ORITINAL ARTICLE

# IS PROXIMAL GASTRIC CANCER A DIFFERENT ENTITY FROM DISTAL GASTRIC CANCER? ANATOMICAL SITE DISTRIBUTION OF SIGNET RING CELL CARCINOMA AND ITS ASSOCIATION WITH *HELICOBACTER PYLORI* INFECTION

**Muhammad Rizwan Khan, Najiha Bilal Farooqi, Noman Shahzad**
**Department of Surgery, Aga Khan University & Hospital Karachi-Pakistan**

**Background:** Despite many known variables affecting the outcome, little is known about the impact of histology on the location of tumour and outcomes. The objective of our study was to describe pattern of gastric cancer at single centre and association with *H. Pylori* and Signet ring cell variant with site of tumour in stomach. **Methods:** This was a cross sectional study conducted at the Department of Surgery of Aga Khan University Hospital, Karachi, Pakistan. A total of 105 patients who underwent surgery for gastric adenocarcinoma were classified to have a proximal, distal or whole stomach cancer. An association was determined between the tumour histology and helicobacter pylori infection with the location of tumour in the stomach. **Results:** Proximal gastric cancer was present in 27 (25.7%) patients and distal gastric cancer was present in 69 (65.7%) patients. There were 9 (8.6%) patients in whom tumour involved the whole stomach. Fifty-two patients (49.5%) had signet ring cell variant of gastric carcinoma and these patients were more like to have higher grade and advanced stage. Further analysis showed that that odds of proximal gastric tumour to have signet ring cell histopathology was 3.22 as compared to distal gastric tumour ($p$=0.017). *Helicobacter Pylori* infection status did not have any significant association with either grade of tumour or stage at the time of presentation. **Conclusion:** Despite limitations our data suggests that proximal gastric cancer may be biologically different from distal gastric cancers in terms of frequency of signet ring cell histology.

**Keywords:** Gastric cancer; Signet ring cell; *Helicobacter pylori*; Prognosis; Outcome; *H.pylori*

**Citation:** Khan MR, Farooqi NB, Shahzad N. Is proximal gastric cancer a different entity from distal gastric cancer? Anatomical site distribution of signet ring cell carcinoma and its association with *Helicobacter pylori* infection. J Ayub Med Coll Abbottabad 2020;32(2):194–7.

## INTRODUCTION

Site of gastric cancer in stomach is known to have association with prognosis. Proximal gastric cancer is reported to have worse short and long term survival as compared to distal gastric cancer.[1] Various factors have been implicated as being the cause of this difference, including different surgical approaches, different rates of R0 resections and difference in operative morbidities and mortalities.[1,2] Little is known about differences in tumour biology, if any.

Some studies suggest that signet ring histology is associated with more advanced stage of disease at presentation.[3] It has long been thought that signet ring histology is an independent predictor of a worse prognosis as compared to other forms of gastric cancer.[4] Though some studies have suggested that signet ring variant has site predilection in stomach and proximal tumours having more frequency than the distal ones.[5] There has been no conclusive data on this.

*Helicobacter pylori* has been recognized as a risk factor in development of both diffuse and intestinal varieties of gastric cancer.[6,7]

However many studies suggest *H. pylori*-associated preneoplastic lesions to be a feature of intestinal-type gastric cancer while diffuse-type gastric cancer having genetic etiology.[8] The relationship of proximal gastric cancers with *H. pylori* infection and their association with preneoplastic atrophic gastritis/intestinal metaplasia has been questioned.[9] But there are reports that at least a subset of proximal cancers represents a separate subtype from distal gastric cancers.[10]

*H. pylori* infection of stomach is endemic in Pakistani population.[11] There is lack of data from our region about how it is related to gastric cancer, its severity and site predilection if any. The objective of our study was to describe pattern of gastric cancer at single centre and association with *H. pylori* and Signet ring cell variant with site of tumour in stomach.

