



The Analysis of Human Epidermal Growth Receptor-2 (HER-2) in Gastric Cancer in a Tertiary Hospital in Sub-Saharan Africa

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Abstract

Background: In Ghana, gastric cancer contributes significantly to cancer morbidity and mortality. However, the recent usage of HER-2 monoclonal antibody in combination with chemotherapy has greatly improved the overall survival of patients. This study, therefore, aims at evaluating the pattern of HER-2 over expression in gastric carcinomas in Kumasi, Ghana

Methodology: Demographic data and histological diagnosis were retrieved from the surgical daybook of the Department of Pathology, Komfo Anokye Teaching Hospital, Kumasi. The slides were retrieved and reviewed to confirm the diagnosis, grading and classification of gastric cancer and immunohistochemistry was done with anti-HER-2 antibody to confirm HER-2 over-expression. Results: Of the 99 cases of gastric cancer seen over the 8 years, there were 57 males and 42 females. There were 91 adenocarcinomas, 5 GIST and 3 Non-Hodgkin Lymphoma. The age range of the study population was 8-90 years with a modal age group in the 6th decade. Of the adenocarcinomas, 45 were poorly differentiated, 38 moderately differentiated and 8 well differentiated. The diffuse type was most common with 47 cases followed by intestinal-type with 41 cases and mixed type with 3 cases. Three of the 4 patients under the age of 30 years had lymphoma. HER-2 over expression was seen in 14 out of the 47 tested and all were intestinal type.

Conclusion: HER -2 over-expression was seen in 30% of patients with gastric carcinoma especially those with intestinal-type.

Keywords: Gastric Adenocarcinoma; HER 2 Expression; Immunohistochemistry.

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Introduction

Gastric carcinoma ranks 5th among the top ten cancers in the world. East Asians, blacks and low socioeconomic groups have recorded very high incident rates^{2,3}.

HER-2/ERBB2 is a member of a family of receptors associated with tumour cell proliferation, apoptosis, adhesion, migration, and differentiation and its potential role as a predictive marker of responsiveness to chemotherapy and radiotherapy is supported by a retrospective analysis of HER-2 gene amplification and overexpression in gastric cancer cases. HER-2 amplification/overexpression serves as a therapeutic target for trastuzumab in both localized and metastatic gastric and gastroesophageal cancer, which is associated with significant improvements in progression-free (PFS) and overall survival.

Despite advances in therapy, the prognosis of advanced gastric cancer remains poor⁶. However, Human Epidermal Growth Factor Receptor-2 (HER-2) monoclonal antibody therapy (Trastuzumab) in combination with chemotherapy has been demonstrated to improve survival of gastric cancer patients. Thus, this study aims to evaluate the pattern of HER-2 overexpression in gastric carcinomas in Kumasi, Ghana as a baseline for the introduction of Trastuzumab in treatment of our patients.

Methods

Demographic data and histological diagnosis were retrieved from the surgical daybook of the Pathology Department of Komfo Anokye Teaching Hospital (KATH), Kumasi of 99 consecutive cases of gastric cancer diagnosed over 8 years. Slides of biopsies (36) or surgical specimens (64) were retrieved and reviewed to confirm the diagnosis, grading and classification of gastric cancer. One of the biopsies was inadequate and was not included. Histological typing was done for all cases according to Lauren's classification⁸. Immunohistochemistry: Microtome was used to cut about 3µm-thick sections from each block and spread onto SuperFrosted Plus slides. The slides were deparaffinised in xylene and rehydrated using graded series of ethanol (100%, 90%, 70%) diluted with tris buffered saline (TBS). This was followed by washing the slides in distilled water. The slides were then incubated in citrate buffer in a pressure cooker for antigen retrieval. Peroxidase methanol and casein solutions were used to block background and non-specific staining respectively. Immunohistochemical dilution for human epidermal growth factor receptor 2 (HER2), was carried out following the manufacturer's instructions (Antibody (HER-2); Clone (CB 11); Pretreat (ER1/20); Dilution (RTU); Control (Breast CA); Company (DAKO); Address (Carpinteria, CA) and the optimized tissue sections were incubated respectively in the diluted primary antibodies. The sections were then immersed in secondary antibody conjugated with Peroxidase and Anti Peroxidase and later developed in diaminobenzidine tetrahydrochloride (DAB). They were subsequently counterstained in haematoxylin, dehydrated in increasing grades of alcohol (70%, 80%, 90%, 95% and 100%) and mounted in DPX Mountant. The scoring was done using the ASCO/CAP guidelines⁹. The data were analysed with SPSS version 17. Photomicrographs of relevant histologic sections were taken.

