

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 persontime 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

Chapter 1 Introduction	10
1.1 Background on Nepal and the burden of cancer in Nepal	10
1.2 Cancer treatment centres in Nepal	13
1.3 Rationale of the study	14
Chapter 2 Introduction to Stomach and Gastric Cancer	18
2.1 Anatomy of stomach	18
2.2 Types of gastric cancer	19
2.3 Signs and symptoms of gastric cancer	20
2.4 Diagnosis of gastric cancer	21
2.5 Classification system for stage of disease at diagnosis	22
2.5.1 Tumour Node Metastasis (TNM)	23
2.5.2 Surveillance, epidemiology, and end results (SEER) summary stage	24
2.5.3 Japanese Classification of Gastric Carcinoma (JCGC) staging system	24
2.6 Histologic subtypes of gastric cancer	24
2.7 Histologic tumour grade of gastric cancer	25
2.8 Dissection of lymph node	26
Chapter 3 Literature Review	29
3.1 Methods for Literature Review	29
3.2 Survival and gastric cancer	33
3.3 Survival and sex	34

3.4 Survival and Age	34
3.5 Survival and tumour location	36
3.6 Survival and histology	37
3.7 Survival and stage at diagnosis	39
3.8 Survival and histologic tumour grade	40
3.9 Survival and tumour size	41
3.10 Survival and treatment	41
3.10.1 Surgery	42
3.10.2 Endoscopic resection	42
3.10.3 Lymphadenectomy	42
3.10.4 Gastrectomy	45
3.11 Chemotherapy	45
3.11.1 Adjuvant chemotherapy	46
3.11.2 Neoadjuvant chemotherapy	46
3.12 Radiotherapy	47
3.13 Survival and socioeconomic status	47
3.14 Survival and race and ethnicity	50
3.15 Other influences on gastric cancer survival	52
3.16 Summary	54
Chapter 4 Research Design and Methodology	55
4.1 Aim and objectives	55

4.1.1 Aim	55
4.1.2 Specific objectives	55
4.1.3 Research questions	56
4.2 Study design	56
4.2.1 Study variables	56
4.2.2 Study procedure	59
4.3 Inclusion criteria	61
4.4 Exclusion criteria	62
4.5 Data collection procedure	62
4.6 Sample size calculation	63
4.7 Statistical analysis	64
4.8 Ethical approval	65
Chapter 5 Results	67
5.1 Patient characteristics	67
5.2 Survival of Gastric Cancer	73
5.3 Factors associated with mortality of gastric cancer in Cox regression un	nivariable analysis
	88
5.4 Factors associated with mortality of gastric cancer based in Cox regress	sion multivariable
analysis	90
Chapter 6 Discussion and Conclusion	94
6.1 Research problem and question	94

6.2 Overall survival from gastric cancer	95
6.2.1 Age and stage at diagnosis as significant factors for survival	96
6.2.2 Tumour location	98
6.2.3 Treatment by surgery	99
6.2.4 Treatment by chemotherapy	99
6.2.5 Treatment by radiotherapy and chemotherapy	100
6.3 Factors identified as not significantly impacting on survival	101
6.3.1 Sex	101
6.3.2 Histologic type	102
6.3.3 Tumour grade	102
6.3.4 Tumour size	103
6.3.5 Extent of cancer	104
6.4 Strengths and limitations	104
6.5 Implications and recommendations	107
6.5.1 Implications for policy	107
6.5.1.1 Implications for health system funding	107
6.5.1.2 Implications for health promotion policy	109
6.5.2 Implications for health information systems	111
6.6 Conclusions	111
References	113
Appendix 1: Patient information sheet	126

Appendix 2: Script for telephone conversation	133
Scenario A: Patient answers the phone call	133
Scenario B: Someone else answers the phone, and not the patient	134
Scenario C: If the patient is unavailable to answer the phone	135
Appendix 3: Distress protocol	137
Appendix 4: TNM clinical classification and TNM pathological classification	137
Appendix 5: The clinical and pathological stages based on the 8 th edition of the AJCC/	UICC
TNM system	140
Pathological stage (pTNM) of gastric cancer based on the 8 th edition of AJCC/UICC	141
Appendix 6: Stata syntax for data generation	142
Appendix 7: Literature database searches	144

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.