UTS UNIVERSITY OF TECHNOLOGY SYDNEY

Predictors of the survival of gastric cancer patients diagnosed at Bhaktapur Cancer Hospital, Nepal – A retrospective cohort study

by Krishna Kanta Poudel

Thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy

under the supervision of Professor Andrew Hayen and Dr Daniel Demant

University of Technology Sydney
Faculty of Health

30/08/2022

CERTIFICATE OF ORIGINAL AUTHORSHIP

I, *Krishna Kanta Poudel*, declare that this thesis is submitted in fulfilment of the requirements for the award of *Doctor of Philosophy*, in the School of Public Health, *Faculty of Health* at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

This research is supported by the Australian Government Research Training Program.

Production Note:
Signature: Signature removed prior to publication.

Date: 20/07/2023

Abstract

Gastric cancer was the fourth most common cause of cancer-related deaths worldwide in 2020. In Nepal, gastric cancer was the second most common cause of cancer deaths in males and the fifth most common cause of cancer deaths in females in 2020. Although gastric cancer is a significant public health problem, there have been no studies undertaken in Nepal to determine the survival and predictors of gastric cancer survival.

This retrospective cohort study investigated the overall survival rate of people with gastric cancer and predictors of survival. We included 817 people who were diagnosed with gastric cancer between 1 January 2010 and 31 December 2021 at Bhaktapur Cancer Hospital, Nepal.

The median overall survival for patients with gastric cancer was 19 months. The total person-time of follow-up was 17,808 months. Survival at one year was 70%, 37% at two-years, 23% at three-years, 18% at four- years, and 12% at five-years. Factors that affected survival included age, tumour locations, tumour stage at diagnosis, treatment by surgery, and treatment by chemotherapy.

This study was limited by the data that was available in the routine medical records, however; to investigate additional potential predictors for survival of gastric cancer, and reduce survival bias, future research should include a prospective study design.

Acknowledgements

First and foremost, I would like to thank my supervisors, Professor Andrew Hayen and Dr Daniel Demant, for their patient guidance, helpful feedback and huge investment of time in me. It has been a privilege to work under their supervision over the past four years.

I gratefully acknowledge the funding received towards my PhD through the International Research Scholarship and UTS President Scholarship. I am also grateful to University of Technology Sydney for providing me the financial support to collect the data for my study. I thank the Bhaktapur Cancer Hospital for providing the data used in this thesis.

Finally, I wish to express my deepest gratitude to my family Bhuminda Poudel (father), Tulasi Devi Poudel (mother), Janaki Kharel Poudel (wife), Sakrish Poudel and Shirish Poudel (sons). This would not have been possible without their strong support and love at all times.

Table of Contents

Abbreviations

AAPC:	Average Annual Percent Change
AJCC:	American Joint Committee on Cancer
API:	Asian Pacific Islander
ASIR:	Age Standardised Incidence Rate
BCH	Bhaktapur Cancer Hospital
BPKMCH:	B P Koirala Memorial Cancer Hospital
CI:	Confidence Interval
CID:	Cancer Identification Number
CT:	Computed Tomography
DFS:	Disease Free Survival
GI:	Gastrointestinal
HDI:	Human Development Index
HICs:	High Income Countries
HR:	Hazard Rate
IARC:	International Agency for Research on Cancer
ICD:	International Classification of Disease
IHC:	Immunohistochemistry
JCGC:	Japanese Classification of Gastric Carcinoma
LMICs:	Low-and Middle-Income Countries

MDCT:	Multidetector Computed Tomography
MRI:	Magnetic Resonance Imaging
NHRC:	Nepal Health Research Council
NPR:	Nepalese Rupees
OR:	Odds Ratio
OS:	Overall Survival
PET-CT:	Positron Emission Tomography-Computed Tomography
RCT:	Randomized Controlled Trial
RR:	Relative Risk
SEER:	Surveillance Epidemiology and End Results
SES:	Socioeconomic Status
SIR:	Standardised Incidence Ratio
SPSS:	Statistical Package for the Social Sciences
SRC:	Signet Ring Cell
TNM:	Tumour Node Metastasis
UHC:	Universal Health Coverage
UICC:	International Union Against Cancer Classification
UTS:	University of Technology Sydney
WHO:	World Health Organization

Impact of COVID 19 pandemic on study

This PhD project was impacted by the COVID-19 pandemic and significant changes to the originally intended research were necessary. It was originally intended to deploy a case-control study design. This was intended to determine the comprehensive potential risk factors for gastric cancer in Nepal across a variety of risk factors (medical, biological and social) that are not fully researched within the Nepalese context. This process also included the collection of blood samples from 145 case participants at the B. P. Koirala Memorial Cancer Hospital and 290 matched control participants from the community. This would have required the researcher to go to Nepal. However, the researcher was unable to visit Nepal to gather any samples because the COVID 19 travel restrictions imposed on University of Technology Sydney (UTS). It was furthermore in this environment not possible to task local hospitals or health services with the collection of samples.

Based on the consultation with supervisors and experts in the field, it was decided to refocus the PhD as well as the associated methods to focus on survival analysis that would allow to effectively use secondary data that could be gathered by medical record employees at the Bhaktapur Cancer Hospital in Nepal. In addition to developing a new study design and receiving relevant ethics approvals from UTS and Nepalese authorities, the researcher was also required to recruit, train and manage the hospital medical record staff in Nepal and provide them with data collection scripts, data collection procedures and survey software questionnaires. These activities were essential to ensure the data was accurately collected and securely transferred to the UTS survey software.

For the first 20 months of the PhD candidature, the original case-control study design was maintained. Within 28 months, the new study design was developed, implemented, obtained ethical approval, data collected, data analysed and the thesis completed.

Chapter 1 Introduction

This chapter discusses the burden of cancer in Nepal and presents background information and the significance of the gastric cancer in Nepal This chapter also provides further contextual information on Nepal including its development, information on its geography and population, and an overview of the top ten cancers in Nepal. Background information on the global burden of gastric cancer and cancer treatment is also provided, including support for cancer patients in Nepal. In addition, this chapter explores the global survival rate of gastric cancer, why gastric cancer is an important public health issue in Nepal and discusses the lack of evidence on predictors of gastric cancer survival in Nepal.

1.1 Background on Nepal and the burden of cancer in Nepal

Nepal is a lower-middle-income country (LMIC) situated between China and India (World Bank Group 2020). In 2021, Nepal ranked 142 out of 185 countries in the Human Development Index (HDI) (HDI score, 0.60), and India, which is the culturally similar neighbouring country, ranked 131 (HDI score, 0.64). The HDI is a composite of health, education, and income as domains of well-being. In 2021, the life expectancy at birth was 70.8 years, health expenditure was 5.6% of the gross domestic product, and expected years of schooling was 12.8 years – Nepal performed slightly better across these domains when compared to India (69.7 years life expectancy at birth, 3.5% gross domestic product, 12.2 expected years of schooling) (United Nations Development Programme 2022).

Nepal has seven provinces, 77 districts, six metropolitan cities, 11 sub-metropolitans, 276 municipalities, and 460 rural municipalities. In 2021, the total population of Nepal was 29,192,480 (Government of Nepal 2021). Nepal's population has 125 ethnic backgrounds, with

Chhetri being the largest ethnic group comprising 16.4% of the population in 2021, followed by Brahmin (11.2%), and Magar (6.9%). Nepal is a multi-religious country with most people identifying as Hindus (81.2%), followed by Buddhists (8.2%) and Muslims (5.0%) in 2021 (Government of Nepal 2021).

Gastric cancer (also referred to as stomach cancer) is a disease in which abnormal cells form in the mucosa of the stomach (Hamilton & Aaltonen 2000). Gastric cancer remains an important public health issue globally. It is the fifth most diagnosed cancer, and the fourth leading cause of cancer death worldwide, with more than a million (1,089,103) gastric cancer cases and almost 770,000 deaths in 2020 alone (Sung et al. 2021). In 2020, gastric cancer accounted for 9.1% of all cancer deaths in men and 6.0% of all cancer deaths in women (Sung et al. 2021). Incidence and deaths are projected to increase globally, with a disproportionate increase in the burden in developing countries (Ferlay et al. 2020m). Countries with a low human development index (LHDI) or medium human development index (MHDI) are predicted to see an increase of about 80% (in both sexes) from 2020 to 2040, compared to just 45% in high HDI countries (Ferlay et al. 2020m).

Cancer is a major health issue in Nepal (World Health Organization 2018b). In Nepal, Globocan[1] estimated in 2020 the total number of new cancer cases to be 20,508 (8,943 men and 11,565 women) (World Health Organization 2018c); and the number of all cancer deaths to be 13,629 (6,244 men and 7,385 women) (Ferlay et al. 2020f). Lung cancer was the most

[1] Globocan (Global Cancer Incidence, Mortality and Prevalence), "a project of the International Agency for Research on Cancer, provides estimates by cancer site and sex using the best available data in each country" (International Agency for Research on Cancer 2020).

common newly diagnosed cancer (18.0% of new cases) followed by gastric cancer (10.9%) in men in Nepal in 2020 (Ferlay et al. 2020j). In women, cervix uteri (19.4%) was the most common cancer, followed by breast cancer (17.1%) (Ferlay et al. 2020k). In 2020, gastric cancer accounted for 10.2% of all cancer deaths in Nepal (Ferlay et al. 2020f) and 7.7% of all cancer deaths globally (Ferlay et al. 2020h).

Owing to the lack of population-based cancer registries in Nepal, it is difficult to estimate accurately the incidence, survival and mortality rate of cancers, including gastric cancer (Neupane et al. 2017; Poudel 2016a, 2016b, 2017; Poudel, Huang & Neupane 2016; Poudel et al. 2017). In order to estimate the incidence and mortality rates of cancer in Nepal, Globocan used the data of neighbouring countries (Ferlay et al. 2020i). Lung cancer had the highest age-standardised incidence rate in men (14.7 per 100,000), followed by gastric cancer in 2020 in Nepal (9.0 per 100,000) (Ferlay et al. 2020d). In women, cancer of the cervix had the highest age-standardised incidence rate (16.4 per 100,000), followed by breast cancer (13.9 per 100,000) (Ferlay et al. 2020c). Age-standardised incidence rates of the top 10 cancers for men and women in 2020 is presented in Table 1.1.

Table 1.1: Age-standardised incidence rates (per 100,000) of top 10 cancers by sexes in 2020, Nepal (Ferlay et al. 2020c, 2020d).

Cancer site (females)	Incidence (females) per 100,000	Cancer site (males)	Incidence (males) per 100,000
Cervix uteri	16.4	Lung	14.7
Breast	13.9	Stomach	9.0
Lung	6.8	Lip, oral cavity	5.5
Gallbladder	5.1	Colorectum	5.5
Stomach	4.1	Liver	3.7
Ovary	3.7	Thyroid	3.2
Colorectum	3.4	Prostate	3.0
Thyroid	1.9	Gallbladder	2.9
Leukaemia	1.8	Bladder	2.9
Lip, oral cavity	1.7	Larynx	2.7

There is a wealth of literature about the survival rate of gastric cancer in high-income countries that report tumour location, histologic type, tumour grade, tumour size, extent of cancer, tumour stage, and treatment as the predictors for gastric cancer survival (see chapter 2) (Petrelli et al. 2017a; Qi et al. 2016). However, there is no original research and data on the survival rate and predictors of gastric cancer survival in Nepal.

1.2 Cancer treatment centres in Nepal

The initial presentation for any cancer patient may be made at local, regional or central-level or primary health care centres or hospitals. The decision of where to seek care is made by the patient, according to their geographical location and their financial situation, as there is no public insurance program in Nepal (B P Koirala Memorial Cancer Hospital 2017b; Banstola et al. 2019; Siwakoti et al. 2019; Subedi 2012). However, the government of Nepal started to provide a fixed amount of US$925.92 from 2019 to all cancer patients for cancer treatment (Gyawali et al. 2020; Khatiwoda et al. 2019). Any further costs incurred must be covered by out-of-pocket expenses directly from the patients, the hospital type for treatment for gastric cancer is also determined by the patient, according to their geographical location or their financial situation rather than by clinical assessment or established referral pathway (B P Koirala Memorial Cancer Hospital 2017b; Siwakoti et al. 2019; Subedi 2012).

There are currently 14 hospitals in Nepal treating and diagnosing gastric cancer. The B P Koirala Memorial Cancer Hospital (BPKMCH), which is the biggest cancer-specific hospital by beds and the number of patients treated, opened in 1992 with the aims of research, prevention and control of cancer in Nepal. BPKMCH was the first tertiary level cancer hospital in Nepal delivering multiple types of cancer treatment services, including surgical oncology, medical oncology, radiation oncology, pathology services, radiodiagnosis imaging and nuclear

medicine services (B P Koirala Memorial Cancer Hospital 2017a). As the number of total patients increased in the cancer hospitals of Nepal in recent years (Poudel 2016b, 2017; Poudel, Huang & Neupane 2016; Poudel et al. 2017), the government and the private sectors opened new cancer hospitals in different urban areas of the country. If people suspect they have gastric cancer, other cancer-specific hospitals, including the Bhaktapur Cancer Hospital and the Nepal Cancer Hospital and Research Centre also offer treatment. Bhaktapur Cancer Hospital (BCH) is the oldest national level cancer specific hospital located in Kathmandu Valley (Nepal Cancer Relief Society 2021). In addition to the three cancer-specific hospitals in Nepal, gastric cancer can be diagnosed and treated at a hospital with oncology services. Oncology services in other hospitals include Bir Hospital, B & B Hospital, Kathmandu Medical College, Nepal Medical College, and Tribhuvan University Teaching Hospital (Piya & Acharya 2012).

1.3 Rationale of the study

Survival[2] of gastric cancer varies between countries and regions. Parkin et al. (2005) reported variation in the five-year survival rate of gastric cancer worldwide ranging from 6% to 52% in several countries (sub-Saharan Africa (6%), North America (21%), Western Europe (27%), and Japan (52%). The CONCORD-3 program reported the highest five-year survival rate between 2010 and 2014 of gastric cancer in Korea (68.9%), followed by Japan (60.3%) while the lowest five-year survival rate was in India (4%) (Allemani et al. 2018). Globocan reported variation in five-year relative survival [3]of gastric cancer in 2014 among high-income countries,

[2] Survival defines the length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive (Dos Santos Silva 1999).

[3] In cancer, relative survival represents the probability of surviving cancer in the absence of other causes of death. It is used to give an estimate of the percentage of people who will survive their cancer (Dos Santos Silva 1999).

including the UK (20%), Denmark (22%), New Zealand (24%), Norway (26%), Canada (30%) and Australia (31%) (Ferlay et al. 2020b).

A recent study on gastric cancer, that collected data from 48 countries between 1980 to 2018, reported that Thailand has the strongest increasing trend in mortality, with an average annual percent change in mortality of AAPC 3.92 (95% CI: 2.14 to 4.74, p=0.001) in males and in AAPC in females of 5.30 (95% CI, 4.38 to 6.23, P<.001) (Wong et al. 2021). The country that had the greatest decrease in gastric cancer mortality was Norway with AAPC -2.69 (95% CI, –4.16 to –1.20, p=0.003) in males and AAPC in females of –5.86 (95% CI, –7.56 to –4.13, p<.001). However, this multi-country gastric cancer study does not include mortality trend information from either Nepal or India (culturally similar neighbouring country), where gastric cancer is a major public health concern.

Although gastric cancer is one of the top four causes of cancer-related death worldwide in 2020 (Ferlay et al. 2020h), there have been no studies to determine the survival and predictors of gastric cancer in Nepal. It is essential to study the survival rate and predictors of gastric cancer in Nepal as, in 2020, gastric cancer was the second most common cause of cancer death in males (14.2% out of 6,244 total male cancer cases death), and fifth in females (6.7% out of 7,385 total females cancer cases death) (Ferlay et al. 2020g). There is limited research, inadequate investment and low healthcare capacity in Nepal because Nepal is a lower-middle-income country (United Nations Development Programme 2022). This paucity of resources increases the urgency to investigate the epidemiology of gastric cancer in Nepal. Globocan estimates that the burden of gastric cancer will be increased by 86.7% from 2020 (1,552) to

---

The difference between survival and relative survival is that survival in this study is based on crude (accurate) survival however relative survival is used for estimating survival for all causes of death (this study did not calculate the relative survival).

2040 (2,897) in Nepal (Ferlay et al. 2020i). In addition, Globocan estimated that number of deaths to gastric cancer in Nepal will increased by 87.1% from 2020 (1,384) to 2040 (2,589) (Ferlay et al. 2020l). The number of estimated deaths due to gastric cancer is higher than the expected population increase from 2020 to 2040, of 20% in Nepal (Population Pyramid 2023). However, Globocan projected that the total number of deaths of gastric cancer in very high HDI countries will increased by only 45.0% from 2020 (182,375) to 2040 (264,415) (Ferlay et al. 2020e).

There are several reasons for the lower survival rate of gastric cancer in LMICs. One potential reason for lower survival rates in low-and middle-income countries (LMICs) may be the result of late diagnoses and hence people being more likely to be diagnosed in advanced stages (Allemani et al. 2018). In LMICs, there is often a lack of access to timely and effective cancer diagnosis and care, resulting in poorer treatment outcomes for those diagnosed (Allemani et al. 2018; Sullivan et al. 2015; Wilson et al. 2018); cancer-screening programs in LMICs are often either not available poorly developed or had a lead-time bias (Sankaranarayanan 2014).

The above gap in knowledge and existing studies warrants further empirical studies to assess the association between predictors and gastric cancer survival in Nepal. The proposed retrospective cohort study will investigate a comprehensive list of clinical predictors for gastric cancer survival such as tumour location, histologic type, tumour grade, tumour size, extent of a cancer, tumour stage and treatment (surgery, chemotherapy, radiotherapy) (for detailed explanation of these variables see appendix 1 patient information sheet). The findings of this study may assist policymakers in the prevention and increase the survival of gastric cancer in Nepal in future. By evaluating the potential predictors associated with gastric cancer survival, this study will reduce the existing gap in the current literature on predictors for gastric cancer survival and contribute to public health policy on gastric cancer prevention. Furthermore, the

outcomes of this study will also assist in comparing the predictors of gastric cancer in other regions and Nepal that may inform health guidelines in Nepal.

The current cohort study, therefore, aims to determine the association between potential predictors and gastric cancer survival in Nepal.

Chapter 2 Introduction to Stomach and Gastric Cancer

This chapter discusses the basic anatomy of the stomach, definition of gastric cancer and its types. This chapter also includes signs and symptoms, diagnosis of gastric cancer by endoscopy, multidetector computed tomography, or magnetic resonance imaging. In addition, this chapter explores the classification system for stage of disease at diagnosis based on the Tumour Node Metastasis, Surveillance, Epidemiology, and End Results (SEER), and Japanese Classification of Gastric Carcinoma (JCGC) staging system. Predictors for gastric cancer survival are also provided, including histologic subtypes of gastric cancer, tumour grade and dissection of lymph node.

2.1 Anatomy of stomach

The stomach is one of the major parts of the upper gastrointestinal (GI) tract, which is part of the digestive system (Cancer Council Australia 2017). It is J-shaped, relatively vertical in tall people, and more horizontal in short people, and lies at the upper left abdominal cavity immediately inferior to the diaphragm. The peritoneum covers the stomach, a muscular sac, and the widest part of the alimentary canal located in the upper left abdominal cavity, continuous with the abdominal oesophagus proximally and with the duodenum distally. The stomach is relatively mobile except at its proximal and distal ends, where it is fixed to nearby structures (Mahadevan 2014).

An empty stomach appears flat, showing its anterior and posterior surfaces, separated by lesser and greater curvature. The lesser curvature of the stomach extends the short distance from the oesophagus to the duodenum along the medial to superior aspect, while the greater curvature extends the longer distance from the esophagus to duodenum on the lateral to inferior aspect. The stomach has two orifices, proximally termed as a cardiac orifice that communicates with

the esophagus, and distally termed as a pyloric orifice that lies at the gastroduodenal junction. The stomach is divided into four regions (Mahadevan 2014), (see Figure 2.1).

1. "The cardiac region (cardia) is a small area immediately inside the cardiac orifice.
2. The fundic region (fundus) is the dome-shaped portion superior to the oesophageal attachment.
3. The body (corpus) makes up the greatest part of the stomach inferior to the cardiac orifice.
4. The pyloric region is a slightly narrower pouch at the inferior end; it is subdivided into a funnel-like antrum and a narrower pyloric canal."

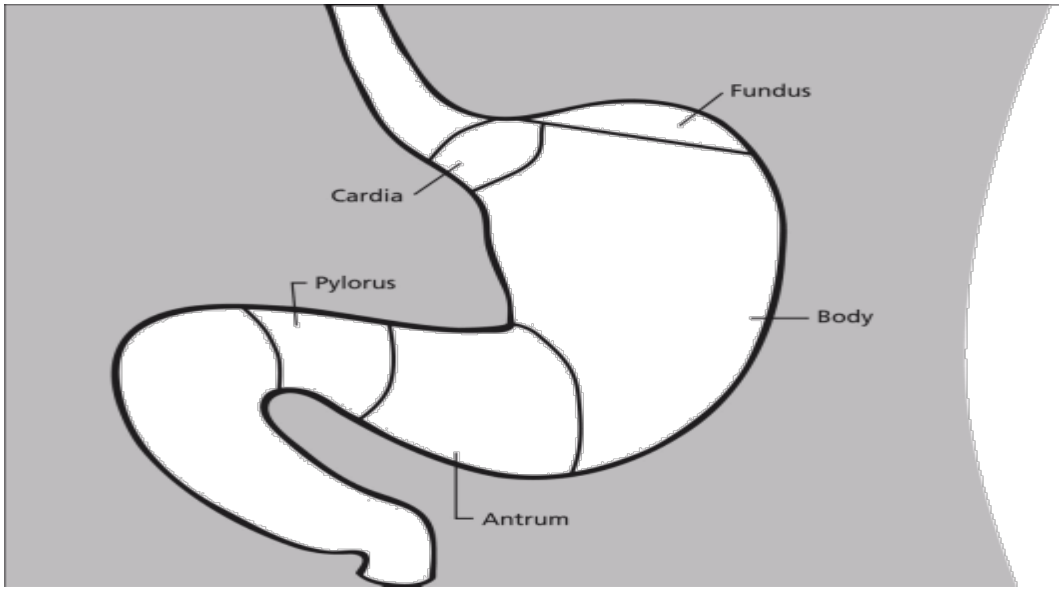


Figure 2.1: Parts of the stomach (Source: American Cancer Society 2017a).

2.2 Types of gastric cancer

Tumours generally arise from the inner surface of the stomach where glandular tissues are located and are called adenocarcinoma of the stomach (American Cancer Society 2017a). Avital et al. (2016) reported that the most common type of gastric cancer, adenocarcinoma is

responsible for 95% of cancer of the stomach. The remaining five percent of gastric cancers are squamous cell carcinoma, carcinoid tumours, adenoacanthoma, mucinous carcinoma, small cell carcinoma, lymphoepithelioma-like carcinoma, carcomatoid carcinoma, adenocarcinoma with rhabdoid features, gastrointestinal stromal tumour, hepatoid adenocarcinoma, gastric carcinoma with osteoclast-like giants cells, neuroendocrine tumour (Avital et al. 2016).

There are two types of gastric cancer by anatomical site of origin (World Cancer Research Fund & American Institute for Cancer Research 2018). They are gastric cardia cancer (cardia cancer) and non-cardia gastric cancer (non-cardia cancer). Cardia cancer occurs around the gastro-oesophageal junction, whereas non-cardia cancer occurs outside this portion, in the lower part of the stomach (Colquhoun et al. 2015).

2.3 Signs and symptoms of gastric cancer

Gastric cancer is not frequently diagnosed in its early stages [4](American Cancer Society 2017b; Cancer Council Australia 2017), with only about one in five gastric cancers in the United States detected in Stage I, before it has extended to other organs of the body (American Cancer Society 2017b). Because of the indefinite and nonspecific signs and symptoms that characterise gastric cancer, many cases are detected at an advanced stage of disease (Avital et al. 2016).

A combination of signs and symptoms are found in gastric cancer patients, including anorexia (5% to 40%); fatigue, discomfort, epigastric pain (62% to 91%); weight loss (22% to 61%); and postprandial fullness[5], indigestion, vomiting, heartburn, and nausea (6% to 40%), and some

[4] Early stage gastric cancer is a carcinoma limited to the mucosa or the mucosa and submucosa, regardless of nodal status (Hamilton & Aaltonen 2000).

[5] Postprandial fullness is defined as an unpleasant sensation like prolonged persistence of food in the stomach (DeVita, Lawrence & Rosenberg 2016).

cases may be asymptomatic (4% to 17%) (Avital et al. 2016). Stomach pain and weight loss are the most common symptoms at an early stage. History or symptoms of peptic ulcer disease are found in 25% of the patients. Similarly, hematemesis does arise in nearly 10% to 15% of cases, and anaemia in 1% to 12% of cases (Avital et al. 2016).

2.4 Diagnosis of gastric cancer

The diagnosis of gastric cancer is typically made by endoscopy, multidetector computed tomography, or magnetic resonance imaging:

A systematic review of 31 studies (twenty-two endoscopic ultrasound, five computed tomography, one combined endoscopic ultrasound and computed tomography, and three magnetic resonance imaging) reported the sensitivity and specificity of endoscopy for T stage gastric cancer with involvement serosal [6] was 78% to 100% in endoscopy (Wang & Chen 2011). A Korean study (a total of 277 patients) conducted in 2006 observed that the sensitivity and specificity of endoscopy for N stage gastric[7] cancer with serosal involvement was 68% to 100% (Hwang et al. 2010). A Chinese study conducted in 2006 identified that confocal laser endoscopy provides sensitivity 90% and specificity 99.5% (Liu et al. 2008).

Multidetector computed tomography (MDCT): The sensitivity and specificity of MDCT for T stage gastric cancer with serosal involvement was 83% to 100% (Wang & Chen 2011). The sensitivity and specificity of MDCT for N stage gastric cancer with serosal involvement was 80% to 97% (Hwang et al. 2010). The sensitivity and specificity of MDCT for lymph node

[6] T Stage gastric cancer with involvement serosal is defined as the Outermost layer of stomach (Hamilton & Aaltonen 2000).

[7] N Stage gastric cancer with serosal involvement is defined as cancer localized on the serosa of the stomach with cancer cells spread to the lymph node (Hamilton & Aaltonen 2000).

metastasis of gastric cancer was 86% and 76%, respectively, in a Chinese study conducted between 2000 and 2008 (Yan et al. 2009).

The sensitivity and specificity of Magnetic resonance imaging (MRI) for T stage gastric cancer with serosal involvement was 89% to 93% for MRI (Wang & Chen 2011). The sensitivity and specificity of MRI for N stage gastric cancer with serosal involvement was 91% to 100% (Hwang et al. 2010).

Based on these individual studies, the three approaches are similar, although the MRI study has showed superior sensitivity and specificity and the endoscopy study and the MDCT study showed lower accuracy in the diagnosis of gastric cancer (Hwang et al. 2010; Liu et al. 2008; Wang & Chen 2011; Yan et al. 2009). Although all three types of approaches, including endoscopy, multidetector computed tomography, and magnetic resonance imaging, are used to diagnose gastric cancer, endoscopy is the most common approach to diagnose gastric cancer in Nepal (B P Koirala Memorial Cancer Hospital 2017a).

2.5 Classification system for stage of disease at diagnosis

The classification system for stage of disease at diagnosis is an important concept for the purpose of this study. The classification system for stage of disease at diagnosis will be used throughout the thesis including the Research Design and Methodology, collection and analysis of the primary data.

The stage of disease at diagnosis is essential to determine the correct treatment of the patient. Gastric cancer can be staged either clinically or pathologically (Compton et al. 2012). Clinical staging of cancer utilizes a diagnostic method to determine the extent of the cancer. Pathological staging of cancer utilizes diagnostic methods for clinical staging as well as findings from surgical resections and histologic examinations (Compton et al. 2012).

Tumour spread, location, size, node involvement and metastasis are all relevant factors in the staging of gastric cancer. The common staging systems used for gastric cancer are the American Joint Committee on Cancer/International Union against Cancer Classification (AJCC/UICC) Tumour Node Metastasis (TNM) system; the Surveillance, Epidemiology, and End Results (SEER) program's Summary Stage 2000, and the Japanese Classification of Gastric Carcinoma (JCGC) staging system. All four of these systems provide similar information on stage at diagnosis.

2.5.1 Tumour Node Metastasis (TNM)

The Tumour (T) Node (N) Metastasis (M) classification system is one method that is used for staging gastric cancer. This system uses (T) to denote the size and extent of the primary tumour, (N) to signify the presence and extent of regional lymph node metastasis, and (M) to indicate the absence or presence of metastasis. Stages I to IV are then determined from the combination of these T, N and M values. In order to determine the T, N and M categories, results from physical examinations, imaging, endoscope and/or surgical examination may be required (Brierley, Gospodarowicz & Wittekind 2017). TNM clinical classification and TNM pathological classification can be found in Appendix 4.

The American Joint Committee on Cancer (AJCC) staging manual and International Union Against Cancer Classification (UICC) updated the tumour node metastasis (TNM) system in 2017 (Brierley, Gospodarowicz & Wittekind 2017). The clinical and pathological stages based on the 8th edition of the AJCC/UICC TNM system can be found in Appendix 5.

2.5.2 Surveillance, epidemiology, and end results (SEER) summary stage

Surveillance, epidemiology, and end results (SEER) summary stage informs the pattern of distribution and burden of cancer in the United States (National Cancer Institute n.d.). The SEER summary stage groups cancer into localised, regional, and distant. Cancer diagnosed only in the part of the body where it started is termed 'localised' or stage I. Cancer that has spread to nearby lymph nodes, tissues, or organs is termed 'regional', while cancer that has spread to distant organs or distant lymph nodes is termed distant metastatic cancer (Fritz et al. 2013; National Cancer Institute n.d.).

2.5.3 Japanese Classification of Gastric Carcinoma (JCGC) staging system

Japan has a different method of staging gastric cancer, based on where the lymph nodes with cancer are located around the stomach. This is different from the U.S. system, which uses the number of lymph nodes and not their location (Japanese Gastric Cancer Association 2021). Description of the clinical stages (cTNM) and pathological stages of TNM (pTNM) of gastric cancer based on the 15th edition of the Japanese Classification of Gastric Carcinoma (JCGC), which is identical to the 8th edition of the International Union Against Cancer (UICC/TNM) classification (Japanese Gastric Cancer Association 2021).

2.6 Histologic subtypes of gastric cancer

Gastric cancer is categorized into several types by histology based on the microscopic features of the tumour (Borrmann 1926; Lauren 1965; Ming 1977; Sano & Aiko 2011). Ming (1977)

divided gastric cancer types into expanding or infiltrating, whereas Borrmann (1926) divided histology of gastric cancer into Borrmann I[8], Borrmann II[9], Borrmann III[10], Borrmann IV[11].

