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Expression of SOX9 in Gastric Adenocarcinoma – An Immunohistochemical Study.

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KEYWORDS

SOX 9(SRY- related high–mobility group (HMG) box), gastric carcinoma, prognosis, biological behaviour.

ABSTRACT:

Background:

Gastrointestinal tract (GIT) malignancies constitute about 27% of total cancers and 20% of all cancer deaths, with the highest burden of 62% in Asia. As GIT malignancies are on the rise in developing countries, SOX9, a potential biomarker belonging to the SOX family, helps in evaluating the clinicopathological and prognostic implications of gastric carcinomas.

Methodology:

After obtaining ethical clearance, the study was done after reviewing patients' medical records in the Department of Pathology, Tertiary Care Hospital located in Kanchipuram. Histopathological and immunohistochemical evaluation was done on 40 representative blocks of gastric carcinoma. Data was entered in MS Excel worksheet and analyzed using SPSS software version 27.

Results:

In the present study, SOX9 showed >3 weighted score in 5 cases of poorly differentiated carcinoma (41.6%), 4 cases of moderately differentiated carcinoma (30.76%) and <3 weighted score in all well differentiated carcinomas. Statistical significance was found between histological grading and the weighted score of SOX9 (p-value <0.005).

Conclusion:

In this study, we observed that high expression of SOX9 was related to tumor progression. This indicated that there is a strong association between SOX9 expression and gastric carcinogenesis. Therefore, SOX9 can be used as a novel prognostic marker for the diagnosis of gastric carcinoma.

Introduction:

Gastric cancer ranks as the fifth most common malignancy and it is the third most cause of cancer related death worldwide[1]. Gastric cancer in young adults is increasing day by day and they are more aggressive and presents at an advanced stage[2]. Eastern Asia, Eastern Europe and South America have higher incidence and mortality rates for gastric carcinoma[3].The etiology of gastric carcinoma is multifactorial and various genetic and dietary factors have been attributed. H.pylori infection remains the main cause of gastric adenocarcinoma and recognized by WHO as class I carcinogen[4] . The major prognostic tool in gastric carcinoma is TNM staging, but still there is a bizarre aggressiveness of the disease within the TNM stage[5]. And also due to tumor heterogeneity, there is variable prognosis and treatment resistance in gastric carcinoma patients[6]. Therefore, acquiring a novel prognostic biomarker is necessary for the early detection of gastric carcinoma, for distinguishing the tumor biology and to develop individualized treatment strategies.

A member of the SOX family, SOX9 (SRY- related high-mobility group (HMG box) the transcription factor, is a versatile regulator of development, proliferation and tumorigenesis[4]. The physiological function of SOX9 includes chondrogenesis, neurogenesis, male sex determination, neural crest development and stem cell maintenance[7]. Also, SOX9 is expressed in all developing gastric epithelial cells during embryonic development[8]. Surface epithelial progenitors lose SOX9 expression whereas non-surface epithelial cells (i.e. glandular) maintain SOX9 expression in the first week of postnatal period and during the second week expression becomes sparser in the base and by day 28 it is most enriched in the mucous neck cells and isthmus regions[9].

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SOX9 affects differentiation, cell proliferation, apoptosis, invasion and migration in many cancer[10]. It has the ability of self-renewal and differentiation to both SOX9 positive and SOX9 negative cells[11]. According to the specific tissue, the function and expression of positivity and negativity in SOX-9 is altered in various cancers[4].

SOX9, being a cancer stem cell marker is involved in initiation of tumor through Wnt/β-catenin pathway and also invasion of tumor through TGFb/Smad signaling along with co-activation of NOTCH pathway[12]. Epithelial-mesenchymal transition, high proliferative ability and chemotherapy resistance are seen in SOX 9 positive cells[13]. Also on the contrary, SOX 9 expression was decreased in gastric cancer due to tumor methylation and is inversely related with advanced tumor stage, vascular invasion and nodal metastasis[14]. Therefore, the underlying mechanism of SOX 9 function in gastric carcinoma still remains unclear and it is less studied in the literature. This study aims to assess the immunohistochemical expression of SOX9 and its association with clinicopathological factors of gastric carcinoma patients for better understanding of the disease.

Materials & Methods:

This retrospective and prospective study was carried out in the Department of Pathology, Tertiary Care Hospital located in Kanchipuram over a period of 13 months from November 2022 to November 2023. 40 gastrectomy specimens in the age group of 40-80 years were studied. This study was conducted after getting approval by Institutional ethics Committee (IEC) with reference number MMCH&RI IEC/PG/44/OCT/22.

