BIOMEDICINSKA ISTRAŽIVANJA
2025;16(2):1–9

UDK: 616.33-006:616-092
DOI: 10.59137/BII202502507C

Original article

The prognostic significance of HER2 in gastric adenocarcinoma

Mirjana Ćuk[1], Radoslav Gajanin[2], Svjetlana Kulić[1], Milena Vasić Milanović[1]

[1]University of East Sarajevo, Faculty of Medicine Foča, Foča, Republic of Srpska, Bosnia and Herzegovina
Faculty of Medicine, Banja Luka, Republic of Srpska, Bosnia and Herzegovina

Primljen – Received: 14/06/2025
Prihvaćen – Accepted: 15/07/2025

Corresponding author:
Mirjana Ćuk, MD, PhD
Studentska 5, 73300 Foča
e-mail: akicuk@yahoo.com

Copyright: ©2025 Mirjana Ćuk et al. This is an Open Access article distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) license.

Summary

Introduction. Gastric adenocarcinoma is a major cause of global cancer mortality. The HER2 receptor plays a critical role in cell proliferation and survival and is overexpressed or amplified in a subset of gastric cancers, particularly of the intestinal type. The objective of this study was to evaluate HER2 protein expression and gene amplification in gastric adenocarcinoma and determine diagnostic concordance between immunohistochemistry (IHC), chromogenic in situ hybridization (CISH), and fluorescence in situ hybridization (FISH) methods.

Methods. This retrospective study analyzed 96 patients with histologically confirmed gastric adenocarcinoma who underwent radical surgery (2006–2014). HER2 expression was assessed using IHC and scored according to Hofmann's system. All tumors with 2+ or 3+ scores were further analyzed for HER2 gene amplification using CISH and FISH. Concordance was evaluated using Cohen's kappa coefficient.

Results. HER2 expression was negative (score 0 and 1+) in 76.1% of cases, equivocal (2+) in 10.4%, and positive (3+) in 13.5%. All patients with a 3+ score showed HER2 gene amplification using both CISH and FISH. In the 2+ group, amplification was detected in 30% (CISH) and 50% (FISH). Concordance between CISH and FISH was high ($\kappa = 0.78$, $p < 0.001$). HER2 positivity correlated significantly with the intestinal type and was associated with poorer survival, particularly in early-stage tumors.

Conclusion. HER2 is a relevant biomarker in intestinal-type gastric adenocarcinoma. FISH is more sensitive than CISH in equivocal IHC cases. IHC score 3+ can be considered definitive, while FISH is recommended for 2+ cases to confirm gene amplification.

Key words: gastric adenocarcinoma, HER2, immunohistochemistry, CISH, FISH, gene amplification

Introduction

According to IARC data for 2022, gastric cancer ranks the fifth in incidence and mortality among malignant diseases worldwide, with 968,350 new cases and 659,853 deaths reported that year [1]. In the European Union, incidence and mortality rates are estimated at 76 and

52 per 100,000 inhabitants, respectively [2]. Gastric cancer typically affects older adults, with a mean age at diagnosis of 68 years, and occurs more frequently in men [3]. Its incidence varies geographically, being highest in East Asia and Eastern Europe and lowest in Africa, Northern Europe, and North America [4]. A rising trend has been observed among individuals under 50 years of age. Major risk factors include Helicobacter pylori infection, genetic predisposition, dietary habits, alcohol, and tobacco use. Due to nonspecific early symptoms and limited screening, most cases are diagnosed at advanced stages [5].

Gastric cancer is genetically heterogeneous. Key genetic alterations include mutations or aberrant expression of genes such as TP53, APC, CDH1, KRAS, MYC, MET, and HER2 [4–6]. HER2 is a membrane-bound tyrosine kinase receptor encoded on chromosome 17q21, implicated in cell proliferation and survival [7, 8]. In gastric cancer, HER2 overexpression or amplification promotes oncogenic behavior, particularly in the intestinal subtype.

HER2 interacts with EGFR and other tyrosine kinase receptors to activate proliferative and anti-apoptotic pathways [9, 10]. Immunohistochemistry (IHC) was first used to detect HER2 overexpression in gastric cancer in 1986 [11]. Today, CISH and FISH are standard methods for detecting HER2 gene amplification, with FISH considered the gold standard in gastric cancers [12–14].

