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Assessment of Vascular Endothelial Growth Factor Receptor 2 in Gastric Adenocarcinoma at the Jos University Teaching Hospital: A Ten-year Retrospective Study

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Abstract

Background:

Gastric cancer (GC) represents a heterogeneous group of malignant tumors of the stomach and remains a significant contributor to global cancer-related morbidity and mortality. Over 90% of gastric cancers are adenocarcinomas. Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) plays a critical role in tumorigenesis, invasion, and metastasis. Anti-VEGFR2 agents, such as ramucirumab and apatinib, have demonstrated favorable outcomes in patients with gastric adenocarcinoma.

Objective:

To evaluate VEGFR2 expression in gastric carcinoma and determine its relationship with histopathological parameters.

Methodology:

This was a descriptive, retrospective cross-sectional study involving 95 histologically confirmed cases of gastric adenocarcinoma diagnosed at Jos University Teaching Hospital between 2012 and 2021. Tumors were classified according to the Lauren and World Health Organization (WHO) classification systems, graded histologically, and analyzed for VEGFR2 expression using immunohistochemistry.

Results:

The mean age of patients was 53.5 years, with a male-to-female ratio of 1:1. The gastric antrum was the most commonly affected site (74.8%). The intestinal type was the predominant histological subtype (65.3%), while the diffuse type accounted for 34.7%. Well-differentiated tumors were the most frequent grade (30.5%). VEGFR2 expression was positive in 78 (82.1%) of cases. A statistically significant association was observed between VEGFR2 expression and both histologic grade and Lauren classification.

Conclusion:

VEGFR2 expression was higher in diffuse-type and moderately to poorly differentiated tumors. Its significant association with histologic grade suggests that patients with these pathological features may benefit from targeted anti-VEGFR2 therapy.

Introduction

Gastric cancers (GC) are a heterogenous group of malignant tumors of the stomach and it is a major contributor to the worldwide morbidity and mortality of cancers.[1] According to the GLOBOCAN 2022, It is the 5th most common cancer worldwide accounting for over one million new cases in both sexes; the

4th most common cancer in men and 7th most common cancer in women.[1]The disease burden per 100,000 individuals show male dominance worldwide.[1,2]

Gastric cancer is the 8th most common cancer in Nigeria.[1,2] Studies in Jos North Central and Ibadan South Western Nigeria showed that gastric cancers accounted for 3.59% and 2.73% of all malignant tumors.[3,4] However, Port Harcourt (South South) reported a lower prevalence of 1.9%.[5]The overall incidence of gastric cancer (GC) in Nigeria is 1.1-6.0% of all malignant tumors.[6,7]A hospital based retrospective study in Lagos (South West) that involved 105 cases of GC showed that 90% of GCs are adenocarcinomas.[8]This is similar to the study in Jos that reported 85.5% of 205 cases of GCs as adenocarcinomas.[3]

Gastric cancers (GC) are the 4th leading cause of cancer mortality worldwide accounting for 7.7% of cancer deaths in year 2020.[2] It is the 9th most common cancer deaths in Nigeria with a mortality.[1,2]

The treatment of GC depends mainly on the stage at presentation.[9,10]Total or subtotal gastrectomies with neoadjuvant chemotherapy is the commonest treatment modality worldwide as majority of patients present with advanced disease.[3,5,6,7] The overall outcome is poor as the 5-year survival of patients with resectable tumors is 10–30%.[9,10,11]

The Pathogenesis of gastric cancer is largely linked to environmental factors.[12] The major contributory risk factor is diet especially salted and smoked foods.[12,13] Lack of refrigeration of foods, nitrosamine containing foods, low dietary vegetables and fruits have also been associated with increased risks.[12,13,14] There is also the role of genetic factors in the development of GC involving polymorphism in the proinflammatory gene, Interleukin 1 beta (IL-1β)[15]and Interleukin – 10 (IL-10).[16]

Vascular endothelial growth factor receptor 2 (VEGFR2) is involved in the signal transduction that culminates in angiogenesis, a key hallmark of carcinogenesis and is gaining recognition as a marker of prognostication and therapeutic intervention.[17]

Overexpression of VEGFR2 is associated with depth of invasion and lymph node metastasis.[17]The Anti-VEGFR2 drug, ramucirumab targets the extracellular domain of VEGFR2 and prevent its binding to VEGF and thereby preventing the VEGF/VEGFR2 angiogenic signaling pathway.[17,18]Licoflavone has been shown to suppress gastric cancer growth by blocking VEGFR2 signaling pathway.[19]

The associated high morbidity and mortality of gastric cancer makes the exploration of molecular characteristics and possible targeted therapies necessary worldwide. This might result in better outcomes and reduce the morbidity associated with extensive surgeries and broad acting cancer chemotherapeutics.[1]

Gastric cancer is the fifth commonest cancer globally and the fourth commonest cause of cancer death.[1]In Nigeria, late presentation has maintained GC as a major contributor of cancer related morbidity

and mortality.[6,7] This is largely due to the asymptomatic and non-specific symptoms of early gastric cancer that mimics peptic ulcer disease or Gastroesophageal reflux disease (GERD) and as such patients present when weight loss, hematemesis, and early satiety begins.[7]The median survival period worldwide is less than 12 months.[6,7] In a study in Maiduguri, North eastern Nigeria, only 8.3% of individuals survived beyond 2 years of commencement of treatment.[7]This is in addition to the toxic effects of chemotherapy and non-availability of specialized surgical interventions. There is therefore a need to explore the possibility of a more individualized targeted therapy to reduce the toxic effects of the broad acting chemotherapeutic agents presently in use.

The paucity of data on VEGFR2 status of gastric adenocarcinoma in Africa, Nigeria and especially in Jos makes this study valuable. This study aims to describe the histopathologic patterns of adenocarcinomas diagnosed in JUTH and to determine their VEGFR2 expression using IHC. It will show the disease burden, and possible emerging patterns of Gastric adenocarcinoma in Jos, North Central Nigeria.

This study will also show to VEGFR2 expression in gastric adenocarcinoma and possibly justify the use of the Anti-VEGFR2 drugs like Ramucirumab and Licoflavone in gastric adenocarcinoma.[18, 19]

Methodology

Study setting

The study was carried out at the Department of Anatomical Pathology and Forensic Medicine of the Jos University Teaching Hospital, JUTH, Lamingo, Plateau State.

Study design

This is a ten-year cross-sectional retrospective study of all gastric biopsies and gastrectomy specimens with a histologic diagnosis of gastric adenocarcinomas received at the Department of Anatomic Pathology and Forensic Medicine of the Jos University Teaching Hospital, JUTH, Lamingo, Jos, Plateau State between january 2012 to december 2022 to assess for expression of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) by immunohistochemistry.