Inclusion criteria:

1. All cases of gastrectomy diagnosed as gastric adenocarcinomas are included in the study.

2. Most representative blocks are chosen.

Exclusion criteria:

1)Tissue blocks of known patients of gastric carcinomas who underwent preoperative therapeutic chemotherapy or radiotherapy.

2)Recurrent cases of any gastrointestinal tract malignancies.

3)Patients diagnosed as neuroendocrine tumors and lymphomas.

4) Samples received as small biopsies.

The data was collected after reviewing the medical records from department of pathology and all the clinicopathological details of the patient were retrieved. All the prospective gastrectomy specimens received were fixed with 10% formalin for 24 hours. The specimens were grossly examined and then multiple bits were taken from representative areas. The tissue bits were processed and embedded in paraffin blocks. Along with it the retrospective blocks were also collected.

Immunohistochemical analysis of SOX9 was carried out in 3-4µm sections of gastric carcinoma cases. First tissues were deparaffinized and hydrated. Heat induced antigen retrieval with enzyme blockage was done, following which primary and secondary antibody were added and then counterstained with hematoxylin and mounted. Section from salivary gland was taken as positive control for SOX9. Immunohistochemical expression of SOX 9 was evaluated by two independent observers using light microscopy.

The total score of SOX 9 was done after assessing the following parameters[21]:

1. Intensity of stain

2. Percentage of positive tumor cells (Nuclear positivity)

Intensity of SOX 9 immunostaining were scored as follows:

0 - Negative

1+ - Weak

2+ - Moderate

3+ - Intense

Percentage of positive tumor cells were scored as follows:

0 - <5%

1 - 5-25%

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2- 26-50%

3 - 51-75%

4 - >75%

Weighted score = staining intensity x percentage of positive tumor cells

< 3 – Negative

>3 – Positive

Statistical Analysis:

The data collected was entered in Microsoft excel sheet, compared and analyzed for statistical significance by SPSS version 27.0 IBM. Chi-square test was used to assess the association between variables and the p value of < 0.05 was considered statistically significant.

Results:

In the present study, the age of the patients ranged from 41-80years with a mean age of 61.5 years.

Out of 40 gastric carcinoma cases, 25(62.5%) were male and 15(37.5%) were female with a M:F ratio of 1.6:1 **(Table 1).** Most of the tumor is located in the (30%) antrum followed by (25%) pylorus, (17.5%) pyloric antrum and remaining (15%) were located in body, (10%) lesser curvature and (2.5%) in greater curvature **(Table 1)**.

Table 1: Distribution of clinicopathological variables - age, gender and location of gastric cancer cases

Clinicopathological Variables	**Frequency (n)**	**Percentage (%)**
Age (years)		
41-60	18	45%
61-80	22	55%
Gender		
Male	25	62.5%
Female	15	37.5%
Location		
Antrum	12	30%
Pylorus	10	25%
Pyloric antrum	7	17.5%
Body	6	15%
Lesser curvature	4	10%
Greater curvature	1	2.5%

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The majority of the patients presented with (40%) abdominal pain followed by (22.5%) weight loss, (15%) vomiting, (12.5%) loss of appetite and (10%) early satiety **(Figure 1).**

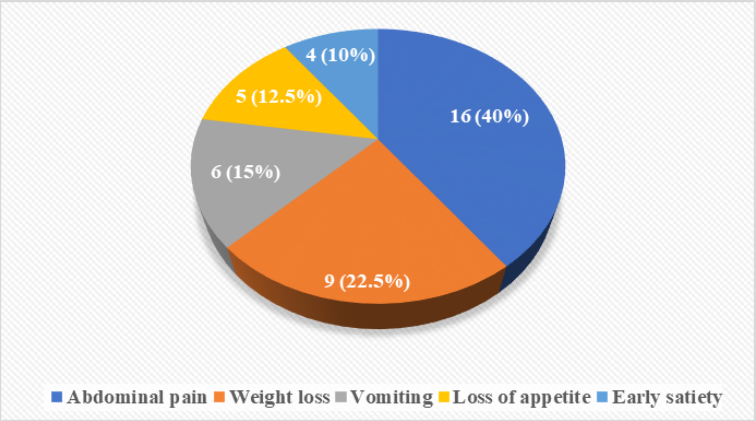

Figure 1: Distribution of clinical features among the study population

According to Lauren's classification, 25(62.5%) were intestinal type, 12 (30%) were diffuse type and remaining 3(7.5%) were mixed type **(Figure 2).** Among the 40 cases, 15(37.5%) were well differentiated, 13(32.5%) were moderately differentiated and 12(30%) were poorly differentiated **(Figure 3)**

