International Surgery Journal
*Chatterjee J et al. Int Surg J. 2025 Mar;12(3):356-361*
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20250568

**Original Research Article**

# A study of the incidence of malignancy and clinicopathological correlation of incidence of malignancy in peptic perforation disease

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**Received:** 19 December 2024
**Revised:** 21 January 2025
**Accepted:** 24 January 2025

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## ABSTRACT

**Background:** Gastrointestinal perforation, a common emergency in surgery, often results from peptic ulcer disease but can also be caused by gastric cancer. Peptic ulcers, with a lifetime risk of 10%, are more prevalent in developing countries and linked to factors like *H. pylori* infection, NSAID use, smoking, and stress. Complications include bleeding, perforation, obstruction, and cancer. Perforation leads to peritonitis, requiring treatment via perforation closure. Although gastric cancer accounts for 10-16% of perforations, many patients don't undergo post-operative biopsy, potentially missing cancer diagnoses. This study aimed to determine the true incidence of malignancy in perforation cases as well as in specific demographics and identify contributing factors.
**Methods:** The present study was aimed at determining the true incidence of malignancy in perforation cases as well as in specific demographics and identify contributing factors. Biopsies taken from the margins of gastric (antral) perforation during the operation, were subjected to histopathological examination.
**Results:** Our study found only 1 case of perforation in a male patient, in the 61-70-year age bracket with history of both smoking as well as alcohol, to have an associated malignancy.
**Conclusions:** The incidence of malignancy in gastric perforation is very low and as a result, often goes undiagnosed, resulting in lack of appropriate treatment of the underlying cancer.

**Keywords:** Adenocarcinoma, Gastric perforation, Malignancy

## INTRODUCTION

Gastric cancer is the 5th most commonly diagnosed cancer globally, with over one million new cases annually. It is more prevalent in males, especially in developed countries, and has higher incidence rates in East Asia and Latin America. The cumulative risk of developing gastric cancer is 1.87% for men and 0.79% for women.[1] Although its incidence is declining, gastric cancer remains the third leading cause of cancer deaths worldwide, responsible for 5.7% of all new cancer cases.[2] It is considered one of the most preventable cancers, influenced by behavioral factors such as diet and lifestyle.

Perforated gastric cancer (PGC) is a rare condition with a reported incidence of 0.3-3.9%, and generally present with histories and symptoms that do not differ obviously from those of benign gastric perforation.[3] In most instances, gastric carcinoma is not suspected as the cause of perforation prior to emergency laparotomy. Even during surgery the gastric ulcer is often difficult to be characterized as benign or malignant.[4] A retrospectively descriptive study of perforated gastric cancer was conducted in 2008 on 13 patients. The incidence of

perforated gastric cancer was found to be 9.6% of all gastric carcinoma cases, and 4.2% of all gastric perforation cases.[5]

Peptic ulcer disease (PUD) affects 4 million people worldwide annually, with 10-20% developing complications, and 2-14% of ulcers leading to perforation.[6] Perforated peptic ulcer (PPU) is rare but life-threatening, with a mortality rate of 10-40%.[7] Incidence rates in northern Europe have remained stable at 4-11 per 100,000 annually, though recent data is limited. A study at R. G. Kar Medical College (2016-2017) found most cases in the 15-30 age group, predominantly male (97%), as shown in Figure 1.[8]

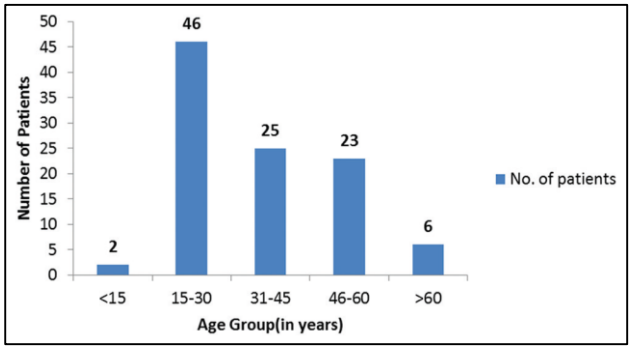


**Figure 1: Distribution of incidence of patients with PPU by age group.**

Causes of peptic perforation are multi factorial, the most common being *Helicobacter pylori* antral gastritis and NSAID's.[9] Rarer causes include Crohn's disease, hypergastrinemia and hyperparathyroidism.