## MATERIAL AND METHODS

This was a retrospective cross-sectional study conducted at the Aga Khan University Hospital Karachi. Data was retrieved from medical record using ICD-9 codes. All adult patients who underwent surgery for gastric cancer at Aga Khan University Hospital were eligible for inclusion into study. The patient who underwent surgery for gastric adenocarcinoma were identified using ICD 9 codes. Files of all patients who met selection criteria were reviewed. Data was collected on a specifically designed questionnaire which included information related to demographics of the patients, patterns of presentation, management of gastric cancer and final histopathology. Site of tumour in the stomach was labelled as proximal if tumour involved distal oesophagus, cardia or fundus, or more than 50% of the tumour was in this territory. Distal gastric cancer tumours included those arising from body, antrum and pylorus and limited to these anatomical areas or more than 50% confined to these areas. If all anatomical areas were involved simultaneously, tumour was said to have involved the whole stomach.

All the patients were classified to have a proximal, distal or whole stomach cancer. The variables analysed in detail included the histopathology of the patients with consideration of signet ring cells, degree of differentiation, stage of the disease on pathology, and presence or absence of helicobacter pylori. An association was determined between the tumour histology and helicobacter pylori infection with the location of tumour in the stomach. Data was entered and analysed using STATA version 11. Qualitative variables are reported in terms of proportion and percentages. Quantitative variables are reported in terms of mean ± standard deviation or median ± interquartile range whichever was applicable depending upon distribution of data. Association of qualitative variables was checked using Chi Square test or Fischer Exact test, whichever was applicable according to distribution of data. Multivariable logistic regression analysis was done to establish independent predictor of signet ring cell histopathology. Variables with univariate *p*-value of 0.1 were included for multivariable logistic regression analysis and excluded if adjusted *p*-value was less than 0.05.

## RESULTS

Over a period of 17 years from Jan 1995 till Dec 2011, there were 105 patients who underwent surgery for gastric cancer at our institution. Mean age of the patients was 50.6±11.9 years. Males were 86 (82%) and females were 19 (18%). Proximal gastric cancer was present in 27 (25.7%) patients and distal gastric cancer was present in 69 (65.7%) patients. There were 9 (8.6%) patients in whom tumour involved the whole stomach. Histopathology of all the patients was adenocarcinoma of stomach. Half of all the patients had poorly differentiated tumours. Almost half of the patients had stage 3 disease at the time of presentation. Details of histopathological grade and stage at the time of presentation are shown in table-1. Of all the patients, 52 (49.5%) had signet ring cell variant of gastric carcinoma. *H. Pylori* testing were done in 78 patients, out of which 60% tested positive and 40% tested negative for *H. Pylori* infection. Signet ring cell variant of histopathology was significantly associated with higher grade of differentiation ($p < .001$). Similarly, advanced stage of tumour at presentation was significantly associated with greater percentage of patients having signet ring cell histopathology ($p = .016$). So, signet ring cell tumour patients were more like to be of higher grade and at advanced stage at the time of presentation. Results are shown in table 2 and 3, respectively. On the other hand, *Helicobacter pylori* infection status did not have any significant association with either grade of tumour or stage at the time of presentation. Looking at various factors associated with signet ring cell variant histopathology, it was found that odds of proximal gastric tumour to have signet ring cell histopathology was 3.22 as compared to the odds of distal gastric tumour to have signet ring cell histopathology. The result was statistically significant with *p*-value of 0.017. *Helicobacter pylori* positive patient were more likely to be of non-signet ring cell variety, but the result did not reach statistical significance with *p*-value of 0.076. Results are as shown in table-4. Site of tumour in the stomach remained the only potential independent predictor of Signet ring cell histopathology after adjusting for *H. Pylori* status in multivariable logistic regression analysis with *p*-value < 0.05.

**Table-1: Histopathological grades and stage of gastric adenocarcinoma**

| Variable | | Number | Percentage |
|---|---|---|---|
| **I. Grade of the Tumour** | | | |
| | Well Differentiated | 10 | 09.5 |
| | Moderately Differentiated | 32 | 30.5 |
| | Poorly Differentiated | 53 | 50.5 |
| | Undifferentiated | 10 | 09.5 |
| **II. Stage of the Tumour** | | | |
| | Stage 0 | 0 | 0 |
| | Stage 1 | 14 | 13.33 |
| | Stage 2 | 27 | 25.71 |
| | Stage 3 | 49 | 46.67 |
| | Stage 4 | 15 | 14.29 |