Nowadays, the most commonly used categorizations are those of Lauren (1965) and the World Health Organization (WHO) (Bosman et al. 2010). Lauren (1965) categorized gastric cancer into those with gland formation (intestinal type) and those without glandular characteristics (diffuse type). Intestinal type cancer occurs more commonly in older male patients, whereas diffuse-type cancer is more likely to occur in younger age groups Lauren (1965).

World Health Organization (WHO) classified gastric adenocarcinoma into several histologic sub-groups in 2010, including tubular, papillary, mucinous, signet-ring cell carcinoma and poorly cohesive carcinomas (Fritz et al. 2013). The most common type of gastric cancer is the tubular adenocarcinoma, followed by papillary adenocarcinoma and this type usually follows under the Lauren intestinal type. Mucinous adenocarcinoma can be intestinal or diffuse. Finally, signet-ring cell carcinoma is of the diffuse type; however, not all the diffuse-type gastric cancers are signet-ring cells as other poorly cohesive carcinoma exist (Hu et al. 2012).

2.7 Histologic tumour grade of gastric cancer

Tumour grade is the description of a tumour by the abnormality of tumour cells and tissue (American Joint Committee on Cancer 2010). It is an indicator of how likely a tumour is to grow and spread rapidly. If the cells of the tumour and the organization of the tumour's tissue

---

[8] Mainly exogenous growth, usually broad-based polypoid carcinomas with protruding (Borrmann 1926).

[9] With a central, bowl-shaped ulcer in the centre and elevated margins, with a relatively clear boundary between the cancer and the surrounding environment (Borrmann 1926).

[10] Centrally ulcerating carcinoma without a rige, elevated margins and not distince from the surrounding environment (Borrmann 1926).

[11] Diffuse tumour infiltration of the gastric wall (Borrmann 1926).

are close to those of normal cells and tissue, the tumour is categorised as well differentiated. These tumours tend to grow and spread at a slower rate than tumours categorised as undifferentiated or poorly differentiated, which have abnormal-looking cells and may lack normal tissue structures (American Joint Committee on Cancer 2010). If a grading (G) system for a tumour type is not specified, the following system is generally used (American Joint Committee on Cancer 2010; Brierley, Gospodarowicz & Wittekind 2017; Fritz et al. 2013):

(a) GX: Grade cannot be assessed (undetermined grade)

(b) G1: Well-differentiated (low grade)

(c) G2: Moderately-differentiated (intermediate grade)

(d) G3: Poorly-differentiated (high grade)

(e) G4: Un-differentiated (high grade)

(f) Grade or differentiation not determined, not stated or not applicable.

2.8 Dissection of lymph node

Lymph node metastasis is considered an important prognostic factor in cancer survival. The type of dissection of lymph nodes (D1, D2, D3) determined by the lymph node stations that will be removed. Limited dissection (D1) is performed for removal of primary tumour and peri gastric lymph nodes (N1). D2 Lymphadenectomy involves additional removal of extra peri gastric nodes on the left gastric, common hepatic, splenic, and left hepatoduodenal artery (N2). D3 dissection involves removal of N1 and N2 nodes as well as removal of para-aortic nodes (celiac, superior mesenteric and inferior mesenteric nodes) (Strong 2015). Anatomical borders of all lymph node stations have presented in Table 2.1.

Table 2.1: Lymph node stations and their anatomical border (Strong 2015).

station	Description	Anatomical border
1	Right cardiac	Perigastric nodes on the right of the cardia. Nodes along the cardio-esophageal branch of the left gastric artery, from its origin to the oesophageal hiatus (N1).
2	Left cardia	Perigastric nodes on the left side of the cardia (N2).
3	Lesser curvature	Nodes along the inferior branch of the left gastric artery to right gastric artery distal to the first gastric branch (N2).
4	Greater curvature	This location is divided into a left and right part defined by the water shed. The left part is divided into proximal and distal part (N2).
5	Suprapyloric	Nodes at the origin of the right gastric artery including the first gastric branch (N2).
6	Infrapyloric	Perigastric nodes on the greater curvature of the pylorus (N2).
7	Root left gastric artery	Nodes on the left gastric artery from its origin to the bifurcation into the cardioesophageal and lower branch (N2).
8	Common hepatic artery	Nodes around the common hepatic artery from the celiac trunk to the branching off of the gastroduodenal artery (N2).
9	Celiac axis	All nodes on the celiac axis including the origins of the common hepatic and splenic artery (N2).
10	Splenic hilum	All nodes at the splenic hilus, distal to the pancreas tip (N2).
11	Splenic artery	Nodes along the splenic vessels up to the distal end of the pancreas tail. These nodes are divided into proximal (p) and distal (d) nodes (N2).
12	Hepatoduodenal ligament	Group number 12 is divided in three parts: 1. Left side of the hepatic artery (12a), 2. Right side of the ligament and posterior to the choledochal duct (12b), 3. Just posteriorly to the portal vein (12p) (N2).

13	Retropancreatic	Nodes along the superior and inferior posterior pancreatidoduodenal arteries on the posterior side of the pancreas (N2).
14	Root of mesentery	Nodes along the superior mesenteric vessels (N2).
15	Middle colic vein	Nodes in the transverse mesocolon (N2).
16	Para-aortic	Nodes around the abdominal aorta and inferior caval vein.

Chapter 3 Literature Review

This chapter discusses the methods for the literature review including databases and search terms and provides a comprehensive review of the literature on predictors for gastric cancer survival. The current body of evidence is presented by different characteristics including age, sex, tumour location, histology, stage at diagnosis, tumour grade, tumour size, socioeconomic status, race and ethnicity, and treatment.

3.1 Methods for Literature Review

The aim of this literature review is to describe survival of gastric cancer, including predictors of survival, such as: sex, age, tumour location, histology, stage at diagnosis, tumour grade, tumour size, treatment and socioeconomic status.

The researcher searched PubMed, Scopus, Ovid Medline, Embase (Ovid) databases for subject headings and MeSH terms related to key concepts that are potential predictors for gastric cancer survival. (“gastric cancer” or “stomach neoplasms”) OR (“stomach cancer”) AND (“survival” or “mortality”) AND (“treatment or “therapeutics”) OR (“surgery” or “general surgery”) OR (“radiotherapy”) OR (“chemotherapy” or “drug therapy”) OR (“stage”) OR (“grade”) OR (“size”) OR (“histology”) AND (“socioeconomic”) OR (“race” or “racial groups”) OR (“ethnicity”) OR (“male” or “female”) OR (“sex” or “gender”) OR (“age”). Table 3.1 shows the search terms for the literature review.

Table 3.1: Literature review search terms for the study.

Gastric cancer		Survival		Treatment		Socioeconomic
Gastric cancer OR Stomach neoplasms OR Stomach cancer	AND	Survival OR Mortality	AND	Treatment OR Therapeutics OR Surgery OR General surgery OR Radiotherapy OR Chemotherapy OR Drug therapy OR Stage OR Grade OR Size OR Histology	AND	Socioeconomic OR Race OR Racial groups OR Ethnicity OR Male OR Female OR Sex OR Gender OR Age

These databases returned 2,765 potentially relevant articles. Out of 2,765 articles, 901 were duplicates. Remaining original peer-reviewed articles with complete information (abstract, material and methods, results, discussion and conclusion) related to the research question of the study were included (see section 4.1.3 Research questions). Following the review of these abstracts, 52 full text articles were exported into Endnote for analysis and comparison of association between predictors and gastric cancer survival. Data were extracted manually. The Prisma diagram of the literature review procedure is presented in Figure 3.1.

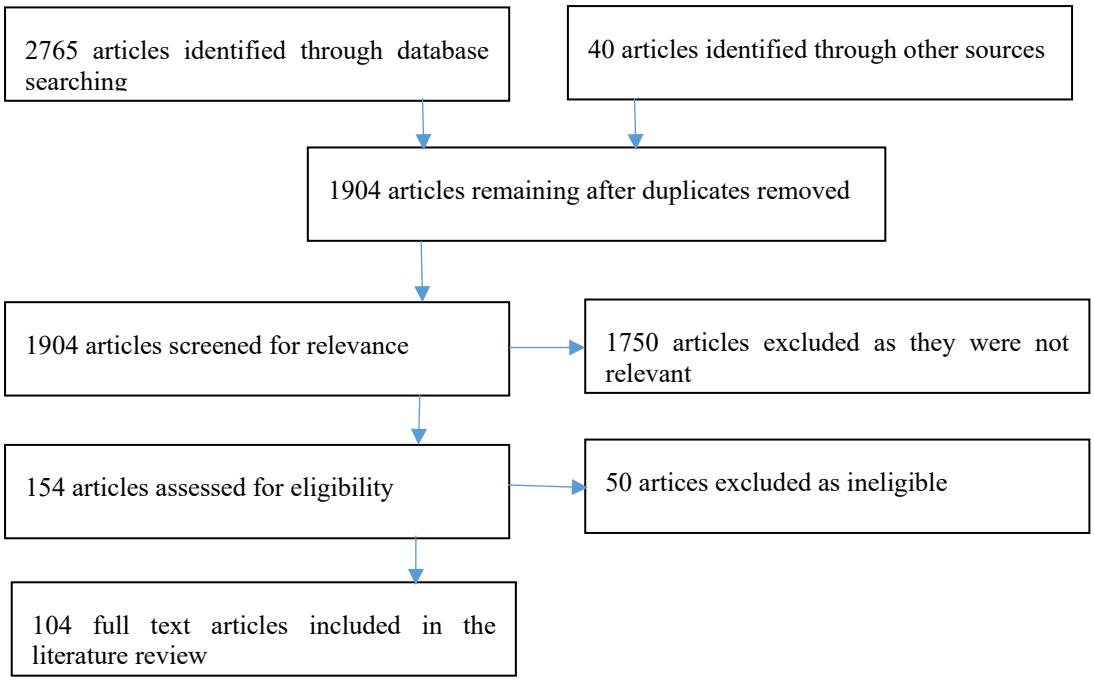


Figure 3.1: The Prisma diagram of the literature review procedure.

Additional articles were added through hand searching and a search of grey literature. A review of the references from the studies found in the initial search 40 articles. Searches for 'gastric cancer survival', 'stomach cancer survival', 'gastric cancer mortality', 'stomach cancer mortality' in the grey literature were undertaken in Google Scholar, or the website of World Health Organisation, or International Agency for Research on Cancer, World Cancer Research Fund, and American Institute for Cancer Research to provide 64 more articles. This yielded 104 articles.

The review was limited to articles published up to 2022 in peer reviewed journals and grey literature, articles in English language and adult human populations. The outcome of articles after using the data bases and key words can be found in Appendix 7 (literature database searches). Data were extracted manually. As only high-quality evidence was included in this literature review, the reader can be confident that this information on risk factors is accurate.

3.2 Survival and gastric cancer

The time that elapses between a cancer diagnosis and subsequent death or end of follow-up is defined as the survival time of a cancer patient. Five-year observed survival is a common epidemiological measure of survival, representing the percentage of patients who are alive five years after their date of diagnosis (Larsen 2019).

The five-year overall survival of gastric cancer varies between geographical regions ranging from 8.9% in India to 68.9% in Korea. The CONCORD-3 program, conducted among 68 countries between January 2010 and December 2014, reported the highest five-year survival rate (68.9%) of gastric cancer in Korea, followed by Japan (60.3%). Survival ranged between 30% to 40% in 16 countries, including Canada, the USA, Puerto Rico, Martinique, Malaysia, Singapore, China and Taiwan, Israel, Italy, Portugal, Austria, Belgium, Germany, Switzerland and Australia; the lowest five-year survival rate (8.9%) was determined in India (Allemani et al. 2018). An explanation for higher survival rates in Korea may be the implementation of a nationwide gastric cancer-screening program. This program doubled the chances of early diagnosis compared with unscreened patients (OR: 2.10, 95% CI = 1.90 to 2.33) (Choi et al. 2015). The low rate of survival in India could the result of higher rates of diagnoses with advanced diseases, low socioeconomic status, inadequate health facilities and health care access (Allemani et al. 2018; Vaccarella et al. 2019).

Because of delays in diagnosis in low and middle income countries, due to inadequate screening (i.e., most countries do not have screening) and diagnostic services, the mortality rate of gastric cancer in LMICs will be around 35% higher than in high HDI countries by 2040 (Ferlay et al. 2020m). As an example, Globocan estimates that the burden of Gastric cancer in Nepal will increase by 86.7% from 2020 to 2040, with an increase in gastric cancer-related deaths of 87.1% from 1,384 in 2020 to 2,589 in 2040 (Ferlay et al. 2020m). However, Globocan

was unable to estimate the survival rate of gastric cancer due to the lack of post diagnosis follow-up data in Nepal (Poudel 2016a, 2016b, 2017; Poudel, Huang & Neupane 2016; Poudel et al. 2017).

3.3 Survival and sex

Studies have reported that survival from gastric cancer may be affected by sex. A higher risk of death was observed in males compared to female gastric cancer patients (HR: 1.25, 95% CI: 1.12 to 1.41, p <0.001) diagnosed between 1995 and 2006 in Netherlands (Dassen 2014). Sex and ethnicity were considered in an American study that determined that, both white and African American, males had a significantly higher risk of dying compared to their females' counterparts (HR: 1.08, 95% CI: 1.00 to 1.16) among 13,840 patients diagnosed with metastatic gastric cancer between 1988 and 2004 in the USA. In Asian, Hispanic, and Native American populations, there was no significant difference in survival for males and females. Males also had a significantly higher risk of dying compared to females in patients whose tumours were poorly differentiated or undifferentiated (HR: 1.23, 95% CI: 1.16 to 1.30), or had unknown tumour grade (HR: 1.10, 95% CI: 1.02 to 1.18) (Yang et al. 2011). Although stage at diagnosis is a significant predictor for gastric cancer survival (Dassen 2014); Yang et al. (2011) did not account for the effect of stage at diagnosis and SES that examined the influence of sex on gastric cancer survival rates (Dassen 2014; Singh & Jemal 2017).

3.4 Survival and Age

The age at diagnosis may influence the survival rate of gastric cancer patients. In younger age groups, survival rates are higher than in older age groups. A similar five-year observed survival rate in the age group 35 to 44 years (18.61%) and those aged 45 to 54 years (18.13%) was reported among 15,401 Chinese gastric cancer patients diagnosed between 1972 and 2011

(Chen et al. 2015). However, Chen et al. (2015) reported a higher five-year observed survival rate in the age group 55 to 64 years (13.59%) compared to those 65 to 74 years (9.31%), and 75 years and older (2.86%). Additional factors that also influence survival include clinical stage, the pathological subtype of tumour, the degree of tumour cell differentiation influence the survival rate of gastric cancer (Matz 2017; Vaccarella et al. 2019).

In another study among 3,930 Chines gastric cancer patients diagnosed between January 2005 and December 2010 (Wang et al. 2016), a significantly higher five-year survival rate (60.8%) was found in those aged 40 years or less compared with those aged 41 years or older (53.07%, $p = 0.01$). Although Wang et al. (2016) accounted for important clinical predictors such as histologic type, disease stage, differentiation, and treatment in their study, this study lacks information on the influence of socioeconomic status (SES) on gastric cancer survival. Based on the Japanese retrospective study (Katai et al. 2018) in 118,367 gastric cancer patients diagnosed between 2001 and 2007, elderly patients (≥80 years) had a worse five-year overall survival than patients in other age groups for every stage. As an example, patients in the age group ≤39 years ($n = 1,135$) in stage IA had a significant ($p <0.001$) higher five-year overall survival rate (99.1%) compared to patients in the age group ≥80 years 72.8% ($n = 3,772$). Using SEER data of 13,840 metastatic gastric cancer patients diagnosed between 1988 and 2004, the median overall survival was six months in patients of aged ≤ 44 years old as compared to three months in patients aged 75 years and older (Yang et al. 2011).

Although the current body of evidence suggests a link between patient age and survival, no such studies have been conducted in Nepal. However, such studies are necessary as gastric cancer cases are commonly diagnosed in advanced stages in Nepal due to an inadequate number of oncologists, modern diagnostic techniques and the overall socio-economic position of Nepal (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer

Hospital 2017b; Piya & Acharya 2012; Poudel et al. 2018). Further research is required to determine the link between patient age and five-year gastric cancer survival rate to fill this gap in current knowledge. This situation may impact meaningfully on the epidemiology of gastric cancer survival in Nepal.

3.5 Survival and tumour location

Gastric cancer can be classified into two distinct anatomical sites: proximal and distal stomach. The first three parts of the stomach (cardia, fundus, and body) are in the proximal stomach, whereas the lower two parts (antrum and pylorus) are in the distal stomach (Gunderson et al. 2014). The location of tumours within the stomach may be a potential predictor for gastric cancer survival. Worse overall survival of patients with proximal gastric cancer compared with distal gastric cancer was reported in a meta-analysis of 50 studies on tumour location with 128,268 patients (HR: 1.25, 95% CI: 1.12 to 1.41, p <0.001) (Petrelli et al. 2017b), although this study has some limitations, such as only including non-metastatic patients and retrospective studies and differences in received treatments and adjuvant therapies between studies, furthermore, no studies from LMICs were included. Hence, the findings of this study may not apply to LMICs. In another study among 47,295 Dutch gastric cancer patients diagnosed 1989 between 2008, Cardia gastric cancer patients had a worse five-year survival rate (20%) compared with non-cardia gastric cancer patients (30%) for stage I-III, and unknown stage (Dassen 2014). However, for stage IV, the five-year survival rate was poor for cardia cancer (1.0%) and non-cardia cancer (1.9%). The lower survival rate for patients with cardia gastric cancer may be because cancer that primarily originates in the cardia shows more aggressive behaviour, and the diagnosis is more likely to be made at more advanced stage compared to non-cardia cancer (Maeda et al. 2008; Saito et al. 2006).

Although evidence has shown that the tumour's anatomical location is a predictor for gastric cancer survival, this has not been established in the Nepalese context. The survival rate of gastric cancer by tumour location may differ in Nepal, a LMIC, compared to high income countries (HICs). In some HICs, including UK and USA, cardia cancer is more prevalent, and have a higher proportion of cardia than non-cardia cancer (de Martel, Forman & Plummer 2013; Devesa & Frameni 1999; World Cancer Research Fund & American Institute for Cancer Research 2018). Non-cardia gastric cancer is most prevalent in Asian countries, although the incidence rate of non-cardia cancer is declining (Colquhoun et al. 2015; World Cancer Research Fund & American Institute for Cancer Research 2018). As non-cardia cancer is most prevalent in Asian countries, it may be extrapolated that the number of deaths due to non-cardia cancer will be higher for LMICs, including Nepal, compared to HICs, including UK and U.S. Reasons for this increased non-cardia cancer burden in Asian LMICs may include lifestyle, SES and lack of health resources that reduce access to timely and effective diagnosis and care and increasing the likelihood that diagnosis will not be made until advanced stages of the cancer (Poudel et al. 2018; Vaccarella et al. 2019).

3.6 Survival and histology

Histology is a predictor for gastric cancer survival. There are two systems that classify the histology of gastric adenocarcinoma: Lauren and WHO. The Lauren classification system represents a simple and robust classification approach, developed in 1965, is still widely accepted and employed by pathologists and oncologists. Based on the Lauren classification, gastric cancer can be classified into two distinct histological patterns: diffuse and intestinal (Lauren 1965).

The management of gastric cancer is relying on prognostic assessment based on clinical and pathological stage, while histology needs to be validated as a prognostic or even predictive

factor in gastric cancer patients as evidence suggested that diffuse-type cancers are associated with worse survival than intestinal-type cancers (Liu et al. 2013; Petrelli et al. 2017a). Intestinal type histology had a higher five-year survival rate (36%) compared with diffuse-type of histology (20%; p = 0.03) with 224 patients diagnosed between May 1984 and July 2002 in US study (Cunningham et al. 2005). In a meta-analysis of 21 studies by Liu et al. (2013), intestinal-type had a higher five-year survival rate (61.7%) compared with diffuse-type of histology (41%; p < 0.001) among 11,073 patients; however, Liu et al. (2013) did not take common clinical and pathological variables such as disease stage, treatment into account. A recent meta-analysis of 73 studies, including 61,468 patients by Petrelli et al. (2017a) indicated (23%) worse overall survival in gastric cancer patients with diffuse-type (HR: 1.23, 95% CI: 1.17 to 1.29, p <0.0001) compared with intestinal subgroup. However, this meta-analysis was limited to those published in English. All studies were retrospectives and no studies from LMICs were included.

The other histological system used to classify gastric adenocarcinoma is the WHO classification system. The WHO classification of gastric adenocarcinoma was used to determine gastric cancer survival in a Japanese study, conducted between 1993 and 2006, which found associations between histology and survival for 517 gastric cancer patients (RR: 1.29, 95% CI: 1.08 to 1.53, p = 0.003) (Hua et al. 2010); although this study was based at a single hospital.

Signet ring cell (SRC) histology type was associated with poorer survival (HR: 1.12, 95% CI: 1.01 to 1.23, p = 0.03) among 9,636 patients reported in a meta-analysis of 21 studies (Zhao et al. 2020). However, the subgroup analysis (8 studies) found that SRC histology type had better survival than non-SRC type for early gastric cancer (HR: 0.60, 95% CI: 0.48 to 0.75, p <0.001). However, the survival of SRC type was worse than that of non-SRC type for advanced gastric

cancer (HR: 1.18, 95% CI: 1.07 to 1.29, p <0.001), when excluding stage IV patients in three studies. As this study did not include any prospective study, the level of current evidence is not high enough, the majority of studies were included from East Asian Countries that may not be representative of the characteristic of South Asian countries such as Nepal.

Although gastric cancer patients diagnosed with intestinal-type histological patterns have better survival than patients diagnosed with diffuse type, survival rates of gastric cancer by histologic type may be different in Nepal compared to other countries due to the lack of pre-metastatic diagnosis in Nepal. WHO classification of histology for gastric adenocarcinoma is common in Nepal (B P Koirala Memorial Cancer Hospital 2018); no studies have established this link.

3.7 Survival and stage at diagnosis

Most cancer patients with regional or distant metastasis have lower survival compared with the local stage of disease, which is also true for patients diagnosed with gastric cancer. The five-year relative survival rate for localised gastric cancer (69.5%) was higher compared to regional (26%) and distant gastric cancers (36%) based on the SEER data of stomach cancer diagnosed between 2010 and 2016 (National Cancer Institute n.d.). A Norwegian report analysing all gastric cancer cases between 2014 to 2018 found a higher five-year relative survival rate in localised gastric cancer patients (72.9%) compared with regional (37.3%) and distant (3.5%) in males, while the survival rate in females was slightly lower: localised (69.5%), regional (30%) and distant (3.2%) (Larsen 2019). A Japanese study analysing data from 118,367 patients with primary gastric carcinoma who underwent resection between 2001 and 2007, found a higher five-year overall survival rate in patients with pathological stage IA (91.5%) compared with II (70.6%), IIIA (53.6%), IIIB (34.8%), and IV (16. 4%) (Katai et al. 2018). Although this study collected data from 367 institutions and included data on 53 items such as surgical procedures and pathological diagnosis among others, data were gathered

retrospectively seven years after surgery. A meta-analysis of 73 studies with 61,468 patients by Petrelli et al. (2017a) found lower survival in both stages I-III (25 studies, HR: 1.21, 95% CI: 1.12 to 1.3, p< 0.01) and more advanced stages (7 studies, HR: 1.25, 95% CI: 1.04 to 1.5, p = 0.014) with diffuse histology.

The difference in overall survival of gastric cancer is not explained by international differences in the staging of diagnosis. Factors that influence survival include tumour biology, diagnostic delay, staging procedure and treatment (Singh & Jemal 2017; Vaccarella et al. 2019). Staging guidelines must be accurate across regions to enable global comparisons of stage-specific survival (Brierley, Gospodarowicz & Wittekind 2017).

3.8 Survival and histologic tumour grade

For any histologic cancer site, including the stomach, a well-differentiated histologic tumour grade was shown to have a higher survival rate than and moderately differentiated, poorly differentiated or undifferentiated tumours. A significant association (p = 0.012) between tumour differentiation and survival was reported in a retrospective study (Zu et al. 2014) of 741 Chinese patients diagnosed with advanced gastric cancer between 1997 and 2007. This study identified a higher five-year survival rate of patients with well-differentiated (87.1%) than moderately differentiated (57.1%) and poorly differentiated tumours (50.6%). However, there was no association between tumour differentiation and survival in early gastric cancer patients. Similarly, a worse overall survival in poorly differentiated tumours compared with moderately or well-differentiated tumours (HR: 1.19, 95% CI: 1.13 to 1.25, p <0.001) was reported among 13,840 metastatic gastric cancer patients diagnosed between1988 and 2004 in the USA (Yang et al. 2011).

Although the classification of tumour grade, based on the World Health Organization, is used in Nepalese cancer hospitals (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b), the link between tumour grade and gastric cancer survival rate for Nepalese people have not been investigated. The survival rate of gastric cancer by tumour grade may differ in Nepal compared with other countries due to not being diagnosed in the early stages.

3.9 Survival and tumour size

Most cancer patients with large-sized tumours had a lower survival rate than those with small-sized tumours, which may also be true for patients diagnosed with gastric cancer. Better overall survival in small-sized-tumours (< 5 cm) compared with large-sized tumours (5 to 7 cm, HR: 1.35, 95% CI: 1.03 to 1.75, p = 0.03) and (> 7 cm, HR: 2.09, 95% CI: 1.48 to 2.94, p <0.001) was found in 508 Chinese gastric cancer patients diagnosed between 2004 and 2013 (Gao et al. 2020). Wang et al. (2012) also reported significantly higher five-year overall survival in small-sized-tumours (<4.8cm) compared with large-sized tumours (≥4.8cm) (RR: 2.14, 95% CI: 1.68 to 2.72,p <0.01) in 430 Chinese advanced gastric cancer patients diagnosed between 1998 and 2004.

Although the classification of tumour size is common in Nepal (B P Koirala Memorial Cancer Hospital 2018), there have been no studies in Nepal that establish this link between tumour size and survival rate. The survival of gastric cancer by tumour size may differ in Nepal compared with other countries due to a larger proportion being diagnosed in advanced stages.

3.10 Survival and treatment

Treatment of gastric cancer options available to patients depends on different factors, including the location and stage (extent of spread) of the tumour (American Cancer Society 2017c). This

section aims to discuss the survival rate of gastric cancer by three types of treatment: surgery, chemotherapy, and radiotherapy.

3.10.1 Surgery

Surgery can be part of the treatment of gastric cancer at different stages (American Cancer Society 2017c; Avital et al. 2016). Type of surgery usually depends on the part of the stomach the cancer is located and its spread into the surrounding tissue. Multiple kinds of surgery, including endoscopic resection, lymphadenectomy, gastrectomy (partial gastrectomy, subtotal gastrectomy, and total gastrectomy) may be used to treat gastric cancer (Avital et al. 2016):

3.10.2 Endoscopic resection

Endoscopic mucosal resection (EMR) and endoscopic submucosal resection can be used to treat some very early-stage cancers, where the chance of extent to the lymph nodes is very low (Avital et al. 2016). These procedures are not as common in the United States as in countries like Japan, where gastric cancer is more prevalent and more often diagnosed at an early stage due to population-based screening program (Avital et al. 2016; DeVita, Lawrence & Rosenberg 2016). However, a meta-analysis of five studies with 1,428 patients reported no significant difference for five-year overall survival between patients with endoscopic resection and those with gastrectomy (HR: 1.06, 95% CI: 0.61 to 1.83, p = 0.83) (Wang et al. 2015).

3.10.3 Lymphadenectomy

Evidence suggested that extended lymph node dissection may be associated with improved long-term survival. A randomized controlled trial (RCT) was conducted in the United Kingdom between 1986 and 1993 in 737 patients with histologically proven adenocarcinoma of the stomach who underwent a staging laparotomy (Cuschieri et al. 1999). Of these patients, 400 patients were eligible for the study (defined as stage I – III gastric cancer without positive

infracolic para-aortic nodes). Eligible patients were randomized at the time of laparotomy, 200 to each group, to undergo lymph node dissection D1 or D2. The difference in overall five-year survival rates was not significant, with 35% in the D1 dissection group and 33% in the D2 group (Cuschieri et al. 1999).

In a large RCT of 1,078 Dutch patients between 1989 and 1993, there was no significant difference found between D1 and D2 lymph node dissection (Bonenkamp, Songun & Hermans 1995). The eligible 711 patients underwent curative resection were randomized D1 dissection (n = 380) or D2 dissection (n = 331). The overall five-year survival rates were 34% for the D1 dissection group and 37% for the D2 group (Bonenkamp, Songun & Hermans 1995). After a median follow-up of 11 years, no difference in overall survival was detected between the D1 group D2 group with 30% and 35% survival, respectively. (Hartgrink et al. 2004). With a median follow-up of 15 years, a new report on this study was published in 2010, 174 (25%) patients were alive out of 711 patients (Songun et al. 2010). The fifteen-year overall survival in the curative resection group was 21% in the D1 group (82/711) and 29% in D2 group (92/711), the difference was again not significant.

In an RCT at 24 Japanese hospitals between 1995 and 2001, no statistical difference was found for the five-year overall survival for patients undergoing D2 lymphadenectomy plus para-aortic node dissection (PAND) (n = 263 patients) 70.3% versus D2 lymphadenectomy alone (n = 260 patients) 69.2% (HR = 1.03; p = 0.85) (Sasako et al. 2008).

An RCT from Italy conducted between June 1998 and December 2006, compared D1 (n = 133 patients) and D2 (n = 134 patients) lymphadenectomy for gastric adenocarcinoma with the primary outcome of overall survival over median follow-up 8.8 years (Degiuli et al. 2014). There was no significant difference in five-year overall survival (66.5% versus 64. 2%; p = 0.69) in patients undergoing D1 and D2 gastrectomy. However, subgroup analysis showed

significantly higher five-year disease-specific survival rate for D2 (59%) than D1 (38%) gastrectomy ($p = 0.05$) in patients with advanced T-stages (pT2-4) and node-positive disease.

A RCT conducted in Taiwan, compared D1 (110 patients) and D3 (111 patients) dissection group between October 7, 1993 to August 12, 1999 (Wu et al. 2006). At median follow-up 94.5 months, D3 dissection showed better overall five-year survival 59.5% (95% CI = 50.3 to 68.7) versus D1 dissection 53.6% (95% CI = 44.2 to 63.0; $p = 0.04$).

However, some RCTs have shown a significant difference in gastric cancer mortality between D1 and D2 dissection groups. For example, hospital mortality rates in the United Kingdom were significantly higher in the D2 group (13%) versus in the D1 group (6%; $p < 0.04$) (Cuschieri et al. 1999). Similar results were found in a Dutch trial for D2 group (10%) versus D1 group (4%; $p = 0.004$) (Bonenkamp, Songun & Hermans 1995). However, other studies have shown similar or no difference between D1 and D2 groups. An Italian RCT found no significant difference in mortality (3% versus 2.2%) in patients undergoing D1 dissection and D2 gastrectomy (Degiuli et al. 2014), and a Japanese trial reported a similar mortality rate in each dissection group of 0.8% (D1 and D2) (Sasako et al. 2008). For patients who underwent D2 dissection, no significant difference in survival compared to patients who underwent D1 dissection, as demonstrated by these five studies (Bonenkamp, Songun & Hermans 1995; Cuschieri et al. 1999; Hartgrink et al. 2004; Sasako et al. 2008; Songun et al. 2010). However, mortality was demonstrated to be higher in patients who underwent D2 dissection compared to patients who underwent D1 dissection based on the two studies that were eligible (Bonenkamp, Songun & Hermans 1995; Cuschieri et al. 1999).