During the 20th century gastric cancer was considered a consequence of preexisting or coexisting conditions (i.e., chronic atrophic gastritis), poor lifestyles, or para physiological conditions (i.e., diet poor in fibers, menopause, etc.), and to a genetic predisposition (gene mutations, group A blood, etc.). Most of these links were never confirmed, except the causative role of *H. pylori*.[10]

Genetic factors linked to gastric cancer include type A blood, pernicious anemia, family history, hereditary nonpolyposis colon cancer, and Li-Fraumeni syndrome, though these are not modifiable.[11] Modifiable risk factors for distal gastric cancer include high salt and nitrate intake, low vitamins A and C, smoking, and *Helicobacter pylori* infection. The pathogenesis of *Helicobacter*-associated gastric cancer involves mucosal atrophy, increased gastric pH, and bacterial overgrowth, leading to intestinal metaplasia. This process is further aggravated by nitrites and N-nitroso compounds. Recent research suggests Epstein-Barr virus genes may also play a role in gastric cancer development.[12] Additionally, prior gastric ulcer surgery and radiation exposure increase risk.

Acid secretion in the stomach is regulated by specialized gastric mucosal cells. G cells in the antrum release gastrin, which stimulates enterochromaffin-like cells to release histamine and directly activates parietal cells to secrete acid. Histamine $H_2$ receptor antagonists block histamine's effect on parietal cells, while proton pump inhibitors inhibit the enzyme responsible for acid production.[13] Somatostatin, released by somatostatin cells, inhibits these processes. *H. pylori* infection affects acid secretion by targeting different gastric regions, influencing specific cell types.[14] Gastrin also promotes the growth of enterochromaffin-like and parietal cells, reinforcing its central role in acid regulation.

Tumor classification by anatomical location is crucial, as true gastric (non-cardia) and gastro-oesophageal junction (cardia) cancers differ in incidence, geography, causes, clinical progression, and treatment. The Siewert classification divides gastro-oesophageal junction cancers into three types: type I (distal esophageal adenocarcinomas), type II (true cardia carcinomas), and type III (subcardial gastric cancers).[15] However, it lacks precise criteria for gastro-oesophageal junction adenocarcinomas and faces criticism. The TNM system simplifies classification: tumors with an epicenter in the distal esophagus, junction, or proximal 5 cm of the stomach extending into the esophagus are classified as esophageal carcinomas; others are gastric carcinomas.[16]

Gastric adenocarcinomas are highly heterogeneous in structure, growth, differentiation, and molecular pathogenesis, leading to diverse classification systems.[17] The Lauren classification divides gastric carcinomas into diffuse (poorly differentiated, with solitary tumor cells and no gland formation) and intestinal types (well to moderately differentiated, forming glandular structures similar to colorectal adenocarcinoma's), as well as mixed and indeterminate types.[10] The WHO classification, aligned with histological schemes for other gastrointestinal cancers, categorizes tumors into five types based on predominant histological patterns: tubular, papillary, mucinous, poorly cohesive (including signet ring cells), and rare variants.[18] WHO's system enhances classification consistency and aligns with Lauren's categories.

The Cancer Genome Atlas identified four molecular subtypes of gastric adenocarcinomas: Epstein-Barr virus-positive (9%), microsatellite unstable (22%), genomically stable (20%), and chromosomally unstable (50%).[19] Genomically stable tumors often align with diffuse-type cancers, while chromosomally unstable tumors are common in gastro-oesophageal junction cancers. Microsatellite instability, linked to defective DNA mismatch repair, favors intestinal-type tumors and offers better prognosis. HER2-positive tumors (12-20%) may worsen prognosis but respond well to trastuzumab therapy, as shown in the ToGA trial.[20] HER2 testing is routine for advanced disease. Molecular subtyping could refine prognosis, guide treatment, and improve outcomes in gastric cancer management.

***Objective***

The objective of this study was to investigate the occurrence of malignancy in peptic perforation, evaluating the relationship between risk factors and cancer development. It analyzed the impact of age, sex, and personal habits (such as addictions) on the incidence of malignancy in peptic perforations and identify the various histopathological types associated with cancer in these cases.

