DO PERFORATED GASTRIC ULCERS REQUIRE ROUTINE INTRA-OPERATIVE BIOPSY?

Meryl Dache Oyomno

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Master of Medicine (General Surgery).

Johannesburg, 2018

DECLARATION

I, Meryl Dache Oyomno, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine (General Surgery) at the University of the Witwatersrand, Johannesburg. It has not been submitted before either whole or in part for any degree or examination at this or in any other university.

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On the ……. day of……. 2017

DEDICATION

To my parents, Violet and Gordon Oyomno.

ACKNOWLEDGEMENTS

I owe a great debt of gratitude to **Dr. Martin Brand**, a remarkable supervisor! He was an enormous help in the formulation of the research question and protocol and read multiple drafts of the written report. I appreciate the quick responses and helpful feedback, the guidance and expert advice.

In the same breath, I would like to thank **Professor Damon Bizos** for not only helping me come up with the research topic but for his constant guidance and support.

I would also like thank the Wits postgraduate Hub statistical consultation team and **Dr. Petra Gaylard** of Data management and statistical analysis DMSA for their assistance in the data analysis and statistics.

PRESENTATIONS ARISING FROM RESEARCH REPORT

Oral Presentation

1. Do perforated gastric ulcers require routine intra-operative biopsy? A study in three Gauteng public hospitals.

   Bert Myburgh Research Forum 2015

ABSTRACT

Background.

It is recommended that perforated peptic ulcers undergo intraoperative biopsy to rule out an occult malignancy. Furthermore, there is a recommendation for routine postoperative outpatient follow-up gastroscopy to examine and biopsy residual ulcers. In view of the low incidence of malignancy (<1%) and the changing epidemiology of perforated gastric ulcers, evidenced by an increased incidence of patients younger than the typical gastric cancer age group (60-79 years), presenting with this condition, the question is raised: *is it necessary to biopsy all perforated gastric ulcers at the time of surgical repair?*

Objectives

To determine the demographics and potential risk factors for perforated peptic ulcers as well as the incidence of occult malignancy in these ulcers.

Methods

A retrospective study was carried out from 1 January 2010 to 31 December 2011 in three public university affiliated hospitals in Johannesburg. Data analysis was conducted using Microsoft Excel^{TM} spreadsheet tools. The descriptive analysis was carried out as follows. First, categorical variables were summarized by frequency and percentage tabulations and illustrated by means of bar charts. Second, continuous variables were summarized by mean, standard deviation, median, and interquartile range and their distribution illustrated by histograms. The X^2 test was used to assess the association between age category, gender, and ulcer location. Fischer's exact test was used for 2x2 tables and where the requirements for the X^2 test could not be met. Finally, the Phi coefficient and Cramer's V were used to measure the strength of association.

Results

During the study period 171 patients underwent operative management of perforated ulcers. Most were young (20 – 39 years) with a median age of 42 years, 54.4% of the ulcers were gastric ulcers and intra-operative biopsy was performed in 72% of cases. Of these 25 (26.88 %) were adequate biopsies. Of the inadequate biopsies

97.62% had no mucosa in the biopsy specimen. 90.2% of the biopsies were benign and 2.4% malignant. One case of *H. pylori* infection was noted. There was a non-attendance rate of 72% for follow-up gastroscopy. For the perforated gastric ulcers, the most prevalent risks factors include smoking (55.9%), NSAIDS (40.0%), and alcohol (34.4%).

Conclusion

A South African protocol for the management of perforated peptic ulcers, recognizing that most patients do not return for follow-up gastroscopy, should be developed. Intra-operatively biopsy should be performed in view of the low patient follow-up rate, however the biopsy specimen must include mucosa to improve the diagnostic rate of malignancy and *H. pylori*.

LIST OF ABBREVIATIONS.

Ab	Antibody
AIDS	Acquired immune deficiency syndrome
ARV	Antiretroviral
CHBAC	Chris Hani Baragwanath Academic Hospital
CLO	Campylobacter-like organism test
CMJAH	Charlotte Maxeke Johannesburg academic hospital
CMV	Cytomegalovirus
CO_2	Carbon dioxide
CT	Computerized tomography scans
D1	The first part of the duodenum
D2	Second part of the duodenum
DMSA	Data management and statistical analysis
DU	Duodenal ulcer
EGC	Early gastric cancer
ELISA	Enzyme linked immunoassay
EOGC	Early onset gastric cancer
EUS	Endoscopic ultrasound
EZ-HBT	Urea blood test
GDU	Gastroduodenal ulcer
GIT	Gastrointestinal
GOJ	Gastroesophageal junction
GOO	Gastric outlet obstruction
GORD	Gastroesophageal reflux disease
GU	Gastric ulcers
H&E	Heamatoxylin and eosin stains
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
HJH	Helen Joseph Hospital
HOCL	Hypochlorus acid
ICU	Intensive care unit
Ig G	Immunoglobulin
IncRNA	Long non-coding ribonucleic acid
LN	Lymph node

MDT	Multidisciplinary team
NHLS	National Health laboratory Services
NICE	The National Institute of Health and Care Excellence
NSAIDS	Non-steroidal anti-inflammatory drugs
OG	Oesophago-gastric
PCR	Polymerase chain reaction
pH	Potential of Hydrogen
PPI	Proton pump inhibitors
PPU	Perforated peptic ulcers
PUD	Peptic ulcer disease
RCT	RCT randomized control trial
SBP	Systolic blood pressure
SMS	Short message service
TB	Tuberculosis
UBT	Urea breath test
ZE	Zollinger Ellison syndrome

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1 INTRODUCTION AND BACKGROUND

1.1 Introduction

The management of perforated gastric ulcers follows two approaches: operative or non-operative. Operative management (via laparotomy or laparoscopy) may include either a simple omentopexy or excision and primary closure of the ulcer. For ulcers occurring along the body, antrum and greater curvature of the stomach, wedge resection may be done with closure using a linear stapler. More extensive procedures such as a partial gastrectomy may be used for giant ulcers. Regardless of the choice of operative procedure, the recommendation is to send off an intra-operative tissue specimen of the perforated ulcer for histopathological assessment either as a biopsy (incisional or excisional) or the resected specimen (Søreide, Thorsen et al. 2014). Thereafter there should be an outpatient follow up gastroscopy and biopsy approximately six to eight weeks postoperatively; this is performed to diagnose a missed malignancy or false negative intra-operative biopsies (Kasakura, Ajani et al. 2002).

1.2 Research problem

The etiology of perforated gastric ulcers is broadly divided into malignant or benign factors. The recommendation for intraoperative biopsy of the perforated ulcers aims to detect an occult malignancy or infective etiological agent, such as *Helicobacter pylori (H. pylori)* which may subsequently have an impact on decision making with regards to patient management and follow up (Kasakura, Ajani et al. 2002). For example, whether or not to institute *H. pylori* eradication therapy or in case of a malignancy, whether or not to do staging computerized tomography (CT) scans or manage the patient in a multidisciplinary team (MDT) setting for the best outcome in oncological therapy etc.

Two issues emerged during our weekly combined gastrointestinal (GIT) surgery and pathology meetings held in CMJAH during which all biopsy results are reviewed. Firstly, it was noted that rarely was the intra-operative biopsy specimen of the

perforated ulcer malignant, nor were *H. pylori* identified. This raised doubt as to whether there was a need for routine intra-operative biopsy when positive results are rarely obtained. Furthermore there is a significant cost involved with each biopsy specimen's histological assessment. Each specimen costs approximately R 4000.00 to process and analyze. The second issue concerns the current state of medical technology and practice, characterized by access to endoscopy and H. pylori diagnostic tests. Some of the new *H. pylori* diagnostic tests are non-invasive (Urea breath test) and can be rapidly administered in the endoscopy suite (Rapid urease test/ Campylobacter-like organism CLO test). With these less- and non-invasive tests available, the routine use of more invasive tests such as intra-operative biopsies may potentially become obsolete. Therefore, during the follow up gastroscopy procedure a gastric mucosal biopsy may be obtained for testing to rule out malignancy, *H. pylori* or any other infective etiological agents.

These two issues cast doubt on the need to continue the current practice of routine intraoperative biopsy in all patients with a perforated gastric ulcer and hence support the need for this study

1.3 Hypothesis

- Routine intraoperative biopsy of perforated gastric ulcers to rule out malignancy is not necessary, nor does it diagnose *H. pylori* infection.
- The commonest cause of perforated gastric ulcers diagnosed on intra-operative biopsy at the time of ulcer repair is neither *H. pylori* nor malignancy.
- Locally, the mean age of presentation for perforated gastric ulcers is 20 - 40 years (much younger than what is documented in Western literature).

1.4 Aims/ objectives

Primary aims

- To determine patient demographics (whether the age of presentation in South Africa is lower than is documented in literature), risk factors, clinical presentation and yield of intraoperative biopsies for perforated gastric ulcers.
- To determine whether or not *H. pylori* is the commonest cause of perforated gastric ulcers diagnosed on intra-operative biopsy at the time of ulcer repair.

Secondary aims

- To determine post-operative outcome (mortality rate)
- To determine patient compliance and timing of follow up gastroscopy.

1.5 Definition of terms

1.5.1 Gastroduodenal ulcers

The pyloric canal (pyloric channel) is the segment (approximately 2 -3 cm in length) of the stomach distal to the antrum that ends at the gastroduodenal junction/pylorus. The term gastroduodenal is defined as relating to or simultaneously involving the stomach and the duodenum.

The assumption is that for ulcers that were documented as being gastroduodenal ulcers in the operative notes, these were either gastric ulcers that occurred in the distal pyloric channel very close to the pylorus/gastroduodenal junction or duodenal ulcers that occurred in the proximal area of the D1 (D1 is the first part of the duodenum) very close to the pylorus/gastroduodenal junction and intra-operatively the surgeon was unable to identify the exact site of the pylorus/ gastroduodenal junction either firstly on inspection and/or secondly did not employ any techniques such as use of a sterile Foley urinary catheter gently inserted proximally and distally into the hollow viscus (stomach or duodenum) via the perforation site, insufflated gently with 5mm of saline and retracted gently back towards the site of the perforation taking care to note where the site of resistance if any (an assumption being made that the site of resistance will be the site of the pyloric sphincter [NB: of course not the perforation site which will be a few mm to cm in size]) and identifying the ulcer site in relation to this in order to determine whether this was a gastric or duodenal ulcer. Gastric ulcers GU will be those proximal to the pyloric sphincter while duodenal ulcers will be those distal to the pyloric sphincter. There were cases in which the pathologist described the ulcer biopsy specimen as being gastroduodenal though the surgeon had described the ulcer as being “distal gastric at the level of the pylorus”.

2 LITERATURE REVIEW

2.1 Introduction

The literature is organized into three themes:

- Prevalence of *H. pylori*,
- Prevalence of malignancy and
- Compliance in follow-up gastroscopy.

2.2 Gastric ulcers

The stomach wall consists of mucosa, submucosa, muscularis externa and serosa. The epithelium, lamina propria and muscularis mucosa (smooth muscle) form the mucosa while the submucosa is formed from a collagen rich connective tissue matrix that makes it the strongest layer of the stomach wall. The inner oblique, middle circular and outer longitudinal smooth muscle layers constitute the muscularis externa (muscularis propria). The serosa is the peritoneal layer encasing the stomach.

A breach of the gastric mucosa that extends beyond the muscularis mucosa is referred to as a gastric ulcer. If the breach penetrates the muscularis mucosa but doesn't extend beyond the submucosa it is referred to as an acute gastric ulcer while chronic gastric ulcers occur when the full thickness of the muscularis propria is penetrated and the ulcer base is in the serosal layer or there is perforation and the ulcer completely goes through the entire stomach wall.

The etiology of perforated gastric ulcers may be divided into malignant or benign factors. Malignant causes include primary gastric malignancy e.g. adenocarcinoma, lymphoma etc. and secondary /metastatic disease e.g. metastatic breast cancer.

An imbalance between mucosal protective mechanisms and the injurious effects of gastric hydrochloric acid and pepsin is usually responsible for benign gastric ulcers. Mucosal defensive/protective mechanisms include adequate mucosal bicarbonate secretion and mucus production, optimal blood flow, sufficiency of growth factors and

endogenous prostaglandins and timely cell renewal (Townsend C. M. 2012, Cameron and Cameron 2013). There are several factors that work either alone or in concert with *H. pylori* to decrease mucosal protective mechanisms and thus predispose to gastric ulcer formation. These are considered to be risk factors for gastric ulcer formation. They include:

- Smoking (causes decreased blood flow to the mucosa and thus inhibits healing),
- Peptic ulcer disease (PUD) and acid hypersecretory states e.g. Zollinger Ellison syndrome (ZE). Co-morbidities such as renal failure and hyperparathyroidism result in hypercalcaemia that stimulates gastrin release with resultant hyperacidity,
- Drugs: Chronic use of non-steroidal anti-inflammatory drugs (NSAIDS), steroids or oral glucocorticoids cause direct damage to the gastric mucosa and also inhibits the synthesis of protective mucosal prostaglandin while crack cocaine induces gastric mucosal ischemia (Ergul and Gozetlik 2009),
- Infectious causes e.g. *H. pylori*, tuberculosis (TB), candida (Gall and Talbot 1964),
- Hypoxic and ischemic states e.g. due to gastric volvulus, gastric bypass/gastric-restrictive surgery, extracorporeal circulation or complications of cardiac surgery,
- Iatrogenic injury e.g. during endoscopic biopsy,
- Caustic ingestion,
- Chronic alcohol ingestion is associated with immunodeficiency and gastroparesis,
- Duodenal bile reflux.

The management of perforated gastric ulcers varies. Broadly speaking it is either non-operative (conservative) or operative. Non-operative management is implemented in patients without peritonitis, or patients who are either unfit for surgery or have sealed perforations with no or small collections that can be drained radiologically (percutaneously or via endoscopic ultrasound (EUS)). During this period antibiotic use, serial blood tests and abdominal examinations are carried out

to ensure the patient is improving. Should the patient deteriorate, operative management should be implemented.

Operative management options (via laparotomy or laparoscopy) for perforated gastric ulcers include omentopexy, simple excision and primary closure, wedge resection of ulcers occurring along the body, antrum and greater curvature of the stomach with closure using a linear stapler or a more extensive procedure such as a partial gastrectomy. Regardless of the choice of operative procedure, the current recommendation is that an intra-operative tissue specimen of the ulcer be sent off for histopathological assessment either as a biopsy (incisional or excisional) or as the resected specimen (Søreide, Thorsen et al. 2014). A further recommendation is to take four quadrant full thickness incisional biopsies of the perforated ulcer and then proceed to omentopexy. Another option is to carry out ulcer excisional biopsy and simple primary closure by over sewing it. This should then be followed by outpatient gastroscopy and biopsy, usually six to eight weeks postoperatively, to diagnose a missed malignancy or false negative intra-operative biopsies (Kasakura, Ajani et al. 2002).

Over the years, a general decline in the incidence of peptic ulcer complications has been noted, a feature attributed to multiple factors e.g. use of proton pump inhibitors (PPIs), *Helicobacter pylori (H. Pylori)* eradication therapy and the advent of gastroscopy for early diagnosis, initiation of therapy and follow up of patients to confirm successful treatment (Søreide, Thorsen et al. 2014).

2.3 Prevalence of *H. pylori*

Literature describing *H. pylori* prevalence in perforated gastric ulcers is organized into the following five sub-topics: conceptualization, prevalence, diagnostic tests, treatment and deficiencies in the studies.

2.3.1 Conceptualization

H. pylori are slow growing helical-shaped gram-negative microaerophilic bacteria often found in the mucoid lining of the gastric mucosa. In humans, *H. pylori* causes gastritis and is linked to the development of gastric and duodenal ulcers, gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma (Brown 2000,

Somily and Morshed 2015). It uses various adaptations to flourish and decrease mucosal protective mechanisms. It utilizes its urease enzyme to break urea down into ammonia and bicarbonate that buffer the gastric acid adjacent to the bacteria, thus providing a suitable environment for the bacteria to flourish. The alkaline ammonia stimulates G cells resulting in increased gastrin secretion that also stimulates the parietal cells to secrete hydrochloric acid resulting in hyperacidity.

The presence of flagella allows it increased mobility to swim through the viscous mucus environment. This leads to increased neutrophil infiltration and myeloperoxidase production that catalyzes the reaction between hypochlorous acid HOCL and ammonia to produce monochloramine that is toxic to mammalian cells. H. pylori damages the surface epithelial cells and lamina propria endothelial cells causing release of bacterial platelet activating factor. This results in thrombotic occlusion of the vessels with subsequent ischemia and decreased washing away of gastric acid. Epithelial breach leads to nutrient leakage with increased nutrient availability for the *H. pylori*. Antigen and lipopolysaccharide (endotoxin) production thus pro-inflammatory cells and mediators are attracted to the site causing chronic mucosal inflammation and damage. Ultimately all these factors work together leading to decreased gastric mucosal protective mechanisms and increased aggressive effects of acid and pepsin and this imbalance results in formation of gastric ulcers.