The difference in gastric cancer survival rates between D1 dissection group and D2 dissection group among different studies could be because of the difference in diagnostic criteria of gastric

cancer stage migration and treatment. There is limited evidence from LMICs, such as Nepal, to determine these factors for gastric cancer survival and mortality.

3.10.4 Gastrectomy

Gastrectomy surgery (partial gastrectomy, subtotal gastrectomy, and total gastrectomy) could be an influenced factor for gastric cancer survival. A partial gastrectomy is a surgical procedure that is performed to remove a portion of the stomach to treat stomach cancer and benign stomach tumours whereas a subtotal gastrectomy includes removing the cancerous part of stomach, nearby lymph nodes, and possibly parts of other organs near the tumour. But a total gastrectomy involves removing the entire stomach, nearby lymph nodes, and parts of oesophagus and small intestine (American Cancer Society 2017c).

A meta-analysis of 11 studies with 5,447 patients on gastrectomy showed a higher accumulated five-year overall survival rates of distal subtotal gastrectomy groups (55.9%) compared with total gastrectomy groups (49.6%). This study also showed that the distal gastrectomy subgroup had higher survival compared with the total gastrectomy subgroup (HR: 0.91, 95% CI: 0.85 to 0.97, p = 0.006) (Qi et al. 2016). In addition, a meta-analysis of 11 studies with 3,554 patients reported a better five-year overall survival in the distal gastrectomy group than in the total gastrectomy group (OR: 0.62, 95% CI: 0.43 to 0.89, p = 0.009) (Li et al. 2018).

3.11 Chemotherapy

This section examines the survival of gastric cancer by adjuvant chemotherapy and neoadjuvant chemotherapy.

3.11.1 Adjuvant chemotherapy

There have been studies reporting advantages of adjuvant chemotherapy for the survival of gastric cancer patients. A meta-analysis of 16 trials (n = 3,710) by Buyse & Pignon (2009) revealed an overall survival benefit in favour of adjuvant chemotherapy[12] compared with surgery alone (HR: 0.83; 95% CI: 0.76 to 0.91; p<0.0001). In addition, another meta-analysis of 17 trials (n = 3,838) by Sugarbaker, Yu & Yonemura (2003) reported a higher overall survival from adjuvant chemotherapy compared with surgery alone (HR: 0.82; 95% CI: 0.75-0.90; p > 0.001). The estimated median overall survival (OS) was lower in the surgery only group 4.9 years (95% CI: 4.4 to 5.5), whereas OS was 7.8 years (95% CI: 6.5 to 8.7) in the group receiving adjuvant chemotherapy.

3.11.2 Neoadjuvant chemotherapy

Although the outcome of neoadjuvant chemotherapy in gastric cancer has been widely studied, the data of survival benefit are still unclear (DeVita, Lawrence & Rosenberg 2016). A meta-analysis of six randomized controlled trials (n = 781) by Liao et al. (2013) reported no significant difference for overall survival when comparing neoadjuvant chemotherapy [13]and surgery to surgery alone (OR: 1.16; 95% CI: 0.85 to 1.58; p = 0.36).

---

[12] Adjuvant chemotherapy takes place after the first-line treatment, such as surgery to remove a cancerous tumour. The main goal of adjuvant chemotherapy is to lower the chance that the cancer will return, and to improve the outcome of first-line treatment (DeVita, Lawrence & Rosenberg 2016).

[13] Neoadjuvant chemotherapy is chemotherapy that a person with cancer receives before their primary course of treatment. The aim is to shrink a cancerous tumour using drugs before moving onto other treatments, such as surgery (DeVita, Lawrence & Rosenberg 2016).

No studies have been found investigating the association between adjuvant chemotherapy, and neoadjuvant chemotherapy to determine the survival rate of gastric cancer patients in Nepal. This is particularly important, considering that adjuvant chemotherapy and neoadjuvant chemotherapy for gastric cancer patients is common in Nepal (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b) as well as other low-to-middle income countries (Horton & Gauvreau 2015).

3.12 Radiotherapy

Postoperative radiotherapy improves the survival for patients with gastric cancer (Nitin et al. 2013). A meta-analysis of 13 randomized controlled trials determined that for resect-able gastric cancer adjuvant radiation and surgery improved survival compared to surgery alone (Nitin et al. 2013). Postoperative radiation was associated with a significant improvement in both overall survival (HR: 0.78; 95% CI: 0.70 to 0.86; $p<0.001$) and disease-free survival (HR: 0.71; 95% CI: 0.63 to 0.80; $p <0.001$) (Nitin et al. 2013).

In Nepal radiotherapy is commonly used to treat gastric cancer (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b), however, no studies have examined the association between radiotherapy and the survival of Nepalese gastric cancer patients.

Due to the diagnosed in advanced stages of gastric cancer, survival rate of gastric cancer by treatment (surgery, radiotherapy and chemotherapy) may be different in Nepal comparing with other countries.

3.13 Survival and socioeconomic status

Socioeconomic status (SES) is intricately related to income, occupation and education (Vaccarella et al. 2019). Evidence shows that survival is associated with socioeconomic status

for many different types of cancer. Inequalities in cancer survival are affected by socioeconomic differentials in diagnosis stages (Matz 2017; Vaccarella et al. 2019). Cancer survival may be related either to the tumour (e.g., stage at diagnosis and biological characteristics), to the patients (host factors, susceptibility to treatment, psychosocial factors) or the health care system (treatment received, medical expertise and screening). All of these factors may be affected by socioeconomic status as access to health care may affects the spread, tumour size and stage of progression at the time of diagnosis (Brierley, Gospodarowicz & Wittekind 2017; Matz 2017; Vaccarella et al. 2019).

SES affects diagnostic staging with patients with a higher SES background more likely to be diagnosed at a localised stage with a higher survival rate, whereas those with a lower SES more likely to be diagnosed at an advanced stage with lower survival rates (Matz 2017). Patients with low SES may have inadequate access to health resources, including to diagnostic investigation and are more likely to experience a misclassification of localised disease (Singh & Jemal 2017; Vaccarella et al. 2019).

The lack of access to timely and effective cancer diagnosis and care in LMICs has been shown to influence gastric cancer survival (Allemani et al. 2018; Wilson et al. 2018), as well as availability and efficacy of cancer-screening program (Sankaranarayanan 2014). In addition, due to inadequately sourced laboratories and a lack of skilled staff caused by low resources, most gastric cancer cases may not be diagnosed at pre-metastatic or early stages in LMICs, resulting in a higher mortality rate in LMICs compared to HICs (Wilson et al. 2018). Other factors include a lack of established guidelines and protocols for referral of gastric cancer patients, a lack of national health insurance schemes, inadequately resourced cancer treatment facilities, and the unavailability of early detection programs (Wilson et al. 2018).

Patients who relocate to higher SES locations may have better chance of survival through improved access to diagnostic techniques that re-categorise the tumour to a higher diagnostic stage. Patients who relocate following an initial incorrect staging of localised disease may be correctly staged with advanced disease and subsequently provided with higher-level treatment and increased chance of survival (Feinstein, Sosin & Wellis 1985; Matz 2017). Patients in high SES locations, who have access to modern diagnostic techniques, are more likely to be staged accurately than patients from low SES locations (Kurkure & Yeole 2006; Singh & Jemal 2017; Vaccarella et al. 2019; Yoshikawa et al. 2006).

The association between SES and gastric cancer survival varies by country and population. Italian case-control study of 122 gastric cancer patients determined significantly better survival for patients higher-income jobs (HR: 0.59; 95% CI: 0.37 to 0.94; p = 0.03) compared to to those with lower-income jobs, and for those with a higher education level (more than five years of schooling) (HR: 0.40; 95% CI: 0.22 to 0.70; p = 0.003) compared to those with a lower level of education (less than five years of schooling) (Fontana et al. 1997).

A Japanese prospective study reported that unemployed patients (HR: 2.23; 95% CI: 1.27 to 3.92) and manual labourers (HR: 1.68; 95% CI: 1.07 to 2.62) had an increased risk of gastric cancer death compared to professionals or office workers. However, there was no significant association between education and gastric cancer death (Kuwahara et al. 2010). A Colombian study (de Vries et al. 2015) conducted between 1998 and 2007 among 117,597 reported all cancer deaths, inequalities of gastric cancer mortality by educational level. Patients with only primary education had a higher mortality rate (RR: 2.56; 95% CI: 2.29 to 2.86) than patients with tertiary education, although the association differed by the histological site. In the USA National Longitudinal Mortality study conducted between 1979 to 1998 (Singh & Jemal 2017), reported that males with less than a high school education had a 92% higher gastric cancer

mortality than those with a college degree. Similarly, females with less than a high school education had a 74% higher gastric cancer mortality than those with a college degree. This study also showed that males living below the poverty level had a 65% higher gastric cancer mortality than males in the highest income level, while females living below the poverty level had a 20% higher gastric cancer mortality than those of the highest income level. A study from Taiwan Wu et al. (2014) conducted among patients diagnosed with gastric cancer (3,396) between 2002 and 2006 found that high individual SES had a 68% lower risk of mortality than low SES (OR: 0.32; 95% CI: 0.17 to 0.61; p = <0.001) for patients younger than 65 years. However, there was no significant association between SES and gastric cancer death for those patients aged 65 years and older (OR: 1.17; 95% CI: 0.49 to 2.80; p = <0.71). Wu et al. (2014) did not report the association between education and gastric cancer death.

High mortality from gastric cancer in patients with low SES may be due to insufficient fund for health, lack of cancer screening, limited access to care or delay in disease diagnosis.

3.14 Survival and race and ethnicity

This synthesis of information is based on the WHO model of systematic and institutional racism as a cause of inequity in health outcomes (World Health Organization 2017). However, no evidence was available to understand systematic and institutional racism, as a cause of inequity in health outcomes in LMICs. Research suggests that SES and deprivation levels do not fully account for racial and ethnic disparities in cancer incidence, mortality, and survival in the USA (Gopal et al. 2003; Singh et al. 2011). In a U. S. study conducted between 2003 and 2007 (Singh et al. 2011), African Americans were found to have a higher mortality for all cancer (lung, colorectal, prostate, breast and cervical) when compared to White Americans within each deprivation group. Indeed, the overall cancer mortality and incidence rates for African Americans in the most-affluent group are similar to or exceed those for White

Americans in the most-deprived group (Gopal et al. 2003; Singh et al. 2011). Such marked racial inequalities may exist partly because African Americans are socially and materially worse off than White Americans across different socioeconomic strata (Singh et al. 2011). Moreover, they are more likely to experience disadvantages than White Americans in health-risk behaviours, health care access and use, and cancer treatment and survival within each deprivation group (Gopal et al. 2003; Singh et al. 2011).

The National Longitudinal Mortality Study in the U.S. by Singh & Jemal (2017) reported a 2.42 times higher mortality of gastric cancer in males in Asian/Pacific Islanders compared with Non- Hispanic white, whereas in females, mortality was 3.12 times higher in Asian/Pacific Islanders (API) than in non- Hispanic White between 1979 and 1998.

Cancer patients (lung, colorectal, prostrate, breast, cervical, stomach, liver and oesophageal) diagnosed during 1988 and 1999, in the most-deprived decile (low SES) had a 56% higher adjusted risk of mortality (age and period of diagnosis, sex, race/ethnicity, marital status, area deprivation, and rural-urban residence) than those in the least deprived decile (high SES) (Singh & Jemal 2017). After adjusting for deprivation and other covariates, American Indians/Alaska Native (HR: 1.46, 95% CI: 1.40 to 1.54), non- Hispanic Black (HR: 1.20, 95% CI: 1.19 to 1.21), and Hispanics (HR: 1.05, 95% CI: 1.03 to 1.06), experienced significantly higher mortality than non-Hispanic Whites. Several Asian/Pacific Islanders such as Chinese (HR: 1.22, 95% CI: 1.20 to 1.25), Koreans (HR: 1.54, 95% CI: 1.48 to 1.60), Vietnamese (HR: 1.47, 95% CI: 1.41 to 1.54), and Hawaiians (HR: 1.40, 95% CI: 1.34 to 1.46), had higher overall patient mortality when compared to non-Hispanic Whites (Singh & Jemal 2017).

However, Yang et al. (2011) reported not difference in the overall survival of patients with metastatic gastric cancer among different races (White, African American, Asian, Hispanic, Native American) diagnosed between 1988 to 2004 in the USA.

Inequalities in mortality from gastric cancer by racial and ethnic could be due to lack of health insurance, lower cancer screening rate, limited access to care, or delayed disease diagnosis among deprived groups.

3.15 Other influences on gastric cancer survival

There is also evidence of factors that influence gastric cancer survival beyond age, sex, tumour location, histologic type, stage at diagnosis, histologic tumour grade, tumour size, SES, race/ethnicity, and treatment. Some of these additional factors may explain some of the disparities in survival rates of gastric cancer between LMICs and HICs.

Higher rates of *H. pylori* infection may moderate the association between low socioeconomic status, region, age and a higher risk of gastric cancer (Brown 2000). *H. pylori* infections can cause gastritis, which can sometimes be symptomatic (Correa 1992). Symptomatic infection with *H. pylori* in the Antrum[14] leads to a higher acid output that in turn may cause duodenal ulcers. In contrast, the infection in the body of the stomach leads to low acid production, leading to gastric adenocarcinoma (Correa 1992). The average prevalence of *H. pylori* was higher in LMICs at 50.8% (95% CI: 46.8 to 54.7) compared with HICs at 34.7% (95% CI: 30.2 to 39.3) in a review of data from 183 studies conducted in 73 countries between 2000 and 2017 (Zamani et al. 2018). Due to inadequate resources, *H. pylori* may be diagnosed late in LMICs. Delays in the diagnosis of *H. pylori* infections in LMICs may increase the number of metastatic gastric cancer cases and results in lower survival rates of gastric cancer in LMICs.

Lifestyle factors in LMICs increase the risk of tumours of the stomach and may result in inequalities in mortality in both sexes. One example is tobacco use with 80% of the 1.3 billion

[14] Lower portion of the stomach (Hamilton & Aaltonen 2000)

tobacco users worldwide living in LMICs (World Health Organization 2020a). A meta-analysis of 32 studies (five nested case-control studies and 27 cohort studies) on tobacco use, observed that current smokers had an elevated risk of developing gastric cancer compared with those who never smoked among men (RR = 1.62; 95% CI: 1.50 to 1.75; $I^2 = 46.0\%$) and women (RR = 1.20; 95% CI: 1.01 to 1.43; $I^2 = 49.8\%$) (Ladeiras-Lopes et al. 2008). Higher rates of tobacco use are one of the lifestyle risk factors that may be responsible for the higher mortality due to gastric cancer in LMICs.

Another risk factor for gastric cancer is use of alcohol. Higher consumption of alcohol may increase the risk of gastric cancer (World Cancer Research Fund & American Institute for Cancer Research 2018). The annual per capita unrecorded consumption (APC) of alcohol is almost four times higher in LMICS (43.6%) compared with HIC (11.4%) (World Health Organization 2018a). An analysis of 14 studies on alcohol consumption reported a significantly increased risk of gastric cancer in Asians cohorts (RR = 1.03; 95% CI: 1.01 to 1.04; per 10 grams per day) compared with European cohorts (RR = 1.02; 95% CI: 0.98 to 1.06; per 10 grams per day, in seven studies) (World Cancer Research Fund & American Institute for Cancer Research 2018).

Insurance coverage may be another factor that influences the lower survival rate of gastric cancer survival. The overall five-year survival rate of gastric cancer was higher in the national health insurance registered group (64.3%) compared with the medical aid covered group (43.9%) among 247 gastric cancer patients diagnosed between January 1999 and December 2010 in Korea (Jang et al. 2013); although this study was based in a single medical centre.

3.16 Summary

From the available literature, it is clear that histologic type, stage at diagnosis, tumour size, and treatment are predictors of gastric cancer survival. However, in terms of Nepal, there are no studies regarding the factors associated with survival from gastric cancer. The results from the proposed study might assist to help understand the effectiveness of various treatment strategies for better survival from the disease.

Chapter 4 Research Design and Methodology

This chapter discusses the research aim and objectives, study design, study variables, study procedure, inclusion criteria, and exclusion criteria. This chapter also discusses data collection procedures, sample size calculation and statistical analysis. Furthermore, script for telephone conversation with participants, distress protocol, and ethical approval are all presented.

4.1 Aim and objectives

4.1.1 Aim

The overall aim of this study was to determine the five-year survival rate and the predictors of survival from newly diagnosed gastric cancer cases at Bhaktapur Cancer Hospital (BCH) in Nepal between 1st January 2010 and 31st December 2021.

4.1.2 Specific objectives

Specific objectives of this study were:

i. To determine the five-year survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021.

ii. To determine potential predictors of survival from gastric cancer. These include sex (male, female), age at diagnosis, tumour location (proximal, distal); histologic type (tubular adenocarcinoma, papillary adenocarcinomas, mucinous adenocarcinomas, signet-ring-cell carcinomas, poorly cohesive carcinomas); tumour grade (well-differentiated, moderately-differentiated, poorly-differentiated, un-differentiated); tumour size (<3 cm, 3 to 6 cm, >6 cm); extent of cancer (localised, regional, distant metastases; tumour stage (I, II, III, IV); and treatment (surgery, chemotherapy, radiotherapy). Three discrete variables were analysed and interpreted: ‘surgery only’, ‘chemotherapy only’; ‘both radiotherapy and chemotherapy’. As

this dataset does not include socioeconomic status (SES), SES is not included as a potential predictor of gastric cancer.

4.1.3 Research questions

i. Which and to what degree did predictors affect the five-year survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021 in Nepal?

ii. What is the overall survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021?

4.2 Study design

A retrospective cohort study was deployed to determine the predictors of gastric cancer survival at BCH, Nepal. This research included all gastric cancer cases (diagnosed between 1st January 2010 and 31st December 2021 at BCH) within the relevant categories of the International Classification of Disease for Oncology (ICD-10) published by World Health Organization (Fritz et al. 2013).

4.2.1 Study variables

Relevant demographic and clinical information were extracted from patients' medical records. Selected potential predictor variables for gastric cancer survival are listed in Table 4.1. Clinically important variables were included based on the Cancer Principles and Practice of Oncology (DeVita, Lawrence & Rosenberg 2016). These included sex, age, tumour location, histologic type, tumour grade, tumour size, extent of cancer, tumour stage and treatment related data that were obtained from the patients' records at BCH (for detail, see appendix 1 for study variables). The date of diagnosis was retrieved from the patient medical record. The date of

death was retrieved from the medical record only if the patient had died in hospital. For all patients in this study the cause of death was gastric cancer.

Table 4.1: Demographic and clinical variables for the study.

Demographic variables	
Sex	**Residential-Province**
Male	Province No. 1
Female	Madhesh Pradesh
Age	Bagmati Pradesh
18 to < 50	Gandaki Pradesh
50 to < 65	Lumbini Pradesh
≥ 65	Karnali Pradesh
	Sudurpashchim Pradesh
Clinical variables	
Sign and Symptoms	**Tumour size**
Abdominal pain	<3 cm
Anorexia	3 to 6 cm
Nausea	>6 cm
Fatigue	Unknown
Weight loss	**Extent of cancer**
Heartburn	Localised
Black-coloured feces	Regional
Vomiting	Locally advanced
Anaemia	Distant metastases
Tumour location	Unknown
Distal (non-cardia cancer)	**Tumour stage**
Proximal (cardia cancer)	Stage I and II
Unknown	Stage III
Histologic type	Stage IV
Tubular adenocarcinoma	Unknown
Mucinous adenocarcinoma	**Treatment by surgery only**
Papillary adenocarcinoma	Partial radical gastrectomy
Poorly cohesive carcinoma	Total radical gastrectomy
Signet-ring cell carcinoma	Bypass surgery
Unknown	Palliative gastrectomy
Tumour grade	No surgery
Well-differentiated	**Treatment by chemotherapy only**
Moderately-differentiated	Yes
Poorly-differentiated	No
Un-differentiated	**Treatment by both radiotherapy and chemotherapy**
Unknown	Yes
	No

Note: Only one surgical procedure to remove or bypass the stomach will be performed.

Some signs and symptoms and some potential predictors variables were unknown. In Nepal, hospitals do not have electronic records systems to record the presence or absence of a

predetermined list of signs and symptoms. Only those signs and symptoms that were observed by the clinician or reported by the patient are included in the patient record. For this study where signs and symptoms were not included these may have either not been experienced or were not reported by the patients. Hospitals in Nepal do not have sufficiently modern equipment or expert oncologist to accurately determine the potential predictors for gastric cancer survival - tumour stage, extent of cancer, tumour grade, tumour locaiton and histology type. Only demographic and treatment outcome variables were included in the patient record and therefore had been included in this study. Those outcome variable that were not documented in the patient record have been coded as 'unknown'.

The gastric cancer patietns who were diagnosed at stage I were merged with the gastric cancer patientns who were diagnosed at stage II as only nine patients had been diagnosed at stage I.

4.2.2 Study procedure

Each BCH patient receives an individual Cancer Identity number (CID) (Nepal Cancer Relief Society 2021). The CID was used to link patient to the contact information for next of kin. If a date of death was recorded in the patient medical record, then this date was used. If no date of death was recorded in the medical records, we contacted the patients or their next of kin by telephone to determine the patients' vital status using contact information contained in the patient's records. The day, month and year of death was obtained for every patient that was included in this study. The vital status at the last known follow-up was recorded for each participant.

Data collectors were provided by the researcher with research training, via Zoom. The training included the scope and design of the project as well as the key issues related to data collection such as voluntary participation, confidentiality, and privacy of data. In addition, the researcher

will inform them about the aim, objectives and information regarding the study. Appendix 2 provides the details of the script for telephone conversation scenarios: (A) Patient answers the phone call (B) Someone else answers the phone, and not the patient (C) If the patient is unavailable to answer the phone. Appendix 3 provides the details of distress protocol. Data collectors called each patients a maximum of three times. If the patients did not answer the phone, the data collector contacted their next of kin to inquire about the survival status of the patient, with a maximum of three attempts at contact. Patients were considered to be lost to follow-up where either: their phone number was not recorded or if no response was obtained after three contact attempts with their next of kin. For patients who were lost to follow-up, the date of lost to follow-up was obtained from the patients' files based on their last presentation at BCH. The vital status of each patient was assessed between 1st January 2022 (starting date for data collection) to 15th February 2022 (study completion date) as dead, alive or lost to follow-up. The flowchart of the data collection procedure is presented in Figure 4.1.

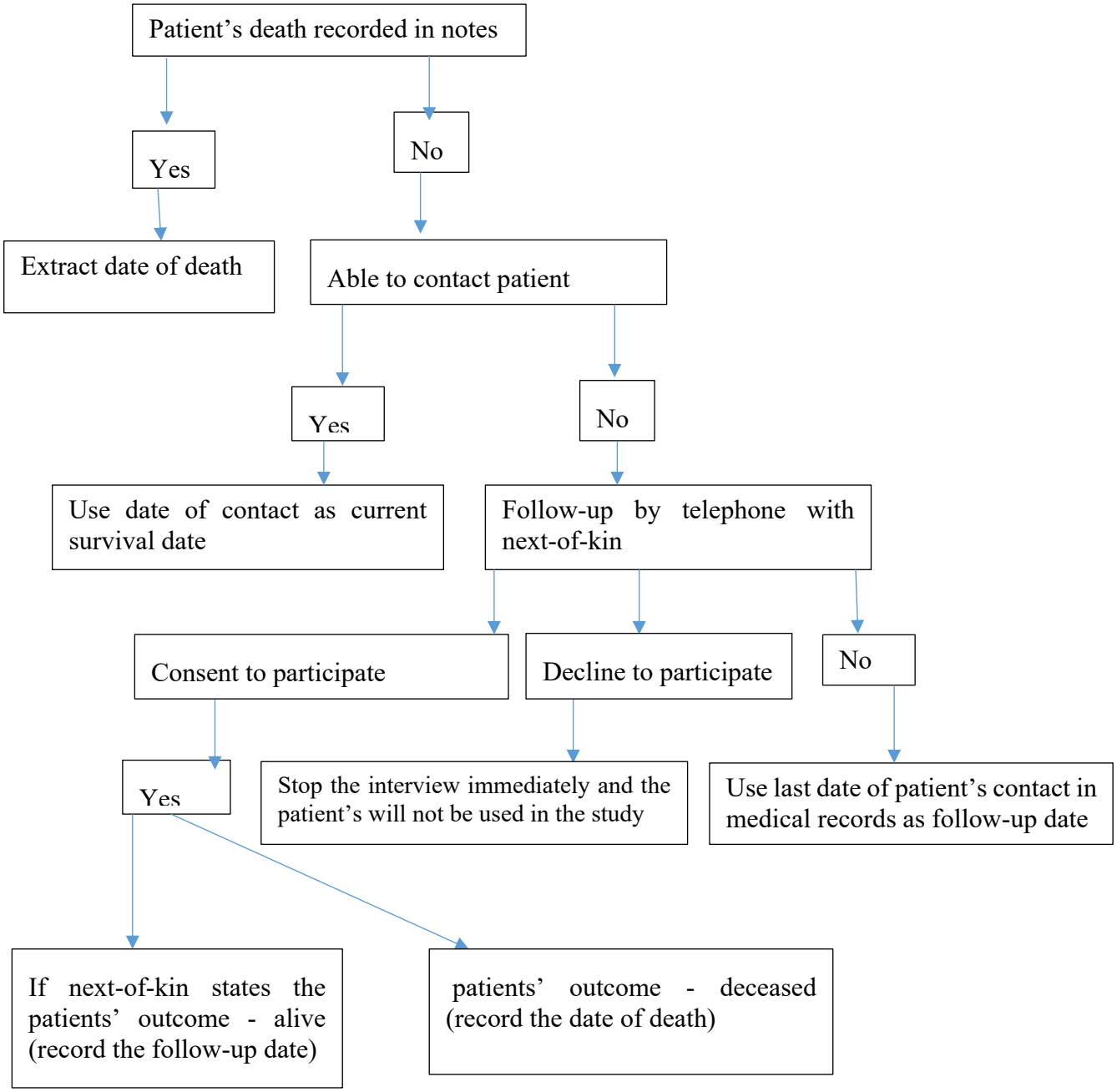


Figure 4.1: Flowchart for the data collection procedure.

4.3 Inclusion criteria

Adults (18 years of age or older) who met the eligibility criteria and were diagnosed with gastric cancer 1st January 2010 and 31st December 2021at BCH were included in the study. Only gastric adenocarcinoma confirmed histologically using the World Health Organization

classification (tubular adenocarcinomas, papillary adenocarcinomas, mucinous adenocarcinomas, signet-ring cell carcinomas, and poorly cohesive carcinomas) were eligible (Fritz et al. 2013).

4.4 Exclusion criteria

Patients with missing information on age, sex, residential address, date of diagnosis, method of diagnosis, or unknown histological findings were excluded from the study. Patients were also excluded if the next of kin declined to report to the data collectors if the patient was deceased or not deceased the patient status . Missing information was not confirmed with the next of kin prior to exclusion.

4.5 Data collection procedure

Three data collectors from the medical record department of BCH were recruited and trained by the researcher via Zoom or Skype on the scope and design of the project as well as key issues related to data collection such as confidentiality and privacy of data consistent with the National Statement on Ethical Conduct in Human Research, and National Health and Medical Research Council, Australia.

Using the data collection tool, data collectors transferred data securely via Qualtrics to UTS. The director of BCH acted as the local supervisor of this study to monitor the work of data collectors, audit collected data, and ensure the overall quality of the data collection. The researcher contacted the director of BCH and the data collectors at least two times a week to receive regular updates regarding the data collection and to enquire about potential issues. All electronic data was stored on the e-Research Storage, as specified in the research data management plan. Only the researchers had access to the research data.

4.6 Sample size calculation

The primary outcome for this research was the time since diagnosis to death, contact date with the data collectors or loss to follow-up. We calculated the survival time using the date of diagnosis and date of loss to follow-up, death, or date of contact with the data collectors, as appropriate.

The assumed parameters of this study were: power = 0.80, minimum hazard ratio (HR) to be detected = 1.5 or smaller for comparing various potential factors that may affect survival in which the two groups are equally sized. Based on these assumed parameters, this study would require 191 gastric cancer deaths. Given that there is a ~ 10% five-year survival rate from gastric cancer in similar settings (e.g., in India (Allemani et al. 2018), this research would then be able to include this number of participants in this study. The proposed study assumed minimum hazard ratio to be detected = 1.5 or smaller based on an earlier studies conducted between February 2003 and January 2007 in India (Pourhoseingholi et al. 2009).

The initial power calculation determined that a sample size of 191 gastric cancer deaths was required to undertake a survival analysis. Over a 10-year period, there were 951 cases of gastric cancer recorded at Bhaktapur Cancer Hospital. Following application of exclusion criteria, 817 participants eligible for inclusion in the study, which was sufficient for a survival analysis.

The sample size was calculated using statistical software STATA (StataCorp 2017). Based on the annual report of BCH, the estimated number of newly diagnosed gastric cancer cases were 951 between 1st January 2010 and 31st December 2021.

4.7 Statistical analysis

Demographic, clinical and pathological predictors of survival are described using frequencies and percentages. The survival rate and median survival[15] was estimated using the Kaplan-Meier method (Kaplan & Meier 1958). The Kaplan-Meier method estimate the survival over time (Kirkwood & Sterne 2003). For each time interval, the survival probability is calculated as the number of subjects surviving divided by the number of patients at risk. An advantage of the Kaplan-Meier curve is that the method can take into account some types of censored data, particularly right-censoring, which occurs if a patient withdraws from a study, is lost to follow-up, or is alive without event occurrence at last follow-up. A limitation of the Kaplan-Meier method is that the log-rank test is purely a significance test and cannot provide an estimate of the size of the difference between the groups and its related confidence interval. Another limitation of the Kaplan-Meier method is that it only provides unadjusted mortality (and survival) probabilities. In contrast to the Kaplan-Meier method, Cox regression model can provide an effect estimate by quantifying the difference in survival between patient groups and can adjust for confounding effects of other variables (Kalbfleisch & Prentice 1980; Kirkwood & Sterne 2003). The advantage of cox regression model is that one can adjust the association of interest for potential confounders. A limitation of Cox regression model is that in the event of violation of the proportionality of hazard assumption, the use of a simple Cox regression model is incorrect. Treating variables that strengthen as a hazard factor changes and/or

[15] The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that half of the patients in a group of patients diagnosed with the disease are still alive (National Cancer Institute 2023).

disappear during follow-up as constant, significant risk factors of death, may result in a false inference (Kalbfleisch & Prentice 1980; Kirkwood & Sterne 2003).

