CLINICO-PATHOLOGICAL CHARACTERISTICS AND OUTCOMES OF GASTRIC CANCER AMONG PATIENTS AT KENYATTA NATIONAL HOSPITAL

A RETROSPECTIVE CHART REVIEW

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DECLARATION

This dissertation is my own original work and has not been presented for a degree at any other University.

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DEDICATION

I dedicate this work to all cancer patients seen at Kenyatta National Hospital

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I am grateful to the following for their contribution to this project:

Almighty God, for giving me good health to carry out this project

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LIST OF ABBREVIATIONS

5FU	Fluorouracil
AJCC	American Joint Committee on Cancer
CRT	Chemotherapy and radiotherapy
ECX	Etoposide, Cisplatin, Xeloda
EOX	Etoposide, Oxaplatin, Xeloda
FOLFOX	Folinic acid, 5 Fluorouracil, Oxaplatin
GC	Gastric Cancer
GEJ	Gastro oesophagal junction
GIST	Gastrointestinal Stromal tumour
HER2	Human epidermal growth factor receptor 2
ICD	International Classification of Diseases
KNH	Kenyatta National Hospital
MALT	Mucosa-Associated Lymphoid Tissue
RT	Radiotherapy
UICC	Union for International Cancer Control

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ABSTRACT

Background: Despite a decrease in new cases, gastric cancer (GC) is the third-highest cause of death from cancer around the world. According to the Globocan data 2012, Kenya is estimated to have the highest incidence of gastric cancer seen on the continent of Africa. Clinical data on gastric cancer in Kenya is lacking.

Aims: The study describes the clinicopathological characteristics and outcomes of gastric cancer patients seen at the Kenyatta National Hospital (KNH) between January 2014 to December 2018.

Methods: This was a hospital-based retrospective study. We included consecutive patients with a histological diagnosis of gastric cancer from January 2014 December 2018. Patients' socio-demographic data, clinical and pathological characteristic and outcome were recorded into the Data Collection form and analyzed. The mortality rate was calculated at 6 months and the survival rate throughout the period of study.

Results: We enrolled 438 confirmed gastric malignancy. The male to female ratio was 3:2, with a median age among enrolled patients of 58 years. The commonest presenting complaints were abdominal pain, vomiting and weight loss. Approximately three-quarters (n=298,74%) patients had advanced disease (stage III and IV). Anatomically antral tumours were the most commonly seen in 196 (46.4%) while adenocarcinoma was the commonest histological type found in, 405 (93.5%) patients. Diffuse subtype was seen in 144 (58.8%) while intestinal subtype was present in 72 (29.4%). 153 (43.3%) of the patients had surgery and 267 (75.9 %) of the patients had chemotherapy with the majority having palliative chemotherapy in 197 (53.1%). Platinum-based

chemotherapy was the therapy of choice in 197 (67.2 %) patients with EOX 76 (25.9 %) being the commonest regimen of prescribed.

Conclusion: Gastric cancer in our population present at a younger age and in advanced stages resulting in poor outcomes. Early diagnosis and curative intent in treatment will likely improve survival.

CHAPTER 1: INTRODUCTION

Gastric cancer is the third most fatal cancer around the globe, with about a million diagnosed cases and over 700,000 deaths reported annually. About 70% of the cases occur in low and middle-income countries. Additionally, half of these cases occur in Eastern Asia. (1) There are wide variations of gastric cancer incidence in the world. In Africa, the geographical and regional variations have also been observed. According to the Globocan data; Kenya, Zimbabwe and Algeria were noted to have a higher incidence than Sudan, Chad and Nigeria. (1). More so regional variations have also been reported in Nigeria; the southern part has double the incidence of the northern part of the country (2, 3). According to the Nairobi cancer registry, GC ranks fourth and fifth among male and female cancers, respectively. In males, GC accounts for 6 % of all male cancers and 4% in female (4). In the Globocan data, Kenya has the highest incidence in Africa at 9.5%. (1)

Anatomically, a gastroesophageal junction (GEJ) is the junction between the distal esophagus and the proximal stomach (cardia). GEJ adenocarcinoma is often regarded as gastric carcinoma in most studies. Although the incidence of gastric cancer is reducing, that of cardia and GEJ cancers has increased (5, 6). These proximal tumours differ from the distal ones, as they are more aggressive and strongly associated with chemical carcinogens or environmental factors(7).

Anatomically GC are tumours not only arising from the stomach mucosa but also include tumours of GEJ. The definition of the GEJ is not standardized. The anatomists, physiologists, endoscopists, and pathologists define it differently. In the 2017 review of American Joint Committee on Cancer (AJCC) classification of gastric tumours, GEJ tumours with their epicentre

located more than 2cm into the proximal stomach are staged as stomach cancers, while those with an epicentre less than 2 cm into the stomach are regarded as esophagal cancer (8).

GC as a disease stems from several different causes, indicting environmental as well as genetic risk factors. The most implicated risk factors for gastric cancer as reported in multiple studies are increased levels of dietary salt and nitrates, infection with Helicobacter pylori, high alcohol intake, smoking, chronic atrophic gastritis, pernicious anaemia, positive family history of gastric, prior radiation exposure, as well as obesity (9, 10). Patients with HIV have also increased risk to develop gastric and esophagal cancer (11). These risk factors vary among the different population groups studied.

The clinical and pathological features of GC patients vary from region to region, mostly according to risk factor trends and patterns. The prognosis of GC has remains poor even in good centres due to late presentation of GC(12). This is more so in low-income countries partly due to a dearth of effective screening, radiological and endoscopy facilities. However, in developed countries with these resources like Japan, almost two-thirds of patients with gastric cancer are diagnosed early(13). The commonest presenting complaints are weight loss, abdominal pain and dysphagia. Other complaints include nausea, early satiety, occult and overt gastrointestinal bleeding. Upon physical examination, the most frequently reported finding is a palpable mass, although this signifies advanced disease(14).

Lauren classifies gastric cancer in the two histological subtypes, diffuse and intestinal. The two subtypes are different in most of their characteristics that include the epidemiology, aetiology, pathogenesis and tumour behaviour (15). Often attributed to environmental factors, the intestinal subtype mostly affects males, older people and those in high-risk areas. The diffuse (infiltrative) type, has an equal distribution of incidence between the two sexes, mostly affects younger people, and its prognosis is poorer in comparison to the intestinal type.

For the intestinal type, its incidence has decreased globally in the last several years (16). In a retrospective study of 44 patients with GC at KNH Lodenyo et al found 59% with diffuse; the more aggressive type and 39% patients with intestinal subtype(17). A larger study is needed to characterize the GC patients in our set up, and how the histological subtype affects survival. The clinical and pathological features of gastric cancer often vary age. The poor prognosis among youthful patients attributed to slower diagnosis and hyper-aggressive tumour behaviour (18). Other studies show an equivalent or better prognosis to that of older patients at the same stage (19, 20). These characteristics remain unknown in our population.

The management of GC depends on the location, size, stage and surgical candidacy. The current treatment modalities of gastric cancer include surgical resection, neoadjuvant chemoradiotherapy, adjuvant chemotherapy or palliative care(21). The management of GC is difficult in resource-constrained countries: because of the low index of suspicion, dearth of screening programs, radiological and endoscopic facilities(22). The outcome of gastric cancer is generally poor worldwide, more so in resource-limited countries like Kenya. The recent change in trend in gastric and GEJ cancer has led to the proliferation of many studies, few in Kenya. With this background, the study of the clinicopathological characteristics and outcomes of gastric cancer

patients in Kenya is a medical research priority. This study will raise the awareness of gastric cancer among local clinicians to enable early identification and prompt management of these patients.

CHAPTER 2: LITERATURE REVIEW

2.1 Epidemiology

2.1.1 Incidence and geographical variations

Gastric cancer (GC) is considered among the most rampant malignancies rated fifth with over one million estimated new cases in 2012 worldwide, this represents a substantive change as gastric cancer was the commonest malignancy in the 1980s. At least two-thirds of GC cases of cancer mostly occur in developing countries with China recording the highest number of cases of gastric cancer. Age-adjusted incidence ratio of male to female is 2:1. Eastern Europe and Eastern Asia have recorded the highest incidence of gastric cancer which is comparatively lower in the USA and Canada(1).

The incidence of GC has been on the decline in the recent decades, although this decline has been interrupted by an increase in gastric cancer in younger populations(23). Part of this trend can be linked to identifying Helicobacter pylori as a risk factor, moving away from salting as a food preservation method to refrigeration and changes in dietary and environmental factors. In countries with high incidence like China, the decline has been slower with an observed increase in the younger population(24). Similarly, North American data from 1977- 2006 shows a decreased incidence of non-cardia GC in all person groups except for white people and those aged 25 – 39 years. (25).

In Africa, there is a paucity of data and lack of reliably established registries to inform us on the burden of gastric cancer. GC in Africa still demonstrates geographical and regional variations. According to the Globocan cancer registry, GC incidence rates are reported higher in

Kenya, Zimbabwe and Algeria than Sudan, Chad and Algeria(1). Regional variation has also been reported in many countries. Two retrospective studies done in Nigeria found the incidence of gastric cancer in Southwest Nigeria at 4.1%, this was double the rate in the north part of Nigeria (2, 3). In Tanzania, a higher incidence rate was observed around the Mt Kilimanjaro region than the lower Southern parts (26).

2.1.2 Burden of Gastric cancer in Kenya

Despite the lack of data on GC and GEJ in Kenya, the Globocan cancer registry indicates an incidence rate of 9.5% for gastric cancer in Kenya making it the highest rate in Africa (1).

A retrospective study by McFarlane G et al reviewing data of gastric cancer patients in eight hospitals in Meru, Eastern part of Kenya, between 1991 to 1993 reported 200 cases of gastric cancer over the three years with "an annual crude incidence of 7.01 per 100000 males and 3.7 per 100000 females (world standardized rate of 14.3 for males and 7.1 for females). These rates in this part of Kenya were comparable to the rates in Eastern Europe and similar to the rates reported in some highlands of Africa."(27) The reliability of this data may be questionable as only 24 % of the patients had an endoscopic diagnosis, with only 18% (9 patients) having a histological diagnosis and the majority of the patients 52% (103 patients) diagnosed by laparotomy. This may also have underestimated the incidence of GC in this study(27).

A retrospective study reviewing 1200 patients with dyspeptic symptoms who underwent endoscopy at KNH between 2014 and 2016 found a relatively high prevalence of 3.6 % (44 patients) with a male to female ratio of 1.8: 1. Females were affected earlier than males by about one decade with more than 52.5% of the female with gastric cancer below 50 years and 11.8 %

diagnosed below 40 years while only 11. 1% of the males diagnosed below 40 years(17). The percentage of younger patients diagnosed with GC was higher than many other studies (28). Although this study had a small sample of 44 patients, it brought out important patient characteristics of gastric cancer patients in Kenya that needs to be explored further.

An earlier retrospective study to evaluating endoscopy and the prevalence of *H. pylori* among patients in Kenya between June 1993 and September 1994 demonstrated gastric cancer prevalence of 17.4% of 120 patients who underwent endoscopy, with none of them being below 50 years(29). Lodenyo et al in 2014 to 2016 reported gastric cancer in patients in an age range of 23 to 85 with 37.9% of patients below 50 years. Another study by Ogutu et al between 1987 and 1989 at Kenyatta National Hospital found a higher male predominance among 53 patients with histologically proven gastric cancer with a male to female ratio of 3.4:1 with a peak age recorded at the 6^{th} decade(30).

