Association of HER2 Expression with Clinical, Endoscopic, and Histopathological Features in Gastric Adenocarcinoma

Virly Nanda Muzellina

Division of Gastroenterology, Pancreatobiliary and Digestive Endoscopy, Department of Internal Medicine, Cipto Mangunkusumo General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta

Gastric cancer is the fifth most common malignancy and the fourth leading cause of cancer-related death worldwide. Its incidence varies markedly across geographic regions, with the highest rates reported in East Asian countries, particularly China, Japan, and Korea which reflects differences in environmental exposures, *Helicobacter pylori* infection, dietary patterns, genetic susceptibility, and access to early detection.[1]

Several environmental and genetic factors are related to the development of gastric cancer. Most gastric cancer cases occur sporadically, whereas approximately 5–10% of patients have a family history of gastric cancer.[1] Some of the most relevant risk factors include dietary patterns characterized by high salt intake, low consumption of vitamins A and C, and frequent consumption of smoked or cured foods, as well as alcohol use, smoking, high body mass index, gastroesophageal reflux, and infection with *Helicobacter pylori* and Epstein–Barr virus.

Gastric cancer is frequently diagnosed at an advanced stage because early disease is often asymptomatic or associated with nonspecific symptoms. Clinical manifestations may include dyspepsia, persistent abdominal discomfort, early satiety, nausea, vomiting, anorexia, weight loss, dysphagia, fatigue, gastrointestinal bleeding, and iron deficiency anemia. Upper gastrointestinal endoscopy remains the principal diagnostic modality because it permits direct visualization of the gastric mucosa and acquisition of multiple biopsies for histopathological and molecular assessment. [1,2]

According to the Lauren classification, gastric adenocarcinoma is broadly divided into two major histological subtypes, such as intestinal and diffuse types. The intestinal subtype is more common which characterized by gland formation, resembling adenocarcinomas of the intestine. Its development is considered multifactorial and is strongly associated with environmental factors, particularly *Helicobacter pylori* infection, smoking, and dietary factors. *H. pylori* is regarded as a major initiating factor in carcinogenesis, with the intestinal subtype following a multistep sequence of gastric carcinogenesis. [1,3]

In contrast, the diffuse subtype is characterized by poorly differentiated tumor cells that diffusely infiltrate the gastric wall, with either signet-ring or non-signet-ring morphology. Unlike the intestinal subtype, diffuse-type gastric cancer generally lacks identifiable precursor lesions and arises from normal gastric mucosa. It is more frequently observed in younger patients and women, may occur more commonly in regions with a lower incidence of gastric cancer and strongly associated with hereditary genetic abnormalities.[1,3]

RELEVANCE OF HER2 IN GASTRIC CANCER

The development of molecularly targeted therapies has subsequently expanded treatment options for advanced gastric cancer. Among these, human epidermal growth factor receptor 2 (HER2) has emerged as an important therapeutic biomarker. HER2, also known as CerbB-2 or ERBB2, is a proto-oncogene located on chromosome 17q21 that encodes a transmembrane receptor with tyrosine kinase activity belonging to the HER receptor family. [3,4] HER2 is involved in intracellular signal transduction pathways regulating cell proliferation, differentiation, growth, and survival. Amplification of the *HER2* gene and overexpression of its protein were initially identified in breast cancer and were subsequently recognized in several other malignancies, especially gastric adenocarcinoma.[5,6]

In gastric cancers, the reported frequency of HER2 overexpression ranges from 4.4% to 53.4%, with an estimated mean of approximately 17.9%. This substantial variation reflects differences in tumor location, histological subtype, patient characteristics,

and methods used for HER2 assessment. Large-scale validation studies have demonstrated that HER2 expression is influenced more by the anatomical site and histological characteristics of the tumor.[7,8]

