NATURAL HISTORY OF GASTRIC ADENOCARCINOMA AND TREATMENT OUTCOMES IN A UNITED KINGDOM-BASED POPULATION

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DECLARATION

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Thesis Abstract

There are clear unmet needs for effective therapeutic strategies in patients with advanced gastric cancer. Unanswered questions include whether baseline characteristics can predict treatment benefit and enable personalised treatment decisions, and which groups of patients stand to benefit the most from novel therapeutic strategies.

Overarching aims are:

(1) To describe current outcomes in patients with gastric adenocarcinoma (including Siewert III gastro-oesophageal junction adenocarcinoma) in the United Kingdom;
(2) To identify patient and disease factors associated with poor outcomes in this population; and
(3) To highlight unmet needs that may serve as meaningful endpoints in future trials as well as subgroups of patients who might stand to benefit from novel therapeutic modalities.

Findings are presented from a single tertiary centre cohort study of 540 patients with gastric adenocarcinoma between 2011 and 2021. A predictive model for 1-year survival identifies performance status, disease stage, surgical resection and chemotherapy as key prognostic factors. A case is made for gastrectomy and other aggressive modes of treatment in older patients with operable disease and adequate performance status, although intervention may not necessarily be in the best interests of patients with poor performance status. A chain of associations linking suboptimal preoperative optimisation with poor prognosis in surgical patients is demonstrated. Novel adjuvant strategies are therefore needed to optimise outcomes in patients undergoing emergency surgery or with other risk factors for recurrence. The current evidence base is insufficient to inform treatment recommendations for resectable linitis plastica, indicating a need for larger multinational research collaborations. Prognosis in patients with peritoneal disease is poor regardless of baseline characteristics or treatment offered. Intraperitoneal chemotherapy is discussed as a therapeutic modality that may improve outcomes in patients with peritoneal disease.

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List of Abbreviations

AJCC	American Joint Committee on Cancer
CI	Confidence interval
CRS	Cytoreductive surgery
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECF	Epirubicin, cisplatin and 5-fluorouracil
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FLOT	Fluorouracil, leucovorin, oxaliplatin and docetaxel
GOJ	Gastro-oesophageal junction
HIPEC	Hyperthermic intraperitoneal chemotherapy
IQR	Interquartile Range
MDT	Multidisciplinary team
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNUH	Norfolk and Norwich University Hospitals NHS Foundation Trust
NOGCA	National Oesophago-Gastric Cancer Audit
NOS	Newcastle-Ottawa Scale
OG	Oesophago-gastric
OR	Odds ratio
PCI	Peritoneal cancer index
PIPAC	Pressurised intraperitoneal aerosolised chemotherapy
PMGC	Peritoneal metastasis of gastric cancer
PS	Performance status
QoL	Quality of Life
RCT	Randomised controlled trial
REC	Research Ethics Committee
RoB	Risk of bias
ROC	Receiver Operating Characteristic
RR	Relative risk/risk ratio
SEER	Surveillance Epidemiology and End Result Registry
SCR	Somerset Cancer Registry
SD	Standard deviation
TNM	Tumour, node, metastasis
ULN	Upper limit of normal
US(A)	United States (of America)
UK	United Kingdom
WHO	World Health Organisation

CHAPTER 1- Gastric cancer in the United Kingdom

ABSTRACT

Clinical Context

Gastric cancer is the sixth most common malignancy and the fifth leading cause of cancer death worldwide. Although the prevalence of gastric cancer is relatively low in the United Kingdom and other western countries, a majority of UK patients with gastric cancer are diagnosed at advanced stages and suffer from poor outcomes regardless of treatment. There are clear unmet needs for effective therapeutic strategies in patients with advanced and metastatic gastric cancers as well as patients with resectable disease at high risk of cancer recurrence. Unanswered questions include whether baseline characteristics can be used to predict treatment benefit and enable personalised treatment decisions, and which groups of patients stand to benefit the most from novel therapeutic strategies.

Overarching Aims

The overarching aims of this thesis are:

(1) To describe current outcomes in patients with gastric adenocarcinoma (including Siewert III gastro-oesophageal junction adenocarcinoma) in the United Kingdom;
(2) To identify patient and disease factors associated with poor outcomes in this under-researched population; and
(3) To highlight unmet needs that may serve as meaningful endpoints in future trials as well as subgroups of patients who might stand to benefit from novel therapeutic modalities.