The burden of gastric and GEJ cancer is relatively high in Kenya contrary to other parts of the world and there are obvious differences and change of trend in gastric cancer patients in these studies. The sample size of GC in these studies was small thus the need for a large sample sized study to fully characterize these patients in our population.

2.2 Clinical presentation

A majority of the gastric cancer patients are often diagnosed when the diseases are on the incurable stage. The patients usually experience severe abdominal pain and encounter significant weight loss during the first diagnosis. They also complain about dysphagia especially in patients

with a proximal or GEJ tumour (14). Other symptoms are inclusive of nausea, early satiety attributed to tumour mass and *linitis plastic* which is attributed to distensibility of the stomach. An advanced distal tumour may also cause gastric outlet obstruction among patients. A retrospective conducted by Mabula et al also revealed that a majority of the patients who encounter advanced forms of the disease such as epigastric mass were 69.8%, symptoms of obstruction 79% and gastrointestinal bleeding 19.4% (31).

2.2 Pathological Characteristics

Different classification systems have been used to describe GC based on both macroscopic and histopathological characteristics. These include Borrman, the World Health Organization (WHO) system, The Japanese system and Lauren classification (15, 32). The Lauren classification is the most widely used system and characterizes the tumours in accordance to the histological appearance and pattern. This system, sub-classifies gastric adenocarcinoma into two sub-types which are inclusive of intestinal and diffuse histological which differ markedly in their epidemiology etiology, pathology and biological behaviour (15).

2.2.1 Histological Subtypes

The intestinal subtype of GC is the most frequent worldwide and in particular in areas with a high prevalence of the malignancy(33). It is twice more common among males contrary to females and usually in the older age group. Additionally, it is also prevalent in areas which are considered to be high-risk and are highly linked to environmental influences. Often occurs in the distal lower stomach (antrum) and has well defined glandular formation (34). The intestinal

subtype usually develops in a stepwise sequence that is preceded by atrophic gastritis, metaplasia, dysplasia and to finally overt GC (35).

The diffuse or infiltrative subtype of gastric adenocarcinoma develops frequently in the stomach and unlike the intestinal type, it is associated with the lack of recognizable pre-cancerous lesion(34). It is also linked with genetic abnormalities, and though to arise out of single-cell mutations in the previous normal gastric glands (36, 37). It doesn't demonstrate gender predilection, although more rampant among younger patients, and often more aggressive with poorer outcomes than the intestinal type.

The diffuse type accounts for 30% of GC in some published studies(16), Lodenyo et al in the series reviewing 44 patients with histologically confirmed gastric at KNH cancer found 59% with diffuse; the more aggressive type and 39% patients with intestinal subtype. These histological variations and their effect on the survival rate has not been studied in our local population of gastric cancer patients.

The anatomical location of tumours is also been shown to be an indispensable parameter for the classification of GC and GEJ malignancies. Concerning anatomical location, there are two subtypes GC which are recognized which is inclusive of tumours in the stomach (usually in the distal parts) and from the most proximal part which includes the cardia and the GEJ (38).

Different studies in Africa have reported varied results on the anatomical location of gastric and GEJ malignancy. Osime et al in a retrospective review of GC patient in 2010 at a teaching and referral hospital in Nigeria over 5 year period found that at least 78% of the cases were related to

gastric antrum (39). A Tanzanian retrospective study of 232 with GC between January 2007 and December 2011 found a slightly lower antral predominance at 56.5% with cardia accounting for the least at 5.2% (31).

Many studies done in the last one decade have demonstrated and a significant increase in the cancers of the cardia and the GEJ. It has been found as reported in some studies that the proximal tumours are different entity at all (5). The tumours are associated with demographic and histopathological characteristics with Barrett's mostly being linked with esophageal cancer which is more common in males, as with the distal esophageal cancer. A study evaluating forty-nine patients with surgically resected adenocarcinomas of the gastric cardia captured 23 cases which contribute to resected adenocarcinomas which were as a result of Barrett's columnar lined lower esophagus contrary to the histological and clinical aspects. These two groups are were also identical in relation to the degree of differentiation, histopathological pattern and the level of tumour extension and the time of resection."(7) They are more aggressive than those with distal antecedents. Additionally, chemical and environmental carcinogens (such as cigarette and alcohol) which had stronger associations as opposed to cardiac distal carcinomas (7).

The epidemiological and geographical variation between the two anatomical types of gastric tumours has been reported in many studies. Non-cardia tumours contribute to a majority of the cases in the world and are commoner in high prevalence countries. In contrast, cardia sub-types of gastric cancer is homogeneously distributed worldwide with a rising incidence(38). In a Descriptive study that conducted by the National Cancer Institute's Surveillance in the United States from 1977 through 2006, of 83 225 gastric cancer found the incidence rates of non-cardia to have declined in all races and age groups except in white younger patients between the ages of

25-39 years who recorded an increased. The increased incidence of non-cardia GC among younger individuals that is worth noting that may result in the introduction of environmental factors (25).

2.5 Diagnosis

2.5.1 Upper gastrointestinal endoscopy

The upper gastrointestinal endoscopy is typically performed for tissue examination and anatomic localization of the primary tumour. Although it is more aggressive and costly, the upper endoscopy has greater sensitivity and specificity to diagnose a range of gastric tumours than alternative diagnostic approaches that include barium studies with increased sensitivity as the number of biopsies taken increases (40). Most of the endoscopic equipment in Kenya are found in major towns, and in private hospitals where the procedure is expensive. This contributes to the delays in diagnosis and treatment of GC.

In a comparative retrospective study of 100 randomly selected patients who were examined with either endoscopy or barium meal, it was found that endoscopy and barium studies had a sensitivity of 92% and 54% with a specificity of 100% and 91% respectively. The diagnosis of "linitis Plastica" an aggressive form of GC is usually cumbersome through the use of endoscopy largely due to the fact the tumours are deep the submucosa making superficial mucosal biopsies give false-negative results. Authorities, therefore, make the recommendation of using both strip and bite biopsy approaches in the diagnosis of the diffuse type of GC (41).

2.5.2 Barium studies

Barium studies are instrumental in the identification of malignant gastric ulcers and infiltrating lesions, and sometimes can locate early GC, however, as many as 50 % of the cases identified might be false-negatives(41). The sensitivity reduces to as low as 14% in early GC(42). Thus, in most if not all settings, upper endoscopy is the most ideal initial diagnostic test for patients suspected of GC. A high clinician suspicion level, health education and the provision of endoscopic facilities may instrumental during early diagnosis and it helps in improving the outcomes.

2.5.3 Screening

Early detection of GC has been shown to improve mortality, however, screening for GC has been controversial and different screening protocols vary based on the cancer incidence. Countries such as Korea, Venezuela and Chile record the highest incidence of GC captured through population-based screening (43-45). The two modalities used for cancer screening has been upper endoscopy and double-contrast barium radiographs or digital radiography which is deemed to be superior (40). Barium sensitivity in a study that focused early GC was 14%(41). Although some observational studies propose that screening in areas with high GC incidence contributed to the early detection cancer and a general decline in mortality from GC, there are no data from large randomized trials showing lower mortality from GC (43, 46)

In Japan, population-based screening for stomach cancer is suggested for individuals over 50 years of age with conventional double-contrast photofluorography barium radiography every year or upper endoscopy every two to three years(45). In Korea, upper endoscopy is endorsed for

individuals between 40 and 75 years every two years (47). In areas that record low GC incidence, screening with upper endoscopy is endorsed for specific high-risk subgroups.

2.6 Management

GC management poses a major challenge in resource-limited countries around the world, such as Sub-Saharan Africa. If the disease is characterized with a late presentation due to a lack of standardized and appropriate screening services, clinical knowledge and suspicion coupled with a lack of endoscopic facilities lead to high morbidity and mortality in sub-Saharan Africa(48).

2.6.1 Staging

Many staging systems have been documented worldwide, with two being the major classification system used. The Japanese classification, which is founded on the defined anatomic site, and the lymph node status(49). The commonest and the more widely used staging system, developed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), are commonly used (8). The staging schema for AJCC/UICC are usually founded on the AJCC/UICC is based upon the tumour, node, and metastasis (TNM) classifications. The latest revision of the classification is the 8^{th} edition which was developed in 2017 (AJCC/UICC-TNM).

Surgical pathology staging is the most accurate to determine GC stage, however, clinical staging mostly directs approach to therapy initially. Patients with a locoregional disease (stage I to III) after preoperative evaluations are potentially curable, while those with advanced-stage IV disease, contingent on the symptoms and functional capabilities (palliative therapy). Multiple studies show systemic therapy which contributes to longer survival and better life quality.

2.6.3 Treatment

The determinants of treatment modality of gastric cancer include the location, stage, histological type, patient's age, comorbidities, and general health of the patient.

2.6.3.1 Local/locoregional disease

Role of surgery

Surgical resection of GC, especially in early stages, can be curative in centres with experienced surgeons. However, even good experienced centres up to 40% of patients can encounter relapse after surgical resection, combination therapies that include perioperative chemotherapy or radiotherapy is the standard in a majority of the guidelines for ≥ Stage IB disease(50). Endoscopic resection of very early GC (T1a) that doesn't extend beyond the mucosa, non-ulcerated, well-differentiated and with a tumour size of ≤2 cm can be attempted in centres experienced with the procedure (51).

Radical gastrectomy either subtotal or total is indicated stage IB–III gastric cancer. If a proximal macroscopic margin of 5cm is attained between the tumour and its free margins, subtotal gastrectomy may be performed, otherwise, total gastrectomy should be performed. For these patients, perioperative therapy is indicated (52)

The degree of nodal dissection following gastrectomy has elicited intense and inconclusive debate.D1 resection entails the dissection and removal of perigastric lymph nodes only while D2 involves removal of perigastric lymph nodes with those along surrounding vessels that include the left gastric, splenic and the hepatic arteries and the coeliac axis. Several studies comparing the two

nodal dissection modalities have revealed conflicting results. Studies from Asian countries that include observational and randomized control trials have demonstrated superiority of D2 over D1 nodal dissection, while studies in the western countries, Italy and Holland has failed to show the above(53-55). A consensus report by the specialists is that, for patients who are clinically fit in high volume, specialized and experienced centres with appropriate post-operative care should undergo D2 resection(52).

Meta-analysis and randomized studies have shown significant survival benefits of adjuvant chemoradiotherapy, perioperative (preoperative plus postoperative) chemotherapy through surgery alone among patients with potentially resectable cardia and GEJ tumours (56).

Perioperative chemotherapy

Neoadjuvant chemotherapy is recommended as the initial treatment in resectable and unresectable GC with no metastasis as a way of "downstaging" a locally advanced tumour before surgical resection. A platinum/fluoropyrimidine combination is recommended perioperatively for patients with ≥ Stage IB resectable GC. This was informed by the MAGIC trial of the United Kingdom Medical Research Council, which showed a 5-year survival benefit for patients with resectable stage II and III stomach cancers treated with 6 cycles of ECF (Epirubicin, Cisplatin and 5-fluorouracil) compared to surgical resection alone. This is one of the largest and influential studies in GC (56)

One of the largest meta-analysis of 12 trials including the influential MAGIC trial comparing different preoperative chemotherapy regimens with surgery alone deduced that

neoadjuvant chemotherapy was linked with benefits that contributed to overall survival, progression-free survival, higher R0 tumor resection rate and without significantly worsening the operative complications, perioperative mortality, or grade 3 or 4 adverse effects(57). There has been the variability of practice on the choice of chemotherapy as the best chemotherapy regimen to be used for the above has not been conclusively established.