Methods

A total of 96 patients with histologically confirmed gastric adenocarcinoma who underwent radical surgical resection between January 2006 and July 2014 at the University Hospital Foča or Clinical Center Banja Luka were retrospectively included. Tumor tissue and lymph node samples were collected from resected specimens, fixed in 4% formalin, and embedded in paraffin. Sections 4 μm thick were cut and stained with hematoxylin-eosin (HE) for standard histopathological analysis. One representative tumor area per patient was selected for immunohistochemistry (IHC).

HER2 protein expression was assessed using the HercepTest™ (DAKO, USA) and scored according to Hofmann's system (0–3+). Cases scored as 2+ and 3+ underwent further testing for HER2 gene amplification using both chromogenic in situ hybridization (CISH) and fluorescence in situ hybridization (FISH). For CISH, the HER2 pharmDx™ Kit (SK109, DAKO) was used. Following pretreatment, hybridization, and enzymatic detection, HER2/CEP17 ratios were calculated in at least 20 tumor nuclei. Amplification was defined as a HER2/CEP17 ratio ≥2 or presence of HER2 signal clusters.

For FISH analysis, a PATH Vysion HER2 kit (Abbott Vysis, USA) was applied to 2 μm sections using HER2 and CEP17-specific fluorescent probes. After denaturation and overnight hybridization, slides were analyzed under a Leica fluorescence microscope. Amplification was defined as HER2/CEP17 ≥2 or presence of signal clusters. Equivocal cases (HER2/CEP17 ratio 1.8–2.0) were reassessed in an additional 20 nuclei.

Tumor heterogeneity was evaluated at low magnification prior to signal counting. Only tumors with IHC scores of 2+ or 3+ were tested for gene amplification. Positive and negative controls were included in all staining runs. Agreement between CISH and FISH results was analyzed using Cohen's kappa (κ) coefficient. Statistical analysis was performed using SPSS v15 (SPSS Inc., Chicago, IL, USA).

Results

Immunohistochemical analysis of HER2 expression showed: score 0 – 50 patients (52.1%), score 1+ – 23 patients (24.0%), score 2+ – 10 patients (10.4%), score 3+ – 13 patients (13.5%), (Figure 1a).

Tumor samples from paraffin blocks of all patients categorized as 2+ and 3+ on IHC stained slides were analyzed for HER2 gene amplification by CISH method (Figure 1b, Figure 1c). In all 13 patients with an IHC score of 3+, HER2 gene amplification was found. Out of a total of 10 patients with a score of 2+ on IHC stained slides, HER2 gene amplification was found in 3 patients.

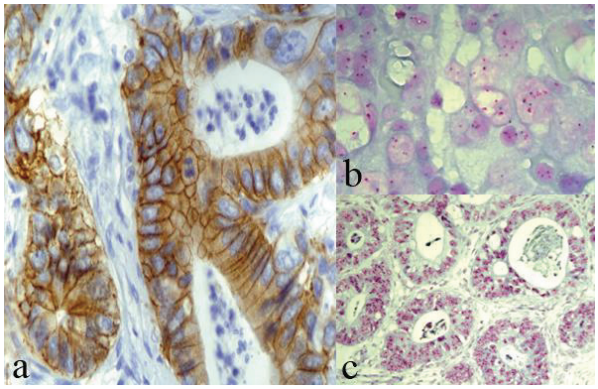


Figure 1a. Adenocarcinoma ventriculi, intestinal type, positive HER2 protein expression (score 3+), IHC, HER2 x400; **b.** Adenocarcinoma ventriculi, intestinal type, no HER2 gene amplification present, CISH method x400; **c.** Adenocarcinoma ventriculi, intestinal type, HER2 gene amplification present, CISH method x200

Tumor samples from paraffin blocks of all patients categorized as 2+ and 3+ on IHC stained slides were analyzed for HER2 gene amplification by FISH method (Figure 2). In all 13 patients with an IHC score of 3+, HER2 gene amplification was found. In the group of 10 tumors with a score of 2+ on IHC stained slides, HER2 gene amplification was found in five patients. Analysis of patients categorized as 3+ on IHC slides showed complete concordance of all three methods used for detecting HER2 positivity. In all 13 tumors positive by IHC staining with HER2 antibody, the presence of HER2 gene amplification was confirmed by both CISH and FISH methods. In the group of 10 patients whose tumors were categorized as 2+ (equivocal positivity) on histological slides stained by IHC with HER2 antibody, three patients were found to have HER2 gene amplification by CISH, and five patients by FISH method (Graph 1).

