Questions Relating to Immunohistochemistry for HER2 on Gastric and Gastroesophageal Junction Carcinomas

Do the ASCO/CAP guidelines for HER2 testing in breast cancer also apply to gastric cancer?

No. The ASCO/CAP guidelines for breast cancer do not apply to HER2 IHC as performed on gastric cancer.

Are the grading criteria for HER2 IHC on gastric carcinoma the same as those for breast carcinoma?

No. The criteria for interpreting HER2 IHC on gastric carcinoma differ significantly from the breast cancer criteria in three important ways. Firstly, in contrast to the grading scheme in breast cancer, the gastric carcinoma interpretation criteria use 10% tumor cell staining as a cutoff to distinguish negative from 1+. In gastric carcinoma, the distinction between 1+, 2+, and 3+ depends on the intensity of staining presuming that more than 10% of tumor cells show HER2 expression (see table below).

Secondly, in strongly staining cases, HER2 3+ gastric cancers may only show expression along the basolateral or lateral cell membranes; apical membranes do not always show stain. Thus, the criteria for 2+ and 3+ staining in gastric cancer require only lateral or basolateral staining, unlike the breast cancer criteria which require complete, circumferential staining.

Thirdly, the criteria for HER2 overexpression differ when interpreting biopsy and resection specimens due to increased heterogeneity of HER2 expression in gastric and gastroesophageal junction carcinomas (see table below).

<table>
<thead>
<tr>
<th>Surgical Specimen Staining Pattern</th>
<th>Biopsy Specimen Staining Pattern</th>
<th>HER2 Overexpression Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No reactivity or membranous reactivity in &lt;10% of tumor cells</td>
<td>No reactivity in any tumor cell</td>
<td>Negative</td>
</tr>
<tr>
<td>Faint or barely perceptible membranous reactivity in 10% or more of tumor cells; cells are reactive only in part of their membrane</td>
<td>Tumor cell cluster* with faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Negative</td>
</tr>
<tr>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in 10% or more of tumor cells</td>
<td>Tumor cell cluster* with weak to moderate complete, basolateral or lateral membranous</td>
<td>Equivocal</td>
</tr>
</tbody>
</table>
reactivity irrespective of percentage of tumor cells stained

| Strong complete, basolateral or lateral membranous reactivity in 10% or more of tumor cells | Tumor cell cluster* with strong complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained | Positive |


**Tumor cell cluster** is defined as a cluster of 5 or more tumor cells (Ruschoff et al, HER2 diagnostic in gastric cancer –&38211; guideline validation and development of standardized immununohistochemical testing. Virchows Arch 457:299-307. 2010.)

**Do the LAP questions that specifically apply to HER2 immunohistochemistry on breast cancer apply to gastric cancer?**

No. However, general questions pertaining to IHC assays that provide independent predictive information do apply to HER2 IHC performed on gastric cancer (see ANP.22969 and ANP.22970).

Exception: Laboratories that interpret and report the results of HER2 testing by FISH in which the hybridization is performed at an outside laboratory should not enroll in proficiency testing for that assay due to PT Referral prohibitions; such laboratories must perform alternative assessment. This exception does not apply to laboratories that interpret and report the results of HER2 testing by immunohistochemistry when staining is done at an outside facility.

**Do I need to separately validate my HER2 IHC assay for gastric cancer?**

Yes. While the assay conditions between HER2 IHC performed on breast and gastric carcinomas need not differ, the interpretation criteria differ significantly (see above). As such, we recommend that a small revalidation be performed to assure that the correlation between IHC results and those of FISH are adequate. The required level of correlation and the number of cases that should be included in the revalidation is best determined by the immunohistochemistry laboratory director. However, 90-95% concordance between FISH and IHC is recommended.

**Does a proficiency testing product exist for HER2 IHC on gastric cancer?**

Yes, the CAP Gastric HER2 (GHER2) Survey offers one 10-core tissue microarray slide in each of 2 shipments per year.
What are the published benchmarks for HER2 expression in gastric cancer?

Depending on the series, the prevalence of HER2 expression in gastric cancer seems to be 15-25%. The level of expression of intestinal type gastric cancer seems to be much higher (~32%) compared with diffuse-type gastric cancer (~6%). Also, tumors that are primarily located at the gastroesophageal junction seem to have higher HER2 positive rates compared to tumors that occur in the rest of the stomach (33% versus 21%).

References