AN OVERVIEW OF RISK FACTORS AND TREATMENT OUTCOMES IN GASTRIC CANCER PATIENTS AT TYGERBERG HOSPITAL

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LITERATURE REVIEW

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GLOSSARY

AIDS	Acquired Immune Deficiency Syndrome
CI	Confidence Interval
CT	Computed Tomography
DOR	Diagnostic Odds Ratio
GC	Gastric cancer
GIT	Gastro intestinal tract
HIV	Human Immunodeficiency Virus
HR	Hazards Ratio
JGCA	Japanese Gastric Cancer Association
NNT	Number Needed To Treat
OR	Odds Ratio
PET	Positron Emission Tomography
RCT	Randomized Controlled Trials
RR	Relative Risk/Risk Ratio
SEER	Surveillance, Epidemiology and End Results programme
SIR	Standardized Incidence Ratio
UK	United Kingdom
USA	United States of America

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Literature Review

1. Search Methodologies

A literature search was performed to gain information on the risk factors associated with the carcinogenesis of gastric cancer, in particular *Helicobacter pylori (H Pylori).* The search also focused on guidelines/recommendations for the management of gastric cancer and prognostic factors related to poor local control. The literature review included published research related to the search question-*H Pylori* infection in patients with gastric cancer.

Articles relevant to the topic were searched via Scopus, Google scholar, PubMed and MedLine search engines. This included Reviews & Meta-analyses, Randomized Controlled Trials (RCT) and non-RCT. Only articles that were published in English were evaluated.

The researched articles reviewed were assessed according to the following categories:

1. General risk factors associated with gastric cancer
2. *Helicobacter pylori (H Pylori)* as a pro-carcinogen for gastric cancer
3. Clinical presentation and diagnosis of gastric cancer
4. Management strategies for gastric cancer
5. Prognostic factors associated with poor local control

2. Background

Cancer is the leading cause of death worldwide.[1] In 2012 alone, there were estimated 14.1 million cancer cases globally and of those, 7.4 million cases were males and 6.7 million females. This number is expected to double in the next 2 decades.[1]

Gastric cancer is reported as the fifth most common cancer in the world, and it is the second most frequent cause of cancer related deaths.[1,2]

In East Africa the incidence of gastric cancer is estimated to be 5.6 per 100 000 per year in men and 4.0 per 100 000 per year in women,[3] while the incidence for most cancers in African countries remains unknown due to inaccurate data. Furthermore, the risk factors associated with gastric cancer in the developing countries are neither well studied nor documented.

3. Epidemiology

According to the South African National Cancer Registry, in 2010, of all histologically diagnosed cancers, gastric cancer accounted for 2.48% of all cancers in males and 1.43% of cancers in females.[4] The peak incidence in 2010 was 55-59 years for males and 60-64 years for females.[4]

A marked decline in the incidence of gastric cancer has been observed in many countries in the developed world[5] , but with an increase in the ageing population, the total number of deaths from gastric cancer might rise in the future.[6]

4. Risk Factors

The risk factors for gastric cancer have been extensively investigated through numerous epidemiological studies. The International Agency for Research on Cancer (IARC), as well as the World Cancer Research Fund (WCRF) who are considered to be the leaders in cancer epidemiology, have reviewed available data on gastric cancer risk factors.

4.1. Helicobacter Pylori Infection

Helicobacter pylori (*H. Pylori*) is an independent, definite (Group 1) carcinogen in the human population according to the World Health Organization (WHO).[7] *H Pylori* is a gram-negative spiral bacterium that specifically targets the gastric lining. The bacterium will continue colonizing the gastric lining in the infected individual, unless it is specifically targeted and treated appropriately.[8]

Causal association between *H Pylori* and GC has been established by several studies. In the UK, *H Pylori* is associated with 32% of gastric cancer[9], but the association is as high as 90% in South Korea & Japan.[10]

Several meta-analyses of cohort and case control studies reported a strong association between *H Pylori* infection and GC (OR 3.00 CI 2.42-3.72 p<0.001).[10]

4.1.1. Mechanism

Majority of data supports the view that *H Pylori* bacterium is transmitted by means of person to person contact or via consumption of contaminated water and food.[2]

H Pylori's mechanism of action on gastric epithelium is through activation of chronic inflammatory changes that present as chronic superficial gastritis.[11] Malfertheiner and Graham proposed a specific multistep model of gastric carcinogenesis namely chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and development of gastric cancer.[11,12]

Evidence is mounting that *H Pylori* infection also causes biochemical, genetic and epigenetic changes in the gastric lining. The epigenetic changes lead to genetic instability in gastric epithelial cells resulting in the development of GC.[12]

4.1.2. Diagnostic modalities

It is of paramount importance to identify the presence of *H Pylori* bacterium timeously in order to manage the disease appropriately. Bacteriological methods are ideal confirmatory tests for *H Pylori* diagnosis but are difficult to perform , so various easier stains are used but their specificity and sensitivity varies.[13]

The invasive methods necessitates a biopsy specimen in order to detect *H Pylori* through rapid urease activity, histology (hematoxylin-eosin, Toluidine Blue and Giemsa staining) or on molecular basis (polymerase chain reaction).[14,15] The non-invasive methods to detect *H Pylori* infection consist of serology, the urea breath test and the detection of the *H Pylori* antigen in urine, blood or stool samples.[16] Generally, the choice of test is a careful balance between sensitivity, specificity, practicality and cost-effectiveness.
Immunohistochemical (IHC) stains detect an antibody antigen reaction and has a sensitivity of >90% and high specificity, and is a better test than GIEMSA stain for the detection of *H Pylori* infection.[17] The sensitivity and specificity of GIEMSA was reported by Wabinga[13] to be 85% and 89%, respectively. In contrast Tajalli *et al*.[15] found GIEMSA to have sensitivity of 53.4% and specificity of 95.4%. However, with Toluidine blue staining the sensitivity was 76.7% and specificity 100%. Both staining methods are user friendly, inexpensive, readily available and can be performed in any laboratory.[13,15]