Results

Data of 99 reviewed cases of gastric cancer seen over the 8 years showed adenocarcinoma (n=91, 91.9%), GIST (n=5, 5.05%) and Non-Hodgkin's Lymphoma (n=3, 3.03%).

57 males were constituting 57.6% and 42 females constituted 42.4% giving a male: female ratio of 1.4:1. The age range was 8 to 90 years with patients aged 50-59 years constituting the highest number of patients (23.2%) while age ranges 0-9 and 90-99 recorded the least cases (1%). (Table 1).

There were more biopsies (63) than resections (36). Of the 91 adenocarcinomas, 45(49.5%) were poorly differentiated, 38(41.8%) moderately differentiated and 8(8.8%) well differentiated. The diffuse-type gastric carcinoma was the most common adenocarcinoma type with 47(51.6%) cases followed by intestinal-type (n=41,45.1%) and mixed type (n=3,3.3%) as shown in Table 2. The diffuse type (n=17) is more common in the younger age group than the intestinal type (n=10) in patients less than 50 years.

Three of the 4 patients under the age of 30 years had lymphoma while the 4th case was diagnosed as adenocarcinoma. Only forty-seven blocks were suitable for IHC and were selected. HER-2 overexpression was seen in 14(30%) of the 47 tested and all were of the intestinal type.

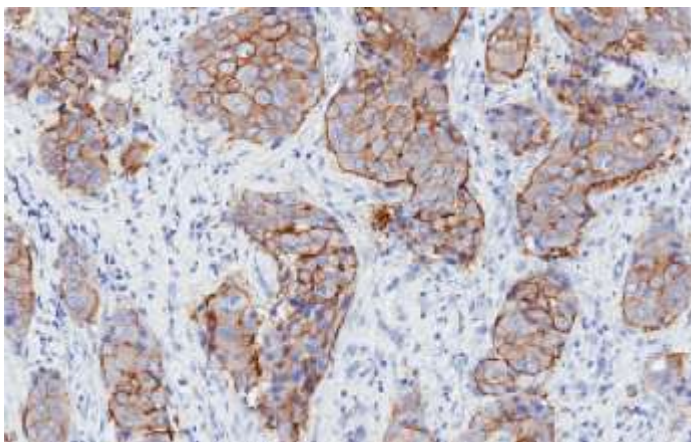
The staining pattern of HER 2 immunohistochemistry is shown in Figure 1. HER-2 overexpression was seen in a small cohort (30%) of our patients with gastric carcinoma especially those with intestinal-type. An additional 10% have equivocal (2+) staining requiring FISH for confirmation.

Table 1: Age and sex distribution of patients with gastric cancer

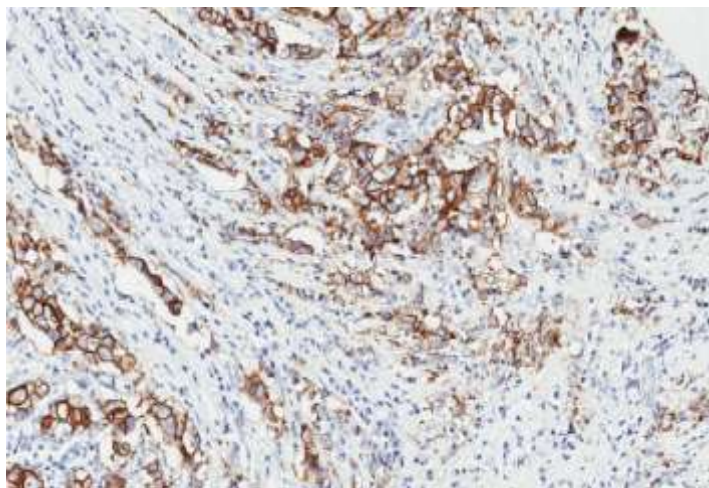
Demographics	Frequency	Percentage (%)
Gender	(n)	
Male	57	57.6
Female	42	42.4
Age		
0-9	1	1.0
20-29	3	3.0
30-39	6	6.1
40-49	21	21.2
50-59	23	23.2
60-69	21	21.2
70-79	16	16.2
80-89	7	7.1
90-99	1	1.0
Total	99	100