Inclusion and exclusion criteria

All slides and Formalin Fixed Paraffin Embedded (FFPE) tissue blocks of histologically diagnosed gastric adenocarcinoma within the stipulated study period were included in the study. Missing tissue blocks, damaged blocks and the blocks in which the tissue has been exhausted were excluded from the study. Cases that had incomplete biodata were also excluded.

Materials and data collection

Formalin fixed paraffin embedded (FFPE) tissue blocks of all cases of gastric adenocarcinoma diagnosed between January 2012 and December 2022 were retrieved following collation of biodata and clinical information of patients from the laboratory database. Archived slides stained with Hematoxylin and Eosin were examined and classified using the Lauren and WHO classification systems by me and two supervising consultants of the department. Archived FFPE blocks from each representative block were selected for immunohistochemical staining, which was carried out at the University College Hospital, Ibadan

Immunohistochemistry for VEGFR2

FFPE blocks were sectioned at 3–4μm and tissue slices deparaffinized in xylene twice for 10 minutes at room temperature, rehydrated with 100% ethanol for 10 minutes, 95% ethanol for 5 minutes and 75% ethanol for 5 minutes, all at room temperature and then placed in 3% H_2O_2 dissolved in methanol for 10 minutes at room temperature. Tissue slices were incubated with 10% normal goat serum (biotechnne R&D system Ltd.) for 60 minutes at room temperature. After overnight incubation at 4^{o}C with primary antibody with VEGFR-2 (Human VEGFR2/KDR/Flk-1 Antibody: AF375) and then incubated with secondary antibody TM detection kit. Finally, the slices were incubated with diaminobenzidine for 3–5 minutes and counter stained with hematoxylin stain for 30 seconds at room temperature.

For VEGFR-2 expression, the immunoreactive score was used. Staining intensity is scored as follows: i)0, no coloration ii) 1, light brown iii) 2, brown and iv)3, dark brown. The percentage staining is usually scored as 0, 1, 2, 3, 4 for 0–5%, 6–25%, 26–50%, 51–75%, 76–100% of positively stained cells, respectively. Total scores of 0–1, 2–4, and 5–12 are scored as VEGFR2 (-), VEGFR2 (+), VEGFR2 (++/+++).[17,18]

The VEGFR2 stained slides were viewed under a LEICA DM500 light microscope at x 40 magnification. VEGFR2 expression in gastric adenocarcinoma was determined using the combined Immunoreactive Score (IRS) which is expressed as the number of positive VEGFR2 neoplastic cells staining cells including tumor cells divided by the total number of viable tumor cells multiplied by 100. The intensity of staining is also assessed as mild, moderate and strong positivity for light brown, dee brown and dark brown stain respectively.

Evaluation of VEGF2 staining of tumour cells will be started at 20x magnification. VEGFR2 positive will be counted at 40x magnification in ten contiguous fields which show distribution, maximal number of tumour cells, and minimal desmoplastic stroma and necrosis, only immunoreactive cells in direct contact with tumour cells will be counted. Immuno positive cells will be defined as those which show partial or complete staining of the cell membrane and/or cytoplasm. Intensity of staining will be classified as: 0- negative, 1-weak, 2-moderate, 3-strong. A score of 2 or 3 will be considered positive. The average number of cells per high power field will be calculated. The median value of VEGFR2 positive cells per HPF will be derived and the tumours classified into low or high VEGFR2 expression based on the median value.

Evaluation of cytoplasmic staining of tumor cells was done at 40x magnification (LEICA DM500 light Microscope) consistent with other studies in China studies on VEGFR2 expression in gastric adenocarcinoma.[17]. Positive-staining cells were defined as those which showed partial or complete staining of the cytoplasm. Intensity of staining was classified as: 0- negative, 1-weak, 2-moderate, 3-strong. A score of 2 or 3 was considered positive.

Data analysis

The data obtained was analyzed using the SPSS for Windows version 27 (IBM Corp., Amok, N.Y., USA) using inferential and descriptive statistical methods. Mean, median, frequency, and percentage were used to analyze descriptive variables.

The analysis of variables that show association was carried out using the chi-square test. A confidence level of 95% which correlates with a p-value of < 0.05 was considered significant. The results obtained were presented in charts, tables, and figures.

The frequency of VEGFR2 expression was reported as percentages and represented in charts and tables showing the proportion of gastric adenocarcinoma expressing VEGFR2. Statistical correlation between VEGFR2 expression and clinicopathological parameters including age, sex, histologic type (Lauren and WHO classifications), degree of differentiation (classified as well, moderately, or poorly differentiated; 8th edition of the AJCC staging system and the World Health Organization systems were made).

Results

Frequency of gastric carcinoma

Table 1 shows ninety-five (95) cases of gastric adenocarcinomas were diagnosed during the study period and all met the inclusion criteria. Figure 1 show yearly distribution of GC during the study period. Of the 95 cases, 10 (10.5%) were gastrectomy specimen and 85 (89.5%) were endoscopic biopsy specimens.

Age distribution of gastric carcinoma

Table 2 shows the mean age was 53.5 (SD = 17.1). It revealed that the 19 cases (20.0%) occurred in patients younger than 40 years, 38 cases (40.0%) in the 40–59 years age group, and another 38 cases (40.0%) in patients aged 60 years and above.

Sex distribution of gastric carcinoma

Regarding sex distribution, the data showed a higher prevalence of GC in males, with 53 cases (55.8%), compared to females, who accounted for 42 cases (Fig. 2)

Anatomic site distribution of gastric carcinoma

The Antrum is the most commonly affected site (74.8%). This is followed by both the Fundus and the Pylorus, each with 10 cases (10.5%). The Cardia is the least affected site, with only 4 cases (4.2%). Table 3

Histologic type of gastric carcinoma

Using the Lauren's classification, 62 cases (65.3%) were the intestinal type, while 33 cases (34.7%) were classified as diffused type. The WHO typing revealed a diverse distribution: tubular type was found in 42.1% of cases, papillary in 16.9%, PCC(NSRC) in 14.8%, mucinous in 10.5%, PCC(SRC) in 7.4%, micropapillary in 5.3%, medullary in 2.1%, and hepatoid in 1.1% of cases. (Table 4)

Histologic grade of gastric carcinoma

Using the AJCC grading, Majority of cases, 29(30.5%) were classified as G1 (Well differentiated), 26 cases (27.4%) as G2 (Moderately differentiated), 26 cases (27.4%) as G3 (Poorly differentiated), and 14 cases (14.7%) were non-gradable.

In the WHO classification, 52 cases (54.7%) were categorized as Low-grade, and 43 cases (45.3%) as High-grade. (Table 5).

