# HER2 Assessment in Upper Gastrointestinal Tract Adenocarcinoma

## A Practical, Algorithmic Approach

Jon M. Davison, MD, Reetesh K. Pai, MD*

**KEYWORDS**

• HER2 • Trastuzumab • Herceptin • Esophageal adenocarcinoma • Gastric adenocarcinoma

## ABSTRACT

Gastric and gastroesophageal junction adenocarcinomas constitute a major health problem. For localized disease, adjuvant treatment is multidisciplinary and usually includes a combination of surgery, radiation, and chemotherapy. For advanced disease, there is no formal consensus or evidence-based rationale regarding the best chemotherapy regimen. Although treatment of patients with unresectable or metastatic disease remains palliative and survival rates low, chemotherapy improves survival and quality of life compared with best supportive care. The purpose of this review is to provide pathologists with practical guidance in HER2 assessment of upper gastrointestinal tract adenocarcinomas to accurately identify patients eligible for trastuzumab therapy.

## OVERVIEW OF UPPER GASTROINTESTINAL TRACT ADENOCARCINOMA

Gastric and gastroesophageal junction adenocarcinomas constitute a major health problem. Gastric cancer is the fourth most prevalent malignancy and the second leading cause of cancer death worldwide.[1] In the United States, an estimated 21,000 cases of gastric cancer were diagnosed and 10,570 patients died from this disease in 2010.[2] Carcinoma of the esophagus and gastroesophageal junction is overall less common, but the incidence has risen faster than any other malignancy in the past 25 years in the United States and other Western countries.[3] For localized disease, adjuvant treatment is multidisciplinary and usually includes a combination of surgery, radiation, and chemotherapy. For advanced disease, there is no formal consensus or evidence-based rationale regarding the best chemotherapy regimen. Although treatment of patients with unresectable or metastatic disease remains palliative and survival rates still low, chemotherapy improves survival and quality of life compared with best supportive care.[4] The median time to progression for advanced disease is 4 to 6 months and median overall survival is 7 to 10 months.

Until recently, targeted agents have not shown a significant survival advantage in advanced upper gastrointestinal (GI) tract cancers. Trastuzumab (Herceptin) is a targeted anticancer therapy that functions by binding to the human epidermal growth factor 2 (HER2 and also called HER2/neu) receptor, preventing its constitutive activation, blocking receptor dimerization, and facilitating immune recognition of tumor cells through antibody-dependent cell-mediated cytotoxicity.[5,6] HER2 is a membrane-associated receptor tyrosine kinase that transduces extracellular signals to mitogen-activated protein kinase and phosphatidylinositol 3-kinase intercellular signaling networks, which

Department of Pathology, University of Pittsburgh Medical Center, 200 Lothrop Street, Pittsburgh, PA 15213, USA

* Corresponding author. Department of Pathology, Presbyterian Hospital, University of Pittsburgh, 200 Lothrop Street, Room A-610, Pittsburgh, PA.

*E-mail address:* pair@upmc.edu

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are major signal transduction pathways stimulating cell growth in many cancer types.[6] HER2 protein may be overexpressed in gastric, gastroesophageal junction, and esophageal adenocarcinomas as well as several other types of tumors, most frequently in breast,[7] and is highly correlated with amplification of the HER2-encoding gene, *ERBB2*, located on chromosome 17 (Chr17).[8] A phase III study investigating trastuzumab was presented by the Trastuzumab for Gastric Cancer (ToGA) investigators first at the 2009 American Society of Clinical Oncology (ASCO) annual meeting and then published.[9] In the ToGA study, 594 patients with HER2-positive, advanced gastric or gastroesophageal junction adenocarcinoma were randomized to standard therapy with a fluoropyrimidine and cisplatin with or without trastuzumab. HER2 positivity was defined by immunohistochemistry (IHC 3+) or amplification by fluorescence in situ hybridization (FISH) (*HER2*:Chr17 ratio >2). Patients receiving trastuzumab had a significantly longer median overall survival (13.8 vs 11.1 months, $P = .0046$), progression-free survival (6.7 vs 5.5 months, $P = .0002$), and response rate (47% vs 35%, $P = .00175$). The ToGA trial also showed evidence of a greater survival benefit for trastuzumab with tumors that expressed higher levels of HER2 protein expression.