Stage at diagnosis was adjusted to determine the survival by treatment including surgery, chemotherapy and radiotherapy chemotherapy. Differences in the survival rate by different characteristics using the log-rank test, and, where crude differences were deemed statistically significant, the variable was then included in the multivariable analysis (Kalbfleisch & Prentice 1980). Variables that met certain threshold in univariable models using log-rank tests (p-value < 0.25) as covariates to fit the multivariable Cox regression model; variables showing statistical significance (determined at $p < 0.05$) in multivariable Cox regression analysis were considered as significant predictors associated with survival of gastric cancer patients. Global p values for results are based on Wald statistics. Survival was analysed through a multivariable model that followed a backwards-stepwise approach and included only significant predictors. This efficient analysis limited the number of predictors and reduce the risk of overfitting by removing the least important variables early in the model and leaving the most important variables to determine predictors of survival (Kalbfleisch & Prentice 1980). All analysis was conducted using the StataBE version 17 (StataCorp 2017). Stata syntax for survival curves of this study is attached in appendix 6.

4.8 Ethical approval

Ethical approval was first obtained from the University of Technology Sydney Medical Research Ethics Committee (UTS MREC) (approval number ETH21-6718), and then obtained from the Nepal Health Research Council (NHRC) prior to collection any data. Approval from the BCH was recently obtained and UTS MREC was obtained as per relevant protocols. A

waiver of consent was granted as the vast majority of information for this study was extracted from medical records.

A waiver of consent was granted by the ethics committee for patients who provided data by telephone. A waiver for patient consent is possible if the patient answered the telephone, as there was a valid assumption that the patient was surviving at the time of the telephone call. Therefore, no consent was required to obtain this information. However, if the patient did not answer the telephone and the next of kin did answer the telephone than an oral consent to participate in the study was obtained from the next of kin to determine the vital status of the patient. These processes including the script for telephone conversation between data collectors and participants can be found in appendix 2. Additionally, the distress protocol of this study is attached in appendix 3.

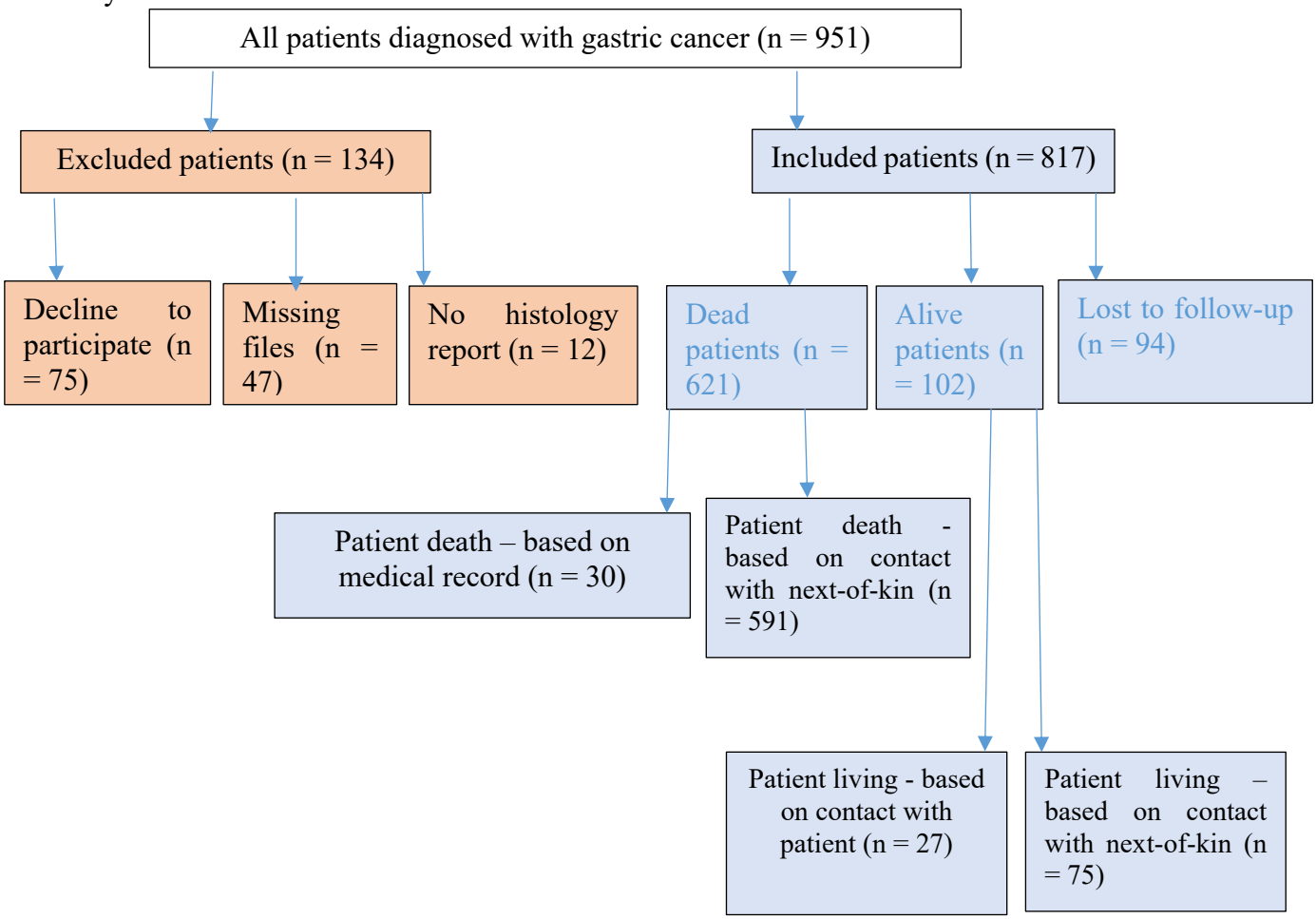
Chapter 5 Results

This chapter reports characteristics of patients diagnosed between 1 January 2010 and 31 December 2021 at Bhaktapur Cancer Hospital (BCH), their survival, and factors associated with survival.

5.1 Patient characteristics

There were 951 patients newly diagnosed with gastric cancer at BCH between 1 January 2010 and 31 December 2021. Data for 134 patients were unavailable as either patients declined to participate (n = 75). As some patients would have relocated to another country for treatment, and as there is no electronic record system in this hospital, the patient would be required to remove their physical medical record; this was the case for forty-seven persons why were censored as a result or patients for whom there was no histology report available in their medical record (n = 12) (see figure 4.1 for flowchart of data collection procedure and figure 5.1 for inclusion and exclusion criteria). The remaining 817 participants with data available to determine vital status, after some participants were lost to follow up. Figure 5.1 shows the vital status at the time of data collection; 621 patients had died, of whom 591 were confirmed through next-of-kin and 30 were based on medical records. A total of 102 patients were still alive at the time of data collection, of whom 75 were confirmed through their next-of-kin and 27 by the patients themselves. Between 1st January and 15 February 2022, 94 (11%) gastric cancer patients were lost to follow-up as either no phone number was recorded, or no response was obtained after three contact attempts by trained data collectors.

Figure 5.1: Flowchart showing inclusion and exclusion of gastric cancer patients in the analyses.



In the final sample included for data analyses, there were more men (n = 520, 63.6%) than women (n = 297, 36.4%). Based on age at diagnosis 22 percent of participants were in the 18 to < 50 age group (n = 179), 46.5% were in the 50 to < 65 age group (n = 377) and 31.5% were in the ≥65 aged group (n = 261). Based on residential province, participants were from Baghmati Pradesh (n = 443, 54.3%), Province 1 (n = 142, 17.4%), Gandaki Pradesh (n = 83, 10.2%) and Madhesh Pradesh (n = 74, 9.0%), respectively. The most common sign and symptoms recorded for participants were abdominal pain (n = 787, 95.9%), anorexia (n = 687, 84%), nausea (n = 618, 76%) and fatigue (n = 602, 73.7%). Table 5.1 shows the presence or absence/unknown of these common signs and symptoms for all patients. For those who met exclusion criteria there was no baseline data collected, therefore no comparison in their characteristics was able to be determined.

Table 5.1: Demographic data and signs and symptoms for gastric cancer patients diagnosed between 1st January 2010 and 31st December 2021 at BCH, Nepal.

Variables	Frequency	Percent (%)
Sex		
Male	520	63.6
Female	297	36.4
Age		
18 to < 50	179	22.0
50 to < 65	377	46.5
≥ 65	261	31.5
Residential Province		
Province No. 1	142	17.4
Madhesh Pradesh	74	9.0
Bagmati Pradesh	443	54.3
Gandaki Pradesh	83	10.2
Lumbini Pradesh	35	4.2
Karnali Pradesh	22	2.7
Sudurpashchim Pradesh	18	2.2
Signs and Symptoms		
Abdominal pain	787	95.9
Anorexia	687	84.0
Nausea	618	76.0
Fatigue	602	73.7
Weight loss	537	65.7
Heartburn	366	44.8
Black-coloured faeces	312	38.3
Vomiting	292	35.8
Anaemia	257	31.6

Note: Where signs/symptoms were not included these may have either not been experienced or were not reported by the patient. Following data on signs and symptoms for patients with gastric cancer were missing: 4.1% abdominal pain, 16.0% anorexia, 24.0% nausea, 26.3% fatigue, 34.3% weight loss, 55.2% heartburn, 61.7% black-coloured faeces, 64.2% vomiting and 68.4% anaemia.

Patient data were available for analysis by survival based on the following variables Table 5.2): tumour location (796), histologic type (714), tumour grade (772), tumour size (773), extent of

cancer (781), tumour stage (776), treatment by surgery (817), treatment by chemotherapy (817), treatment by radiotherapy chemotherapy (817).

Table 5.2: Potential factors affecting the survival of gastric cancer patients diagnosed between 1st January 2010 and 31st December 2021 at BCH, Nepal.

Variables	Frequency	Percent (%)
Tumour location		
Distal (non-cardia cancer)	666	81.5
Proximal (cardia cancer)	130	16.0
Unknown	21	2.5
Histologic type		
Tubular adenocarcinoma	336	41.1
Mucinous adenocarcinoma	146	18.0
Papillary adenocarcinoma	16	1.9
Poorly cohesive carcinoma	34	4.2
Signet-ring cell carcinoma	182	22.3
Unknown	103	12.5
Tumour grade		
Well-differentiated	68	8.3
Moderately-differentiated	342	41.9
Poorly-differentiated	309	37.8
Un-differentiated	53	6.5
Unknown	45	5.5
Tumour size		
<3 cm	155	18.9
3 to 6 cm	266	32.6
>6 cm	352	43.1
Unknown	44	5.4
Extent of cancer		
Localised	19	2.3
Regional	133	16.3
Locally advanced	355	43.4
Distant metastases	274	33.6
Unknown	36	4.4
Tumour stage		
Stage I and II	145	17.8
Stage III	356	43.6
Stage IV	275	33.6
Unknown	41	5.0
Treatment by surgery		
Partial radical gastrectomy	348	42.6
Total radical gastrectomy	76	9.3
Bypass surgery	62	7.6
Palliative gastrectomy	153	18.7
No surgery	178	21.8
Treatment by chemotherapy		
Yes	726	88.8

No	91	11.2
Treatment by radiotherapy chemotherapy		
Yes	148	18.0
No	669	82.0

5.2 Survival of Gastric Cancer

The median overall survival for gastric cancer patients was 19 months (month is defined as 30 days) since diagnosis. The total person-time of follow-up was 17,808 months. The survival rate was 70% at one year, 37% at two years, 23% at three years, 18% at four years, and 12% at five years (see Figure 5.2).

Male gastric cancer patients had a significantly lower median survival of 17 months (95% CI: 15.7 to 18.4) since diagnosis compared with female patients' survival of 22 months (95% CI: 20.3 to 23.9, P <0.001) since diagnosis. Survival was also dependent on age at diagnosis; a significantly lower median survival (10 months, $P < 0.001$) was determined for those aged greater or equal to 65 years, compared with 30 months for those aged between 18 and 50 years. Based on the IARC (WHO) classifications, both extent of cancer and of tumour stage are included in order to provide a comprehensive description of survival (DeVita, Lawrence & Rosenberg 2016).'The extent of the cancer was linked with survival rate; patients with distant gastric cancer metastases had significantly lower median survival (71 months, $P < 0.001$), compared with localise cancer (see Table 5.3). Staging was associated with survival rate; patients diagnosed with stage IV gastric cancer had significantly lower median survival (13 months) compared with stage I and II (67 months, $P < 0.001$). Treatment was also related to survival rate; patients who did not receive any surgery had significantly lower median survival (9 months) compared with patients who had partial radical gastrectomy (30 months, $P < 0.001$). Bypass surgery and palliative gastrectomy had significantly lower median survival (10 and 15

months respectively) compared with partial-radical gastrectomy (30 months, $P < 0.001$) and total gastrectomy (30 months, $P < 0.001$). Patients who did not receive treatment by chemotherapy had significantly lower median survival (7 months) compared with patients who did receive chemotherapy (21 months, $P < 0.001$). Patients who did not receive radiotherapy had significantly lower median survival (17 months) compared with those who did receive radiotherapy (26 months, $P < 0.005$).

Table 5.3: Covariates and median survival time since diagnosis (months) of gastric cancer patients diagnosed between 1st January 2010 and 31st December 2021 at BCH, Nepal.

Variables	Median survival time (months)	95% CI	p value (Log-rank)
Sex			0.001
Male	17	15.7 to 18.4	
Female	22	20.3 to 23.9	
Age (years)			<0.001
18 to <50	30	26.3 to 33.6	
50 to <65	21	19.3 to 22.6	
≥ 65	10	9.1 to 10.8	
Tumour location			0.25
Distal cancer	19	17.4 to 20.5	
Proximal cancer	18	13.9 to 22.1	
Histologic type			0.79
Tubular adenocarcinoma	18	15.9 to 20.0	
Mucinous adenocarcinoma	20	16.6 to 23.3	
Papillary adenocarcinoma	23	10.7 to 35.2	
Poorly-cohesive carcinoma	19	12.9 to 25.0	
Signet-ring-cell carcinoma	18	15.5 to 20.4	
Tumour grade			0.44
Well-differentiated	21	16.2 to 25.8	
Moderately-differentiated	19	16.9 to 21.1	
Poorly-differentiated	17	14.9 to 19.1	
Un-differentiated	17	13.4 to 20.5	
Tumour size			0.85
<3 cm	18	14.2 to 21.7	
3 to 6 com	18	15.5 to 20.4	
>6 cm	19	16.9 to 21.1	
Extent of cancer			<0.001
Localised	71	55.9 to 86.1	
Regional	63	52.9 to 73.1	
Locally advanced	22	20.6 to 23.9	

Distant metastases	11	10.0 to 12.1	
Tumour stage			<0.001
Stage I and II	67	59.1 to 74.8	
Stage III	22	20.5 to 23.4	
Stage IV	13	11.5 to 14.4	
Treatment-by surgery			<0.001
Partial-radical gastrectomy	30	26.9 to 33.1	
Total-radical gastrectomy	30	22.9 to 37.0	
Bypass surgery	10	8.5 to 11.4	
Palliative gastrectomy	15	13.8 to 16.1	
No surgery	9	8.1 to 9.8	
Treatment by chemotherapy			<0.001
Yes	21	19.3 to 22.6	
No	7	5.9 to 8.1	
Treatment by radiotherapy chemotherapy			0.005
Yes	26	22.5 to 29.4	
No	17	15.5 to 18.4	

Figure 5.2 shows the overall survival rate. Figures 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 and 5.10 show survival rate and potential predictors for survival including sex, age, tumour location, extent of cancer, stage at diagnosis, treatment by surgery, treatment by chemotherapy and treatment by radiotherapy-chemotherapy). Potential predictors except sex and extent of cancer, histologic type, tumour grade, tumour subtype were not significant in the univariable analysis. However, in multivariable analysis, there were no associations between mortality and these variables (sex and extent of cancer).

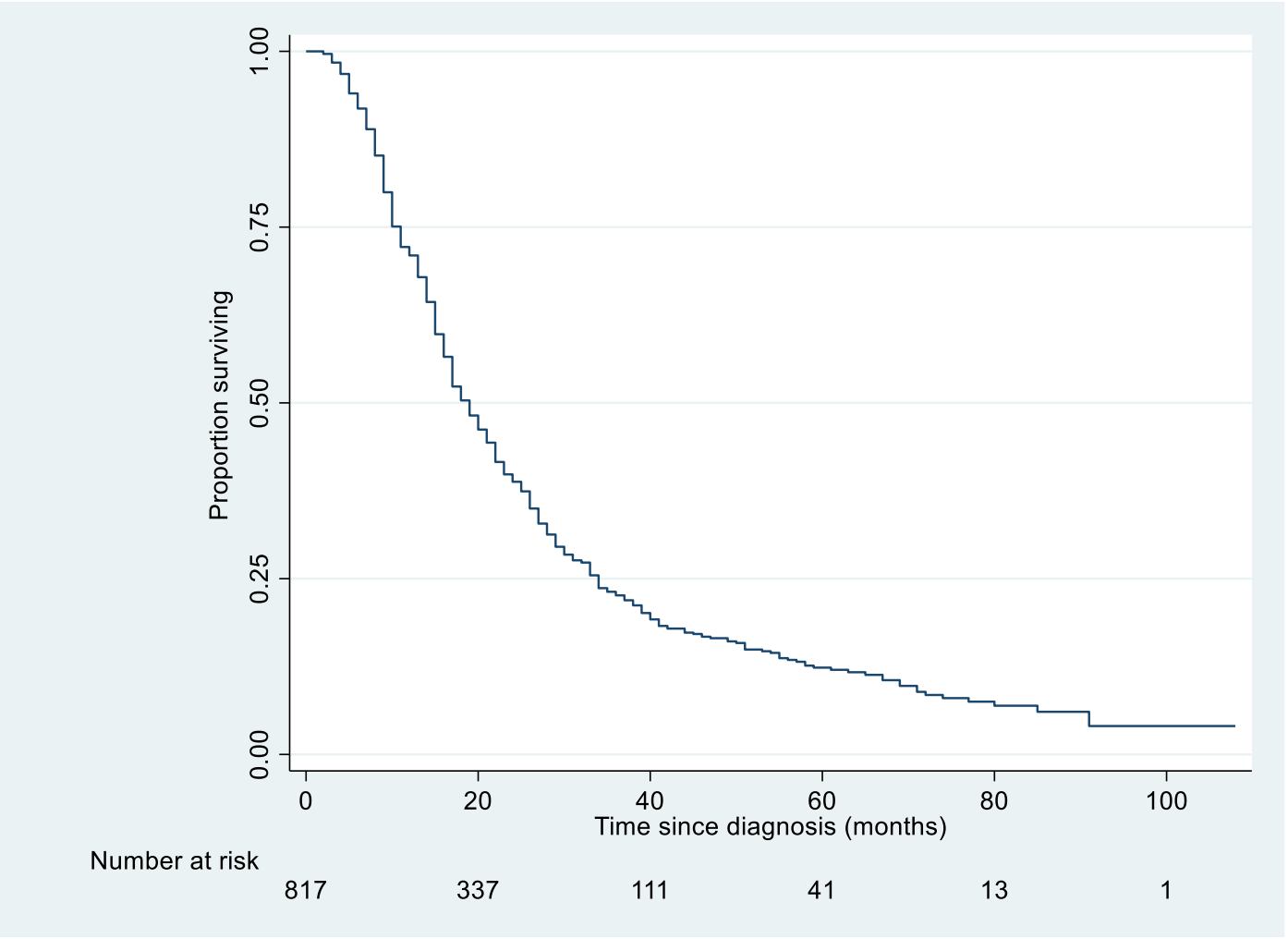


Figure 5.2: Overall survival rate of patients with gastric cancer diagnosed at BCH between 1 January 2010 and 31 December 2021.

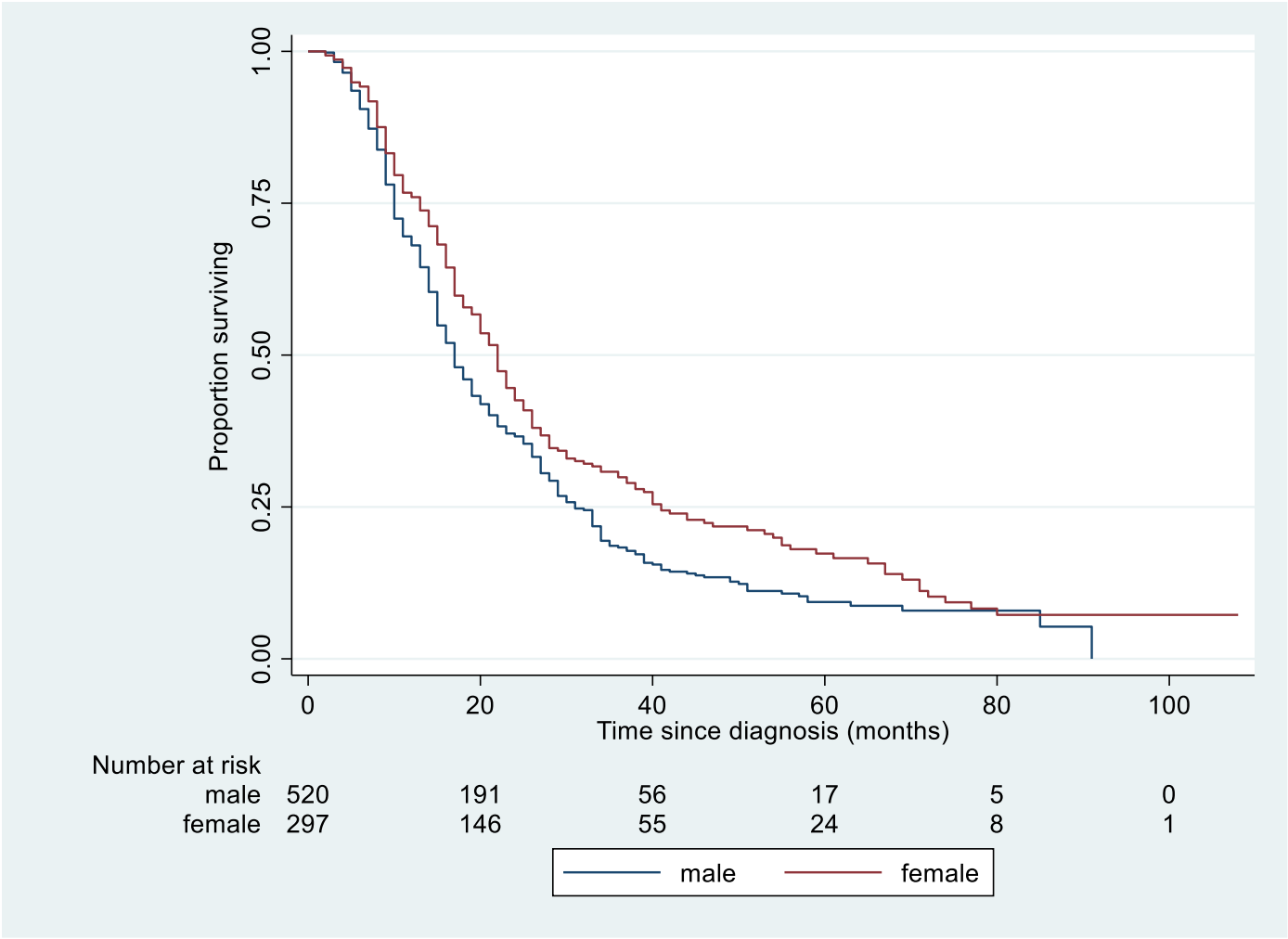


Figure 5.3: Survival from gastric cancer by sex at Bhaktapur Cancer Hospital.

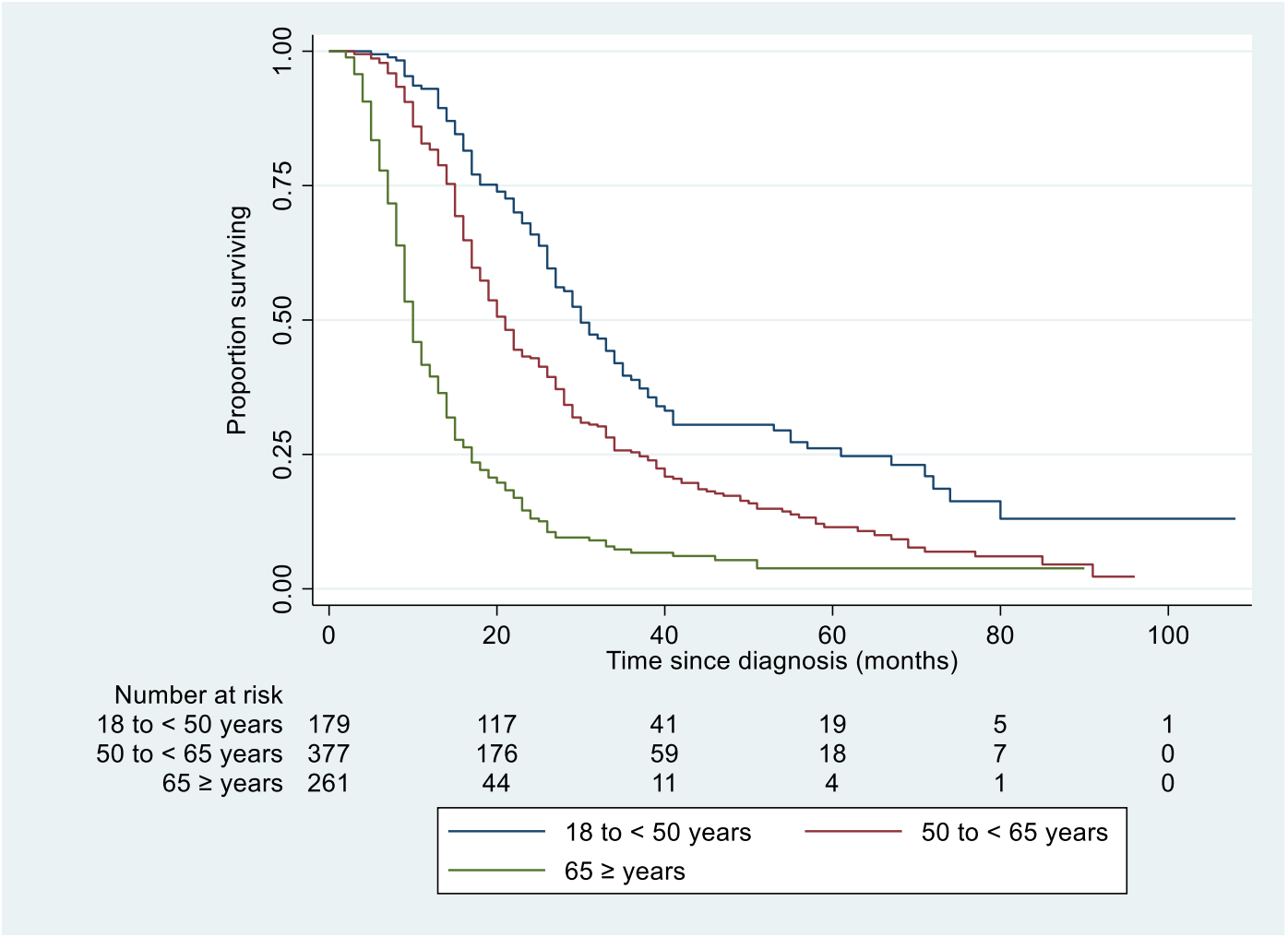


Figure 5.4: Survival from gastric cancer by age group at Bhaktapur Cancer Hospital. The median overall survival for gastric cancer patients in the age group 18 to <50 years was higher (30 months) compared to the age group 50 to <65 years (median overall survival 20 months) and age group ≥65 years (median overall survival 10 months).

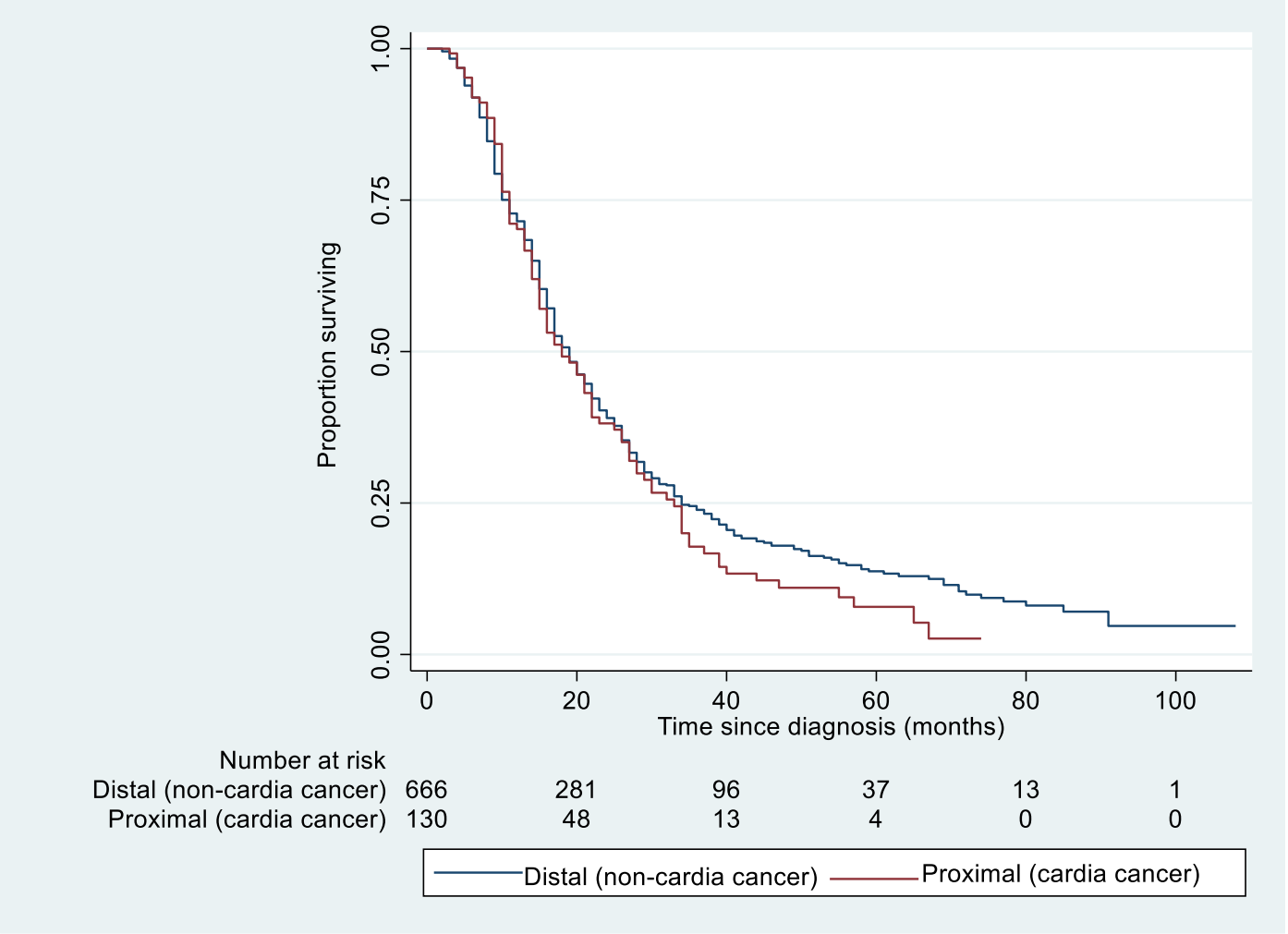


Figure 5.5: Survival from gastric cancer by tumour location at Bhaktapur Cancer Hospital.

