

P53 and ki67 Immunostaining in Gastric Biopsies: A Histopathological Study

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Abstract

Background: Gastrointestinal (GI) tract tumors are most common malignancies in western countries. The esophagus, stomach, and colon (including rectum) are the most common site of malignancy.

Objective: The present study was conducted to show the advantages of immunohistochemistry, which includes not only its remarkable sensitivity and specificity but also its applicability to routinely processed formaline fixed material.

Materials and Methods: The present study has been conducted in the Department of Pathology, BRD Medical College, Gorakhpur, Uttar Pradesh. The patients included were both in-patient department and out-patient department patients in whom endoscopic biopsies were conducted for gastric lesions. Further, all these biopsies were studied by immunohistochemical (IHC).

Result: The present study included 30 cases of gastric endoscopic biopsy. Benign lesions amounted to 10 and malignancies were 20. The significant findings in this study showed p53 and ki-67 positivity in only 30% of benign gastric tumors. However, it was interesting to note that malignant gastric tumors were highly positive for p53 (80%) and ki-67 had a high positive index (85%).

Conclusion: Most GI tumors can be differentiated by their unique IHC profile. P53 and ki-67 show much more positivity in case of malignant gastric tumors. In case of p53, Yate's Chi-square is 5.185 and *P* value came out to be 0.023 i.e. significant, whereas ki-67 showed Yate's Chi-square to be 6.769 and *P* value to be 0.0009, which is also significant.

Key words: Gastric biopsies, Immunohistochemistry, Ki-67, P53

INTRODUCTION

Gastrointestinal (GI) tract tumors include a wide variety of vastly different tumors and on a whole are one of the most common malignancies in western countries.¹ These tumors often present as distant metastasis at late stages, which are difficult to differentiate on biopsy.¹ The esophagus, stomach, and colon (including rectum) are the most common site of malignancy.² Collectively, GI cancers account for more than 250,000 new cases each year and over 100,000 deaths each year World Wide.³ The American Cancer Society estimates that GI cancers accounted for

19% of all new cases diagnosed and more than 24% of all cancer death in 2009.⁴

Usually, GI tract cancers occur in the age group of 60 years and above but in the last couple of years, the cancers are occurring in the age group of 20-40 years. This is mainly because of smoking, high fat diet, junk food, sedentary lifestyle, more of non-vegetarian food rather than the fiber rich fruits and vegetable.⁵

Most GI tumors can be differentiated by their unique immunohistochemical (IHC) profile. As the size of biopsies decrease, the role of IHC stains will become even more important in determining the origin and differentiation of GI tract tumours.⁶

Gastric adenocarcinoma is the second most common cancer World Wide with the highest rates in Asia. It is more common in males and has been associated with risk factors such as low socioeconomic status, cigarette

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Month of Submission : 12-2014
Month of Peer Review : 01-2015
Month of Acceptance : 01-2015
Month of Publishing : 02-2015

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smoking, nitrites, chronic gastritis and *Helicobacter pylori*.⁶ The expression of p53 was closely related to the potential for tumor advance and a poorer post-operative prognosis for patients with gastric cancer.⁷

Ki-67 is an excellent marker to determine the growth fraction of a given cell population. The fraction of ki-67-positive tumor cells (the ki-67 labeling index) is often correlated with the clinical course of cancer.⁸ High ki-67 is a sign of poor prognosis associated with a good chance of clinical response to chemotherapy, but its independent significance is modest and does not merit measurements in most routine clinical scenarios.⁹

MATERIALS AND METHODS

The present study has been conducted in the Department of Pathology, BRD. Medical college, Gorakhpur, on the patients attending surgery indoor and out patient department in Nehru Chikitsalaya during a period ranging from August 2012 to October 2013.

Freshly biopsied specimens were subjected to overnight fixation and were processed routinely in the histopathology laboratory, and retrospective study has also been performed on preserved blocks.

All the paraffin blocks were preserved for section cutting. Thin sections of 4-5 μ have been cut after dewaxing, and then were stained by hematoxylin and eosin stain. Histopathological diagnosis was made, and then freshly cut sections were also used for immunostaining.

Sections from 2 representative paraffin blocks of each case were immunostained with p53 (mouse monoclonal antibody, clone DO-1) and ki-67 (mouse monoclonal antibody, clone MIB1).

