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HER2 immunohistochemical expression and its association with clinicopathological features of gastric adenocarcinoma in Uganda

Mohamed Kahiye[1], James Yahaya[2], Sam Kalungi[3], Hawa Nalwoga[4]

[1] Department of Pathology, Sahan Pathology Laboratories, Mogadishu, Somalia
[2] Department of Pathology, Soroti University Faculty of Medicine, Soroti, Uganda
[3] Department of Pathology, Mulago National Referral Hospital, Kampala, Uganda
[4] Department of Pathology, Makerere College of Health Sciences, Kampala, Uganda

ABSTRACT

Objective: Despite the remarkable improvement in gastric adenocarcinoma treatment modalities, the prognosis of gastric adenocarcinoma remains poor. The purpose of this study was to determine the prevalence of HER2 immunohistochemical expression and its association with clinicopathological features of patients with gastric adenocarcinoma.

Material and Methods: This was a cross-sectional study which was conducted at the department of pathology. A total of 86 formalin fixed paraffin embedded tissue blocks of the patients who were confirmed histologically with gastric adenocarcinoma from January 2009 to December 2019 were included in the analysis. Laboratory requisition form and patients' files were used to extract the clinical and pathological data of the cases. Immunohistochemistry to assess HER2 overexpression was done using monoclonal (SP3 clone) rabbit anti-HER2/neu (Thermo Fisher Scientific-USA). Chi-square statistical test was used to determine the association of the clinicopathological characteristics with HER2 expression. P< 0.05 was considered statistically significant.

Results: Mean age of the patients included in the study was 58.5 ± 14.3 years, and over half 54.7% (n= 47) of the patients were males. Poorly cohesive non-signet ring types contributed most (47.7%) (n= 41) of the cases, and diffuse/mixed histological subtypes were more prevalent (57%) (n= 49) subtypes. Poorly differentiated cases accounted for the majority (66.3%) (n= 57) of the cases. The prevalence of HER2 immunohistochemical expression was 8.1% (n= 7). None of the clinicopathological characteristics were associated with HER2 expression.

Conclusion: This study has shown almost every one in 10 patients with gastric adenocarcinoma may express HER2 when using immunohistochemistry test. However, the HER2 in this study was not associated with age, sex, tumor location, the nature of biopsy, histological subtypes, and tumor grade.

Keywords: Gastric adenocarcinoma, HER2 overexpression, prognosis, clinicopathological characteristics

INTRODUCTION

Gastric adenocarcinoma is the fifth most common malignancy globally accounting for 5.7% of all adenocarcinomas with an incidence of 11.4 per 100.000 population annually (1). It ranks third among the causes of adenocarcinoma-related deaths in both sexes worldwide, accounting for 8.2% of adenocarcinoma deaths with a rate of 8.45 per 100.000 population annually (1,2). There is a geographical variation in the incidence of gastric adenocarcinoma globally, and over 50% of the cases occur in developing countries (2,3). The highest incidence is in Eastern Asia, and the lowest in Central Africa (3). In Uganda, the incidence of gastric adenocarcinoma has increased by more than 11-fold from 0.8 per 100.000 population reported in the 1960s to nine per 100.000 population reported in 2014 (4,5). It is now one of the main causes of cancer-related deaths in Uganda with a mortality rate of 8.7 per 100.000 population (5). In most countries including Uganda, gastric adenocarcinoma is usually diagnosed at an advanced stage when curative surgical resection is no longer possible, which contributes to poor prognosis (6). Several poor prognostic factors such as diffuse histological subtype, high grade, and overexpression of proteins like human epidermal receptor 2 (HER2) among many others have been identified by independent studies (7,8).

HER2 protein, which is involved in various aspects of tumor cell biology, has previously been shown to be an independent poor prognostic factor in gastric adenocarcinoma (9). HER2 positive tumors behave more aggressively and have higher

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Corresponding Author
James Yahaya
E-mail: mashimba2009@yahoo.com

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chances of recurrence than HER2 negative tumors (7,8). Moreover, HER2 protein overexpression in gastric adenocarcinoma is also considered a predictive biomarker for response to HER2 targeted therapy (7,10). The prognosis of HER2 positive gastric adenocarcinoma has been relatively improved by the use of the targeted therapies against HER2 (11). Nonetheless, a wide range of variation in the frequency of HER2 protein overexpression in gastric adenocarcinoma, ranging from 8% to 53.4%, which also with different populations, histological subtypes of gastric adenocarcinoma and tumor grade has been demonstrated by previous studies (12-14). The wide range of HER2 overexpression is attributed to many factors including geographical differences, tumor biology and heterogeneity, and methodological differences (14,15).

In Uganda, the prevalence of HER2 protein overexpression in gastric adenocarcinoma remains unknown. Therefore, this study aimed to determine the immunohistochemical expression of HER2 protein and its association with demographic and pathologic features of gastric adenocarcinoma.