**Table-2: Association of signet ring cell variant with grade of disease**

| Histopathological Grade | Signet ring variant | | Total* | *p*-value |
|---|---|---|---|---|
| | No | Yes | | |
| Well Differentiated | 7 | 3 | 10 | < 0.001 |
| Moderately Differentiated | 24 | 7 | 31 | |
| Poorly Differentiated | 15 | 36 | 51 | |
| **Total** | 46 | 46 | 92 | |

*Reporting of signet ring variant of 3 patients was missing. *Reporting of histopathological grade of 10 patients was missing

**Table-3: Association of signet ring cell variant with stage at presentation**

| Stage at Presentation | Signet ring variant | | Total# | *p*-value (Pearson's Chi Square) |
|---|---|---|---|---|
| | No | Yes | | |
| 1 | 11 | 3 | 14 | 0.016 |
| 2 | 12 | 13 | 25 | |
| 3 | 17 | 31 | 48 | |
| 4 | 10 | 5 | 15 | |
| **Total** | 50 | 52 | 102 | |

#Signet ring variant type of 3 patients was missing

**Table-4: Univariable analysis for associations of various predictors of signet ring variant**

| Variable | Reference Category | Tested Category | Odds Ratio | *p*-value |
|---|---|---|---|---|
| **Age** | < 50 year | ≥50 years | 1.36 | 0.439 |
| **Gender** | Male | Female | 0.84 | 0.727 |
| **Site of Tumour in Stomach** | Proximal | Distal | 3.22 | 0.017 |
| | | Whole Stomach | 4.75 | 0.058 |
| ***H. pylori* Status** | Negative | Positive | 2.36 | 0.076 |

# DISCUSSION

Worse prognosis of proximal gastric cancers has been attributed to different surgical approaches to proximal gastric cancers, relatively less surgical cure rate and relatively high operative morbidities and mortalities.[1,2] Less attention has been given to the difference in biology of disease. Our study highlights two important tumour biology features of gastric cancer, i.e., signet ring cell variant and associated *H. Pylori* infection.

When intracellular mucin is abundant, it pushes aside the nucleus of the individual cells, resulting in the so-called signet ring carcinoma. Our results show that signet ring cell histopathology is significantly associated with higher grade of tumour and advanced stage of disease at presentation. These findings are consistent with data from previous studies suggesting that signet ring cell tumours are pathologically high-grade tumours and are fairly advanced at the time when patient presents to hospital.[12] This type of data points towards the fact that signet ring cell tumours may be biologically different from non-signet ring cell tumours. Our study also found that site of tumour in the stomach was the only significant predictor after multivariable regression analysis that tuned out to have significant association with signet ring cell histopathology. This finding points toward the worse tumour biology of proximal gastric cancer than distal gastric cancer, and can potentially be the contributory factor in worse prognosis in addition to operative factors.

*Helicobacter pylori* infection is an established risk factor of gastric cancer.[13] but little is known about its site predilection is stomach and severity of gastric cancer arising as a result of chronic *H. pylori* gastritis. Our study has shown that *H. pylori* positive gastric cancers are more likely to be of non-signet ring cell variety. Though no site predilection of *H. pylori* associated gastric cancer has been seen in our data, its association with non-signet ring cell histology points toward a better biology of tumour. Some studies have shown that *H. pylori* associated gastric cancer is more common in distal part of stomach,[14] but no conclusive evidence has been established yet.

Our study is a retrospective study with its limitations and some potential for missing data. Despite limitations, our data suggests that proximal gastric cancer is biologically different from distal gastric cancers in terms of frequency of signet ring cell histology. Worse prognosis of proximal gastric cancers as compared to distal gastric cancers is potentially contributed by worse tumour biology in addition to different surgical approach. Further studies from high volume centers might help clarify the subject.

# CONCLUSION

Our data suggests that proximal gastric cancer may be biologically different from distal gastric cancers in terms of frequency of signet ring cell histology. Prospective studies with large numbers are needed to further address this question.