Neoadjuvant Chemoradiotherapy

Chemotherapy and radiation therapy combinations preoperatively are mostly used for cardia and GEJ adenocarcinoma, and less commonly used for the noncardia tumors. Neoadjuvant chemoradiotherapy was matched with induction chemotherapy alone in the multicenter German POET randomized control trial, which was limited to patients with GEJ adenocarcinoma. While the primary endpoint of survival benefit was insignificant in the long-term follow-up showed benefit especially in relation to the local progression-free survival when radiotherapy was combined to preoperative chemotherapy in patients with GEJ locally advanced adenocarcinoma (58). In addition, it is indistinct whether the findings can be extrapolated to patients with true noncardia gastric cancers. Comparable also show that in three randomized postoperative CRT studies demonstrating a significant survival benefit contrary to surgery alone after the completion of GC and GEJ cancer resection (59-61).

The largest and most recent of these trials is the United States Intergroup 0116, which provides strong data to prove the benefit of adjuvant CRT following complete surgical resection. The study showed improved overall survival with a combination of adjuvant therapy of 5-FU plus fractionated radiotherapy compared with surgery alone. The analysis shows a statistically significant increase in survival rates, 50% 3-year survival for CRT-treated patients versus 41% for

surgical only treated patients. In a 10 year follow-up period, the OS progress remained substantially favourable for the CRT arm (61)

2.6.3.2 Advanced/metastatic disease

Patients who experience advanced GC or GEJ cancer and good PS a platinum /fluoropyrimidine-based chemotherapy is recommended. The effectiveness of systemic chemotherapy in advanced GC was assessed in an RCT in which 61 patients who were randomized to chemotherapy and best supportive care or best supportive care alone. A majority of the patients undergoing chemotherapy recorded an enhancement in life quality which contributes to better-survival rates as opposed to supportive treatment alone. However, the systemic chemotherapy should be offered only after evaluation of the patients' PS, comorbidities, organ function and patients preferences (62).Second line chemotherapy in carefully selected with taxanes, ramucirumab or irinotecan have demonstrated efficacy as single agents or combinations in advanced GC (63).

Targeted therapy

The prevalence of HER2 positivity has been variable in different studies. In a local study, Hussein et al found 42.4 % prevalence of HER2 positivity in 66 gastric cancer patients at KNH, a referral hospital in Kenya, a higher prevalence than in most of the other studies (64). The Phase III, Trastuzumab for Gastric Cancer, ToGA study that captured statistically significant gains in overall survival, performance scales and response rate, with the addition of trastuzumab to a doublet of cisplatin/fluoropyrimidine in HER2-positive gastric (65).

2.7 Outcomes and prognostic factors

There has been variable survival rate of GC and GEJ cancers. GC has shown to having worse prognosis among the solid tumors. Despite the advancement and success of current modern chemotherapy in relation to the treatment of large intestinal cancers, the five-year survival of patients with GC and GEJ cancers in most regions is below 30% and is projected to be lower in developing countries (66).

Prognostic factors in gastric adenocarcinoma need to be identified in order to establish the staging and determining therapeutic strategies. TNM staging is the most significant factor in gastric cancer. In a study done in Oman, Al- Mundhir et al found tumor size >5 cm having a strong prognostic significance (67, 68). In some reported series, the Lauren histological subtype determines the prognosis. Studies have shown that the diffuse or the infiltrative type tends to be aggressive leading to poor outcomes(15). Location of the tumor has been shown to predict patient's outcome. Data from many studies report an explosive increase in the incidence of cancers of the gastric cardia and GEJ (5, 6). Tumors of the cardia and the GEJ tend to be more aggressive contrary to those from distal sites.(7).

The clinical and pathological properties of gastric cancer often vary between younger and older patients, and the prognosis is believed to be poorer in younger patients due to late diagnosis and more aggressive tumor activity (18). Other studies have shown that the prognosis is equivalent to (69, 70) or better to that of older patients at the same stage (19, 20). These characteristics remain controversial and would differ from different populations studied.

The last one decade has seen a growing number of studies comparing the clinicopathological characteristics, outcomes and prognosis in the two age groups. Yukiko Takatsu et al in 2015, in a single centre retrospective study investigating clinicopathological characteristics of GC in young patients, it was observed that early onset of GC is likely to occur with lymph node metastasis than in older patients (25% vs. 16 % respectively). However, the survival rate of GC among young patients was equivalent compared to patients in their 60s (71). In another retrospective study in Portugal, comparing the outcome of GC in the two age groups found that diffuse adenocarcinoma was a common histological type among young patients while in older patients it was intestinal subtype. The survival for stage III and IV was significantly worse in younger patients compared to older patients with gastric cancer in the same cohort(72). Similar study design in Turkey found that young GC patients had more aggressive histopathological features with more than half had metastatic disease at the time of diagnosis (73).

Survival rates of GC and GEJ cancers in Africa has been lower than the reported rates in developed countries. Table 1 shows a summary of outcomes reported in some selected African countries. All these studies have had conflicting results as they were done in different geographical regions with differing basic clinical characteristic of the patients. These characteristics are not known in our patients; knowledge on the above will help clinical stratification and prognostication among our local patients with GC

Table 1: Outcomes of Gastric Cancer in African counties.

Country	Year of publication and study design	Author	Sample size	Overall survival	Treatment	Post-operative		Incidence and Mortality rate per Globocan
						Complication	Mortality	
Tanzania	2012, retrospective review	Mabula et al(31)	232	5 year survival: 32.8%	Surgery: 223/232 (96.1%) Chemotherapy: 56 (24%) Radiotherapy: 12 (5.1%)	37.1%	18.1%	2/100000 2/100000
Mali (Abstract, French article)	2012	Dembele et al(74)	425	1 year survival: 15.5%	200 (65%): surgery 105(34.3) no surgery 4 (1.3%) chemotherapy	-	-	20.3/100000
Nigeria	2011, retrospective review	Ahmed et al(75)	179	1 year 70.1% 5 years: 20%	Surgery: 155 (86.6%)	43 (27.7%)	25 (16.1%)	2.2/100000

CHAPTER 3: JUSTIFICATION

GC is among the most common causes of death and it is ranked in the world. The Nairobi Cancer Registry revealed that GC is also ranked the third leading cause of death among both males and females after cancer of the prostate and esophagus in males and cancer of the breast and cervix in females, with the Globocan Data reporting the highest incidence in Africa at 9.5% of all cancers. The management of GC is a major public health concern worldwide. It is often detected late, more so in resource-limited countries in Africa leading to high morbidity and mortality.

There is a limitation of studies in relation to GC has not been recently studied in Kenya, and the worldwide change in the clinicopathological characteristics have not been documented in our set up. There has been an increase in the interest of various stakeholders on cancer and its management. This study provides information on the clinicopathological characteristics and outcomes of gastric cancer bridging the gap in knowledge and forming a basis for further research to improve patient's outcomes.

CHAPTER 4: RESEARCH QUESTION AND OBJECTIVES

4.1 Study question

What are the clinicopathologic characteristics and outcomes of patients with gastric cancer at KNH?

4.2 Study objectives

4.2.1 Broad objective

To determine the clinicopathological characteristics and outcomes of patients with gastric cancer at KNH between 1st January 2014 and 31st 2018.

4.2.1 Primary objectives

1. Describe the socio-demographic characteristics of patients with GC at KNH
2. Describe the clinical characteristics of patients with GC at KNH
3. Describe the pathological characteristics of patients with GC at KNH

4.2.2 Secondary objectives

1. Determine the outcomes of patients with gastric cancer at KNH.
2. Correlate mortality with clinicopathological characteristics.

CHAPTER 5: METHODOLOGY

5.1 Study Site

This study was conducted at KNH, the largest referral hospital in Kenya, with 1800 bed capacity located in Nairobi County, Kenya. The catchment is largely from the metropolis with referrals from all over Kenya and East Africa. It has established outpatient oncology clinic, radiotherapy department and oncology wards seeing more than 5000 new cancer patients a year from different parts of the country. The study was undertaken at the KNH Cancer Treatment Centre registry and them main hospital registry where patients details were retrieved from the files.

5.2 Study Design

A single centre retrospective study approach was implemented. This design allowed the evaluation of clinicopathological characteristics and outcomes of patients with gastric cancer.

5.3 Study Population

Data was retrieved from case records of patients with biopsy-proven Gastric and GEJ cancers aged 13 years and above, who were seen at the Kenyatta National Hospital between January 2014 and December 2018. Patient records from the main KNH records office and the Cancer treatment Centre were studied

5.4 Eligibility Criteria

5.4.1 Inclusion Criteria

All patients above 13 years with biopsy-proven gastric or gastroesophageal junction cancer seen at KNH between January 2014 and December 2018.

5.4.2 Exclusion criteria

Records of patients having insufficient or incomplete medical records were excluded Incomplete records were described as any case with no data on variables of interest (age, histological subtype).

5.5 Sample size determination

The Fisher's formula((76) was used;

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = value from standard normal distribution corresponding to the desired confidence level (Z=1.96 for 95% CI)

P = expected true proportion (estimated at 56.5%, from a retrospective study conducted by Mabula JB et al. (2012) from January 2007 to December 2011 at Bugando Medical Center, Tanzania;

looking at histologically confirmed cases of gastric cancer, found that antrum was the most frequent anatomical site at 56.5%

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.565(1-0.565)}{0.05^2} = 347$$

A Sample size of 347 patients was required for the study.

5.6 Sampling Method

All patients diagnosed with GC during the study duration who also met the eligibility criteria were enrolled. Since all the patients meeting the eligibility criteria were enrolled, the calculation of a sample size wasn't required. However, a minimum sample size was calculated.

5.7 Research tools

Study data were sourced from the patient's medical records. Missing records e.g. histology results, imaging reports were from the relevant department. Data collection tool was used to collect variables of interest.

5.8 Data collection

Through a retrospective review of the medical records at KNH both at the main registry and at the Cancer Treatment Centre.GC files from 1st January 2014 to 31st December 2018 were retrieved using ICD- 10 code, C16.9 that includes GEJ cancer. The review was done by the

investigators with assistance from medical records officers. Missing information on histology was supplemented by retrieving histology reports from the histopathology department. We included all consecutive patients with a confirmed histological diagnosis of gastric cancer in the 5 year period. Files that didn't meet the criteria were excluded. Variables of interest were recorded into the Data Collection form. The outcome at 6 months was recorded as indicated in the records as dead, alive or lost to follow up.