Based on the results of the ToGA trial, the US Food and Drug Administration (FDA) has approved the use of trastuzumab for the treatment of metastatic upper GI tract (gastric, esophageal, and gastroesophageal) adenocarcinomas that meet the ToGA inclusion criteria.[10] The European Medicines Agency has approved trastuzumab for IHC 3+ or IHC 2+/FISH-amplified tumors.[11] The optimal protocol for HER2 assessment is rapidly evolving as more information has become available. The purpose of this review is to provide pathologists with practical guidance in HER2 assessment of upper GI tract adenocarcinomas to accurately identify patients eligible for trastuzumab therapy.

## SAMPLE COLLECTION AND TISSUE PROCESSING

### SPECIMEN TYPE

Because the therapy regimen, including trastuzumab, for upper GI tract adenocarcinoma, is typically reserved for those patients with inoperable locally advanced or metastatic disease in the United States, HER2 assessment is often performed on small endoscopic biopsies. In contrast to breast carcinoma, where there is a high concordance between HER2 assessment in needle core biopsy and subsequent surgical resection,[12,13] HER2 testing can yield discordant results between biopsy and resections in upper GI tract carcinomas. In an analysis by Lee and colleagues,[14] 54 paired biopsy and gastrectomy specimens were analyzed for HER2 and only 87% of cases had concordant results between biopsy and resection specimens. Of the 7 discordant cases, 3 tumors showed 3+ HER2 on the resection specimen but were HER2-negative on the biopsy specimen. The small tissue fragments obtained by endoscopic biopsies of carcinomas allow for only a limited area of each tumor to be analyzed for HER2 expression. Such false-negative HER2 results on biopsy specimen are likely due to the frequent occurrence of heterogeneous HER2 expression in upper GI tract adenocarcinomas. To compensate for heterogeneous HER2 expression, it is recommend that a minimum of 6 to 8 endoscopic biopsy fragments be submitted for HER2 assessment.[15] One potential benefit of assessing HER2 status on endoscopic biopsy specimens is superior antigen preservation in the smaller biopsy fragments due to more complete formalin penetration. In the analysis by Lee and colleagues,[14] 4 of the 7 discordant cases were tumors with negative HER2 results on surgical resection but 3+ HER2 results on preoperative biopsy samples. Whether the advantage of better antigen preservation in biopsy specimens outweighs the disadvantage of sampling error in small biopsy samples from tumors with significant HER2 heterogeneity is a subject of debate in the literature.

Another consideration in HER2 assessment is whether to test the primary carcinoma or sites of metastatic disease.[16–19] Some literature reports have demonstrated discordant HER2 expression between metastatic tumor deposits and the primary tumor. Kim and colleagues[18] tested 250 paired primary and metastatic lesions and demonstrated 6 (2.4%) cases of HER2-positive metastatic disease and HER2-negative primary tumor. Similarly, Perrone and colleagues[16] reported 3/27 (11%) discordance between metastatic tumor deposits and primary tumor. Other literature reports have found a much less frequent (approximately 1.5%) occurrence of discordant results between primary and metastatic tumor with discordant cases. Most discordant results between primary and metastatic tumor reported in the literature are due to positive HER2 conversion in the metastatic tumor. These few data suggest that testing metastatic tumors in addition to the primary tumor may provide a better assessment of HER2 status to identify patients eligible for trastuzumab therapy.

### TISSUE PROCESSING

Preanalytic variables, such as cold ischemia and formalin-fixation times, in HER2 assessment