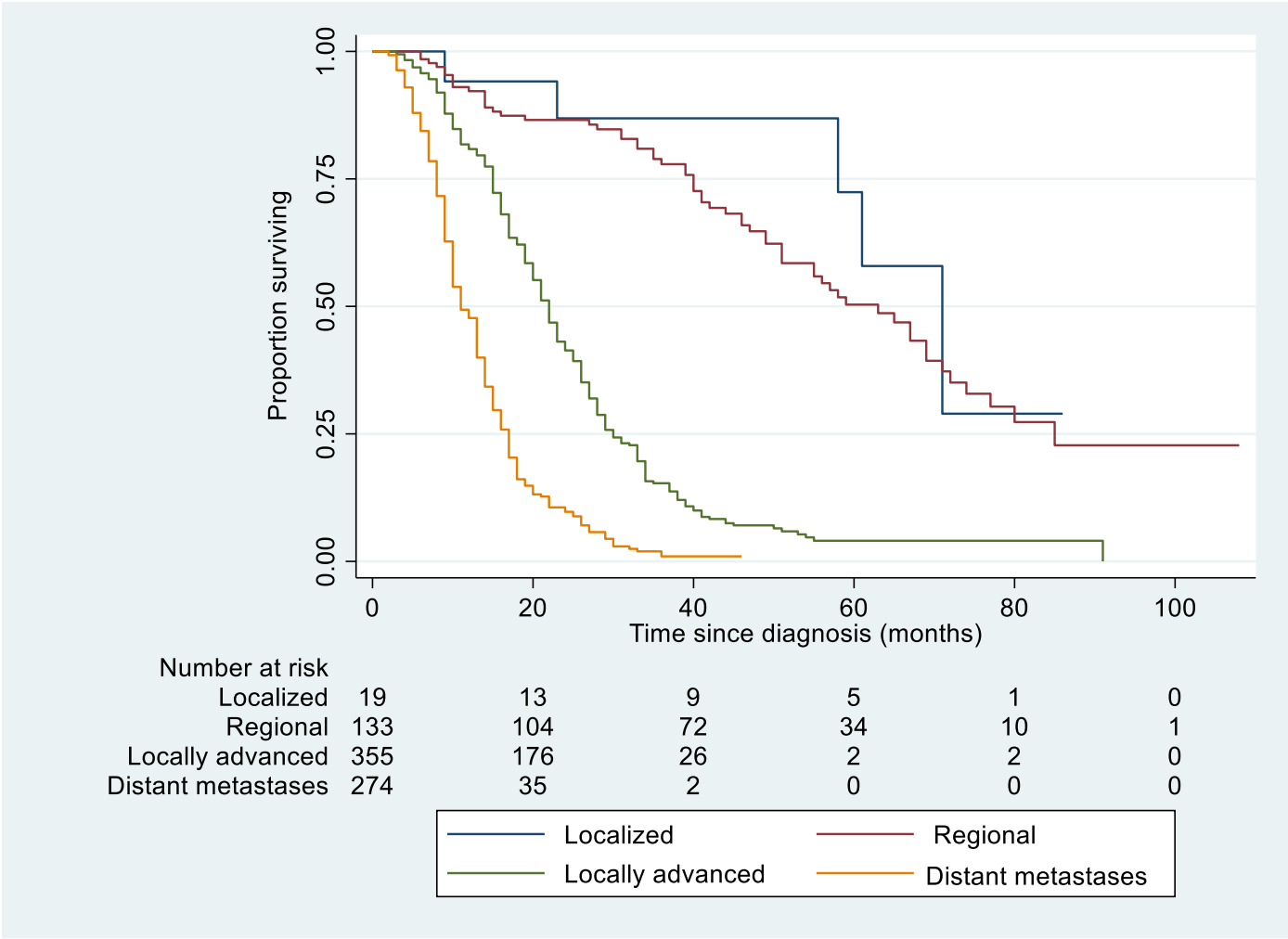


Figure 5.6: Survival from gastric cancer by extent of cancer at Bhaktapur Cancer Hospital.

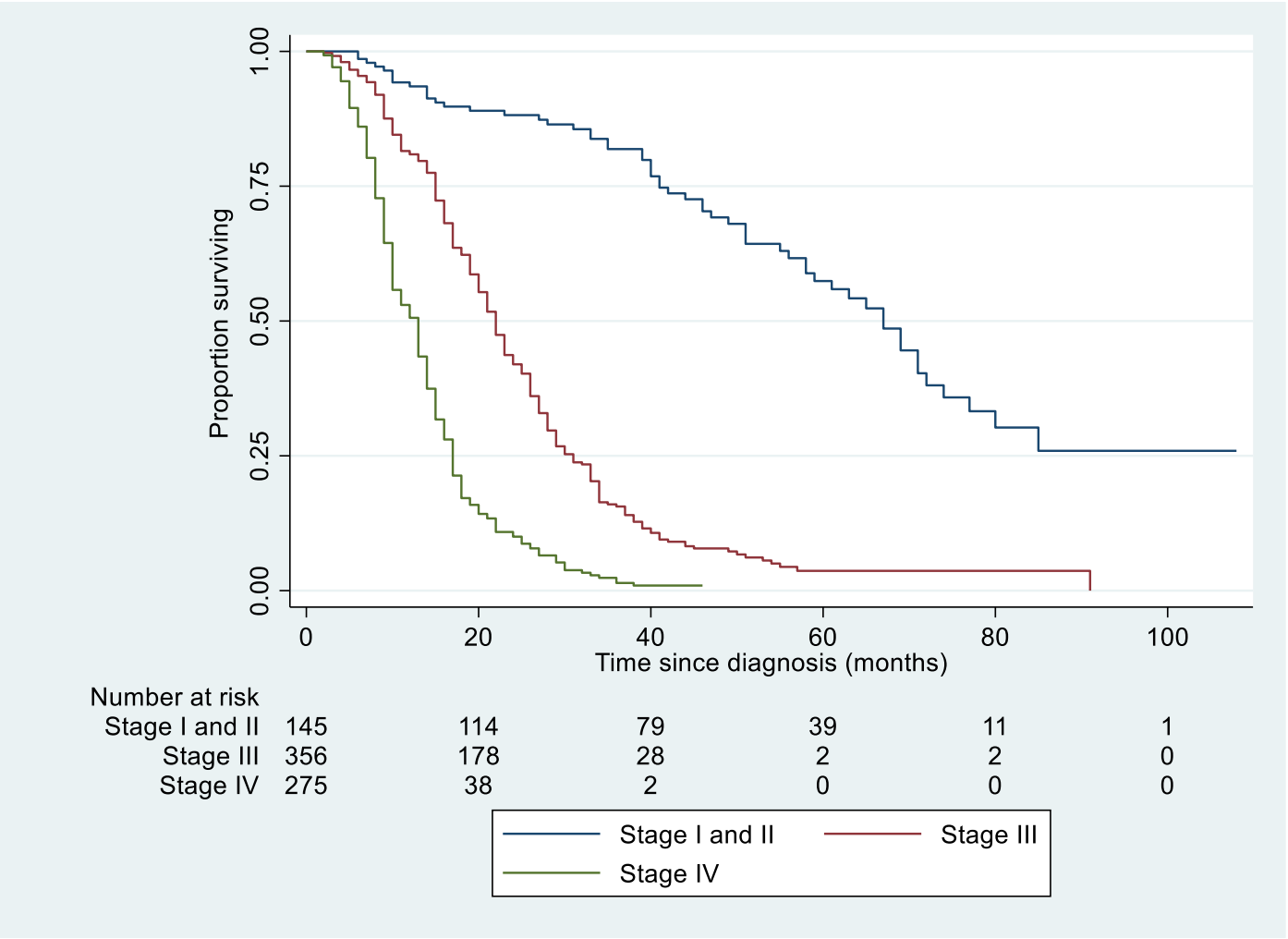


Figure 5.7: Survival from gastric cancer by stage at diagnosis at Bhaktapur Cancer Hospital.

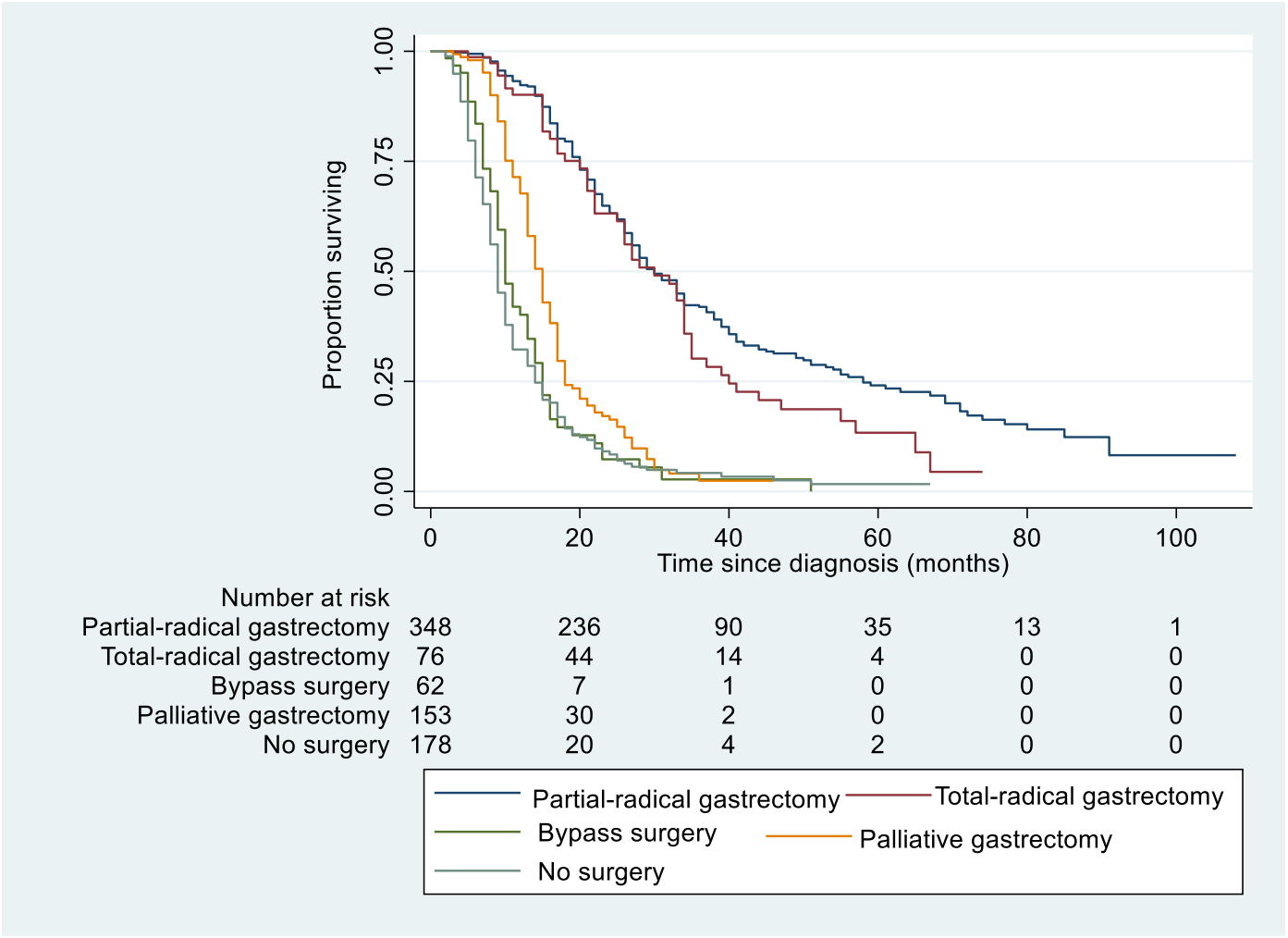


Figure 5.8: Survival of gastric cancer patients' treatment by surgery and no-surgery at Bhaktapur Cancer Hospital.

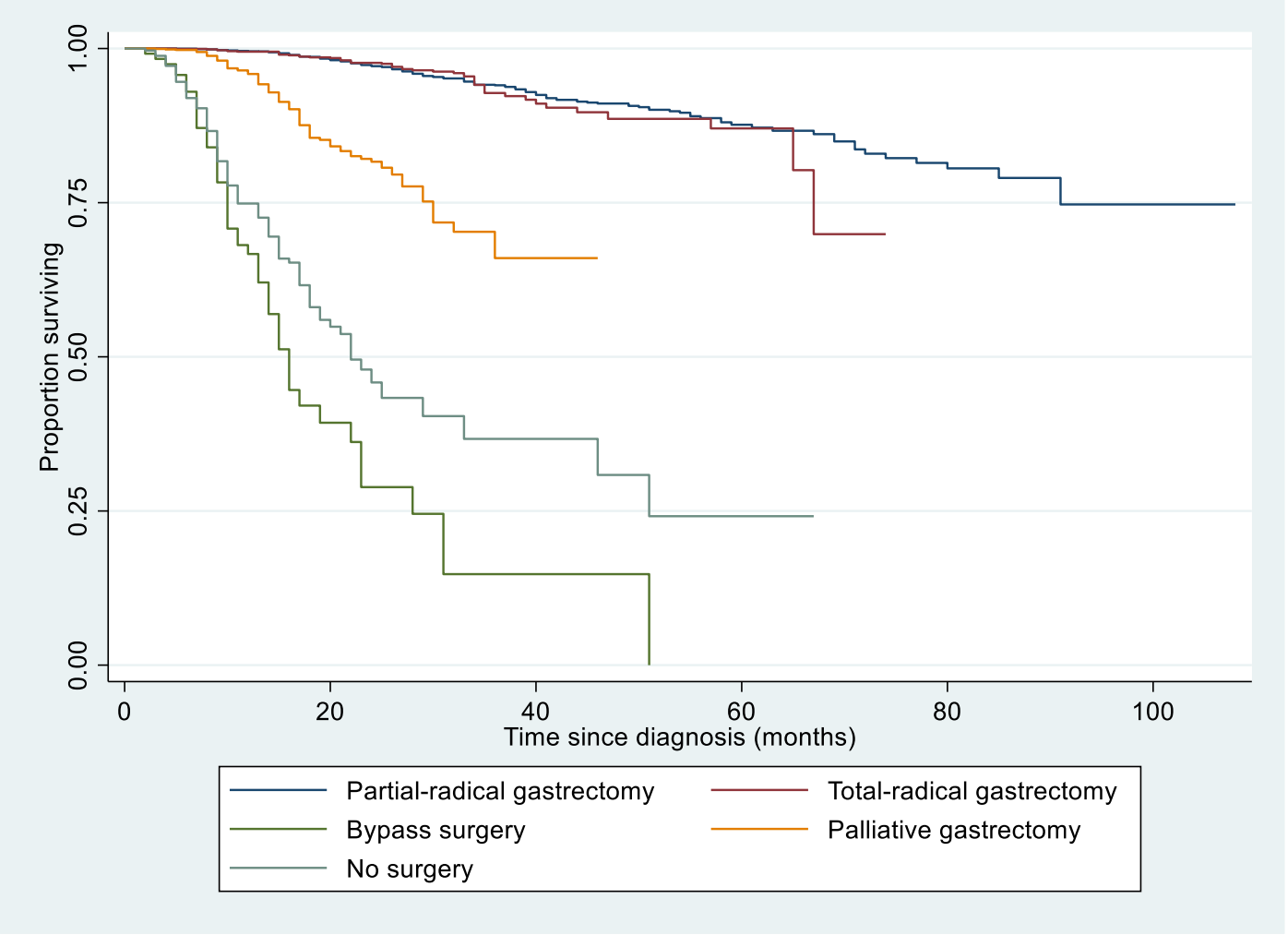


Figure 5.8.1: Survival of gastric cancer patients' treatment by surgery and no-surgery (adjusted for stage at diagnosis).

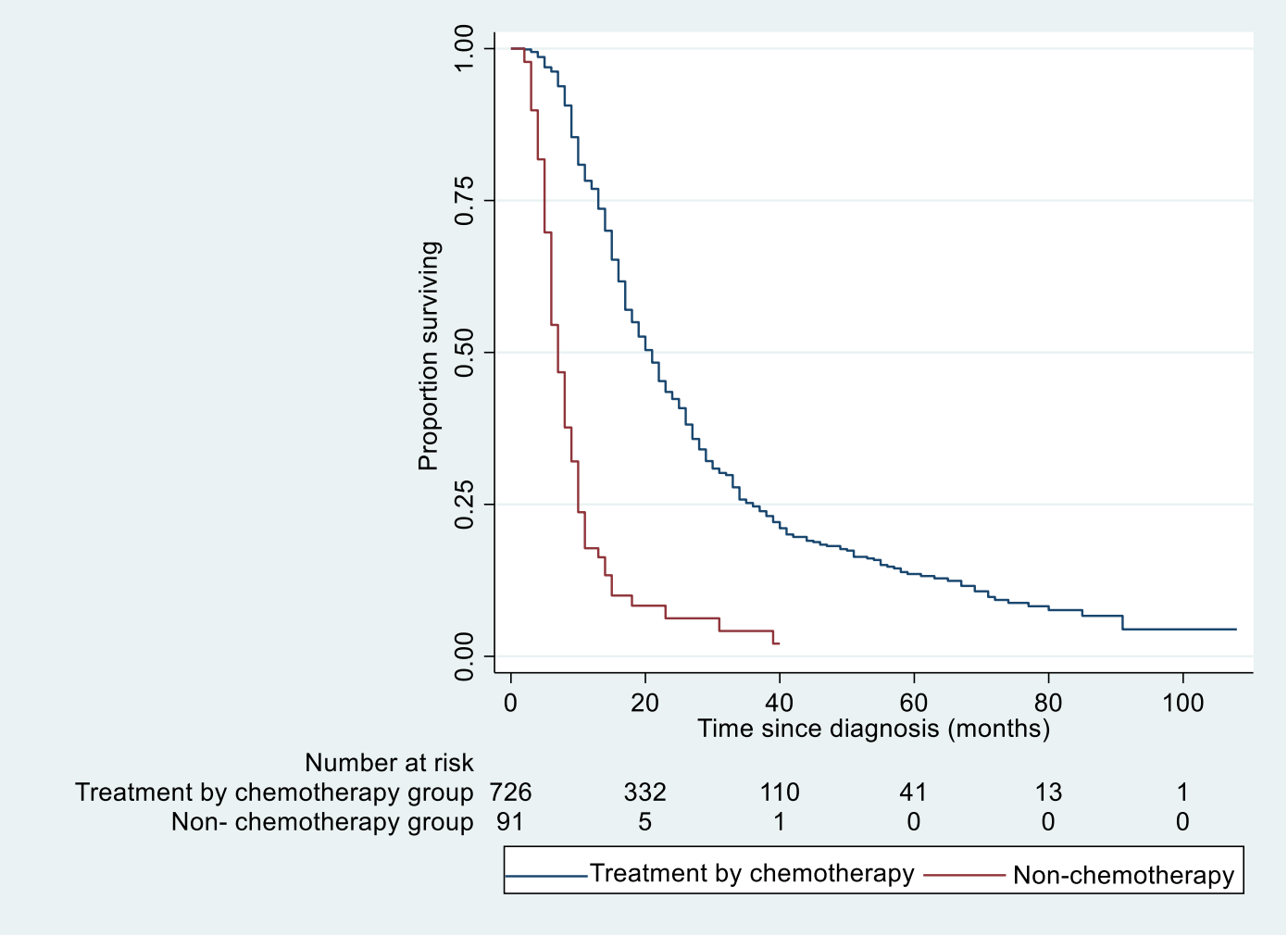


Figure 5.9: Survival of gastric cancer patients' treatment by chemotherapy and non-chemotherapy at Bhaktapur Cancer Hospital.

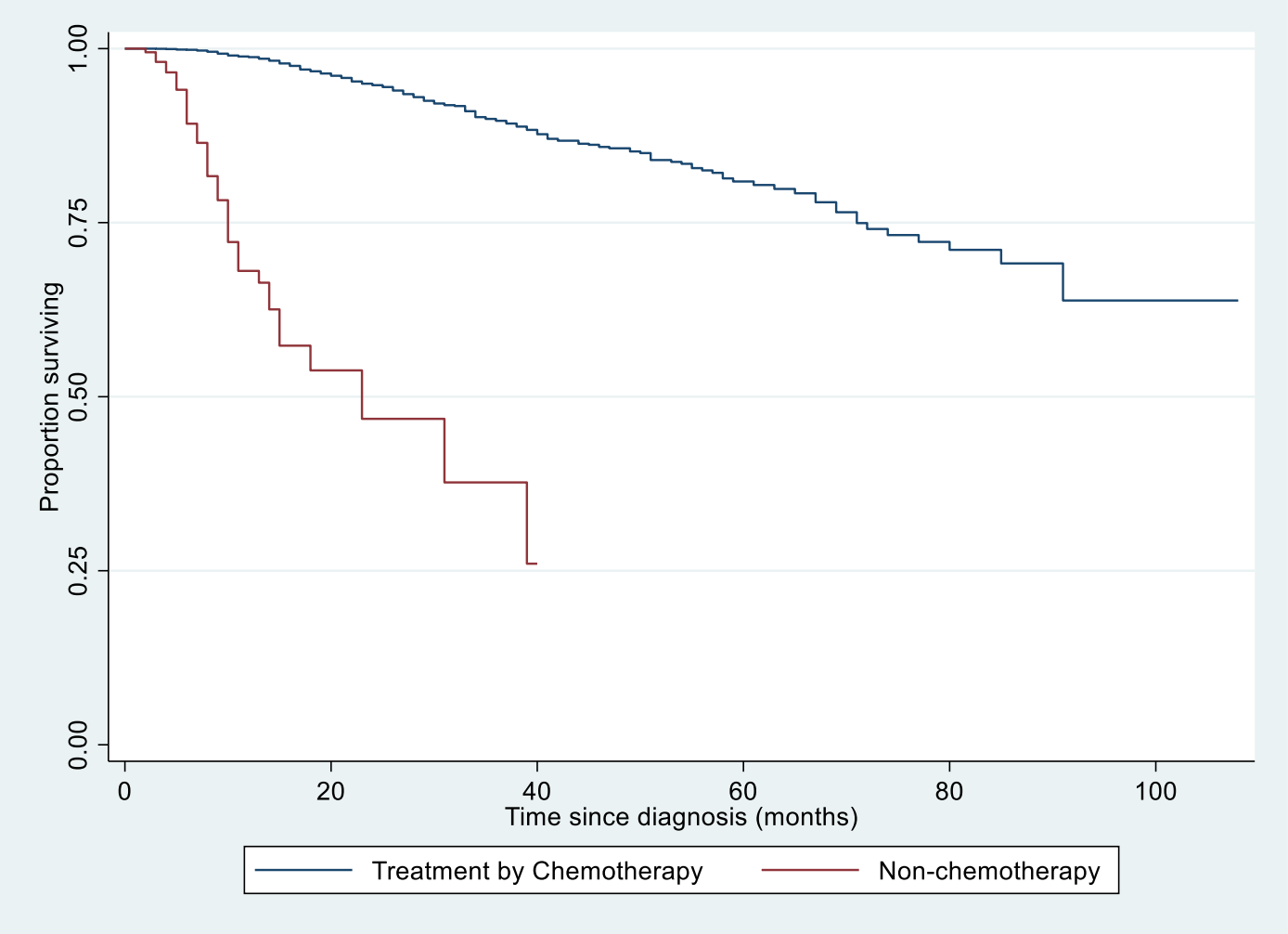


Figure 5.9.1: Survival of gastric cancer patients' treatment by chemotherapy and non-chemotherapy at Bhaktapur Cancer Hospital (adjusted for stage at diagnosis).

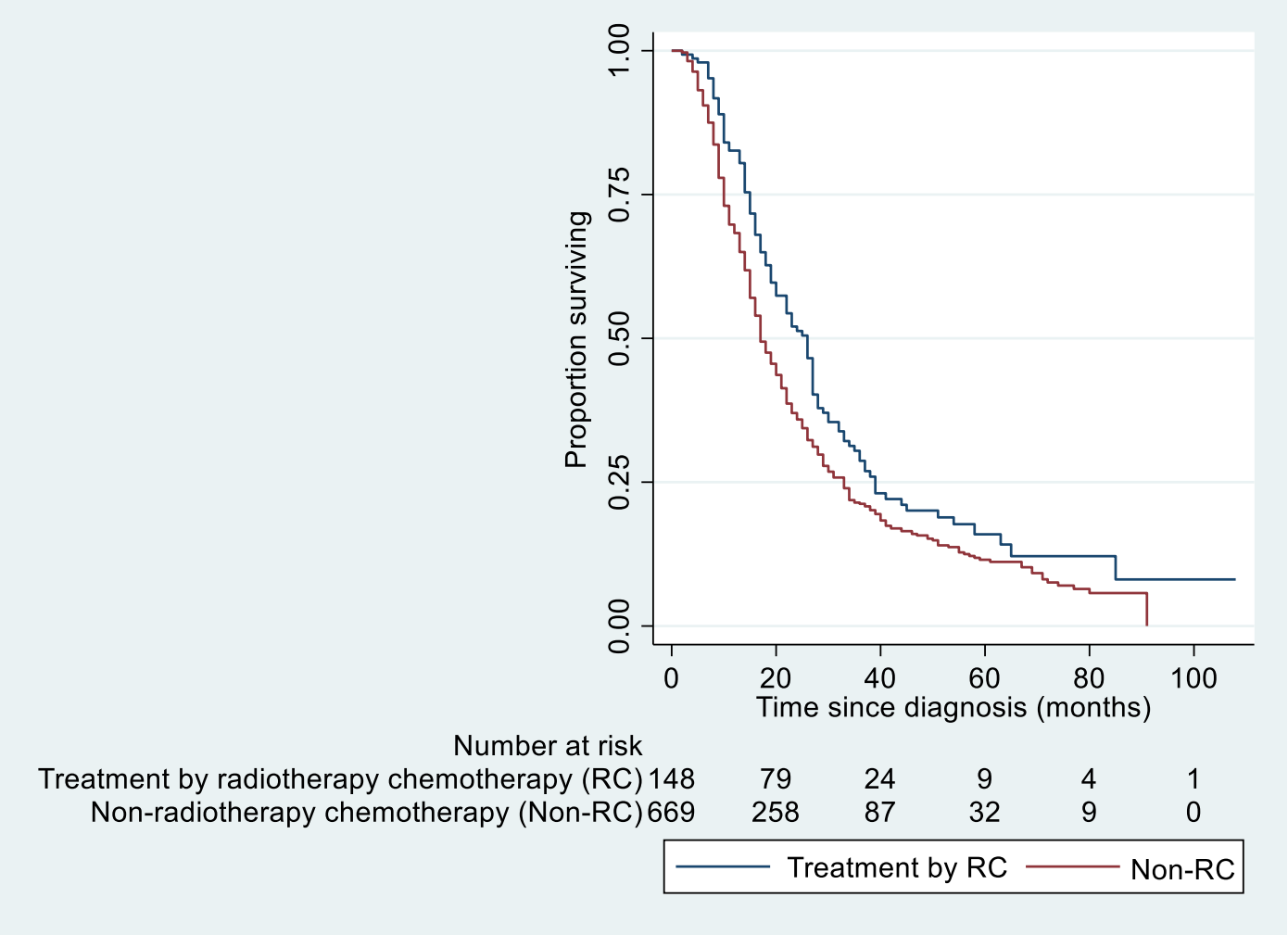


Figure 5.10: Survival of gastric cancer patients' treatment by radiotherapy chemotherapy (RC) and non- radiotherapy chemotherapy (Non-RC).

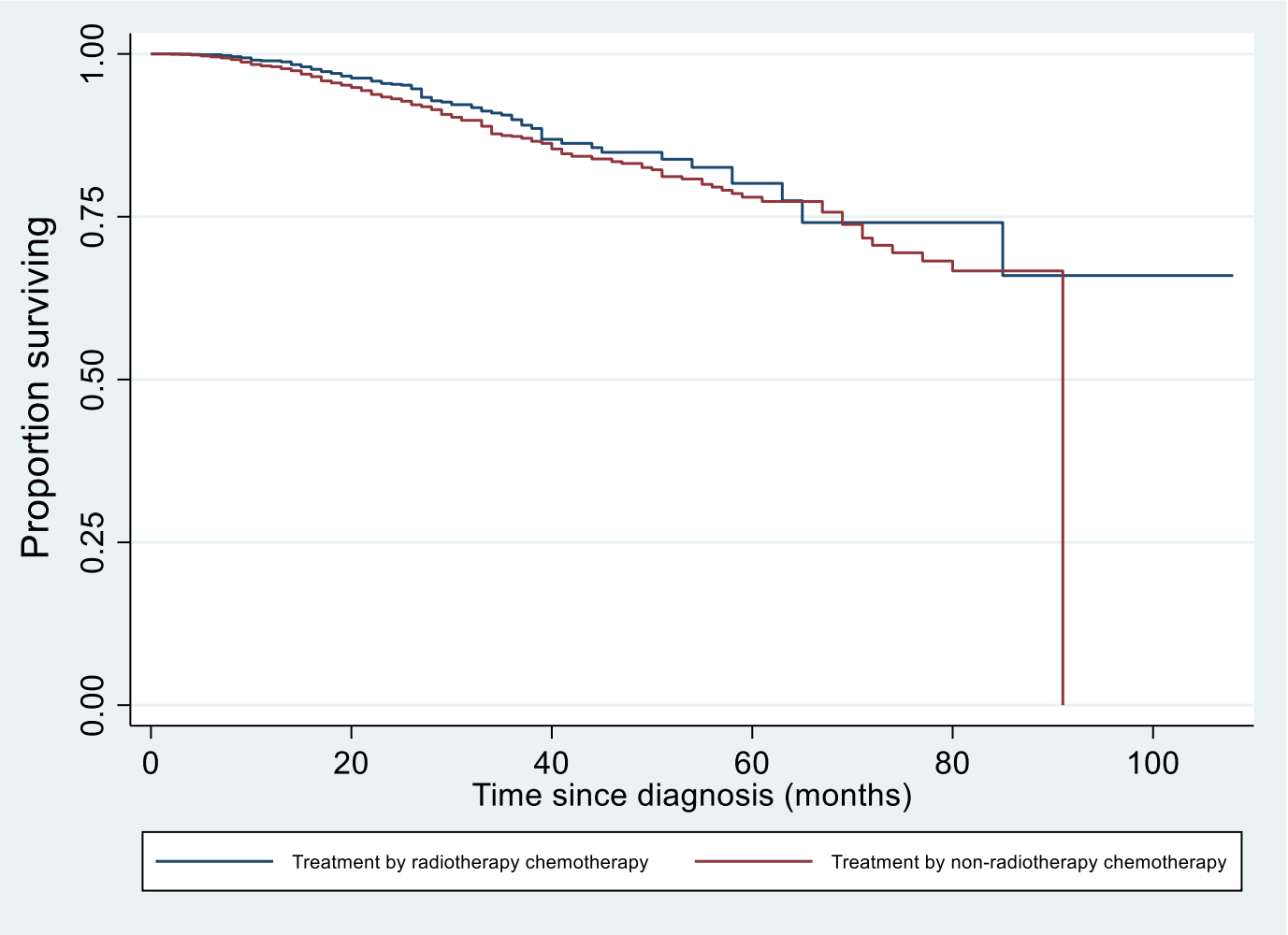


Figure 5.10.1: Survival of gastric cancer patients' treatment by radiotherapy chemotherapy and non- radiotherapy chemotherapy (adjusted for stage at diagnosis).