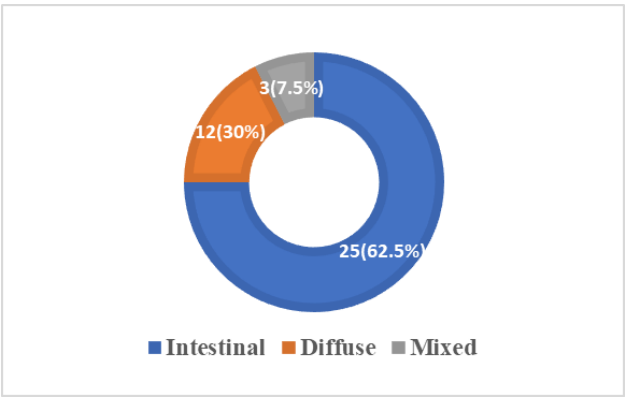

Figure 2: Distribution based on histological type

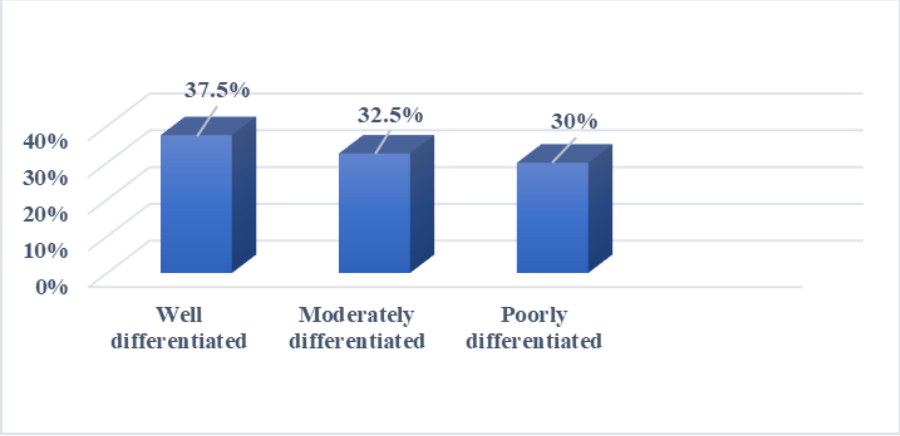

Figure 3: Distribution based on histological grades of gastric carcinoma

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Table 2: Distribution of gastric carcinoma cases based on TNM staging and lymph node (LN) status

		Frequency (n)	Percentage (%)
TNM stage	T1	2	5%
	T2	8	20%
	T3	7	17.5%
	T4	23	57.5%
LN status			
	Present	34	85%
	Absent	6	15%

Out of 40 gastric carcinoma cases, 57.5% were categorized as T4, 17.5% were categorized as pT3, 20% were categorized as pT2 and remaining 5% were categorized as pT1**(Table 2)**. Lymph node metastasis was present in 34(85%) cases and absent in 6(15%) cases **(Table 2).**

Among the 40 gastric carcinoma cases, 9(22.5%) showed positive and 31(77.5%) showed negative scoring for SOX9 **(Table 3).**

Table 3: Distribution of gastric carcinoma cases based on SOX9 weighted score

SOX9 Weighted score = (Staining intensity x Percentage of positive tumor cells)	**Frequency (n)**	**Percentage (%)**
Positive, >3	9	22.5%
Negative, <3	31	77.5%

In this study, there is a positive association between age and weighted score of SOX9 (p-value = 0.023) **(Table 4)**. Among the 18 (45%) patients of 40-60yrs age group, 1 showed positive scoring and 17 showed negative scoring for SOX9. And among the 22(55%) patients of 61-80yrs, 8 were SOX9 positive and 14 were SOX9 negative.