## METHODS

This study was a hospital based, observational, cross-sectional study, including a total of 117 patients of peptic perforation, conducted in the department of general surgery, Dr. BRAM Hospital, Raipur, Chhattisgarh, over a period of one year, from June 2021 to June 2022. All patients who presented to surgery OPD/emergency of Dr. BRAM Hospital, Raipur with symptoms suggestive of perforation peritonitis and operated for the same were included in this study. All cases of GIT perforation other than antral perforation, such as jejunal or ileal perforation or even perforations of the large gut were excluded. Traumatic perforation as well as diagnosed cases of malignancy presenting with perforation were also excluded. The major variables which were studied included the age, sex, socioeconomic background, diet, site of perforation, use of NSAID's and personal habits. The outcome variables included histopathology, incidence of malignancy and clinical correlation with malignancy.

Patients with suspected cases of perforation who presented to the department of surgery were diagnosed on the grounds of a thorough history, clinical examination as well as imaging studies- x-ray chest PA view showing air under diaphragm, USG abdomen showing free fluid in peritoneum and CT scan. The cases were first resuscitated and then operated. Biopsies were taken from the margin of gastric (antral) perforation during the operation, and sent for histopathology and examination to look for presence of malignancy. Subsequently, the data was analyzed using the SPSS Statistics 22.0 software to study the trends with respect to outcome variables such as age, sex, location of perforation and association with smoking and drinking.

## RESULTS

The Table 1 shows the age distribution of patients who have been diagnosed with perforation peritonitis. The ages of the 117 patients were divided into the following seven categories: 1) under 20 years of age (7.69%), 21-30 years of age (17.95%), 31-40 years of age (15.38%), 41-50 years of age (21.37%), 51-60 years of age (23.08%), 61-70 years of age (11.11%), and 71-80 years of age (3.42%). In our study group, the incidence was found to be the highest between the ages of 51 and 60.

**Table 1: Age distribution.**

| Age group (years) | N | % |
|---|---|---|
| **≤20** | 9 | 7.69 |
| **21-30** | 21 | 17.95 |
| **31-40** | 18 | 15.38 |
| **41-50** | 25 | 21.37 |
| **51-60** | 27 | 23.08 |
| **61-70** | 13 | 11.11 |
| **71-80** | 4 | 3.42 |
| **Total** | 117 | 100 |

The incidence of perforation was found to be significantly higher among the males with 80.34% of cases in males and only 19.66% in females.

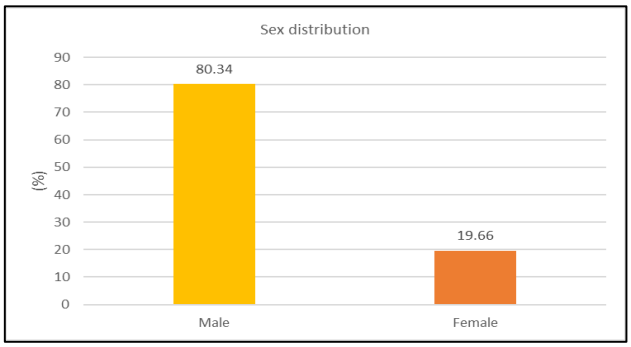


**Figure 1: Gender distribution.**

**Table 2: Frequency distribution for addictions.**

| Personal history | N | % |
|---|---|---|
| **Smoking** | 85 | 72.65 |
| **Alcohol** | 33 | 28.21 |
| **Tobacco** | 2 | 1.71 |

Among the study population smoking was found to be the most common addiction with 72.65% of the study population giving history of smoking addiction.

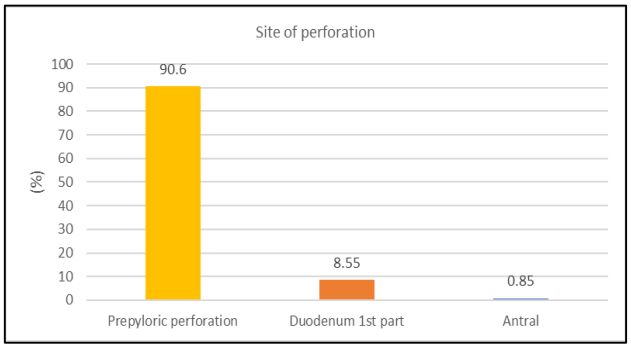


**Figure 2: Perforation site distribution.**

The most common site of perforation in the study was found to be pre pyloric perforation with 90.60% of all recorded cases, followed by 10 cases having involvement

of 1st part of duodenum and only 1 case with antral perforation.

