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Original Research Article

Clinico-pathological evaluation of gastric adeno carcinoma with reference to ki-67 LI immuno-staining

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ABSTRACT

Background: Gastric cancer is a life-threatening disease accounting for the one of the most common types of disease and second most that cause the cancer which lead to death. Many molecular markers were established as a possible prognostic factor apart from routine grading and TNM staging. The variable prognosis of gastric cancer within a pathological grade necessitates a newer marker which can be correlated with the prognosis and aggressiveness of the disease. ki-67 is a nuclear protein that is known as a marker of cellular proliferation and ribosomal RNA transcription. According to analysis, the ki-67 is a nuclear proliferation antigen affecting the health of the people as it cannot be cycle in the resting phase. Moreover, the fraction of ki-67 is clinical course of various cancers.
Aim: To evaluate the expression of ki-67 LI in gastric cancer and correlate the findings with various clinico-pathological features.
Materials and Methods: Prospective study was conducted from October 2018 to September 2021 at the department of Pathology, MKCG Medical College, Berhampur, Odisha. Two sets of 3–4-micron thickness of tissue sections prepared from blocks of histologically confirmed cases of gastric adenocarcinoma were taken, one for routine H&E and other for ki-67 LI IHC study. IHC protocol of DAKO was followed along with DAB visualisation. The results were correlated with different clinico-pathological features of Gastric cancer.
Results: Higher ki-67 LI was correlated significantly with tumour location, histological grade and type but not with age and sex.
Conclusion: In our study, IHC assessment of ki-67 LI correlates well with histological grade and type of tumour. ki-67 LI can be taken as a useful method in identifying aggressiveness of the tumour with an indication of adjuvant chemotherapy. Post-operative follow-up and large sample size could throw more light.

1. Introduction

Diseases of stomach are a frequent cause of morbidity and mortality worldwide. Inflammatory lesions of stomach like chronic gastritis and peptic ulcer disease are most common cause of morbidity while adenocarcinoma of stomach is the leading cause of death and comprises more than 90% of all gastric cancers.[1]

There are different types of epidemiologic that indicating the issues related to the GC and influencing the health of the individual. These are including high salt intake, cigarette smoking, high fat, blood group A, whereas H.

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pylori infection is established as an independent factor in the development of gastric cancer.[2] According to analysis, the deaths in both sexes worldwide (723,000 deaths, 8.8% of the total).[3,4]

There is multistep process is being used for managing the issues related to GC and having a significant impact on the Gastric glands, intestinal metaplasia (IM), dysplasia (DYS), and ultimately gastric cancer.[5]

Though overall prognosis for all patients is between 4% to 13% According to analysis, the 5-year survival rate was 46% and 89% for "early" carcinoma.[6]

The outcome of the gastric cancer depends upon the prognostic factors as tumour staging and size, lymph node status, lympho-vascular invasion and molecular biomarkers like tumour suppressor gene & proliferation marker like ki-67.[7]

ki-67 is a nuclear protein that is known as a marker of cellular proliferation and ribosomal RNA transcription.[8] It is widely used in routine pathological investigation and is an established prognostic and predictive marker in various cancer.[9] Recently various researches have been focused on ki-67 LI in many cancers and correlation as a prognostic marker.[10] It has been observed that the ki-67 proliferating index increased during the process of gastric carcinogenesis from intestinal metaplasia (IM) to gastric cancer (GC).[11]

According to analysis of the previous reports the high level of ki-67 is having direct impact on the behaviour of the individual that because of the aggressive tumour that known as adverse predictors.

2. Aim

To evaluate the expression of ki-67 LI in gastric cancer and correlate the findings with various clinico-pathological features.

3. Materials and Methods

The present prospective study was conducted in the Department of Pathology, M.K.C.G Medical college, Berhampur. Study duration was for a period of 3 years, from October 2018 till September 2021. Detail clinical data collected from records and Immuno-histochemical evaluation of ki-67 LI done, on histologically diagnosed cases of gastric adeno-carcinoma.

Routine H&E stain and IHC [Dako] for ki-67 LI done on each selected block. We used, primary antibody as ready to use Biogenex rabbit monoclonal Ab in PBG with carrier protein and preservative. Secondary antibody used was ready to use Dako envision TM,Flex/HRP SM802. DAB was used as the visualising agent. The reaction was considered positive for any positive nuclear staining. Quantification was done through assessment of marking index (MI). MI-ki67 was expressed as percentage of nuclear positivity after counting 500 cells in hotspot areas.

The ki-67 LI score was correlated with clinic-pathological factors, like age, sex, location, type, and grade of tumour. We found varied ki67 scores ranging from 10 to 90 percentages, with an average of 45%. As there is no unanimous decision on ki-67 LI score to level as high or low, we took the average score of 45% i.e. carcinomas with more than 45% positivity were taken as high ki-67LI and less than 45% as low ki-67LI.

3.1. Statistical ***analysis***

For the analysis of the data Chi-Square and IBM SPSS were applied.