In a meta-analysis by Jiang Jian-hui *et al*[18] which included 22 studies, they concluded that PCR had the best performance with diagnostic odds ratio(DOR) of 6.7(5.5-7.8) followed by urea breath test and Enzyme Linked Immunosorbent Assay (ELISA) with DOR 6.4 (5.4-7.4) and 4.5(3.8-5.2), respectively. Therefore, non-invasive tests are appropriate methods to screen *for H Pylori* but invasive tests are best used to confirm diagnosis in suspected patients.[18]

4.1.3. H pylori infection eradication

Eradication of *H Pylori* has been demonstrated in in vitro studies to reduce the levels of epidermal growth factors (EGF), which are proteins linked with carcinogenesis.[11] *H Pylori* eradication heals active gastritis and reduce the recurrence of peptic ulcer disease[5], and subsequently reduce the risk of gastric cancer.[12] Unfortunately, an already established intestinal metaplasia or dysplasia is unlikely to be reversible.[11,19]

The standard of care for the eradication of *H Pylori* infection consists of triple therapy, which entails a combination of a proton pump inhibitor (PPI) and two antibiotics.[20] The antibiotic combination can either be clarithromycin and amoxicillin or amoxicillin and metronidazole.[11,19,20]

The same first line treatment is recommended for use globally but dosages used and length of treatment may vary per country or region.[11] Effective treatment of *H Pylori* depends on the utilization of sensitive and accurate diagnostic tests, as well as appropriate chemotherapeutic agents.

4.2. Diet

The results from various studies of association between the consumption of fruit and/or vegetables with the development of gastric cancer have been conflicting and inconsistent. A study by Epplein *et al*[21],reported no association between gastric cancer risk and highest intake of fruit(HR=1.02 CI 0.68-1.54 p=0.87) or vegetables(HR=0.89 CI 0.60-1.31 p=0.32) in women. However, in men, increased fruit intake was associated with decreased risk of distal gastric cancer but no association was seen with increased intake of vegetables.[21]

A meta-analysis of cohort studies, which included large prospective studies with >2.4 million individuals and median follow up of 10 years, also found an inverse association between fruit consumption and gastric cancer (GC) risk.[22] The protective effect of fruit consumption on GC risk was similar in both males and females. However, possible confounding factors common in observational studies , the likelihood of lower prevalence of smoking and alcohol consumption in individuals with high fruit intake, as well as measurement error effects, could not be ruled out.[22]

4.3. Alcohol

Alcohol consumption has been linked to an increased risk of GC. Meta-analyses by Tramacere *et al*[23], and Bagnardi *et al*[24], established a definite quantification of the association between alcohol intake and risk of GC in heavy drinkers(≥4 drinks/day) when compared with non-drinkers. The pooled RR was 1.07(CI 1.01-1.13) for moderate drinkers (<4 drinks /day) and 1.20(CI 1.01-1.44) for heavy drinkers. In contrast, drinking cessation is reported not to have significant effect on risk of GC (OR = 0.99 CI: 0.97-1.02).[10] These results are to be interpreted with caution due to small number of studies in that field.

4.4. Smoking

Although the mechanism by which tobacco smoking increases the risk for the development of GC is not well understood, it is still considered a risk factor.[10]

Meta-analysis including 23 articles, concluded that there is a positive association between smoking and increased risk of GC in current smokers RR: 1.53), when compared to non-smokers.[25] Subsequent meta-analysis had similar findings (OR: 1.69 CI 1.35-2.11) when non-smokers and current smokers were compared.[26]

4.5. Salt Intake

D'Elia *et al*[27], showed that dietary salt intake may be associated with increased risk of gastric cancer across various consumption levels. Although there is a 68% increased risk (RR 1.68 CI 1.17-2.41

p=0.005) of GC in high salt intake group compared to low salt intake group, there was significant heterogeneity between studies.

Several mechanisms by which salt intake may increase the risk of GC have been suggested but none have been proven.

As part of health eating lifestyle, low salt intake strategy is cheap and simple and should therefore be encouraged despite lack of convincing evidence.

4.6. HIV Infection

In a systematic review by Persson *et al*[28], people living with HIV/AIDS had an increased risk of GC (SIR1.44 CI 1.17-1.76). When compared to the general population, people living with HIV/AIDS have an even greater risk of developing carcinoma of the gastric cardia (SIR,1.36 CI 0.83-2.11) and non cardia (SIR 1.53 CI 1.12-2.05).The risk of GC may be elevated due to association with immunosuppression and the co-existence of other risk factors such as obesity and smoking.

A similar pattern of risk of GC in people with HIV/AIDS was observed in a meta-analysis by Grulich *et al*[29] (SIR 1.90 CI 1.53-2.36).The pattern of risk of developing GC was much the same in transplant recipients(SIR 2.04 CI 1.49-2.36), suggesting that the risk of GC is associated with immune deficiency.[29]

4.7. Low socio economic status

Several studies reported an increased risk of developing malignancies, including gastric cancer, in patients with low socio economic background and the observed difference is attributed to differences in diet and living standards.[30–32] Therefore, it is anticipated that the developing countries will experience an increased burden of gastric cancer.

