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HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline from the College of American Pathologists, American Society for Clinical Pathology and the American Society of Clinical Oncology

www.asco.org/her2-gastric-guideline

Introduction

- Gastroesophageal adenocarcinoma (GEA) is estimated to represent up to 43,280 cancer cases in the US in 2016,[1] and represents the eighth (esophageal) and fifth (stomach) most common cancers worldwide.[2]

- In 2010, results of an open-label, international, phase 3 randomized controlled trial (Trastuzumab for Gastric Cancer, ToGA), showed that the anti-HER2 humanized monoclonal antibody trastuzumab (Herceptin) statistically significantly prolonged overall survival compared with chemotherapy alone in patients with HER2–positive advanced GEA.[3]

- In 2007, a joint expert panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for *HER2* in patients with breast cancer, which is amplified and/or overexpressed in up to 30% of cases.[4]

- Because there are important distinct differences in HER2 expression, scoring, and outcomes in GEA relative to breast carcinoma, the need for HER2 guidelines (that include critical clinical and laboratory considerations) was recognized.

CAP/ASCP/ASCO Guideline Development Methodology

The process for this guideline included:

- a systematic literature review
- an expert panel provided critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by the CAP independent review panel, ASCP Special Review Panel, and ASCO CPGC

The full guideline methodology supplement can be found at:

www.asco.org/her2-gastric-guideline

Clinical Questions

What is the optimal testing algorithm for the assessment of *HER2* status in patients with GEA?

What strategies can help ensure optimal performance, interpretation, and reporting of established assays in patients with GEA?

Target Population and Audience

Target Population

Patients with Gastroesophageal Adenocarcinoma

Target Audience

Medical and surgical oncologists; oncology nurses and physician assistants; pathologists; general practitioners; and patients

Summary of Recommendations

CLINICAL QUESTION 1

What is the optimal testing algorithm for the assessment of *HER2* status in patients with GEA?

Recommendation 1.1

In patients with advanced GEA who are potential candidates for HER2 targeted therapy, the treating clinician should request *HER2* testing on tumor tissue (Type: Evidence based; Quality of evidence: High; Strength of recommendation: Strong).

Recommendation 1.2

Treating clinicians or pathologists should request *HER2* testing on tumor tissue in the biopsy or resection specimens (primary or metastasis) preferably prior to the initiation of trastuzumab therapy if such specimens are available and adequate. *HER2* testing on FNA specimens (cell blocks) is an acceptable alternative (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate).

Recommendation 1.3

Treating clinicians should offer combination chemotherapy and HER2-targeted therapy as the initial treatment for appropriate patients with *HER2* positive tumors who have advanced GEA (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Summary of Recommendations

CLINICAL QUESTION 2

What strategies can help ensure optimal performance, interpretation, and reporting of established assays in patients with GEA?

Recommendation 2.1

Laboratories/pathologists must specify the antibodies and probes used for the test and ensure that assays are appropriately validated for HER2 IHC and ISH on GEA specimens (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Recommendation 2.2

When GEA HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first followed by ISH when IHC result is 2+ (equivocal). Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing (Type: Evidence based; Quality of evidence: High; Strength of recommendation: Strong).

Recommendation 2.3

Pathologists should use the Ruschoff/Hofmann method in scoring HER2 IHC and ISH results for GEA (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Summary of Recommendations

Recommendation 2.4

Pathologists should select the tissue block with the areas of lowest grade tumor morphology in biopsy and resection specimens. More than one tissue block may be selected if different morphologic patterns are present (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate).

Recommendation 2.5

Laboratories should report HER2 test results in GEA specimens in accordance with the CAP biomarker "Template for Reporting Results of *HER2 (ERBB2)* Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction"[5] (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Summary of Recommendations

Recommendation 2.6

Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in GEA specimen for subsequent ISH scoring when required (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