VEGFR2 expression status in gastric carcinoma

Out of 95 cases, 78 (82.1%) showed positive VEGFR2 expression, while 17 (17.9%) were negative. Among the 78 positive cases, 43 (55.1%) exhibited a single positive (+) staining intensity, 15 (19.2%) showed double positive (++), and 20 (25.7%) had triple positive (+++) staining. (Table 6)

Relationship between VEGFR2 expression and patient's age, gender, histologic type and AJCC grade of GC

Table 7 shows among the patients younger than 40, 84.2% tested positive for VEGFR2 expression, compared to 86.8% in the 40–59 age group and 76.3% in the 60 and above age group. The statistical analysis showed no significant association between age and VEGFR2 expression ($X^2 = 1.505$, $p = 0.471$). Regarding sex, 85.7% of male patients and 79.2% of female patients were positive for VEGFR2 expression. The difference between males and females in terms of VEGFR2 expression was not statistically significant ($X^2 = 0.667$, $p = 0.414$).

Using Lauren's classification, 82.3% of GC were positive for VEGFR2 expression, compared to 81.8% of diffused-type cancers. This difference was not statistically significant ($X^2 = 0.003$, $p = 0.958$).

Based on WHO grade, in the low-grade group, 86.5% were positive for VEGFR2 expression, whereas in the high-grade group, 76.7% were positive. The association between WHO grade and VEGFR2 expression was not statistically significant ($X^2 = 1.537$, $p = 0.215$).

Using the AJCC grading system, 80.0% of well-differentiated tumors had negative-low VEGFR2 expression, whereas 20.0% had high expression. In poorly differentiated tumors, 40.0% had negative-low

expression, and 60.0% had high expression. This association was statistically significant ($X^2 = 15.924$, $p < 0.001$), suggesting that poorly differentiated tumors are more likely to express VEGFR2 at high levels.

Table 8 shows the summary of the association between age, sex, histologic type, grade and VEGFR2 expression. There is significant statistical association between the degree of VEGFR2 expression and the WHO and AJCC grade as well as Lauren classification of GC.

The Degree of VEGFR2 expression is illustrated in a well deffrentiated (Fig. 3) and poorly diffrientiated (Fig. 4) gastric adenocarcinoma

Table 1
Ten Year prevalence of GC in Jos University Teaching Hospital

Cancer	Frequency	Percent
GC	95	2.6
Others	3513	97.4
Total	3608	100.0

Table 2
Distribution of GC in Jos University Teaching Hospital according to Age

Variable	Frequency	Percent
Age group(years)		
< 40	19	20.0
40–59	38	40.0
≥ 60	38	40.0
Mean ± SD	53.5 ± 17.1	100.0

Table 3
Distribution of GC in Jos University Teaching Hospital according to Site

Site	Frequency	Percent
Antrum	71	74.8
Fundus	10	10.5
Pylorus	10	10.5
Cardia	4	4.2
Total	95	100.0

Table 4
Classification of GC in Jos University Teaching Hospital according to Lauren and WHO Typing

Typing	Frequency	Percent
Lauren		
Intestinal	62	65.3
Diffused	33	34.7
WHO		
Tubular	40	42.1
Papillary	16	16.9
PCC(NSRC)	14	14.8
Mucinous	10	10.5
PCC(SRC)	7	7.4
Micropapillary	5	5.3
Medullary	2	2.1
Hepatoid	1	1.1

Table 5
Grading of GC in Jos University Teaching Hospital

Grading	Frequency	Percent
AJCC		
G1	29	30.5
G2	26	27.4
G3	26	27.4
GX	14	14.7
WHO		
Low	52	54.7
High	43	45.3

Table 6
VEGFR2 Expression in GC

VEGFR Expression	Frequency	Percent
Positive	78	82.1
Negative	17	17.9
Total	95	100.0

Table 7
Association between Age, Sex, Grade and Levels of VEGFR2 expression

Variable	VEGFR2			X^2	P-Value
	Negative-low -/+n = 60	High ++/+++n = 35	Total		
Age (years)				3.054	0.217
< 40	9(47.4)	10(52.6)	19(20.0)		
40–59	27(71.1)	11(28.9)	38(40.0)		
≥ 60	24(63.2)	14(36.8)	38(40.0)		
Sex				0.051	0.822
Male	34(56.7)	19(54.3)	53(55.8)		
Female	26(43.3)	16(45.7)	42(44.2)		
WHO grade				26.990	< 0.001*
Low	45(86.5)	7(13.5)	52(547)		
High	15(34.9)	28(65.1)	43(45.3)		
AJCC grade				15.924	< 0.001*
Well differentiated	44(80.0)	11(20.0)	60(63.2)		
Poorly differentiated	16(40.0)	24(60.0)	35(36.8)		
Lauren typing				32.909	< 0.001*
Diffused	8(24.2)	25(75.8)	33(34.7)		
Intestinal	52(83.9)	10(16.1)	62(65.3)		

Table 8
Association between selected Characteristics and VEGFR2 expression

Variable	VEGFR2		Total	X^2 (p-value)
	Yes n = 78 Freq (%)	No n = 17 Freq (%)	N = 95 Freq (%)	
Age				1.505(0.471)
< 40	16(84.2)	3(15.8)	19(20.0)	
40–59	33(86.8)	5(13.2)	38(40.0)	
≥ 60	29(76.3)	9(23.7)	38(40.0)	
Sex				0.667(0.414)
Male	36(85.7)	6(14.6)	53(55.8)	
Female	42(79.2)	11(20.8)	42(44.2)	
WHO grade				1.537(0.215)
Low	45(86.5)	7(13.5)	52(54.7)	
High	33(76.7)	10(23.3)	43(45.3)	
AJCC grade				4.339(0.037*)
Well differentiated	49(89.1)	6(10.9)	55(57.9)	
Poorly differentiated	29(72.5)	11(27.5)	40(42.1)	
Lauren typing				0.003(0.958)
Intestinal	51(82.3)	11(17.7)	62(65.3)	
Diffused	27(81.8)	6(18.2)	23(24.2)	
WHO typing				15.465(0.030*)
Tubular	38(95.0)	2(5.0)	40(42.1)	
Papillary	12(75.0)	4(25.0)	16(16.9)	
PCC(NSRC)	11(78.6)	3(21.4)	14(14.8)	
Mucinous	5(50.0)	5(50.0)	10(10.5)	
PCC(SRC)	5(71.40	2(28.6)	7(7.4)	
Micropapillary	5(100.0)	0(0.0)	5(5.3)	
Medullary	1(50.0)	1(50.0)	2(2.1)	

Variable	VEGFR2		Total	X^2 (p-value)
	Yes n = 78	No n = 17	N = 95	
	Freq (%)	Freq (%)	Freq (%)	
Hepatoid	1(100.0)	0(0.0)	1(1.1)	

Discussion

Age, sex, anatomic site distribution, histologic type and pathologic grade of GC

This study revealed that the 19 cases (20.0%) occurred in patients younger than 40 years, 38 cases (40.0%) in the 40-59-year age group, and another 38 cases (40.0%) in patients aged 60 years and above.