MATERIAL and METHODS

Study Design and Setting

This was a cross-sectional study design which was conducted at the department pathology, Makerere College of Health Sciences (MakCHS) in Kampala, Uganda. The college is located in the same area with Mulago hospital. Therefore, the department of pathology receives most of samples from Mulago National Hospital and also from other health facilities which perform surgery mainly within the central region where Kampala is located. The department serves the roles of teaching, research, as well as offering diagnostic services for histological, cytological and autopsy services within Kampala, other parts of the country, and other areas of the neighboring countries such as Kenya, Rwanda, and Democratic Republic of Congo.

Study Population

The study analysed archived formalin-fixed paraffin-embedded (FFPE) tissue blocks of patients who were diagnosed with various histological types of gastric adenocarcinoma from January 2009 to December 2019. Laboratory requisition forms and patients' files were used to select the required cases. Cases with available clinical information and confirmed histological diagnosis and also available FFPE tissue blocks with good quality were retrieved and included in the study. However, cases with poorly fixed or processed FFPE tissue blocks, those with necrotic tissue blocks, cases with missing patients' files, and those with prior history of chemotherapy and/or radiotherapy al were excluded from the analysis.

Sample Size Estimation

The sample size was determined using the Kish Leslie formula in which the sample size was calculated as $n= Z^2 P (1-P)/e^2$; n= sample size, z= standard normal deviate at a 95% confidence interval corresponding to 1.96, and e= margin of error of 5% (16). The p= prevalence of HER2 protein overexpression in gastric adenocarcinomas was assumed to be 42.2% from a study done in Kenya (17). Therefore, $n= (1.96)^2 \times 0.422 (0.578)/(0.05)^2= 0.9370/0.0025= 374.81$. The possible population size for cases with gastric adenocarcinoma was estimated to be around 110. Therefore, the calculated sample size of approximately 375 was not possible which necessitated to apply the finite population correction formula so as to reduce the calculated sample size to an achievable sample size as follows: n= (calculated sample size x population size)/(calculated sample size) + (population size - 1). n= (374.81 x 110)/(374.81 + (110-1)). Therefore, n= 85.2. The obtained minimum sample size required for this study was approximately 86 (18).

Sampling Method

The required number of the cases were sampled using convenience sampling method, and all eligible number of FFPE tissue with confirmed histological diagnosis of gastric adenocarcinoma were retrieved consecutively from the archive of FFPE tissue blocks in the department of pathology. Retrieval of the FFPE tissue blocks was done by a laboratory technician using the inclusion criteria.

Haematoxylin and Eosin Staining

Each retrieved FFPE tissue block was processed and stained with haematoxylin and eosin (H,E) as it was previously done for re-confirmation of the previous diagnosis (19). Histological classification and grading of the tumors were done in accordance with the Lauren and World Health Organization 2010 report classification systems using an Olympus CX23 microscope (20,21). The evaluation of the microscopic tissue slides was done by two independent experienced pathologists.

Immunohistochemistry Staining

Immunohistochemistry (IHC) staining was performed to detect HER2 protein using a previously optimized protocol by a qualified technician (22). Monoclonal SP3 clone rabbit anti-HER2/neu (Thermo Fisher Scientific, USA) antibody was used. A known HER2 positive breast adenocarcinoma case was used as positive control while omitting the primary antibody served as the negative control. The percentage of tumor cells with HER2 positivity was recorded along with the strength of staining as done in a previous study (23). Tumors with score 0 or score 1+ in which there was no membranous staining or weak staining detected in only one part of the membrane were considered as negative. Cases with moderate or weak complete or basolateral membranous staining were regarded equivocal cases and were given score of 2+. Tumors with score 3+ in which there was strong complete or basolateral membranous staining were considered positive for HER2 protein. Background staining and

cytoplasmic staining were considered as nonspecific staining. Only complete or basolateral membranous staining was considered as true positive. The cut-off points of at least five cohesive, unequivocal tumor cells in endoscopic biopsies, and at least 10% of tumor cells in resection biopsies were used to evaluate HER2 over-expression.

Data Analysis

Data analysis was performed using STATA programme version 15.0. Continuous and categorical variables were presented in mean ± standard deviation and proportions, respectively. Pearson Chi-square statistical test was used to assess the association of the clinicopathological characteristics with HER2 immunohistochemical expression. $P< 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological Characteristics of the Patients

Table 1 presents the clinicopathological characteristics of the patients. Mean age of the patients with gastric adenocarcinoma was 58.5 ± 14.3 years, with an age range of 28-87 years. Majority of the patients (74.4%) (n= 64) were older than 50 years, and over half (54.7%) (n= 47) of the patients were males, and the male to female ratio was 1.2:1. Most of the cases of gastric adenocarcinoma (52.3%) (n= 45) were non-cardia tumors and endoscopic biopsies dominated the specimens (62.8%) (n= 58). Regarding Lauren and WHO classification of the cases, 57.0% (n= 49) and 47.7% (n= 41) were of diffuse type and poorly non-cohesive signet ring type, respectively. Majority (66.3%) (n= 57) of the tumors were poorly differentiated adenocarcinomas. Various histopathological variants of gastric adenocarcinoma are shown in Figure 1.