SOX9 expression is proportionate with the histological grading of the tumor. Among the 12 cases of poorly differentiated gastric carcinomas, 5 showed positive scoring and among 13 moderately differentiated carcinomas 4 showed positive scoring and all the 15 well differentiated carcinomas showed negative scoring for SOX9. Statistical significance exists between weighted score of SOX9 and histological grade i.e positive expression was more in poorly differentiated than moderately and well differentiated gastric carcinomas

(p-value = 0.025)**(Table 4).**

SOX9 weighted score did not show any significant association with gender, clinical features, location,

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histological type, tumor stage and lymph node metastasis (**Table 4)**.

Table 4: Correlation of SOX 9 expression with clinicopathological variables

Clinicopathological Variables	SOX 9		P-Value
	>3 - Pos	< 3 - Neg	
Age (years)			
41-60	1	17	0.023*
61-80	8	14	
Gender			
Male	8	17	0.067
Female	1	14	
Clinical features			
Abdominal pain	6	10	0.219
Weight loss	1	8	
Vomiting	2	4	
Early satiety	0	4	
Loss of appetite	0	5	
Location			
Antrum	4	8	
Pylorus	2	8	0.767
Pyloric antrum	2	5	
Body	1	5	
Lesser curvature	0	4	
Greater curvature	0	1	
Histological type (Lauren's)			
Intestinal	5	21	0.135
Diffuse	4	7	
Mixed	0	3	

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Histological grade			
Well differentiated	0	15	0.025*
Moderately differentiated	4	9	
Poorly differentiated	5	7	
TNM staging			
T1	0	2	
T2	1	7	0.543
T3	1	6	
T4	7	16	
Lymphnode metastasis			
Present	9	25	0.192
Absent	0	6	

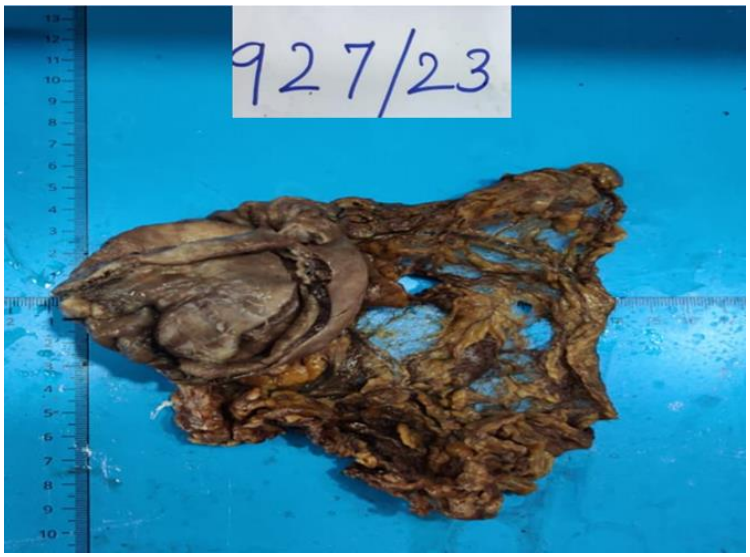

Figure 4: Macroscopic image of distal gastrectomy specimen

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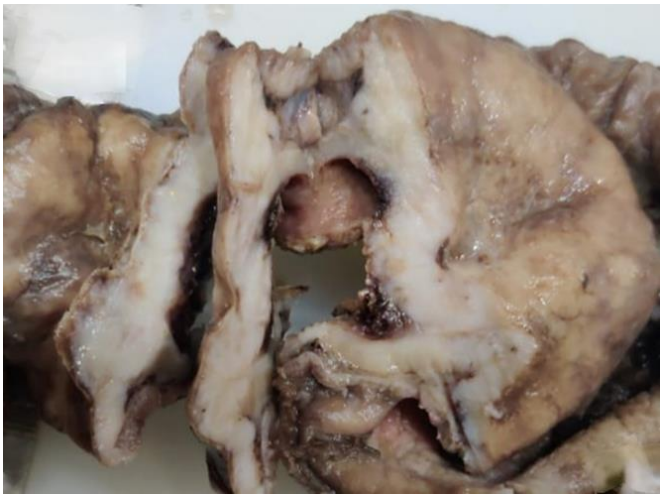