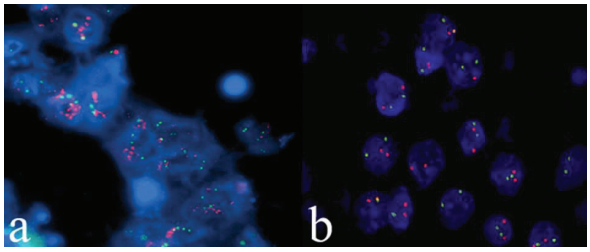
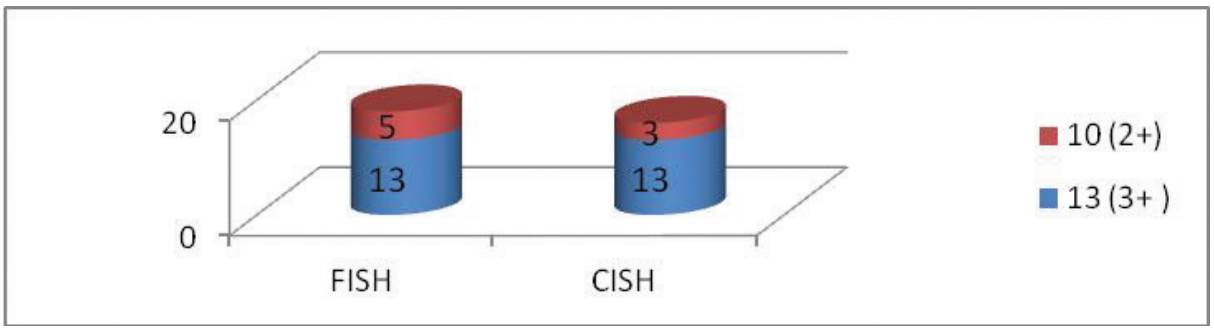


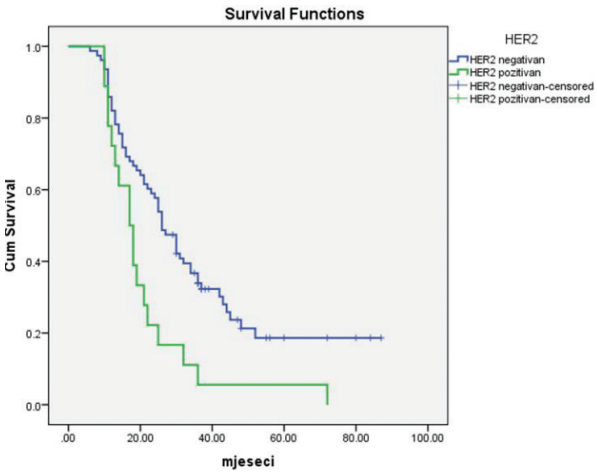
Figure 2a. Adenocarcinoma ventriculi, intestinal type, HER2 gene amplification, FISH x 400, **b.** Adenocarcinoma ventriculi, intestinal type, no HER2 gene amplification, FISH x 400

Kappa coefficient was used to determine the level of agreement between CISH and FISH methods for determining HER2 gene amplification for the group of patients with HER2 equivocal and positive expression (score 2+ and score 3+). The level of agreement between these two methods was high and statistically significant, Kappa = 0.78 ($p < 0.001$).



Graph 1. Distribution of HER2 gene amplification results determined by CISH and FISH methods

Three-year survival of patients with negative HER2 expression/amplification was 33.9%, while in patients with positive HER2 expression/amplification it was 5.6% (Graph 2).



Graph 2. Kaplan-Meier survival curve in relation to HER2 expression/amplification

Discussion

Amplification of the human epidermal growth factor receptor 2 (HER2/neu) gene and/or overexpression of the HER2 protein is present in a large number of cancers including breast, colon, endometrium, uterine cervix, urothelial carcinomas, lung carcinomas, ovarian carcinomas, and gastric and gastroesophageal junction carcinomas [15]. Tumors with amplification/overexpression of the HER2 gene have a poorer prognosis, and it is necessary to apply targeted biological therapy in these patients [15, 16].