5.10 Study variables

5.10.1 Independent variables

Measures that will be obtained include:

- Socio-demographic data: Age, gender, residence, occupation
- Clinical presentation: Abdominal pain, dysphagia, vomiting, weight loss
- Duration of symptoms in months as recorded by the clinician in the file
- Date of diagnosis: Defined as the date of histological diagnosis.
- Anatomical site – As defined by the endoscope or laparotomy
- Histological type – Adenocarcinoma /squamous cell carcinoma/adenosquamous
- Histological subtype – According to Lauren classification as either intestinal or diffuse.
- Staging: American Joint Committee on Cancer (AJCC)
- Information regarding treatment: type of chemotherapy, type of surgery

5.10.2 Dependent variables

Outcome measures were recorded as alive, dead or lost to follow up at the end of the five year study period. Outcomes included all-cause mortality at 6 months after diagnosis and survival rates. The date of diagnosis was assumed to be the date of the first histological proven gastric cancer.

5.11 Data Analysis

The data was exported to Microsoft Excel Package and Statistical Package for Social Sciences (SPSS). Categorical variables were analyzed and reported as frequencies with percentages. Continuous data variables e.g. age was expressed as means and standard deviations if normally distributed or median and interquartile range if skewed.

Person time was calculated from the time of first histological diagnosis of gastric cancer to death or end of the follow-up period. The mortality rate was calculated at 6 months. Kaplan-Meier analysis method was used to show to determine survival and Log Rank test was used to compare the survival distribution across the groups of the covariates with statistical significance at $p<0.05$.

Cox proportional hazard regression was modelled to identify the factors associated with mortality among patients with gastric cancer. First, a univariate Cox regression analysis was done to estimate unadjusted Hazard Ratios (table 3). Variables significant at $p <0.05$ in the univariate analysis were analyzed using multivariate cox regression to estimate adjusted Hazard Ratios with 95% confidence intervals.

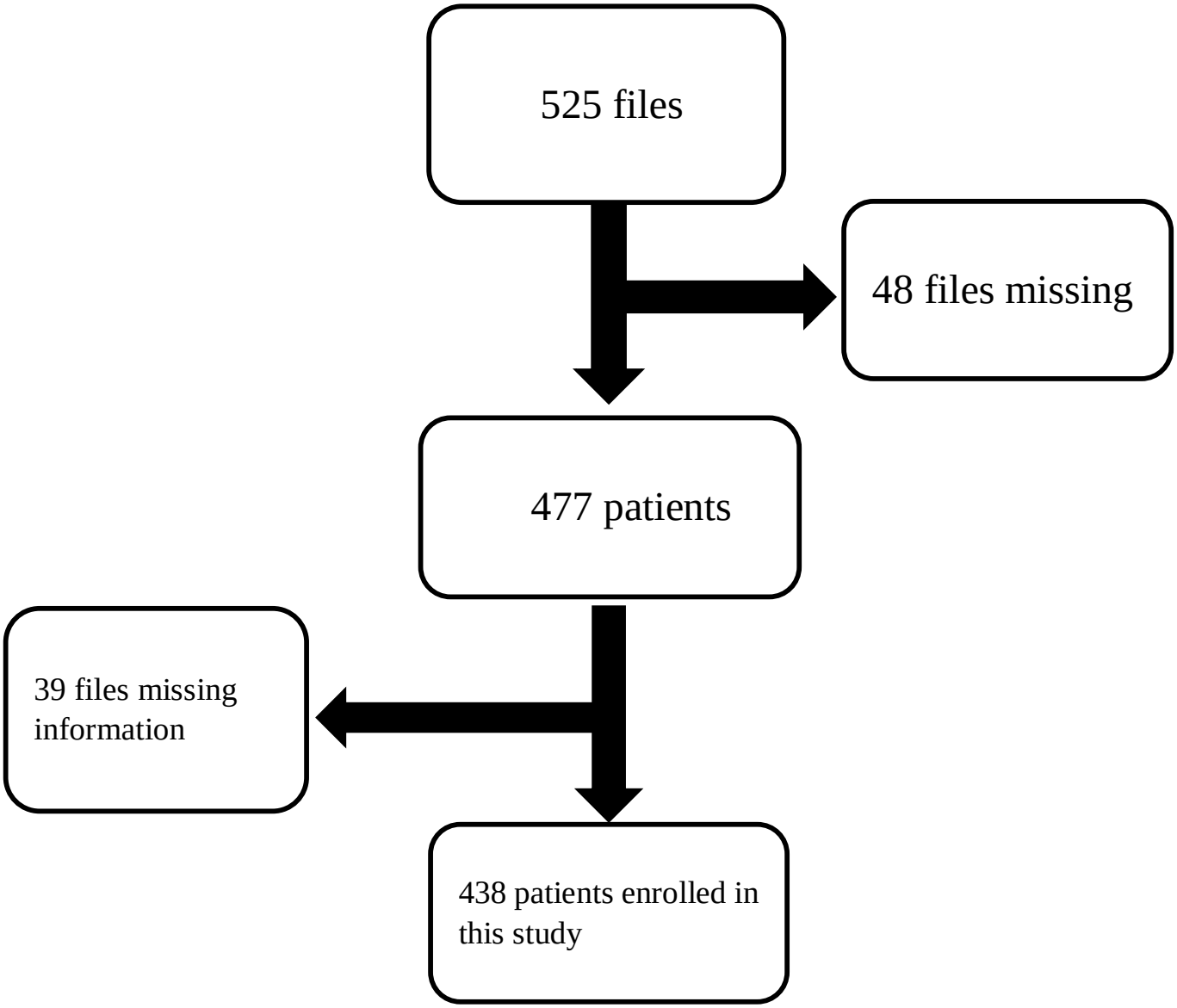
5.13 Ethical Considerations

Data collection proceeded after ethical approval was obtained from the Ethics Committee at the KNH. Absolute confidentiality was observed. Data collected was kept by the primary researcher which was inclusive of the computer used to analyze the data under lock and key. The identification of patients was made through the use of unique numbers to ensure confidentiality. Data obtained from this study was not used for any other purpose apart from meeting the objectives of the study.

CHAPTER 6: RESULTS

There were 24669 patients with malignancies registered at KNH in the 5 year period studied of which 525 were gastric cancer, representing 2.13 % of the total malignancies.48 files were missing and 39 had missing information, therefore 438 were enrolled (Figure 1)

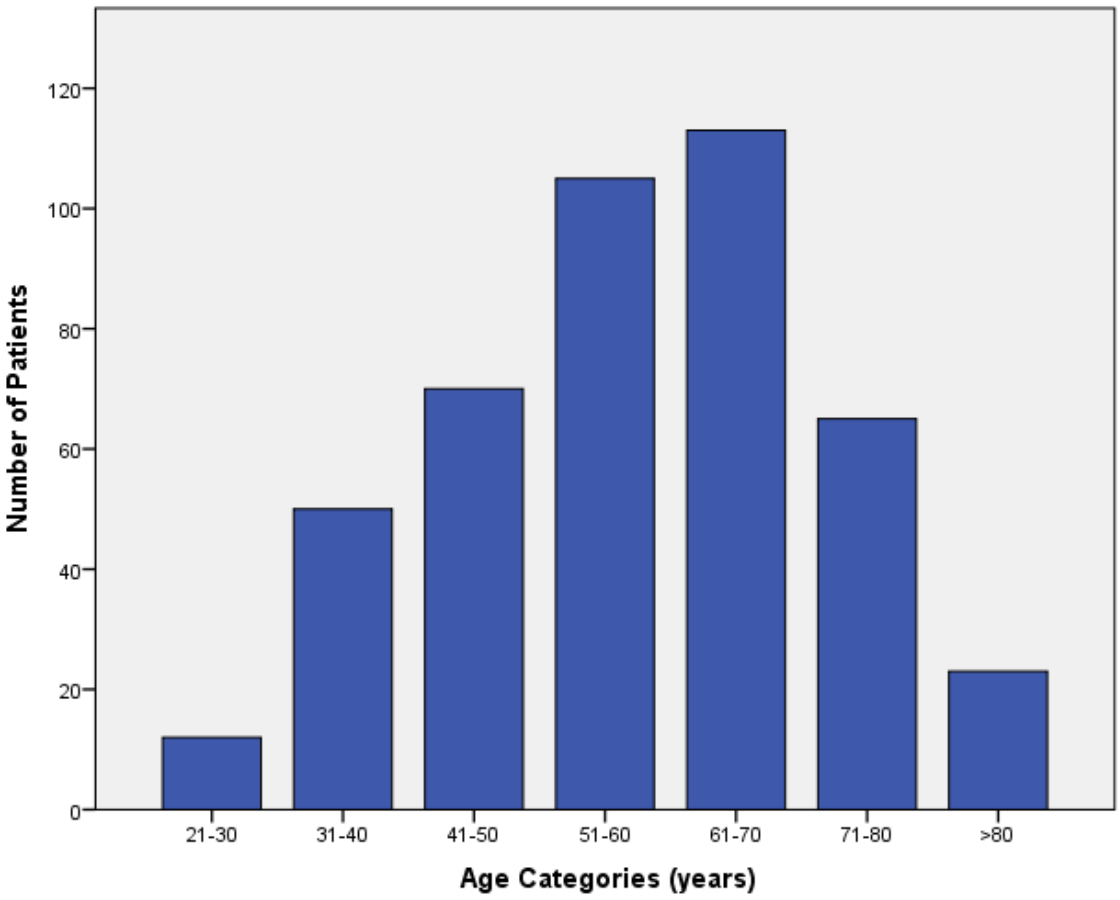
Figure 1 Flow diagram showing the selection of the study cohort



6.1 Socio-demographic Characteristics

Out of the 438 enrolled there were 264 (60.3%) males and 174 (39.7%) females with the M: F ratio at 1.5: 1. The age range was from 21 to 100 years with the mean age at 58.1 (SD=14.4) years, while the median age was 59.0 (IQR=21.0) years. The age distribution is represented in a bar graph as shown in Figure 2 below. The mean age for female was slightly lower at 55.9 years than that of males at 58.3 years although this was not statistically significant. (P-value = 0.17)