The fact that *H. pylori* and it's oncoprotein CagA can reprogram epithelial cells and affect gastric mucosal progenitor cells together with the acknowledgement that gastric microbiota, essential micronutrients and dietary factors alter the ability of *H. pylori* to act as a commensal or as a potentially carcinogenic pathogen in the stomach are important factors that are currently the subject of research in gastric cancer. (Amieva and Peek 2016)

2.3.2 Prevalence

Though it is more common in developing countries than developed (Western) countries, *H. pylori* is present in more than 50% of all people worldwide but symptomatic in less than 20% of those infected (Brown 2000, Yamaoka 2008, Amieva and Peek 2016).

There is a high prevalence of H. pylori in uncomplicated duodenal ulcers (approximately 90%) however in complicated (perforated) peptic ulcers the frequency is not well established (Gisbert and Pajares 2003). Kumar S et al (2003) in a study on the prevalence of H. pylori in patients with perforated duodenal ulcers found it to be between 33-50% and Sebastian M et al (1995) found the prevalence of H. pylori to be 82- 86% in perforated peptic ulcers (i.e. both gastric and duodenal ulcers included) (Sebastian, Chandran et al. 1995, Kumar, Mittal et al. 2003).

Kumar S. et al (2003) identified 86 patients with perforated duodenal ulcers who underwent operative management with intra-operative biopsies done. The biopsy specimen was then subjected to three different investigations in an attempt to identify H. pylori infection. For each patient, one biopsy specimen was put in urea broth and a rapid urease test conducted, another was put in Brucella broth transport medium and cultured and finally one was put in 10% formalin and assessed histopathologically.

Of these 86 patients with perforated duodenal ulcers, the rapid urease test was positive in 43/86 (50%). No culture was positive. *H. pylori* were identified in 29/86 (33.7%) of the histology specimens, compared to 2/30 (6.7%) on histology and 5/30 (16.7%) with rapid urease test in 30 normal healthy volunteers that underwent gastroscopy and biopsy. Therefore, while H. pylori was detected in 50% of perforated duodenal ulcers, in normal healthy individuals *H. pylori* was diagnosed in 16.7%; therefore supporting the association between *H. pylori* and perforated duodenal ulcers.

The strength of this prospective study lies in the fact that not only did they use three different techniques in an attempt to increase their chances of identifying *H. pylori* organisms; they also managed to obtain multiple mucosal biopsies by intra-operatively introducing a biopsy forceps through the perforation site. This is relevant owing to the fact that the organisms are often found in the mucosal and submucosal layers of the gastric wall; consequently biopsies of the ulcer edge were inadequate if no mucosa is represented (only muscle layer or fibrous tissue is present) as the detection rate of *H. pylori* is decreased.

Gisbert and Pajares (2003) carried out a meta-analysis including 19 studies (1169 patients). They found the mean prevalence of *H. pylori* infection in perforated peptic ulcers was 68.1% (95% confidence interval CI, 65-71%) (Gisbert and Pajares 2003). Other peptic ulcer complications e.g. gastric outlet obstruction (GOO) had a similar prevalence of *H. pylori* infection. Of note is the fact that this meta-analysis was of perforated peptic ulcers i.e. both duodenal and gastric ulcers were included in the studies. Only two out of the 19 studies in this meta-analysis specifically investigated *H. pylori* prevalence in perforated gastric ulcers (independent of duodenal ulcers) and it was found to be 67% and 100% respectively on serology (serum Antibody Ab test) (Lanas, Serrano et al. 1997, Matsukura, Onda et al. 1997).

Matsukura et al (1997) conducted an age-and gender-matched case-control study between perforated and non-surgical peptic ulcer with *H. pylori* infection and examined the differences in the cytotoxin genes cagA and vacA. In the duodenal ulcers the serum *H. pylori* Ig G Ab (ELISA) was positive in 20/21 (95%) of perforated versus 37/40 (93%) of non-perforated ulcers. In the gastric ulcers the serum *H. pylori* Ig G Ab (ELISA) was positive in 5/5 (100%) perforated versus 24/28 (86%) non-perforated ulcers (Matsukura, Onda et al. 1997).

Lanas et al (1997) carried out a two-year prospective trial evaluating the evidence of NSAID (Aspirin) use in upper and lower GIT perforation. A total of 76 patients with GIT perforation (60 upper and 16 lower GIT included) were enrolled and 152 control patients (age, sex and neighborhood matched so as to preserve the same rural-urban population). Among the upper GIT perforations 28 were gastric ulcers, 31 were duodenal ulcers and one patient had an esophageal ulcer (Lanas, Serrano et al. 1997). In the perforated gastric ulcer group, 18/27 (66.7%) and 22/29 (75.7%) in the perforated duodenal ulcer group were serology positive for *H. pylori*. The frequency of *H. pylori* in perforated peptic ulcers was not found to be more than in their control group.

Sebastian M et al (1995) analyzed the incidence of *H. pylori* in perforated peptic ulcers and the relationship between the presence of *H. pylori* and the persisting ulcer. A high rate of duodenal ulcer persistence was noted in the presence of *H. pylori.* (Sebastian, Chandran et al. 1995) Twenty-nine patients with perforated peptic ulcers (did not differentiate gastric or duodenal location) underwent operative

management. On the 8th postoperative day, a 13C urea breath test was done and at six weeks after discharge both gastroscopy with mucosal biopsy for rapid urease test (e.g. CLO test) and a urea breath test were carried out. The urea breath test at day eight postoperatively was positive in 24/29 patients (82.8%) and at week six-post discharge was positive in 14/17 patients (82.4%). The mucosal biopsy specimen rapid urease test was positive in 12/14 patients (85.7%). During post-operative gastroscopy (six weeks post discharge), seven patients among those with positive urease and urea breath test were found to have persistent duodenal ulceration. Based on these findings, they suggested that all patients with perforated peptic ulcers should receive empiric antibiotic eradication therapy.

2.3.3 Diagnostic tests

The diagnosis of *H. pylori* can be determined by either invasive or non-invasive tests. Invasive tests include: mucosal biopsy for a rapid urease test (Campylobacter-like organism CLO Test), histology assessment (microscopy), culture and molecular (Polymerase chain reaction PCR) tests or brush cytology. The rapid urease test involves the use of urea, a pH indicator phenol red, bacteriostatic agents and buffers into which the mucosal biopsy specimen is placed. If *H. pylori* is present, it produces urease enzyme that hydrolyzes the urea to ammonia increasing the pH and resulting in a color changing from yellow to red. Patchy distribution or low numbers of *H. pylori* can result in false-negative results.

Non-invasive tests include: Serology (ELISA, the urea breath test (UBT), rapid stool antigen test, urine antibody test, serum antibody test (serology), saliva and dental plaque PCR and stool antigen tests. (Somily and Morshed 2015) These non-invasive tests can be utilized post operatively for the detection of *H. pylori* induced perforated gastric ulcers that would require eradication therapy. Rapid transportation of *H. pylori* in Stewart's transport media is recommended to avoid drying of this microaerophilic organism, if unavailable, normal saline with 20% glucose and glycerol can be used as a substitute transport media for *H. pylori* culture. Locally, *H. pylori* culture is rarely requested. Normal saline is used as the transport media for *H. pylori* mucosal biopsies intended for culture. Often formalin is used as the transport media and for preservation of the biopsy specimen intended for histological assessment.

2.3.4 Treatment

Triple therapy, the traditional treatment of *H. pylori*, consists of a proton pump inhibitor e.g. Omeprazole for one month, and the antibiotics, Clarithromycin (a macrolide antibiotic) and Amoxicillin for two weeks. Bismuth may be added to this classical triple therapy regime making it a quadruple therapy regimen. These standard regimes have a similar *H. pylori* eradication rate of approximately 70- 85%. A *H. pylori* eradication rate of 87% for clarithromycin triple therapy was noted in a recent meta-analysis of five randomized control trials RCT (Chey and Wong 2007). In tropical countries, metronidazole resistance rates are approximately 80-90% as opposed to 50% in European countries (Somily and Morshed 2015).

Sequential therapy is strategy that has been used to combat Clarithromycin resistant *H. pylori* strains. This entails giving a PPI and Amoxicillin for five days, then Tinidazole, clarithromycin, and a PPI for the next five days. The efficacy of sequential therapy (82%) has been found to be greater than that of the classical clarithromycin triple therapy (44%) $P < 0.0155$ (De Francesco, Margiotta et al. 2006). For patients with persistent *H. pylori* infection, other salvage therapies that avoid the use of previously used antibiotics, may be implemented, once compliance has been confirmed. These salvage therapies may include: 14 days use of bismuth based quadruple therapy or ten day use of Levofloxacin-based triple therapy.

2.3.5 Deficiencies in the studies

There is limited data regarding *H. pylori* infection and perforated gastric ulcers as few studies focus on this patient subgroup. Most of the published data either concentrate on perforated duodenal ulcers, or both duodenal and gastric ulcers together, or discuss the treatment of *H. pylori* in non-perforated ulcers.

Low enrolment figures were noted in most studies. Often the number of patients with perforated gastric ulcers was less than 30 patients (for example five, 24, 28, 29 etc. perforated gastric ulcers per study).

Most published data available originates from European, Asian (Japan) or American Centre's despite *H. pylori* being more prevalent in developing countries. No published South African data was found.

2.4 Prevalence of malignancy

Literature describing prevalence of malignant perforated gastric ulcers is organized into four sub-topics:

- Conceptualization
- Prevalence
- Diagnostic tests
- Deficiencies in the studies

2.4.1 Conceptualization

Perforated gastric cancer is rare and when it does occur 64-68% of these patients will present with advanced disease i.e. stage III and IV (Lim, Tay et al. 2013). Even more rare than the incidence of perforated gastric cancer is the incidence of perforation in early gastric cancer (EGC). EGC is gastric adenocarcinoma confined to mucosa or submucosa with or without regional lymph node involvement i.e.T1, any N. Though rare in the rest of the world, EGC is common in Japan. It is associated with a better prognosis and lower long-term mortality.

The fact that H. pylori and it's oncoprotein CagA can reprogram epithelial cells and affect gastric mucosal progenitor cells together with the acknowledgement that gastric microbiota, essential micronutrients and dietary factors alter the ability of *H. pylori* to act as a commensal or as a potentially carcinogenic pathogen in the stomach are important factors that are currently the subject of research in gastric cancer. (Amieva and Peek 2016).

Table 1: TNM Classification of Gastric Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1	(a)Tumor invades lamina propria or muscularis mucosae, (b) invades the submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

2.4.2 Prevalence

The incidence of perforated peptic ulcers (PPU) is 3.77 to 14 cases per 100,000 (Lau, Sung et al. 2011, Thorsen, Soreide et al. 2013, Wilhelmsen, Møller et al. 2015). The mean age of presentation in Africa is lower with a peak incidence in the 4th decade (31 – 40 years), as opposed to Europe where it's higher (≥65 years) (Roviello, Rossi et al. 2006, Chalya, Mabula et al. 2011, Thorsen, Soreide et al. 2013, Ugochukwu, Amu et al. 2013, Wilhelmsen, Møller et al. 2015). In two South African studies, one reported a mean age of 43 years for perforated gastric ulcers and the other in 1984 reported a mean age of 55 years for PPU (Schein, Saadia et al. 1986, Madiba, Nair et al. 2005). The Italian research group for gastric cancer reported a mean age of 68 years for perforated gastric cancer (Roviello, Rossi et al. 2006).

Perforation in gastric cancer is rare, and when it does occur 64-68% of these patients will present with advanced disease i.e. stage III and IV adenocarcinoma (Lim, Tay et al. 2013). The perforation is often secondary to not just infection (H. pylori) but also central necrosis and ischemia that occurs due to tumor neovascularization and rapid increase in size.

Primary gastric lymphoma accounts for 1- 5 % of all gastric cancers. Spontaneous perforation is rare, however perforation may occur during chemotherapy. (Ohkura, Lee et al. 2015) The incidence of perforated gastric adenocarcinoma is reported as 0.56 – 3.9% by Shyh-chuan Jwo et al (2005), 0.72 % (16/2218) by Kasakura et al (2002) and ≤1% by Roviello et al (2006) and Ergul E. et al (2009). (Kasakura, Ajani et al. 2002, Jwo, Chien et al. 2005, Roviello, Rossi et al. 2006, Ergul and Gozetlik 2009) In other words gastric adenocarcinoma rarely perforates.

2.4.3 Diagnostic tests

While the standard diagnosis of gastric cancer may be easy to make and involves endoscopy (gastroscopy) and biopsy for tissue histology combined with imaging modalities such as a staging CT scan, the clinical pre-operative diagnosis of malignancy in perforated gastric ulcers is unusual (30%). The only factor that may give the surgeon a suspicion of malignancy is the age of the patient e.g. > 65 years. (Lau, Sung et al. 2011)

Currently, the recommendation is that all patients with perforated gastric ulcers should have an intraoperative biopsy for histology and frozen section analysis if a pathologist is available (Lau, Sung et al. 2011). If unavailable, Ergul and Gozetlik (2009) suggest that the following factors may indicate gastric malignancy with 98.7% specificity, 53.7% sensitivity, 93.4% negative predictive value and an 85.7% positive predictive value:

- Age >60 years
- An ulcer diameter (edema included) >6cm
- Diameter of the perforation >0.5cm
- Duration of symptoms >20hrs
- White blood cell count of $<15.10^3/\mu L$

This study, which had significantly more patients than other similar studies (513 total gastric ulcer perforations, 67 malignant and 446 benign) also suggested that females with perforated gastric ulcers had nearly two times greater risk of it being malignant compared to males (Ergul and Gozetlik 2009).

2.4.4 Deficiencies in studies

Some of the concerns in this study by Ergul and Gozetlik (2009) and the factors hypothesized to be suggestive of malignancy in perforated gastric ulcers include:

- Though the benefits of laparoscopic surgery over open surgery are well established and laparoscopic closure of the perforation is safe and currently considered the first choice in treatment if the patient's condition allows it and the technical expertise is available. In this study all patients underwent open surgery (Laparotomy). None underwent laparoscopic surgery due to lack of technical expertise.
- Ulcer diameter (Edema included) is often not easy to determine from the outside of the stomach if it isn't a perforated giant ulcer that allows one to easily visualize the inside of the stomach.

- Immunocompromised patients (e.g. HIV/AIDS, the very old etc.) may not mount an immune response and may present with a low white blood cell count.
- In a resource constrained environment patients may delay in presenting to hospital. Duration of symptoms may also be prolonged due to delays in patient transfers to appropriate facilities i.e. from local clinics to facilities where emergency surgery may be undertaken).

Recent research has shown that high levels of *H. pylori* infection and the increased expression the IncRNA (H19) in serum is associated with an increased risk of gastric cancer and may serve as a potential cancer diagnostic biomarker (Yang, Zeng et al. 2016).

While in the past, perforated gastric ulcers were commonly seen in older patients i.e. classically in the fifth to seventh decade of life (Roviello, Rossi et al. 2006), studies undertaken in Africa demonstrate an increase in incidence in younger patients (20-40 years) (Chalya, Mabula et al. 2011). It is evident that the epidemiology of perforated gastric ulcers is changing and malignant perforated gastric ulcers are rare. The need for routine intra-operative biopsy may therefore be unwarranted due to a low probability of gastric malignancy in younger patients.

2.5 Compliance with follow-up gastroscopy

A Chinese case report describes a patient who presented with a perforated early gastric cancer EGC (pT1b, No, Mo) and underwent operative management with an omentopexy (Lim, Tay et al. 2013). The biopsy conducted during the initial surgery failed to diagnose the cancer, which was diagnosed at routine post-operative gastroscopy six weeks later. This case supports the need for routine post-operative gastroscopy and mucosal biopsy of all perforated gastric ulcers even in the absence of malignant features or negative intraoperative biopsy histology; instead of that conducted during intraoperative management. Adopting this as a practice, however, must take into account the potential effect of a six-week delay on patients and the number of patients that actually return for their six-week gastroscopy. Numerous

studies have reported very low attendance/ return rates for these patients (Sola-Vera, Sáez et al. 2008, Deng, Wang et al. 2015, Zhang, Li et al. 2016). In their study, Zhang (2016) and others investigated the efficacy of gastric cancer screening in a high-risk rural Chinese population (Henan province) over a period of five years in which over 88,000 people underwent screening for gastroscopy. The compliance/ attendance rate for follow-up gastroscopy was only 66.32%.