3.2. Observation and Result

Table 1: Age distribution of patients taken for study

Age in years	No of patients	Percentage (%)
31 – 40	8	15
41 – 50	11	21
51 – 60	15	28
61 – 70	16	30
71 – 80	3	6
Total	53	100

In present study, age range from 32-80 yrs & mean age was 64.65 years. Majority, 16 (30%) cases belonged to 61-70 years.Table 1

Table 2: Gender Based Distribution

Gender	No of patients	Percentage (%)
Male	40	75
Female	13	25
Total	53	100

In our study, maximum no. of cases were Male, 40 (75%).Table 2

Table 3: Location of tumour

Site	No. of Cases	Percentage (%)
GEJ & Cardia	7	13.2
Body	18	33.9
Pylorus	24	45.2
Pan-gastric	4	8
Total	53	100

In our study, Maximum No. of cases were located in Pyloric region, 24(45.2%).Table 3

In our study, Majority of cases were, 33 (62%) Fungating in gross appearance.Table 4

In our study, Majority of cases were of Intestinal type - 39(73.5%).Table 5

In our study, Majority of cases were Tubular 53%, followed by signet –ring carcinoma 26% and mucinous 4%.Table 6

Table 4: Endoscopic appearance of the tumour

Appearance	No of patients	Percentage (%)
Fungating	33	62.4
Ulcerative	17	32
Infiltrative	3	5.6
Total	53	100

Table 5: Lauren classification of tumour

Type	No. of cases	Percentage (%)
Intestinal	39	73.5
Diffuse	14	26.5
Total	53	100

Table 6: WHO classification of gastric tumour

Type	No. of cases	Percentage (%)
Tubular	28	53
Mucinous	02	04
Signet ring	14	26
Mixed	09	17
Total	53	100

Table 7: Histological grade of the tumour

Grade	No. of cases	Percentage (%)
Well (G1)	16	30
Moderate (G2)	27	51
Poor (G3)	10	19
Total	53	100

In our study, maximum no. of cases were moderately differentiated i.e. 51%.Table 7

Table 8: ki67 correlation with Age

Age	ki67 high LI	ki67 low LI	Percentage (%)	p-value
<50	8[42%]	11[58%]	19[35.8%]	
>50	13[38.2%]	21[62%]	34[64.1%	0.782
Total	21[39.6%]	32[60.3%]	53 [100%]	

In the present study, ki-67 LI positive status is high in 38 %(> 50yrs) cases and 38.8%(<50yrs) respectively. This variation of ki-67 LI correlation with age is not statistically significant ie. P value > 0.05. Table 8

Table 9: ki67correlation with sex

Sex	ki67 high LI	ki67 low LI	Percentage (%)	p-value
Male	15(37.5%)	25(62.5%)	40(100%)	
Female	6(46%)	07(54%)	13(100%)	0.579
Total	21(40%)	32(60%)	53(100%)	

We found a greater number of male patients i.e., 51% showing high ki-67 LI value compared to female showing 33% but ki-67 LI was not statistically significant when compared.Table 9

Table 10: i67 co- relation with location

Location	ki67 high LI	ki67 low LI	Percentage (%)	p-value
GEJ-cardia	1[33%]	2[66%]	3[100%]	
Body	6[26.8%]	17[73.9]	23[100%]	0.012
Pylorus	13[56%]	10[43.4]	23[100%]	
Pan – gastric	1[25%]	3[75%]	4[100%]	
Total	21[39.6%]	32[60.3%]	53[100%]	

In this present study – expression of ki-67 LI was high in majority of cases from pylorus (56%), followed by GEJ-cardia [33%]. Location of tumour was statistically correlated with ki67 and found significant.Table 10

Table 11: ki67 correlation with histological type

Type	ki67 high	ki67 low	%	p-value
Intestinal	20[41%]	19[59%]	39[100%]	
Diffuse	1[33.3%]	136.6%]	12[100%]	0.003
Total	21[39.6%]	32[60.4%]	53[100%]	

When Lauren's classification was taken into account, we found significant high value of Ki-67 LI in intestinal variant [41%] in comparison with diffuse variant [33%].Table 11

Table 12: ki67 correlation with grade of tumour

G1	1[6.25%]	15[93.75%]	16[100%]	p-value
G2	11[40.74%]	16[59.26%]	27[100%]	
G3	9[90%]	1[10%]	10[100%]	0.001
Total	21[40%]	32[60%]	53[100%]	

From the analysis, it has been carried out that ki-67 is increased up to 40% and moderately level of the tumour was also increased up to 6%. There was a significant percentage of 90% of G3 that shows the high level of ki-67 LI. We observed good correlation between degree of tumour differentiation and label of Ki-67 score. Poorly differentiated cancers show statistically significant high Ki-67 score when compared to well differentiated cancers.Table 12

4. Discussion

Gastric cancer is causing cancer that leads the people to death. The issues related to GC are found across the world and having a significant impact on the health of the people and affecting the health care system. [12,13] Although the incidence of stomach cancer is decreasing, it is still considered as a major cause of cancer death in East Asia. [14–16] Gastric carcinogenesis is finally adenocarcinoma as postulated by Correa. [17,18]