Gastric and gastroesophageal junction carcinomas generally represent a large share as a cause of death from malignant diseases worldwide, with a combined incidence of about 1.4 million new cases per year and a 5-year survival rate of less than 20% [17]. Standard chemotherapeutics given to these patients—5-fluorouracil, cisplatin, epirubicin, and docetaxel—have quite limited effects, and numerous new studies are based on identifying molecular "targets" and appropriate targeted biological therapy from which better therapeutic response and survival are expected in these patients [18]. HER2 gene amplification and HER2 protein overexpression in gastric and gastroesophageal junction carcinomas were first discovered in 1986 and have since been studied in a large number of studies [19]. Gastroesophageal junction carcinomas have a 1.8 to 2.6 times higher incidence of HER2 amplification/expression with an incidence of 24%–32% compared to the rest of the stomach, where the incidence according to various authors ranges from 9.5% to 18% [20].

Differences in the prevalence of HER2 amplification/expression, in addition to differences in the primary tumor location in the proximal third and the rest of the stomach, can also be the result of differences in sample size, inter-population differences, interobserver differences, differences in fixation and sample preparation, as well as the results of applying different staining methodologies [21].

The prognostic significance of HER2 amplification/expression in gastric cancer is partly controversial. Recent literature review studies on the impact of HER2 overexpression on survival have published results showing that HER2 overexpression had no impact on patient survival in 20 published studies (57%), two studies (6%) reported significantly better survival for patients with HER2 overexpression compared to HER2-negative patients, and 13 studies (37%) found significantly worse survival for patients with HER2 overexpression/amplification [22]. Chua and colleagues in their study published results showing that the median percentage of HER2-positive gastric carcinomas was 18% (range 4%–53%) [23]. Terashima and colleagues in their study found a HER2 score of 2+ in 101 (12.2%) carcinomas and a HER2 score of 3+ in 75 (9.0%) gastric carcinomas. These authors analyzed gene amplification by FISH method in carcinoma samples

that were scored 2+ and 3+ on immunohistochemically stained slides [24].

In patients with a 3+ score on IHC slides, gene amplification was found in 97.3%, while in patients with a 2+ score, gene amplification was found in 37.6% of patients. HER2 positive expression/amplification was significantly associated with well-differentiated tumors, male sex, older age, and lower tumor stage. These authors did not find a significant correlation between positive HER2 expression/amplification and patient survival [24, 25].

In our study, according to Hofmann's scoring recommendations on IHC stained slides, 73 (76.1%) patients were classified as HER2 negative, 10 (10.4%) patients in the 2+ category (HER2 equivocal), and 13 (13.5%) patients were classified as 3+ (positive HER2 expression). Our results are largely consistent with the results of He and colleagues, who in their study of 197 patients found HER2 expression distribution according to Hofmann's scoring: 9.64% positive tumors (3+), 12.69% equivocal tumors (2+), and 77.66% of tumors scored as 0 and 1+ (negative HER2 expression) [25].

Begnami and colleagues in their study found only 3% of gastric tumors with a 3+ score on IHC slides and 9% with a 2+ score. A score of 1+ was found in this study in 38% of patients, and a score of 0 in 50% of patients. Gene amplification by FISH method was found in 8% of patients with gastric carcinoma. A positive correlation between expression on IHC slides and gene amplification determined by FISH method was found in 62.5% of patients. In this study, 99.9% of patients who were negative (score 0 and 1+) on IHC slides were also negative for gene amplification determined by FISH method. These authors found statistically significantly worse survival for patients with HER2 positive expression/amplification compared to patients with HER2 negative expression/amplification. They also found a statistically significant positive association between HER2 positive expression/amplification and intestinal type adenocarcinoma, as well as low-grade adenocarcinoma [26].

In our study, analogously to other studies, we investigated HER2 gene amplification using CISH and FISH methods. The CISH method is standardized for determining HER2 gene amplification in breast cancers. The FISH method is, in numerous studies, the method of choice for determining gene amplification in gastric cancers [27]. Some authors have reported perfect concordance between these two methods (CISH and FISH) in determining HER2 gene amplification [13]. Analogous to the results of Begnami et al. and Marx et al., who confirmed negative HER2 gene amplification by FISH method in 99.9% and 100% of patients with negative HER2 protein expression, we did not analyze gene amplification in patients with scores 0 and 1+ [26, 27]. Marx and colleagues examined the correlation between HER2 protein expression results on IHC slides and HER2 gene amplification determined by FISH method. Their results showed a very high correlation between these two methods. All tumors that were positive for expression on IHC slides (score 3+) had present gene amplification, and five out of six tumors with a score of 2+ on IHC slides had present gene amplification. All tumors scored negative on IHC slides (score 0 and 1+) were negative for gene amplification determined by FISH method [27].