Figure 4.1: Cut surface showing a grey white tumor along the lesser curvature

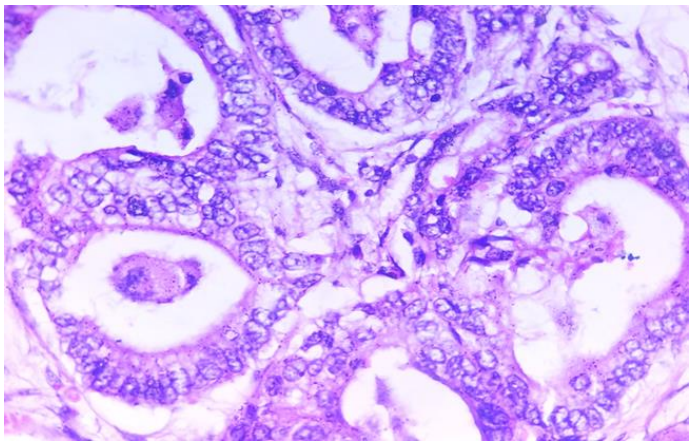

Figure 5: H&E 40x showing well differentiated gastric adenocarcinoma

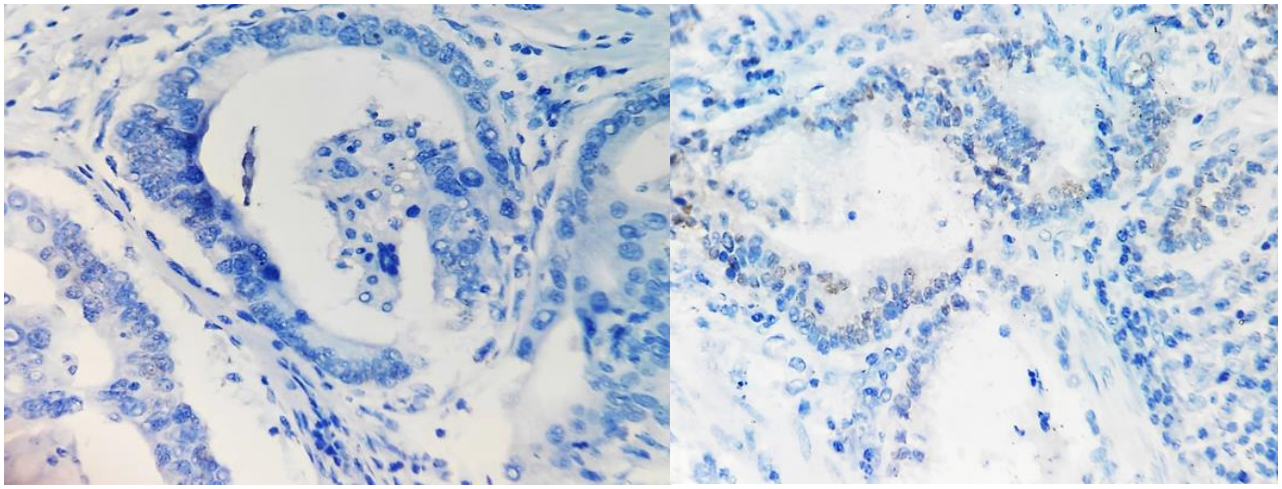

Figure 5.1 & 5.2: IHC 40x - showing negative expression of SOX9 in well differentiated gastric adenocarcinoma i.e. < 3 weighted score (Negative (Fig 5.1) and weak (Fig 5.2) nuclear intensity for SOX9).

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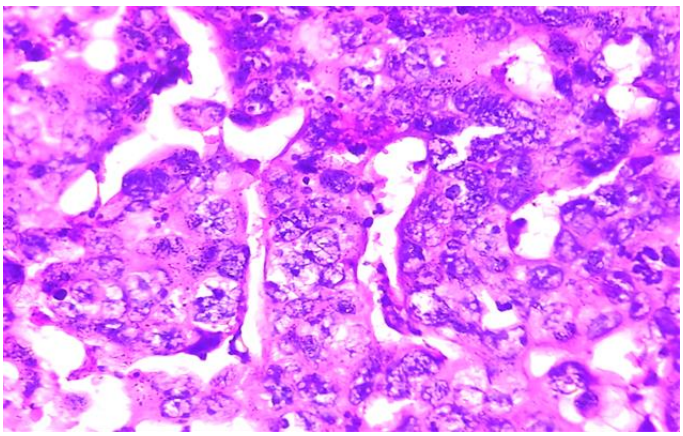