The mean age of the patients in this study was 53.5years, which is similar to the findings reported by Komolafe et al who also reported a mean age incidence of 53.5 years and Abdulkareem et al who observed a mean age of 55.3years for gastric cancer patients.[8,20] It also corelates closely to values reported in other parts of Nigeria. Bakari et al in Maiduguri and Kwaghe et al in Jos reported a median age of 51.35 years and 54.6 years respectively.[7,21]Obiorah et al and Ebili et al in Port Harcourt and Ibadan respectively reported slightly higher values of 55 years.[5,22]Studies in other parts of Africa are comparable to our finding in this study. Mabula et al in Tanzania reported a median age of 52 years in a review of 232 cases, this was similar to the value in Egypt reported by Elmajjaoui who also reported same mean age of 52 years.[23,24] However, Lodenyo et al in Kenya reported a mean age for the 44 cancer patients as 58.3yrs with values for males as 61.8 years and that for females was 53.5 years.[25] This higher mean age incidence could be due to the relatively low study population. In Asia however, the peak age incidence of gastric cancer is higher possibly owing to higher endoscopic surveillance and disease burden. Xueru et al in China reported 63 years as the mean age incidence,[26]Xiu-Feng et al however reported 54 years as peak age incidence, probably due to their smaller sample size.[17]

In this study, Males are more affected than females which is consistent with findings in other parts of the world.[22,24,25,26].

The Antrum was the commonest affected anatomic site (74.8%). This is followed by both the Fundus and the Pylorus, each with 10 cases (10.5%). The Cardia was the least affected site, with only 4 cases (4.2%). This is in tandem with reports in most parts of the world and in Nigeria. Mabula et al in Bugando, Tanzania reported 56.5% cases occurred in the antrum while the cardia was least affected with 5.2% involvement.[23]Lodenyo in Kenya also reported the antrum with the highest (56.5%) involvement followed by the fundus (12.7%), the cardia was the least involved.[25]In Jos, Kwaghe et al and Mandong et al all

reported similar findings.[11,21]The picture was also similar with studies in Asia by Xueru et al and Xiu-Feng et al as well as other parts of the globe.[17,26]

The Intestinal type accounted for 65.3% of the cases, while diffuse type constituted 34.7% of the cases. This is similar to the findings by Abdulkareem et al in Lagos that showed intestinal type being the most common histologic type.[8]In Ibadan, Ebili et al also reported the intestinal type as the most common (47%), with diffuse type accounting 35.1% and the mixed ,17.9% of the cases.[22]Studies in other parts of the world puts the intestinal type of gastric carcinoma as the most common histologic type in many parts of Africa, Asia.[6,7,8,17,21,22]In contrast however, Lodenyo et al in Kenya, reported that diffuse gastric cancer was commoner, and accounted 59.1% of the cases they studied while intestinal type made up 34.9%.[25]The campaign on Helicobacter pylori eradication programs is a possible explanation of this phenomenon as H. pylori is a dominant factor in the pathogenesis of intestinal type adenocarcinoma.[25]

Using the American Joint Committee on Cancer system, the most common grade of gastric carcinoma in this study are the well-differentiated tumours accounting 30.5%, the moderately and poorly differentiated tumors each account for 27.4% of the cases, the remainders are non-gradable tumours. This is in tandem with reports by both Mandong et al and Kwaghe et al in Jos who reported the well-differentiated tumours was the most common (51.2% and 54.3% of cases respectively).[11,21]Studies by Bakari et al in Maiduguri and Obiorah et al in Port-Harcourt also reported well differentiated carcinomas as the most common grade, while the least common were the poorly differentiated group.[5,7] Ebili et al in Ibadan however reported a higher proportion of poorly differentiated tumors in their study.[22]Mabula et al in Tanzania reported a higher proportion of well-differentiated tumours (38.8%) and moderately-differentiated tumours constituted (32.8%), while poorly-differentiated tumours made up 19.8% which is similar to values reported by Lodenyo et al in Kenya.[23,25]

VEGFR2 expression in gastric carcinoma

In this study, 78 (82.1%) showed positive VEGFR2 expression, while 17 (17.9%) were negative of the 95 cases reviewed. Xueru et al in China reported similar findings of 218 (85.1%) tumours showing VEGFR2, with 38 (14.8%) VEGFR2 negative categories.[26]This is consistent with values reported by Xiu-Feng et al who also reported high (75%) expression of VEGFR2 in early gastric cancer.[17]Li et al also in China however reported lower values not consistent with other studies, with values of 17.6%, 32.2% for mild and moderate positivity of VEGFR2 in 255 cases they reviewed.[27]However, overall expression was also high, suggesting that gastric carcinomas commonly express higher levels of VEGFR2.[10,11,17,26,27]

Correlation between VEGFR2 and the Lauren/WHO types of GC

Using Lauren's classification, 82.3% of GC were positive for VEGFR2 expression, compared to 81.8% of diffused-type cancers. This difference was not statistically significant ($X^2 = 0.003$, $p = 0.958$). WHO typing revealed significant variability in VEGFR2 expression among different subtypes of GC. Tubular

type had the highest VEGFR2 expression at 95.0%, followed by micropapillary type at 100%, and papillary type at 75.0%. Mucinous and PCC (non-signet ring cell) types had the lowest expression rates at 50.0% each. This association was statistically significant ($X^2 = 15.465$, $p = 0.030$), indicating that the type of GC significantly influences VEGFR2 expression. This finding is consistent with reports by Li et al in China which showed no significant statistical correlation of VEGFR2 with the Lauren and WHO types of gastric adenocarcinomas.[27]Teng et al and Hongxia et al also reported similar findings.[18,19]

Relationship between VEGFR2 and clinicopathologic indices

In this study, there was significant statistical association between VEGFR2 degree of expression, the AJCC and World Health Organization grades of gastric adenocarcinomas. Among patients with low-grade tumors, 86.5% had negative-low VEGFR2 expression compared to 13.5% with high expression. Conversely, in the high-grade group, 34.9% had negative-low expression and 65.1% had high expression. This association was statistically significant ($X^2 = 26.990$, $p < 0.001$), indicating that high-grade tumors are more likely to express VEGFR2 at high levels. Using the AJCC grading system, 80.0% of well-differentiated tumors had negative to low VEGFR2 expression, whereas 20.0% had high expression. In poorly differentiated tumors, 40.0% had negative to low expression, and 60.0% had high expression. This association was statistically significant ($X^2 = 15.924$, $p < 0.001$), suggesting that poorly differentiated tumors are more likely to express VEGFR2 at high levels. Li et al reported statistically significant correlation between VEGFR2 expression and grade of gastric cancer. This is in keeping with findings in this study. Similar findings were also reported by Xueru et al and Xiu-Feng et al in China,[17,27] which were also corroborated by Hongxia et al and Teng et al.[18,19] However more studies need to be done in other parts of the world.