5.3 Factors associated with mortality of gastric cancer in Cox regression univariable analysis

Variables included were sex, age, tumour location, extent of cancer, stage at diagnosis, treatment by surgery, treatment by chemotherapy, treatment by radiotherapy and chemotherapy were used in Cox regression univariable analysis to fit in Cox regression multivariable analysis.

Table 5.4: Univariable analysis of factors associated with mortality of gastric cancer diagnosed at BCH.

Variables	Hazard ratio (HR)	95% CI	P value
Sex			0.002
Male	Reference		
Female	0.77	0.6 to 0.9	
Age (per 5-year increase)	1.26	1.2 to 1.3	<0.001
Tumour locations			0.26
Distal cancer	Reference		
Proximal cancer	1.13	0.9 to 1.4	
Extent of cancer			<0.001
Localised	Reference		
Regional	1.55	0.6 to 3.8	
Locally advanced	7.67	3.1 to 18.7	
Distant metastases	21.39	8.7 to 52.5	
Tumour stage			<0.001
Stage I and II	Reference		
Stage III	5.72	4.2 to 7.7	
Stage IV	15.36	11.71 to 21.30	
Treatment-by surgery			<0.001
Partial radical gastrectomy	Reference		
Total radical gastrectomy	1.27	0.9 to 1.7	
Bypass surgery	5.48	4.4 to 7.4	
Palliative gastrectomy	3.58	2.8 to 4.5	
No surgery	5.83	4.7 to 7.2	
Treatment-by chemotherapy			<0.001
Yes	Reference		
No	4.85	3.7 to 6.2	
Treatment-by radiotherapy chemotherapy			0.004
Yes	Reference		
No	1.34	1.1 to 1.7	

Note: Age at diagnosis of all patients (n = 817) were dividied by 5 to report per five year increase in the risk of death.

Based on the univariable analysis, tumour locations did not influence survival of gastric cancer patients diagnosed at BCH. However, other factors include sex, age, extent of spread of cancer, stage at diagnosis, treatment by surgery, treatment by chemotherapy, treatment by radiotherapy and chemotherapy affected on survival.

5.4 Factors associated with mortality of gastric cancer based in Cox regression multivariable analysis

A total of 730 gastric cancer patients were included in the multivariable analysis. The covariates determined as significant in the log-rank test (p-value < 0.25) were used to fit the multivariable Cox regression model (backward stepwise). Multivariable analysis was used to adjust the variables (sex, age, tumour location, extent of cancer, tumour stage, treatment by only surgery, treatment by only chemotherapy, treatment by both radiotherapy and chemotherapy) in this model of analysis. The variable showing statistical significance in multivariable Cox regression analysis (p <0.05) are age, tumour locations, tumour stage, treatment by surgery and treatment by chemotherapy. These variables are presented in Table 5.5.

Table 5.5: Multivariable analysis of factors associated with mortality of gastric cancer diagnosed at BCH.

Variable	Hazard ratio (HR)	95% CI	P value
Age	1.15	1.1 to 1.2	<0.001
Tumour location			0.02
Distal cancer	Reference		
Proximal cancer	1.44	1.1 to 2.9	
Tumour stage			<0.001
Stage I and II	Reference		
Stage III	6.81	4.9 to 9.3	
Stage IV	8.27	5.7 to 12.2	
Treatment by surgery			<0.001
Partial radical gastrectomy	Reference		
Total radical gastrectomy	0.81	0.5 to 1.2	
Bypass surgery	2.84	1.9 to 4.1	
Palliative gastrectomy	2.03	1.4 to 2.9	
No surgery	2.94	2.7 to 4.2	
Treatment by chemotherapy			<0.001
Yes	Reference		
No	2.51	1.8 to 3.4	

Note: Variable that were adjusted for – sex, age, tumour location, extent of cancer, tumour stage, treatment by surgery, treatment by chemotherapy, and treatment by radiotherapy chemotherapy.

Table 5.5 shows that an increased age at diagnosis by five-years was associated with increased risk of death by 15% (HR: 1.15; 95% CI: 1.1 to 1.2, P <0.001). There was a higher risk of death for patients with proximal gastric cancer compared to distal gastric cancer (HR: 1.44; 95% CI: 1.1 to 2.8, P = 0.02). There was a higher risk of death for patients in stage III (HR: 6.81; 95% CI: 4.9 to 9.3, P < 0.001) and stage IV (HR: 8.27; 95% CI: 5.7 to 12.2, P < 0.001) compared to patients in stage I and II. There was a higher risk of death for patients in the non-surgical treatment group (HR: 2.94; 95% CI: 2.7 to 4.2, P < 0.001) compared with partial radical gastrectomy.

A higher risk of death was observed in palliative gastrectomy (HR: 2.03; 95% CI: 1.4 to 2.9, $P < 0.001$) and bypass surgery (HR: 2.84; 95% CI: 1.9 to 4.1, $P < 0.001$) compared to partial radical gastrectomy. The risk of death by total radical gastrectomy (HR: 0.81; 95% CI: 0.5 to 1.2, $P < 0.001$) was lower compared with partial radical gastrectomy. There was a higher risk of death for patients to treatment by non-chemotherapy group compared to treatment by chemotherapy (HR: 2.51; 95% CI: 1.8 to 3.4, $P < 0.001$).

Table 5.6: Multivariable analysis of factors associated with mortality of gastric cancer (without treatment by surgery and without treatment by chemotherapy) diagnosed at BCH.

Variable	Hazard ratio (HR)	95% CI	P value
Age	1.26	1.2 to 1.4	<0.001
Tumour location			0.15
Distal cancer	Reference		
Proximal cancer	1.18	0.9 to 1.5	
Tumour stage			<0.001
Stage I and II	Reference		
Stage III	6.43	4.7 to 8.7	
Stage IV	15.96	11.4 to 22.2	

Table 5.6 shows that an increased age at diagnosis by five-years was associated with increased risk of death by 26% (HR: 1.26; 95% CI: 1.2 to 1.4, P <0.001). There was a higher risk of death for patients in stage III (HR: 6.43; 95% CI: 4.7 to 8.7, $P < 0.001$) and stage IV (HR: 15.96; 95% CI: 11.4 to 22.2, $P < 0.001$) compared to patients in stage I and II. However, there was no significant association between tumour location and death (HR: 1.18; 95% CI: 0.9 to 1.5, $P = 0.15$).

In summary, this chapter reported the characteristics of patients with gastric cancer, the overall survival, and factors associated with survival. The most common sign and symptoms for participants with gastric cancer were abdominal pain, anorexia, nausea and fatigue. For gastric cancer patients, the median overall survival from diagnosis was 19 months. The total person-time of follow-up was 17,808 months. The one-year survival rate was remarkable higher compared with the five-year survival rate. Age, tumour locations, tumour stage, treatment by surgery and treatment by chemotherapy affected the survival of gastric cancer patients. However, sex, histologic type, tumour grade, tumour size and extent of cancer were not associated with survival for these gastric cancer patients at BCH.

Chapter 6 Discussion and Conclusion

This study was undertaken at Bhaktapur Cancer Hospital (BCH), the government specialist cancer hospital with the largest number of beds, in Kathmandu Valley, Nepal. Data from patients diagnosed with gastric cancer at BCH between 1st January 2010 and December 31st 2021 were included. The study shows that the five-year overall survival rate was 12% and identified significant predictors for survival: age at diagnosis, tumour location, tumour stage at diagnosis, treatment by surgery and treatment by chemotherapy. This study also found that sex, histologic type, tumour grade, tumour size, extent of cancer, and treatment by radiotherapy and chemotherapy did not affect the survival of patients with gastric cancer.

6.1 Research problem and question

A recent multi country gastric cancer study collected data from 48 countries between 1980 to 2018, reported that Thailand had the highest increasing trend in mortality, whereas Norway had the greatest decrease in gastric cancer mortality (Wong et al. 2021). However, this gastric cancer study did not include mortality trend information from either Nepal or India (culturally similar neighboring countries), where gastric cancer is a major public health concern. There is no data published by Globocan[16] about the predictors and overall survival rates of gastric cancer in Nepal, despite data suggesting that gastric cancer was the second most common cause of cancer deaths in males, and fifth most common cause of cancer deaths in females in 2020 (Ferlay et al. 2020g).

[16] Globocan (Global Cancer Incidence, Mortality and Prevalence), "a project of the International Agency for Research on Cancer, provides estimates by cancer site and sex using the best available data in each country".

The two research questions were: i. Which and to what degree did predictors affect the five-year survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021 in Nepal? ii. What is the overall survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021? The new evidence from this study has answered the research question to determine the significant covariates and the survival rate of newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021 in BCH.

6.2 Overall survival from gastric cancer

Although there is very limited global data on survival from cancer, there is information available through Globocan, on number of new cases of cancer and deaths. In 2020, Globocan estimated that the number of deaths due to lung cancer was higher in Nepal compared to HICs. Also, that the number of deaths due to breast cancer was higher in Nepal compared to HICs. And the number of deaths due to cervical cancer was higher in Nepal compared to HICs (Ferlay et al. 2020m). Globocan estimated that a number of deaths to gastric cancer was higher in Nepal (10.2%) than in India (6.2%), a culturally similar neighbouring country.

The findings from this study for the median overall survival for gastric cancer patients, between January 2010 to December 2021, was 19 months since diagnosis, overall survival rate at one-year was 70%, and five-year the overall survival rate was at 12%. The overall survival rate in this study is significantly lower compared to the overall survival rate in HICs countries. Between January 2010 and December 2014, the overall survival rate was 20 to 29% in Kuwait, Turkey, Finland, France; 30 to 40% in Canada, USA, Malaysia, Italy, Belgium, Switzerland; and 60 to 70% in Korea and Japan (Allemani et al. 2018). The exception was in India, a

culturally similar neighbouring country to Nepal. The 12% overall survival rate in this study was slightly higher than 8.9% overall survival rate in India (Allemani et al. 2018).

In this study, significant covariates were age at diagnosis, tumour location, tumour stage at diagnosis, treatment by surgery, and treatment by chemotherapy. The non-significant covariates were sex, histology type, tumour size, extent of cancer, and treatment by radiotherapy chemotherapy. These will be discussed in light of the existing evidence on survival and covariates.

6.2.1 Age and stage at diagnosis as significant factors for survival

This study found that age and stage at diagnosis are significant factors for survival of patients with gastric cancer. In this study, the median age at diagnosis of gastric cancer patients was 60 years, and the overall five-year survival rate was 12%, which was lower than in HICs (Allemani et al. 2018). In HICs, such as Australia, Canada, Denmark, United Kingdom, New Zealand, the median age at diagnosis of gastric cancer patients was 70 to 75 years and the overall five-year survival was 20 to 40% (Allemani et al. 2018; Arnold et al. 2021). The survival of patients with gastric cancer is associated with age at diagnosis (DeVita, Lawrence & Rosenberg 2016; Strong 2015).

The highest proportion of patients (45.9%) was classified at stage III gastric cancer, 35.4% of patients were classified at stage IV and the lowest proportion of patients, 18.7% were classified in stage I and II. In this study the three-year survival for Stage I and II was 88%. This may due to the combination of stage I and stage II that determined a high percentage of patients in the early stage of diagnosis which may increase data skewness and reduce effectiveness of the model used for analysis. The early diagnosis survival was lower in Canadian study, which determined a three-year survival of 62% for Stage I and 50 % for stage II (Ferlay et al. 2020a).

For Stage III, the three-year survival rate was lower in this study (20%) compared to survival in HICs. In Canada, the three-year survival rate for diagnosis at stage III was 34% (Ferlay et al. 2020a). In Denmark, the three-year survival rate, for diagnosis at stage was III 29.7% (Ferlay et al. 2020a). However, in this study the three-year survival for diagnosis at stage IV was higher, at 5% compared to both Canada and Denmark, where the three-year survival for diagnosis at stage IV was only 4%. In Ireland, the three-year survival was higher for diagnosis at all stages compared to Nepal; for stage I was 85%, for stage II 58%, stage III 40% and for stage IV 8% (Ferlay et al. 2020a).

A recent study from HICs, also showed a higher proportion of gastric cancer patients had advanced staging, classified stage IV gastric cancer, compared with stage I and II. In Canada, 50% of patients were diagnosed at stage IV, compared to 20% diagnosed at stage I and II. In New Zealand 59% of patients were diagnosed at stage IV, compared to 16% diagnosed at stage I and II. In the United Kingdom, 50% of patients were diagnosed at stage IV, where only 11% were diagnosed at stage I and II. In Denmark, 48% of patients were diagnosed at stage IV, compared to 11% of patients diagnosed at stage I and II (Arnold et al. 2021). The higher proportion of gastric cancer patients diagnosed at stage IV may be due to late presentation of symptoms and lack of pathognomonic signs of gastric cancer (Dassen 2014; Strong 2015).

In this study, 40.4% of the patients in the older aged group (≥65 years) were diagnosed at stage IV gastric cancer compared with 16.0% of the patients in the younger age group (18 to <50 years) diagnosed at stage IV. The higher proportion of stage IV gastric cancer in the older aged group, compared to the younger age group may contribute to a lower overall survival of gastric cancer patients in the older age group in Nepal. Previous studies also reported a lower overall survival for patients in the older age group that were diagnosed with stage IV gastric cancer, compared to patients in the younger age group that were diagnosed with stage IV gastric cancer

(Katai et al. 2018; Wang et al. 2016; Yang et al. 2011). The information on age and stage of diagnosis indicates that at BCH, a higher proportion of older age patients diagnosed at stage IV affected the lower survival of gastric cancer and that early diagnosis is thus important for improved survival. In India, older people were also diagnosed at a later stage similarly to Nepal, as there is a lower awareness of the signs and symptoms of gastric cancer (Maheshwari et al. 2022; Poudel et al. 2017; Sirohi et al. 2014).

The survival based on age and stage was expected. This is the same as previous studies, where increase age and stage was associated with decreased survival. This comparison is based on peer-reviewed studies that were published in English journals providing the reader with confidence in the evidence.

6.2.2 Tumour location

The body of literature has shown that tumour location of gastric cancer can influence survival (Dassen 2014; Petrelli et al. 2017b). In this study, survival of patients with gastric cancer was dependent on the tumour location; most (83.7%) patients were diagnosed with distal gastric cancer compared to just 16.3% of patients being diagnosed with proximal gastric cancer. The five-year survival for patients with proximal gastric cancer was lower (10%) than in patients with distal gastric cancer (15%). This difference in survival between tumour locations is confirmed by previous studies where patients with proximal gastric cancer had a lower survival compared with distal gastric cancer (Dassen 2014; Petrelli et al. 2017b). This result supports previous evidence or poorer survival rate for proximal gastric cancer. However, no studies in comparable countries have been published. The lower survival rate for patients with proximal gastric cancer may be because cancer that primarily originates in the cardia demonstrates more

aggressive behaviour, and the diagnosis is more likely to be made at a more advanced stage compared to distal gastric cancer (Dassen 2014; Saito et al. 2006).

6.2.3 Treatment by surgery

The body of evidence has shown that surgical treatment of gastric cancer can influence survival (DeVita, Lawrence & Rosenberg 2016; Strong 2015). In this study, survival of patients with gastric cancer was dependent on the surgical treatment. Patients who underwent partial radical gastrectomy had a higher five-year survival (25%) compared to patients who underwent total radical gastrectomy (15%), while patients who did not undergo surgery had a significantly lower five-year survival (5%). This difference was also found in other studies. In HICs, Italy and Japan, patients who underwent partial radical gastrectomy had a higher five-year survival (65.3% and 76.3%) compared to patients who underwent total radical gastrectomy (62.4% and 55.9%) (Federico et al. 1999; Kakeji et al. 2022). However, in India, patients who underwent partial radical gastrectomy and total radical gastrectomy, there was no survival at five-year (Sugoor et al. 2016). A major limitation of all three of this study was that no information was included for patients who did NOT undergo surgery. International oncology clinical guidelines recommend that patients diagnosed at stage IV gastric cancer are ineligible for surgical treatment (DeVita, Lawrence & Rosenberg 2016; Matz 2017; Strong 2015). The high proportion of patients who were ineligible of surgical treatment due to diagnosed at stage IV gastric cancer at BCH may have contributed to the lower overall survival.

6.2.4 Treatment by chemotherapy

The body of literature has shown that chemotherapy treatment of gastric cancer can influence survival (DeVita, Lawrence & Rosenberg 2016; Strong 2015). In this study, the survival of patients with gastric cancer was dependent on the use of chemotherapy treatment and that,

survival was significantly higher for patients who received chemotherapy compared to patients who did not. The five-year survival for patients who received chemotherapy was 15% compared to 0% in patients who did not receive chemotherapy. This was lower than findings from a similar study from Iran that found a 30% five-year survival for patients who received chemotherapy, although in the Iranian study the five year survival for patients who did not receive chemotherapy was also 0% (Akhondi-Meybodi et al. 2017). Further, these findings were confirmed by previous evidence that determined a positive impact of chemotherapy on survival (Buyse & Pignon 2009; Sugarbaker, Yu & Yonemura 2003). Although 88% of gastric cancer patients did receive chemotherapy treatment at BCH, the five-year survival was significantly lower in Nepal compared to HICs countries. Although the lower survival following chemotherapy may bring into question the effectiveness of the chemotherapy treatment in Nepal, this is beyond the scope of the study.

6.2.5 Treatment by radiotherapy and chemotherapy

In univariable analysis, this study determined significant association between treatment by radiotherapy and chemotherapy and survival of patients with gastric cancer. However, in the multivariable analysis, there was no association between survival and patients' treatment by radiotherapy and chemotherapy.

The lack of association between survival and treatment by both radiotherapy and chemotherapy could be due to lack of data to compare adjuvant and neoadjuvant radiotherapy chemotherapy. Alternatively, for patients with gastric cancer, other treatment factors, including surgery and chemotherapy, may be more important than radiotherapy and chemotherapy. A previous study by Nitin et al. (2013) observed that adjuvant radiation and surgery improved survival compared to surgery alone.

6.3 Factors identified as not significantly impacting on survival

6.3.1 Sex

Based on univariable analysis, sex did significantly impact survival, there was a higher risk of death in male gastric cancer patients compared to female gastric cancer patients. The higher risk of death in males may be due to the higher proportion of males diagnosed at stage IV compared to females diagnosed at stage IV for all age groups (18>65). In age group 18 to <50, this study found a higher proportion of stage IV gastric cancer in males (54.5%) compared to females (45.5%). In the age group 50 to <65, this study found a higher proportion of stage IV gastric cancer in males (68.3%) compared to females (31.7%). And in the ≥65 years age group, a higher proportion of stage IV gastric cancer in males (67.7%) was found compared to females (32.3%). , Based on multivariable analysis, there was no significantly higher risk of death in male gastric cancer patients compared to female gastric cancer patients. Sex, although not a predictor of gastric cancer, is associated with survival in explanation of tumour location and stage of cancer treatment (DeVita, Lawrence & Rosenberg 2016; Strong 2015). Although the association between sex and survival has not been shown to be significant, this finding is unexpected as other studies found a significant association (Dassen 2014; Yang et al. 2011).

This study demonstrated that sex, was not a predictor for overall survival rate of gastric cancer. This study did not look at sex in association with tumour location or sex in association with stage of treatment, as this was beyond the scope of the study aim - to determine overall survival rate.

6.3.2 Histologic type

This study did not find any association between histological subtype (tubular adenocarcinoma, mucinous cell carcinoma, papillary adenocarcinoma, poorly-cohesive carcinoma, and signet-ring cell carcinoma) and survival of patients with gastric cancer in either the univariable or the multivariable analysis. However, studies from HICs showed a significant association between histological subtype and survival of patients with gastric cancer (Cunningham et al. 2005; Liu et al. 2013; Petrelli et al. 2017a). Inaccuracy in the classification of histology subtype may be the reason why there is no association between histological subtype and survival of patients with gastric cancer at BCH. Immunohistochemistry (IHC) is the most accurate technique to classify the histological subtype (Inamura 2018; Selves et al. 2018). Since IHC facilities are not available in Nepal (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b, 2018), classification of histological subtype may be less accurate and treatment decision may be impacted (DeVita, Lawrence & Rosenberg 2016; Horton & Gauvreau 2015; Matz 2017). Hence, the inaccurate classification or misclassification histological subtype may be one factor that reduced survival for gastric cancer patients at BCH.

6.3.3 Tumour grade

Similarly, to histological subtype, this study did not identify any association between tumour grade subtype (well-differentiated, moderately differentiated, poorly differentiated, and un-differentiated) and survival of gastric cancer patients in either univariable or multivariable analysis. This is inconsistent with previous studies which identified a significant association between tumour grade subtype and survival of patients with gastric cancer (Yang et al. 2011; Zu et al. 2014).

Due to the unavailability of IHC facilities in Nepal (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b, 2018), classification of tumour grade subtype may be less accurate and treatment decision may be influenced (DeVita, Lawrence & Rosenberg 2016; Horton & Gauvreau 2015; Matz 2017). Hence, the inaccurate classification or misclassification of tumour grade subtype which may be a factor affecting the lower overall survival for gastric cancer patients at BCH.

6.3.4 Tumour size

This study did not show any association between tumour subtype (<3 cm, 3 to 6 cm, and >6 cm) and survival. As with previous points, other studies showed that there is a significant association between increased tumour subtype and reduced survival (Gao et al. 2020; Wang et al. 2012). However, accurately classification of tumour subtype is also depend on specialised IHC pathology services (DeVita, Lawrence & Rosenberg 2016; Matz 2017) that are currently not available. IHC facilities are important to provide accurate classification of tumour grade and subtype that provides essential information for treatment decisions that can safeguard patients outcomes (DeVita, Lawrence & Rosenberg 2016). As there was no specialised IHC facilities at BCH (Nepal Cancer Relief Society 2021), classification of tumour subtype may be inaccurate at BCH. Inaccurate tumour subtype classification may affect the treatment decision and reduce the survival of patients with gastric cancer (DeVita, Lawrence & Rosenberg 2016; Horton & Gauvreau 2015; Matz 2017; Strong 2015). Thus, development of specialised IHC service is important that may increase overall survival of gastric cancer patients diagnosed at BCH.

6.3.5 Extent of cancer

In a recent study of patients with gastric cancer, multivariate analysis determined that extent of cancer was associated with survival (Jin et al. 2017). In this study, univariable analysis found a significantly higher risk of death in patients with distant metastases compared to patients with localised gastric cancer. However, multivariable analysis showed no association between extent of cancer (localised, regional, locally advanced, and distant metastases) and the survival of patients with gastric cancer.

Positron Emission Tomography-Computed Tomography (PET-CT) radiodiagnosis techniques are important to provide accurate information on the extent of cancer, essential for treatment decision that can safeguard patient outcomes (DeVita, Lawrence & Rosenberg 2016). Due to the unavailability of Positron Emission Tomography-Computed Tomography (PET-CT) scan machine at BCH, the assessment of extent of cancer may be less accurate. Inaccuracy in assessment of the extent of cancer may affect the treatment decision and reduce the survival of patients with gastric cancer (DeVita, Lawrence & Rosenberg 2016; Horton & Gauvreau 2015; Strong 2015). Thus, development of PET-CT scan service is important which may increase overall survival of gastric cancer patients diagnosed at BCH.

6.4 Strengths and limitations

This is a quantitative non-experimental study design undertaken in the form of a retrospective cohort study that allowed multiple exposures and multiple outcomes to be examined in regard to gastric cancer.

One of the strengths of this study is the sample size. Based on the power calculation, the number of participants was adequate to determine the survival rate of gastric cancer patients. Another

strength can be seen in the adequate time frame for follow-up of up to 12 years. Newly diagnosed gastric cancer patients between 1st January 2010 and 31st December 2021 were collected to determine the five-year survival rate. A further strength of this study is the wide range of clinical predictors that enable the determination of associations with survival. And finally, the high participation rate of 89% reduced attrition bias.

As this study design was retrospective, the data available had originally been collected for treatment purposes and not for scientific purposes. Therefore, the data collection tools were specifically created to obtain maximum information from existing variables, while retaining study feasibility. This study employed a retrospective study design, using definitive date of diagnosis and definitive date of death, that ensured accurate and complete data to support internal validity of the results.

As data were unavailable regarding; socioeconomic status, ethnicity and the specific type of treatment, this study was unable to determine the association between these variables and survival of gastric cancer patients. Additionally, this study was unable to compare survival associated with the type of treatment: chemotherapy (adjuvant vs neo-adjuvant) and radiotherapy (adjuvant vs neo-adjuvant). This study did not look at differences in the age at diagnosis for men and women, or at age and sex-related differences in tumour location, stage and treatment, as the study aimed to determine overall survival rate and the predictors of gastric cancer.

Where patient death was reported by next of kin, either grief or the retrospective nature of the data collection may have affected memory of the next of kin and resulted in recall bias regarding the date of patient death. Where the death date was provided by the next of kin, the accuracy and assumptions that were made may have caused the results to be incorrect. The

collection of data from only one site limited external validity; therefore, the finding may not be generalisable to the overall survival situation in Nepal. Although in Nepal there is no population-based cancer registry, as gastric cancer treatment is provided through cancer hospitals, the annual reports for BPKMCH, similar to BCH, suggests the same pattern of new cases of gastric cancer, over the same time period.

In addition, the exclusion of participants who declined to participate, resulted in a selection bias that may influence the result of the study if those declining to participate have different survival statuses compared to those who participated. One aim of this study was to determine the five-year survival rate of newly diagnosed gastric cancer patients, based on the IARC(WHO) standards. Further, the percentage lost to follow-up was 11% (94/817). Evidence suggests that <5% lost to follow-up is unlikely to result in bias, while >20% lost to follow-up poses threats to validity (Sacket, Richardson & Rosenberg 1997). Therefore, the proportion lost to follow-up in this study may be considered as a limitation of the study. As only the median overall survival is required to answer the research question, the median survival for each age range would be superfluous.

A further limitation was the inability to separately determine survival for patients who were diagnosed at stage I and survival for patients who were diagnosed at stage II. As there was an inadequate number of stage I gastric cancer patients the staging variables stage I and stage II were merged together. A lack of IHC and PET-CT scan services at BCH, implied that the classification of histological subtype, tumour grade and extent of cancer may have been inaccurate. As data on socioeconomic status such as occupation, education, income as well as race/ethnicity of patients was unavailable, the data was not included in our study.

Survival bias may have resulted from delay following diagnosis that resulted in commencement of treatment, duration of treatment or cyclical nature of the treatment (Kirkwood & Sterne 2003; Matz 2017). Also, there may be some confounding by indication on the treatment status of patients, however we have adjusted the effect of potential confounders (sex, age, tumour location, extent of cancer, tumour stage and treatment). As this study is limited to survival analysis, the predictors of gastric cancer survival have been explored, however providing evidence on risk factors, causal factors and explanatory factors will require further research using case-control or cohort study design. This study did not determine censoring statistics.

A further limitation of this study is the use of a backwards stepwise approach to select variables for inclusion in this survival model. This approach does not consider all possible combinations nor consider the causal relationships between variables. However, this model does remove the least important variables early and leaves the most important variables in order to determine predictors of survival (Sengul & Kaya 2023).

6.5 Implications and recommendations

6.5.1 Implications for policy

The results of this study have implications for policy and practice in Nepal and BCH. The implications for policy include changes to health system funding, health promotion policy, professional practice and specialised cancer care are outlined below.

6.5.1.1 Implications for health system funding

The results of this study have determined significant survival factors that may inform policy and practice to improve diagnosis and access to appropriate health care services for gastric cancer in Nepal. The Ministry of Health funds hospital costs in Nepal, based on diagnosis-

related funding rather than based on health services or the number of bed days (Gyawali et al. 2020; Khatiwoda et al. 2019). For cancer care, the maximum amount of funding available is equivalent to US$ 925.92; and the patient is required to cover all additional costs above this threshold (Gyawali et al. 2020; Khatiwoda et al. 2019). The Universal Health Coverage (UHC) policy in Nepal provided healthcare services, enabled access to health facilities and protected against financial risk of patients, however, UHC included neither gastric cancer early detection programs nor cancer care for patients with gastric cancer (Banstola et al. 2019).

The cancer care funding available in Nepal is lower than in the neighbouring country India where the cost of care is less expensive, more care is available for the same amount of money and there is a higher ratio of expert oncologist in India, therefore the overall survival of patients with gastric cancer was similar to this study (Dey 2014). The total cost of care for a newly diagnosed gastric cancer patient in India was between US$ 4,000 to 8,000 (Cancer Treatment India 2021). Evidence suggested economic status influenced the survival of patients with cancer (Horton & Gauvreau 2015; Vaccarella et al. 2019). Due to economic barriers, especially in LMICs, patients failed to complete cancer treatment even when cancer was diagnosed at early stage (Horton & Gauvreau 2015; World Health Organization 2020b). Although no evidence has been published, the lower survival of patients with gastric cancer in Nepal may be due to economic barriers that prevent access to cancer care. This strongly suggests that a significant increase in funding for gastric cancer care would be required to improve survival.

There are few oncologists in Nepal compared with other countries with only 0.4 oncologists per 100,000 population (Gyawali et al. 2020), this is lower than comparable country, India (Dey 2014). In England and Wales, there are 5 oncologists per 100,000 population, and in Northern Ireland there are 7 oncologists per 100,000 population (The Royal College of Radiologists 2021). The evidence had demonstrated that survival of gastric cancer patients was

dependent on the availability of expert oncology care (DeVita, Lawrence & Rosenberg 2016; Peter, Davis & Takeshi 2001). The development of specialised cancer treatment services commenced recently in Nepal in 2002 (B P Koirala Memorial Cancer Hospital 2017a; B P Koirala Memorial Cancer Hospital 2017b, 2018). This suggests that more places are needed to support graduated medical doctors to specialise in oncology. These places are so limited that Nepalese medical doctors may benefit from specialist education and training in countries that provide a higher level of cancer care.