The present study showed that the age range of gastric adenocarcinoma was from 31 years to 80 years with the

mean age of 55.04 years, with the highest prealance in the sixth decade. According to the study of Y.E.Joo et al[19] who has observed a mean age of 58.7 years with a range from 28 to 79 years. Moreover, the study of Y.E . Joo et al[19] the incidence of gastric cancer ratio among the male and female was 84% and 35%, 74% and 26% respectively. Present study also revealed male preponderance [75%]

In our study, the pyloric antrum was the most common site (45.2%). According to the study by Zohreh et al[20]Ekta Tiwari et al[21] and Casasola et al.[22] [47.5%], histological subtype (Lauren) in our study was of the Intestinal variant (64%), The GC is increasing the Lauren and that is affecting the cells of the people that causing the issues related to cancer. The early diagnose of the problem is helpful for the individual to manage the health and counter the health problem related to cancer.

Biological behaviour of cancer is influenced by many oncogenes and tumour suppressor genes that influence kinetics of cell proliferation. Ki-67 LI is a widely used proliferation index marker in many cancers including breast where it is validated as an important prognostic marker. The cellular proliferation is used for predicting the cancer and helping to respond to the issues that increase the health problem. Its role as a prognostic marker in gastric carcinoma is controversial and still under evaluation.

There are different types of markers are used for analysing the issues related to the GC and predicting the management of the issues related to cancer. These are including high salt intake, cigarette smoking, high fat, blood group A, whereas H. pylori infection is established as a independent factor in the development of gastric cancer.

In gastric cancer Ki-67 has been reported to be useful in predicting prognosis as studied by Al Moundhri et al and Tzanakis NE et al.[23,24] But its role remain controversial, as studies by Wu A et al, De Manjoni G et al, tsamandas AC et al. and Huang G et al.[25–28] have identified that Ki-67 is having relationships with poor prognosis whereas study by Lee-et-al[29] showed high Ki-67 level associated with good prognosis. An Italian study by de Manjoni G et al[30] additionally showed that high Ki-67LI associated with poor prognosis in elderly gastric cancer cases. On the other hand, Boger et al[31]reported that Ki-67LI didn't have any prognostic value.

We found no significant difference in high ki-67 LI with age or sex in contrast to findings of de Manjoni G et al.[30] who emphasised on importance of high ki-67 LI in elderly, as an unfavourable prognostic marker.

In our study high ki-67 LI was associated with antrally located tumour, also it was the most common site of gastric carcinoma in our study. Studies by Muller wW et al and Inada T et al have shown that intestinal type of gastric neoplasms presents a significant high Ki-67LI[32,33]. When ki-67 lebelling index compared with type of gastric carcinoma according to Lauren classification, we also found it high in intestinal type, in contrast to study done by Vander Woude CJ et al and Kikuyama S et al.[34,35]

When ki-67 labelling index was compared with histological grading of tumor, we found poorly differentiated tumours showing high values in comparison to well differentiated tumours in concurrence with study done by few studies like by Igarashi N et al, Mori M et al and Maeda k et al reported ,rapidly proliferative tumours with high ki67 index, associated with unfavourable clinical outcome.[36–38] whereas study done by Victorzon et al, Tsamandas AC et al and Brien TP et al demonstrated limited role of ki-67 as an independent prognostic marker.[39–41]

Casasola et al (2004) has shown that Ki-67 is associated with length of the survival and considered as a significant prognostic factor.[22] Zohreh Sanaat et al (2013)[20] studied 100 gastric patients in Iran and found there were no significant association between positive ki67 with age, anatomic site, histological type and stage.

The present study showed ki67 over-expression in relation to site, type and grade, but not with age or sex.

Biological behaviour of cancers influenced by many oncogenes and tumour suppressor genes that influence kinetics of cell proliferation. Ki-67 is a widely used proliferation index used in many cancers including breast, where it is validated as an important prognostic marker.[42] As a prognostic marker in gastric adeno-carcinoma it is still under evaluation.

5. Conclusion

Significant global strides have been made in the prevention and treatment of gastric cancer. Nevertheless, the Gastric carcinoma remains the 4th most commonly diagnosed, and the 2nd most deadly amongst all.

Clinico-pathological correlation of gastric adeno-carcinoma in the present study revealed a predominance of male sex in the 6th decade of life with a moderately differentiated and intestinal type in the pyloric region.

Ki-67 is a nuclear protein that is known as a marker of cellular proliferation and ribosomal RNA transcription. Many studies correlate high ki-67 LI with aggressiveness of tumour and advocate an adjuvant chemotherapy as in carcinoma breast. Its role as a prognostic marker in gastric carcinoma is yet to be established, in the present study we found significant association between high ki-67 LI with location, histological type and grade of adenocarcinoma

To conclude, the Ki-67 is prognostic markers for GC and larger sample and period could affect the independent management of the cancer issues.

6. Conflict of Interest

None.

7. Source of Funding

None.

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