Using Lauren's classification, 24.2% of diffuse-type tumors had negative-low VEGFR2 expression, while 75.8% had high expression. For intestinal-type tumors, 83.9% had negative-low expression, and 16.1% had high expression. This difference was statistically significant ($X^2 = 32.909$, $p < 0.001$), indicating that diffuse-type GC are more likely to have high VEGFR2 expression compared to intestinal-type cancers. This is not consistent in other studies which reported no statistically significant relationship between VEGFR2 expression and Lauren type of gastric carcinomas. Xueru et al, Xiu-Feng et al and Li et al in China all reported no significant correlation in their studies.[17,26,27]The statistical relationship in this study may not be unconnected to the relatively low sample size associated with this study. A larger sample size and multicenter based study may be necessary to establish statistical relationship.

There was no significant association between VEGFR2 expression and age, or sex in this study. This is consistent with findings of no statistical correlation between VEGFR2 and age or sex of the patients.

Conclusion

The study has shown that gastric carcinoma in our environment is more common in the 5th decade, which is similar to findings reported in most studies. It is also more common in males than in females. The common anatomic site involved is the antrum. The intestinal type has a higher prevalence. The majority of gastric carcinomas are well differentiated tumours.

The expression of VEGFR2 was seen in both the intestinal and diffuse type. There was statistical association between VEGFR2 and the histologic type and grade of gastric carcinomas. There was no association between other clinicopathologic parameters and VEGFR2 expression.

Limitations of the study

This is a retrospective a study and as such the number of samples for the period over review are relatively small. Also, some of the archived records and FFPE blocks were either missing or damaged making immunohistochemical stain difficult. Percentage expressivity of VEGFR2 in some samples may not be well analyzed as majority were small endoscopic biopsy tissues.

Recommendations

More studies need to be done involving larger sample size and multi-centre based to fully establish relationship between VEGFR2 with clinicopathologic parameters of gastric carcinoma. Studies outside Nigeria should also be done to see if there are variabilities in various study populations in different geopolitical regions.

A prospective study with clinical information on Bormann's class, depth of invasion, nodal metastasis and other relevant clinical variables is advised to demonstrate relevant clinicopathologic relationships.

VEGFR2 testing should be encouraged in high prevalence areas as many recent studies have shown high expression in gastric carcinomas and is gaining recognition as a prognostic marker and for therapeutic intervention.

Declarations

a. Ethics approval and consent to participate

In accordance with the Declaration of Helsinki, ethical approval for the study was obtained from the Health and Research Ethics Committee of the Jos University Teaching Hospital, Lamingo, Plateau State, Nigeria with the reference number: JUTH/DCS/IREC/127/XXXI/385.

Confidentiality and anonimity of data extracted was ensured.

Clinical trial number: not applicable.

Human Ethics and Consent to Participate declarations: Not applicable.

This study adhered to the Declaration of Helsinki.

b. Consent to publish

Not applicable.

c. Availability of data and materials

The data used and analyzed as well as materials for this study are available on request from the corresponding author.

d. Conflicts of interest

There is no potential conflict of interest

e. Funding

There is no funding recieved for this study.

f. Authors contributions

Conceptualization: IAO; Methodology: IAO, BVK, POA; Investigation: IAO; Microscopy; IAO, BVK, POA, Original draft: IAO, DAA, OM, MBL, Writing and editing: IAO, DAA, OM, MBL. All authors have read and approved the final version of the manuscript.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A. Global Cancer Statistics 2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;3(2):209–49.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Pineros M et al. Global Cancer Observatory: Cancer Today. International Agency for Research on Cancer; 2020. Accessed May, 30 2022.gco.iarc.fr/today
3. Mandong BM, Madaki AJ, Manasseh AN. Malignant Disease in Jos: A Follow Up. Ann Afr Med: 2003; (2):42–6.
4. Ogunbiyi JO. Epidemiology of Cancer in Ibadan: Tumors in Adults. Arch Ib Med. 2000;1:9–12.
5. Obiorah CC, Ray-Offor E. Epidemiology of Gastrointestinal Malignancies in Nigeria: Port Harcourt Cancer Registry Study. Oncol J India. 2020; (4):1–7.
6. Oluwasola AO, Ogunbiyi JO. Gastric Cancer: Aetiological, Clinicopathological and Management Pattern in Nigeria. Niger J Med. 2003;12:177–86.
7. Bakari AA, Ibrahim AG, Gali BM, Dogo D, Ngadda HA. Pattern of Gastric Cancer in North Eastern Nigeria: A Clinicopathological Study. J Chin Med. 2010;5:211–5.