Sections were mounted on silanized slides, deparaffinised, and rehydrated through graded alcohol to water. Next, slides were microwaved at 95°C for 6 cycles of 5 min each in a 10-mm ol/l concentration of sodium citrate buffer (pH 6.0) for ki-67 or for 7 cycles of 5 min each for p53. Then the slides were allowed to cool for approximately 1 h at room temperature to enhance antigen retrieval.

Then specimens were treated with 10% normal rabbit serum for 10 min at room temperature in a cover plate. Primary antibodies were incubated with tissue sections for 18 h at 4°C. After washing with a 0.01-mol/l concentration of phosphate-buffered saline, they were incubated with biotin-conjugated antimouse immunoglobulin for 10 min at room temperature and then incubated with peroxidase-

conjugated streptavidin for 5 min at room temperature using a histofine kit. Demonstration of binding sites with the peroxidase reaction was achieved with 3,3-diaminobenzidine tetrahydrochloride (0.25 mg dissolved in 1 ml of 0.02% hydrogen peroxide). Faint nuclear staining, sufficient to aid in orientation but not enough to influence the judgment of positivity, was performed with Mayer hematoxylin solution. The p53 label was determined as positive or negative by calculating the number of positive nuclei per 500 gastric epithelial cells and cancer cells in 1 representative section. The count was performed under low magnification ($\times 100$) using a double-headed light microscope. The staining intensity was arbitrarily graded on a scale of four grades: 0, no staining of cancer cells; 1, weak staining; 2, moderate staining; 3, strong staining. The percentage of staining area was also graded on a scale with four grades: 0, none; 1, <10%; 2, 10-50%; 3, >50%. Theoretically, the overall scores could range from 0 to 8. The specimens with a score of more than 4 were regarded as positive expression and those with a score ≤ 4 as a negative expression.

The intensity of positivity for ki67 was scored as follows: 0 negative; 1 weak; 2 moderate; 3 strong. The extent of positivity was scored according to the percentage of cells showing positive staining: 0, <5%; 1, >5-25%; 2, >25-50%; 3, >50-75%; 4, >75% of the cells in the respective lesions. The final score was determined by multiplying the intensity of positivity and the extent of positivity scores, yielding a range from 0 to 12. Any score that was above 4 was interpreted as positive for ki-67.

- Stain positive nuclei - Brown
- Counter stained areas - Blue.

All gastric biopsies, which were processed for IHC by p53 and ki-67. They were processed along with positive and negative controls. The positive controls were previously positive p53 colonic carcinomas with high ki-67 labeling index.

RESULTS

The present study included 30 cases of gastric endoscopic biopsy. Benign lesions amounted to be 10 (33.3%) and malignancies were 20 (66.6%). The relative incidence of gastric tumors was found to be 10.2%.

Most common age group of gastric cancer was found to be 75-85 years. According to our study 5 cases (25%) of adenocarcinoma and 1 case (5%) of lymphoma lie in this group. In age group of 65-75 years, 5 cases have been found (3 [15%] adenocarcinoma and 2 [10%] lymphoma). 4 cases (2 [10%] adenocarcinoma and 2 [10%] lymphoma) have been seen in age group between 55 and 65 years. 2 (1 [5%]

adenocarcinoma and 1 [5%] undifferentiated carcinoma) cases were seen beyond 85 years and only 3 cases (1 [5%] adenocarcinoma, 1 [5%] adenosquamous carcinoma and 1 [5%] lymphoma) were seen <55 years. Mean age for gastric cancer came out to be 70 years.

Most common benign gastric tumor shown in our study was gastrointestinal stromal tumors (GIST). 8/10 cases (80%) p53 was positive in 3 (30%) out of the 10 benign cases, and incidentally all were GIST's. ki-67 score in all 3(30%) cases of GIST was 4. All GIST was confirmed with CD117.

Our study included 20 cases of malignancy in the stomach. The most common malignancy was adenocarcinoma (12/20 cases [60%]) (Figure 1), followed by non-hodgkins lymphoma (6/20 cases [30%]). Two other malignancies were encountered in our study, which included one case of adenosquamous and one case of undifferentiated carcinoma.

11 out of 12 cases of adenocarcinoma were positive for p53, which amounted to 91.6%. 5 cases of 6 lymphomas were positive for p53, which amounted to 83.3%. One case each of adenocarcinoma and lymphoma were negative for p53. Adenosquamous and undifferentiated carcinoma was also negative for p53.