Figure 2: Age distribution



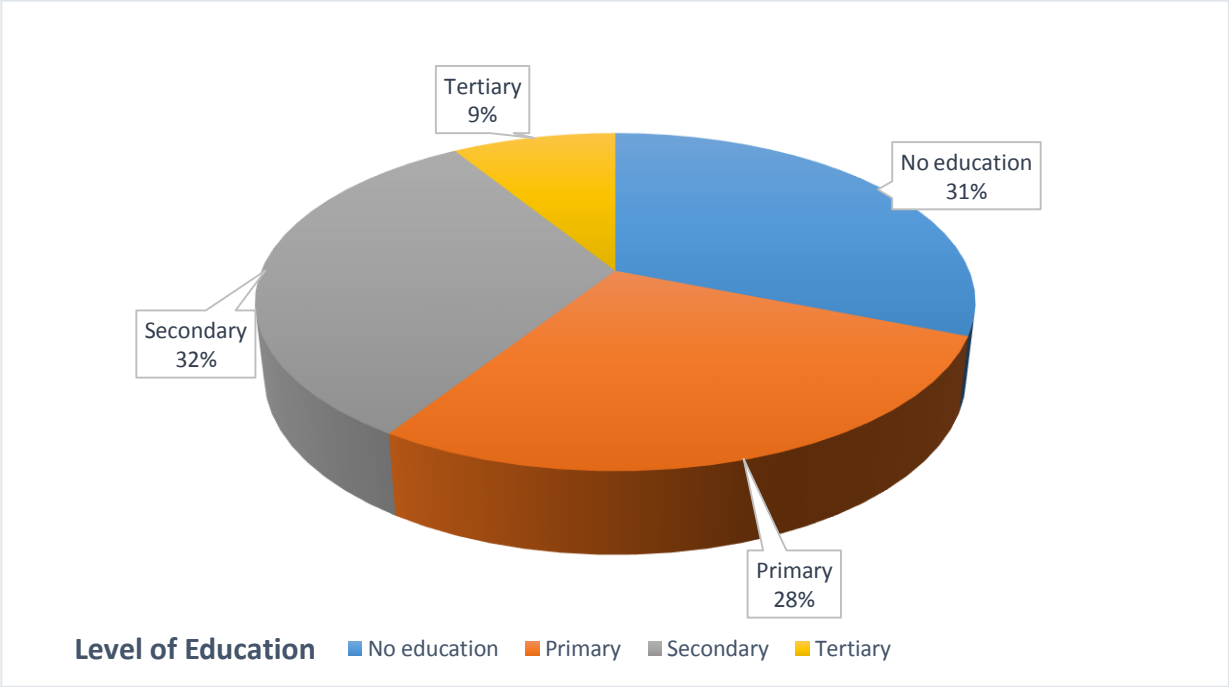
Majority of patients had either no education or primary education 118(59 %) while 62 (32.1%) had secondary education. Only 17 (8.8%) had tertiary education from either college or university (Figure 3). There were 64 (35 %) unemployed patients, while the majority of employed were in business or farming. Patients seen with GC at KNH were from Nairobi and its environs. Fifty-five patients (13.1%) were from within Nairobi, while central Kenya accounted for the most, with 57 (13.6 %), 53 (12.6%) and 49 (11.7%) coming from Kiambu, Muranga and Nyeri respectively. Table 2 below summarizes the patients' socio-demographic characteristics.

Table 2: Patient Socio-demographic characteristics

	Frequency n (%)
Mean	58.1 (SD=14.4)
Median	59.0 (IQR=21.0)
Gender *(n=438)*	
Male	264 (60.3)
Female	174 (39.7)
Level of education *(n=193)*	
No education	60 (31.1)
Any formal education	133 (68.9)
Occupation *(n=183)*	
Employed	37 (20.2)
Unemployed	64 (35.0)

Self-employed	82 (44.8)
Residence *(n=419)*	
Kiambu	57 (13.6)
Nairobi	55 (13.1)
Muranga	53 (12.6)
Nyeri	49 (11.7)
Meru	38 (9.1)
Others	167 (39.9)

Figure 3 : level of education



6.2 Clinical Presentation

As shown in Table 3 below, the commonest presenting complaint was abdominal pain, documented in 337 (76.9%) of the patients, while 200 (45.7%) patients had vomiting, with

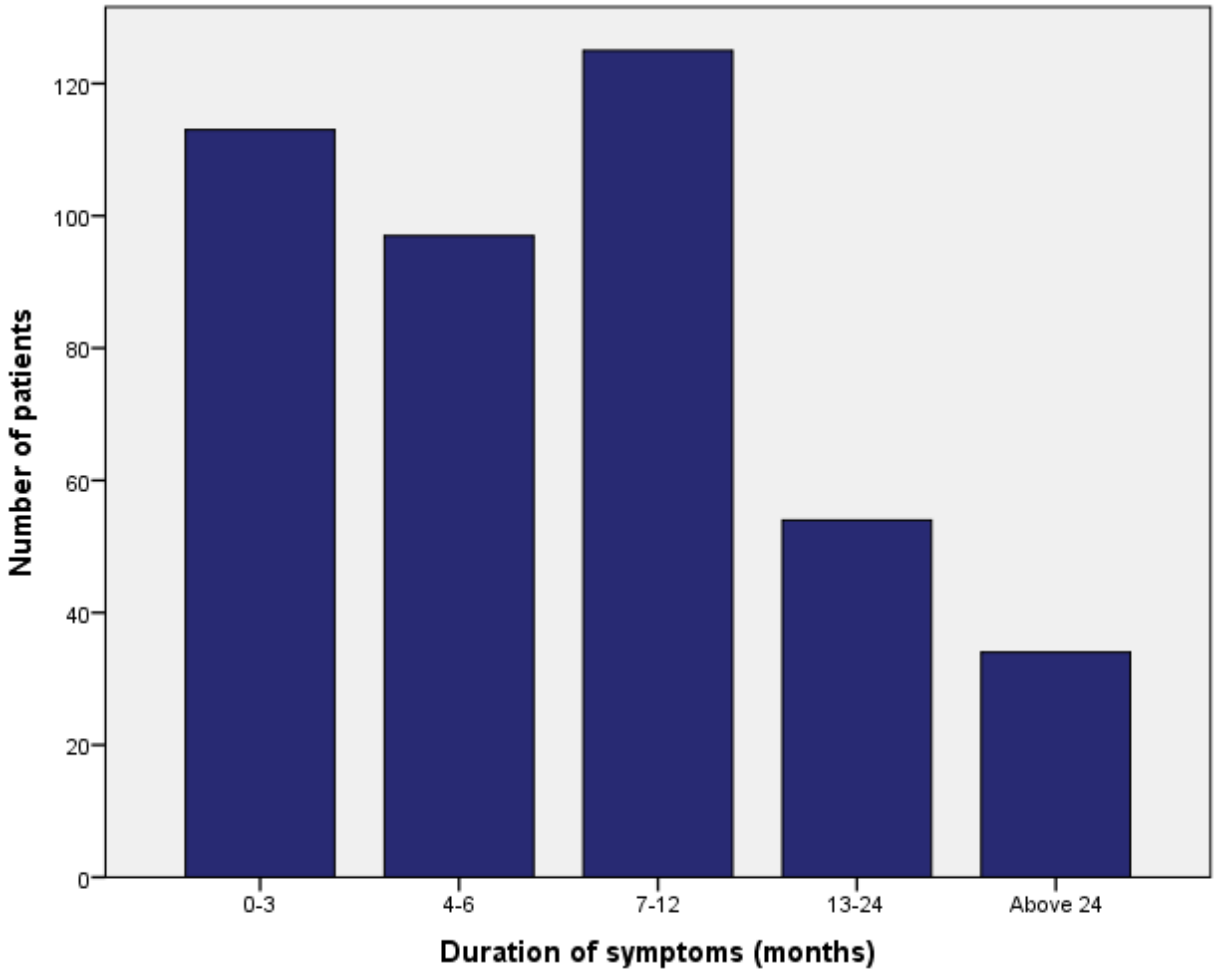
143(32.6%) patients presenting with the combination of abdominal pain and vomiting. Twenty-nine (6.6%) patients had dyspepsia as their chief complaints. One hundred and thirty-two patients (30.1%) had weight loss documented at presentation. 27 patients (6.2%) presented with bowel obstruction while forty-eight (11.0 %) patients had evidence of gastrointestinal bleeding, either as melena stool or frank hematemesis.Some patients presented with symptoms of metastatic disease, with jaundice reported in 32(7.3) patients. Anemia was evident in 246 (66.7%) patient while 16.3 % had severe anemia at a hemoglobin less than 7g/dl.

The duration of symptoms ranged from 1 month to 29 years and the mean duration was 11.9 (SD=20.9) months, and the median duration was 7 months. This is illustrated in figure 3 below.

Table 3: Clinical characteristics.

	Frequency (%)
Clinical signs and symptoms N=438	
Abdominal pain	337 (76.9)
Vomiting	200 (45.7)
Weight loss	132 (30.1)
Dysphagia	91 (20.8)
Upper GI bleeding	48 (11.0)
Jaundice	32(7.3)
Dyspepsia	29 (6.6)
Gastric outlet obstruction	27 (6.2)
Epigastric mass	24 (5.5)
Hemoglobin *(n=369)*	
Severe (<7g/dl)	60 (16.3)
Moderate (7.0-9.9 g/dl)	83 (22.5)
Mild (10.0-11.9 g/dl)	103 (27.9)
Normal (>11.9 g/dl)	123 (33.3)
Duration of symptoms (n=423)	
Mean, SD (months)	11.9 (SD=20.9)

Figure 4: Duration of symptoms



6.3 Diagnosis of gastric cancer.

Majority of the cases were first diagnosis in 425(97%) patients while 13 (3.0 %) cases were recurrent disease with a mean duration of 3.2 years since first diagnosis. The diagnosis was made endoscopically in 400 patients while surgery mainly due to bowel obstruction was used to diagnose 38(8.7%) cases. This is illustrated in table 4 below.

Table 4: Diagnosis of Gastric cancer

Type of diagnosis *(n=438)*	**Frequency (%)**
New diagnosis	425 (97.0)
Recurrence	13 (3.0)
Diagnosis done *(n=438)*	
Endoscopic	400 (91.3)
Surgical	38 (8.7)

6.4 Histopathological characteristics.

Most of the patients had tumors of the antrum, seen in 196 (46.0%), while 138 (32.3%) patients had tumors of the cardia and the GEJ. Nineteen (4.5%) patients had the diffuse form gastric cancer (figure 4). Macroscopically according to the Bormann Classification System, ulcerating tumor (Type III) was present in 102 (36.0%) cases while 73 (25.8%) of them had fungating/polyploid masses. Linitis Plastica was documented in 13 (4.6%) patients with 38.5% of them diagnosed surgically.

Histologically, 405 (93.5%) had adenocarcinoma with 5(1.2%) patients having squamous cell carcinoma and all five patient had GEJ tumor. GIST was present in 12 (2.8%) patients. Lymphoma as a histological diagnosis was documented in only 2(0.5 %) of the cases. According

to Lauren classification, diffuse subtype was seen in 144 (58.8%) while intestinal subtype was present in 72 (29.4%). Signet cell type adenocarcinoma was seen in 29 (11.8%). Most of the tumors had a well-differentiated grade in 45 percent of the cases. This is summarized in table 5 below

Figure 5 Anatomic Site

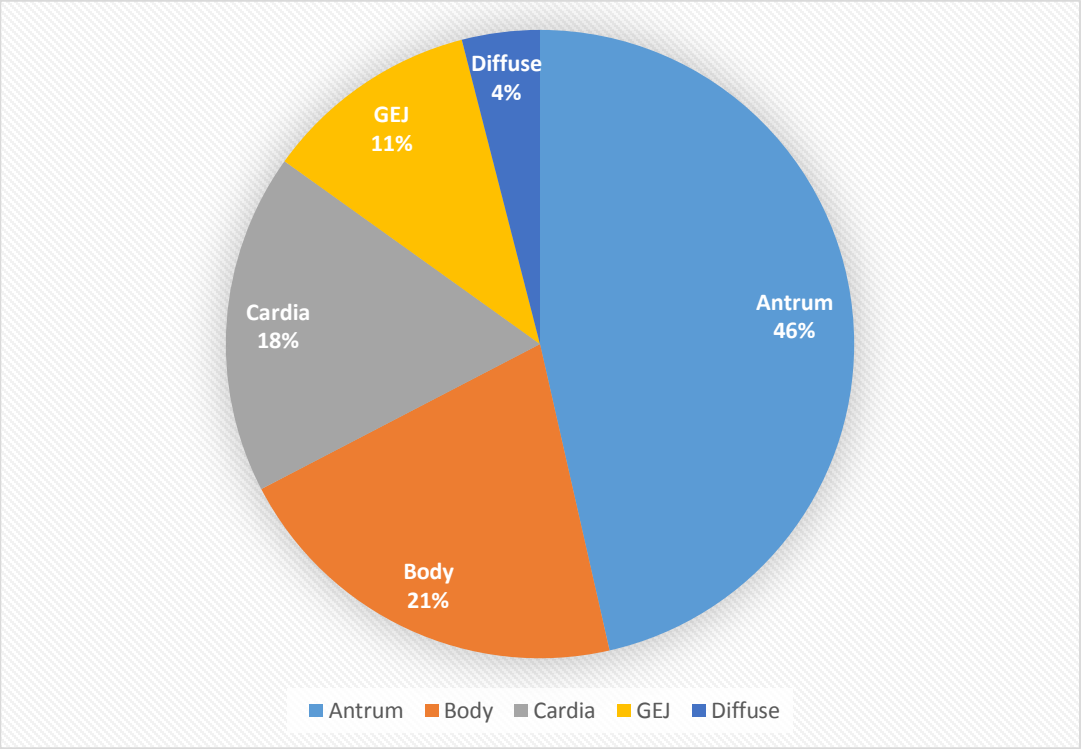


Table 5: Macroscopic appearance and histological characteristics.

