HER2 assessment in solid malignancies at many institutions. HER2 IHC staining criteria differs amongst solid tumor types, and approved algorithms with differing scoring parameters exist for HER2 expression and amplification in breast and gastric carcinomas[1-2].
- Historically, a binary categorization of HER2 status (positive vs. negative) defined the prognosis and treatment of patients with HER2 expressing tumors based on the activity of trastuzumab[3].
- With the development of HER2-ADCs, there is evidence of anti-tumor activity in cancers across a full range of HER2 expression, including equivocal staining[3-4].
- Enrollment in recent trials such as the DESTINY-PanTumor02 was based on HER2 diagnostic criteria for gastric carcinoma[4], while institutions commonly utilize breast cancer scoring algorithms 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 endometrioid endometrial cancer when gastric versus breast HER2 diagnostic criteria are used.

Methods

- 263 endometrioid endometrial cancer specimens were randomly selected.
- Previously stained HER2 IHC (4B5) specimen 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 statistical significance determined using unpaired t-test.

Results

- Nearly all HER2 positive cases (49/51, 96%) were concordant between breast/gastric criteria
- HER2 equivocal tumors showed a lower rate of concordance (51%)
- Of the discordant HER2 equivocal tumors, 44% were negative by breast criteria, but equivocal by gastric criteria
- 86% of HER2 negative cases were concordant
- Concordant HER2 equivocal cases had a median of 2.5 copies of ERBB2, compared to tumors that were negative by breast criteria/equivocal by gastric criteria which had 1.8 median copies ($p<0.02$)

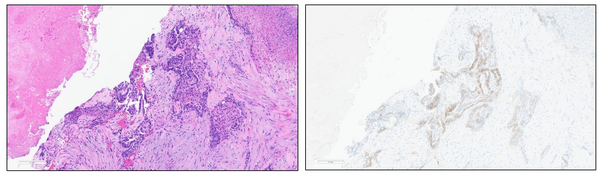

Figure 1: Example of discordant standing. Hematoxylin and eosin staining (left), 20x magnification, and companion HER2 IHC (clone 4B5) staining (right), 20x magnification), demonstrating a focus of endometrioid adenocarcinoma with 2+ staining intensity in 5% of neoplastic cells by breast IHC criteria,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

		Gastric		
	IHC call	**P**	**E**	**N**
Breast	**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

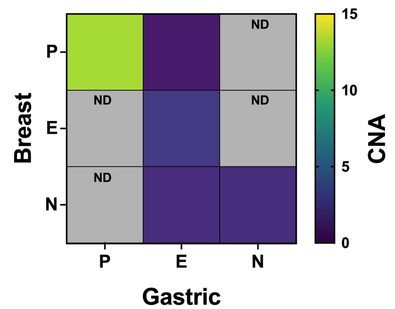

Figure 2: Copy number alterations (CNA) of ERBB2 stratified by HER2 IHC staining

Study Highlights

- There is a high level of concordance between gastric and breast criteria for HER2 IHC staining in identifying EEAs positive for HER2 overexpression
- Equivocal staining was more often documented with gastric scoring criteria (negative by breast scoring criteria).
- As clinical benefit of HER2 ADCs has been established in patients with HER2 equivocal tumors (by gastric scoring criteria), this discrepancy highlights a need for validation and standardization of scoring criteria to matching trial inclusion criteria.

Conclusions

- Gastric and breast criteria for HER2 IHC staining demonstrate high levels of concordance in identifying EEAs positive for HER2 overexpression
- Equivocal staining was more often documented with gastric scoring.
- This greater frequency of equivocal results may suggest a preference for gastric criteria in the assessment of EEA, matching trial inclusion criteria where clinical benefit of HER2 ADCs has been established in patients with HER2 equivocal tumors.
- Further work is focused on expanding this analysis to other histologic subtypes of endometrial cancer.

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