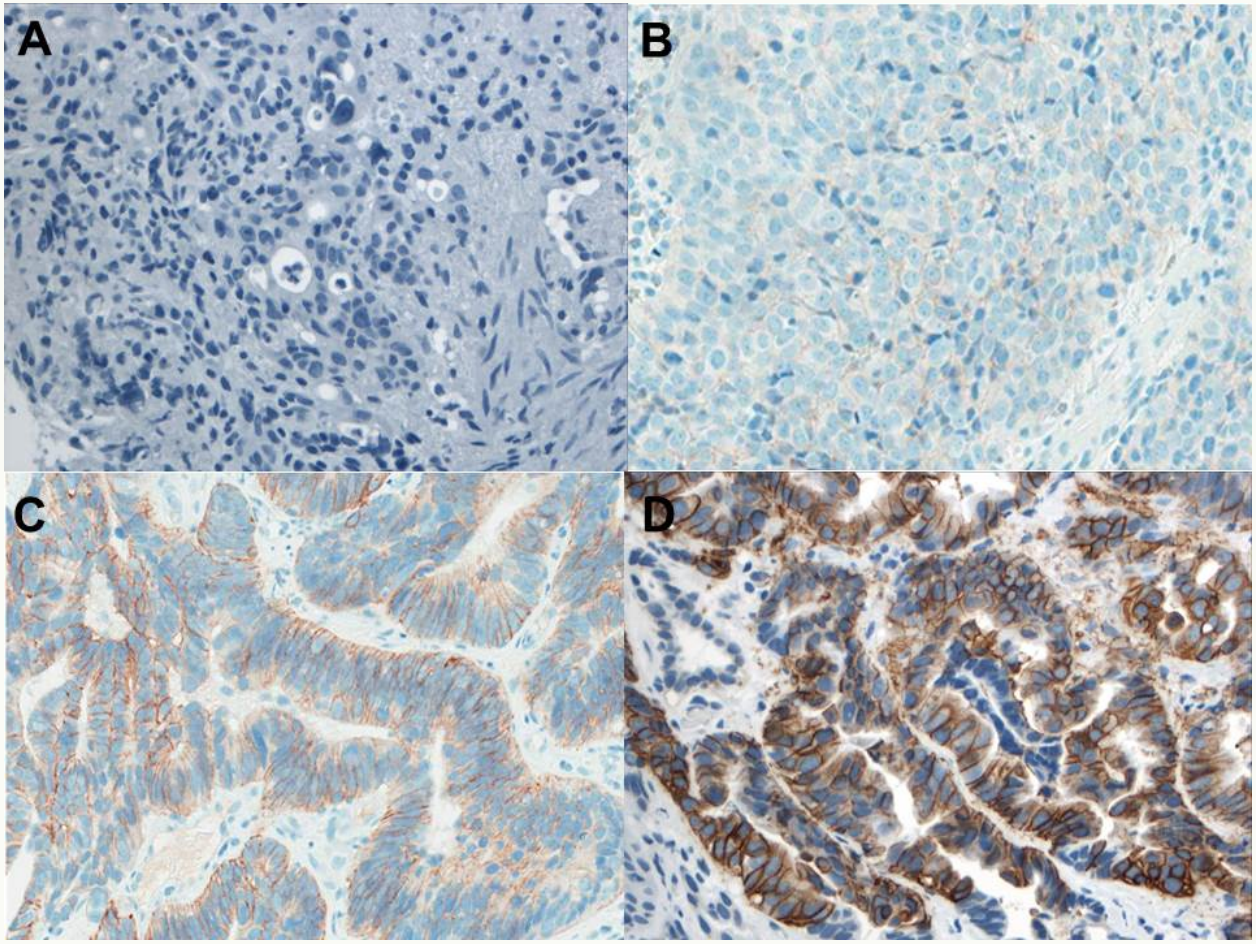
Recommendation 2.7

Laboratories must incorporate GEA HER2 testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to assure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing GEA HER2 testing should participate in a formal proficiency testing program, if available, or an alternative proficiency assurance activity (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Recommendation 2.8