CLINICAL FEATURES OF HER2 EXPRESSION

Gastric cancer may present with a broad spectrum gastroinestinal symptoms, including epigastric or upper abdominal discomfort, dyspepsia, early satiety, nausea, vomiting, abdominal pain, loss of appetite, and weight loss. As the disease progresses, patients may develop more prominent symptoms such as persistent vomiting, progressive intolerance to oral intake, gastrointestinal bleeding manifested by hematemesis or melena, anemia-related symptoms, and symptoms related to gastric outlet obstruction. Several studies evaluating HER2 expression in gastric adenocarcinoma have demonstrated that HER2-positive and HER2-negative tumors can present with similar clinical symptoms. Therefore, symptoms such as epigastric pain, dyspepsia, nausea, vomiting, anorexia, early satiety, gastrointestinal bleeding, and weight loss should be considered clinical manifestations of gastric adenocarcinoma rather than specific indicators of HER2 positivity. In a prospective study of 111 patients with gastric cancer, weight loss was the most common presenting symptom (61%), followed by vomiting (48%), abdominal pain (45%), early satiety (39%), and dysphagia (26%). This study showed that clinical symptoms of gastric adenocarcinoma are not specific to HER2 expression because they are primarily influenced by tumor location, size, growth pattern, and local effects on gastric function rather than by HER2 status itself. Symptoms such as weight loss, vomiting, abdominal pain, early satiety, and dysphagia can therefore occur in both HER2-positive and HER2-negative tumors.[9]

From a clinical perspective**,** liver metastasis was observed in 27.9% of patients, and HER2 positivity showed a numerical tendency to be more frequent among patients with liver metastasis than among those without liver metastasis (17.6% vs. 10.2%). However, this difference was not statistically significant (p = 0.355), indicating that the presence of liver metastasis was not significantly associated with HER2 expression in this cohort.[10]

A similar pattern was observed in another study of 58 patients with gastric adenocarcinoma with a mean age of 58.8 years and predominance of males (74.1%). HER2 overexpression was identified in 16 patients (27.6%). HER2 positivity was observed in 31.8% of patients aged >65 years compared with 25.0% of those aged <65 years, and in 27.9% of males compared with 26.7% of females. Overall, these findings suggest that HER2 expression is not strongly determined by clinical characteristics of gastric cancer and not statistically significant.[11] Therefore, the clinical symptoms observed in gastric cancer patients should be interpreted as manifestations of the disease itself, whereas HER2 expression appears to be more closely related to specific anatomical and morphological characteristics of the tumor rather than to a distinct symptom profile.

ENDOSCOPIC FEATURES OF HERS2 EXPRESSION

Endoscopic examination plays an important role in characterizing gastric adenocarcinoma, particularly by determining the macroscopic appearance, tumor location, and extent of the lesion. Gastric adenocarcinoma may present with different endoscopic morphologies, including ulcerative, fungating or exophytic, polypoid, and infiltrative lesions. In advanced gastric cancer, the macroscopic appearance of the tumor can be described using the Borrmann classification, which categorizes lesions according to their predominant growth pattern. Borrmann type I represents a polypoid or fungating tumor that protrudes into the gastric lumen and has relatively well-defined margins. Borrmann type II is characterized by a localized ulcerative lesion with distinct margins and raised edges, whereas Borrmann type III presents as an ulcerative lesion with poorly defined margins and infiltration into the surrounding gastric wall. Borrmann type IV represents diffuse infiltrative disease, characterized by extensive thickening and rigidity of the gastric wall and may correspond to *linitis plastica*.[12]

In the study by Le Viet Nho et al., the most common endoscopic appearance was fungating carcinoma (42.2%), followed by ulcerative (25.0%), polypoid (20.3%), and infiltrative lesions (12.5%). This study showed that HER2 overexpression was significantly associated with the gross endoscopic appearance according to the Borrmann classification (p = 0.04). HER2 positivity was observed in 37.0% of fungating lesions and 30.8% of polypoid lesions, compared with 6.3% of ulcerative lesions, while none of the infiltrative lesions demonstrated HER2 overexpression.[13]

In contrast, a study by Larasati et al. showed that there is not significant association between

HER2 expression and tumor location or endoscopic morphology. HER2 expression occurred in 14.3% of well- or moderately differentiated tumors compared with 11.0% of poorly differentiated tumors (RP 1.304, 95% CI 0.505–3.363; p = 0.789).[10]