Figure 6: H&E 40x showing moderately differentiated gastric adenocarcinoma

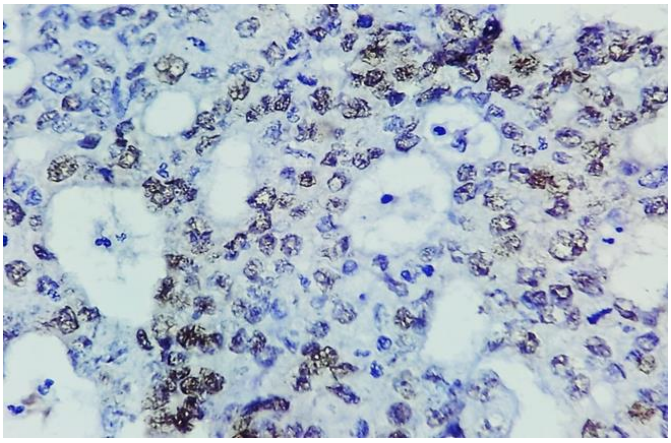

Figure 6.1: IHC 40x – showing positive expression of SOX9 in moderately differentiated gastric adenocarcinoma i.e. >3 weighted score (Moderate nuclear intensity for SOX 9)

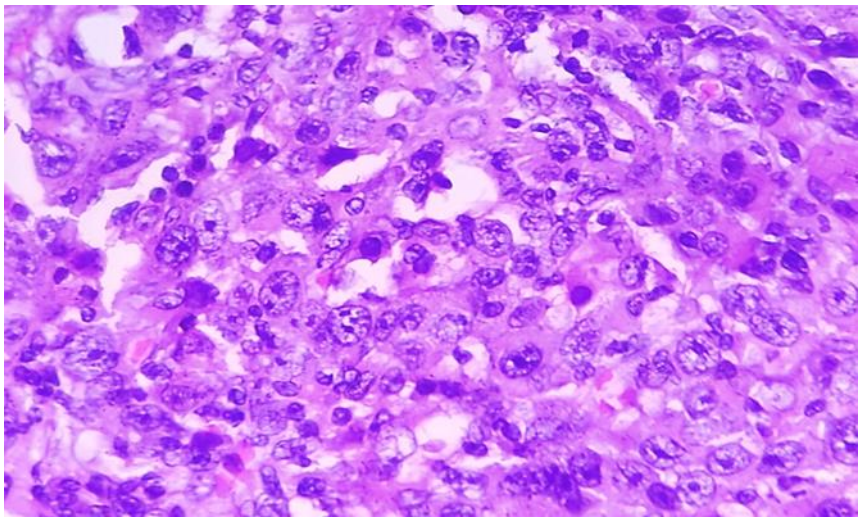

Figure 7: H&E 40x showing poorly differentiated gastric adenocarcinoma

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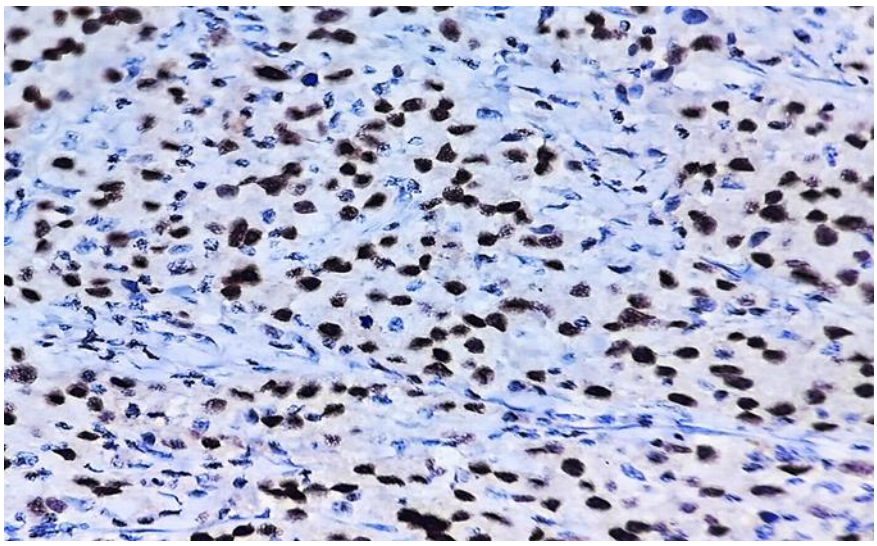

Figure 7.1: IHC 40x – showing positive expression of SOX9 in poorly differentiated gastric adenocarcinoma i.e. >3 weighted score (High nuclear intensity for SOX 9).