4.8. Genetic predisposition

Major risk factors for development of GC had initially appeared to be environmental but it has since been established that 1-3% of GC occur as a result of inherited gastric cancer predisposition syndromes.[33] These encompass hereditary diffuse GC (HDGC) and other syndromes including LiFraumeni and Familial Adenomatous polyposis.[34]

A Korean study by Yoon and Kim also showed that the risk of GC increased 3-fold in individuals with first-degree relatives with history of GC (OR 2.85, CI 1.83-4.46), when compared with control.[10]

5. Diagnosis of Gastric cancer

5.1. Clinical Presentation

Patients with suspected gastric cancer present with non-specific symptoms which may range from unexplained weight loss, stomach pain, vomiting, early satiety and bloating.[35]

5.2. Diagnosis

The diagnosis of gastric cancer is based on histological diagnosis which is achieved through gastroscopy and tissue biopsy.[35] Barium meal can assist with differential diagnoses in cases where patients present with gastric outlet obstruction.

Contrast enhanced computed tomography (CT) of thorax and abdomen and Positron Emission Tomography (PET) scan can be used to stage the disease.[35]

6. Treatment Options

6.1. Surgery

According to Orditura *et al*,surgery is the only curative treatment modality in T1b-T4 resectable gastric cancers.[36]

Orditura et al, also stated that globally, there is general consensus that subtotal gastrectomy should be performed for antral tumours and total gastrectomy is then performed for other gastric tumour sites.[36] For radical/curative treatment, the aim of surgery is to achieve negative margins in order to reduce possibility of local recurrence. The Japanese Gastric Cancer Association(JGCA) has provided guidelines with respect to size of surgical margins required per stage and histological type of disease .According to JGCA "a proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (Types 1 and 2) and 5 cm is recommended for those with infiltrative growth pattern (Types 3 and 4)" [37] The guidelines have provided clarity regarding the sizes of the margins required for gastric resections.

With technological advances, early gastric cancer (T1a) can be treated with endoscopic resection and laparoscopic gastric surgery has extended from treating benign gastric diseases to include advanced gastric cancer requiring total gastrectomy and lymphadenectomy.[36]

The extent of lymph node dissection in the treatment of gastric adenocarcinoma continues to be debated. According to JGCA D2 lymphadenectomy is performed as a standard of care in Japan for several decades because it offers survival benefit when compared to D1 lymphadenectomy.[37] The retrospective review of SEER data by Schwarz showed that number of lymph nodes(LN) examined is an independent prognostic survival predictor($p<0.0001$) and best long term survival were observed in negative LN counts of >15.[38] Songun et al published their RCT (The Dutch D1D2 trial) findings that supported this approach

because they reported a significant benefit of D2 lymphadenectomy over D1 lymphadenectomy in terms of loco-regional control with local recurrence of 22% in D1 and 12% in D2 groups and regional recurrence was 19% in D1 versus 13% in D2 groups. But, there were higher operative mortality rates in D2 group. The study was adequately powered with a substantial follow up period of 15 years. .[39]

On the contrary, a meta-analysis by Jiang *et al*,[40] including 12 RCT's has shown no significant differences in overall survival between D1 and D2 lymphadenectomy(HR = 0.92, 95% CI: 0.77-1.10, P = 0.36).

6.2. Chemotherapy

The published results of both the Medical Research Council Adjuvant Gastric Cancer Infusional Chemotherapy (MAGIC)[41] and FFCD9703 trials,[42] supported the use of neoadjuvant chemotherapy in patients with resectable gastric cancer. In both trials, neoadjuvant chemotherapy groups showed higher curative resectability rates and higher likelihood of 5 year survival, progression- free survival and overall survival rates when compared to surgery alone. The MAGIC trial reported 5-year survival rates of 23% (95% CI 16.0-29.4) with surgery alone and 36% (95%CI 29.5-43) with perioperative chemotherapy. In patients who received preoperative chemotherapy there was some degree of tumor down-staging but none achieved complete pathological response to chemotherapy and only 42% of patients completed all the protocol treatment.

The FFCD9703 trial reported a 38% (29-47%) vs 25% (17-33%) 5 year OS benefit of perioperative chemotherapy when compared with surgery alone.[42]

6.3. Radiotherapy

In the RCT by Zhang,*et al*[43] ,230 patients were randomized to receive preoperative radiotherapy and surgery(R+S) vs surgery(S) alone. The 5 year survival rate and recurrence rate in the R+S group and S group were 30% vs 20%, 39% vs 52%($p<0.025$) respectively. The results of the trial proved that radiotherapy improved surgical outcomes.

A systematic review and meta-analysis to assess impact of radiotherapy on survival in patients with resectable gastric cancer was conducted by Valentini, et al[44] Their results indicated radiotherapy had a 5 year survival benefit with the overall 5-year RR 1.26 (95% CI: 1.08-1.48; NNT=17). The studies included radiotherapy used preoperatively, postoperatively and/or intraoperatively.

6.4. Adjuvant chemoradiotherapy

The results of the RCT by MacDonald *et al*,[45] proved that chemoradiotherapy after resection of gastric cancer significantly improved relapse free survival and overall survival. Chemotherapy drugs used were Fluorouracil and Leucovorin. The hazard ratio for relapse was 1.52 (95% CI 1.23 to 1.86; P<0.001) and median overall survival in the surgery only group was 27 months when compared with 36 months in the chemoradiotherapy group.

The ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) phase 3 trial failed to demonstrate similar findings in patients that were randomized to receive concurrent chemoradiotherapy (using Capecitabine and Cisplatin) vs chemotherapy alone. The addition of radiotherapy to chemotherapy did not significantly prolong disease-free survival (DFS; P = .0862).[46] The treatment was completed by 82% of patients in the chemoradiotherapy group vs 75% in the chemotherapy alone group indicating that treatment was well tolerated.

7. Prognosis

Resected gastric cancer has a high rate of local recurrence.[36] Addition of adjuvant chemoradiotherapy or chemotherapy alone has been studied and used to prolong disease free survival rates.[46] In a study by Yoo *et al*[47] mean time to recurrence was 21.8 months and pathological features associated with early recurrence(<24 months) were differentiated tumour, serosal invasion, lymph node metastases, diffuse type of cancer and patients who had total gastrectomy.