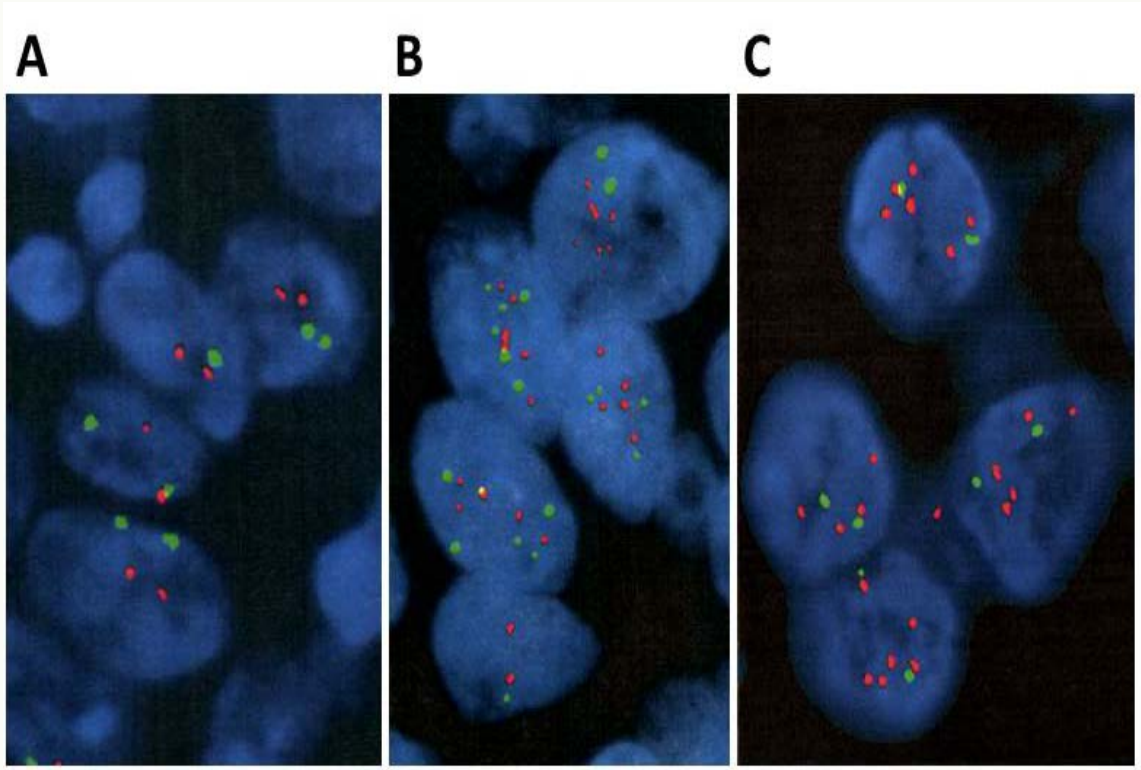
There is insufficient evidence to recommend for or against genomic testing in GEA patients at this time.

HER2 immunochemistry showing representative cases for scoring.



(A) Negative 0: No reactivity, specifically no membranous reactivity is seen in any of the tumor cells. Any cytoplasmic staining is disregarded for scoring purposes; (B) Negative 1+: Tumor cells with faint/barely perceptible membranous staining; (C) Equivocal 2+: Tumor cells with weak to moderate complete, basolateral and lateral membranous staining. Columnar cells that are sectioned tangentially tend to show a complete membranous staining pattern; (D) Positive 3+: Tumor cells with a strong complete, basolateral and lateral membranous reactivity. Also note that cells showing a complete membranous staining pattern are often tangentially sectioned columnar cells.

HER2 and CEP 17 fluorescence in situ hybridization (FISH) shows scores of representative cases



(A) Not amplified: Ratio 1.0. Mean number of *HER2* signals per cell is 1.9; mean number of CEP 17 signals per cell is 1.8; (B) Not amplified: Ratio 1.3. Mean number of *HER2* signals per cell is 3.4; mean number of CEP 17 signals per cell is 2.7. Segmental duplication (or polysomy) likely accounts for signal numbers over 2 per cell; (C) Amplified: Ratio 3.0. Mean number of *HER2* signals per cell is 5.2; mean number of CEP 17 signals per cell is 1.7.

Conclusion

- GEA continues to be a major healthcare burden throughout the world.
- Advanced GEA that is not amenable to effective local therapy remains incurable and patients have limited therapeutic options.
- Other than *HER2*, there is no biomarker available for selection of therapy for patients with advanced GEA.
- Trastuzumab is the only approved HER2-directed therapy that has resulted in modest but statistically significant prolongation of overall survival of HER2 positive GEA patients.

Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/her2-gastric-guideline

Patient information is available at www.cancer.net

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References

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2. World Cancer Research Fund International: Cancer facts & figures - Worldwide data. http://www.wcrf.org/int/cancer-facts-figures/worldwide-data (Accessed June 28, 2016)

3. Bang YJ, Van Cutsem E, Feyereislova A, et al: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 376:687-697, 2010

4. Wolff AC, Hammond ME, Schwartz JN, et al: American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 131:18-43, 2007

5. Bartley AN, Christ J, Fitzgibbons PL, et al: Template for reporting results of HER2 (ERBB2) biomarker testing of specimens from patients with adenocarcinoma of the stomach or esophagogastric junction. Arch Pathol Lab Med 139:618-620, 2015

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