	Frequency n (%)
Macroscopic *(n=283)*	
Polypoid/fungating	73 (25.8)
Superficial spreading	3 (1.1)
Ulcerating	102 (36.0)
Linitis plastic	13 (4.6)
Unclassified	2 (0.7)
Not documented	90 (31.8)
Histological type *(n=433)*	
Adenocarcinoma	405 (93.5)
Squamous cell	5 (1.2)
Adenosquamous	1 (0.2)
GIST	12 (2.8)
Carcinoid	5 (1.2)
Others	1 (0.2)
Other Lymphomas	2 (0.5)
MALT	2 (0.5)
Histological subtype *(n=245)*	
Diffuse/infiltrative	144 (58.8)
Intestinal	72 (29.4)
Signet cell	29 (11.8)
Tumor grade *(n=353)*	
Well differentiated	49 (13.9)
Moderately differentiated	161 (45.6)
Poorly differentiated	143 (40.5)

GIST: Gastrointestinal Stromal Tumors, MALT: Mucosa-Associated Lymphoid Tissue

6.5 TNM Staging

Of the 402 cases where staging was documented 96 % clinical staging while 16 (4.0%) cases had only pathological staging documented.

Most of the patients were stage 4 at the time of diagnosis, documented 234 (58.1%). Only 9 (2.2 %) of the cases presented with early disease at stage 1 and 47 (11.7 %) patients at stage 2.Five of the stage 2 patients had locally advanced in operable disease. Stage 3 disease was documented in 64 (15.9%) of the cases with 25 (39 %) being inoperable due to locally advanced disease. At the time of diagnosis, lymph node involvement was present in 331 (82.1%). This is illustrated in tables 6 and 7 below. The commonest site of metastasis was the liver seen in 167 (79.1 %) cases. Lung and peritoneal metastasis were present in 49 and 48 patients respectively. Krukenberg tumor was present in 6 cases, 3.4 % of the females with GC. Other sites of metastasis include renal –adrenal, bones and thyroid seen in 6 (2.8%), 3 (1.4 %) and 2 (0.9 %) cases respectively. (Figure 6).

Table 6: Staging

	Frequency n (%)
Staging *(n=404)*	
Clinical ¶	388 (96.0)
Pathological ¥	16 (4.0)
Nodal involvement *(n=404)*	
Absent	72 (17.8)
Present	332 (82.2)
Metastasis *(n=399)*	
Absent	165 (41.4)
Present	234 (58.6)

¶ Staging done after CT scan imaging ¥ pathological report after surgery.

Figure 6 : Site of metastasis

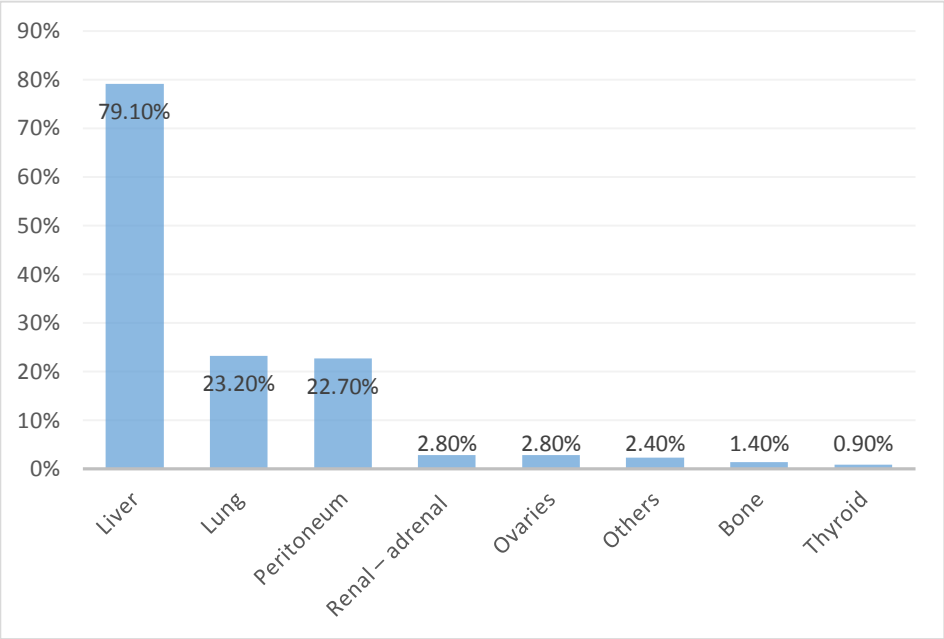


Table 7: AJCC Staging

AJCC Stage *(n=403)*	**Frequency n (%)**
Stage 1	9 (2.2)
Stage 2	47 (11.7)
Stage 3	64 (15.9)
Stage 4	234 (58.1)
Not documented	49 (12.2)

AJCC: American Joint Committee on Cancer.

6.6 Treatment modalities.

Palliative treatment was given in 284 (74 %) of patients while curative treatment was given in 100 (26 %). Only 153 (43.3%) of the patients had surgery, and partial gastrectomy was the commonest procedure done in 63 (41.2%) of the patients, while 19 (12.4) patients had total gastrectomy. Gastrojejunostomy was done in 50 (32.7 %) patients. Esophageal surgery was done in 10 (6.5%) patients, of which 6 had esophageal stenting and 4 had lower esophagectomy this was done in patients with GEJ tumors. Forty eight patients (31.3%) with stage 4 disease had surgery of which half of them had gastrojejunostomy.

Chemotherapy was documented in 267 (75.9 %) of the patients, with the majority having palliative chemotherapy in 187 (53.1%) cases of whom 31 patients (16.6%) also received concurrent palliative radiotherapy. Chemotherapy as an adjuvant was given in 67 (19 %), while additional 4 patients had concurrent chemoradiotherapy. Neoadjuvant chemotherapy was the least used treatment modality only given in 9 patients. Platinum-based chemotherapy was the therapy of choice in 197 (67.2%) patients with EOX being the commonest regimen of choice. Fifty one patients had 5 FU based regimen with FOLFOX given in 35 patients. Capacitabine single therapy was documented in 27 patients, with stage 4 or advanced disease. Above is summarized in table 8 below

Table 8: Treatment intention and types

	Frequency n (%)
Treatment Intention *(n=384)*	
Curative	100 (26.0)
Palliative	284 (74.0)
Treatment types *(n=352)*	
BSC	33 (9.4)
Palliative CT	134 (38.1)
Palliative CRT	31 (8.8)
Adjuvant CT	67 (19.0)
Adjuvant CRT	4 (1.1)
Neoadjuvant CT	10 (2.9)
Surgery only	52 (14.9)
Surgery plus palliative CT	22 (6.3)

BSC Best supportive care, CT Chemotherapy, CRT Chemotherapy and radiotherapy

Table 9: Types of Surgery performed

Surgery *(n=153)*	**Frequency (%)**
Gastrojejunostomy	50 (32.7)
Partial gastrectomy	63 (41.2)
Total gastrectomy	19 (12.4)
Exploratory laparotomy + biopsy	10 (6.5)
Surgery type not documented	1 (0.7)
Lower esophageal stenting	6 (3.9)
Lower esophagectomy	4 (2.6)

Table 10: Types of Chemotherapy regimens

Chemotherapy type *(n=293)*	**Frequency (%)**	**Chemotherapy type *(n=293)***	**Frequency (%)**
EOX	76 (25.9)	Docetaxel,Cisplatin, 5FU	2 (0.7)
ECX	39 (13.3)	Imatinib	4 (1.4)
FOLFOX	35 (11.9)	Carboplatin/Docetaxel	3 (1.0)
Capecatabine single agent	27 (9.2)	Etoposide /cisplatin	7 (2.4)
Cispalstin-Docetaxel	13 (4.4)	Oxaliplatin/Xeloda	5 (1.7)
Epirubicin-Cyclophosphamide	2 (0.7)	Cisplatin/Doxorubicin	4 (1.4)
Cisplatin/5FU	13 (4.4)	No chemotherapy	59 (20.1)

EOX Etoposide, Oxaliplatin, Xeloda. ECX Etoposide, Cisplatin, Xeloda. FOLFOX Folinic acid, Oxaliplatin, Fluorouracil. FU Fluorouracil

6.7 Clinical characteristics according to the age of the patients

There was a total of 62 (14.1 %) patients below 40 years, with significantly more females than males (54.8 % vs. 45.2 % P < 0.009). Younger patients presented later than older patients with the mean duration of symptoms 17.2 months for a younger and 11.1 months for the older patients (P = 0.034).Stage at presentation didn't differ between the two groups, 29 (50.0 %) younger and 201 (58.3), older patients presented at stage IV (P = 0.240).

In treatment modalities, older patients had adjuvant chemotherapy after surgery (34.0 % vs. 51 % <0.005). None of the younger patients received radiotherapy, with 31 (10.2 %) of the older patients getting radiotherapy (p <0.022).The same proportion of the patients had surgery only, 7 (14.9) in the younger group and 45 (14.8) in the older group (p <0.978). This is summarized in Table 11 below.

Table 11 : Clinical characteristics according to age.

	ALL (N=Total Number)	**Young patients (≤ 40 years)**	**Older patients (> 40 years)**	**p-value**
Gender				
Male	264	28 (45.2)	236 (62.8)	0.009
Female	174	34 (54.8)	140 (37.2)	

Symptoms duration (months)					
Mean ±SD		17.2 ±19.2	11.1 ±21.1		0.034
Absent	72	9 (15.3)	63 (18.3)	0.571	
Present	331	50 (84.7)	281 (81.7)		
AJCC Staging					
Stage 1	9	0 (0.0)	9 (2.6)		0.213
Stage 2	48	10 (17.2)	38 (11.0)		0.176
Stage 3	65	11 (19.0)	54 (15.7)		0.526
Stage 4	230	29 (50.0)	201 (58.3)		0.240
Not documented	51	8 (13.8)	43 (12.5)		0.762
Treatment modality					
BSC	33	3 (6.4)	30 (9.8)		0.450
Palliative CT	134	17 (36.2)	117 (38.4)		0.773
Palliative CRT	31	0 (0.0)	31 (10.2)		0.022
Adjuvant CT	67	16 (34.0)	51 (16.7)		0.005
Adjuvant CRT	4	0 (0.0)	4 (1.3)		0.429

Neoadjuvant CT	9	2 (4.3)	7 (2.3)		0.419
Surgery only	52	7 (14.9)	45 (14.8)	0.978	
Palliative CT + surgery	22	2 (4.3)	20 (6.6)		0.534

AJCC American Joint Committee on cancer, BSC Best supportive care, CT Chemotherapy, CRT Chemo radiotherapy *P<0.05 was considered significant.