Hospitals in the United Kingdom and America have been providing specialised cancer treatment services as early as 1850 (Memorial Sloan Kettering Cancer Center 2022; Royal Marsden 2022). Care in specialisation cancer hospitals have been demonstrated as a potential factor in the higher overall survival of patients with gastric cancer (Morishima et al. 2022). Development of specialised cancer hospitals would contribute to increase survival of patients with gastric cancer in Nepal.

6.5.1.2 Implications for health promotion policy

In Nepal, there are currently no health promotion strategies related to gastric cancer. The lack of public awareness of gastric cancer symptoms means that a significantly higher number of cases were diagnosed at more advanced stage, resulting in lower survival (Horton & Gauvreau 2015; Strong 2015). Earlier diagnosis may be more likely through implementation of gastric cancer awareness program that may include media and social campaigns. There are successful public health promotion strategies in Nepal, regarding maternal health (Khanal 2021), and cervical cancer screening programs (B P Koirala Memorial Cancer Hospital 2018), that may be adapted to increase awareness of symptoms of gastric cancer.

In Nepal, a larger proportion of gastric cancer cases were diagnosed at later stage IV rather than at an earlier stage I and II. Therefore, one of the main implications of this study is that the implementation of an early detection screening programs that may enable a larger proportion of gastric cancer cases to be diagnosed at an earlier stage, increasing survival and decreasing mortality. Although an evidence based approach is required in order to evaluate screening programs and minimise lead-time bias (Jacklyn, Bell & Hayen 2017), a recent systematic review and meta-analysis highlighted that screening programs significantly reduced the mortality of gastric cancer (Faria et al. 2022). Although the highest age-standardised incidence rate of gastric cancer was observed in men of the Republic of Korea (39.7 per 100, 000) in 2020 (Ferlay et al. 2021), the Republic of Korea also had the highest survival of patients with gastric cancer (Allemani et al. 2018). This may be due in part to the establishment in 1999 gastric cancer endoscopic early detection program 50 to 60% gastric cancer cases were diagnosed at early stage (Choi et al. 2015; Jeong & Park 2011; Jung et al. 2013).

H. pylori was linked to 78% of gastric cancer cases (Forman & Sierra 2014) and *H. pylori* eradication therapy was successful in reducing the risk of gastric cancer (Ford et al. 2014). *H. pylori* screening program such as the urea breath test, may increase the proportion of patient's diagnosis prior to the onset of symptoms. However, the effect of a *H. pylori* screening program on mortality is not yet evident. Indeed, in HICs that do not have gastric cancer screening programs, the higher overall survival for gastric cancer patients may be due to other factors such as availability of oncology specialist and specialised cancer services (DeVita, Lawrence & Rosenberg 2016; Horton & Gauvreau 2015; Strong 2015). For those already diagnosed with gastric cancer, programs that provide access to primary care and to community health may reduce risk of progression, minimise treatment complications, increase quality of life and improve survival (DeVita, Lawrence & Rosenberg 2016; Strong 2015).

6.5.2 Implications for health information systems

The finding from this study may inform health information systems including availability of treatments and development of clinical and medical record guidelines that may improve healthcare delivery. In Nepal, there may be less accuracy in the classification of histological subtype, which may affect treatment decision and reduce the survival of gastric cancer patients diagnosed at BCH. This suggests improvement in the ability to classify histological subtype, such as development of immunohistochemistry (IHC) services, may improve the diagnostic capacity for gastric cancer. Improvement in the assessment of extent of cancer, such as development of PET-CT scan services may improve the diagnostic capacity for gastric cancer. Future research would include investigating of the impact of diagnostic services and detailed assessment of histological subtypes on the extent of cancer.

The overall survival of patients with gastric cancer following chemotherapy treatment is lower in Nepal, compared to HICs. Evidence on gastric cancer treatment has demonstrated that the survival benefit and response rate differs between chemotherapy agents; fluorouracil, docetaxel, oxaliplatin, capecitabine, cisplatin and epirubicin (DeVita, Lawrence & Rosenberg 2016; Strong 2015). Therefore, future studies may investigate the survival and the effectiveness of chemotherapy agents used at BCH.

6.6 Conclusions

The overall survival of patients with gastric cancer was lower in Nepal compared with other HICs. Factors affecting overall survival were age, tumour locations, tumour stage, treatment by surgery and treatment by chemotherapy. However, sex, histologic type, tumour grade, tumour subtype and extent of cancer were not associated with survival. Though this was a retrospective, single-site, hospital-based study, this study included a wide range of clinical

predictors to determine the survival. Future research would include a prospective study design that includes ethnicity, SES, patients treated by type of chemotherapy and type of radiotherapy, as well as patients' screening status to determine overall survival and effect of predictors on survival. The implications for Nepal on cost, staffing, and medications may apply to other types of cancer.

Implementation of pathology (immunohistochemistry) and radiology (Positron Emission Tomography-Computed Tomography scan) services at BCH, would increase the accuracy of assessment of histologic subtype and extent of cancer. Following the implementation of these services, future research would be required to determine the association between subtype of histology, tumour grade, and extent of cancer in relation to overall survival of patients with gastric cancer.

References

Akhondi-Meybodi, M., Ghane, M., Akhondi-Meybodi, S. & Dashti, G. 2017, 'Five-year Survival Rate for Gastric Cancer in Yazd Province, Central Iran, from 2001 to 2008', *Middle East Journal of Digestive Disease*, vol. 9, no. 1, pp. 39-48.

Allemani, C., Matsuda, T., Di Carlo, V., Harewood, R., Matz, M., Nikšić, M., . . . Lewis, C. 2018, 'Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries', *The Lancet*, vol. 391, no. 10125, pp. 1023-75.

American Cancer Society 2017a, *About stomach cancer*, viewed 14 September 2018, <https://www.cancer.org/content/dam/CRC/PDF/Public/8838.00.pdf>.

American Cancer Society 2017b, *Stomach cancer early detection, diagnosis, and staging*, American Cancer Society, viewed 20 September 2018, <https://www.cancer.org/content/dam/CRC/PDF/Public/8840.00.pdf>.

American Cancer Society 2017c, *Treating Stomach Cancer*, American Cancer Society, viewed 22 September 2018, <https://www.cancer.org/content/dam/CRC/PDF/Public/8841.00.pdf>.

American Joint Committee on Cancer 2010, *AJCC Cancer Staging Manual*, Springer New York.

Arnold, M., Morgan, E., Bardot, A., Rutherford, M.J., Ferlay, J., Little, A., . . . Soerjomataram, I. 2021, 'International variation in oesophageal and gastric cancer survival 2012-2014: differences by histological subtype and stage at diagnosis (an ICBP SURVMARK-2 population-based study)', *Gut*, viewed 25 November 2021, <https://www.ncbi.nlm.nih.gov/pubmed/34824149>.

Avital, I., Stojadinovic, A., Pisters, P.W.T., Kelsen, D.P. & Willet, C.G. 2016, 'Cancer of the stomach', in V.T. DeVita, T.S. Lawrence & S.A. Rosenberg (eds), *Colon and other gastrointestinal cancers: cancer: principles and practice of oncology*, 10th edn, Wolters Kluwer, Philadelphia, pp. 1086-169.

B P Koirala Memorial Cancer Hospital 2017a, *Annual Report*, B P Koirala Memorial Cancer Hospital, Chitwan.

B P Koirala Memorial Cancer Hospital 2017b, *National cancer registry programme: Hospital based cancer registry 10 years consolidated report (2003-2012)*, B P Koirala Memorial Cancer Hospital, Chitwan.

B P Koirala Memorial Cancer Hospital 2018, *Annual Report*, B P Koirala Memorial Cancer Hospital, Chitwan.

Banstola, A., Panta, P.R., Bhatta, S. & Adhikari, S.R. 2019, *Amrit Banstola et al: Achieving universal health coverage in Nepal*, The BMJ Opinion, viewed 26 February 2019, <https://blogs.bmj.com/bmj/2019/02/15/amrit-banstola-et-al-achieving-universal-health-coverage-in-nepal/>.

Bonenkamp, J.J., Songun, I. & Hermans, J. 1995, 'Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients', *Lancet (London, England)*, vol. 345, pp. 745-8.

Borrmann, R. 1926, 'Tumours of the stomach and duodenum', in H. Borchardt, R. Borrmann, E. Christeller, A. Dietrich, W. Fischer, E. Gierke, . . . O. Stoerk (eds), *Manual of Special Pathological Anatomy and Histology*, vol. 4, Springer, Vienna, pp. 812–1054.

Bosman, F., Carneiro, F., Hruban, R. & Theise, N. 2010, *WHO classification of tumours of the digestive system*, vol. 3, World Health Organization, viewed 15 September 2020, <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-The-Digestive-System-2010#!>.

Brierley, J.D., Gospodarowicz, M.K. & Wittekind, C. (eds) 2017, *TNM classifcation of malignant tumours*, 8th edn, Union for International Cancer Control, Geneva.

Brown, L.M. 2000, 'Helicobacter pylori: epidemiology and routes of transmission', *Epidemiologic Reviews*, vol. 22, pp. 283-97.

Buyse, M.E. & Pignon, J. 2009, 'Meta-analyses of randomized trials assessing the interest of postoperative adjuvant chemotherapy and prognostic factors in gastric cancer', *Journal of Clinical Oncology*, vol. 27, no. 15, p. 4539.

Cancer Council Australia 2017, *Understanding stomach and oesophageal cancers: a guide for people with cancer, their families and friends*, Cancer Council Australia, Sydney.

Cancer Treatment India 2021, *Stomach cancer treatment cost in India*, viewed 23 June 2022, <https://hmsdesk.com/cost/stomach-cancer-treatment-cost-in-india/>.

Chen, Y.S., Zhu, J., Zhang, Y.H., Ding, L.L. & Chen, J.G. 2015, 'Long-term survival trends of gastric cancer patients between 1972 and 2011 in Qidong', *Chinese Journal of Cancer*, vol. 34, no. 12, pp. 1-6.

Choi, K.S., Jun, J.K., Suh, M., Park, B., Noh, D.K., Song, S.H., . . . Park, E.C. 2015, 'Effect of endoscopy screening on stage at gastric cancer diagnosis: results of the National Cancer Screening Programme in Korea', *British Journal of Cancer*, vol. 112, no. 3, pp. 608-12.

Colquhoun, A., Arnold, M., Ferlay, J., Goodman, K.J., Forman, D. & Soerjomataram, I. 2015, 'Global patterns of cardia and non-cardia gastric cancer incidence in 2012', *Gut*, vol. 64, no. 12, pp. 1881-8.

Compton, C.C., Byrd, D.R., Garcia-Aguilar, J., Kurtzman, S.H., Ojawaiye, A. & Washington, M.K. (eds) 2012, *Cancer Staging Atlas: A companion to the seventh edition of the AJCC cancer staging manual and handbook second edition*, Springer, Chicago.

Correa, P. 1992, 'Human gastric carcinogenesis: a multistep and multifactorial process first American Cancer Society Award lecture on cancer epidemiology and prevention', *Cancer Research* vol. 52, pp. 6735-40.

Cunningham, S.C., Kamangar, F., Kim, M.P., Hammoud, S., Haque, R., Maitra, A., . . . Schulick, R.D. 2005, 'Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution', *Journal of Gastrointestinal Surgery*, vol. 9, no. 5, pp. 718-25.

Cuschieri, A., Weeden, S., Fielding, J.W.L., Bancewicz, J., Craven, J., Joypaul, V., . . . Fayers, P. 1999, 'Patient survival after D1 and D2 resections for gastric cancer: long-term

results of the MRC randomized surgical trial', *British Journal of Cancer*, vol. (9/10), pp. 1522–30.

Dassen, A.E. 2014, *Gastric cancer trends and treatment strategies in the Netherlands*, Erasmus University, Rotterdam, Netherlands.

de Martel, C., Forman, D. & Plummer, M. 2013, 'Gastric Cancer: Epidemiology and Risk Factors', *Gastroenterology Clinics of North America*, vol. 42, no. 2, pp. 219-40.

de Vries, E., Arroyave, I., Pardo, C., Wiesner, C., Murillo, R., Forman, D., . . . Avendano, M. 2015, 'Trends in inequalities in premature cancer mortality by educational level in Colombia, 1998-2007', *Journal of Epidemiology Community Health*, vol. 69, no. 5, pp. 408-15.

Degiuli, M., Sasako, M., Ponti, A., Vendrame, A., Tomatis, M., Mazza, C., . . . Italian Gastric Cancer Study, G. 2014, 'Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer', *British Journal of Surgery*, vol. 101, no. 2, pp. 23-31.

Devesa, S.S. & Frameni, J.F. 1999, 'The rising incidence of gastric cardia cancer', *Jounal of National Cancer Institute*, vol. 91, no. 9, pp. 747-9.

DeVita, V.T., Lawrence, T.S. & Rosenberg, S.A. 2016, *Colon and other gastrointestinal cancers : cancer: principles & practice of oncology*, 10th edn, Wolters Kluwer Health, Philadelphia, United States.

Dey, S. 2014, *India has 1.8 mn cancer patients but only one oncologist to treat every 2,000*, New Delhi, viewed 23 August 2022, <https://www.business-standard.com/article/current-affairs/india-has-1-8-mn-cancer-patients-but-only-one-oncologist-to-treat-every-2-000-114052401140_1.html>.

Dos Santos Silva, I. 1999, *Cancer epidemiology: principles and methods*, International Agency for Research on Cancer, Lyon.

Faria, L., Silva, J.C., Rodriguez-Carrasco, M., Pimentel-Nunes, P., Dinis-Ribeiro, M. & Libanio, D. 2022, 'Gastric cancer screening: a systematic review and meta-analysis', *Scandinavian Journal of Gastroenterology*, pp. 1-11.

Federico, B., Ettore, M., Giuliano, B., Rosalba, M., Chiara, P. & Leandro, G. 1999, 'Subtotal versus total gastrectomy for gastric cancer: Five-year survival rates in a multicenter randomized Italian Trial', *Annals of Surgery*, vol. 230, no. 2, pp. 170-8.

Feinstein, A.R., Sosin, D.M. & Wellis, C.K. 1985, 'The Will Rogers phenomenon: stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer', *The New England Journal of Medicine*, vol. 312, pp. 1604-8.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Pineros, M., . . . Bray, F. 2020a, *Age-standardized net survival, both sexes, age (15-99), stomach cancer, 2012-2014*, International Agency for Research on Cancer, Lyon, viewed 21 August 2022, <https://gco.iarc.fr/survival/survmark/visualizations/viz7/?mode=%22circle%22&groupby=%22country%22&period=%221%22&cancer=%22GAST%22&country=%22Australia%22&gender=0&stage=%22TNM%22&age_group=%2215-99%22&show_ci=%22%22&countries=%5B%22Ireland%22%5D>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020b, *Age-standardized incidence, mortality rates (25-99 years) and 5-year net survival (15-99 years) in 2014, stomach, both sexes*, International Agency for Research on Cancer,

Lyon, viewed 11 January 2021, <https://gco.iarc.fr/survival/survmark/visualizations/viz1/?groupby=%22country%22&period=%225%22&cancer_site=%22Stomach%22&country=%22Australia%22&year=%222014%22&gender=%22All%22&sorting=%220%22>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020c, *Estimated age-standardized incidence and mortality rates (world) in 2020, Nepal, females, all ages*, International Agency for Research on Cancer, Lyon, viewed 15 Janauary 2021, <https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=524&key=asr&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Atrue%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020d, *Estimated age-standardized incidene and mortality rates (world) in 2020, Nepal, males, all ages*, International Agency for Research on Cancer, Lyon, viewed 13 January 2021, <https://gco.iarc.fr/today/online-analysis-multi-bars?v=2020&mode=cancer&mode_population=countries&population=900&populations=524&key=asr&sex=1&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=10&group_cancer=1&include_nmsc=1&include_nmsc_other=1&type_multiple=%257B%2522inc%2522%253Atrue%252C%2522mort%2522%253Atrue%252C%2522prev%2522%253Afalse%257D&orientation=horizontal&type_sort=0&type_nb_items=%257B%2522top%2522%253Atrue%252C%2522bottom%2522%253Afalse%257D#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020e, *Estimated number of deaths from 2020 to 2040, both sexes, age (0-85+) stomach*, International Agency for Research on Cancer, Lyon, viewed 20 January 2021, <https://gco.iarc.fr/tomorrow/en/dataviz/bars?sexes=0&mode=population&populations=981&cancers=7&types=1>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020f, *Estimated number of deaths in 2020, Nepal, both sexes, all ages*, International Agency for Research on Cancer, Lyon, viewed 20 January 2021, <https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=524&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020g, *Estimated number of deaths in 2020, Nepal, females, all ages*, International Agency for Research on Cancer, Lyon, viewed 13 January 2021, <https://gco.iarc.fr/today/online-analysis-

pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=524&key=total&sex=2&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020h, *Estimated number of deaths in 2020, worldwide, both sexes, all ages*, International Agency for Research on Cancer, Lyon, viewed 3 January 2021, <https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020i, *Estimated number of new cases from 2020 to 2040, both sexes, age (0-85+) stomach*, International Agency for Research on Cancer, Lyon, viewed 12 January 2021, <https://gco.iarc.fr/tomorrow/en/dataviz/bars?sexes=0&mode=population&populations=524&cancers=7>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020j, *Estimated number of new cases in 2020, Australia, both sexes, all ages*, International Agency for Research on Cancer, Lyon, viewed 3 August 2022, <https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=524&key=total&sex=1&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020k, *Estimated number of new cases in 2020, Nepal, females, all ages*, International Agency for Research on Cancer, Lyon, viewed 10 January 2021, <https://gco.iarc.fr/today/online-analysis-pie?v=2020&mode=cancer&mode_population=continents&population=900&populations=524&key=total&sex=2&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0#collapse-group-0-3>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020l, *Global Cancer Observatory: About*, International Agency for Research on Cancer, Lyon, viewed 10 November 2021, <https://gco.iarc.fr/today/about?fbclid=IwAR0h3euZHCpTBexy_vOMczscw0aYEp7RkRgM2si_AU6XYtPUZoOBk-g5eGo>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2020m, *Global Cancer Observatory: Cancer Today*, International Agency for Research on Cancer, Lyon, viewed 7 January 2021, <https://gco.iarc.fr/today>.

Ferlay, J., Ervik, M., Lam, F., Colombet, M., Mery, L., Piñeros, M., . . . Bray, F. 2021, *Number of new cases in 2020, both sexes, all ages*, International Agency for Research on

Cancer, Lyon, viewed 11 June 2022, <https://gco.iarc.fr/today/data/factsheets/populations/410-korea-republic-of-fact-sheets.pdf>.

Fontana, V., Decensi, A., Orengo, M.A., Parodi, S., Torrisi, R. & Puntoni, R. 1997, 'Socioeconomic status and survival of gastric cancer patients', *European Journal of Cancer*, vol. 34, no. 4, pp. 537-42.

Ford, A.C., Forman, D., Hunt, R.H., Yuan, Y. & Moayyedi, P. 2014, 'Helicobacter pylori eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials', *BMJ*, vol. 348, p. g3174.

Forman, D. & Sierra, M.S. 2014, 'The current and projected global burden of gastric cancer', in IARC *Helicobacter pylori* Working Group (ed.), *Helicobacter pylori eradication as a strategy for preventing gastric cancer*, vol. 8, International Agency for Research on Cancer, Lyon, pp. 5-15.

Fritz, A., Percy, C., Jack, A., Shanmugaratnam, K., Sobin, L.H., Parkin, D.M. & Whelan, S. (eds) 2013, *International Classification of Diseases for Oncology (ICD-O)*, 3rd edn, World Health Organization, Geneva.

Gao, Z., Ni, J., Ding, H., Yan, C., Ren, C., Li, G., . . . Jin, G. 2020, 'A nomogram for prediction of stage III/IV gastric cancer outcome after surgery: A multicenter population-based study', *Cancer Medicine*, vol. 9, no. 15, pp. 5490-9.

Gopal, K.S., Barry, A.M., Benjamin, F.H. & Brenda, K.E. 2003, *Area socioeconomic variations in U.S. cancer incidence, mortality, stage,treatment, and survival, 1975–1999*, NCI Cancer Surveillance Monograph Series, National Cancer Institute, Bethesda.

Government of Nepal 2021, *National population and housing census 2021: National report*, vol. 01, National Planning Commission Secretariat Central Bureau of Statistics, Kathmandu.

Gunderson, L.L., Donohue, J.H., Alberts, S.R., Ashman, J.B. & Jaroszewski, D.E. 2014, *Cancer of the stomach and gastroesophageal junction*, American Cancer Society, viewed 30 November 2020, <https://www.cancer.org/cancer/stomach-cancer/about/what-is-stomach-cancer.html?fbclid=IwAR2lUljQeDp01fkWdaHoJaw35kyw1jWFETcaqH_bS7pwYF5Sxiv9kOJdNNk#references>.

Gyawali, B., Sharma, S., Shilpakar, R., Dulal, S., Pariyar, J., Booth, C.M. & Poudyal, B. 2020, 'Overview of delivery of cancer care in Nepal: current status and future priorities', *Global Oncology*, vol. 6, pp. 1211-7.

Hamilton, S.R. & Aaltonen, L.A. (eds) 2000, *Pathology and genetics of tumours of the digestive system*, International Agency for Research on Cancer, Lyon.

Hartgrink, H.H., van de Velde, C.J., Putter, H., Bonenkamp, J.J., Klein Kranenbarg, E., Songun, I., . . . Sasako, M. 2004, 'Extended lymph node dissection for gastric cancer: who may benefit? Final results of the randomized Dutch gastric cancer group trial', *Journal of Clinical Oncology*, vol. 22, no. 11, pp. 2069-77.

Horton, S. & Gauvreau, C.L. 2015, *Cancer in low- and middle-income countries: an economic overview*, vol. 3, The International Bank for Reconstruction and Development / The World Bank, <https://www.ncbi.nlm.nih.gov/books/NBK343620/>.

Hu, B., El Hajj, N., Sittler, S., Lammert, N., Barnes, R. & Meloni-Ehrig, A. 2012, 'Gastric cancer: Classification, histology and application of molecular pathology', *Journal of Gastrointestinal Oncology*, vol. 3, no. 3, pp. 251-61.

Hua, C.Z., Yu, S.Z., Pu, X., Xiao, Y.X., Ya, X., Hiroyuki, T., . . . Yasuo, T. 2010, 'The pathobiological behaviors and prognosis associated with Japanese gastric adenocarcinomas of pure WHO histological subtypes', *Histology and Histopathology*, vol. 25, pp. 445-52.

Hwang, S.W., Lee, D.H., Lee, S.H., Park, Y.S., Hwang, J.H., Kim, J.W., . . . Song, I.S. 2010, 'Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography', *Journal of Gastroenterology and Hepatology*, vol. 25, no. 3, pp. 512-8.

Inamura, K. 2018, 'Update on Immunohistochemistry for the Diagnosis of Lung Cancer', *Cancers*, vol. 10, no. 3, viewed Mar 14, 2022, <https://www.ncbi.nlm.nih.gov/pubmed/29538329>.

International Agency for Research on Cancer 2020, *Global Cancer Observatory*, World Health Organization, viewed 10 July 2023, <https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa/>.

Jacklyn, G., Bell, K. & Hayen, A. 2017, 'Assessing the efficacy of cancer screening', *Public Health Research & Practice*, vol. 27, no. 3.

Jang, J.S., Shin, D.G., Cho, H.M., Kwon, Y., Cho, D.H., Lee, K.B., . . . Kim, I.M. 2013, 'Differences in the Survival of Gastric Cancer Patients after Gastrectomy according to the Medical Insurance Status', *Journal of Gastric Cancer*, vol. 13, no. 4, pp. 247-54.

Japanese Gastric Cancer Association 2021, 'Japanese gastric cancer treatment guidelines 2018 (5th edition)', *Gastric Cancer*, vol. 24, no. 1, pp. 1-21.

Jeong, O. & Park, Y.K. 2011, 'Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients', *Journal of Gastric Cancer*, vol. 11, no. 2, pp. 69-77.

Jin, H., Pinheiro, P.S., Callahan, K.E. & Altekruse, S.F. 2017, 'Examining the gastric cancer survival gap between Asians and whites in the United States', *Gastric Cancer*, vol. 20, no. 4, pp. 573-82.

Jung, K.W., Won, Y.J., Kong, H.J., Oh, C.M., Shin, A. & Lee, J.S. 2013, 'Survival of korean adult cancer patients by stage at diagnosis, 2006-2010: national cancer registry study', *Cancer Research and Treatment*, vol. 45, no. 3, pp. 162-71.

Kakeji, Y., Ishikawa, T., Suzuki, S., Akazawa, K., Irino, T., Miyashiro, I., . . . Registration Committee of the Japanese Gastric Cancer, A. 2022, 'A retrospective 5-year survival analysis of surgically resected gastric cancer cases from the Japanese Gastric Cancer Association nationwide registry (2001-2013)', *Gastric Cancer*.

Kalbfleisch, J.D. & Prentice, R.L. 1980, *The statistical analysis failure time data*, 2nd edn, John Wiley and Sons, New York.

Kaplan, E.L. & Meier, P. 1958, 'Nonparametric estimation from incomplete observations', *Journal of the American Statistical Association*, vol. 53, pp. 457–81.

Katai, H., Ishikawa, T., Akazawa, K., Isobe, Y., Miyashiro, I., Oda, I., . . . Nashimoto, A. 2018, 'Five-year survival analysis of surgically resected gastric cancer cases in Japan: a retrospective analysis of more than 100,000 patients from the nationwide registry of the Japanese Gastric Cancer Association (2001–2007)', *Gastric Cancer*, vol. 21, no. 1, pp. 144-54.

Khanal, N. 2021, *The aama program: Maternal health in Nepal*, weblog, The Borgen Project, Kathmandu, <https://borgenproject.org/about-us/>.

Khatiwoda, S.R., Dhungana, R.R., Sapkota, V.P. & Singh, S. 2019, 'Estimating the direct cost of cancer in Nepal: a cross-sectional study in a tertiary cancer Hospital', *Front Public Health*, vol. 7, p. 160.

Kirkwood, B.R. & Sterne, J.A.C. 2003, *Essential Medical Statistics*, Blackwell Publishing, Hoboken.

Kurkure, A.P. & Yeole, B.B. 2006, 'Social Inequalities in cancer with special reference to South Asian countries', *Asia Pacific Journal of Cancer Prevention*, vol. 67, pp. 36-40.

Kuwahara, A., Takachi, R., Tsubono, Y., Sasazuki, S., Inoue, M., Tsugane, S. & JPHC Study Group 2010, 'Socioeconomic status and gastric cancer survival in Japan', *Gastric Cancer*, vol. 13, no. 4, pp. 222-30.

Ladeiras-Lopes, R., Pereira, A.K., Nogueira, A., Pinheiro-Torres, T., Pinto, I., Santos-Pereira, R. & Lunet, N. 2008, 'Smoking and gastric cancer: systematic review and meta-analysis of cohort studies', *Cancer causes & control : CCC*, vol. 19, no. 7, pp. 689-701.

Larsen, I.K. (ed.) 2019, *Cancer in Norway 2019 : Cancer incidence, mortality, survival and prevalence in Norway*, Cancer Registry of Norway, Oslo.

Lauren, P. 1965, 'The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma: an attempt at a histo-clinical classification', *Acta Pathologica, Microbiologica, et Immunologica Scandinavica*, vol. 64, pp. 31-49.

Li, Z., Bai, B., Xie, F. & Zhao, Q. 2018, 'Distal versus total gastrectomy for middle and lower-third gastric cancer: A systematic review and meta-analysis', *International Journal of Surgery (London, England)*, vol. 53, pp. 163-70.

Liao, Y., Yang, Z.L., Peng, J.S., Xiang, J. & Wang, J.P. 2013, 'Neoadjuvant chemotherapy for gastric cancer: A meta-analysis of randomized, controlled trials', *Journal of Gastroenterology and Hepatology (Australia)*, vol. 28, no. 5, pp. 777-82.

Liu, H., Li, Y.Q., Yu, T., Zhao, Y.A., Zhang, J.P., Zhang, J.N., . . . Desmond, P.V. 2008, 'Confocal endomicroscopy for in vivo detection of microvascular architecture in normal and malignant lesions of upper gastrointestinal tract', *Journal of Gastroenterology and Hepatology*, vol. 23, no. 1, pp. 56-61.

Liu, L., Wang, Z.W., Ji, J., Zhang, J.N., Yan, M., Zhang, J., . . . Yu, Y.Y. 2013, 'A cohort study and meta-analysis between Histopathological classification and prognosis of gastric Carcinoma', *Anti-Cancer Agents in Medicinal Chemistry*, vol. 13, no. 2, pp. 227-34.

Maeda, H., Okabayashi, T., Nishimori, I., Sugimoto, T., Namikawa, T., Dabanaka, K., . . . Hanazaki, K. 2008, 'Clinicopathologic features of adenocarcinoma at the gastric cardia:

is it different from distal cancer of the stomach?', *Journal of the American College of Surgeons*, vol. 206, no. 2, pp. 306-10.

Mahadevan, V. 2014, 'Anatomy of the stomach', *Surgery (Oxford)*, vol. 32, no. 11, pp. 571-4.

Maheshwari, U., Sharma, M., Goel, V., Goyal, P., Jain, P., Agarwal, C., . . . Koyyala, V.P.B. 2022, 'Clinical Profile and Outcomes of Treatment in Gastric Cancer in Young Patients in India', *Asian Journal of Oncology*.

Matz, M. 2017, 'Factors influencing ovarian cancer survival worldwide', PhD thesis, London School of Hygiene and Tropical Medicine, London.

Memorial Sloan Kettering Cancer Center 2022, *History and milestones*, New York, viewed 12 June 2022, <https://www.mskcc.org/about/history-milestones>.

Ming, S.C. 1977, 'Gastric carcinoma: a pathobiological classification', *Cancer*, vol. 39, no. 6, pp. 2475-85.

Morishima, T., Okawa, S., Koyama, S., Nakata, K., Tabuchi, T. & Miyashiro, I. 2022, 'Between-hospital variations in 3-year survival among patients with newly diagnosed gastric, colorectal, and lung cancer', *Scientific reports*, vol. 12, no. 1, p. 7134.

National Cancer Institute 2023, *Median Survival*, viewed 25 July 2023, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/median-survival>.

National Cancer Institute n.d., *Cancer stat facts: stomach cancer*, Seer, viewed 19 November 2020, <https://seer.cancer.gov/statfacts/html/stomach.html>.

Nepal Cancer Relief Society 2021, *Bhaktapur Cancer Hospital*, Nepal Cancer Relief Society, Bhaktapur, viewed 5 November 2021, <http://ncrs.org.np/page/13/programs/curative_programs/bhaktapur_cancer_hospital>.

Neupane, P.R., Poudel, K.K., Huang, Z.B., Steel, R. & Poudel, J.K. 2017, 'Distribution of cancer by sex and site in Nepal', *Asian Pacific Journal of Cancer Prevention*, vol. 18, no. 6, pp. 1611-5.