8. Abdulkareem FB, Onyekwere CA, Awolola NA, Ajekigbe AT. Clinicopathological Review of Malignant Gastric Tumors in Lagos, Nigeria. Nig Q J Hosp Med. 2010;20(2):49–54.
9. National Comprehensive Cancer Network (NCCN). Gastric Cancer. 2020. www.nncn.org accessed July 6, 2022.
10. Green D, Ponce de Leon S, Leon- Rodriguez E, Sosa-Sanchez R. Adenocarcinoma of the Stomach: univariate and multivariate analysis of factors associated with survival. Am J Clin Oncol. 2002;25(1):84–9.
11. Mandong BM, Manasseh AN, Tanko MN, Echejoh GO, Madaki AJ. Epidemiology of Gastric Cancer in Jos University Teaching Hospital, Jos: a 20-year review of cases. Niger J Med. 2010;19(4):451–4.
12. Chew-Wun W, Chin-Wen C, Wen- Chang L. Gastric Cancer: Expert Reviews Mol Med. 2002;4(6):1–12. 10.1017/S1462399402004337.
13. Normark S, Nilson C, Normark BH, Homef MW. Persistent Infection with Helicobacter Pylori and The Development of Gastric Cancer. Adv Cancer Res. 2003;90:63–89.
14. Edington GM, Maclean CM. A Cancer Rate Survey in Ibadan Western Nigeria. Brit Cancer. 1965:1947–181.
15. El-Omar EM, Carrington M, Chow H. Interleukin – 1 Polymorphism Associated with Increased Risk of Gastric Cancer. Nature. 2000;404:308–402.
16. El-Omar EM, Rabkin CS, Gammon MD. Increased Risk of Non-cardia Gastric Cancer Associated with Proinflammatory Cytokine Gene Polymorphisms. Gastroenterol. 2003;124:1193–201.
17. Xiu-feng L, Yun-Xiang Z, Ting-goo, Z, Yang M. The Expression of VEGFR2 and VEGFR3 in Early Gastric Cancer and its Clinical Significance. J Bioprocess Biotech.2018; (8):325. Doi: 10:4172/2155-9821.10000325.
18. Teng L, Jing Y, Xinyu L, Weiguo R, Yue Z, Bangwei C. VEGFR2 as a Novel Predictor of Survival in Gastric Cancer: A Systematic Review and Meta-analysis. Elsevier Pathol Pract. 2018;214:560–4.
19. Hongxia G, Xiaoje J, Guangxian L, Min Z, Shiwei N, Wangjie C. Licoflavone A Suppresses Gastric Cancer Growth and Metastasis by Blocking the VEGFR2 Signaling Pathway. J Oncol. 2022 (2).
20. Komolafe AO, Ojo SO, Olasode BJ. Gastric Malignancies and Associated Premalignant Lesions in a Teaching Hospital in South West Nigeria. Afr J Biotechnol. 2008;7(13):2104–11.
21. Kwaghe BV, Mandong BM, Manasseh AN, Ngadda HA, Emmanuel I, Amos AG. Clinicopathological Study of Gastric Malignancies in Jos University Teaching Hospital, Jos, Nigeria. Jos J Med 2012; (11): 51–9.
22. Ebili HO, Oluwasola AO, Akang EU, Ogunbiyi JO. Clinicopathological Features of Gastric Carcinoma in Ibadan, Nigeria. Niger Med J. 2015;11(2):126–31.
23. Mabula JB, Mchembe MD, Koy M, Chalya PL, Massaga F, Rambau PF, et al. Gastric Cancer at a University Teaching Hospital in Northwestern Tanzania: A Retrospective Review of 232 Cases. World J Surg Oncol. 2012;10(257). https://doi.org/10.1186/1477-7819-10-257.

24. Elmajjaoui S, Ismaili N, Zaidi H, Elkacemi H, Hassouni K, Kebdani T, et al. Epidemiology, Clinical, Pathological and Therapeutic Aspects of Gastric Cancer in Morocco. Clin Cancer Investig J. 2014;3(1):3–8.
25. Lodenyo HA, Rogena E, Sitati S. Gastric Cancer in Kenya. Afr J Health Sci. 2017;31(1):51–8.
26. Xueru Z, Yiwei W, Wenji X, Ruifen W, Lifeng W, Mei-ling Z, et al. The VEFGR2 Protein and The VEGFR2 rs1870377 A > T Genetic Polymorphism are Prognostic Factors for Gastric Cancer. Cancer Biol Therapy. 2019;4:497–504.
27. Li X, Zhu X, Wang Y, Wang R, Wang L, Zhu ML, Zheng L. Prognostic value and association of Lauren classification with VEGF and VEGFR-2 expression in gastric cancer. Oncol Lett. 2019;18(5):4891–9.