All 11 cases which were positive for p53 also showed a high ki-67 labeling index (Figure 2). A mean score of 8 was obtained for adenocarcinomas. All 6 cases of lymphomas showed a high ki-67 score which was scored as 7-9. Incidentally, adenosquamous and undifferentiated carcinoma showed low ki-67 labeling index.

Among 30 gastric cases, 22 cases (73.4%) were males and 8 cases (26.6%) were females with male:female ratio of 2.7:1. In the present study, it was found that gastric cancers

are more prevalent in hindus (73%) of urban places (80%) as compared to rural places (20%).

The most common mode of presentation of gastric tumor is epigastric pain (36%) which was seen in 11 cases. Among these 11 cases 6 (54.5%) cases were of adenocarcinoma, 3 (27.2%) cases were of GIST and 2 (18.2%) cases were of lymphoma. Next common presentation is vomiting and hematemesis (25%) which included 5 (71.4%) cases of adenocarcinoma and 2 (28.5%) cases of lymphoma. Other mode of presentation was mass abdomen, dysphagia, malena and anemia, i.e. 40% and these included rest 12 cases.

According to our study the most common location of gastric tumors were found to be antrum (47.5%), which included 14 cases (6 [42.8%] cases of adenocarcinoma, 3 [21.4%] cases of lymphoma, 3 [21.4%] cases of GIST and 2 [14.2] cases of adenoma). Next in sequence comes body which includes 12 cases i.e. 4 (33.3%) cases of adenocarcinoma and GIST, 2 (16.6%) cases of lymphoma and 1 (8.33%) undifferentiated carcinoma and adenosquamous carcinoma each. Least common location of gastric tumors is cardiac which included 4 cases. 1 cases of lymphoma, 1 case of GIST and 2 cases of adenocarcinoma were seen at this location.

The significant findings in this study showed p53 and ki-67 positivity in only 30% of benign gastric tumors. However, it was interesting to note that malignant gastric tumors were highly positive for p53 (80%) and ki-67 had a high positive index (85%) (Table 1). Statistically for p53, Yate's chi square is 5.185 and P value came out to be 0.023, i.e. significant, whereas ki-67 showed Yate's chi square to be 6.769 and P value to be 0.0009 which is also significant (Table 2).

Table 1: Comparative evaluation of p53 and ki67 in gastric tumours

Distribution	p53+cases	%	ki67+cases	%
Benign	3	30	3	30
Malignant	16	80	17	85

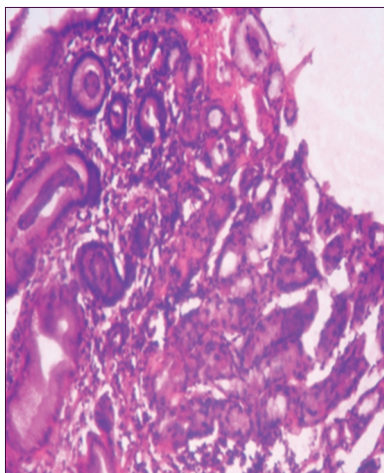


Figure 1: Well differentiated gastric adenocarcinoma (H and E x400)

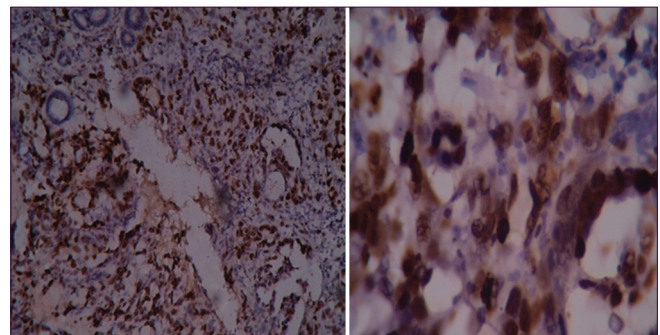


Figure 2: Well differentiated gastric adenocarcinoma (same case) tumor cells show nuclear positivity for Ki67 and p53 (H and E x400)

In the present study, the sensitivity and specificity of p53 in gastric cancer came out to be 80% and 70% respectively. Whereas sensitivity and specificity of ki-67 in gastric cancer was found to be 85% and 70%, respectively (Table 3).

DISCUSSION

In the present study, the relative incidence of gastric tumors (among all GI lesions) received in our department was found to be 10.2%.

We studied 30 cases of gastric tumors out of which 10 (33.3%) cases were benign and 20 cases (66.6%) were malignant.