6.8 Pathological characteristics according to age

Pathologically, diffuse adenocarcinoma was present in 18 (42.9%) patients in the younger age group and in 119 (59.5 %) patients in the older age group (p-value < 0.051). More proportion of the patients in the younger group than the older group had signet cell, 21.4 % vs. 10.0 % p-value of 0.038. Poorly differentiated GC was more in the younger age group than in the older group, 26 (56.5%) vs.117 (38.1%) p-value < 0.018. Inversely more older patients had well-differentiated GC at 47 (15.3 %) while only 2 patients younger patients had a well-differentiated tumor with a significant p-value at 0.045. (Table 12).

Table 12: Pathological characteristics according to age

	ALL (N=Total Number)	Young patients (≤ 40 years)	Older patients (> 40 years)	p-value
Histological subtype				
Diffuse/infiltrative	137	18 (42.9)	119 (59.5)	0.051
Intestinal	72	14 (33.3)	58 (29.0)	0.577
Not documented	4	1 (2.4)	3 (1.5)	0.684
Signet cell	29	9 (21.4)	20 (10.0)	0.038
Tumor grade				
Well differentiated	49	2 (4.3)	47 (15.3)	0.045
Moderately differentiated	161	18 (39.1)	143 (46.6)	0.344
Poorly differentiated	143	26 (56.5)	117 (38.1)	0.018

*P<0.05 was considered significant.

6.9 Outcome

The six month mortality rate amongst the gastric cancer patients is 29.7%, there were 246 patients with known status at 6 months, out of which 73 died. The calculated person-time in this instance for the gastric cancer is 5 per 100 person-months. There were 73 deaths within the 6

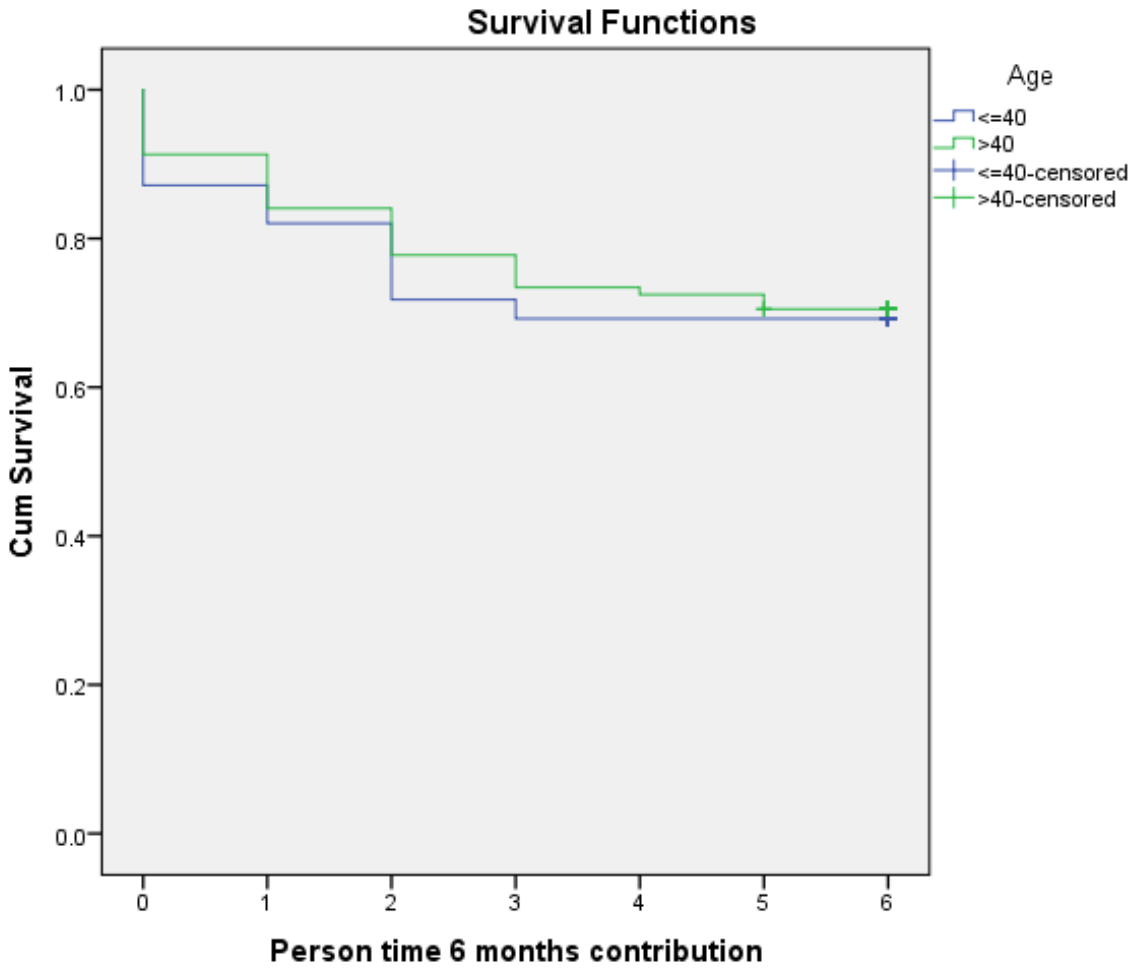
months, and a total of 1,511 contributed months from the patients. The calculated person-time for gastric cancer is 4 per 100 person-months. There were 114 deaths within the study period, and a total of 2,894 contributed months from the patients. As shown in table 13 below overall survival at 6 months, 1 year, and 5 years were, 77 %. 62 % and 30 % respectively.

Table 13: Survival rate

	Probability of survival (%) ±SD
6 months	7 7 ±2
1 year	62 ±3
3 year	46 ± 5
5 year	30 ± 13

The Kaplan-Meier survival curves for the overall cohort, and according to the age group are shown in Figure below. The younger patients (< 40 years) showed a trend towards a worse outcome although not statistically significant, p-value 0.87.

Figure 7: Six months survival functions



	Chi-Square	Sig.
Log Rank (Mantel-Cox)	.060	.807

6.91 Prognostic factors of mortality.

The relationship between mortality and prognostic factors was assessed in a univariate Cox regression model, recurrence, lymph node involvement, distant metastasis and stage IV was prognostic. However, when placed in a multivariate cox regression model significant recurrent disease, stage 1V and distant metastasis were associated with poor mortality while male gender was associated with good prognosis. This is summarized in table 14 below.

Table 14: Factors associated with mortality

Variable	Unadjusted Hazard Ratio (95% CI)	p-value	Adjusted Hazard Ratio (95% CI)	p-value
Age (≤40)	1.1 (0.6-2.0)	0.814	1.5 (0.7-3.3)	0.309
Gender (male)	0.6 (0.4-1.0)	0.053	0.5 (0.3-0.9)	0.023
Recurrent disease	3.1 (1.4-7.2)	0.008	2.7 (1.1-6.6)	0.026
Diffuse subtype	1.7 (0.9-3.1)	0.088	1.1 (0.6-2.1)	0.761
LN involvement	.2 (1.2-8.8)	0.024	0.5 (0.1-2.9)	0.457
Distant metastasis	9.6 (3.9-23.8)	<0.001	7.8 (0.7-18.6)	0.037
Stage 4	8.7 (3.8-20.1)	<0.001	7.5 (0.2-11.5)	0.048

LN Lymph node, *P<0.05 was considered significant.

CHAPTER 7: DISCUSSION.

In our review, in the study period of 5 years, GC represented 2.13% of cancers seen at the KNH. This is similar to what is reported in other African countries with incidences ranges of 1.1% to 6.0 % of all malignancies (2, 26, 31). Mabula et al reported an incidence of 4.5 % in Northwestern Tanzania, while an earlier study in Northeastern Tanzania reported higher incidences at 15.7 %(26). Due to the retrospective nature of our study, the rate in our study may be an underestimate of the actual proportion of patients with GC.

The mean age of patients with gastric cancer in our study was 58.1 (SD=14.4) years, with the age ranging between 21 and 100 years, this concurs with most African studies which recorded peak age group between 6^{th} and 7^{th} decade (31, 74). Our results showed that up to 30.1 % of the patients were aged 50 years and below, this is in contrast with an earlier study by Ogutu et al in 1993 to 1994, where they found no patient below 50 years with GC(29). The higher number of younger patients in our study is due to the increase rate of GC diagnosis in recent years, and the worldwide rise in GC in the younger population (28). The peak age of GC in our study was more than one decade earlier than what is established in the developed world. The mean age recorded in France and South Korea was higher at 72.7±11 and 59.2±11.9 years, respectively (77, 78). The high numbers of GC in a younger age group in our population can be partly explained by the lower life expectancy in our population, nonetheless, other factors favoring younger patients have to be investigated.

The male predominance in our study confirms what most of the studies in the world had reported before. However, our study showed a higher proportion of females, with the male to female ratio at 1.5: 1 in contrast to other studies which found a male to female of 1.8 -3.4: 1(1, 17,

30, 31). Ogutu et al, in a retrospective study of 53 patients with GC, from 1987 to 1989 reported one of the highest male predominance ratio at 3.4: 1. Albeit GC rates, being reported to be decreasing worldwide, stable rates or even increasing numbers have been reported especially in young female patients (5, 28). This can explain the higher number of females affected in our study more so at a younger age. Whether health-seeking behaviour has changed over time with more female patients seeking treatment can only be speculated.

Majority of the patients had low social economic status, a major health determinant, with 118(59 %) having no education or just primary education and 64 (35 %) of the patients being unemployed. However, our study site, KNH is a public hospital where majority of the patients seen are from the less privileged communities. Similar findings were demonstrated in a study in northeastern Tanzania (31).

Our clinical presentation data are similar to those reported in a series of other studies; most of our patients presented in late signs and symptoms (2, 26). The red flag symptoms that included dysphagia, vomiting, GIT bleeding and obstructive symptoms were present in more than 85 % of the cases. Abdominal pain presented in 337 (76.9%) of the patients, while 200 (45.7%) had vomiting. GIT bleeding was documented in fewer patients in our study. Only 11 % of the cases in our study had documented GIT bleeding, whereas 19.4% and 26 % were reported in Tanzania and Nigeria respectively. (31, 75).

The duration of symptoms ranged from 2 weeks to 29 years. The emergency or acute symptoms that included GIT bleeding, obstructive symptoms had shorter duration prior to presentation. The patients with longer duration of symptoms of more than 1 decade represent the group of patients who had dyspeptic symptoms prior to the GC symptoms. Strikingly younger

patients had a longer duration of symptoms before presentation than the older population (17.2 months for a younger and 11.1 months for the older patients (P = 0.034).).We postulate this could be due to the lower index of suspicion in a younger age group prolonging the time from symptom onset to diagnosis.