Verlato *et al*[48] also found depth of tumour invasion, pathological nodal status and size of tumour as poor prognostic factors for recurrence. However, only depth of tumour invasion was independently associated with timing of recurrence.

A retrospective study conducted by McMillan *et al*[49] found that delay during delivery of adjuvant radiation therapy has an impact in the overall survival of patients with gastric cancer. Median OS were worse in patients with prolonged (delay of >7 days) radiotherapy treatment when compared with those whose treatment was delivered without interruptions. However, patients with pathological high risk features for recurrence, namely positive margins, lymph node positivity or inadequate surgical nodal staging, and those who had a cycle of chemo prior to chemoradiotherapy demonstrated worse survival with interruptions of <7 days.[49]

Therefore every effort has to be made to deliver adjuvant radiotherapy without delays especially in patients with pathological high risk features for recurrence.

A retrospective study offers low level of evidence (Level 4) due to the inherent biases of the study design.

8. Summary

Diagnosis of GC carries a poor prognosis and because it presents with non-specific clinical symptoms, confirmation of diagnosis is usually delayed.

H Pylori infection is a strong independent risk factor for development of gastric cancer. Eradication of the *H Pylori* bacteria, when performed early, may lead to regression of pre-cancerous lesion in the gastric mucosa with subsequent reduction in gastric cancer.

There is increased risk for development of gastric cancer in patients with immunodeficiency, as well as those with inherited gastric cancer predisposition syndromes.

Surgical resection of the tumour is still the only curative treatment modality, with mean time to recurrence of <24 months in patients with pathological high risk features for recurrence. Neoadjuvant chemotherapy offers survival benefit and delay in delivery of adjuvant radiotherapy has poor outcomes.

9. Recommendations

In a high risk population, there may be merit in screening patients with even mild GIT symptoms for *H Pylori* infection and providing empiric eradication therapy. This will be of greatest value in developing countries were access to laboratory testing is difficult.

South Africa has a high prevalence of people living with HIV/AIDS who might benefit from early screening and treatment of *H Pylori* infection.

Mobilization of resources for the development of a vaccine study would be invaluable towards the prevention of gastric cancer and to the reduction of mortality rates due to gastric cancer, globally.

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Title: The prevalence of Helicobacter pylori infection in patients with gastric cancer at a single institution

Abstract:

Background: In South Africa, gastric cancer accounts for 2.48% of all cancers in males and 1.47% of cancers in females. The risk of developing gastric cancer is 6 times higher in individuals infected with Helicobacter Pylori (*H. pylori*), and in the United Kingdom, *H. pylori* infection is associated with 32% of gastric cancers. In developing countries, including South Africa, data reporting risk factors for development of gastric cancer is lacking.

Aim: To determine the prevalence of *H. pylori* infection among patients managed for gastric adenocarcinoma.

Setting: A single academic oncology unit

Methodology: It is an observational, retrospective chart review. Information including demographic data, clinical details, histological reports, and gastroscopy findings was collected using only the patient's folder numbers. Relevant imaging studies and laboratory results were also collected.

Results: One-hundred and sixteen patient records were evaluated. Of these, 75 were conclusively tested for of *H. pylori* and the prevalence was found to be 13.3% (n=10). The most used testing modality in this study was Giemsa staining, an accounted for 94.7% of the tested patients (n=71). Of the 56 patients who were tested for the human immunodeficiency virus (HIV), only 4 (7.1%) were found to be positive. Use of alcohol and smoking (past/present) were reported in 6% (n=7) and 16.4% (n=19) of the study cohort, respectively.

Conclusion: This study has shown prevalence of *H. pylori* infection of 13.3% in gastric cancer patients, and that Giemsa staining is the commonest modality used for *H. pylori* testing in our institution's setting.

Keywords: *H. pylori*, Gastric cancer, Risk factors, Low resource, Alcohol & smoking

Title: The prevalence of Helicobacter pylori infection in patients with gastric cancer at a single institution

Introduction:

Cancer is a leading cause of death worldwide, accounting for 8.2 million deaths in 2012, with gastric cancer being the third leading cause of cancer related deaths.[1] Data on incidence of most cancers in Africa are inaccurate, but in East Africa the incidence of gastric cancer is estimated to be 5.6 per 100 000 per year in men and 4.0 per 100 000 per year in women.[2] In South Africa, gastric cancer accounts for 2.48% of all cancers in males and 1.47% of cancers in females. It has a peak incidence in the 55-59 years age group for males and 65-69 years age group for females, respectively.[3]

The risk factors for gastric cancer have been extensively investigated through numerous epidemiological studies. The International Agency for Research on Cancer (IARC), as well as the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) who are considered to be the gold standard in cancer epidemiology, have reviewed available data on gastric cancer risk factors.[4] They have listed Helicobacter Pylori (*H. pylori*) infection, working in environments associated with rubber production, tobacco smoking, and exposures to X-radiation and gamma radiation as definite risk factors for gastric cancer.[4] There is, however, also an increased risk with older age, male gender and poor socio-economic status.[5,6] *H. pylori* infection is associated with 32% of gastric cancers in the United Kingdom.[7] A combined analysis estimated that the risk of developing gastric cancer is 6 times higher in individuals infected with *H. pylori*.[8] *H. pylori* is a gram-negative spiral bacterium that specifically targets the lining of the stomach.[9] The bacterium continuously colonises the gastric lining in the infected individual, unless it is specifically targeted and treated with appropriate antibiotics.[10]If the infection persists

for a long time, it can cause chronic gastritis, gastric ulceration, gastric cancer or even mucosa-associated lymphoid tissue lymphoma.[11]

The prevalence of *H. pylori* is inversely related to socio-economic status.[12] The infection is usually acquired in childhood and is transferable from one person to the other.[13] Many populations are not informed about the early signs and symptoms of gastric cancer, as well as the risk factors leading to this dismal diagnosis.[14] The latter, together with unavailability of sufficient screening programs to identify high risk individuals at an early stage, also account for the high burden of disease in many resource limited countries.[15,16] Therefore, developing countries are likely to experience an increased burden of gastritis, peptic ulcer disease, and subsequently gastric cancer as a sequele of *H. pylori* infection, if left untreated.