Age Distribution According to Sex of the Patients with Gastric Adenocarcinoma

The frequency of the gastric adenocarcinoma cases was not linear for both age and sex of the patients. There was a kind of trend to some extent, and there was an increase (35-39 years) and decrease (40-44 years) of the frequency of the cases with age and sex of the patients in the study. Moreover, at the age group of 55-59 years, there was a steep decrease (one case) in the fre-

Table 1. Clinicopathological characteristics of the patients included in the analysis (n= 86)

Variables	Frequency n (%)
Age (years)	
≤50 years	22 (25.6)
>50 years	64 (74.4)
Sex	
Male	47 (54.7)
Female	39 (45.3)
Tumor Location	
Cardia	4 (4.7)
Non-cardia	45 (52.3)
Not specified	37 (43.0)
Nature of Biopsy	
Endoscopic biopsy	54 (62.8)
Surgical biopsy	32 (37.2)
Tumor Grades	
Well differentiated	(16.3)
Moderately differentiated	(17.4)
Poorly differentiated	(66.3)
Lauren Classification	
Intestinal type	37 (43.0)
Diffuse type	49 (57.0)
World Health Organization 2010 Classification	
Mucinous	6 (7.0)
Papillary	8 (9.3)
Poorly cohesive signet ring	8 (9.3)
Tubular	23 (26.7)
Poorly non-cohesive signet ring	41 (47.7)
Tumor Grades	
Well differentiated	14 (16.3)
Moderately differentiated	15 (17.4)
Poorly differentiated	57 (66.3)

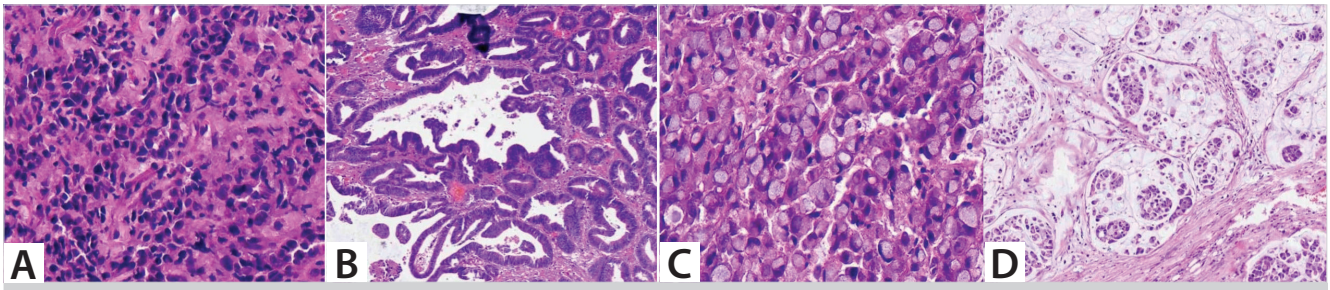

Figure 1. A. The above micrograph shows sheets of neoplastic epithelial cells with marked cytological atypia diffusely invading a desmoplastic stroma. **B.** Photomicrograph showing well differentiated papillary/intestinal adenocarcinoma under H&E stain (x100). **C.** Photomicrograph showing cohesive signet ring carcinoma under H&E stain (x400), and **D.** photomicrograph showing moderately differentiated mucinous/intestinal adenocarcinoma under H&E stain (x100).

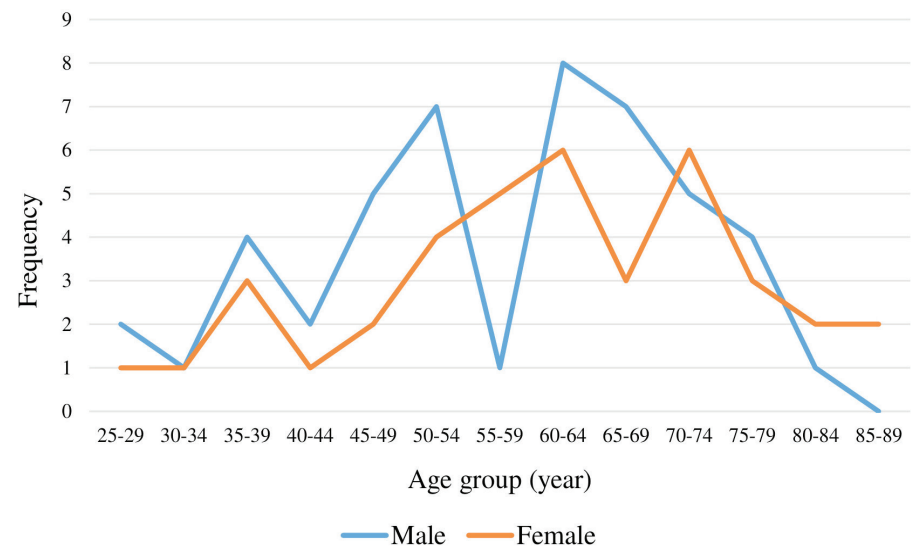

Figure 2. Age distribution according to sex of the patients with gastric adenocarcinoma.

quency of cases among males whereas a significant increase (five cases) in the frequency of cases among females was noticeable. Conversely, at the age group of 65-69 years, there was a decrease (three cases) in the frequency of cases among females whereas a significant increase (eight cases) in the frequency of cases among males was observed (Figure 2).