More than 91.3 % of the patients were diagnosed after endoscopy while the remaining few were diagnosed after surgery. An earlier study in the eastern part of Kenya, reported very low rates of endoscopically diagnosed GC at only 48 (24 %) patients, while 103 (52%) diagnosed after laparotomy (28). None of the patients in our study had a record of barium study in the file, however, there is still a possibility that some patients had done a barium study as their initial test before being referred to for endoscopy. Although barium study is inferior to upper endoscopy in the diagnosis of GC, studies have demonstrated its utility for screening in countries with high incidence (40, 41). It is not clear whether barium meal can be used as a diagnostic tool in the low income countries with a low incidence of GC. The higher number of endoscopies done to diagnose GC in our study, compared to previous ones is due to the increasing number of endoscopy centres in the country although still few.

The anatomical location of tumors in the stomach has also been considered as an important parameter for the classification of gastric cancer. Our study showed a higher number of proximal tumors than other African studies, with an inverse lower proportions of the distal tumors. Tumors of the cardia and the GEJ accounted for 138(32.8%) of the cases, while tumors of the antrum were seen in 196 (46 %). In 2011, Ahmed et al in Nigeria found only 14 (7.7 %) patients had tumors of the cardia, with higher proportions of the patients with antral tumors at 116 (64%), almost similar findings were reported in a Tanzanian study (31, 75). Our study confirms the increase in the

incidence of cancer of the gastric cardia and GEJ. The change in trend from distal to proximal stomach may in part be due to the decrease in the distal cancers. However, it has also been proposed that carcinoma at the cardia and GEJ is a different entity from the rest of the gastric carcinoma (5). Proximal tumors share similar histopathological and demographics with the esophageal tumors, and tend to be more aggressive. Kenya is among the countries with the highest incidence of esophageal cancer, our study confirms the relationship between the two.

More than 93 % of the patients had adenocarcinoma. This agrees with many studies done worldwide (15, 33, 34). Lymphomas were only seen in 2 (0.5 %) cases, lower than what is reported in other studies (31). The lower documented cases of gastric lymphomas could be attributed to the ICD coding and filling systems as patients with Gastric lymphoma are mostly coded under lymphomas, underestimating the cases in our study.

There has been a worldwide decline in the incidence of the intestinal subtype in recent few decades that parallels the overall decline in the incidence of GC.(16). The above is reflected in our study, according to Lauren classification diffuse subtype was seen in 137 (56.6%) while intestinal subtype was present in 72 (29.8%). An earlier Kenyan study by Lodenyo et al in the series reviewing 44 patients with histologically confirmed GC at KNH found 59% of the patients had the diffuse type and 39% of patients with the intestinal type. Infiltrative type occurred more commonly in the older patients seen in 119 patients vs 18 of the younger population (P-value <0.051). Although the numbers in our study were relatively small, the findings are in contrast with other studies around the world which showed that the diffuse infiltrative type occurred more commonly in the younger patients (34, 72).

GC has been traditionally known to present in late stages, our study didn't differ from this. Advanced gastric cancer (Stages III and IV) was present in 298 (74%). Most of the African studies have reported similar presentations of the disease, with more than 90% presenting with advanced disease (2, 26, 31). This is implicated to the low level of suspicion, non-specific symptoms of early disease, low social economic status, lack of screening programs or guidelines, fewer health facilities and endoscopic centres among others. Our study didn't show a significant difference in the stage of presentation of the disease between the younger and the older patients.

The management of gastric cancer poses a great challenge in resource-limited areas, like Africa. Late presentation of the disease due to lack of endoscopic facilities, lack of adequate screening programs which leads to high morbidity and mortality are characteristic of gastric cancer patients in our set up (48). Majority of patients were treated on palliative intent, with only 153 (43.3%) of the patients undergoing surgery. Partial gastrectomy was the commonest procedure done in 63 (41.2%) of the patients. This in agreement to most African studies. Mabula et al reported a slightly higher rate of surgeries at 223 (96.1%), and only 2.2% of patients had gastric surgery with curative intent. (31). It is evident from many studies that a multidisciplinary approach of GC treatment, with surgery being the fundamental management modality should be adopted to achieve the best results (50, 52). The late presentation of our patients due to the reasons alluded to above accounted for the low rates of surgery, and more so, surgeries with curative intent.

Chemotherapy was documented in 267 (75.9 %) of the patients, with the majority having palliative chemotherapy in 187 (53.1%) cases of whom 31 patients (16.6%) also received concurrent palliative radiotherapy. Radiotherapy was given in patients with cardia and GEJ (proximal tumors) but mostly for palliation. The Germany POET study, which was limited to

patients with GEJ adenocarcinoma, demonstrated benefit in local progression-free survival when radiotherapy was added to preoperative chemotherapy in patients with locally advanced adenocarcinoma of the GEJ (58). The MAGIC trial showed increase survival in patients when given perioperative chemotherapy in resectable tumors (56). Although our study showed more than 75 % of patient had chemotherapy less than half of them had chemotherapy with curative intent, this was attributed to the late presentation of the GC in our set up. Mabula et al reported lower rates of chemotherapy than our study at 31.8% (57 patients) (32)

The six-month mortality rate amongst the gastric cancer patients is 29.7%, there were 246 patients with known status at 6 months, out of which 73 died. 192 patients were lost to follow up at 6 months. Overall survival at 6 months, 1 year, and 5 years were, 77 %. 62 % and 30 % respectively. Similar survival rates were reported in African studies, the 5-year survival rates in Tanzania and Nigeria were 32.8 % and 20 % respectively (32). In countries like Japan, where there has been vigorous effort to diagnose GC early, with good screening programs, the 5-year survival rate is reported up to 90 %(50). Although still at an alarming level, the survival rates in our study might have been underestimated due to loss of follow up of many patients. The low survival rate in our study can be explained by the late presentation, late diagnosis and poor follow up of the patients which makes therapy with curative intent unachievable.

In multivariate cox regression model recurrent disease, stage 1V and distant metastasis were associated with poor survival significantly. These factors have been associated with poor outcomes in most of the studies (64, 65). In contrast to what has been reported before, our study didn't show infiltrative subtype to be associated with poorer outcomes, this could be due to the fewer pathologist using Laurens Classification for GC histological reporting. Younger age group showed

a trend towards a poorer outcome, as shown in figure 6 above this was not statistically significant. This agrees with the study by Takatsu et al in 2015, in a single centre retrospective study looking at clinicopathological features of gastric cancer in young patients found that survival rate of gastric cancer in young patients was equivalent to that in patients in their 60s (66), in contrast to other studies which found poorer outcomes in younger patients (67.68). The younger patients' trend towards poorer outcome was attributed to the longer duration of symptoms and a more advanced stage at presentation.

CHAPTER 8: CONCLUSIONS AND RECOMMENDATIONS.

The study was set out to describe the clinical and pathological characteristics of gastric cancer in Kenya. The findings clearly indicate the GC in our set up occurs in a younger population one to two decades earlier than the developed countries with more women affected at a younger age. The commonest site of the tumor is the antrum, and as postulated from the changing trend worldwide we recorded a higher number of proximal tumors. More than 74 % of the patients presented with advanced disease leading to poor outcomes. The stage at presentation, recurrent disease and distant metastasis are significantly associated with poorer outcomes.

This was one of the biggest studies in sub-Saharan Africa assessing both the clinical and pathological characteristics of GC. To enhance the long-term prognosis for GC patients, greater effort is needed from the multidisciplinary stakeholders. Infrastructure, such as the establishment of endoscopy facilities to provide early diagnosis and treatment of GC needs to be a priority for health system decision-makers in sub-Saharan Africa.

Given the study findings, it is clear that the subject matter might be more amenable to a prospective approach involving multiple centres with more number of patients.

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10.0 APPENDICES

Appendix I: Data Collection Form

SECTION 1: DEMOGRAPHICS			
NO	**Question**	**Response**	**Code**
1	Gender **(GEN)**	F=1 M=2	**[ ]**
2	Age **(A)**	Number	**[ ]**
3	Residence		
4	Occupation		
5	Level of education		
SECTION 2: DISEASE INFORMATION			
6	Presenting signs and symptoms	1. Abdominal pain 2. Weight loss 3. Dysphagia 4. Vomiting 5. UGIB 6. Bowel obstruction 7. Epigastric mass 8. Others	**[ ]**
7	Haemoglobin **(HB)**		
8.	Date of Diagnosis **(DD)**	Number	**[ ]**
9.	Duration of symptoms **(DOS)**	Number	**[ ]**
10.	Type of diagnosis **(TOD)**	1.New diagnosis 2.Recurrence	**[ ]**
11.	How diagnosis made**(HDM)**	1.Endoscopic 2.Barium and surgery 3.Surgical	**[ ]**
SECTION 4: BIOPSY			
12.	Anatomical site **(AS)**	1. Antrum 2. Body 3. Cardia 4. GEJ	**[ ]**

		5. Diffuse 6. Not documanted	
13	Macroscopic appearance	1. Polypoid/finagating 2. Superficial spreading 3. Ulcerating 4. Linitis plastic 5. Unclassified 6. Not documented	
14.	Histological type **(HT)**	1.Adenocarcinona 2. Squamous cell 3. Adenosqaumous 4. Others	**[ ]**
15.	Histological subtype**(HST)**	1.Diffuse/infiltrative 2. Intestinal	**[ ]**
16.	Tumour grade**(TG)**	1. Well differentiated 2. Moderately differentiated 3. Poorly differentiated	**[ ]**
SECTION 5: STAGE			
17.	Staging **(STG)**	1. Clinical 2. Pathological	**[ ]**
18.	Nodal involvement	1. Present 2. Absent	**[ ]**
19.	Metastasis	1. Present 2. Absent	**[ ]**

20.	TNM stage **(TNM)**	1.Stage 0 2. stage I 3.Stage II 4.Stage III 5.Stage IV 7.Not documented	**[ ]**
SECTION 6: TREATMENT			
21.	Treatment intention**(TI)**	1.Curative 2.Palliative	**[ ]**
22.	Surgery plus **(SGR)**	1.Yes 2. No	**[ ]**
23.	Surgery Only **(SGRO)**	Y = 1 N = 2	
	If surgery , type of surgery		
24.	Chemotherapy only(CTO)	Y = 1 N = 2	**[ ]**
25.	Chemo- radiotherapy only(CRTO)	Y = 1 N = 2	**[ ]**
26.	Adjuvant chemotherapy**(AC)**	Y = 1 N = 2	**[ ]**
27.	Adjuvant chemo-radiotherapy **(ACRT)**	Y = 1 N = 2	**[ ]**
28.	Neo- Adjuvant Chemotherapy only **(NAC)**	Y = 1 N = 2	**[ ]**
29.	Neo- adjuvant chemo- radiotherapy**(NACRT)**	Y = 1	**[ ]**

		N = 2	
30.	If chemotherapy given ,regimen given		**[ ]**
SECTION 7: OUTCOMES			
31.	Survival status**(SRVL)**	1. Dead 2. Alive	**[ ]**
32.	If Dead ,date of death **(DOD)**		**[ ]**
33	If alive date last seen		