**Ethical considerations**

All information was collected in coded form. No individual identifiable individual information was collected. Data was kept under lock and key. Results are presented in aggregate form with no individual identifiable information reported separately. The study protocol was reviewed by the institutional ethics review committee and granted exemption.

## AUTHORS' CONTRIBUTION

NBF did the data collection and NS wrote the first manuscript. The idea was worked out by all the authors and was supervised by MRK. All the authors contributed to the analysis and final manuscript.

## REFERENCES


1. Hundahl SA, Phillips JL, Menck HR. The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis. Cancer 2000;88(4):921–32.
2. Bilici A, Selcukbiricik F. Prognostic significance of the recurrence pattern and risk factors for recurrence in patients with proximal gastric cancer who underwent curative gastrectomy. Tumour Biol 2015;368(8):619–9.
3. Bamboat ZM, Tang LH, Vinuela E, Kuk D, Gonen M, Shah MA, *et al*. Stage-stratified prognosis of signet ring cell histology in patients undergoing curative resection for gastric adenocarcinoma. Ann Surg Oncol 2014;21(5):1678–85.
4. Piessen G, Messager M, Leteurtre E, Jean-Pierre T, Mariette C. Signet ring cell histology is an independent predictor of poor prognosis in gastric adenocarcinoma regardless of tumoural clinical presentation. Ann Surg 2009;250(6):878–87.
5. Bang YJ, Yalcin S, Roth A, Hitier S, Ter-Ovanesov M, Wu CW, *et al*. Registry of gastric cancer treatment evaluation (REGATE): I baseline disease characteristics. Asia Pac J Clin Oncol 2014;10(1):38–52.
6. Parkin DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer 2006;118(12):3030–44.
7. Solcia E, Fiocca R, Luinetti O, Villani L, Padovan L, Calistri D, *et al*. Intestinal and diffuse gastric cancers arise in a different background of Helicobacter pylori gastritis through different gene involvement. Am J Surg Pathol 1996;20(Suppl 1):S8–22.
8. Carneiro F, Huntsman DG, Smyrk TC, Owen DA, Seruca R, Pharoah P, *et al*. Model of the early development of diffuse gastric cancer in E-cadherin mutation carriers and its implications for patient screening. J Pathol 2004;203(2):681–7.
9. Siman JH, Engstrand L, Berglund G, Forsgren A, Floren CH. Helicobacter pylori and CagA seropositivity and its association with gastric and oesophageal carcinoma. Scand J Gastroenterol 2007;42(8):933–40.
10. Hansen S, Vollset SE, Derakhshan MH, Fyfe V, Melby KK, Aase S, *et al*. Two distinct aetiologies of cardia cancer; evidence from premorbid serological markers of gastric atrophy and Helicobacter pylori status. Gut 2007;56(7):918–25.
11. Daniyal M, Ahmad S, Ahmad M, Asif HM, Akram M, Rehman SU, *et al*. Risk Factors and Epidemiology of Gastric Cancer in Pakistan. Asian Pac J Cancer Prev 2015;16(12):4821–4.
12. Postlewait LM, Squires MH, Kooby DA, Poultsides GA, Weber SM, Bloomston M, *et al*. The Prognostic Value of Signet-Ring Cell Histology in Resected Gastric Adenocarcinoma. Ann Surg Oncol 2015;22(Suppl 3):S832–9.
13. Yong X, Tang B, Li BS, Xie R, Hu CJ, Luo G, *et al*. Helicobacter pylori virulence factor CagA promotes tumourigenesis of gastric cancer via multiple signaling pathways. Cell Commun Signal 2015;13:30.
14. Al-Marhoon MS, Nunn S, Soames RW. Colonization of cagA-positive Helicobacter pylori is significantly greater in infected human males than females. A possible factor in distal gastric cancer gender difference. Saudi Med J 2006;27(6):898–900.



| *Submitted: June 28, 2018* | *Revised: January 27, 2019* | *Accepted: January 12, 2020* |
|---|---|---|



## Address for Correspondence:

**Dr Muhammad Rizwan Khan,** Professor of Surgery, Aga Khan University & Hospital, Stadium Road, Karachi-74800-Pakistan

**Cell:** +92 300 828 6602

**Email:** doctormrkhan@yahoo.com