Analysis of patients in our study categorized as 3+ on IHC slides showed complete concordance of all three methods used to detect HER2 positivity. In all 13 tumors positive by IHC staining with HER2 antibody, the presence of HER2 gene amplification was confirmed by both CISH and FISH methods. In the group of 10 patients whose tumors were categorized as 2+ (equivocal positivity) on histological slides stained by IHC with HER2 antibody, 30% of patients had HER2 gene amplification by CISH, and 50% by FISH method. The level of agreement between these two methods was high and statistically significant, Kappa = 0.78 ($p < 0.001$). Our results are largely consistent with those of Yan et al. [15].

Shan and colleagues, in their study analyzing HER2 expression in 1,463 patients, found HER2 overexpression on IHC slides (score 3+) in 7.0% of patients with gastric cancer and 14.6% of patients with gastroesophageal junction adenocarcinomas [20]. A score of 2+ was found in 13.0% of patients with gastric cancer and 16.9% of patients with gastroesophageal junction adenocarcinomas. HER2 gene amplification by FISH method was found in 97.5% of patients with a 3+ score on IHC slides, 28.9% of patients with a 2+ score on IHC slides, and 1.3% of patients with scores 0 and 1+. The concordance percentage between IHC and FISH methods in this study was 98.5%. Other authors reported a concordance of 94.5% [20]. In contrast, the ToGA study reported a concordance percentage between the IHC method and the FISH method for determining HER2 positivity of 87.2% [17]. According to the results of this study, 7.5% of patients with scores 0 and 1+ had positive gene amplification determined by FISH, and 54.6% of patients with a 2+ score on IHC slides had positive HER2 gene amplification determined by FISH. The concordance percentage between IHC determination of HER2 protein overexpression and HER2 gene amplification by FISH method in numerous studies ranges from 88.6% to 97.7% [20].

He and colleagues, in their study analyzing the agreement between IHC determination of HER2 overexpression and HER2 gene amplification by FISH method, found 100% agreement in the group of patients with a 3+ score, and 32.26% agreement in the group with a 2+ score [25]. Our results are largely consistent with these authors. When looking at the CISH method, the concordance percentage between IHC and gene amplification determination is identical, and when looking at the FISH method, our study found a higher concordance percentage in the group of patients with a 2+ score, but in the total tested sample with all three methods, there is a high level of agreement. Our results and those of many other studies indicate the necessity of determining gene amplification in the group of patients with a 2+ score on IHC slides. The choice of ISH (in situ hybridization) method is somewhat unclearly defined, but the results of our study suggest that the FISH method has greater sensitivity in identifying gene amplification in gastric adenocarcinoma. Based on our results and those of many other studies, the recommendation is that there is no need for additional testing of gene amplification in patients with a 3+ score on IHC slides, and the results of the IHC test can be accepted as definitive.

Conclusion

Positive HER2 expression/amplification is associated with shorter survival in patients with gastric adenocarcinoma when it comes to the intestinal type adenocarcinoma according to Lauren's classification.

Differences in survival in the entire sample covering all adenocarcinoma subtypes, where patients in the study did not receive anti-HER2 biological therapy, are statistically significant in stages I and II, while in stage III there was no statistically significant difference. Determining HER2 expression/amplification is recommended for the intestinal type adenocarcinoma. The level of agreement in determining HER2 gene amplification using CISH and FISH methods is high and statistically significant. The FISH method is more sensitive and is recommended in routine practice for determining HER2 gene amplification in patients with gastric adenocarcinoma with immunohistochemically equivocal positivity (score 2+). Our results indicate that tumor tissue samples with an IHC score of 3+ do not need to be additionally tested for gene amplification, but the results of the IHC test can be accepted as final.

Funding source. The authors received no specific funding for this work.