HISTOPATHOLOGICAL FEATURES OF HER2 EXPRESSION

The relevance of HER2 also has been investigated to the histopathological behavior of gastric cancer. In the study by Ravutu et al., 20 patients with gastric adenocarcinoma were evaluated histopathologically. Well-differentiated adenocarcinoma was the predominant histological pattern, observed in 14 cases (70%), followed by moderately differentiated adenocarcinoma in 3 cases (15%) and poorly differentiated adenocarcinoma in 3 cases (15%). Most tumors were HER2 negative (18 cases, 90%), while only 2 cases (10%) were HER2 positive with an IHC score of 3+. These findings suggest that HER2 positivity was uncommon and was not clearly related to tumor differentiation. According to the Lauren classification, HER2 expression was observed in 13.9% of intestinal-type tumors and 10.0% of diffuse or mixed-type tumors (RP 1.389, 95% CI 0.505–3.817; p = 0.524). Tumor location also showed no significant relationship with HER2 expression.[14]

These findings are further supported by Larasati et al., who also evaluated HER2 expression and histopathological characteristics. HER2 positivity was observed in 7 of 49 tumors (14.3%) with well or moderately differentiated histology and in 8 of 73 tumors (11.0%) with poorly differentiated histology (RP 1.304, 95% CI 0.505–3.363; p=0.789), indicating no significant association between HER2 expression and tumor differentiation.[10]

Although histological differentiation and Lauren classification do not appear to reliably predict HER2 status, the biological significance of HER2 expression may extend beyond conventional tumor morphology. A systematic review of 42 studies involving 12,749 patients reported that 71% of the included publications found HER2 positivity to be associated with poorer survival and/or adverse clinicopathological characteristics. These findings suggest that HER2 overexpression or amplification may identify a biologically more aggressive subgroup of gastric adenocarcinoma. Therefore, while histopathological examination remains essential for determining tumor differentiation and histological subtype, direct HER2 immunohistochemical assessment is important because HER2 status may provide additional biological and prognostic information that cannot be reliably determined from morphology alone.[15]

CONCLUSION

HER2 expression in gastric adenocarcinoma showed heterogeneous associations with patient characteristics, endoscopic findings, and histopathological features. HER2 positivity was not consistently associated with clinical manifestation, age, sex, tumor location, disease stage, or liver metastasis. Regarding endoscopic appearance, HER2 positivity tended to be more frequent in fungating and polypoid tumors, although this association was not consistently demonstrated across studies. Histopathological assessment showed that HER2 expression occurred across different degrees of tumor differentiation and Lauren subtypes, with no significant association between HER2 status and these histological characteristics.

The prognostic significance of HER2 expression in gastric adenocarcinoma remains uncertain. Although several studies have suggested that HER2 positivity may be associated with poorer survival and adverse clinicopathological characteristics, the findings are inconsistent across studies. In the multicenter Indonesian study, HER2 positivity was identified in 12.3% of patients with gastric adenocarcinoma. HER2 expression tended to be more frequent in patients with liver metastases, Borrmann type I/II tumors, moderately differentiated tumors, and intestinal-type histology. However, despite these clinicopathological patterns, HER2 expression was not a significant prognostic factor for two-year survival. This was supported by the findings that showed the median survival was higher in HER2-positive patients than in HER2-negative patients.[10] Overall, HER2 expression may provide additional prognostic information in gastric adenocarcinoma, but its association with two-year survival remains uncertain.

REFERENCES

1. Caniparoli A, Saenz Briones P, Rezzonico andBarg RAJS. Gastric Cancer. Rev Argent Cir. 2024 Oct 28;26(6):127–8. doi:10.1201/b22898-58 PubMed PMID: 29083746.
2. Ramachandran R, Grantham T, Parvataneni S, Budh D, Gollapalli S, Reddy M, et al. Gastric Cancer: Clinical Features, Screening, Diagnosis, Treatment, and Prevention. J Community Hosp Intern Med Perspect. 2024 Mar 1;14(2):49. doi:10.55729/2000-9666.1304 PubMed PMID: 38966500.