Figures

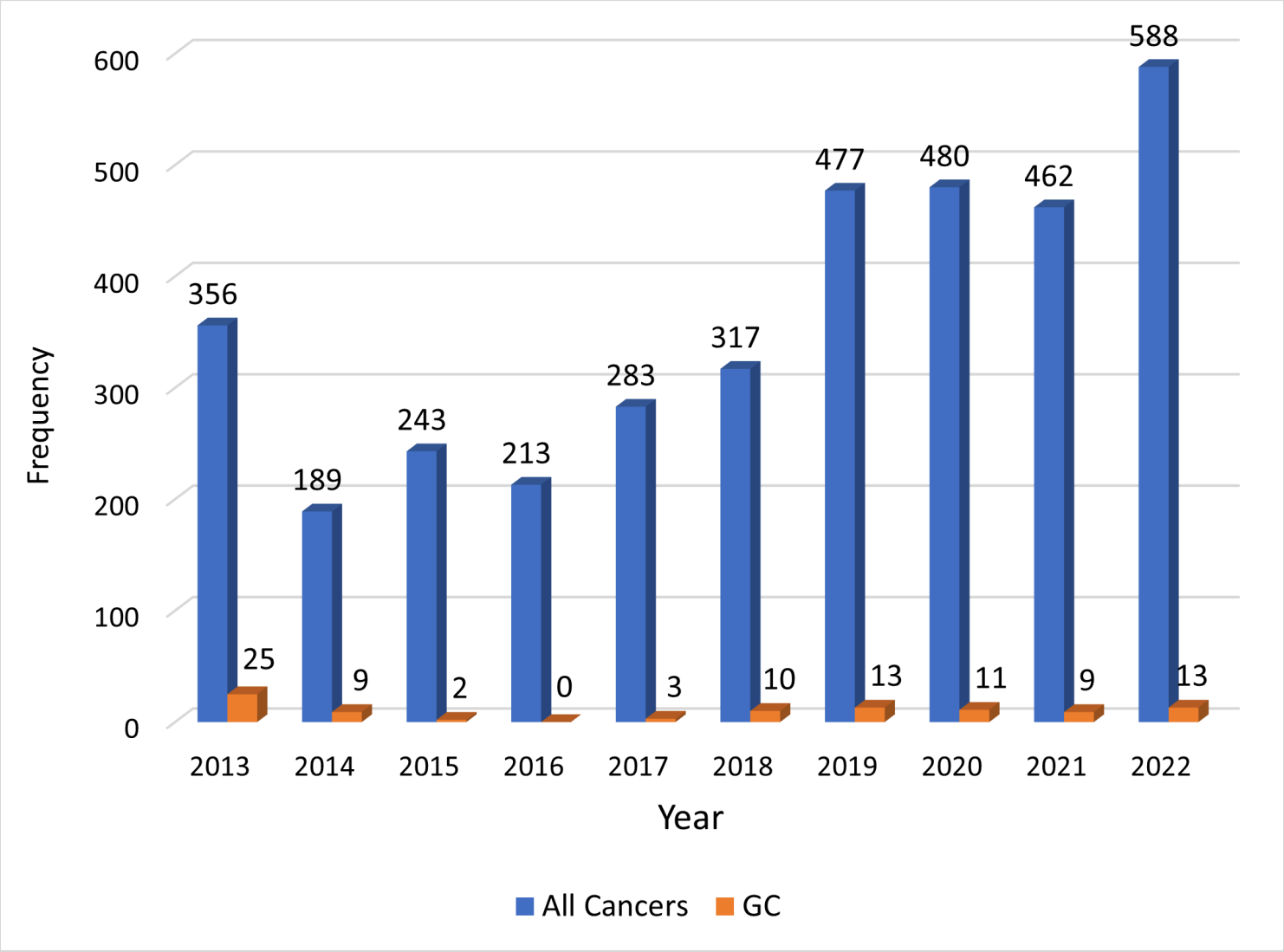


Figure 1

Yearly frequency of GC in Jos University Teaching Hospital Between 2013 to 2022

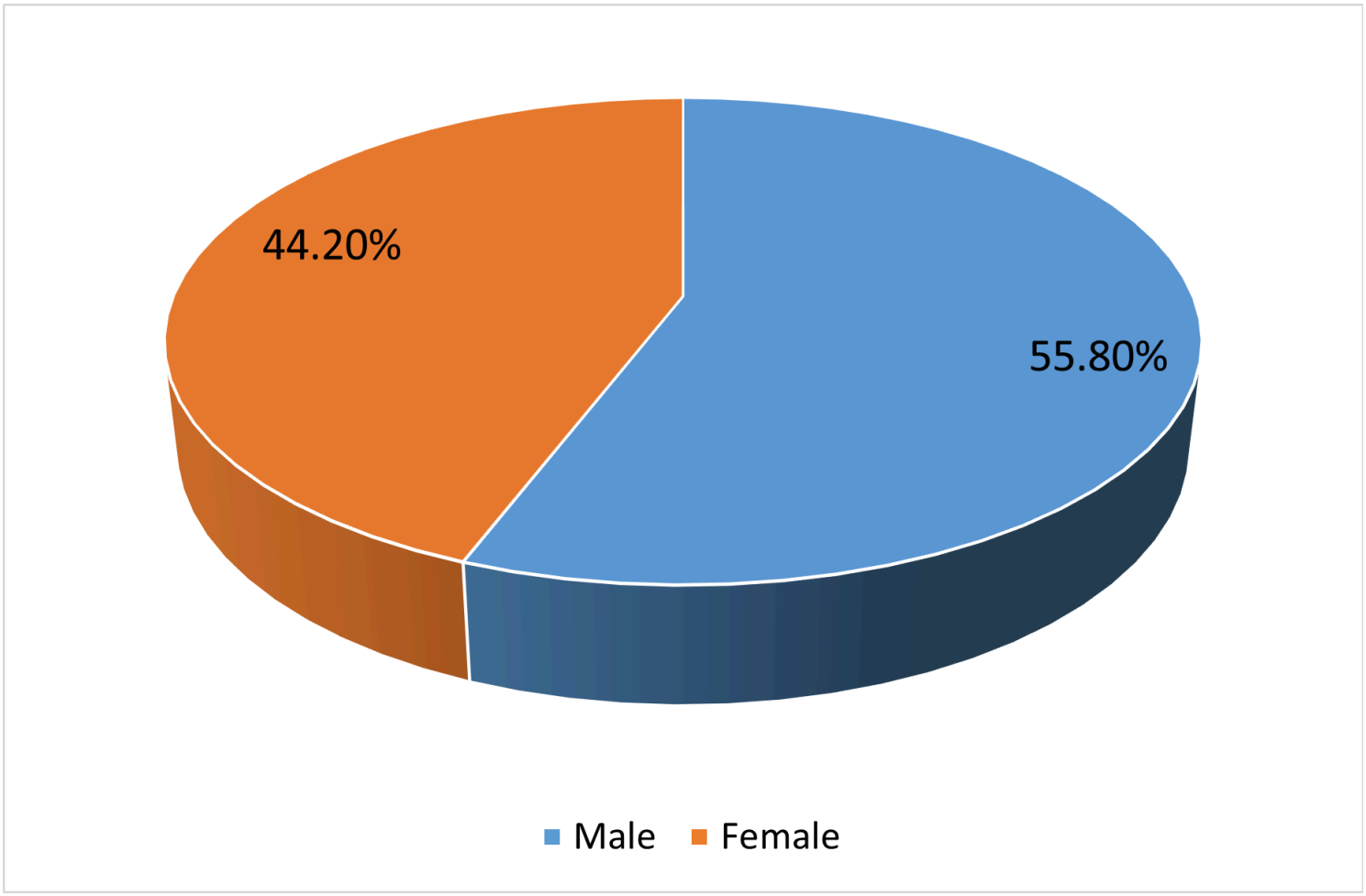


Figure 2

Sex distribution of GC

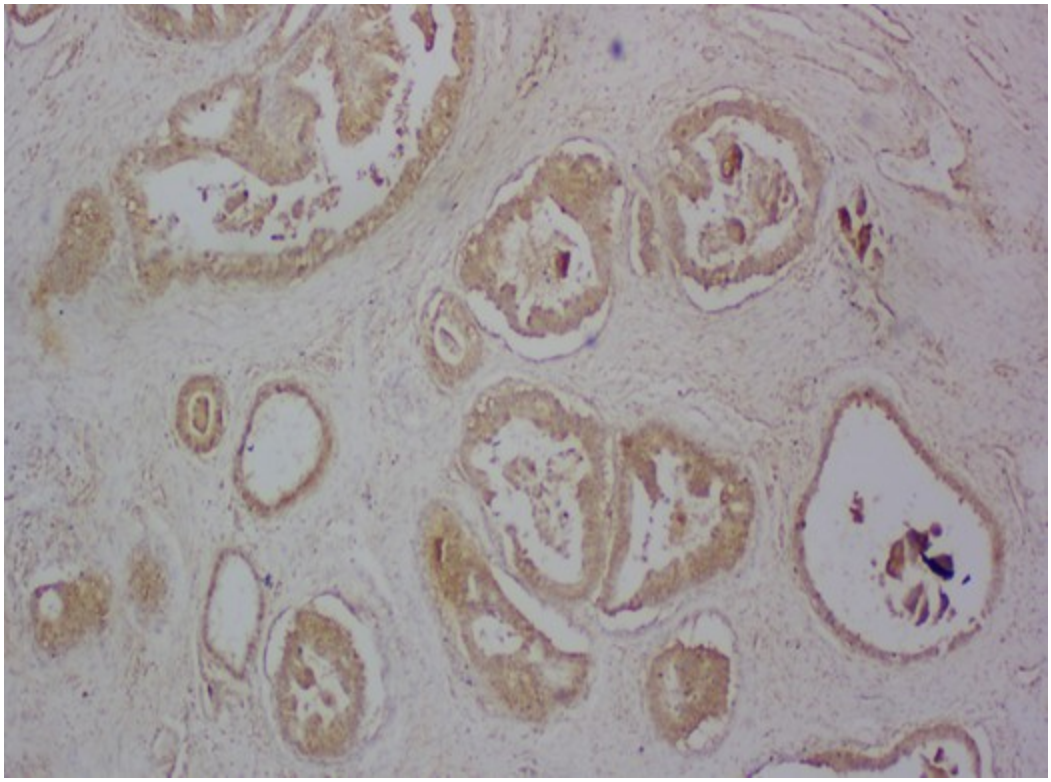


Figure 3