Stomach cancer incidence rates have decreased overall. Much of this can be attributed to a decline in the prevalence of *H. pylori* (a major cause of stomach cancer) and increase in fresh food in the diet.¹⁰ Present study shows GIST as the most common benign gastric tumor, 8/10 cases (80% cases) which was similar to the study of Minnes *et al.* 1936 who also found GIST to be most common benign tumor.¹¹

The most common malignant gastric tumors shown in our study was adenocarcinoma, i.e. 12/20 cases (60%). Similar result was seen by Durrani *et al.* 2009.¹²

In the context to the 30 cases of gastric tumors selected for study maximum number of cases were found to be in their 7th and 8th decade of life. Mean age for gastric cancer is 70 years. On the other hand Khuroo *et al.* 1992 found the peak incidence between 65 and 75 years.¹³

Among 30 gastric cases, 22 cases (73.4%) were males and 8 cases (26.6%) were females with male:female ratio of 2.7:1. Joo *et al.* 2006 reported similar figures with male:female ratio of 2.4:1 in his study.¹⁴ Zohreh Sanaat *et al.* studied 100 patients with gastric cancer and found that 76 (76%) were men and 24 (24%) were women with male to female ratio 3:1.¹⁵

Table 2: Benign versus malignant gastric tumours

Histology	Markers	P value	Significance
Benign versus malignant gastric tumours	p53	<0.05 (0.023)	Significant
Benign versus malignant gastric tumours	ki67	<0.05 (0.009)	Significant

Table 3: Sensitivity and specificity of p53 and ki67 in gastric cancer

	p53 (%)	ki67 (%)
Sensitivity	80	85
Specificity	70	70

Among gastric tumors, majority of cases were Hindus i.e. 22 (73%) and minority were Muslims 18 (27%) which was in concordance with the study of Saha *et al.* 2012.¹⁶

The most common mode of presentation of gastric cancer is epigastric pain (36%), followed by vomiting, hematemesis (25%) and mass abdomen (16%). Other mode of presentation is dysphagia, malena and anemia with frequency of 10%, 6% and 5% respectively. Durrani *et al.* 2009 observed 175 cases and found that the commonest mode of presentation was epigastric pain, followed by vomiting and hematemesis.

As seen in our study the most common anatomic site of gastric cancer is antrum. 10 cases (47.5%) lie in this group, then comes body and cardiac which include 8 cases (38.8%) and 2 cases (13.7%) respectively. Our study was in concordance with the study of Khuroo *et al.* 1992 who found a similar result. However, Zohreh Sanaat *et al.* and Shafiqh *et al.* found different results. In studies conducted by Zohreh Sanaat *et al.* it was found that 63 (63%) patients had a cancer on body of stomach, 33 (33%) on cardia, 3 (3%) on antrum and one (1%) in pylorus. The study by Shafiqh *et al.* reported the frequent sites of gastric cancer as follows: Cardia (50%), fundus (33%), antrum (17%).¹⁷

In the present study, IHC revealed that in case of benign gastric tumors p53 showed positivity in 3/10 cases, i.e. 30% whereas ki-67 showed positivity in 3/10 cases, i.e. 30% only.

Malignant gastric tumors showed p53 positivity in 16/20 cases, i.e. 80% and ki-67 showed positivity (score >4) in 17/20 cases, i.e. 85%. Easterwood *et al.* (2012) in their study showed that out of 27 cases of gastric cancer 84.2% were p53 positive and 88.9% were ki-67 positive.¹⁸ In studies done by Zohreh Sanaat *et al.* p53 was positive in 35 (35%) patients and ki-67 was positive in 53 (53%) patients. There was no significant association between positive ki-67 and p53 and sex, stage, pathology type, and anatomic site.

A study by Shafiqh *et al.* showed that in patients with gastric cancer who were younger than 60 years, p53 was positive in 14% of patients while in patient over 60 years of age it increased to 19%. He reported 75.9% of patients with gastric cancer ki-67 positive. Our study showed that below 65 years of age, 20% of the patients were positive for p53 whereas 60% patients showed positivity above 65 years of age.

Al-Mondhri *et al.* reported the prevalence of p53 in their patients with gastric cancer to be 54% and ki-67 to be 70% positive.¹⁹

On the other hand Chikanori Niimi *et al.* 2002 included in his study 987 cases in which 62% were positive for p53 and 94 % were positive for ki-67.²⁰

Joo *et al.* 2006, in his study observed that out of 119 cases, 34% showed positivity for p53 and 52% showed positivity for ki-67.