Ethical approval. The Ethics Committee of the University of East Sarajevo, Faculty of Medicine Foča, Foča, Republic of Srpska, Bosnia and Herzegovina, approved the study (No. 19.032/961-59/19) and informed consent was obtained from all individual respondents. The research was conducted according to the Declaration of Helsinki.

Conflicts of interest. The authors declare no conflict of interest.

References:

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229–63.
2. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, et al. The European cancer burden in 2020: Incidence and mortality estimates for 40 countries and 25 major cancers. Eur J Cancer 2021;157:308–47.
3. American Cancer Society. Cancer Facts & Figures 2024. Atlanta: American Cancer Society; 2024.
4. Lu L, Mullins CS, Schafmayer C, Zeißig S, Linnebacher M. A global assessment of recent trends in gastrointestinal cancer and lifestyle-associated risk factors. Cancer Commun (Lond) 2021;41(11):1137–51.
5. Lordick F, Carneiro F, Cascinu S, Fleitas T, Haustermans K, Piessen G, et al. Gastric cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 2022;33(10):1005–20.
6. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020;76(2):182–8.
7. Fukushige SI, Matsubara KI, Yoshida M, Sasaki M, Suzuki T, Semba K, et al. Localization of a Novel v-erb B-Related Gene, c-erb B-2, on Human Chromosome 17 and Its Amplification in a Gastric Cancer Cell Line. Mol Cell Biol 1986;6(3):955–8.
8. Roy V, Perez EA. Beyond trastuzumab: small molecule tyrosine kinase inhibitors in HER-2-positive breast cancer. Oncologist 2009;14(11):1061–9.
9. Kaufmann R, Müller P, Hildenbrand G, Hausmann M, Cremer C. Analysis of Her2/neu membrane protein clusters in different types of breast cancer cells using localization microscopy. J Microsc 2011;242(1):46–54.
10. Sakai K, Mori S, Kawamoto T, Taniguchi S, Kobori O, Morioka Y, et al. Expression of epidermal growth factor receptors on normal human gastric epithelia and gastric carcinomas. J Natl Cancer Inst 1986;77(5):1047–52.
11. Wong H, Yau T. Targeted Therapy in the Management of Advanced Gastric Cancer: Are We Making Progress in the Era of Personalized Medicine? Oncologist 2012;17(3):346–58.
12. Kiyose S, Igarashi H, Nagura K, Kamo T, Kawane K, Mori H, et al. Chromogenic in situ hybridization (CISH) to detect HER2 gene amplification in breast and gastric cancer: comparison with immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Pathol Int 2012;62(11):728–34.
13. Satala CB, Jung I, Stefan-van Staden RI, Kovacs Z, Molnar C, Bara T Jr, et al. HER2 Heterogeneity in Gastric Cancer: A Comparative Study, Using Two Commercial Antibodies. J Oncol 2020;2020:8860174.
14. Jørgensen JT. Targeted HER2 treatment in advanced gastric cancer. Oncology 2010;78(1):26–33.
15. Yan B, Yau EX, Bte Omar SS, Ong CW, Pang B, Yeoh KG, et al. A study of HER2 gene amplification and protein expression in gastric cancer. J Clin Pathol 2010;63(9):839–42.
16. Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol 2023;16(1):57.
17. Bang Y, Chung H, Xu J, Lordick F, Sawaki A, Al-Sakaff N, et al. Pathological features of advanced gastric cancer (GC): Relationship to human epidermal growth factor receptor 2 (HER2) positivity in the global screening programme of the ToGA trial. J Clin Oncol 2009;27(Suppl 15):4556.

18. Kunz PL, Mojtahed A, Fisher GA, Ford JM, Chang DT, Balise RR, et al. HER2 expression in gastric and gastroesophageal junction adenocarcinoma in a US population: clinicopathologic analysis with proposed approach to HER2 assessment. Appl Immunohistochem Mol Morphol 2012;20(1):13–24.

19. Tafe LJ, Janjigian YY, Zaidinski M, Hedvat CV, Hameed MR, Tang LH, et al. Human epidermal growth factor receptor 2 testing in gastroesophageal cancer: correlation between immunohistochemistry and fluorescence in situ hybridization. Arch Pathol Lab Med 2011;135(11):1460–5.

20. Shan L, Ying J, Lu N. HER2 expression and relevant clinicopathological features in gastric and gastroesophageal junction adenocarcinoma in a Chinese population. Diagn Pathol 2013;8:76.