**Table 3: HPE of samples in population.**

| Malignancy | N | % |
|---|---|---|
| **Malignant** | 1 | 0.85 |
| **Benign** | 116 | 99.15 |
| **Total** | 117 | 100 |

A single case of malignancy was found in our study population making the incidence 0.85%.

**Table 4: Malignancy in relation to age.**

| Age group (years) | N | No. of malignancy-positive cases | % |
|---|---|---|---|
| **≤20** | 9 | | |
| **21-30** | 21 | | |
| **31-40** | 18 | | |
| **41-50** | 25 | | |
| **51-60** | 27 | | |
| **61-70** | 13 | 1 | 7.69 |
| **71-80** | 4 | | |
| **Total** | 117 | 1 | 0.85 |

P=0.55 NS

A single case of malignancy was found in the age group of 61-70 years.

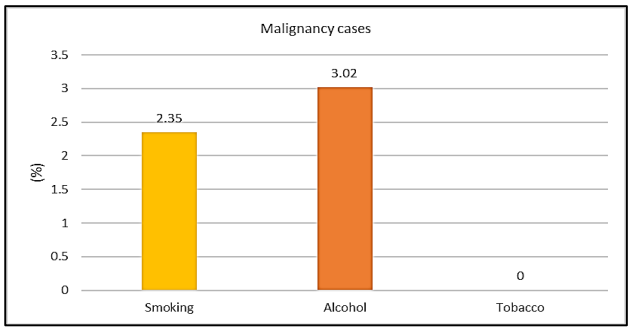


**Figure 3: Distribution of malignancy in relation to addiction.**

In our study, the isolated case of malignancy gave history of both smoking and drinking addiction.

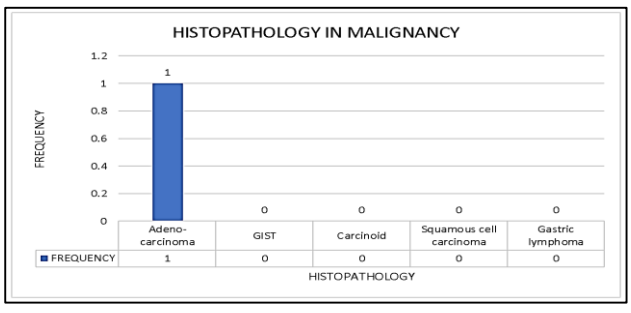


**Figure 4: Histopathology in malignant cases.**

The case of malignancy was histopathologically found to be adenocarcinoma.

## DISCUSSION

This research used a total of ten different kinds of variables in its analysis, including things like name, age, gender, and use of nonsteroidal anti-inflammatory drugs (NSAIDs). The personal history includes three different variables, while the past history includes two different variables, dietary habits, the site of the perforation, histopathology, and the type of cancer that was used. In order to perform an analysis of these variables, the malignancy and logistic regression algorithm, which is implemented in the R programming language, was used. The statistical analysis instrument that was used was R. The following subsection provides a graph and table that describe the variables.

In the current studies, the ages of the 117 patients were divided into the following seven categories: 1) under 20 years of age (7.69%), 21-30 years of age (17.95%), 31-40 years of age (15.38%), 41-50 years of age (21.37%), 51-60 years of age (23.08%), 61-70 years of age (11.11%), and 71-80 years of age (3.42%). In our study group, people between the ages of 51 and 60 were observed the most frequently. Sumit et al, in his study of 60 patients found that the age group with the highest incidence of gastric perforation was 51-60 years (15 cases; 25%) followed by 41-50 years and 61-70 years (12 cases each).[22] Emre et al of the 513 patients treated for gastric perforation had 67 patients had gastric cancer (13.06%), of which the mean age for gastric ulcer perforation was 43.2 years and that with gastric cancer perforation was 64.4 years.[21]

In the population that served as the basis for our research, we located 80.34 percent males and 19.66 percent females. Sumit et al found that among the 60 cases of gastric perforation there was a male preponderance (56 cases; 93%).[22] Emre et al of the 513 patients treated for gastric perforation there were 429 (96.19%) males and 17 (3.81%) females diagnosed with gastric ulcer perforation, while 62 (92.54%) males and 5 (7.46%) females were diagnosed with gastric cancer perforation.[21]