H. pylori has recently been deemed a human carcinogen by the World Health Organization (WHO).[17] For this reason, identification of *H. pylori* infection in individuals mandates treatment aimed at successful eradication.[18]

Eradication of *H. pylori* has been demonstrated *in vitro* following reduced levels of epidermal growth factors, which are proteins linked with carcinogenesis.[18] *H. pylori* eradication heals active gastritis and reduces the recurrence of peptic ulcer disease.[19] Unfortunately, already established intestinal metaplasia and dysplasia are unlikely to be reversible.[18,20] According to Fukase *et al*., eradication of *H. pylori* even after endoscopic resection of early gastric cancer is of value, since it reduces the incidence of metachronous gastric carcinoma.[21] The standard of care for the eradication of *H. pylori* infection consists of triple therapy, which entails a combination of a proton pump inhibitor and two antibiotics. The antibiotic combination can either be clarithromycin and amoxicillin or amoxicillin and metronidazole.[22] Effective antimicrobial treatment depends on sensitive and accurate diagnostic tests, as well as the use of appropriate chemotherapeutic agents.

Numerous techniques can be used to diagnose *H. pylori* infection. The invasive method necessitates a biopsy specimen in order to detect *H. pylori* through rapid urease activity, histology (hematoxylin-eosin and Giemsa staining) or on molecular basis (polymerase chain reaction).[22] The non-invasive detection methods consist of serology, the urea breath test and the detection of the *H. pylori* antigen in urine, blood or stool samples.[23] Generally, the choice of test is a careful balance between sensitivity, specificity, practicality and cost-effectiveness.

There is no published data available for the prevalence of *H. pylori* infection in patients managed for gastric cancer at our institution. Taking into account the poor socio-economic status of the majority of the patients seen at Tygerberg Hospital, there is a need to evaluate the prevalence of *H. pylori* infection amongst our gastric cancer patients and to identify other associated risk factors.

Aim

To determine the prevalence of *H. pylori* infection among patients managed for gastric adenocarcinoma at in a single academic oncology unit.

Objectives

Primary Objective:

To assess the prevalence of *H. pylori* infection in all patients managed for gastric adenocarcinoma in a single institution.

Secondary Objectives:

To identify the most common technique used for the diagnosis of *H. pylori* infection in a single institution. To evaluate the epidemiological risk factors associated with the development of gastric carcinoma. To assess the prognostic factors associated with recurrence of gastric adenocarcinoma.

Methodology

Study design: An observational, descriptive retrospective analysis.

Study setting: A single academic oncology unit.

Study population:

All patients diagnosed and referred with gastric adenocarcinoma in the period of January 2010 to December 2012.

Patient selection:

Inclusion criteria:

All patients referred with proven histological diagnosis of gastric adenocarcinoma from January 2010 to December 2012.

Exclusion criteria:

Patients with histological diagnosis other than adenocarcinoma and patients without confirmed histological diagnosis.

Sampling technique:

Non-random consecutive sampling of records of all the patients referred with gastric adenocarcinoma between January 2010 and December 2012.

Data collection:

Data was sourced from the patients' therapy folders specific to the Division of Clinical and Radiation Oncology, Tygerberg Academic Hospital. This included the demographic profile, clinical data, histological reports, and gastroscopy findings. Imaging studies were collected from the picture archiving and communication system (PACS) and the laboratory results were collected from the DISALAB program. Data were collected using the patient's folder numbers only and no names or identifiable information was used.

Data analysis:

The data was analysed using the most recent version of statistical software, STATA Corp 13, Texas. Descriptive statistics were used to present the different variables within the data set. These were presented in the form of tables, as well as graphics in the form of graphs and charts. Analytical statistics were performed to assess associations between variables and the findings were presented in tables and charts.

Ethical consideration:

The study was approved by the Health Research Ethics Committee of the University of Stellenbosch: Protocol number S14/10/242.

Confidentiality:

All patients were assigned an individual study number that was not be linked to their names or hospital numbers in order to protect their identity and to maintain confidentiality. Identity of patients was only known to the principal investigator who kept the details of the information in a secure office and only accesses the information for verification purposes. The computer used for coding and storing patients' information was password protected.

Declaration: The investigator and the supervisor have nothing to declare.

Results

Clinical records of 116 patients who were diagnosed with gastric adenocarcinoma and other type of gastric cancer at our institution between January 2010 and December 2012 were evaluated.

There was a higher proportion of male patients, who accounted for 71% (n=82), than female patients who constituted 29% (n=34) (Table 1). Amongst the male patients, 80% (n=24) were <50 years of age. There was, however, no significant difference observed amongst other baseline variables. It is important to note that large proportions of the study cohort had no records with regards to HIV status (51.7%), smoking history (79.3%), and alcohol drinking (88.8%) (Table 1).

In this study, the prevalence of *H. pylori* was found to be 13.5% (n=10), but *H. pylori* test was not performed in 35.3% (n=41) of the cases (Table 2). The most common testing modality for *H. pylori* was Giemsa staining, accounting for 94.7% of the tested (n=71). Only in a single case (1.3%) was polymerase chain reaction (PCR) used, and the remaining 3 cases (4%) were tested using other techniques (Table 2).