Prevalence of HER2 Immunohistochemical Overexpression

The variation of HER2 overexpression for the cases of gastric adenocarcinomas is presented in Figure 3. The prevalence of HER2 immunohistochemical overexpression was 8.1% (n= 7) (Figure 3a), all the other 91.9% (n= 79) of the cases were negative (both 0 and 1+ scores) (Figures 3b-d). There was intratumoral heterogeneity of HER2 over-expression in the current study, which occurred in 57% of cases. No equivocal cases were found in this series of tumors regarding HER2 expression.

Association of HER2 Overexpression with Clinicopathological Characteristics of the Patients

Table 2 shows the association of HER2 overexpression with clinicopathological characteristics. HER2 overexpression was higher in patients younger than or of 50 years of age (13.6%, 3/22), than in patients older than 50 years (6.3%, 4/64), although the difference was not statistically significant (p= 0.274). Four out of forty-seven (8.5%) gastric adenocarcinoma tumors from males overexpressed HER2 compared to 3/39 of tumors (7.7%) in females (p= 0.890). Tubular adenocarcinoma had the highest prevalence of HER2 positivity (17.4%, 4/23) compared to other histological subtypes, and we considered the difference was insignificant (p= 0.253). Considering Lauren classification, intestinal subtype of gastric adenocarcinomas had a higher rate of HER2 overexpression (13.5%, 5/37) than diffuse or mixed subtype (4.1%, 2/49), and the difference was also not statistically significant (p= 0.113). Regarding tumor grade, the moderately differentiated

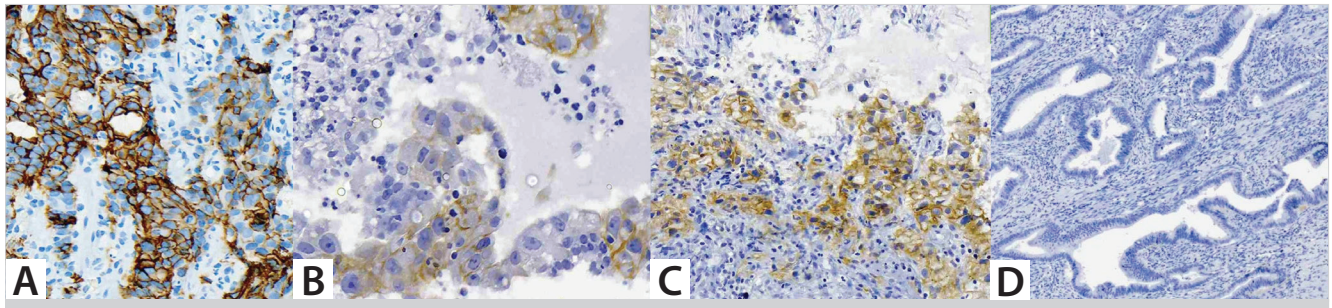

Figure 3. A. Photomicrograph showing HER2 positive score 3+ of a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody x400), **B.** photomicrograph showing HER2 negative score 1+ of a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody, x200), **C.** photomicrograph showing heterogeneous HER2 negative score 1+ in a poorly cohesive non-signet ring adenocarcinoma case (HER2 immunohistochemistry antibody, x200), and **D.** photomicrograph showing HER2 negative score 0 of a well differentiated tubular adenocarcinoma case (HER2 immunohistochemistry antibody, x100).

Table 2. Association of HER2 overexpression with clinicopathological characteristics of the patients

Variables	Positive n (%)	Negative n (%)	p
Age (years)			0.274
≤50 years	3 (13.6)	19 (86.4)	
>50 years	4 (6.3)	60 (93.8)	
Sex			0.890
Male	4 (8.5)	43 (91.5)	
Female	3 (7.7)	36 (92.3)	
Tumor Location			0.658
Cardia	0 (0)	4 (100)	
Non-cardia	3 (6.7)	42 (93.3)	
Not specified	4 (10.8)	33 (89.2)	
Nature of Biopsy			0.190
Endoscopic biopsy	6 (11.1)	48 (88.9)	
Surgical biopsy	1 (3.1)	31 (96.9)	
Histological Subtype (World Health Organization 2010)			0.253
Papillary	1 (12.5)	7 (87.5)	
Tubular	4 (17.4)	19 (82.6)	
Mucinous	0 (0%)	6 (100)	
Poorly cohesive signet ring	1 (12.5)	7 (87.5)	
Poorly cohesive non-signet ring	1 (2.4)	40 (97.6)	
Histological Subtype (Lauren)			0.113
Intestinal	5 (13.5)	32 (86.5)	
Diffuse/mixed	2 (4.1)	47 (95.9)	
Tumor Grades			0.720
Well-differentiated	1 (7.1)	13 (92.9)	
Moderately differentiated	2 (13.3)	13 (86.7)	
Poorly differentiated	4 (7.0)	53 (93.0)	

tumors had more HER2 protein overexpression (13.3%, 2/15) compared to either well differentiated (7.1%, 1/14,) or poorly differentiated cases (7.0%, 4/57) but the difference was not significant (p= 0.720). Also, the overexpression of HER2 protein was not associated with tumor location (p= 0.658) although all four tumors from the cardiac location were negative.