Deng X et al (2015) evaluated the use of short messaging service (SMS) to complement conventional methods, such as leaflets, health worker counseling and education, to improve compliance and reduce cancellations among 1786 patients. They found that the non-attendance/ cancellation rate decreased from 8.0% in the control group to 4.8% ($P<0.001$) in the SMS group. They also noted significantly higher attendance/ compliance scores among young patients and first time patients. Furthermore, gastroscopy patients, patients with lower education levels and those scheduled for morning procedures had higher attendance scores.

In Valencia, Spain, Sola-Vera J. et al (2008) enrolled 1,897 patients in a study to evaluate the extent of non-attendance among out patients for endoscopy (gastroscopy and colonoscopy). Of these patients, 1051 were enrolled for gastroscopy and 756 for colonoscopy. They found that non-attendance was 14% among gastroscopy patients and 15.6% for colonoscopy patients (Sola-Vera, Sáez et al. 2008). This is similar to what is seen in other GIT endoscopy units e.g.12.2% in Australia (Adams, Pawlik et al. 2004, Sola-Vera, Sáez et al. 2008). In Northern Ireland, Murdock et al, found a 14% non-attendance rate among patients in a GIT outpatient clinic (Murdock, Rodgers et al. 2002).

These studies confirm high non-attendance among patients to be a pertinent universal factor to be taken into account when considering the adoption of post-operative management of gastric ulcers. Until suitable mechanisms to improve non-attendance are found, the use of intra-operative biopsy remains necessary.

2.6 Deficiencies in these studies

No published local or African data was found; most of the available data came from European, Asian (Japan) or American Centre's. Similarly, there was no published

data specifically looking at the compliance in follow up outpatient gastroscopy among patients who had surgical operative intervention for a perforated ulcer.

Some of the studies, involved populations at high risk for gastric cancer thus compliance is expected to be higher than in low risk populations such as in South Africa. There is increased patient knowledge and education regarding this risk and presence of easily accessible screening programs in China and Japan.

Resource availability: while the practice of sending SMS texts reminders to patients may be a feasible practice that could improve compliance in developed countries, for now locally, cost is a limiting factor in the public health sector.

In the study by Sola-Vera J. and his colleagues (2008), patients referred by general practitioners as opposed to specialists and those that had a longer time on the waiting list had a higher non-attendance rate (Sola-Vera, Sáez et al. 2008). When patients present with perforated gastric ulcers they are managed within specialist units, i.e. surgical units and thus a specialist will have made their referral for gastroscopy.

The Murdoch et al (2002) study in Northern Ireland looked at non-attendance in a GIT outpatient clinic in general and not specifically within the GIT endoscopic unit and the study in Arizona USA by Guduru et al (2006) had a significantly lower non-attendance rate (4.1%) than the national rate (27%)(Gurudu, Fry et al. 2006).

2.7 Summary of all the literature reviewed

The recommendation for intraoperative biopsy of PPUs is aimed at diagnosing malignancy and *H. Pylori*. However, consider the following:

- The incidence of malignancy in perforated gastric ulcers is low i.e. less than or equal to 1% (Kasakura, Ajani et al. 2002, Jwo, Chien et al. 2005, Roviello, Rossi et al. 2006, Ergul and Gozetlik 2009, Wilhelmsen, Møller et al. 2015).
- The epidemiology of perforated gastric ulcers is changing with an increase in incidence in patients younger than the classical seventh to eighth decade of life (60-79 years); the age group for gastric malignancy. (Roviello, Rossi et al. 2006, Brenner, Rothenbacher et al. 2009)

- False negatives occur (e. g. a false negative/benign intra-operative biopsy results can miss a malignancy which on follow up gastroscopy may be misinterpreted as gastric deformity secondary to the prior ulcer surgery thus not be re-biopsied and ultimately result in a missed malignancy. (Kasakura, Ajani et al. 2002)
- The current recommendation that all patients should have follow up outpatient gastroscopy and at which time multiple biopsies should be done (Kasakura, Ajani et al. 2002).

These factors together with the fact that there are currently multiple non-invasive tests which may be used for the detection of *H. pylori*, raises the question; *is it necessary to biopsy all perforated gastric ulcers intra-operatively, at the time of repair?* In summary, while the evidence appears to suggest that intraoperative biopsy may not be necessary, one must not forget issues such as the incidence of early onset gastric cancer and non-attendance thus we may miss the only opportunity we had to biopsy an ulcer (Milne and Offerhaus 2010).

3 METHODOLOGY

3.1 Introduction

This chapter describes the study design, data collection tools and techniques utilized. The data analysis and the challenges faced are outlined.

3.2 Data required

The data required is organized into the following four categories:

- General demographic information about the patient
- Data about perforated ulcers generally
- Data about perforated gastric ulcers specifically
- Data about compliance in follow-up gastroscopy

The data elements comprising each category are given in appendix 1 as the Data Collection Sheet. Data on prevalence of risk factors (e.g. smoking, NSAID use etc.) is important as various risk factors work in concert with *H. pylori* in the etiology of gastric ulcers. Knowledge of the prevalent risk factors is useful not only for data analysis and interpretation e.g. should the prevalence of H. pylori be low, but also in forming suggestions for future patient advice and education.

The patient's HIV status (whether positive, negative or unknown), CD4 count, viral load and whether or not they were on antiretroviral treatment was recorded. This information was important in the discussion should the findings have been that other AIDS related opportunistic infections (TB, CMV etc.) were found in the biopsy specimen. Due to the high HIV prevalence in South Africa, this was a consideration that would have not only affected etiology but also analysis of patient outcomes. Advanced HIV would be associated with poor outcome and increased morbidity.

Other factors that could influence patient outcome included clinical presentation. Blood pressure and the onset of symptoms i.e. whether early (<24 hours), late (>24 hours) or unknown, was noted. The unknown component was included as some patients were transferred from other institutions intubated or elderly patients with

dementia or confused due to sepsis with no family available to provide collateral history.

The presence or absence of the surgeon's operation notes was noted. Those not found were recorded as missing data while those available were reviewed for information on the size, number and site of the perforations i.e. Size in mm and whether it was a giant ulcers (≥ 3 cm in diameter) and site of the perforations (e.g. gastric, duodenal, gastro-duodenal, pyloric channel or not documented) for analysis of the modified Johnson's classification of ulcers, and the number of perforations noted. The modified Johnson's classification of ulcers is indicated in appendix 3. The perforation site were further subdivided based on whether it involved the anterior or posterior wall of the stomach, lesser or greater curvature, the proximal fundus, body, distal antrum, pyloric channel, first part of the duodenum D1 or second part of the duodenum D2.

Histology reports were reviewed to confirm the findings, but also to check whether or not the pathologist had noted the site of the ulcer based on the tissue mucosa assessed e.g. the surgeon may have labeled the ulcer as being gastric (e.g. a pyloric channel ulcer) in their operative notes but the pathologist may have found duodenal rather than gastric mucosa in the specimen and labeled it as a duodenal ulcer. Thus the site of the perforated ulcer based on the surgeon's and pathologist's opinion was noted and the concordance or discordance noted. If discordant, the pathologist's tissue mucosa assessment was used to determine the final ulcer site/location.

Information on whether or not intraoperative biopsy had been conducted and if so, how many and what type of biopsy was done e.g. ulcer edge incisional biopsy (four quadrant or not), ulcer excisional biopsy (entire ulcer or partial gastrectomy) and information on any other biopsies done e.g. lymph node or omentum biopsy was also recorded.

Type of surgery, whether open laparotomy or laparoscopic was indicated. Laparoscopic surgery would have influenced the length of hospital stay and made it shorter overall. Furthermore, it could account for low biopsy rates among surgeons who should have but didn't carry out intra-operative biopsy.

Biopsy results, whether benign or malignant and if dysplasia or metaplasia or features of chemical etiology were noted. The adequacy of the biopsy specimen submitted to the pathologist was also noted i.e. did the pathologist record that the biopsy specimen was adequate or inadequate and if inadequate, why?

Biopsy specimens were classed as inadequate if no mucosa was represented in the specimen or the specimen received lacked viable tissue (only a mucoid blood clot received) or the specimen wasn't sent in formalin. This was relevant because inadequate specimens compromise the pathologist's ability to detect H. pylori and thus may be used to explain a low prevalence of *H. pylori*.

Knowledge of several aspects of patient management was necessary. Such knowledge include but was not limited to: any infectious etiological agents that have been noted in the specimen, whether subsequent relook operation was undertaken, treatment outcome and mortality rate, compliance with follow-up gastroscopy, length of stay in the hospital and whether or not patient received *H. pylori* eradication therapy.

3.3 Population and sampling

Data was obtained from medical records maintained by three Gauteng public hospitals, namely, Charlotte Maxeke Johannesburg academic hospital CMJAH, Chris Hani Baragwanath Academic Hospital CHBAH, and Helen Joseph Hospital HJH. The study population included all patients operatively treated for perforated ulcers in these three hospitals over a two-year period, from 1st of January 2010 to the 31st of December 2011. However, as explained in the sampling paragraph below, this period was extended to a three-year interval, which resulted in a sample size of 1183 patient records.

3.3.1 Sample size calculation

A sample drawn from this population included all adult patients who were 18 years of age or older. Patients with perforations that were secondary to trauma, caustic ingestion or iatrogenic causes were also excluded.

Theoretical sampling estimates were based on reporting of a 50 percent proportion with five percent accuracy at 95 percent confidence interval. Achieving these statistical thresholds required a sample size of 384. However, after examining 630 records in the three hospitals, a much lower number was obtained. After extending the two-year period to three-years (January 2010 – December 2012), thus increasing the base population to 1,183 records, 171 usable good records were obtained. NB: the final year (January to December 2012) was used to check if any patients who had undergone surgery in 2010 and 2011 had returned for follow up gastroscopy much later.

In this study, the term a good record is used to mean a patient record that included all the information relevant to the study. Such a record includes, legible admission and intra-operative notes documenting whether or not biopsy was done, type of biopsy done and histological results of the biopsy. This number (171) constituted the sample for the study. This study had a considerably lower sample size of 171, which would have resulted in a considerably lower precision e.g. a 50% proportion can only, be reported with 75% precision. For this reason, descriptive reporting of percentages was done.

3.4 Data collection tools

Structured questionnaire was used to guide data collection. A data completeness checklist was drawn from the questionnaire and used to guide physical examination of each record from each hospital for completeness.

3.5 Data collection procedure

Data collection entailed examination of patient records in the three study hospitals. In two hospitals (HJH and CHBAH), the records were kept in paper form while at one hospital the records were stored both in paper and microfilm form (CMJAH). Casualty registers, surgical ward admission registers, and emergency theatre operative registers were scanned and reviewed to determine records of patient meeting the sampling requirements for the study. Furthermore, the National Health laboratory Services (NHLS) computer system in each hospital was used to get histopathology reports on biopsies of perforated ulcers, culture and all blood results

of all the study patients. The NHLS system was also used to check if the patient had subsequent or prior admissions and if so what was the reason for admission. Furthermore if the patient had ever been evaluated at another hospital for a related problem e.g. if there was histology on the system for a gastric mucosal biopsy done on gastroscopy, the history supplied on the request form for that investigation by the endoscopist may reveal a history of prior PUD or a risk factor for peptic ulcer disease PUD such as smoking etc. if the patient had a history of being evaluated at one of the other study hospitals, then a search was done for any other medical records/ files and gastroscopy reports they may have had done at that institution.

During the period, the Endoscopy Unit gastroscopy registers, records and reports were reviewed to capture firstly, any patients who had their surgery towards the latter half of 2011 (e.g. November and December 2011) and thus would only require their follow up gastroscopy (routinely done at six weeks post operatively) in the 2012 period, and secondly any patients who though delayed (the recommended period is six -eight weeks postoperatively), ultimately did return for follow up gastroscopy.

Following examination of hospital records, a questionnaire was used as a template to guide and manually capture the required data for each individual patient. This data collection sheet is included as Appendix 1.

The information from the data collection sheet was then transcribed into a Microsoft Excel™ spreadsheet for analysis. Each patient was assigned a unique study number and the hospital they were treated in noted. All patients from one hospital were given sequential study number i.e. Study No 1 – 61 were from one institution (CMJAH), 62 -98 the next hospital (HJH) and 99 -173 another hospital (CHBAH). The reason for this was to enable easier data analysis and interpretation in areas where the hospitals had differing policies i.e. at one hospital (CMJAH) gastroscopy was done under sedation while at the other two institutions (HJH and CHBAH) sedation was not given. If patient compliance to outpatient follow up gastroscopy had been low in the two institutions that didn't utilize sedation, and high in hospital that did the procedure under sedation, it would have been important to check if this was a compounding factor in the non-attendance i.e. patient fear and discomfort, especially among patients who had previously experienced the procedure.

3.6 Data analysis and presentation

Data analysis was conducted using Microsoft Excel™ spreadsheet tools such as Stata, Statistica and SAS (SAS Institute Inc., SAS Software version 9.3 for windows, Cary, NC, USA: SAS Institute Inc. (2002 – 2010)). The descriptive analysis was carried out as follows. First, categorical variables were summarized by frequencies and percentage tabulations and illustrated by means of bar charts. Second, continuous variables were summarized by mean, standard deviation, median, and interquartile range and their distribution illustrated by histograms. The X^2 test was used to assess the association between age category, gender, and ulcer location. Fischer's exact test was used for 2x2 tables and where the requirements for the X^2 test could not be met. Finally, the Phi coefficient and Cramer's V were used to measure the strength of associations. A 5% significance level was used i.e. p-values <0.05 indicate significant results.

Sample size estimation was based on the reporting of a 50% proportion (worst-case) with 5% precision at the 95% confidence interval. This requires a sample size of 384. This study had a lower sample size of 171, which would have resulted in a lower precision e.g. a 50% proportion can only, be reported with 75% precision. For this reason, descriptive reporting of percentages was done.

3.7 Ethical considerations

Ethics approval was obtained from The University of the Witwatersrand Human Research Ethics committee HREC (Medical) [Clearance certificate No. M111126]. Permission was granted by the respective hospital management teams (Charlotte Maxeke Johannesburg Academic hospital CMJAH, Chris Hani Baragwanath Academic hospital CHBAH and Helen Joseph hospital HJH) and the National Health laboratory Services NHLS to access their records/database. The HREC ethics certificate is attached as appendix 2.

4 RESULTS

4.1 Introduction

In this chapter, the results of the study are presented in four main sections as follows. First, the demographic data obtained is presented organized into main sections each with its relevant subsections and finally in summary, the results pertaining to each research question are presented. The four main sections are:

- Demographic data
- Perforated ulcers data
- Follow-up gastroscopy
- Summary

In the three hospitals over the study period, 1183 records were reviewed and 171 usable good (complete) records obtained. The distribution of the sample by hospital is given in Table 2 below.

Table 2: Hospitals and the records examined

Hospital	Records examined	Good records obtained	Percentage
CMJAH	373	61	16.35 %
CHBAH	507	73	14.40 %
HJH	303	37	12.21 %
Total	1183	171	14.45 %

Over the two-year period, 171 patients underwent operative management for PPU. There were 173 perforated ulcers identified (three patients each had two synchronous perforated ulcers); 93 (54.4%) were gastric ulcers and 74 (43.3%) were duodenal ulcers, four (2.3%) gastroduodenal ulcers and in two (1.2%), the site was not specified.

4.2 Demographics

4.2.1 Age and gender

Overall, 74.9% were male with a male: female ratio of 3: 1. Most patients were in the 3rd and 4th decade of life (20 – 39 years), with the mean age being 44.1 years ±SD

16.9 and the median age was 42 years ±Interquartile range IQR 29-57 years; range 18-91 years). (Figure 2 and 3)

For the patients with perforated gastric ulcers, 65 (69.9%) were male and 28 (30.1%) female, with a male: female ratio of 2.3: 1. The mean age was 47.0 years ±SD 18.3. With regards to perforated duodenal ulcers 81.1% were male and 18.95% female (Male to female ratio of 4.3: 1).

There was no significant association between the presence/absence of perforated gastric ulcers GU and age (p=0.07) or gender (p=0.07), nor the presence/absence of perforated duodenal ulcers DU and age (p=0.10) or gender (p=0.07).