P53 and ki-67 also show overexpression in tumors of other sites also. Khodaeiani *et al.* collected 50 biopsy samples, which included 30 basal cell carcinomas (BCCs), 10 squamous cell carcinomas (SCCs), 8 keratoacanthomas (KAs), and 2 trichoepitheliomas (TEs). These were IHC evaluated for p53 and ki-67 expression. The expression rate of p53 was 67.77% for the BCCs, 50.20% for the SCCs, and null for the KAs. For both TEs, it was 50%. The expression rate of ki-67 was 57.33% for the BCCs, 47.70% for the SCCs, 37.5% for the KAs, and 0.0% for TEs.²¹

Francholumachi *et al.* 2012 retrospectively studied 31 men (median age 65, range 48-75 years) with confirmed Dukes B colorectal adenocarcinoma. The percentage positivity for ki-67 and p53 in cancer tissues was 46.9 ± 19.2 and 48.7 ± 14.2 , respectively.²²

Luminița Nicoleta Giurgea *et al.* studied total number of 125 patients diagnosed with epithelial ovarian neoplasms. There were 26 (50%) malignant cases, 15 (28.8%) borderline and 11 (21.15%) benign. P53 immunoreactions were positive in 41.66% of malignant serous tumors, most of them (90%) high-grade carcinomas; 6.66% of borderline and none benign tumors were positive. Ki-67 was positive in 61.53% of malignant cases, with higher percents in advanced clinical stages. Ki-67 immunoreactions were also positive in borderline and benign tumors, with lower percents, 13.3% respectively 9.09%.²³

Hiroko Yamashita *et al.* studied 506 primary invasive ductal carcinomas in which 29.0% and 53.6% were positive for p53 protein accumulation, and ki-67 expression, respectively.²⁴

According to present study p53 and ki-67 show much more positivity in case of malignant gastric tumors as compared to benign ones. In case of p53, Yate's chi square is 5.185 and P value came out to be 0.023 i.e. significant, whereas ki-67 showed Yate's chi square to be 6.769 and p value to be 0.0009, which is also significant.

In the present study, the sensitivity and specificity of p53 in gastric cancer came out to be 80% and 70% respectively. Whereas sensitivity and specificity of ki-67 in gastric cancer were found to be 85% and 70% respectively. Easterwood *et al.* (2012) who found similar results in his study with sensitivity and specificity of p53 to be 77.8% and 59.5% respectively and sensitivity and specificity of ki-67 to be 88.9% and 76.2% respectively.

CONCLUSION

In the present study, our results showed an altered expression of p53 and ki-67 during the process of carcinogenesis. p53 and ki-67 showed an increasing expression from benign to malignant tumors. The result support that high proliferation measured by ki-67 could predict the extent of the primary tumor and helpful in preoperative pathological diagnosis but these findings require further studies. The tumor suppressor protein p53 is a crucial factor for the maintenance of the genomic stability. Immunostaining pattern of p53 could be used as predictive and prognostic factor in gastric and esophageal tumors. Additional studies should be performed to verify the prognostic role of p53.

ACKNOWLEDGMENT

First of all I would like to thank the almighty for all the blessings and the unconditional love he has showered upon me and making his presence known in every second of my life.

I would like to thank my guide, Dr. Arvind Pallipady, Associate Professor, Department of Pathology, AJ Institute of Medical Sciences and research centre, for his constant suggestions, patience, praise and encouragement.

I would also like to whole heartedly thank Dr. Rajeev Misra, HOD of B.R.D Medical college, Gorakhpur, U.P who have guided me and taught me.

My heartfelt thanks go to each and every patient who agreed to be a part of this study and also my apologies to them in case of any inconvenience caused.

Last but definitely not the least, I would like to thank my precious parents, my in laws and my husband Dr. Saurabh for their unconditional love, support and encouragement in all my endeavors and for believing in me.

Date: 18-12-2014
Place: Mangalore

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How to cite this article: Tiwari E, Pallipady A, Misra R, Mishra S. P53 and ki67 Immunostaining in Gastric Biopsies: A Histopathological Study. *Int J Sci Stud* 2015;2(11):96-101.

Source of Support: Nil, **Conflict of Interest:** None declared.