DISCUSSION

This study aimed to determine the prevalence of HER2 immunohistochemical overexpression among gastric adenocarcinoma cases and to establish its association with clinicopathological features of gastric adenocarcinoma. The prevalence of HER2 overexpression in gastric adenocarcinoma in the present study was 8.1% which is in agreement with previous studies (15,24). A wide range of HER2 immunohistochemical expression of 8%-53.4% among cases of gastric adenocarcinoma has been reported in previous studies (24,25).

The reasons for such a wide range of HER2 expression reported in previous studies and extended by the current study could be due to the nature of biopsies, type of antibody clone, scoring system, and tumor heterogeneity (14,26). Among these, tumor heterogeneity could be the leading factor contributing to the wide variation in HER2 prevalence. Previously, tumor heterogeneity of about 30% of tumor cells exhibiting reactivity or only focal staining of tumor cells in at least 30% of HER2 positive cases has been reported in gastric adenocarcinoma (27). Differences in sensitivity and specificity among the antibodies might have contributed to the variation of HER2 protein overexpression (28). Also, previous studies considered only cases with score 3+ as positive, similar to our study, which provided a positivity ranging from 6% to 10.5% (29,30). However, studies where tumors even with scores 2+ were considered positive reported relatively higher HER2 immunohistochemical overexpression rates. For instance, a study by Barros-Silva et al. showed 9.3% HER2 positivity after combining 3.9% which were

score 2+ cases and 5.5% for score 3+ cases (31). Likewise, Van Trung reported 11.7% of HER2 positivity after combining 6.9% which were score 2+ cases with 4.8% score 3+ cases (32).

The lack of association between HER2 immunohistochemical overexpression with all demographic and pathologic characteristics (age, sex, tumor site, grade, and histological subtype) in this study has also been reported in previous studies, though other studies have reported association of HER2 expression with some of the demographic and pathologic characteristics (33,34). This is likely because in the study of Li et al. it was also found that HER2 protein overexpression which is involved in tumor progression was not associated with age of the patients (35). Although the prevalence of HER2 expression was slightly higher in males compared to females, the difference was not statistically significant, similar to other studies (27,33,36,37). On the contrary, a study done in India found an association between HER2 overexpression and sex of the patients (27). The prevalence of HER2 immunohistochemical overexpression varied with WHO histological subtypes, in which tubular adenocarcinoma showed the highest HER2 overexpression, but the difference was not statistically significant, contrary to the findings in the previous studies (36,37). The intestinal subtype that was least frequent in the current study had a higher HER2 overexpression than the diffuse/mixed subtypes as reported by previous studies (36,38). This could partly explain the low prevalence of HER2 immunohistochemical overexpression in this study compared to previous studies which reported a higher proportion of the intestinal subtype of gastric adenocarcinoma than the diffuse/mixed subtypes (24,33,39). Unlike the finding in the current study, Kataoka et al. and Takehana et al. reported a positive association between histological type and HER2 expression (36,37).

Regarding association of tumor grade with HER2 expression, in this study, moderately differentiated adenocarcinomas showed a higher prevalence of HER2 positivity than poorly differentiated adenocarcinomas, though the difference was not significant similar to previous studies (27,36). However, some studies have shown an association between HER2 overexpression and tumor grade (36,40). This is probably due to the different antibody clones used for HER2 testing. Out of the seven cases with positive HER2 protein overexpression, three were non-cardia, while none of the cardia tumors showed reactivity. Compared with a previous study that showed a significant association between HER2 overexpression and tumor location, the current study is in agreement with another studies, which found no significant association (27,41). HER2 overexpression was more prevalent among endoscopic biopsy specimens (11.1%) than surgical biopsies (3.1%) This was consistent with the findings of previous studies (27,42), which also suggested that since small biopsy specimens fix much quicker than surgical biopsies with less ischemic time, antigens are preserved better resulting in higher positivity (41). Consistent with previous studies, there was no significant association between HER2 overexpression and nature of biopsy, probably because of the similarity of small sample size compared to some studies that showed significant association (27,41).

Study Limitations

We faced difficulty in obtaining a large number of FFPE tissue blocks from the tissue blocks repository due to poor storage despite the identification of potential cases from the laboratory requisition forms and patients' files. Incomplete information because of inadequately filled request forms with some important variables lacking like tumor location, incomplete clinical history on including a history of previous chemotherapy or radiotherapy contributed to failure to associate such factors with HER2 overexpression. Also, inappropriate tissue fixation might have affected antigen retrieval during IHC staining. Endoscopic biopsies contained one or two samples per patient which were not enough to represent the tumor.