A well differentiated carcinoma, light brown VEGFR2 stain

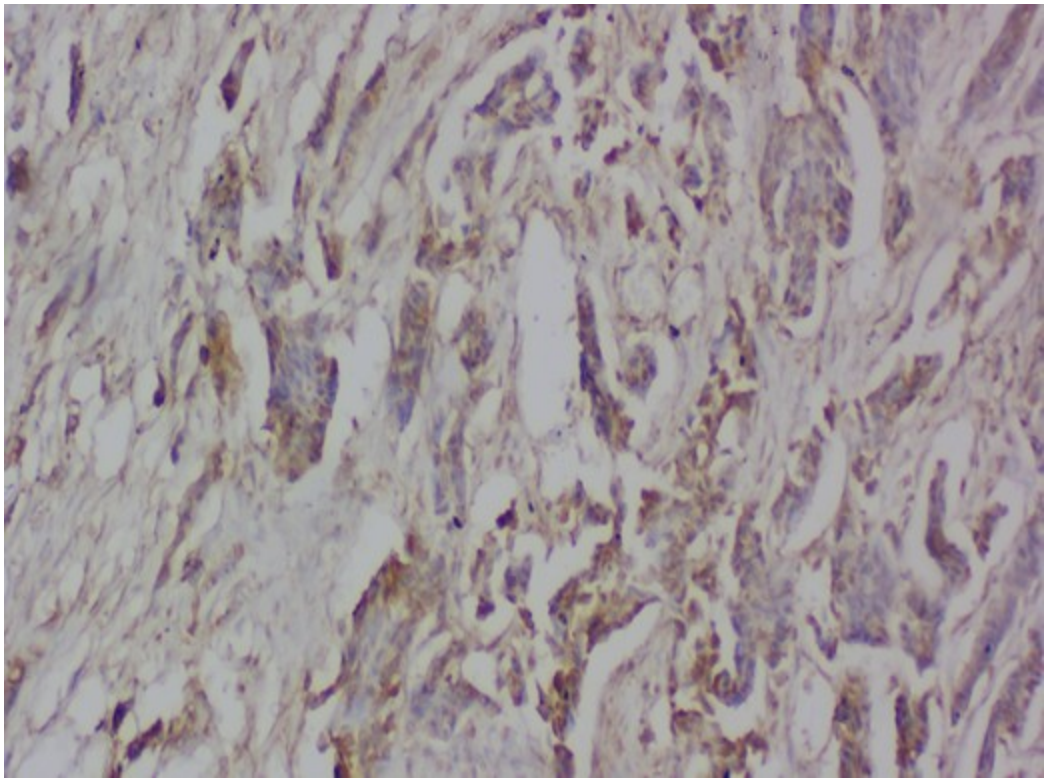


Figure 4

A poorly differentiated carcinoma, dark brown VEGFR2

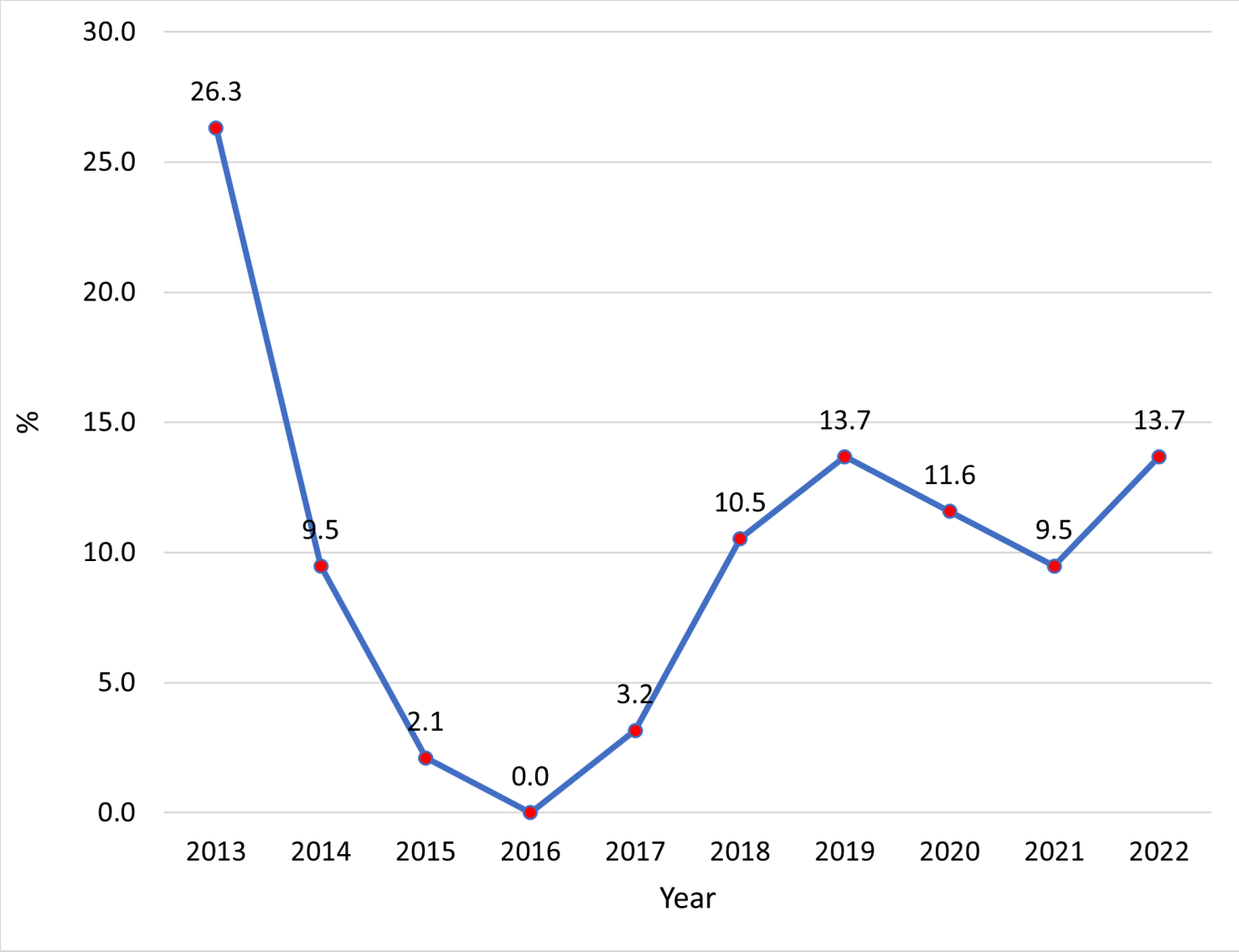


Figure 5

A Ten-Year trend of GC in Jos University Teaching Hospital