In the current study of the seventy-two and a half percent of the people who participated in the research admitted to having a history of dependency on smoking, making it the addiction with the highest prevalence rate in the sample. Sumit et al in his study found that the most common addiction in the patients was addiction to both alcohol and smoking (28 cases; 46%) and tobacco chewing (24 cases; 40%).[22]

In the following study, the perforation distribution was divided into three groups across 117 patients, and they were as follows: 10 cases involving the first part of the duodenum were then reported, and only one case involved antral perforation. 1) Prepyloric perforation

(90.60%), 2) duodenum 1st part (8.55%), and 3) antral (0.85%) were the three types of perforations that were found. Emre et al stated that of the 513 patients with gastric perforation; 69 cases (15.5%) and 377 cases (84.5%) had ulcer perforation in the middle and lower third of stomach respectively, while 4 cases (6%), 13 cases (19.4%) and 50 cases (74.6%) had gastric cancer perforation in the upper, middle and lower third of stomach respectively.[21] Franco et al in his study mentions that there were 8 cases (80%) of gastric perforation in lower third, 1 case (20%) in middle third and 1 case (20%) in upper third of stomach.[23]

In the population that we were studying, we found one case of cancer, which puts the incidence at 0.85 percent. Sumit et al in his study found that there were 5 cases of malignancy among the 60 cases presenting with antral perforation (8.3%).[22] Emre et al noted that out of the 513 patients treated for gastric perforation, 67 patients had gastric cancer (13.06%).[21]

According to our study, the data reveals that patients aged 61-70 years have a positive case rate of 7.69% and a value of p=0.55NS. Sumit et al noted that among the 5 cases of malignancy found within 60 patients, the highest incidence for malignancy was 61-70 years (17%) followed by 52-60 years (13%).[22] Emre et al studied 513 patients with gastric perforation of which 67 patients had gastric cancer perforation; the mean age of those with gastric cancer perforation was 64.4 years.[21] Kotan et al studied 13 cases of gastric cancer perforation and found out that the mean age of 59.0±9.56 years.[24] Franco et al, in his study about gastric cancer perforation noted that the mean age was 68 years (50-82 years).[23] Nebojsa et al, in his study of gastric cancer perforation found that the mean age was (59.90±9.20) years.[25]

In our study, the patient value of p=0.38 was observed in this research, and the percentage of addiction-related malignancy positive cases is 3.02%. Sumit et al found that addiction to both alcohol and smoking has the highest incidence in cases of gastric perforation due to malignancy (2 cases out of 28) followed by cases who are addicted to tobacco chewing (2 cases out of 24) and addicted to smoking (1 case out of 9).[22] Tredaniel conducted a review and meta-analysis and found a relative risk of 1.5-1.6 of developing gastric cancer among smokers versus non smokers.[26]

In our study a single case of perforation came positive for malignancy, which was histopathologicaly found to be Adenocarcinoma. Sumit et al in his study found that out of the 5 cases of malignancy, 4 cases were found to be of adenocarcinoma (80%) making it the most common histopathological variant associated with perforated gastric cancer.[22] Only one case of malignant GIST (20%) was found. Tan et al conducted a study in which 12 patients underwent surgery for perforated gastric cancer.[27] 9 out of the 12 cases were adenocarcinoma (75%) and 3 cases were of B cell lymphoma (25%), making adenocarcinoma the most commonly associated with perforation.

One of the main limitations of this study was the small sample size, which could've been responsible for the single case of malignancy in our study compared to the higher numbers in other similar studies. Another limitation was the biopsy technique where tissue taken from the margin of perforation could've been unhealthy slough and necrotic tissue, giving a false low incidence of malignancy.

## CONCLUSION

Perforation as a complication of gastric malignancy is one of the rarer yet deadlier complications. As a result, most patients of perforation with underlying malignancy go undiagnosed and are treated only as a surgical emergency for hollow viscous perforation. Factors such as inadequate or improper biopsy technique and loss of follow up further add to the pile of undiagnosed malignancy cases. It is important therefore to stay vigilant towards signs of malignancy and to ensure proper biopsy from the perforation margin is taken and adequately followed up. This will ensure that the patient receives adequate chemotherapy and radiotherapy in the post operative period for treatment of the malignancy.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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