CONCLUSION

The present study shows that almost one in 10 patients with gastric adenocarcinoma tumors in Uganda are more likely to have HER2 expression, and for that reason, they may benefit from targeted therapy that specifically targets inhibition of HER2. Moreover, HER2 immunohistochemical overexpression in this study was not significantly associated with age, sex, tumor location, nature of biopsy, histological subtype, and tumor grade. Larger scale prospective studies should be conducted to evaluate HER2 immunohistochemical overexpression in gastric adenocarcinoma cases in Uganda to obtain more generalizable results.

Ethics Committee Approval: This study was approved by Makerere University College of Health Sciences School of Biomedical Sciences Research and Ethics Committee (Decision no: SBS-713, Date: 30.01.2020).

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REFERENCES

1. *Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68(6): 394-424. https://doi.org/10.3322/caac.21492*

2. Ngaiza A, Vuhahula E, Yahaya J, Ndayisaba MC, Kawishe GJ, Grenert JP, et al. Evaluation of human epidermal growth factor receptor 2 expression in gastric and gastroesophageal cancers in Tanzania. Arch Pathol Lab Med 2022; 146(12): 1523-9. https://doi.org/10.5858/arpa.2021-0394-OA
3. Robert S, Małgorzata S, Jerzy M, A OGJ, Ryszard M, P PW. Gastric cancer: Epidemiology, prevention, classification, and treatment. Cancer Manag Res 2018; 10. https://doi.org/10.2147/CMAR.S149619
4. Asombang AW, Rahman R, Ibdah JA. Gastric cancer in africa: Current management and outcomes. World J Gastroenterol 2014; 20(14): 3875-9. https://doi.org/10.3748/wjg.v20.i14.3875
5. Bukirwa P, Wabinga H, Nambooze S, Amulen PM, Joko WY, Liu B, et al. Trends in the incidence of cancer in Kampala, Uganda, 1991 to 2015. Int J Cancer 2021; 148(9): 2129-38. https://doi.org/10.1002/ijc.33373
6. Ibingira CB. Management of cancer of the stomach in Mulago Hospital Kampala, Uganda. East Afr Med J 2001; 78(5): 233-7. https://doi.org/10.4314/eamj.v78i5.9044
7. Gravalos C, Jimeno A. HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. Ann Oncol 2008; 19(9): 1523-9. https://doi.org/10.1093/annonc/mdn169
8. Drubay V, Nuytens F, Renaud F, Adenis A, Eveno C, Piessen G. Poorly cohesive cells gastric carcinoma including signet-ring cell cancer: Updated review of definition, classification and therapeutic management. World J Gastrointest Oncol 2022; 14(8): 1406-28. https://doi.org/10.4251/wjgo.v14.i8.1406
9. Tewari M, Kumar A, Mishra RR, Kumar M, Shukla HS. HER2 expression in gastric and gastroesophageal cancer: Report from a tertiary care hospital in north India. Indian J Surg 2015; 77: 447-51. https://doi.org/10.1007/s12262-013-0871-y
10. Scartozzi M, Galizia E, Freddari F, Berardi R, Cellerino R, Cascinu S. Molecular biology of sporadic gastric cancer: Prognostic indicators and novel therapeutic approaches. Cancer Treat Rev 2004; 30(5): 451-9. https://doi.org/10.1016/j.ctrv.2004.01.001
11. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 2010; 376(9742): 687-97. https://doi.org/10.1016/S0140-6736(10)61121-X
12. 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. https://doi.org/10.7150/jca.4090
13. Guoxiong C, Yijun M, Xiaoming P, Ming L, Suping W. Expression of HER2/c-erbB-2, EGFR protein in gastric carcinoma and its clinical significance. Open Life Sci 2019; 14: 119-25. https://doi.org/10.1515/biol-2019-0013
14. Otsu H, Oki E, Ikawa-Yoshida A, Kawano H, Ando K, Ida S, et al. Correlation of HER2 expression with clinicopathological characteristics and prognosis in resectable gastric cancer. Anticancer Res 2015; 35(4): 2441-6.