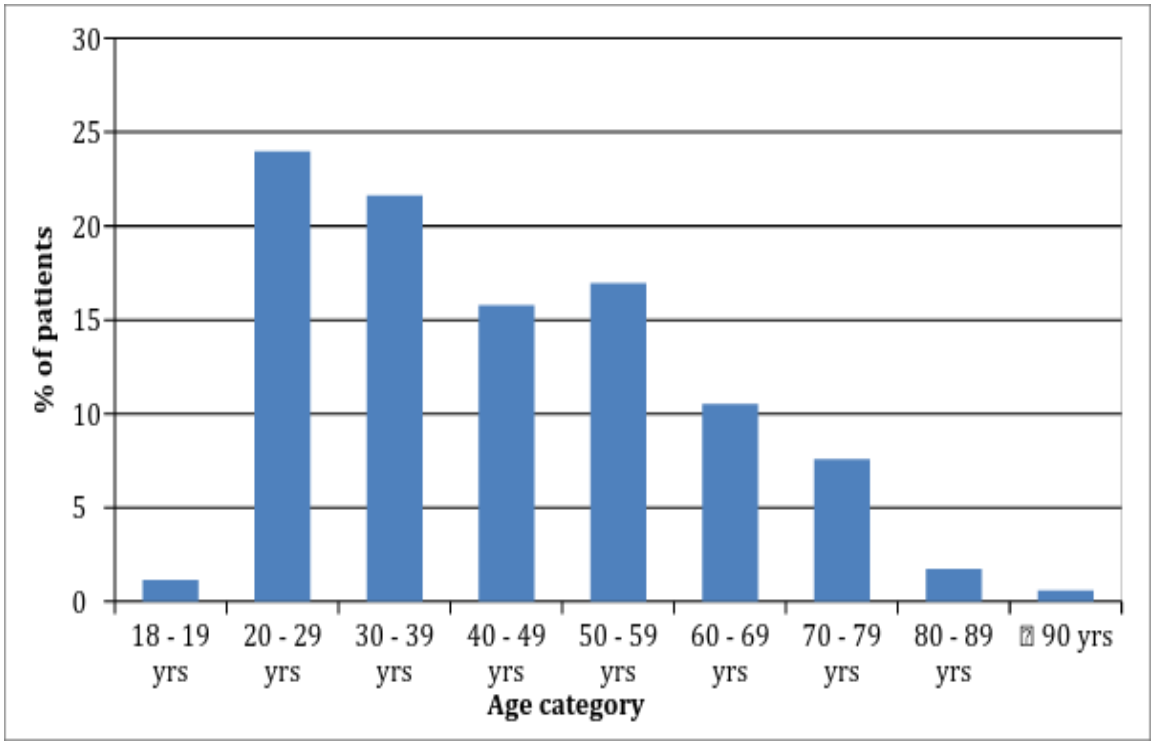


Figure 1: Distribution of patients with perforated ulcers by age

Key: y-axis: Number of patients (0.01=10 patients) x-axis: age in years

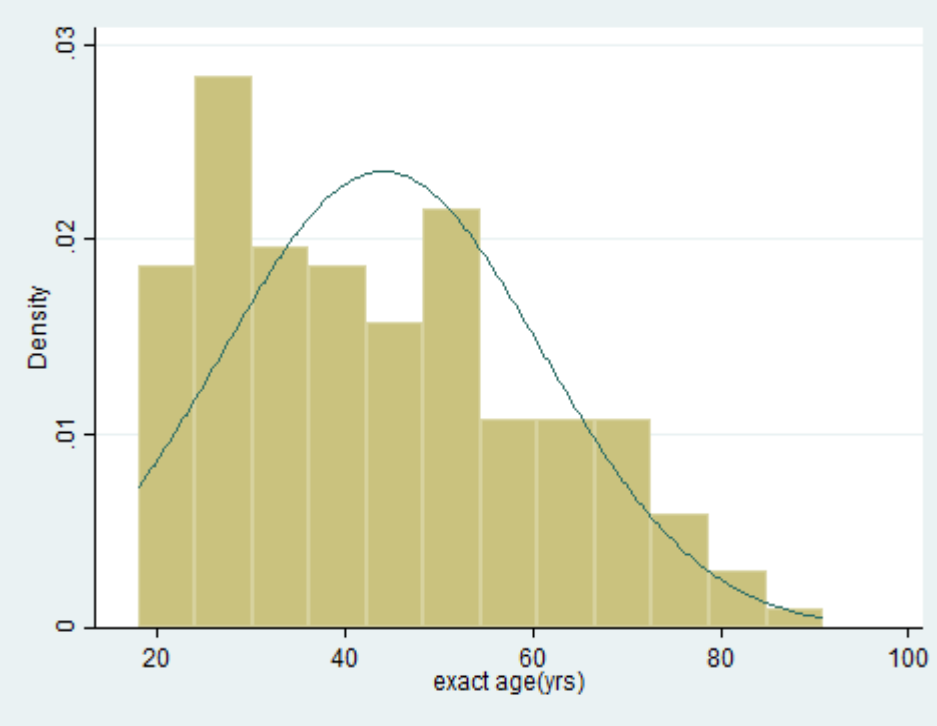


Figure 2: Distribution of patients with perforated ulcers who underwent operating management.

Key: y-axis: Number of patients (0.01=10 patients) x- axis: age in years

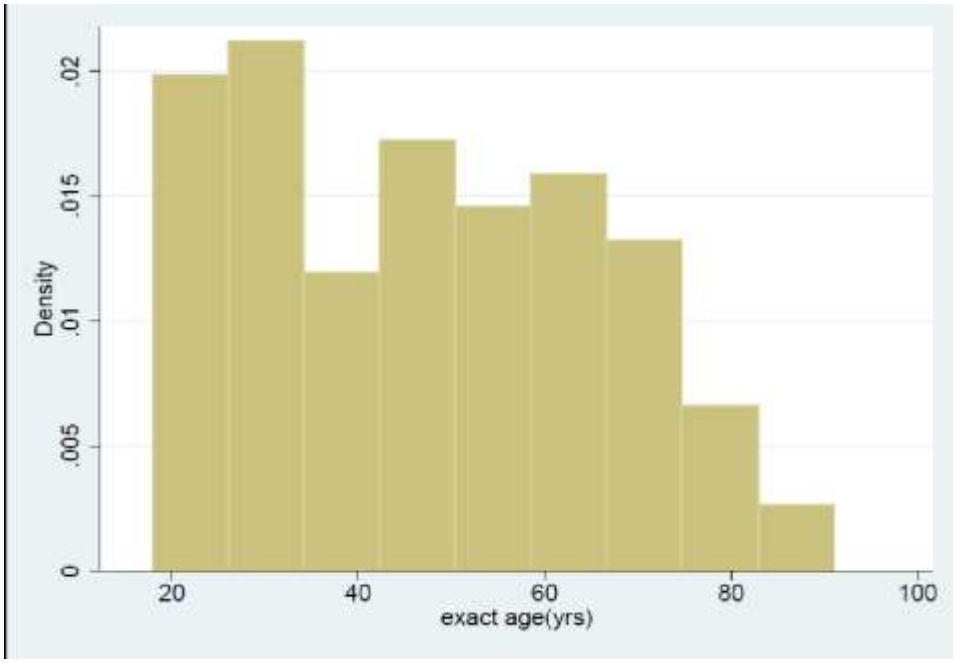


Figure 3: Distribution of patients who underwent operative management by age

4.2.2 Risk factors

Overall for all perforated ulcers, the most prevalent risk factor were history of smoking (49.7%), NSAID use (30.04%) and previous PUD (20.47%) that were present in 85, 52 and 35 patients respectively. History of alcohol use was noted in 60 (35.1%) patients. Some patients had more than one risk factor e.g. smoking and NSAID use or smoking and a history of prior PUD, while some had none documented. For perforated gastric ulcers, the commonest risk factors were smoking 55.9%, NSAID use 40.86%, PUD 24.36% and ethanol use 34.4%. Missing data on these risk factors ranged from 15.8-17.5%. Figure 5 below illustrates the commonest risk factors.

One patient, a 33-year-old male had a history of ingesting traditional herbal medication and no other documented risk factors. Whether the ingested medication resulted in the perforation or whether the medication was ingested in an attempt to treat the symptoms of the perforated ulcer (e.g. abdominal pain) is unknown. Histological evaluation of his intra-operative ulcer biopsy confirmed a perforated duodenal ulcer.

Of all the patients with PUD, 5.85% were not on treatment (treatment non-compliant) despite being known to have peptic ulcer disease PUD.

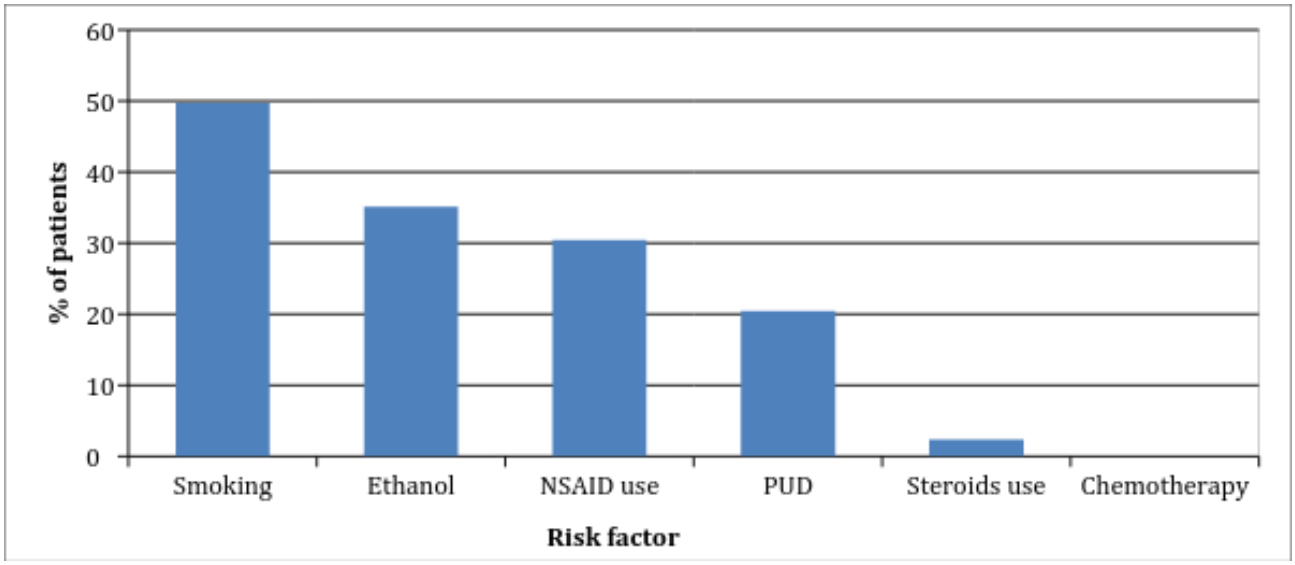


Figure 4: Risk factors for PPU

4.2.3 HIV status

The HIV status of 114/171 patients was unknown (untested). For those in whom the HIV status was known, 9/57 were HIV positive and 48/57 HIV negative with the CD4 count ranging from four to 269 and the highest viral load being 6,612,319. Only 3/9 HIV positive patients were on antiretroviral therapy.

With the HIV status unknown in two thirds of patients, the HIV data and associated variables were insufficient for further analysis.

4.3 Perforated ulcers data

4.3.1 Clinical presentation

In patients with perforated gastric ulcers, 35.5% had early presentation, 49.5% delayed presentation and in 15%, the timing of their presentation was unknown. Table 3 below shows the timing of clinical presentation, in all patients with perforated ulcers who underwent operative management 38.6% had early and 46.2% delayed presentation. In 15.2% of the patient's, presentation was unknown.

Table 3: Timing of clinical presentation in perforate ulcers

Presentation	Number	Percentage
Early	66	38.6
Late/delayed	79	46.2
Unknown	26	15.2
Total	171	100.0

The data on hemodynamic stability is presented in Table 8 below. Majority of patients (63.7%) were hemodynamically stable but a missing data rate of 21.6% is noted.

Table 4: Hemodynamic status

Haemodynamic stability	Number	Percentage
Stable	109	63.7
Unstable	25	14.7
Missing information	37	21.6
Total	171	100.0

Two patients were admitted in shock with unrecordable blood pressure at presentation that improved post resuscitation to 115/50 and 95/65 mmHg respectively.

4.3.2 Characteristics of the perforated ulcer

4.3.2.1 Number of perforated ulcers

In all patients with perforated ulcers who underwent operative management (n = 171), there were a total of 173 ulcers, 93 (54.4%) of these were perforated gastric ulcers. Of the gastric ulcers, a single perforation site was noted in most patients 90 (96.77%).

Overall, a single perforation site was noted in 168 patients (98.2%) while three patients had two synchronous sites of perforation. One had both a perforated gastric ulcer and perforated duodenal ulcer, another had both a perforated gastric ulcer and perforated gastroduodenal ulcer and the third had two perforated gastric ulcers near the incisura.

4.3.2.2 Number of intra-operative biopsies done

Overall, intra-operative biopsy was performed in 48.0% of the cases (1.8% missing data). For the perforated gastric ulcers (n = 93), intra-operative biopsy was performed in 75.27% of the cases. In all but one case, an open laparotomy surgical approach was used.

4.3.2.3 Site of perforation

Based on surgical operative notes (1.8% missing data), 53.2% of the perforated ulcers were gastric GU, 43.3% duodenal DU and 1.8% gastroduodenal GDU. Based on histological assessment of the biopsy specimen: this data was limited since

50.3% of all (n = 173) the cases were not biopsied and of those that were biopsied a further 26.9% of cases could not have the location determined as the specimen did not include mucosa. 0.6% of cases had no evidence of perforation (one partial/ distal gastrectomy specimen assessed by the pathologist was found to have no perforation site); and data for 2.9% of the cases were missing.

Note that the data in the table do not sum to 100% since three patients each had two perforation sites. Cross-tabulation of the sites for which there was both surgeon and histology data available for the site of the perforation (n=34 sites from 32 cases) is presented in Table 5 below.

Table 5: Cross tabulation of sites

Site (surgeon)	**Site (pathologist)**			
	GU	**DU**	**GDU**	**Total**
GU	19	3	2	24
DU	2	5	1	8
GDU	1	1	0	2
Total	22	9	3	34

The agreement between the two site specifications was 25/34 (74%). In the final consolidation, with the site of perforation based firstly on histology and then (in the absence of histology) on the surgical notes, 54.4% of the ulcers were classified as GU, 43.3% as DU and 2.3% as GDU (1.2% missing data). Of the patients with perforated gastric ulcers, 70.3% were male and 29.7% female. (Male to female ratio of 2.3:1) With regards to perforated duodenal ulcers 81.1% were male and 18.95% female. (Male to female ratio of 4.3: 1). Figure 6 below shows the ulcer type based on the modified Johnson classification of ulcers. Of the perforated gastric ulcers GU, 68.8% were Type 3. (15.6% missing data)

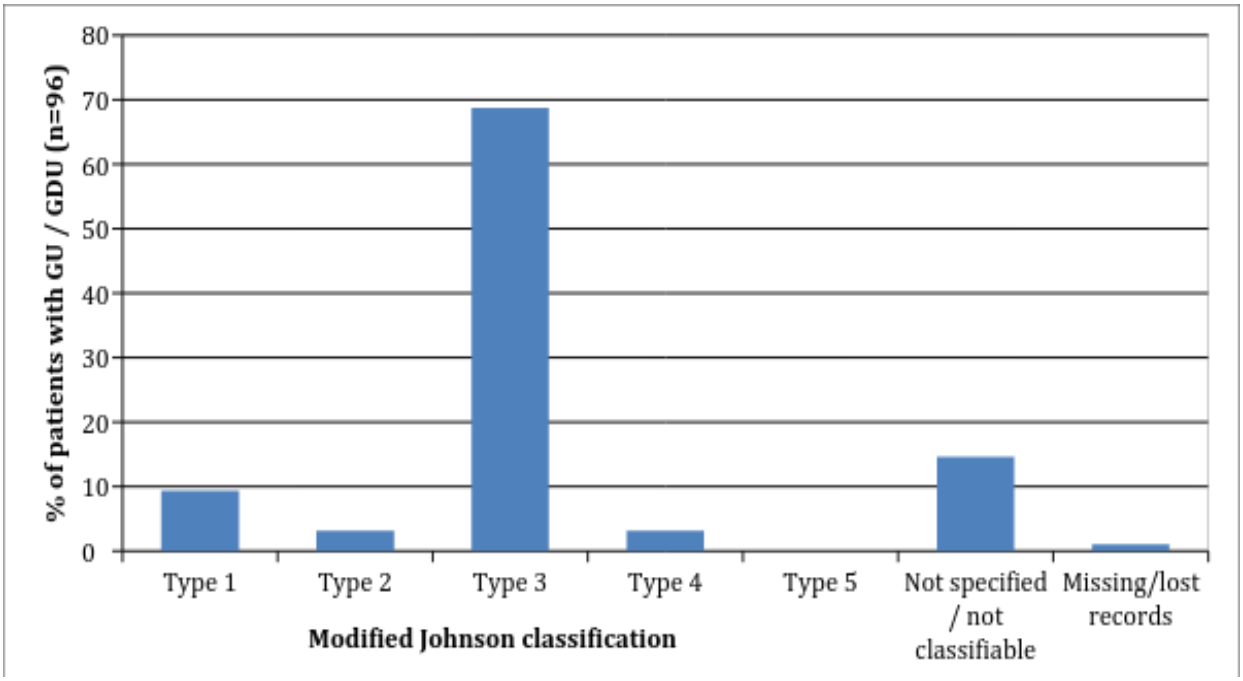


Figure 5: Modified Johnson classification of perforated peptic ulcers

4.3.2.4 Ulcer size

Only 4.3% of the gastric ulcers were giant ulcers. Overall, four Giant ulcers (≥3 cm diameter) were noted out of 173 ulcers. All four were gastric ulcers. No giant duodenal or gastroduodenal ulcers were noted

4.3.2.5 Type of biopsy done

Overall for all perforated ulcers, intra-operative biopsy was conducted in 48.0% cases (1.8% missing data). Of these, 76.8% were incision biopsies and 17.1% were excision biopsies (2.4% unknown). Note that these percentages do not add up to 100 because some patients had more than one type of biopsy.