Table 2: Age and subtypes of gastric adenocarcinoma

Age	LAUREN CLASSIFICATION				Chi square P value
	Diffuse	Intestinal	Mixed	Total	
20-29	3	0	0	3	0.459
30-39	5	0	0	5	
40-49	9	10	2	21	
50-59	11	10	0	21	
60-69	8	10	1	19	
70-79	7	7	0	14	
80-89	4	3	0	7	
90-99	0	1	0	1	
Total	47	41	3	91	



A



B

Figure 1: HER-2 immunohistochemistry of gastric adenocarcinoma. A – Positive control (Breast carcinoma); B – Gastric adenocarcinoma showing 3+ intensity (positive). The golden brown colorations indicate positive test.

Discussion

The age range of the study population of 8-90 years with modal age group in the 6th decade is similar to other studies. It has been reported that gastric cancers correlate with older age and male gender and from the study demographic data, a higher frequency of the disease was observed among men in our study population which agreed with other studies worldwide. More so, the results also confirm that older patients have a higher frequency of gastric cancer. Previous studies^{10,11} have reported adenocarcinoma as the most common histologic type of gastric cancer. Our study interestingly conforms to a very high percentage of gastric adenocarcinoma (91.9%) relative to GIST and Non-Hodgkin's Lymphoma.

Over the past decades, Lauren's classification has been the main histological classification of gastric carcinoma, in which intestinal-type and diffuse-type adenocarcinoma are the major histologic subtypes, with indeterminate type/mixed type as uncommon variant. The numbers of our patients with the diffuse subtype were not significantly different from those with the intestinal subtype ($p = 0.459$). There was no significant difference in the pattern of occurrence of the three histologic types as opposed to a study by Polkowski et al¹⁴ which showed a significant occurrence of intestinal-type. There are indications that the diffuse-type gastric carcinoma is more often seen in females and young individuals,^{8,15} and from our results, the diffuse adenocarcinoma subtype occurs in a much younger age group compared to the intestinal and mixed subtype ($p = 0.102$). Zheng et al¹⁶ and Shibata et al¹⁷ have described a general reduction in incidence rates of gastric carcinoma due to decreasing intestinal carcinoma with no appreciable change in diffuse adenocarcinoma. The results from our study show a preponderance of diffuse gastric carcinoma compared with intestinal-type. This may be attributed to improved sanitation and better food preservation methods since the intestinal subtype is dependent on environmental factors as compared to the genetic aetiology of the diffuse subtype.

Overexpression of the HER-2 receptor was observed in 30% of our cases which correlated well with the established range of 4.4 to 53.4%.^{18,7}

Previous studies have reported an association between HER-2 and histologic type (intestinal, diffuse and mixed)⁶. Conversely, higher HER-2 positivity rates in intestinal-type compared to other types of gastric carcinoma have also been widely identified and our results was not an exception since all the cases tested for HER-2 overexpression were intestinal adenocarcinoma. A small percentage of our cases have equivocal staining requiring FISH for confirmation. These results suggest an association between the intestinal subtype of gastric cancer and HER-2 overexpression and it is consistent with other studies^{18,7}.

Conclusion

The most common stomach cancer in our centre is adenocarcinoma of higher grade, which are predominantly diffuse. HER-2 over-expression was seen in a small cohort of our patients with gastric cancer especially those with intestinal-type, some of which have equivocal staining requiring FISH for confirmation. We recommend that all patients with

gastric adenocarcinoma should be tested for HER-2 over-expression at early stages as they may benefit from target therapy of trastuzumab in addition to standard chemotherapy. A larger study with FISH for confirmation of equivocal cases is also recommended.

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