All the cases were adenocarcinoma (Table 2) and in 80% of the cases, tumour histological subtype was either interstitial or diffuse, with the remaining 20% of cases (n=14) reported as indeterminate (Table 2). In this study, the common tumour locations were the body of the stomach and pylorus/antrum, accounting for 27.6% (n=32) and 25% (n=29), respectively (Table 2). Tumour location was not specified in 27.6% (n=32) of the cases.

With regards to risk factors, only 4 (7.1%) of the 56 patients who were tested for HIV were found to be positive. Sixty (51.7%) of the study cohort were not tested for HIV infection. Alcohol use and smoking (past/present) were reported in 6% (n=7) and 16.4% (n=19) of

all cases, respectively. Information on use of alcohol and smoking was not recorded for as many as 103 (88.8%) and 92 (79.3%) patients, respectively.

Reported prognostic factors in this study include presence of signet rings in 33 (28.5%) of the cases. Of the 53 cases with data on lymphovascular infiltration, 31 (58.5%) had infiltration. Data on tumour grade (75 cases) showed that 37 (31.9%) of tumours were poorly differentiated (Table 2). Furthermore, there was no comment made in the histology reports regarding omental involvement in 73 (63%) of the cases.

Surgery with curative intent was performed in 48% (n=56) of the cases, and total gastrectomy was effected in 16% (n=19) of the cases (Table 3). More than 75% of the cases were operated within 4 months from the time of diagnosis (Fig. 1). Radiotherapy treatment was offered in 66 (57%) cases (34 curative and 32 palliative).In the cohort, 90.7% of cases started adjuvant radiotherapy in less than 16 weeks after surgery (Fig. 2). Adjuvant radiotherapy could be completed without any delays in 22 (64.7%) of the cases. Chemotherapy was offered to 62 patients which constituted 53.4% of cases and included those treated adjuvantly with chemoradiation. Within a 24 month period, recurrence was reported in 3 (8.8%) of the 34 cases that were treated with chemoradiotherapy. Four patients (11.8%) had metastasis and three (8.8%) cases of death were reported. There were 13 (38.2%) cases lost to follow up (Table 3).

Thirty-six (42.9%) of the 84 patients who were either treated with radiotherapy, chemotherapy or chemoradiotherapy developed at least one of nausea/vomiting, bone marrow suppression, and weight loss (Table 3). No treatment related toxicity was observed in 34 (40.4%) of the cases. As many as 14 (16.7%) of the cases had no data on toxicity.

Table 1: Baseline characteristics

Patient variables	**n (%)**	
Age (years)	**Male**	**Female**
<50	24 (80%)	6 (20%)
50 -65	34 (68%)	16 (32%)
>65	24 (66.7%)	12 (33.3%)
Sex		
Male	82 (70.7%)	
Female	34 (29.3%)	
HIV status		
Positive	4 (3.5%)	
Negative	52 (44.8%)	
Unknown	60 (51.7%)	
Smoking history		
Current smoking	11 (9.5%)	
Previous	8 (6.9%)	
Never smoked	5 (4.3%)	
Unrecorded	92 (79.3%)	
Alcohol drinker		
Yes	7 (6.0%)	
No	6 (5.2%)	
Unrecorded	103 (88.8%)	
Performance status		
PS 0	22 (19.0%)	
PS 1	40(34.5%)	
PS 2	23 (19.8%)	
PS 3	18 (15.5%)	
PS 4	10 (8.6%)	
Unrecorded	3 (2.6%)	

Table 2: Disease profile

Disease variables	**n (%)**
Tumour staging	
T1	5 (4.3%)
T2	18 (15.5%)
T3	19 (16.4%)
T4	18 (15.5%)
TX (non-specified/Unknown	56 (48.3%)
Lymph nodes	
N0	8 (6.9%)
N1	30 (25.9%)
N2	10 (8.6%)
N3	9 (7.7%)
NX	59 (50.9%)
Metastasis	
M0	34 (29.3%)
M1	68 (58.6%)
MX	14 (12.1%)
Tumour histology	
Adenocarcinoma	116 (100%)
Tumour histological sub types	
Interstitial	30 (42.9%)*
Diffuse	26 (37.1%)*
Indeterminate	14 (20%)*
	*Statistics based on recorded data (n=70).
Signet Ring	
Present	33 (28.5%)
Absent	83 (71.5%)
Lymphovascular infiltration	
Present	31 (58.5%)*
Absent	22 (41.5%)*
Not specified	63

	*Statistics based on recorded data (n=53).
Tumour grade	
Well differentiated	9 (12.0%)*
Moderately differentiated	29 (38.7%)*
Poorly differentiated	37 (49.3%)*
Not specified	41
	*Statistics based on recorded data (n=75).
Perineural invasion	
Present	4 (3.4%)
Absent	1 (0.8%)
Not specified	111 (95.6%)
Tumour location	
OG (Oesophago-gastric) junction	10 (8.6%)
Fundus	13 (11.2%)
Lesser or greater curvature or Body	32 (27.6%)
Pylorus/Antrum	29 (25.0%)
Not specified	32 (27.6%)
Omentum	
Involved	10 (8.6%)
Uninvolved	33 (28.4%)
Not specified	73 (63%)
H Pylori tests	
Positive	10 (13.3%)*
Negative	65 (86.7%)*
	*Statistics based on recorded data (n=75).
H. Pylori testing modality	
Giemsa	71 (94.7%)*
PCR	1 (1.3%)*
Other	3 (4.0%)*
	*Statistics based on recorded data (n=75).