For the perforated gastric ulcers (n = 93), intra-operative biopsy was conducted in 75.27% of the cases. Intraoperative biopsy was not done in 24.7% of the perforated gastric ulcers. Of those biopsied, 54 (58.06%) were incision biopsies and 12 (12.91%) were excision biopsies.

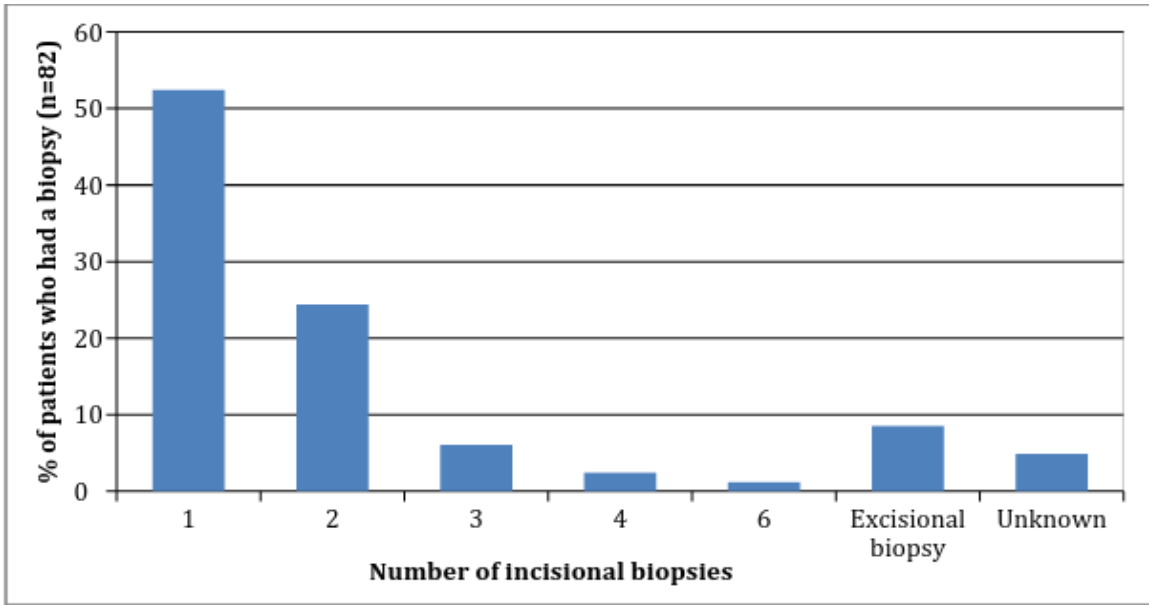


Figure 6: Number and type of intraoperative biopsies for perforated peptic ulcers

For all incision biopsies of perforated ulcers 80.5% were not four quadrant biopsies, most surgeons took only one biopsy. Of the gastric ulcers, six (6.45%) underwent excision biopsy, either as a partial gastrectomy or as a limited excision biopsy of the ulcer, and two had four quadrant incision biopsy done. 88.17% had less than the recommended four quadrant biopsies done (≤ 3 incision biopsies done). Other types of biopsies carried out intra-operatively included biopsies of adjacent lymph nodes, omentum and partial gastrectomies.

4.3.3 Biopsy specimen

4.3.3.1 Adequacy of the intra-operative specimen

Of all the perforated ulcers biopsied, 54.9% of the biopsies were deemed inadequate by the pathologist and 41.45% were adequate biopsies (3.7% missing data). 95.6% of those considered inadequate were classed as such as no mucosa was represented in the specimen.

Of the biopsied perforated gastric ulcers, 25 (26.88%) were adequate biopsies. 42 (45.16%) were considered inadequate, of these 97.62% were due to a lack of mucosa in the biopsy specimen and 2.38% due to a lack of viable tissue in the specimen received by the pathologist.

The table below shows the adequacy of the perforated gastric ulcer biopsy specimen.

Table 6: Adequacy of the perforated gastric ulcer biopsy specimen

Biopsy specimen	Number	Percentage
Adequate	25	26.88
Inadequate	42	45.16
Biopsy not done	24	25.81
Missing data	2	2.15
Total	93	100

4.3.3.2 Biopsy result

Of the 82 perforated gastric and duodenal ulcers biopsied, 73 were benign and 2 were malignant. Of the 93 perforated gastric ulcers, 67 were biopsied, 63 were benign, 2 malignant, 2 demonstrated metaplasia and 1 revealed dysplasia.

Of all perforated ulcers biopsied (gastric and duodenal), two ulcer biopsy specimens (one an incision biopsy [not four quadrants] and the other an excision biopsy) were malignant. Three revealed metaplasia, (perforated GU, distal gastrectomy done and metaplasia noted in sections away from ulcer, another excisional biopsy revealed intestinal metaplasia and the third, a perforated DU, distal gastrectomy done, showed metaplasia at the edges of the duodenum). Two revealed dysplasia and one demonstrated features of a chemical etiology.

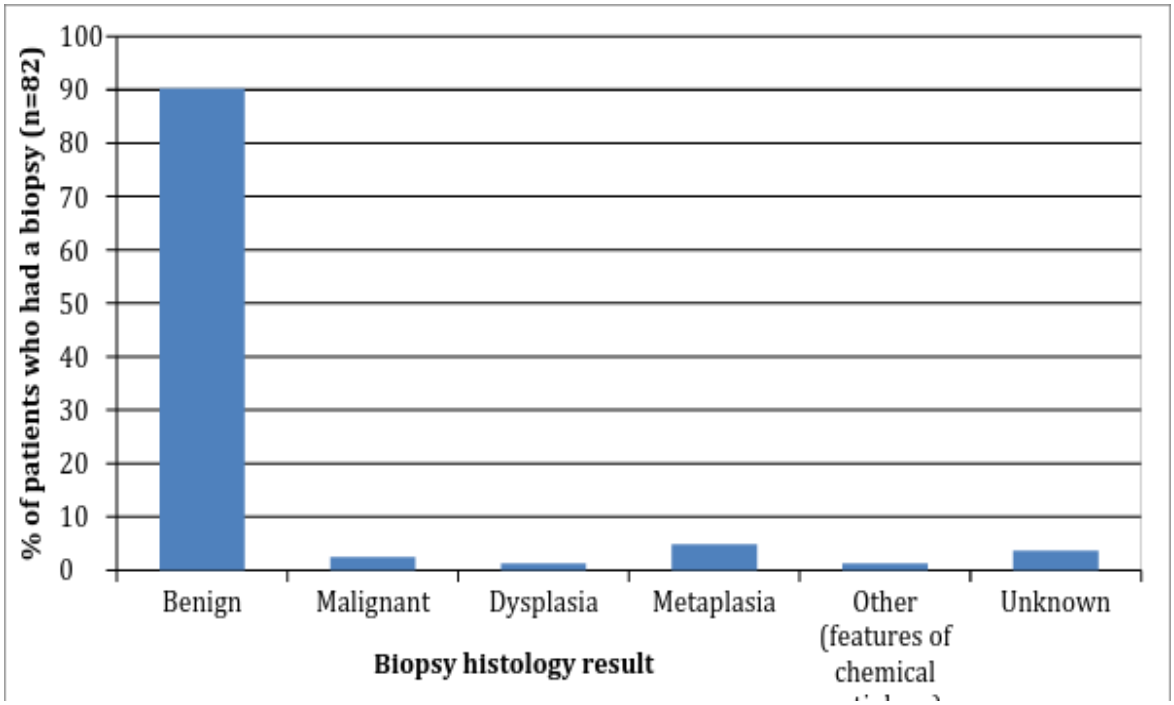


Figure 7: Histology results for intraoperative biopsy of perforated ulcers

One patient was a 72 year old HIV negative male, with no documented risk factors, who had hemodynamic instability (BP 84/65 mmHg) and delayed presentation (>24hrs) of a perforated gastric ulcer on the anterior wall of the stomach (Type 4 modified Johnson classification, proximal/close to the GOJ, size not documented). At laparotomy, two incisional biopsies done, (not four quadrant) that were considered to be adequate i.e. mucosa and viable tissue represented. They revealed invasive poorly differentiated adenocarcinoma with signet ring morphology, extending through the stomach wall (Stage IIIB). No Lymph node LN biopsy was done and there was no comment by the pathologist on the infectious organisms (*H. pylori*) but he received *H. pylori* eradication therapy and the length of hospital stay was 12 days. He returned six weeks later for follow up outpatient gastroscopy, that was found to be suspicious as he had a dilated distal esophagus, distorted oesophago-gastric OG junction and the tumor noted in the proximal stomach at the cardia, fundus, lesser curvature, no obstruction. No biopsy was done at gastroscopy as he already had tissue diagnosis of the tumor from the intra-operative biopsy.

The second malignancy was diagnosed in a 27 year old HIV negative female, risk factors unknown (missing records) who presented with pancytopenia and a single antral perforated gastric ulcer, 15x14x8mm, (<3cm, not a giant ulcer), and excisional

biopsy of the ulcer was done at a laparotomy, this was considered to be adequate by the pathologist as there was representation of both viable tissue and mucosa. It returned as a signet ring cell/diffuse type adenocarcinoma. Stage IIIc: pT4b pN3 If Mo. No infectious organism or H. Pylori was seen. No LN biopsy was done. She was discharged and went on to have a gastrectomy but her records are lost. She probably had her pre-gastrectomy/pre-operative gastroscopy in theatre done by the surgeon, as there seems to be no record of her returning for a follow up gastroscopy.

4.3.3.3 *H. pylori*

59.8% of the biopsies had no infectious etiology (19.6% missing data). One case of *H. pylori* infection was noted in a gastric ulcer biopsy. An incisional biopsy was done and two specimens sent off [not four quadrant] in a 23-year-old male with no risk factors for PPU. His HIV status was unknown and he presented late [>24hrs], hemodynamically stable [sBP>100], with a single perforated prepyloric ulcer [type 3 modified Johnson classification]. A laparotomy and adequate biopsy with mucosa represented was done and no relooks. His length of hospital stay was five days and H. pylori eradication therapy was given but he never returned for a follow-up outpatient gastroscopy.

Of the biopsied perforated gastric ulcers, 12 (12.8%) had fungal elements/candida noted. No tuberculosis TB, cytomegalovirus CMV or any other HIV/AIDS related opportunistic infections were noted in any of the biopsies.

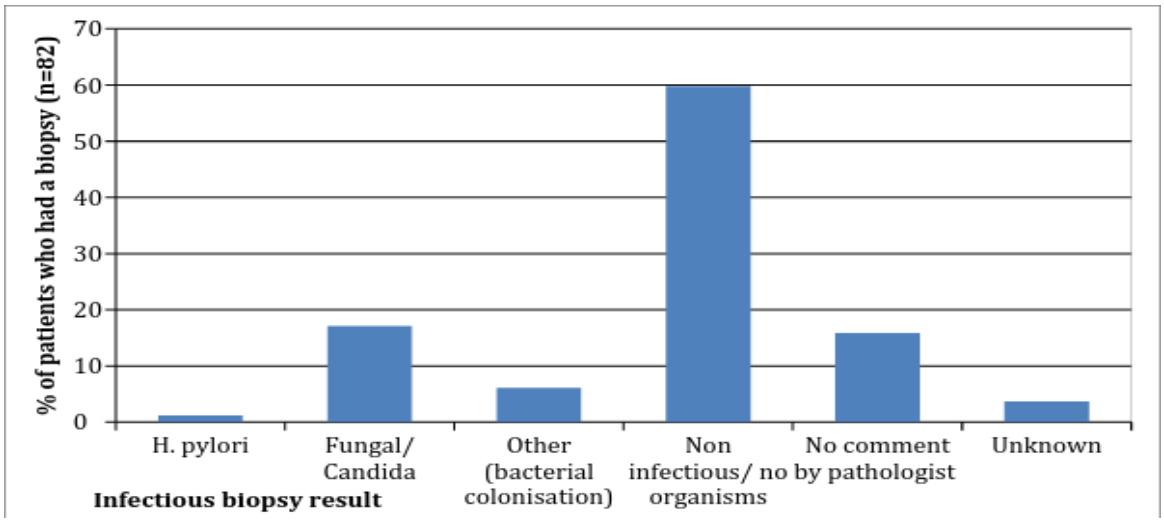


Figure 8: Infectious biopsy results for the intraoperative biopsy

Table 7: Summary of study findings

	ALL PERFORATED ULCERS (GU, DU & GDU)	**PERFORATED GASTRIC ULCERS**
SITE & NUMBER[1]	173	93 (54.4%)
GU	93 (54.4%)	
DU	74 (43.3%)	
GDU	4 (2.3%)	
Unknown	2(1.2%)	
DEMOGRAPHICS		
Mean age (years)	44.1 (SD ±16.9)	47.0 (SD ±18.3)
Male: Female ratio	3 : 1	2.3 : 1
Risk factors[2] (%)		
Smoking	49.7%	55.9%
NSAIDS	30.0%	40.9%
Alcohol	35.1%	34.4%
PUD	20.5%	24.4%
HIV status		
Positive	9/171 (5.3%)	6/93 (6.5%)
Negative	48/171 (28.1%)	29/93 (31.2%)
Unknown	114/171 (66.7%)	58/93 (62.4%)
CLINICAL PRESENTATION		
Early (<24hr)	66 (38.6%)	35.5%
Late (>24hr)	79 (46.2%)	49.5%
Unknown	26 (15.2%)	15%
INTRA-OPERATIVE BIOPSY		
Number of ulcers biopsied	82/173	67/93
Ulcer Size		
No. of Giant ulcers[3]	3/173	3/93
Quality of intra-operative biopsy specimen		
Adequate	34 (41.5%)	25.0%
Inadequate[4]	45 (54.9%)	45.2%
Histology/Biopsy results		
Benign	74/82	63/67
H. pylori	1	1
Fungal/Candida	14/82	

	ALL PERFORATED ULCERS (GU, DU & GDU)	PERFORATED GASTRIC ULCERS
Malignant[5]	2/82	2/67
Dysplasia	2/82	1/67
Metaplasia	3/82	2/67
Other[6]	1/82	
Lymph node LN biopsy	6	3
LN biopsy result		
Malignant[7]	1/6	1/3
Benign	5/6	2/3
Mortality rate[8] (In-hospital)	28 (16.4%)	18 (19.4%)
Follow-up gastroscopy		
Attendance	19	8
Non-attendance	124	67
Biopsy done	2/19	

[1]There were a total of 171 patients. A single perforation site was noted in 168 patients while three patients had two synchronous sites of perforation.

[2] Risk factors: Don't add up to 100% as some patients had more than one risk factor e.g. smoking and NSAID use, while some had none documented.

[3]Giant ulcers were those with a ≥3cm diameter.

[4]An inadequate biopsy specimen is one that lacked mucosa or viable tissue in the specimen or wasn't sent in formalin.

[5]One Signet ring cell type adenocarcinoma and one adenocarcinoma with neuroendocrine differentiation)

[6]Other (features of chemical aetiology)

[7]LN biopsy showing mucinous adenocarcinoma with neuroendocrine features.

[8] Demised during the same admission and therefore did not qualify for follow-up gastroscopy.

4.3.3.4 Intra-abdominal lymph node biopsy

Intra-abdominal lymph node LN biopsy was done in 5/171 (2.9%) of the patients, while one patient had a LN picked up in the omentum. Of the six LN biopsy specimen analyzed, five (83.3%) were benign and one malignant. A mucin producing adenocarcinoma with neuroendocrine features was picked up in the lymph node biopsy of a 24year old male who presented with a perforated gastric ulcer. The incisional biopsy of the gastric ulcer returned as benign/ no malignancy noted while the LN biopsy is the one that revealed the malignancy. Three of these LN biopsies were done in patients with perforated gastric ulcers. One returned as malignant.