15. Uprak TK, Attaallah W, Çelikel ÇA, Ayranci G, Yeğen C. HER-2 incidence in gastric cancer, its association with prognosis and clinicopathological parameters. Turkish J Surg 2015; 31(4): 207-13. https://doi.org/10.5152/UCD.2015.2964
16. Kish L. Sampling survey. New York: John Wiley & Sons; 1965.
17. Hussein A, Rogena E, Omulo TM, Ndaguatha, PLW. HER2/neu protein over-expression in patients with gastric and gastro- esophageal junction carcinoma seen at Kenyatta National Hospital, Kenya. Carcinogenesis Car 2014; 5(5): 1-10.
18. Daniel WW. Biostatistics: A foundation for analysis in the health sciences. Biometrics 1988; 44: 317. https://doi.org/10.2307/2531929
19. Mremi A, Yahaya J, Abraham Z, Mwakigonja A. The role of a minimum immunohistochemical antibody panel in confirming undifferentiated nasopharyngeal carcinoma: A cross-sectional study at the muhimbili national hospital, Dar-es-Salaam, Tanzania. Niger Med J 2019; 60(6): 279. https://doi.org/10.4103/nmj.NMJ_134_19
20. Lauren P. the Two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31-49. https://doi.org/10.1111/apm.1965.64.1.31
21. Fléjou JF. WHO Classification of digestive tumors: The fourth edition. Ann Pathol 2011; 31(5 Suppl): 27-31. https://doi.org/10.1016/j.annpat.2011.08.001
22. Che Y, Ren F, Zhang X, Cui L, Wu H, Zhao Z. Immunohistochemical HER2 recognition and analysis of breast cancer based on deep learning. Diagnostics 2023; 13(2). https://doi.org/10.3390/diagnostics13020263
23. Hofmann M, Stoss O, Shi D, Büttner R, Van De Vijver M, Kim W, et al. Assessment of a HER2 scoring system for gastric cancer: Results from a validation study. Histopathology 2008; 52(7): 797-805. https://doi.org/10.1111/j.1365-2559.2008.03028.x
24. Webb A, Scott-Mackie P, Cunningham D, Norman A, Andreyev J, O'Brien M, et al. The prognostic value of serum and immunohistochemical tumour markers in advanced gastric cancer. Eur J Cancer 1996; 32(1): 63-8. https://doi.org/10.1016/0959-8049(95)00504-8
25. Allgayer H, Babic R, Gruetzner KU, Tarabichi A, Schildberg FW, Heiss MM. c-erbB-2 is of independent prognostic relevance in gastric cancer and is associated with the expression of tumor-associated protease systems. J Clin Oncol 2000; 18(11): 2201-9. https://doi.org/10.1200/JCO.2000.18.11.2201
26. Phan DAT, Nguyen VT, Hua TNH, Ngo QD, Doan TPT, Nguyen ST, et al. HER2 status and its heterogeneity in gastric carcinoma of Vietnamese patient. J Pathol Transl Med 2017; 51(4): 396-402. https://doi.org/10.4132/jptm.2017.04.24
27. 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 2016; 7(1): 18-24. https://doi.org/10.1007/s13193-015-0436-6
28. Dekker TJA, Borg ST, Hooijer GKJ, Meijer SL, Wesseling J, Boers JE, et al. Determining sensitivity and specificity of HER2 testing in breast cancer using a tissue micro-array approach. Breast Cancer Res 2012; 14(3): R93. https://doi.org/10.1186/bcr3208
29. Liang Z, Zeng X, Gao J, Wu S, Wang P, Shi X, et al. Analysis of EGFR, HER2, and TOP2A gene status and chromosomal polysomy in gastric adenocarcinoma from Chinese patients. BMC Cancer 2008; 8: 1-12. https://doi.org/10.1186/1471-2407-8-363
30. Sheffield BS, Garratt J, Kalloger SE, Li-Chang HH, Torlakovic EE, Gilks CB, et al. HER2/neu testing in gastric cancer by immunohistochemistry: Assessment of interlaboratory variation. Arch Pathol Lab Med 2014; 138(11): 1495-502. https://doi.org/10.5858/arpa.2013-0604-OA
31. Barros-Silva JD, Leitão D, Afonso L, Vieira J, Dinis-Ribeiro M, Fragoso M, et al. Association of ERBB2 gene status with histopathological parameters and disease-specific survival in gastric carcinoma patients. Br J Cancer 2009; 100(3): 487-93. https://doi.org/10.1038/sj.bjc.6604885
32. Nghia VT. Identification of HER2 protein overexpression and gene amplification in gastric cancer. 2015.