Table 3: Treatment parameters

Type of surgery	
Total Gastrectomy	18 (15.5%)
Partial Gastrectomy	32 (27.6%)
Gastrectomy and other organs	5 (4.3%)
No surgery performed	61 (52.6%)
Radiotherapy	
Curative	34 (29.3%)
Palliative	32 (27.6%)
Not given	50 (43.1%)
Chemotherapy	
Yes	62 (53.4%)
No	54 (46.6%)
Was adjuvant radiotherapy completed without delays? (n=34)	
Yes	22(64.7%)
No	6(17.65%)
Incomplete treatment	6(17.65%)
Reasons for treatment delay/incompletion (n=12)	
Machine service maintenance	4(33.3%)
Toxicities (Complications)	4(33.3%)
Missed appointments (f/u)	3(25%)
Not specified	1(8.4%)
Cycles of chemotherapy completed	Number (%) of patients
1	7 (11.3%)
2	6 (9.6%)
3	13 (21.0%)
4	7 (11.3%)
5	6 (9.6%)
6	23 (37%)
Treatment related toxicities (n=84)	Number (%) of patients
N + V	11 (13.1%)
Bone marrow suppression	12 (14.3%)
Weight loss	13 (15.5%)
No toxicity	34 (40.4%)
Not specified	14 (16.7%)

End point / outcomes	Curative chemoradiotherapy (n=34)
Recurrence	3(8.8%)
Metastasis	4(11.8%)
Death	3(8.8%)
Follow up	11(32.4%)
Loss to follow up	13(38.2%)

Figure 1: Time from diagnosis to surgery

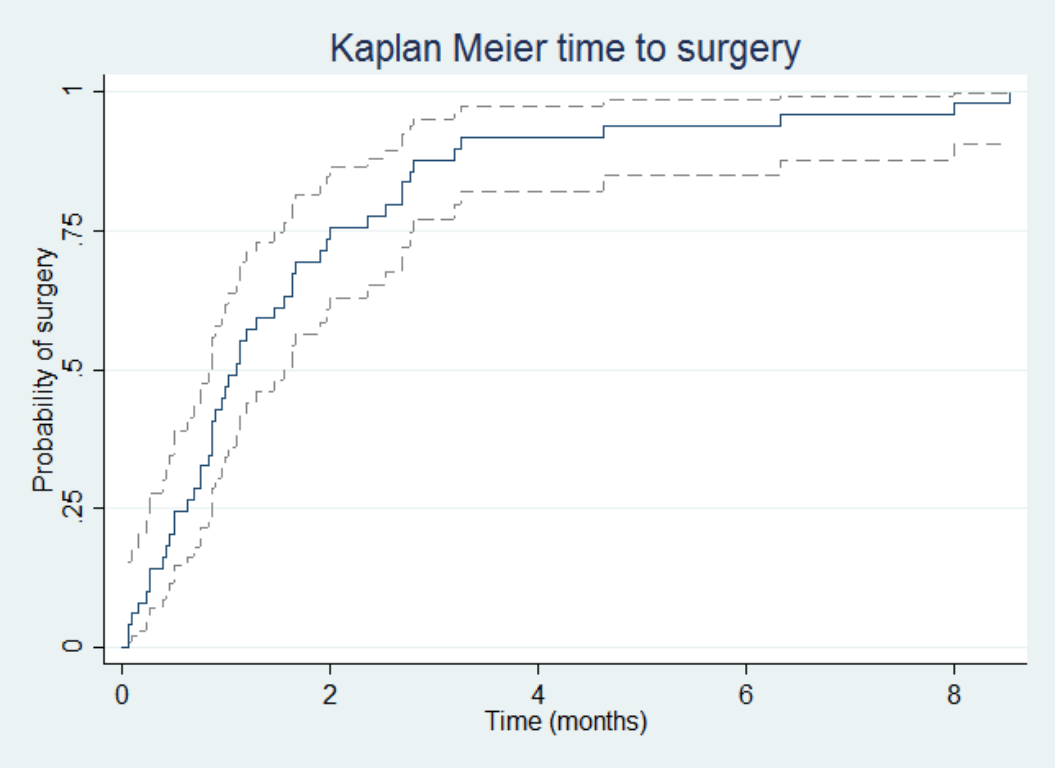
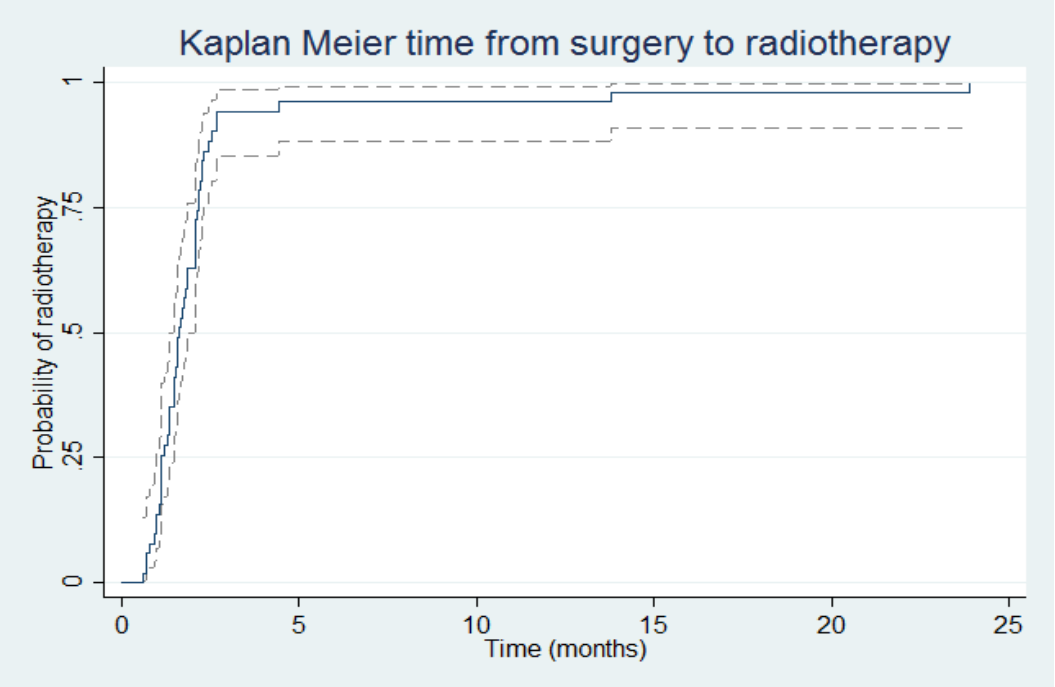