4.3.3.5 Stage and type of malignancy

All the three patients had Stage III disease. (Two signet ring cell type adenocarcinoma and one adenocarcinoma with neuroendocrine differentiation)

4.3.4 Postoperative management

Data on *H. pylori* eradication and relook operations done during the postoperative management of the patients is presented in Table 12.

Table 8: Postoperative management

	Number		**Percentage**
H.pylori eradication therapy	Yes	77	45%
	No	59	34.5%
	Unknown	35	20.5%
Relook operations	Yes	34	19.9%
	No	110	64.3%
	Unknown	27	15.8%

4.3.4.1 H. pylori eradication therapy

Overall, despite one patient having *H. pylori* diagnosed on biopsy, 45.0% of the patients were given *H. pylori* eradication therapy, while 34.5% were not. Of all patients with perforated gastric ulcers, 50% received *H. pylori* eradication therapy.

4.3.4.2 Relook operations

Figure 9 is a bar graph of the frequency and the percentage of patients that underwent relook operations. The median number of relook operations was one (IQR 1-2: range 1-7). Timing of re-look operations (2.9% missing data): 64.7% of the patients had their first re-look surgery days 0-2 postoperatively (with 47.1% of first re-looks occurring on day two), while the rest had their first re-look surgery between day three and 13. Of the gastric ulcer patients that underwent operative management (n = 93), 23 (24.73%) underwent relook operation while 54 (58.06 %) did not. Average length of hospital stay couldn't be assessed due to 35.1% missing data

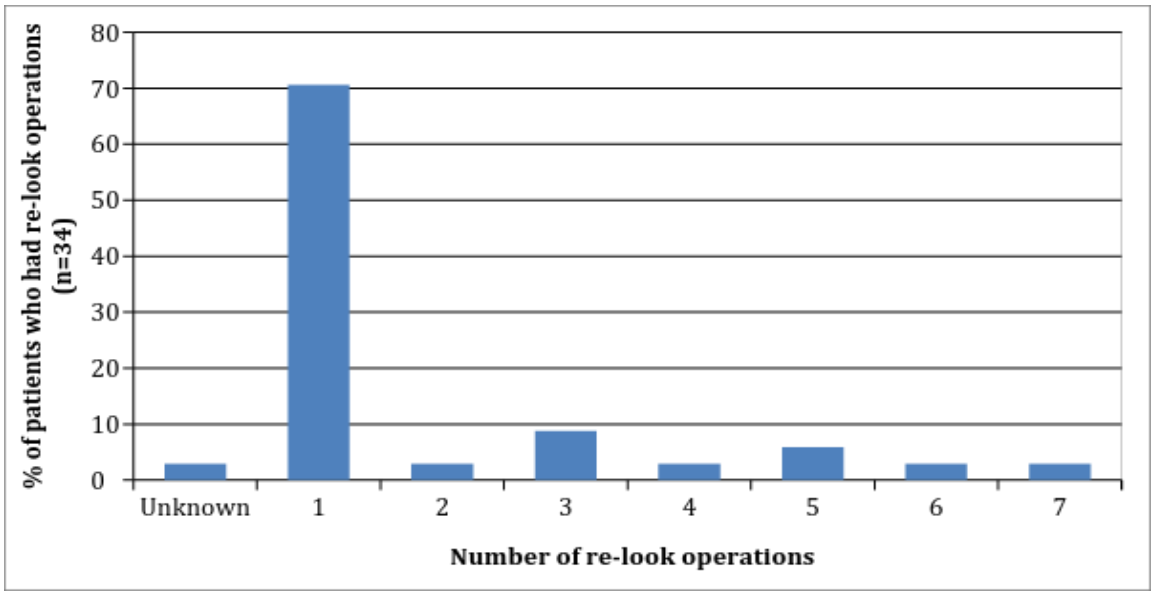


Figure 9: Number of relook operations

4.3.4.3 Outcome

Of all patients with perforated ulcers, 67.3% were discharged. Mortality rate was 16.4%. (16.4% missing data) The median time to death was 5.5 days post operatively. (IQR 2 - 10.5 days: range 0 - 31 days). The mortality rate was 19.35% for perforated gastric ulcers that underwent operative management.

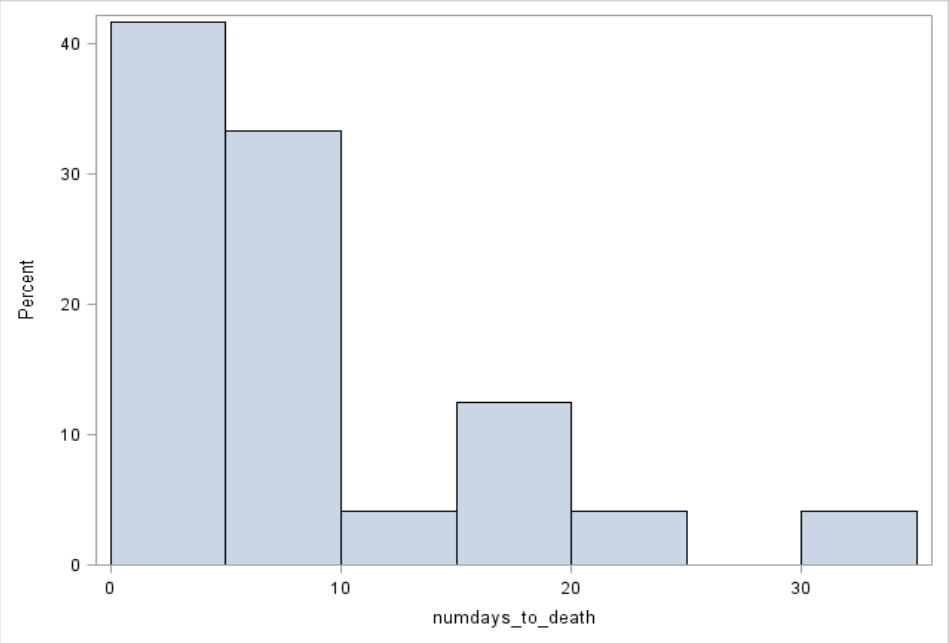


Figure 10: Number of days to in-hospital patient death

Key: y-axis: Number of patients as a percentage (%)
x-axis: Number of days from surgery to patient's death in hospital

4.4 Follow-up gastroscopy

4.4.1 Compliance

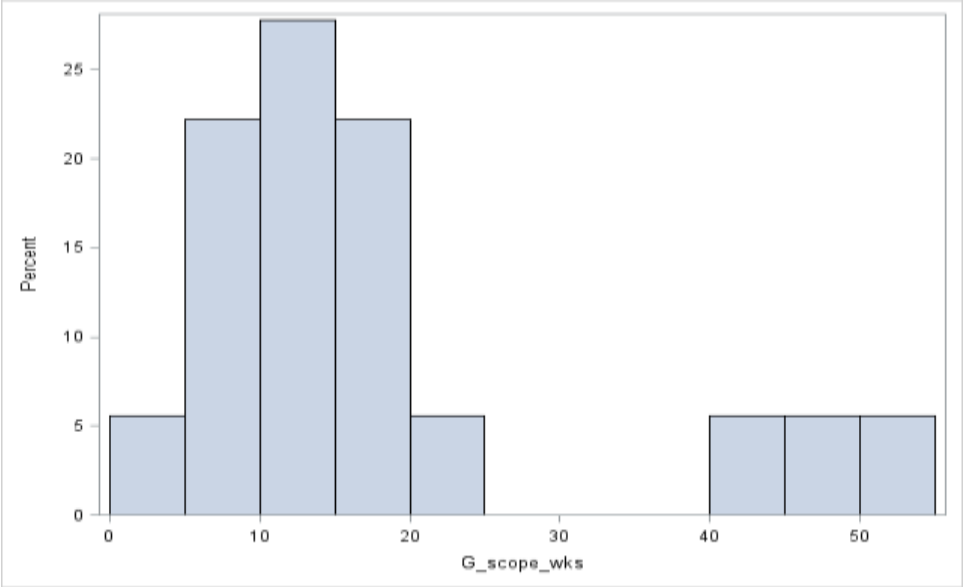
Table 13 below represents data on compliance in follow-up gastroscopy. Overall majority 124 (72.5%) defaulted and only 19 (11.1%) of patients returned for follow up gastroscopy. Post operatively, 16.4% (n = 28) had died in hospital and thus did not qualify for follow up gastroscopy. Of the patients with perforated gastric ulcers, 8/93 (8.06%) returned for follow-up gastroscopy over the three-year period (2010 – 2012). Some patients, 67 (72.04%) patients defaulted and 18 (19.35%) died during the same admission and therefore did not qualify for follow-up gastroscopy.

Table 9: Compliance in follow-up gastroscopy

Follow-up gastroscopy	All perforated ulcers		Perforated gastric ulcers	
	Number	Percentage	Number	Percentage
Done	19	11.1	8	8.6
Not done (Patient died)	28	16.4	18	19.4
Not done (Patient non-attendance)	124	72.5	67	72
Total	171	100.0	93	100.0

4.4.2 Timing

Median duration between surgery and follow up gastroscopy was 12.5 weeks (IQR 8-18 weeks; range 4- 52 weeks) (5.3% missing data)



Timing of post-operative gastroscopy in weeks

Figure 11: Follow up period for outpatient gastroscopy for PPU in weeks

Key: y-axis: Number of patients as a percentage (%)

x-axis: Time from surgery to follow-up gastroscopy (weeks)

4.4.3 Findings and biopsy results

Biopsy during post-operative gastroscopy is recommended but of the 19 (11.1%) patients who returned for follow-up gastroscopy, only two had biopsy done. This was despite the fact that the doctors noted worrisome or suspicious findings during gastroscopy in 26.3% of cases. For example, in one patient, a large fungating (Forrest III) ulcer involving the lesser curvature of the stomach and a prominent antrum were noted and a non-benign lesion NBL or an infiltrative lesion or lymphoma was queried but yet no biopsy was done.

5 DISCUSSION AND CONCLUSIONS

5.1 Summary (Results pertaining to research questions)

5.1.1 Proportion of *H. pylori* in perforated gastric ulcers

For the 93 perforated gastric ulcers, 67 intra-operative biopsy specimens were sent off of which one was positive for *H. pylori* infection (1.5%).

5.1.2 Proportion of malignancy in perforated gastric ulcers

Of the 67 intraoperative biopsy of the ulcer done, two (2.94%) of the biopsy specimen tested positive for malignancy. In one gastric ulcer, the ulcer biopsy did not reveal malignancy but the LN biopsy was positive for malignancy.

5.1.3 Compliance in follow-up gastroscopy

The non-attendance rate for follow-up gastroscopy was more than 70%. Only 8-11% of patients returned and this was after extending the study for one more year. Overall majority 124 (72.5%) defaulted and only 19 (11.1%) of patients returned for follow up gastroscopy. Of the patients with perforated gastric ulcers, only eight (8.6%) out of 93 returned for follow up gastroscopy over the three-year period (2010 – 2012) and 67 (72.04%) defaulted/ did not return.

5.2 Demographics

5.2.1 Age and gender

Unlike European studies that reveal an increase in the age of presentation to 60s and a decrease in the incidence of PPU's in the male population and thus a normalization of the male: female ratio that was previously 4-5:1 to now being almost 1:1, this study was in keeping with other African studies in that most of the patients were young in their 3rd and 4th decades of life (20-39 years) with the mean age being 44.1 (SD ± 16.9) and 47.0 (±SD 18.3) years for all perforated peptic ulcers and perforated gastric ulcers respectively and PPUs being more common in males with a male to female ratio of 3:1 and 2.3:1 for all perforated peptic ulcers and perforated gastric ulcers respectively (Chalya, Mabula et al. 2011, Ugochukwu, Amu et al. 2013, Søreide, Thorsen et al. 2015).

The mean age of patients with perforated ulcers in this study was noted to be 10 years younger than that reported 30 years ago in a similar study done in one of the hospitals included in this study (HJH previously the J. G. Strijdom Hospital) at which time the reported mean age for PPUs was of 55 years then (Schein, Saadia et al. 1986). It is now 44 years in this study while that of perforated gastric ulcers has increased from 43 years to 47 years in this study (Schein, Saadia et al. 1986, Madiba, Nair et al. 2005). In 1980, the life expectancy in South Africa was 58 years. There has been no significant change in the life expectancy (57 years) in South Africa from1980 to date (TheWorldBank , TheWorldBank 2015). Therefore in view of an unchanged life expectancy, a change in life expectancy does not explain the 10-year decrease in age of incidence of perforated peptic ulcers.

Overall for all perforated ulcers, the male: female ratio was 3:1 and more specifically 4.3:1 for perforated duodenal ulcers and 2.3:1 for perforated gastric ulcers. This is also different from the trend noted in Western countries where there is a trend towards an equalizing of the male: female ratio to 1:1. Whether this equalization in the male: female ratio of perforated gastric ulcers is not seen locally as a result of the prevalence of smoking, the main risk factor for perforated gastric ulcers, is still being higher in males than females locally, is unknown.

5.2.2 Risk factors

Smoking, NSAID use and PUD were the most prevalent risk factors in keeping with global findings. This finding is important for public and patient education on the harmful effects of smoking and over the counter NSAID use.

5.2.3 HIV status

The World Health Organization reported a global HIV prevalence of 0.8% for adults aged 15 – 49 years in 2013 (WHO 2013). This figure is an aggregation of prevalence figures over different geographical blocks of regions and/or continents of the world i.e. Africa 4.2 %, South- East Asia 0.3%, Europe 0.4%, Eastern Mediterranean 0.1% and West pacific 0.1% respectively. The Joint United Nations Programme on HIV/AIDS reported the prevalence in South Africa as 18.8% (UNAIDS 2015). For most patients (66.7%) in this study, their HIV status was unknown, resulting in too few observations to draw any conclusions.

The HIV status of the patients was intended to help in the interpretation of the findings of infective causes of ulcers other than H. pylori. It was anticipated, that several AIDS related opportunistic infections such as CMV and TB would be found as aetiological agents especially considering that the prevalence of HIV in South Africa is very high at 18.8%. These infections could then be addressed early on diagnosis and directed treatment initiated promptly when diagnosed. Furthermore with only one third of the patients having their HIV status known, and even fewer having their CD4 count and viral load known, the HIV data and associated variables were insufficient for further analysis or drawing any conclusions.

> **Recommendation:** As a country with an ongoing HIV epidemic and multiple government policies in place trying to combat this problem, greater effort should be exerted by treating physicians to ensure that every contact between physician and patient (admitted patients) serves as an opportunity to recommend HIV VCT.

5.3 Perforated ulcers data

5.3.1 Clinical presentation

For the patients with perforated gastric ulcers 49.5% had delayed presentation, 35.5% had an early presentation and for 15.0% the timing of their presentation was unknown. Some patients come in as transfers from other institutions with insufficient information and history available or documented. At the time of arrival the patient may have been intubated, in shock or having a low Glasgow coma scale and thus unable to supply sufficient history.

The mean SBP at presentation was 121 mm Hg. The majority of patients (63.7%) were hemodynamically stable but the interpretation of this data regarding how ill the patient was at the time of admission must be done with caution. Firstly, data for 21.6% of the patients was missing and secondly, the study hospitals often received patients transferred from other (level 3, 2 and 1) hospitals and surrounding clinics that would have initiated patient resuscitation prior to transfer. Therefore the blood pressure taken at admission in the study hospitals in that case would have been a post resuscitation BP and thus not a true reflection of the patient's severity.

The assumption had been that patients who presented late (>24hrs after onset of symptoms) or who were in shock at the time of presentation would subsequently have a poor outcome e.g. longer hospital stay, more relook operations or subsequent re-operations and may be even ultimately die. But in view of the fact that admission SBP data was unreliable this hypothesis could not be confirmed.

5.3.2 Characteristics of the perforated ulcer

Perforated gastric ulcers were more common than perforated duodenal ulcers (54.4% vs. 43.3%), with a ratio of 1.26: 1. In this respect, the data from this study mimics the changes noted in the West and Europe where there has been a shift from the previously predominantly duodenal ulcers to an increase in the incidence of gastric ulcers (Søreide, Thorsen et al. 2015). The ratio of gastric to duodenal ulcers locally 30 years ago was 1: 2.06 with duodenal ulcers being more common (Schein, Saadia et al. 1986). The reason for this change is unknown. For perforated gastric ulcers GU, the male: female ratio was 2.3:1 and for duodenal ulcers 4.3:1.

Most (68.8%) of the perforated gastric ulcers GU were type 3 of the modified Johnson classification (66 out of 96) i.e. pre-pyloric gastric ulcers within 3cm of the pylorus without duodenal ulceration or scarring, followed by type I (9.4%) and type II and IV were both 3.1%. This is unlike previous studies that had higher rates of type I ulcers i.e. body of the stomach ulcers with no associated abnormalities of the duodenum, pylorus or prepyloric area, than type II ulcers (McGee and Sawyers 1987).