33. *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(1): 1-7. https://doi.org/10.1186/1746-1596-8-76*

34. *Wu HM, Liu YH, Lin F, Xu FP, Luo DL, Zhang F, et al. Association of HER2 protein expression with clinicopathologic features and prognosis in Chinese patients with gastric carcinoma. Zhonghua Bing Li Xue Za Zhi 2011; 40(5): 296-9.*

35. *Li H, Li L, Zhang N, Wang Z, Xu N, Linghu E, et al. Relationship between HER2 overexpression and long-term outcomes of early gastric cancer: A prospective observational study with a 6-year follow-up. BMC Gastroenterol 2022; 22(1): 1-7. https://doi.org/10.1186/s12876-022-02309-7*

36. *Kataoka Y, Okabe H, Yoshizawa A, Minamiguchi S, Yoshimura K, Haga H, et al. HER2 expression and its clinicopathological features in resectable gastric cancer. Gastric Cancer 2013; 16(1): 84-93. https://doi.org/10.1007/s10120-012-0150-9*

37. *Takehana T, Kunitomo K, Kono K, Kitahara F, Iizuka H, Matsumoto Y, et al. Status of c-erbB-2 in gastric adenocarcinoma: A comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. Int J Cancer 2002; 98(6): 833-7. https://doi.org/10.1002/ijc.10257*

38. *Rajagopal I, Niveditha SR, Sahadev R, Preethan KN, Rajendra SG. HER2 expression in gastric and gastro-esophageal junction (GEJ) adenocarcinomas. J Clin Diagnostic Res 2015; 9(3): EC06-EC10. https://doi.org/10.7860/JCDR/2015/12581.5630*

39. *Omulo TM RE. HER2/neu protein over-expression in patients with gastric and gastro- esophageal junction carcinoma seen at Kenyatta National Hospital, Kenya. J Carcinog Mutagen 2014; 05(05). https://doi.org/10.4172/2157-2518.1000186*

40. *Seo KW, Jeon T, Kim S, Kim SS, Kim K, Suh BJ, et al. Epidemiologic study of human epidermal growth factor receptor 2 expression in advanced/metastatic gastric cancer: An assessment of human epidermal growth factor receptor 2 status in tumor tissue samples of gastric and gastro-esophageal junction cancer. J Gastric Cancer 2017; 17(1): 52-62. https://doi.org/10.5230/jgc.2017.17.e6*

41. *Lee S, de Boer WB, Fermoyle S, Platten M, Kumarasinghe MP. Human epidermal growth factor receptor 2 testing in gastric carcinoma: Issues related to heterogeneity in biopsies and resections. Histopathology 2011; 59(5): 832-40. https://doi.org/10.1111/j.1365-2559.2011.04017.x*

42. *Rüschoff J, Dietel M, Baretton G, Arbogast S, Walch A, Monges G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 2010; 457(3): 299-307. https://doi.org/10.1007/s00428-010-0952-2*

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HER2 immünohistokimyasal ekspresyonu ve Uganda'da mide kanserinin klinikopatolojik özellikleri ile ilişkisi

Mohamed Kahiye[1], James Yahaya[2], Sam Kalungi[3], Hawa Nalwoga[4]

[1] Sahan Patoloji Laboratuvarları, Patoloji Kliniği, Mogadişu, Somali
[2] Soroti Üniversitesi Tıp Fakültesi, Patoloji Anabilim Dalı, Soroti, Uganda
[3] Mulago Ulusal Sevk Hastanesi, Patoloji Kliniği, Kampala, Uganda
[4] Makerere Sağlık Bilimleri Fakültesi, Patoloji Anabilim Dalı, Kampala, Uganda

ÖZET

Giriş ve Amaç: Mide kanseri tedavi modalitelerindeki kayda değer gelişmelere rağmen, gastrik adenokarsinomun prognozu kötü olmaya devam etmektedir. Bu çalışmanın amacı HER2 immünohistokimyasal ekspresyonunun prevalansını ve mide kanserli hastaların klinikopatolojik özellikleri ile ilişkisini belirlemektir.

Gereç ve Yöntemler: Bu çalışma patoloji bölümünde yürütülen kesitsel bir çalışmadır. Ocak 2009 ile Aralık 2019 tarihleri arasında histolojik olarak mide kanseri tanısı konmuş 86 hastanın formalin fikse parafine gömülü doku blokları analize dahil edildi. Olguların klinik ve patolojik verilerini elde etmek için laboratuvar talep formu ve hasta dosyaları kullanılmıştır. HER2 aşırı ekspresyonunu değerlendirmek için immünohistokimya monoklonal (SP3 klonu) tavşan anti-HER2/neu (Thermo Fisher Scientific-ABD) kullanılarak yapılmıştır. Klinikopatolojik özelliklerin HER2 ekspresyonu ile ilişkisini belirlemek için ki kare istatistiksel testi kullanılmıştır. P< 0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya dahil edilen hastaların ortalama yaşı 58,5 ± 14,3 yıldı ve hastaların yarısından fazlası (%54,7) (n= 47) erkekti. Olguların %47,7'sini (n= 41) kötü koheziv non-signet halka tipleri oluştururken, diffüz/karışık histolojik alt tipler %57 (n= 49) ile daha sık görülen alt tiplerdi. Kötü diferansiye vakalar vakaların %66,3'ünü (n= 57) oluşturmuştur. HER2 immünohistokimyasal ekspresyon prevalansı %8,1 (n= 7) idi. Klinikopatolojik özelliklerin hiçbiri HER2 ekspresyonu ile ilişkili değildi.

Sonuç: Bu çalışma, immünohistokimya testi kullanıldığında neredeyse her 10 mide kanserli hastadan birinin HER2 eksprese edebileceğini göstermiştir. Bununla birlikte, bu çalışmada HER2 yaş, cinsiyet, tümör yerleşimi, biyopsinin niteliği, histolojik alt tipler ve tümör derecesiyle ilişkili değildi.

Anahtar Kelimeler: Mide kanseri, HER2 aşırı ekspresyonu, prognoz, klinikopatolojik özellikler

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