Figure 2: Time from surgery to radiotherapy



Discussion

The prevalence of *H. pylori* infection in this study is reported to be 13.3%. The figure is low when compared to the findings by Parkin *et al.* that showed that *H. pylori* is associated with 32% of gastric cancers in the UK.[7] *H. pylori* infection is found in as many as 90% of gastric cancer cases in South Korea and Japan.[24] It is also demonstrated that 35% of the patients reported here were not tested for *H. pylori*. The reason for low prevalence of *H. pylori* in our study could be due to poor reporting or under testing, as illustrated in Table 2. *H. pylori* has been ranked as a class 1 carcinogen in the human population by the WHO.[17,25] According to Fukase *et al*., the eradication of *H. pylori* infection even after surgical resection is of great value in reducing the incidence of metachronous gastric cancer.[21] It is, therefore, imperative to ensure that mandatory testing for *H. pylori* is performed in all gastric cancer patients.

The testing for *H. pylori* infection was performed by Giemsa staining in 94.7% of the cases in which infection was evaluated. In a single case, PCR was performed in a laboratory not linked to Tygerberg Hospital. According to Wabinga, Giemsa staining has a sensitivity and specificity of 85% and 89%, respectively, which are reasonably accepted figures.[26] It is considered to be the gold standard invasive test[17], which is one of the reasons why it is a method of choice in our setting. However, other methods of testing, such as immunohistochemical staining with sensitivity of more than 90% and high specificity[27] and the PCR, are better but their application is limited by exorbitant costs.[17,28]

Other risk factors associated with the development of gastric cancers beside the *H. pylori* infection include smoking, alcohol consumption, HIV infection and familial predisposition.[29–32] In this study, we found 9.5% current smokers, 6% alcohol users and only 3.5% HIV positive cases associated with gastric cancer (Table 1). These are in contrast with the high figures reported in the literature by other authors.[29–32] A point of concern

demonstrated in this study is the magnitude of poor reporting as illustrated by 79% of cases unrecorded for smoking history, 88% for alcohol use, and over 50% of cases had unknown HIV infection status. This may be the primary reason why our figures were low when compared to others, and highlights the need to improve data collection and recording of information in order to capture relevant and useful data to improve overall care of our patients.

Surgery is the mainstay of treatment for gastric carcinoma. In this study, 47.4% of patients received surgery and the other 52.6% were either metastatic or irresectable. About 30% of the patients were offered adjuvant chemoradiation with no major side effects reported (Table 3). Adjuvant chemoradiotherapy following surgical resection of gastric cancer significantly improves relapse free survival and overall survival.[33] In our small cohort, majority of patients commenced adjuvant radiotherapy within 3 months, (Fig 2), which is regarded as reasonable.[34] Optimal timing of adjuvant chemotherapy has not been documented,[34–36] and the general recommendation have been to initiate treatment within 8 weeks.[34] In studies on Korean patients, start of chemotherapy longer than 8 weeks post-surgery resulted in poor outcomes,[36,37]but findings of Greenleaf *et al*. demonstrated that time to initiation of adjuvant chemotherapy does not impact survival.[35] In this study, recurrence occurred in 8.8% of cases treated with chemoradiotherapy and this finding compares favourably with other studies which reported recurrent rates as low as 4.9%[38] and as high as 30%.[39] In this study, shorter time from diagnosis to surgery as illustrated in Fig 1 and shorter period from surgery to adjuvant radiotherapy may be contributing factors to improved outcomes. Several other factors influence the rates of recurrence for gastric cancer and they include tumour type, tumour histological subtypes, lymphovascular infiltration, tumour grade, perineural invasion, metastatic spread, and type of treatment modality offered. In this study, a significant proportion of vital information was not recorded and includes tumour grade (35%), omental involvement

(63%), and perineural invasion (95.7%) amongst others (Table 2). Of the 116 patient cohort, there were 21 deaths (18%) recorded during the study period but only 3(8.8%) were treated with curative intent and 44% lost to follow up. The causes of death were not specified.

This is the first study at our institution to audit the prevalence of *H. pylori* infection in gastric cancer patients. The study has gone further to highlight the major pockets of deficiencies in the care delivery system with regards to poor recording of risk factors associated with gastric cancer and insufficient information about the disease profile. The limitations of this study include the design method. As a retrospective audit, it is associated with increased bias and lacks statistical power and robustness to reach any major conclusions.

Conclusion and Recommendation:

This study has shown for the first time a prevalence of 13.3% of *H. pylori* infection in gastric cancer patients at our institution, and that Giemsa staining is the commonest modality used for *H. pylori* testing in our setting. It was not possible to statistically associate any of the risk factors to gastric cancer due to the methodological design of the study, and the high rates of missing information. We therefore recommend a prospective study to evaluate risk factors associated with gastric cancer in our institutional setting, including *H. pylori* infection, smoking, alcohol use, and HIV infection. We also recommend a sound collection of relevant, meaningful, and comprehensive information regarding patient profile, disease parameters, and treatment regimens.

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