While most patients with perforated peptic ulcers usually present with a single perforation site, as demonstrated by 98.2% of the patients in this study who had a single perforation site, synchronous perforated ulcers do occur. Synchronous perforated ulcers are rare, a PubMed search revealed two case reports. Of the 171 patients in this study, three (or 1.75%) had synchronous gastric and duodenal ulcer perforations. Three of the 93 patients with perforated gastric ulcers had synchronous perforations. The synchronous ulcers may require further investigations such as assessment of serum gastrin level to rule out gastrinoma and other causes of atypical PUD, but it was not clear from the patient records if this was done.

5.3.2.1 Number of intra-operative biopsies done

Despite the current recommendation for routine intraoperative biopsy of perforated gastric ulcers only 75.27% of the perforated gastric ulcers were biopsied. The 25% non-biopsy rate becomes more significant in light of the very high non-attendance rate for follow up gastroscopy noted in the local patient population. *Intra-operative biopsy may be the only opportunity available for the surgeon to biopsy the patient's perforated gastric ulcer.*

In this retrospective study 171 patients underwent operative management of PPU. All patients underwent open surgery/ laparotomy except one who had laparoscopic surgery but subsequently needed a relook laparotomy. Most patients had open laparotomy, as the procedures were emergencies often done after hours by trainees who might have lacked proficiency and confidence in their laparoscopic skills. Also when done after hours in most of the hospitals in this study, laparoscopic surgery by trainees might not have been encouraged, and equipment may have been inaccessible.

> **Recommendation**: Expertise in laparoscopic surgery should be encouraged among trainees, as it's a safe and viable option that is comparable to open surgery with regards to repair of the perforated ulcer, and offers the additional benefits of lower rates of surgical site infection SSI, postoperative pain and a shorter hospital stay (Bhogal, Athwal et al. 2008, Tan, Wu et al. 2016).

5.3.2.2 Site of perforation

While in the past the duodenal ulcers were more common, lately there has been a trend worldwide with an increase in the ratio of gastric ulcers compared to duodenal ulcers. This study had more gastric ulcers (54.4%) than duodenal ulcers (43.3%) the significance of this shift is not known. It can't be attributed to an increase in *H. pylori* causing gastric ulcers, as the prevalence of *H. pylori* in this study was very low (one out of 173 perforated ulcers). But the fact that most of the biopsy specimen were considered to be inadequate with no mucosal representation and the fact that *H. pylori* is a microaerophilic bacterium found in the mucosal lining of the stomach, means that if the mucosa is not represented, the chances of *H. pylori* diagnosis in

the gastric ulcer biopsies are significantly reduced. This is why the decision by Kumar S. et al (2004) to not only use three different techniques (rapid urease test, culture and histological examination) in an attempt to increase their chances of identifying the *H. pylori* organisms, but also more specifically to obtain multiple mucosal biopsies by introducing biopsy forceps through the perforation site is unique and should be adopted and encouraged (Kumar, Mittal et al. 2003).

> **Recommendation**: This study has demonstrated that the non-attendance rate for follow up gastroscopy is very high. Furthermore there is a high rate of inadequate intra-operative biopsies, primarily due to lack of mucosal representation.
>
> The technique of intraoperative biopsy of gastric mucosa must be improved. Perhaps by using biopsy forceps e.g. endoscopic biopsy forceps i.e. in addition to doing the four quadrant incisional biopsy, to ensure mucosal representation thus increasing the chances for malignancy and *H. pylori* detection. The incisional biopsy is still important for T staging of malignancy if present, as it will reveal the deepest layer of the stomach wall invaded.

Regarding the ulcer location, the study found that the surgeon and pathologist agreed in 74% of the cases. This error often comes about when dealing with ulcers along the pyloric channel, i.e. distal stomach close to the pylorus and ulcer in the first part of the duodenum very close to the pylorus, in which the position of the pylorus can't be clearly identified. This may arise because most surgeons intraoperatively when in doubt regarding the ulcers site didn't go through the extra effort of trying to put in a catheter and acertain where the ulcer site is, especially for pyloric channel or proximal duodenal ulcers.

> **Recommendation**: In such cases if a laparotomy has been done, a small Foley catheter should be used to try and determine the position of the pylorus in relation to the ulcer by inserting it through the perforated ulcer, insufflate with 2 ml of water or air and then draw back the Foley catheter towards the perforated ulcer site. The pylorus should hold up the catheter bulb and therefore one can determine if the pylorus is proximal (in a duodenal ulcer) or distal (in a gastric ulcer) to the pylorus. If the procedure is done laparoscopically and ulcer site unclear, the surgeon should err on the side of

doing a biopsy. This site of the ulcer can also later be correctly confirmed on follow up gastroscopy.

5.3.2.3 Ulcer size

Ergul and Gozetlik (2009) suggested that an ulcer perforation size of greater than 0.5cm was a feature suggestive of an increased risk of malignancy but unlike their suggestion, none of the four giant gastric ulcers (diameter of greater than 3 cm) noted in this study was malignant (Ergul and Gozetlik 2009).

5.3.2.4 Type of biopsy done

For the perforated gastric ulcers (n = 93), intra-operative biopsy was conducted in 75.27% of the cases. Of those biopsied 54 (58.06%) were incision biopsies, most surgeons took only one biopsy unlike the recommended 4-quadrant biopsy, and 12 (12.91%) were excision biopsies.

Of the gastric ulcers, 6 (6.45%) underwent excision biopsy of the entire ulcer, either as a partial gastrectomy or as a limited excision biopsy of the ulcer, and only two had four quadrant incision biopsy done. 88.17% had less than the recommended four quadrant biopsies done (≤ 3 incision biopsies done). This may be a contributing factor as to why the pick-up of malignancy is low. Other types of biopsies carried out intra-operatively included biopsies of adjacent lymph nodes, omentum and partial gastrectomies and in some cases, while the actual intra-operative ulcer edge biopsy revealed no malignancy.

Recommendation: In cases where the surgeon has a high index of suspicion for a malignant perforated ulcer, biopsy should be done not only of the ulcer edge but also of an adjacent lymph nodes.

5.3.3 Biopsy specimen

5.3.3.1 Adequacy of the intra-operative specimen

Of the perforated gastric ulcers biopsied 25 (26.88%) were adequate biopsies. 42 (45.16%) were considered inadequate. Of those considered to be inadequate, 97.62% were considered so due to lack of mucosa on the biopsy specimen and 2.38% due to a lack of viable tissue in the specimen received by the pathologist or inappropriate transport media e.g. saline instead of formalin.

For detection of *H. pylori*, rapid transportation of *H. pylori* in Stewart's transport media is recommended to avoid drying of this microaerophilic organism, if unavailable, normal saline with 20% glucose and glycerol can be used as a substitute transport media for *H. pylori* culture. Locally, *H. pylori* culture is hardly ever requested. Often, Normal saline alone is used as the transport media for *H. pylori* mucosal biopsies intended for culture and formalin is used as the transport media for preservation of the biopsy specimen intended for histological assessment.

> **Recommendation**: A prospective trial should be conducted comparing the diagnostic rate for *H. pylori* in specimen sent in normal saline versus normal saline with 20% glucose and glycerol to see whether there would be an increased diagnosis of *H. pylori* and whether this would be significant to result in a recommendation in change of practice. The concern though is that the diagnosis of *H. pylori* seems to be multifactorial with multiple influences i.e. not just the transport media but also the quality of the biopsy specimen received (mucosa represented, four quadrant etc.).

5.3.3.2 Biopsy result

Of all the perforated ulcers biopsied (n = 82), 90.2% of the cases were benign and 2.4% were malignant. (The percentages do not sum to 100% as some patients had more than one result).

There were 93 perforated gastric ulcers of which 67 (72%) were biopsied. 26.9% were considered to be adequate by the pathologist. The rest were considered inadequate as they lacked viable mucosa etc. but despite the fact that most (>70%) were considered to be inadequate, the pathologists were still able to report on them. 63 (92.6%) were benign, 2 (2.99%) malignant, 2 (2.9%) demonstrated metaplasia and 1 (1.5%) revealed dysplasia.

Unfortunately, this study failed to achieve the number required for significance as calculated by the power analysis. Thus despite 2.94% malignancies being detected, a strong recommendation cannot be made. But in view of the high non-attendance rate in follow-up gastroscopy in this cohort of patients, i.e. the local patients seen in this study, the suggestion should be that intra-operative biopsy should be done as it may be the only contact with the patient that will offer an opportunity for biopsy to check for malignancy and *H. pylori* infection.

5.3.3.3 H. pylori

The unique aspect was on the results on the H. Pylori prevalence. In that only one patient had H. pylori diagnosed yet studies suggest that prevalence should be higher in young male patients < 40yrs with duodenal ulcer in low and middle income countries (Søreide, Thorsen et al. 2015). This wasn't the case noted in this study. The finding raises the question of whether this is an accurate reflection of the prevalence of H. pylori in the local population or whether the low prevalence is rather a reflection of the inadequate biopsy technique and high non-attendance rate in follow up gastroscopy. This study involved histopathological examination of gastric tissue biopsy specimen the gold standard in the diagnosis of *H. pylori*, therefore the diagnostic technique cannot be faulted. It thus becomes an issue of the quality of the specimen received and this has been demonstrated in this study to be suboptimal/inadequate.

Of the 93 perforated gastric ulcers in this study, 24 (25.81%) did not undergo intraoperative biopsy. Of those biopsied (n=67), only 25 (37.31%) were adequate specimen. 97.62% were considered inadequate due to a lack of mucosa on the biopsy specimen and 2.38% due to a lack of viable tissue in the specimen received by the pathologist. This large number of inadequate specimen compounded by the 25% non-biopsy rate may be the reason why there was only one case with *H. pylori* infection diagnosed out of 67 perforated gastric ulcer biopsy specimen.

Of all the perforated ulcers, no TB, CMV or any other HIV/AIDS related opportunistic infections were noted in any of the biopsies. The question arises as to whether or not this is a true reflection of the local cohort or whether this is another effect of the inadequate biopsy specimen.

5.3.3.4 Intra-abdominal lymph node biopsy

Three LN biopsies were done in patients with perforated gastric ulcers and one returned as malignant. A mucin producing adenocarcinoma with neuroendocrine features was picked up in the lymph node biopsy of a 24 year old male patient who presented with a perforated gastric ulcer. The incisional biopsy of the gastric ulcer returned as benign/ no malignancy noted while the LN biopsy is the one that revealed the malignancy.

Recommendation: In cases where the surgeon has a high index of suspicion for a non-benign cause of the perforated ulcer, biopsy should be done not only of the ulcer edge but also of an adjacent lymph nodes.

5.3.4 Postoperative management

5.3.4.1 *H. pylori* eradication therapy

Overall (171 patients), despite the fact that only one patient had *H. Pylori* diagnosed on biopsy, 45.0% of the patients were given *H. pylori* eradication therapy. Of all patients with perforated gastric ulcers, 50% received *H. pylori* eradication therapy. This is concerning especially on the current background of antibiotic resistance but at the same time one cannot overlook the fact that most of the biopsies done were inadequate and that might explain the low *H. pylori* pick up rate.

Recommendation: To be able to conclusively comment on whether or not *H. pylori* eradication therapy should or shouldn't be given, a prospective trial with optimal intraoperative biopsy and repeat biopsy for histology and CLO- test at follow-up gastroscopy should be undertaken alongside using non-invasive tests to detect *H. pylori* e.g. the Urea breath test. Techniques such as use of endoscopy biopsy forceps intra-operatively or excisional biopsies may be used to ensure adequate mucosal sampling and inclusion in the specimen.

5.3.4.2 Outcome

Despite the fact that 46.6% of the patients in this study had delayed presentation (≥ 24 hrs. after onset of symptoms), which typically should result in a poorer outcome, this wasn't the case. The relook rate was high at 19.9%, which may be anticipated in view of the delayed presentation but considering all but one patient had an open laparotomy at which point adequate exposure and peritoneal washout could be done and not laparoscopic surgery, perhaps the relook rate should've been lower. But remember that delayed presentation may be associated with omental patch failure and resultant leaks, which may explain the high, relook rate. This is all assumption.

The mortality rate, though comparable to what is seen internationally, was still low at 16.4% compared to 30 years ago when it was 25.6% (Schein, Saadia et al. 1986). With a 46.6% delayed presentation rate, it was expected that the mortality rate would be higher than what is seen internationally but the large younger patient

demographic of 20 to 40 years seen locally may mean that these patients have better physiological reserve and thus can tolerate physiological insults better than the 60 -70 age group of patients seen in most western and European countries. This younger patient age must have attributed to better patient outcomes.

5.4 Follow-up gastroscopy

5.4.1 Compliance, timing, findings and biopsy results

This study revealed not only a high follow-up gastroscopy non-attendance rate of greater that 70% but also the patients that did return for the gastroscopy returned late. The median duration between surgery and follow up gastroscopy being 12.5 weeks (over 3 months) and not the recommended 6-8 weeks.

Only eight out of 75 patients who had undergone surgery for perforated gastric ulcers and 19 out of the to 143 patients for all perforated ulcers returned for follow-up gastroscopy. Eighteen of the 93 patients with perforated gastric ulcers and 28 of the 171 patients with all perforated ulcers, died in hospital and therefore weren't eligible for the follow up gastroscopy. This three month delay is significant for patients with a malignancy or for patients with *H. pylori* infection as it could result in progression of their cancer, non-healing ulcers, new bleeding and other complications.

This was a crucial finding of this study. If the thought process was that intraoperative biopsy of the GU's could be waived and the ulcer biopsied at another sitting when the patient returned for follow-up gastroscopy, the high non-attendance rate precludes this. In two of the hospitals included in this study (CHBAH and HJH) gastroscopy is done without any sedation while in the third hospital (CMJAH) conscious sedation is used (Midazolam and Alfentanil) but across the board, compliance/attendance with regards to patients returning for their follow up outpatient gastroscopy was poor at only 11%.

As for the question of whether most of these patients are returning to their primary hospitals for follow-up and gastroscopy, and not the study hospitals where they had their surgery, it's unlikely as some of the referring hospitals and clinics may not have endoscopy facilities. In addition upon discharge, the patients are given follow up gastroscopy and surgical outpatient department OPD appointments at the hospital where the surgery was done.

The other concerning issue was the fact that despite the recommendation for biopsy at follow up gastroscopy, for even the few patients that did return for follow-up gastroscopy, no biopsies were done at the time of the endoscopy.

> **Recommendation**: Intra-operative biopsies should be routinely performed in perforated GU's, with, measures put in place to improve attendance in follow-up gastroscopy and establish the reasons for the low attendance rate. Furthermore, endoscopists should also be reminded of the recommendation for biopsy at follow up gastroscopy.

5.5 Challenges

5.5.1 Sample size

The figure (171) indicates patients with either or both perforated gastric and duodenal ulcers. The reason for collecting both gastric and duodenal ulcers (and not just gastric ulcers as indicated in the study title) was to avoid erroneous exclusion of any patients that met the inclusion criteria. During data collection, it was noted that there were several patients in whom the surgeon didn't document in the operative notes where the actual site of the perforated ulcer was i.e. whether it was a gastric or duodenal ulcer or who loosely used the term "perforated peptic ulcer disease PUD".

There was also the issue of discordance between where the surgeon thought the ulcer was and the histological assessment of the specimen by the pathologist who examined the mucosa in the specimen and was able to specify the exact site of the ulcer e.g. whilst the surgeon may have documented the site of the ulcer as being gastric, assessment of the specimen by the pathologist might have indicated otherwise e.g. that the ulcer was actually situated in the duodenum. In cases of ulcer site discordance, the ultimate ulcer site was taken as that determined by the pathologist on histopathology assessment.

Based on this, the data collection sheet was completed for all patients with perforated ulcers who underwent operative management (171). These were then divided into gastric (93), duodenal (74) and gastroduodenal ulcers (four). In two of the perforated ulcers, despite review of all records, the exact site of the ulcer (whether gastric or duodenal) could not be established and thus were excluded.

The study required a sample size of 384 perforated gastric ulcer intra-operative biopsy specimen, but after first one year then extended to two years, the sample size wasn't achieved and data collection and further enrollment into retrospective review was discontinued. There were three reasons for this. Firstly, despite the fact that very many patients had perforated ulcers, in very many, intra-operative biopsy wasn't done despite the patients undergoing operative management.