3. Pous A, Notario L, Hierro C, Layos L, Bugés C. HER2-Positive Gastric Cancer: The Role of Immunotherapy and Novel Therapeutic Strategies. Int J Mol Sci. 2023 Jul 1;24(14). doi:10.3390/IJMS241411403 PubMed PMID: 37511163.
4. Cetin B, Ozet A. HER2/neu as target in gastric adenocarcinoma. Transl Gastroenterol Hepatol. 2016;1(JULY):59. doi:10.21037/TGH.2016.06.08 PubMed PMID: 28138626.
5. Ma C, Wang X, Guo J, Yang B, Li Y. Challenges and future of HER2-positive gastric cancer therapy. Front Oncol. 2023 Jan 30;13:1080990. doi:10.3389/FONC.2023.1080990/XML
6. Ratti M, Citterio C, Orlandi E, Vecchia S, Anselmi E, Toscani I, et al. Fighting HER2 in Gastric Cancer: Current Approaches and Future Landscapes. International Journal of Molecular Sciences 2025, Vol 26, Page 7285. 2025 Jul 28;26(15):7285. doi:10.3390/IJMS26157285 PubMed PMID: 40806416.
7. Lucas FAM, Cristovam SN. HER2 testing in gastric cancer: An update. World J Gastroenterol. 2016 May 21;22(19):4619. doi:10.3748/WJG.V22.I19.4619 PubMed PMID: 27217694.
8. Boku N. HER2-positive gastric cancer. Gastric Cancer. 2013 Jan;17(1):1. doi:10.1007/S10120-013-0252-Z PubMed PMID: 23563986.
9. B A V, Behera MK, Patne SCU, Shukla SK, Dixit VK. Clinicopathological Significance and Prognostic Role of Her2neu Protein Expression in Patients with Carcinoma Stomach: A Prospective Study from Northern India. South Asian J Cancer. 2023;12(2):135. doi:10.1055/S-0042-1759601 PubMed PMID: 37969677.
10. Larasati D. Hubungan Gambaran Klinis, Endoskopi, Histopatologi terhadap Ekspresi HER2 dan Kesintasan Dua Tahun pada Adenokarsinoma Gaster [Internet]. 2021 [cited 2026 Aug 24]. Available from: //perpus.internafkui.or.id%2Findex.php%3Fp%3Dshow_detail%26id%3D978
11. Aditi R, Aarathi R, Pradeep R, Hemalatha L, Akshatha C, Amar K. HER2 Expression in Gastric Adenocarcinoma—a Study in a Tertiary Care Centre in South India. Indian J Surg Oncol. 2015 Mar 1;7(1):18. doi:10.1007/S13193-015-0436-6 PubMed PMID: 27065677.
12. Jung K, Park MI, Kim SE, Park SJ. Borrmann Type 4 Advanced Gastric Cancer: Focus on the Development of Scirrhous Gastric Cancer. Clin Endosc. 2016 Jul 1;49(4):336. doi:10.5946/CE.2016.057 PubMed PMID: 27456608.
13. Nho LV, Van Huy T, Cong Thuan Đ, To T Van. Endoscopy. histopathological findings and HER2 overespression in gastric adenocarcinoma. Journal of Medicine and Pharmacy. 02(1).
14. Sarkar RN, Ravutu L, Jagadev S, Sumanlatha GR, Polisetty SR, Lakshmi C V. Histopathological Analysis and HER-2/neu Expression in Endoscopic Guided Upper Gastrointestinal Biopsies: An Observational Study. Research Journal of Medical Sciences Research Article Res J Med Sci. 2023;17(11):166–72. doi:10.59218/makrjms.2023.11.166.172
15. Jørgensen JT, Hersom M. HER2 as a Prognostic Marker in Gastric Cancer - A Systematic Analysis of Data from the Literature. J Cancer. 2012;3(1):137–44. doi:10.7150/JCA.4090 PubMed PMID: 22481979.