Adverse prognostic impact of heterogeneous HER2 gene amplification in patients with esophageal adenocarcinoma

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Objective

• To determine the frequency and prognostic impact of intratumor heterogeneous HER2 gene amplification and polysomy 17 in patients with esophageal adenocarcinoma (EAC)
Background

• Among human esophageal adenocarcinomas, 7-40% demonstrate HER2-positivity, as we and others have shown\(^a\).
• Recent data indicate that a subset of primary breast tumors displays intratumor HER2 heterogeneity\(^b\) whose frequency may be higher in gastric cancer\(^c\).
• The reportedly higher rate of HER2 heterogeneity in gastric cancer has led to a change in the interpretive criteria for HER2 staining in esophagogastric cancer biopsies that differs from breast cancers\(^d\).
• Studies to further characterize intratumor HER2 heterogeneity in esophagogastric cancers are needed and may have important clinical implications.
• Routinely ordered HER2 FISH assays include information on chromosome 17 copy number. Extra copies of chromosome 17 (ie, polysomy 17) reflect aneuploidy and chromosomal instability that may confer prognostic information.

\(^a\) — Yoon HH et al Clinical Cancer Research 2012; 18(2): 546-54  
\(^c\) — Hofmann et al. Histopathol 2008; 52;797.  
\(^d\) — Bang et al Lancet 2010.
Study population\textsuperscript{a}

- Patients with adenocarcinoma of the esophagus, gastroesophageal junction, or gastric cardia (termed EAC) who underwent surgery with curative intent at Mayo Clinic, Rochester (1980-97)
- No patient received neoadjuvant or HER2-targeted therapy.

\textsuperscript{a} Yoon HH et al. Clin Cancer Research 2012; 18; 546.
HER2 testing

• Paraffin-embedded EACs were sectioned
• 60 representative malignant nuclei were examined per tumor
• FDA-approved assays (Abbott Molecular) were utilized for assessing HER2 and chromosome 17 copy number by FISH (fluorescence in situ hybridization) a
• HER2 amplification was defined as $\frac{HER2}{CEP17}$ ratio $\geq 2$, in accordance with upper GI cancer criteria and ASCO/CAP (College of American Pathologists) b.
• HER2 heterogeneity was defined per CAP as HER2 amplification in $>5\%$ but $<50\%$ of tumor cells c.

b — Bang et al. Lancet 2010; 376; 687; Wolff et al JCO 2007; 25; 118
c — Vance GH et al, Arch Pathol Lab Med 2009; 133; 611
Intratumor heterogeneous HER2 gene amplification in EAC

The image shows one EAC tumor, with HER2-amplified cells adjacent to HER2-nonamplified cells.

RED = HER2 probe
GREEN = CEP17 centromere probe

WHITE ARROWHEADS = HER2-amplified cells
YELLOW ARROWS = HER2-nonamplified cells

a FDA-approved assay (PathVysion HER2 DNA Probe Kit, Abbott Molecular, Des Plaines, IL) as described in Yoon HH et al Clinical Cancer Research 2012; 18(2): 546-54
Intratumor HER2 heterogeneity

Frequency

HER2-Amplified

N = 117

HER2-Heterogeneous

17%

HER2-Uniform

HER2-Non-Amplified

N = 558

There were no HER2-heterogeneous tumors in the nonamplified group

HER2 heterogeneity was defined utilizing ASCO/CAP guidelines – ie, HER2 amplification present in >5% but <50% of tumor cells, Vance et al, Arch Pathol Lab Med 2009; 133; 611
### HER2 and clinicopathologic variables

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TOTAL (N = 675)</th>
<th>HER2-Non-Amplified (N = 558)</th>
<th>HER2-Amplified (N = 117)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Age, median</td>
<td>64.8</td>
<td>65.2</td>
<td>64.4</td>
<td>63.8</td>
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<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Moderate</td>
<td>399</td>
<td>60</td>
<td>306</td>
<td>55</td>
</tr>
<tr>
<td>High</td>
<td>270</td>
<td>40</td>
<td>249</td>
<td>45</td>
</tr>
<tr>
<td>Signet Ring Cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>606</td>
<td>90</td>
<td>492</td>
<td>88</td>
</tr>
<tr>
<td>Yes</td>
<td>69</td>
<td>10</td>
<td>66</td>
<td>12</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>217</td>
<td>32</td>
<td>169</td>
<td>30</td>
</tr>
<tr>
<td>3-4</td>
<td>454</td>
<td>68</td>
<td>385</td>
<td>70</td>
</tr>
<tr>
<td>No. metastatic nodes, median</td>
<td>2.0</td>
<td>2.0</td>
<td>1.5</td>
<td>1.0</td>
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</table>
## HER2 and polysomy 17

Polysomy 17 = 3 or more copies of CEP17

<table>
<thead>
<tr>
<th>Polysomy 17</th>
<th>HER2-Non-Amplified (N = 558)</th>
<th>HER2-Amplified</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Absent (N = 182)</td>
<td>141</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Present (N = 493)</td>
<td>417</td>
<td>75</td>
<td>18</td>
</tr>
</tbody>
</table>

**Polysomy 17 = 3 or more copies of CEP17**
HER2-heterogeneity and prognosis

Among HER2-amplified EACs

N = 117

Hazard ratios (HRs) are adjusted for histologic grade, the number of malignant lymph nodes, T stage, and polysomy 17. DSS = disease-specific survival. OS = overall survival.

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Polysomy 17 and prognosis

Among HER2-nonamplified EACs

$N = 558$

Hazard ratios (HRs) are adjusted for histologic grade, the number of malignant lymph nodes, T stage. DSS = disease-specific survival. OS = overall survival.

**DSS**
- Polysomy 17
  - Yes ($N=417$) HR 1.36; $P=0.012$
  - No ($N=141$)

**OS**
- Polysomy 17
  - Yes ($N=417$) HR 1.31; $P=0.023$
  - No ($N=141$)
Summary

• Intratumor HER2 genetic heterogeneity is present in 17% of HER2-amplified EACs

• HER2-heterogeneity is independently associated with worse survival in HER2-amplified EACs

• Polysomy 17 is independently associated with worse survival in HER2-nonamplified EACs