Secondly, in majority of those that underwent operative management, the intra-operative biopsy specimen was inadequate e.g. it wasn't a full thickness biopsy and mucosa wasn't represented. Meaning that even if the retrospective study was extended to include ten years and the 384 perforated gastric ulcer biopsies were analysed, if they are inadequate biopsies with no mucosal representation, then bearing in mind that *H. pylori* are found in the mucoid lining of the gastric mucosa and that primary gastric malignancy often begins in the mucosal layer and then grows into the submucosa and muscularis layers, very many cases of *H. pylori* and some of early malignancy are likely to be missed resulting in an erroneously low prevalence rates.

Thirdly, the study aimed to analyse the findings on intraoperative biopsy specimen and compare with the findings in the six weeks postoperative follow up gastroscopy biopsy specimen. But it was found that there was a very high non-attendance rate for the follow up gastroscopy i.e. out of 171 patients, majority 124 (72.5%) defaulted and only 19 (11.1%) patients returned for follow up gastroscopy. 28 patients (16.4%) had died post operatively in hospital and thus did not qualify for follow up gastroscopy.

Taking into consideration the poor attendance rate at follow-up gastroscopy, for accurate analysis of prevalence rates of *H. pylori* and malignancy in perforated gastric ulcers, a prospective study is required during which optimal biopsy specimen (full thickness, four quadrant) transported in optimal media (e.g. one in Formalin and another in Stewart's transport media or a substitute transport media made of normal saline with 20% glucose and glycerol) to ensure the best chance of detecting *H. pylori* and/or malignancy.

5.5.2 Risk Factors

Documentation of the presence or absence of risk factors was necessary i.e. did the doctor specifically ask about and document the absence or presence of these risk

factors. Often the first doctor to assess these patients in casualty and clerks the patient, documenting the history is often the most junior staff member (the intern) who may not realize the significance of the risk factor history and so may not have asked the patient about them or documented it.

History of traditional herbal medication ingestion was also noted. This may have been toxic to the patient causing severe acidosis or alkalosis at presentation or renal dysfunction/acute kidney injury that might have affected the patient's outcome.

5.5.3 Clinical presentation

Caution was used in Interpretation of the data on hemodynamic stability regarding how ill the patient was at the time of admission as firstly, data for 21.6% of the patients was missing. Secondly, the study hospitals included two level 4 [highest level/academic] and one level 3 hospital meaning they often received patients transferred from other level 3, 2 and 1 hospitals and the surrounding local clinics that would have initiated patient resuscitation (fluids, antibiotic therapy and ventilation if necessary) prior to transfer. Therefore the blood pressure taken at admission in the study hospitals in that case would have been a post resuscitation BP and thus not a true reflection of the patient's presenting severity.

5.5.4 Patient records

Missing records included lost files or missing pages from the patient's file. For example, in some patients, the files would be retrieved from the Records Department but some vital pages were found to be missing such as the operative notes, initial casualty notes and vital signs, the ICU daily care charts, discharge summaries indicating whether bookings and follow up appointment dates were made or the medication given e.g. eradication therapy.

When completing the data collection sheet for a single patient, in an attempt to combat the problem of missing data as this was a retrospective study, information was gathered from multiple forums i.e. casualty admission notes, ward admission file, operative notes, discharge summary, NHLS computer system and endoscopy reports.

Despite all these efforts missing data was still noted. It ranged from 1.8% in whether or not an intra-operative biopsy was conducted to 20.5% for data on *H. pylori*

eradication therapy and as high as 86.5% for data on ulcer location (Anterior or posterior wall of the stomach). During data analysis, the missing data was reported as a percentage and if significant, it precluded further analysis or data interpretation e.g. the HIV status of 66.7% of the patients was missing. Thus this and associated variables were not analyzed further but for lower levels of missing data, caution was used in data interpretation.

Currently, in the study hospitals, patient records are stored in film or paper form. And for each admission the patient has a new different file. These different files are often misplaced and unavailable to the treating physician in case of emergencies or during visits to the outpatient clinics and endoscopy units. Meaning that any concerning issues noted and documented by prior doctors are unavailable to the new doctor. Also when carrying out studies, data collection in retrospective studies such as this one becomes very taxing and a lot of missing data is noted.

There were several patients picked up in this retrospective review who had interesting and concerning features noted during their management e.g. a 45-year old female patient whose biopsy revealed free lying atypical cell with features highly suspicious for but not diagnostic for invasive malignancy and repeat biopsy was recommended. Another patient had gastric lymphoma queried. Better and more efficient management of patient records should be implemented. Also an amalgamation of a patient's records in totality should be done i.e. admission records, operative records, ICU records, endoscopy records, and post mortem records if available. Each of these various departments should be linked so that as a physician seeing a patient, one gets a complete picture and can act appropriately e.g. send a 45-year old lady with atypical cell for a repeat biopsy etc. This will also make data collection and analysis during research easier and accurate.

> **Recommendation**: All the records of a patient maintained by the hospital should be interlinked to provide doctors with access to a complete information on any patients of interest.

5.6 Conclusions

5.6.1 Prevalence of *H. pylori* in perforated gastric ulcers

Though the results in this study suggest that the prevalence of *H. pylori* in this study would be very low (one out of 171 patients), this issue of inadequate biopsy specimen and the fact that follow up gastroscopy and biopsy wasn't done to corroborate this data mean that based on the information from this study, this question remains unanswered. A further prospective trial is needed to answer this question.

5.6.2 Prevalence of malignancy in perforated gastric ulcers

Of patients with perforated gastric ulcers, 2.9% had malignancy noted in their intra-operative biopsy specimen. This is in keeping with international data.

5.6.3 Compliance in follow-up gastroscopy

The attendance in follow up gastroscopy was poor with an unacceptably high non-attendance rate of over 72%. This is very high compared to international data where the attendance rate is quoted at 66.3% and non-attendance around 14.7% (Sola-Vera, Sáez et al. 2008, Zhang, Li et al. 2016).

5.7 Significance of the research

The knowledge and understanding resulting from the study should lead to a review of the basic assumptions reinforcing current treatment practices.

The intra-operative biopsy specimen assessment undertaken in this study revealed that the prevalence of infective etiological agents was not high enough to have significant impact on patient management. However, the relatively limited sample size in this study makes further and more rigorous research necessary to confirm the study findings.

While the study expected to result in recommendations for the omission of the mandatory biopsy requirement of all patients and replace it with a selective approach where surgeons only carried out intraoperative biopsy in patients who demonstrated worrisome features, this study has revealed that routine use of intraoperative biopsy

for all patients is justified and mandatory in view of the poor patient compliance in returning for their follow up gastroscopy.

6 REFERENCES

Adams, L., et al. (2004). "Nonattendance at outpatient endoscopy." Endoscopy **36**(05): 402-404.

Amieva, M. and R. M. Peek, Jr. (2016). "Pathobiology of *Helicobacter pylori*-Induced Gastric Cancer." Gastroenterology **150**(1): 64-78.

Bhogal, R. H., et al. (2008). "Comparison between open and laparoscopic repair of perforated peptic ulcer disease." World journal of surgery **32**(11): 2371-2374.

Brenner, H., et al. (2009). "Epidemiology of stomach cancer." Cancer Epidemiology: Modifiable Factors: 467-477.

Brown, L. M. (2000). "Helicobacter pylori: epidemiology and routes of transmission." Epidemiologic reviews **22**(2): 283-297.

Cameron, J. L. and A. M. Cameron (2013). Current surgical therapy, Elsevier Health Sciences.

Chalya, P. L., et al. (2011). "Clinical profile and outcome of surgical treatment of perforated peptic ulcers in Northwestern Tanzania: A tertiary hospital experience." World Journal of Emergency Surgery **6**(1): 1.

De Francesco, V., et al. (2006). "Clarithromycin-resistant genotypes and eradication of Helicobacter pylori." Annals of internal medicine **144**(2): 94-100.

Deng, X., et al. (2015). "Short message service (SMS) can enhance compliance and reduce cancellations in a sedation gastrointestinal endoscopy center: a prospective randomized controlled trial." Journal of medical systems **39**(1): 1-11.

Ergul, E. and E. O. Gozetlik (2009). "Emergency spontaneous gastric perforations: ulcus versus cancer." Langenbeck's archives of surgery **394**(4): 643-646.

Gall, W. and C. Talbot (1964). "Perforated gastric ulcer." British Journal of Surgery **51**(7): 500-503.

Gisbert, J. P. and J. M. Pajares (2003). "*Helicobacter pylori* infection and perforated peptic ulcer prevalence of the infection and role of antimicrobial treatment." Helicobacter **8**(3): 159-167.

Gurudu, S. R., et al. (2006). "Factors contributing to patient nonattendance at open-access endoscopy." Digestive diseases and sciences **51**(11): 1942-1945.

Jwo, S. C., et al. (2005). "Clinicopathological features, surgical management, and disease outcome of perforated gastric cancer." Journal of surgical oncology **91**(4): 219-225.

Kasakura, Y., et al. (2002). "Management of perforated gastric carcinoma: a report of 16 cases and review of world literature." The American surgeon **68**(5): 434.

Kumar, S., et al. (2003). "Prevalence of *Helicobactor pylori* in patients with perforated duodenal ulcer." Tropical gastroenterology: official journal of the Digestive Diseases Foundation **25**(3): 121-124.

Lanas, A., et al. (1997). "Evidence of aspirin use in both upper and lower gastrointestinal perforation." Gastroenterology **112**(3): 683-689.

Lau, J. Y., et al. (2011). "Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality." Digestion **84**(2): 102-113.

Lim, R. H. G., et al. (2013). "Perforated early gastric cancer: uncommon and easily missed a case report and review of literature." Journal of gastric cancer **13**(1): 65-68.

Madiba, T., et al. (2005). "Perforated gastric ulcer-reappraisal of surgical options." South African Journal of Surgery **43**(3): 58-60.

Matsukura, N., et al. (1997). "Role of Helicobacter pylori infection in perforation of peptic ulcer: an age-and gender-matched case-control study." Journal of clinical gastroenterology **25**: S235-S239.

McGee, G. S. and J. L. Sawyers (1987). "Perforated gastric ulcers: A plea for management by primary gastric resection." Archives of Surgery **122**(5): 555-561.

Milne, A. N. and G. J. A. Offerhaus (2010). "Early-onset gastric cancer: Learning lessons from the young." World Journal of Gastrointestinal Oncology [E] **2**(2): 59-64.

Murdock, A., et al. (2002). "Why do patients not keep their appointments? Prospective study in a gastroenterology outpatient clinic." Journal of the Royal Society of Medicine **95**(6): 284-286.

Roviello, F., et al. (2006). "Perforated gastric carcinoma: a report of 10 cases and review of the literature." World journal of surgical oncology **4**(1): 1.

Schein, M., et al. (1986). "Perforated peptic ulcer at the JG Strijdom Hospital. A retrospective study of 99 patients." South African medical journal= Suid-Afrikaanse tydskrif vir geneeskunde **70**(1): 21-23.

Sebastian, M., et al. (1995). "*Helicobacter pylori* infection in perforated peptic ulcer disease." British Journal of Surgery **82**(3): 360-362.

Sola-Vera, J., et al. (2008). "Factors associated with non-attendance at outpatient endoscopy." Scandinavian journal of gastroenterology **43**(2): 202-206.

Somily, A. M. and M. Morshed (2015). "An update of laboratory diagnosis of *Helicobacter pylori* in the Kingdom of Saudi Arabia." The Journal of Infection in Developing Countries **9**(08): 806-814.

Søreide, K., et al. (2015). "Perforated peptic ulcer." The Lancet **386**(10000): 1288-1298.

Søreide, K., et al. (2014). "Strategies to improve the outcome of emergency surgery for perforated peptic ulcer." British Journal of Surgery **101**(1): e51-e64.

Tan, S., et al. (2016). "Laparoscopic versus open repair for perforated peptic ulcer: A meta analysis of randomized controlled trials." International Journal of Surgery **33**: 124-132.

TheWorldBank "World development indicators. Life expectancy at birth, total (years)."

TheWorldBank (2015). "World Development Indicators. Life expectancy at birth, total (years)." Retrieved 17 October 2015, 2015, from http://data.worldbank.org/indicator/SP.DYN.LE00.IN/countries/1W-ZA?display=default

Thorsen, K., et al. (2013). "Epidemiology of perforated peptic ulcer: age-and gender-adjusted analysis of incidence and mortality." World J Gastroenterol **19**(3): 347-354.

Townsend C. M., B. D. R., Evers M. B., Mattox K. L. (2012). Sabiston Textbook of surgery: The biological basis of modern surgical practice. Philadelphia, PA, Elsevier Saunders.

Ugochukwu, A., et al. (2013). "Acute perforated peptic ulcer: on clinical experience in an urban tertiary hospital in south east Nigeria." International Journal of Surgery **11**(3): 223-227.

UNAIDS (2015). "HIV prevalence among adults (15-49 years)." Retrieved 24 October 2015, 2015, from http://aidsinfo.unaids.org/

WHO (2013). "Adult HIV prevalence (15-49 years), 2013 by WHO region ". Retrieved 24 October 2015, 2015, from http://www.who.int/gho/hiv/epidemic_status/prevalence/en/

Wilhelmsen, M., et al. (2015). "Surgical complications after open and laparoscopic surgery for perforated peptic ulcer in a nationwide cohort." British Journal of Surgery **102**(4): 382-387.

Yamaoka, Y. (2008). *Helicobacter pylori*: molecular genetics and cellular biology, Horizon Scientific Press.

Yang, T., et al. (2016). "Helicobacter pylori infection, H19 and LINC00152 expression in serum and risk of gastric cancer in a Chinese population." Cancer Epidemiology **44**: 147-153.

Zhang, M., et al. (2016). "[Analysis of the efficacy of gastric cancer screening in rural population in Henan Province]." Zhonghua zhong liu za zhi [Chinese journal of oncology] **38**(1): 73-77.

7 APPENDICES

7.1 Appendix 1: Data Collection Sheet

Study number_____
I Demographics:

1. Gender: Male___ , Female____

2. Age in years,

- 18-30_____
- 31-40 _____
- 41-50 _____
- 51-60 _____
- 61-70 _____
- 71-80 _____
- >81_____

3. risk factors:
   - known PUD on treatment_____
   - known PUD not on treatment_____,
   - NSAID use _____,
   - Steroid use _____,
   - Chemotherapy_____,
   - Smoking_____

4. HIV status:
   - Positive_____
     - CD4 count_____
     - Viral load_____
   - Negative_____
   - Unknown_____

5. On HAART/ARV treatment:
   - Yes____
   - No_____

II. Clinical presentation:

- Early (<24hours)____
- Late (>24 hours)_____

III Operative notes:

- site of perforation (upper, middle, lower third or fundal and antral),_____

- size/diameter of the perforation_____,
- number of biopsies taken_____,
- type of biopsy
    - excision_____,
    - incision_____,
    - other(specify)_____

- site of biopsy(whether 4quadrant or not)_____
- Type of surgery:
    - open_____ ,
    - laparascopic_____,
    - laparascopic converted to open_____

IV Biopsy results:

- malignancy:
    - Yes _____, specify stage and type_____
    - NO____
- Infectious:
    - yes____, Specify_____
    - No:_____,
- Other,_____ specify_____

V Post operative course:

- Repeat procedure, relook done:
    - Yes___, specify number of procedures and timing (day post Op)____,
    - No____,

- diagnosis at discharge_____,
- Length of stay_____,
- Whether empirical *H. pylori* treatment/eradication therapy was given:
    - Yes____,
    - No_____.

VI Follow up:

- Timing of the EGD i.e. Number of weeks post operatively._____

- EGD/ gastrosopy done: Yes_____, No____
    - Findings____,
    - biopsies taken Yes____, No____,
    - Biopsy results_____

7.2 Appendix 2: Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Meryl Dache Oyomno

CLEARANCE CERTIFICATE	M111126
PROJECT	Do Perforated Gastric Ulcers Require Routine Biopsy? A Study in Three Gauteng Public Hospital
INVESTIGATORS	Dr Meryl Dache Oyomno .
DEPARTMENT	Department of Surgery/Gerneral Surgery
DATE CONSIDERED	25/11/20111
M1111260DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 25/11/2011 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Martin Brand

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Dr M.D Oyomno

7.3 Appendix 3: Modified Johnson's classification of ulcers

The modified Johnson's classification of ulcers as indicated in Table 3 and Figure 1, was used for gastric ulcer site grouping (McGee and Sawyers 1987).

Table 3: Modified Johnson's Classification of Ulcers

Gastric ulcer type	Location
I	Along the body of the stomach often along the lesser curvature. No associated acid hypersecretion.
II	Body of stomach plus a duodenal ulcer. Associated with acid hypersecretion.
III	Pyloric channel within 3cm of the pylorus. Associated acid hypersecretion.
IV	Close to the gastroesophageal junction.
V	Anywhere in the stomach. Associated with chronic NSAID use.

Figure 1: Schematic representation of gastric ulcer sites