21. Hechtman JF, Polydorides AD. HER2/neu Gene Amplification and Protein Overexpression in Gastric and Gastroesophageal Junction Adenocarcinoma. Arch Pathol Lab Med 2012;136(6):691–7.

22. Zhu Y, Zhu X, Wei X, Tang C, Zhang W. HER2-targeted therapies in gastric cancer. Biochim Biophys Acta Rev Cancer 2021;1876(1):188549.

23. Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes—A systematic review. Int J Cancer 2012;130(12):2845–56.

24. Terashima M, Kitada K, Ochiai A, Ichikawa W, Kurahashi I, Sakuramoto S, et al. Impact of Expression of Human Epidermal Growth Factor Receptors EGFR and ERBB2 on Survival in Stage II/III Gastric Cancer. Clin Cancer Res 2012;18(21):5992–6000.

25. He C, Bian XZ, Ni XZ, Shen DP, Shen YY, Liu H, et al. Correlation of human epidermal growth factor receptor 2 expression with clinicopathological characteristics and prognosis in gastric cancer. World J Gastroenterol 2013;19(14):2171–8.

26. Begnami MD, Fukuda E, Fregnani JH, Nonogaki S, Montagnini AL, da Costa WL, et al. Prognostic implications of altered human epidermal growth factor receptors (HERs) in gastric carcinomas: HER2 and HER3 are predictors of poor outcome. J Clin Oncol 2011;29(22):3030–6.

27. Marx AH, Tharun L, Muth J, Dancau AM, Simon R, Yekebas E, et al. HER-2 amplification is highly homogenous in gastric cancer. Hum Pathol 2009;40(6):769–77.

Prognostički značaj HER2 kod želudačnog adenokarcinoma

Mirjana Ćuk[1], Radoslav Gajanin[2], Svjetlana Kulić[1], Milena Vasić Milanović[1]

[1]Univerzitet u Istočnom Sarajevu, Medicinski fakultet Foča, Foča, Republika Srpska, Bosna i Hercegovina

[2]Univerzitet u Banjoj Luci, Medicinski fakultet, Banja Luka, Republika Srpska, Bosna i Hercegovina

Uvod. Adenokarcinom želuca je jedan od vodećih uzroka smrtnosti od malignih bolesti. Receptor HER2 ima važnu ulogu u proliferaciji i preživljavanju ćelija, a njegova prekomjerna ekspresija ili amplifikacija prisutna je kod dijela tumora, naročito intestinalnog tipa. Cilj ovog istraživanja je da procijenimo ekspresiju i amplifikaciju HER2 gena kod adenokarcinoma želuca, te da utvrdimo dijagnostičku usklađenost između metoda: imunohistohemijsko bojenje (IHC), hromogena in situ hibridizacija (CISH) i fluorescentna in situ hibridizacija (FISH).

Metode. U retrospektivnu studiju uključeno je 96 pacijenata sa histološki potvrđenim adenokarcinomom želuca operisanim u periodu 2006–2014. Ekspresija HER2 proteina analizirana je IHC metodom po Hofmanovoj skali. Slučajevi sa ocjenom 2+ i 3+ dodatno su analizirani CISH i FISH metodama radi potvrde amplifikacije HER2 gena. Usklađenost je procijenjena Kappa koeficijentom.

Rezultati. HER2 ekspresija bila je negativna (ocjena 0 i 1+) kod 76,1%, neodređena (2+) kod 10,4%, a pozitivna (3+) kod 13,5% pacijenata. Svi pacijenti sa ocjenom 3+ imali su potvrđenu amplifikaciju HER2 gena i CISH i FISH metodama. U grupi 2+, amplifikacija je potvrđena kod 30% (CISH) i 50% (FISH). Usklađenost između metoda bila je visoka ($\kappa = 0,78$; $p < 0,001$). HER2 pozitivnost bila je značajno povezana sa intestinalnim tipom i lošijom prognozom, posebno u ranoj fazi bolesti.

Zaključak. HER2 je važan biomarker kod intestinalnog adenokarcinoma želuca. FISH metoda je osjetljivija od CISH kod sumnjivih IHC slučajeva, dok se IHC rezultat 3+ može smatrati konačnim bez dodatne potvrde.

Ključne riječi: adenokarcinom želuca, HER2, imunohistohemija, CISH, FISH, amplifikacija gena