Discussion:

Gastric cancer is one of the leading causes of cancer death worldwide because of its high malignant potential and recurrence rate. The incidence varies in different parts of the world and in different ethnic groups based on the lifestyle, food habits and genetic factors. The etiology varies due to clonal evolution of tumor cells and because of that, it is associated with treatment resistance and variable prognosis. SOX 9 plays a key role in stem cell maintenance, thereby regulating tumorigenesis as an oncogene in various cancers including gastric cancer. SOX 9 is expressed in normal gastric mucosa, intestinal metaplasia and gastric carcinoma. So in this study, we performed an immunohistochemical analysis to evaluate the clinicopathologic and prognostic significance of SOX 9 expression in different grades of gastric carcinoma.

In our study, the maximum number of patients with gastric carcinoma were in the age group of 61-80 years (55%). The mean age of the patients recruited in the study was 61.5years. Barad et al[15] also showed that the mean age of gastric carcinoma patients was more than 60 years, which was closer to our study. Kamal et al[16] also showed that gastric carcinoma in male patients (62.5%) were more than female patients (37.5%), which was similar to our study.

In the present study, majority of the patients presented with abdominal pain (40%) followed by weight loss (22.5%), vomiting (15%), loss of appetite (12.5%) and early satiety (10%) which was similar to the study done by Nilam et al[17].In our study, the most common site of gastric carcinoma was in the antral region because of increased H.pylori infection in developing countries and low socioeconomic class. This was similar to the study done by Barad et al[15] and Begnami et al[18]. In the present study, (62.5%) intestinal type was more common than (30%) diffuse type and it was similar to the study by Link et al[19]. Upon histological grading of the tumor, the most common differentiation was well differentiated (37.5%) followed by moderately differentiated (32.5%) and poorly differentiated (30%) gastric carcinoma. This is mainly because of the awareness and availability of medical facilities and screening programmes. But it was contrary to the study done by Warsinggih et al[20] where poorly differentiated carcinoma constituted the most common type.

In our study, we categorized SOX 9 scoring based on staining intensity and percentage of positive tumor cells stained into positive and negative. Among the 40 gastric carcinoma cases, most of the tumors (77.5%) showed low expression and (22.5%) showed high expression. This was consistent with the study done by Zhang et al[21]. Unlike in the larger scale studies of Luo et al[22] and Patricia et al[23], the incidence of high SOX9 expression in gastric carcinoma were 31.8% and 82.6% respectively.

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Only few studies showed a positive correlation of SOX9 expression with age and our study is one among them. The same was said by Wang et al[24], where high expression of SOX9 was significantly associated with age. There is upregulation of SOX9 expression from well differentiated to poorly differentiated gastric carcinoma and it was proportionate with the histological grading. This was similar to the study done by Zhang et al [21]and Wang et al[24], where overexpression of SOX9 had a significant association with tissue differentiation.

Among the study population, 7(30.4%) out of 23 cases showed positive score in pT4 stage, 1(14.2%) out of 7 cases showed positive score in pT3 stage, 1(12.5%) out of 8 cases showed positive score in pT2 stage and all 2 cases in pT1 stage showed negative score and it was not statistically significant. This was similar to the study done by Zhang Et al [21]. But adversely Wang et al[22], Shao et al[25] and Zhou et al[26] showed positive correlation with advanced stage of the tumor and it is related to the emergence of lymphnode metastasis. Lymphnode status showed (85%) positivity and (15%) negativity in metastasis and showed no significance with SOX9 expression. This was in alignment with Zhang et al[21]. But lymphnode positivity was seen more in advanced stage of the disease than early disease and it was concurrent with the study done by Wang et al[22] and Shao et al[25].

And also, other parameters like gender, clinical features, location and histological type did not show any statistical significance with SOX9 expression. This was similar to the study done by Zhang et al[21] and Patricia et al[23].

Conclusion:

In this study**,** we observed that there is over expression of SOX 9 as the tumor progresses and this could be a potential prognostic factor and a therapeutic target for gastric carcinoma patients. However, further studies are needed to understand the role of SOX9 expression in gastric cancer because of the diverging nature of cancer stem cells.

Limitations:

The major limitation of the study was the smaller sample size and lack of post-op follow-up data of the selected cases. Also, the study did not represent the entire population of the region, only cases in our tertiary care hospital were taken as study population.

Conflicts of interest:

The authors of the study declared that there are no conflicts of interest.

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