Nitin, O., Madhur, G., Santiago, A., Andreas, K., Wolfgang, T., Timothy, J.K., . . . Chandan, G. 2013, 'Who benefits from adjuvant radiotherapy for gastric cancer?: a meta-analysis', *International Journal of Radiation Oncology, Biology, Physics*, vol. 86, no. 2, pp. 330-5.

Parkin, D.M., Bray, F., Ferlay, J. & Pisani, P. 2005, 'Global cancer statistics, 2002', *CA: A Cancer Journal for Clinicians*, vol. 55, no. 2, pp. 74-108.

Peter, A., Davis, A. & Takeshi, S. 2001, 'The difference in gastric cancer between Japan, USA and Europe: What are the facts? What are the suggestions?', *Critical Reviews in Oncology Hematology*, vol. 40, pp. 77-94.

Petrelli, F., Berenato, R., Turati, L., Mennitto, A., Steccanella, F., Caporale, M., . . . Barni, S. 2017a, 'Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: A systematic review and meta-analysis', *Journal of Gastrointestinal Oncology*, vol. 8, no. 1, pp. 148-63.

Petrelli, F., Ghidini, M., Barni, S., Steccanella, F., Sgroi, G., Passalacqua, R. & Tomasello, G. 2017b, 'Prognostic Role of Primary Tumour Location in Non-Metastatic Gastric

Cancer: A Systematic Review and Meta-Analysis of 50 Studies', *Annals of Surgical Oncology*, vol. 24, no. 9, pp. 2655-68.

Piya, M.K. & Acharya, S.C. 2012, 'Oncology in Nepal', *South Asian Journal of Cancer*, vol. 1, no. 1, pp. 5-8.

Population Pyramid 2023, *Population pyramids of the world from 1950 to 2100*, viewed 10 July 2023, <https://www.populationpyramid.net/nepal/2040/>.

Poudel, K.K. 2016a, 'Age specific incidence of five major cancers in Nepal, 2012', *Nepal Journal of Epidemiology*, vol. 6, no. 2, pp. 565-73.

Poudel, K.K. 2016b, 'Changes in the distribution of cancer incidence in Nepal from 2003 to 2013', *Asian Pacific Journal of Cancer Prevention*, vol. 17, no. 10, pp. 4775-82.

Poudel, K.K. 2017, 'Hospital-based cancer incidence in Nepal from 2010 to 2013', *Nepal Journal of Epidemiology*, vol. 7, no. 1, pp. 659-65.

Poudel, K.K., Huang, Z. & Neupane, P.R. 2016, 'Trend of cancer incidence in Nepal from 2003 to 2012', *Asian Pacific Journal of Cancer Prevention*, vol. 17, no. 4, pp. 2171-5.

Poudel, K.K., Huang, Z., Neupane, P.R. & Steel, R. 2017, 'Prediction of the cancer incidence in Nepal', *Asian Pacific Journal of Cancer Prevention*, vol. 18, no. 1, pp. 165-8.

Poudel, K.K., Sims, D., Morris, D., Neupane, P.R., Jha, A.K., Lamichhane, N., . . . Weiderpass, E. 2018, 'Cancer Cases Referral system in Nepal', *Nepal Journal of Epidemiology*, vol. 8, no. 4, pp. 748-52.

Pourhoseingholi, A., Bijan Moghimi, D., Azadeh, S., Ebrahim, H., Ali, S. & Zali, M. 2009, 'Prognostic factors in gastric cancer using log-normal censored regression model', *Indian Journal of Medical Research*, vol. 129, pp. 262-7.

Qi, J., Zhang, P., Wang, Y., Chen, H. & Li, Y. 2016, 'Does total gastrectomy provide better outcomes than distal subtotal gastrectomy for distal gastric cancer? A systematic review and meta-analysis', *PloS one*, vol. 11, no. 10, p. e0165179.

Royal Marsden 2022, *NHS Foundation Trust*, National Health Service, viewed 14 June 2022, <https://www.royalmarsden.nhs.uk/>.

Sacket, D., Richardson, W. & Rosenberg, W. 1997, *Evidence-based medicine : how to practice and teach EBM*, Churchill Livingstone, London.

Saito, H., Fukumoto, Y., Osaki, T., Fukuda, K., Tatebe, S., Tsujitani, S. & Ikeguchi, M. 2006, 'Distinct recurrence pattern and outcome of adenocarcinoma of the gastric cardia in comparison with carcinoma of other regions of the stomach', *World Journal of Surgery*, vol. 30, no. 10, pp. 1864-9.

Sankaranarayanan, R. 2014, 'Screening for cancer in low- and middle-income countries', *Annals of Global Health*, vol. 80, no. 5, pp. 412-7.

Sano, T. & Aiko, T. 2011, 'New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points', *Gastric Cancer*, vol. 14, no. 2, pp. 97-100.

Sasako, M., Sano, T., Yamamoto, S., Kurokawa, Y., Nashimoto, A., Kurita, A., . . . Tsujinaka, T. 2008, 'D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer', *New England Journal of Medicine*, vol. 359, pp. 453-62.

Selves, J., Long-Mira, E., Mathieu, M.C., Rochaix, P. & Ilie, M. 2018, 'Immunohistochemistry for diagnosis of metastatic carcinomas of unknown primary site', *Cancers (Basel)*, vol. 10, no. 4.

Sengul, M. & Kaya, I. 2023, 'Use of survival data in multivariate adaptive regression analysis: simulation study', *Turkiye Klinikleri Journal of Biostatistics*, vol. 15, no. 1, pp. 42-51.

Singh, G.K. & Jemal, A. 2017, 'Socioeconomic and racial/ethnic disparities in cancer mortality, incidence, and survival in the United States, 1950-2014: Over six decades of changing patterns and widening inequalities', *Journal of Environmental and Public Health*, vol. 2017, viewed 3 March 2021, <https://www.ncbi.nlm.nih.gov/pubmed/28408935>.

Singh, G.K., Williams, S.D., Siahpush, M. & Mulhollen, A. 2011, 'Socioeconomic, rural-urban, and racial inequalities in US cancer mortality: Part I-all cancers and lung cancer and part II-colorectal, prostate, breast, and cervical cancers', *Journal of Cancer Epidemiology*, vol. 2011, viewed 7 May 2021, <https://www.ncbi.nlm.nih.gov/pubmed/22496688>.

Sirohi, B., Rastogi, S., Dawood, S., Talole, S., Ramadwar, M., Shetty, N. & Shrikhande, S.V. 2014, 'Treatment of patients with advanced gastric cancer: experience from an Indian tertiary cancer center', *Medical Oncology*, vol. 31, no. 10, p. 138.

Siwakoti, B., Subedi, K.P., Mulmi, R., Pradhananga, K.K. & Shrestha, G. 2019, 'Cancer registration in Nepal: current status and way forward', *Journal of Nepal Medical Association*, vol. 57, no. 216, pp. 144-8.

Songun, I., Putter, H., Kranenbarg, E.M.-K., Sasako, M. & van de Velde, C.J.H. 2010, 'Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial', *The Lancet Oncology*, vol. 11, no. 5, pp. 439-49.

StataCorp 2017, *Stata: release 17. statistical software*, Stata Press, College Station, Texas.

Strong, V.E. (ed.) 2015, *Gastric Cancer Principles and Practice*, Springer, New York.

Subedi, K.S. 2012, 'Cancer treatment in Nepal : A historical background, development of treatment facilities, epidemiology and challenges for prevention and control of cancer', *Austral-Asian Journal of Cancer*, vol. 11, no. 3, pp. 205-12.

Sugarbaker, P.H., Yu, W. & Yonemura, Y. 2003, 'Gastrectomy, peritonectomy, and perioperative intraperitoneal chemotherapy: the evolution of treatment strategies for advanced gastric cancer', *Seminars in Surgical Oncology*, vol. 21, no. 4, pp. 233-48.

Sugoor, P., Shah, S., Dusane, R., Desouza, A., Goel, M. & Shrikhande, S.V. 2016, 'Proximal gastrectomy versus total gastrectomy for proximal third gastric cancer: total gastrectomy is not always necessary', *Langenbecks Arch Surg*, vol. 401, no. 5, pp. 687-97.

Sullivan, R., Alatise, O.I., Anderson, B.O., Audisio, R., Autier, P., Aggarwal, A., . . . Purushotham, A. 2015, 'Global cancer surgery: delivering safe, affordable, and timely cancer surgery', *The Lancet Oncology*, vol. 16, no. 11, pp. 1193-224.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. 2021, 'Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *Cancer Journal for Clinicians*, vol. 71, no. 3, pp. 209-49.

The Royal College of Radiologists 2021, *Clinical oncology UK workforce census 2020 report*, London.

United Nations Development Programme 2022, *Human Development Report 2020: The next frontier human development and anthropocene*, United Nations Development Programme, New York.

Vaccarella, S., Lortent-Tieulent, J., Saracci, R., Conway, D.I., Straif, K. & Wild, C.P. (eds) 2019, *Reducing social inequalities in cancer: evidence and priorities for research*, vol. 168, International Agency for Research on Cancer, Lyon.

Wang, H.M., Huang, C.M., Zheng, C.H., Li, P., Xie, J.W., Wang, J.B., . . . Lu, J. 2012, 'Tumour size as a prognostic factor in patients with advanced gastric cancer in the lower third of the stomach', *World Journal of Gastroenterology*, vol. 18, no. 38, pp. 5470-5.

Wang, S., Zhang, Z., Liu, M., Li, S. & Jiang, C. 2015, 'Endoscopic Resection Compared with Gastrectomy to Treat Early Gastric Cancer: A Systematic Review and Meta-Analysis', *PloS one*, vol. 10, no. 12, p. e0144774.

Wang, Z. & Chen, J.Q. 2011, 'Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review', *BMC Gastroenterology*, vol. 11, pp. 1-15.

Wang, Z., Xu, J., Shi, Z., Shen, X., Luo, T., Bi, J. & Nie, M. 2016, 'Clinicopathologic characteristics and prognostic of gastric cancer in young patients', *Scandinavian Journal of Gastroenterology*, vol. 51, no. 9, pp. 1043-9.

Wilson, M.L., Fleming, K.A., Kuti, M.A., Looi, L.M., Lago, N. & Ru, K. 2018, 'Access to pathology and laboratory medicine services: a crucial gap', *The Lancet*, vol. 391, no. 10133, pp. 1927-38.

Wong, M.C.S., Huang, J., Chan, P.S.F., Choi, P., Lao, X.Q., Chan, S.M., . . . Liang, P. 2021, 'Global incidence and mortality of gastric cancer, 1980-2018', *JAMA Network Open*, vol. 4, no. 7, p. e2118457.

World Bank Group 2020, *Nepal development update: post-pandemic Nepal – charting a resilient recovery and future growth directions*, Kathmandu.

World Cancer Research Fund & American Institute for Cancer Research 2018, *Diet, nutrition and physical activity and stomach cancer*, Continuous Update Project, London.

World Health Organization 2017, *Intersectoral factors influencing equity-oriented progress towards universal health coverage: results from a scoping review of literature*, viewed 9 May 2023, <https://www.who.int/publications/i/item/9789241512329>.

World Health Organization 2018a, *Global status report on alcohol and health*, World Health Organization, Geneva.

World Health Organization 2018b, *Nepal–WHO country cooperation strategy (CCS) 2018–2022*, World Health Organization & Government of Nepal Ministry of Health, Kathmandu.

World Health Organization 2018c, *Number of new cases in 2018, both sexes, all ages*, International Agency for Research on Cancer, viewed 1 October 2019.

World Health Organization 2020a, *Leading cause of death, illness and impoverishment*, World Health Organization, viewed 18 June 2021, <https://www.who.int/en/news-room/fact-

sheets/detail/tobacco?fbclid=IwAR2B5r32enm_FzjcrFo246u_vo-nsC9dy_h2jQaH7_ljHsW4QnkIWlHD82A>.

World Health Organization 2020b, *WHO report on cancer setting priorities, investing wisely and providing care for all*, Switzerland.

Wu, C.C., Hsu, T.W., Chang, C.M., Yu, C.H., Wang, Y.F. & Lee, C.C. 2014, 'The effect of individual and neighborhood socioeconomic status on gastric cancer survival', *PLoS One*, vol. 9, no. 2, p. e89655.

Wu, C.W., Hsiung, C.A., Lo, S.S., Hsieh, M.C., Chen, J.H., Li, A.F.Y., . . . Peng, J.W. 2006, 'Nodal dissection for patients with gastric cancer: a randomised controlled trial ', *The Lancet Oncology*, vol. 7, no. 4, pp. 309-15.

Yan, C., Zhu, Z.G., Yan, M., Zhang, H., Pan, Z.L., Chen, J., . . . Lin, Y.Z. 2009, 'Value of multidetector-row computed tomography in the preoperative T and N staging of gastric carcinoma: a large-scale Chinese study', *Journal of Surgical Oncology*, vol. 100, no. 3, pp. 205-14.

Yang, D., Hendifar, A., Lenz, C., Togawa, K., Lenz, F., Lurje, G., . . . Lenz, H.J. 2011, 'Survival of metastatic gastric cancer: Significance of age, sex and race/ethnicity', *Journal of Gastrointestinal Oncology*, vol. 2, no. 2, pp. 77-84.

Yoshikawa, T., Sasako, M., Sano, T., Nashimoto, A., Kurita, A., Tsujinaka, T., . . . Yamamoto, S. 2006, 'Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial', *British Journal of Surgery*, vol. 93, no. 12, pp. 1526-9.

Zamani, M., Ebrahimtabar, F., Zamani, V., Miller, W.H., Alizadeh-Navaei, R., Shokri-Shirvani, J. & Derakhshan, M.H. 2018, 'Systematic review with meta-analysis: the worldwide prevalence of Helicobacter pylori infection', *Alimentary Pharmacology & Therapeutics*, vol. 47, no. 7, pp. 868-76.

Zhao, B., Lv, W., Zhang, J., Zhang, J., Huang, B. & Lin, J. 2020, 'Different prognostic significance of signet ring cell histology for early and advanced gastric cancer patients: a systematic review and meta-analysis', *Expert Review of Gastroenterology and Hepatology*, vol. 14, no. 6, pp. 499-509.

Zu, H., Wang, H., Li, C. & Xue, Y. 2014, 'Clinicopathologic characteristics and prognostic value of various histological types in advanced gastric cancer', *International Journal of Clinical and Experimental Pathology*, vol. 7, no. 9, pp. 5692-700.

Appendix 1: Patient information sheet

Patient code |__|__||__|__|

A. Demographic Data

Data entry date (Day/ Month/ Year): |__|__||__|__| |__|__||__|__|

A.1 Sex |__|__|

01. Male

02. Female

A.2 Patients Age |__|__| (Years)

A.3 Date of diagnosis

01. Day |__|__|

02. Month |__|__|

03. Year |__|__|

A.4 Patients status |__|__|

01. Died

02. Survived

88. Loss to follow-up

A.5 Last visited date at hospital

Day |__|__|

Month |__|__|

Year |__|__||__|__|

A.6 Date of death

Day |__|__|

Month |__|__|

Year |__|__||__|__|

A.6 Province |__|__|

01. Province No.1

02. Madhesh Pradesh

03. Bagmati Pradesh

04. Gandaki Pradesh

05. Lumbini Pradesh

06. Karnali Pradesh

07. Sudurpashchim Pradesh

B. Signs and Symptoms

B.1 Abdominal pain |__|__|

01.Yes

02. No / Unknown

B.2 Anorexia |__|__|

01.Yes

02. No / Unknown

B.3 Nausea |__|__|

01.Yes

02. No / Unknown

B.4 Fatigue |__|__|

01.Yes

02. No / Unknown

B.5 Weight loss |__|__|

01.Yes

02. No / Unknown

B.6 Heartburn |__|__|

01.Yes

02. No / Unknown

B.7 Black-coloured feces |__|__|

01.Yes

02. No / Unknown

B.8 Vomiting |__|__|

01.Yes

02. No / Unknown

B.9 Anaemia |__|__|

01.Yes

02. No / Unknown

C. Pathology of gastric cancer

C.1 Tumour location |__|__|

01. Proximal (cardia cancer)

02. Distal (non-cardia cancer)

88. Unknown

C.2 Histologic type |__|__|

01. Tubular adenocarcinomas

02. Mucinous adenocarcinomas

03. Papillary adenocarcinomas

04. Poorly cohesive carcinomas

05. Signet-ring cell carcinomas

88. Unknown

C.3 Tumour grade |__|__|

01. Well-differentiated

02. Moderately-differentiated

03. Poorly-differentiated

04. Un-differentiated

88. Unknown

C.4 Tumour size: |__|__|

01. <3 cm

02. 3 to 6 cm

03. >6 cm

88. Unknown

C.5 Extent of a cancer |__|__|

01. Localised

02. Regional

03. Locally advanced

04. Distant Metastases

88. Unknown

C.6 Tumour stage |__|__|

01. I and II

02. III

03. IV

88. Unknown

C.7 Treatment by surgery |__|__|

01. Yes (if yes go C. 8)

02. No

C. 8 Type of surgery |__|__|

01. Partial radical gastrectomy

02. Total radical gastrectomy

03. Bypass surgery

04. Palliative gastrectomy

C.9 Treatment by Chemotherapy |__|__|

01. Yes

02. No

C.10 Treatment by Radiotherapy Chemotherapy |__|__|

01. Yes

02. No

Appendix 2: Script for telephone conversation

The following script is based on three potential scenarios between data collectors and participants. They are:

(a) The patient answers the phone call.

(b) the patient does not answer the phone call initially but is available to speak

(c) The patient is unable to speak and the next of kin answers the phone call.

Scenario A: Patient answers the phone call

Hello father / mother/ brother / sister (Colloquial greeting, deemed appropriate within the Nepalese culture).

Am I speaking to (name of the patient here)?

My name is (first name, last name of data collector) I am calling you from Bhaktapur Cancer Hospital medical record department, where I obtained your clinical details.

We are currently conducting a study on gastric cancer survival in Nepal and would like to ask for your assistance in this project. It is important for us to determine gastric cancer survival in Nepal because it is unknown. Furthermore, the outcomes of this study will also assist in comparing the predictors of gastric cancer in other regions and Nepal.

This study has been planned by Krishna Poudel, who is a Nepalese PhD student at University of Technology Sydney.

How are you today? (answer recorded). Thank you.

If you have any questions about this study, please contact directly Kishore Kumar Pradhananga (mobile: +977 [redacted], email: [redacted]@rediffmail.com.

Thanks for receiving the call and I wish you a good day. (Colloquial greeting)

Scenario B: Someone else answers the phone, and not the patient

Hello father / mother/ brother/ sister (Colloquial greeting, deemed appropriate within the Nepalese culture).

Am I speaking to (name of the patient here)?

How are you feeling today? (Rhetorical question).

My name is (first name, last name of data collector) I am calling you from Bhaktapur Cancer Hospital medical record department, where I obtained your clinical details.

We are currently conducting a study on gastric cancer survival in Nepal and would like to ask for your assistance in this project. It is important for us to determine gastric cancer survival in Nepal because it is unknown. Furthermore, the outcomes of this study will also assist in comparing the predictors of gastric cancer in other regions and Nepal.

This study has been planned by Krishna Poudel, who is a Nepalese PhD student at University of Technology Sydney.

May I know how (fill in patient name) is feeling today? (answer recorded). Thank you.

If you have any questions about this study, please contact directly Kishore Kumar Pradhananga (mobile: +977 [redacted], email: [redacted]@rediffmail.com.

Thanks for receiving the call and I wish you a good day. (Colloquial greeting)

Scenario C: If the patient is unavailable to answer the phone

The data collector will contact the next of kin in phone and say:

Hello father / mother/ brother/ sister (Colloquial greeting, deemed appropriate within the Nepalese culture).

Am I speaking to (name of the next of kin)?

How are you feeling today? (Rhetorical question).

My name is (first name, last name of data collector) I am calling you from Bhaktapur Cancer Hospital medical record department, where I obtained your clinical details.

We are currently conducting a study on gastric cancer survival in Nepal and would like to ask for your assistance in this project. It is important for us to determine gastric cancer survival in Nepal because it is unknown. Furthermore, the outcomes of this study will also assist in comparing the predictors of gastric cancer in other regions and Nepal.

This study has been planned by Krishna Poudel, who is a Nepalese PhD student at University of Technology Sydney.

How is (patient first name……..)'s health?

If patient is alive the data collectors will record this.

OR

If the patient has died

I am sorry to hear that (patient's first name) has passed away. Please accept my deepest condolences for your family's loss. Could you please tell me the month and year of his/her death?

If you have any questions about this study, please contact directly Kishore Kumar Pradhananga

(mobile: +977 [redacted], email: [redacted]@rediffmail.com.

Thanks for receiving the call and I wish you a good day (Colloquial greeting).

Appendix 3: Distress protocol

This protocol provides the researcher with guidance to assist if the participant next-of-kin becomes distressed during the data collection telephone call, due to the death of the participant. Prior to the commencement of the study, the researcher will provide sufficient information about the important of research to the participant. Participant and their next of-kin may freely accept or decline participation in the study.

Should a participant (next of kin) become uncomfortable or distressed due to death of the participant (gastric cancer patient), during the telephone interview, the researcher will take the following actions:

1. The researcher will say "I am sorry to hear that (patients full name) has passed away. Please accept my condolences for your family loss." The researcher will suggest that it is appropriate for the interview be terminated. The interview will be ceased without data being collected the death date of participant.

2. In Nepal bereavement support is traditionally provided through family/friends or religious institutions (temples and church). Professional counselling is neither common nor readily accessible. To offer this service would likely be considered an insult to the bereaved person.

3. The participant next-of-kin will not be contacted in the future.

Appendix 4: TNM clinical classification and TNM pathological classification

TNM clinical classification

"T - Primary tumour

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high-grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosa

T1a Tumour invades lamina propria or muscularis mucosae

T1b Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades subserosa

T4 Tumour perforates serosa or invades adjacent structures

T4a Tumour perforates serosa

T4b Tumour invades adjacent structures" (Brierley, Gospodarowicz & Wittekind 2017)

"N - Regional lymph nodes

NX Regional lymph node (s) cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1 to 2 regional lymph nodes

N2 Metastasis in 3 to 6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

N3a Metastasis in 7 to 15 regional lymph nodes

N3b Metastasis in 16 or more regional lymph nodes" (Brierley, Gospodarowicz & Wittekind 2017)

“M- Distant metastasis

M0 No distant metastasis

M1 Distant metastasis” (Brierley, Gospodarowicz & Wittekind 2017).

TNM pathological classification

The pathological assessment of the primary tumour (pT), regional lymph nodes (pN) and distant metastasis (pM1) correspond to TNM categories.

pN0 Generally 16 or more lymph nodes will be included in histological examination of a regional lymphadenectomy specimen. If the lymph nodes are negative, but the number usually examined is not met, categorize as pN0 (Brierley, Gospodarowicz & Wittekind 2017).

Appendix 5: The clinical and pathological stages based on the 8th edition of the AJCC/UICC TNM system

Clinical stage (cTNM) of gastric cancer based on the 8th edition of AJCC/UICC (Brierley, Gospodarowicz & Wittekind 2017).

Stage	Tumour	Node	Metastases
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T1, T2	N1, N2, N3	M0
Stage IIB	T3, T4a	N0	M0
Stage III	T3, T4a	N1, N2, N3	M0
Stage IVA	T4b	Any N	M0
Stage IVB	Any T	Any N	M1

Pathological stage (pTNM) of gastric cancer based on the 8th edition of AJCC/UICC

(Brierley, Gospodarowicz & Wittekind 2017).

Stage	Tumour	Node	Metastases
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1, N2	M0
	T4b	N0	M0
Stage IIIB	T1, T2	N3b	M0
	T3, T4a	N3a	M0
	T4b	N1, N2	M0

Stage IIIC	T3, T4a	N3b	M0
	T4b	N3a, N3b	M0
Stage IV	Any T	Any N	M1

Appendix 6: Stata syntax for data generation

```
*total person-time of follow-up

stset Survivalmonth, failure(status1deathor0alive==1

*overall survival

sts graph, risktable ytitle(Proportion surviving) xtitle(Time since diagnosis (months)) sc

*survival by sex

sts graph, by(Sex) risktable ytitle(Proportion surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by age group

sts graph, by(Agegroup) risktable ytitle(Proportion surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by tumour location

sts graph, by(Tumourlocation) risktable ytitle(Proportion surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by extent of cancer
```

```
sts graph, by(Extentofcancer) risktable ytitle(Proportion
surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by stage at diagnosis

sts graph, by(Stage) risktable ytitle(Proportion surviving)
xtitle(Time since diagnosis (months)) scale(0.8)

*survival by surgery

sts graph, by(Surgery) risktable ytitle(Proportion surviving)
xtitle(Time since diagnosis (months)) scale(0.8)

*survival by surgery (adjusted for stage at diagnosis)

ts graph, by(Surgery) adjustfor(Stage) ytitle(Proportion
surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by chemotherapy

sts graph, by(Chemotherapy) risktable ytitle(Proportion
surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*survival by chemotherapy (adjusted for stage at diagnosis)

sts graph, by(Chemotherapy) adjustfor(Stage) ytitle(Proportion
surviving) xtitle(Time since diagnosis (months)) scale(0.8)

*treatment by radiotherapy and chemotherapy

sts graph, by(RadiotherapyChemotherapy) risktable
ytitle(Proportion surviving) xtitle(Time since diagnosis
(months)) scale(0.8)
```

```
*treatment by radiotherapy and chemotherapy (adjusted for stage
at diagnosis)
sts graph, by(RadiotherapyChemotherapy) adjustfor(Stage)
ytitle(Proportion surviving) xtitle(Time since diagnosis
(months)) scale(0.8)
stcox Fiveyearage i.Tumourlocation i.Stage i.Surgery
i.Chemotherapy
stcox Fiveyearage i.Tumourlocation i.Stage
```

Appendix 7: Literature database searches

Embase <1974 to 2023 March 14>

1	gastric cancer.mp. or Stomach Neoplasms/	116966
2	stomach cancer.mp.	114930
3	1 or 2	156380
4	Survival/ or survival.mp.	2139463
5	Mortality/ or mortality.mp.	1873021
6	treatment.mp. or Therapeutics/	9094762
7	surgery.mp. or General Surgery/	4225929
8	radiotherapy.mp. or Radiotherapy/	680976

9 chemotherapy.mp. or Drug Therapy/ 1857675

10 4 or 5 3600696

11 6 or 7 or 8 or 912002692

12 stage.mp. 1425256

13 grade.mp. 692576

14 size.mp. 1810423

15 Histology/ or histology.mp. 854794

16 12 or 13 or 14 or 15 4330529

17 socioeconomic.mp. or Socioeconomic Factors/ 250906

18 race.mp. or Racial Groups/ 271878

19 ethnicity.mp. or Ethnicity/ 176775

20 Male/ 11189054

21 Female/ 11325449

22 gender.mp. 724008

23 Sex/ or sex.mp. 1296625

24 age.mp. 4809382

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 16150301

26 3 and 10 and 11 and 16 and 25 12000

27 limit 26 to yr="1942 - 2022" 11832

28 limit 27 to (full text and human and (meta analysis or "systematic review") and english and yr="1942 - 2022") 117

29 limit 27 to (full text and human and english language and randomized controlled trial and yr="1942 - 2022") 448

After adding 28 and 29 (565 document results)

Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to March 14, 2023>

1 gastric cancer.mp. or Stomach Neoplasms/ 130559

2 stomach cancer.mp. 7715

3 1 or 2 132549

4 Survival/ or survival.mp. 1460787

5 Mortality/ or mortality.mp. 1360319

6 treatment.mp. or Therapeutics/ 5705362

7 surgery.mp. or General Surgery/ 2996070

8 radiotherapy.mp. or Radiotherapy/ 366756

9 chemotherapy.mp. or Drug Therapy/ 547233

10 4 or 5 2390885

11 6 or 7 or 8 or 97857095

12 stage.mp. 930464

13 grade.mp. 405911

14 size.mp. 1270657

15 Histology/ or histology.mp. 534897

16 12 or 13 or 14 or 15 2888583

17 socioeconomic.mp. or Socioeconomic Factors/ 251948

18 race.mp. or Racial Groups/ 151554

19 ethnicity.mp. or Ethnicity/ 142094

20 Male/ 9319870

21 Female/ 9562019

22 gender.mp. 410626

23 Sex/ or sex.mp. 958963

24 age.mp. 9813046

25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 14858062

26 3 and 10 and 11 and 16 and 25 7418

27 limit 26 to (english language and full text and humans and yr="1942 - 2022" and (meta analysis or randomized controlled trial or "systematic review"))

400 document results

SCOPUS

(((TITLE-ABS-KEY (gastric AND cancer) OR TITLE-ABS-KEY (stomach AND cancer) OR TITLE-ABS-KEY (stomach AND neoplasms))) AND ((TITLE-ABS-KEY (survival) OR TITLE-ABS-KEY (mortality))) AND ((TITLE-ABS-KEY (treatment) OR TITLE-ABS-KEY (therapeutics) OR TITLE-ABS-KEY (surgery) OR TITLE-ABS-KEY (radiotherapy) OR TITLE-ABS-KEY (chemotherapy) OR TITLE-ABS-KEY (drug AND therapy))) AND ((TITLE-ABS-KEY (stage)) OR (TITLE-ABS-KEY (grade)) OR (TITLE-ABS-KEY (size)) OR (TITLE-ABS-KEY (histology))) AND ((TITLE-ABS-KEY (socioeconomic)) OR ((TITLE-ABS-KEY (race) OR TITLE-ABS-KEY (racial AND groups) OR TITLE-ABS-KEY (ethnicity))) OR ((TITLE-ABS-KEY (male) OR TITLE-ABS-KEY (female) OR TITLE-ABS-KEY (sex) OR TITLE-ABS-KEY (gender))) OR (TITLE-ABS-KEY (age)))) AND (multivariate AND analysis) AND (EXCLUDE (PUBYEAR , 2023)) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (EXACTKEYWORD , "Multivariate Analysis"))

848 document results

PUBMED

148

Search: (((((((survival[MeSH Terms]) OR (mortality[MeSH Terms])) OR (survival)) OR (mortality)) AND (((((treatment) OR (therapeutics[MeSH Terms])) OR (general surgery[MeSH Terms])) OR (surgery)) OR ((((radiotherapy) OR (radiotherapy[MeSH Terms])) OR (drug therapy[MeSH Terms])) OR (chemotherapy)))) AND ((stomach neoplasms[MeSH Terms]) OR (stomach cancer) OR (gastric cancer) OR (stomach neoplasms))) AND ((((((stage) OR (grade)) OR (size)) OR (histology)) OR (histology[MeSH Terms])) OR ((((radiotherapy) OR (radiotherapy[MeSH Terms])) OR (drug therapy[MeSH Terms])) OR (chemotherapy)))) AND ((((((((((socioeconomic) OR (race)) OR (racial groups[MeSH Terms])) OR (ethnicity[MeSH Terms])) OR (ethnicity)) OR (male)) OR (female)) OR (gender)) OR (sex)) OR (sex[MeSH Terms]))) **Filters:** Full text, Meta-Analysis, Randomized Controlled Trial, Systematic Review, Humans, English, from 1900 – 2022

953 document results