GENERAL INTRODUCTION

International context

Gastric cancer is the sixth most common malignancy and the fifth leading cause of cancer death worldwide[1]. Population screening programmes in Japan and South Korea have improved survival rates in these countries by identifying tumours at earlier stages[2]. This is not the case in the West, where the overall population incidence does not justify national screening programmes, or in countries with fewer resources per capita such as China[3,4]. Given its comparatively low incidence in Western countries, gastric cancer is also a relatively unpopular topic for clinical research in Europe and North America, especially when compared to colorectal and gynaecological malignancies. The paucity of gastric cancer research in the West comes with serious human consequences. Whereas the 5-year survival of all patients with gastric cancer in East Asia is in the region of 40-60%, the equivalent figure in Europe is only 24.5%[5].

The overall prevalence of gastric cancer has declined worldwide thanks to widespread treatment of *Helicobacter pylori* infection, which historically represented the most significant risk factor[6]. However, cancers involving the gastric cardia and gastro-oesophageal junction (GOJ) are a growing phenomenon. Rates of proximal gastric and junctional cancers have continued to rise, perhaps due to the increasing prevalence of risk factors such as obesity and gastro-oesophageal reflux disease[6]. Incidence of GOJ cancer has risen by nearly 2.5-fold in the United States since the 1970s[7]. The need for clinical research and therapeutic advances in gastric cancer therefore remains as pressing as ever.

United Kingdom context

In the United Kingdom (UK), Cancer Research UK reported 6453 new cases and 4333 deaths from gastric cancer in 2018[8]. As suggested by the high mortality-to-incidence ratio, outcomes of gastric cancer in the UK are generally poor, in keeping with much of the Western world. The UK can rightly be proud of its contributions to upper gastrointestinal cancer research, including the seminal MAGIC trial which established perioperative chemotherapy as the standard of care in Europe and the GO2 trial of reduced-intensity chemotherapy in older and frail patients[9,10]. However, perhaps due to low numbers of patients with gastric cancers, UK-based studies have invariably grouped together gastric and oesophageal cancers despite their differing behaviours and natural history[10–13].

The National Oesophago-Gastric Cancer Audit (NOGCA) State of the Nation Report, published in 2024, provides perhaps the most comprehensive and up-to-date profile of patients with gastric cancer in the UK[14]. The data presented in this report were based on the records of 19 865 patients diagnosed

with gastric or oesophageal cancer in the UK between 2020 and 2022. Siewert III gastro-oesophageal junction cancers were classified as gastric cancers (this classification will apply throughout the present thesis). Patients diagnosed with gastric cancer had a median age of 74 years and were predominantly male (66%). 45.2% of cases were diagnosed at Stage 4, where curative treatment is no longer possible. Only 31.7% of patients with gastric cancer were offered a treatment plan with curative intent. Indeed, the proportion of patients diagnosed with Stage 4 cancer has increased since the audit began. Furthermore, rates of diagnosis following an initial emergency admission have not improved in recent years, holding at 20% after previously declining from very high levels approaching 40% in the early 2000s[14,15].

Current standard of care for gastric cancer in the United Kingdom and Europe

The latest iteration of European Society for Medical Oncology (ESMO) guidelines for the treatment of gastric cancer were published in 2022[16]. Apart from very early T1a gastric cancers that may be treatable by endoscopic resection, combined modality therapy with radical gastrectomy, D2 lymphadenectomy and perioperative chemotherapy is now the standard of care for operable gastric cancers treated with curative intent. The evidence behind this recommendation will be discussed in Chapters 4 and 5.

For locally advanced and metastatic gastric cancer, the standard of care is combination chemotherapy using a platinum-fluoropyrimidine doublet, with additional recommendations for trastuzumab for HER2-positive and nivolumab for PD-L1-positive disease. Whilst the evidence for specific regimens of chemotherapy or immunotherapy is beyond the scope of this thesis, outcomes in patients treated with palliative chemotherapy will be explored in Chapters 3 and 6. The 2022 ESMO guidelines are the first version to acknowledge the potential use of hyperthermic intraperitoneal chemotherapy (HIPEC) in combination with radical resection and pressurised intraperitoneal aerosolised chemotherapy (PIPAC) in highly selected cases of peritoneal metastasis from gastric cancer. These strategies will be explored in Chapter 7.

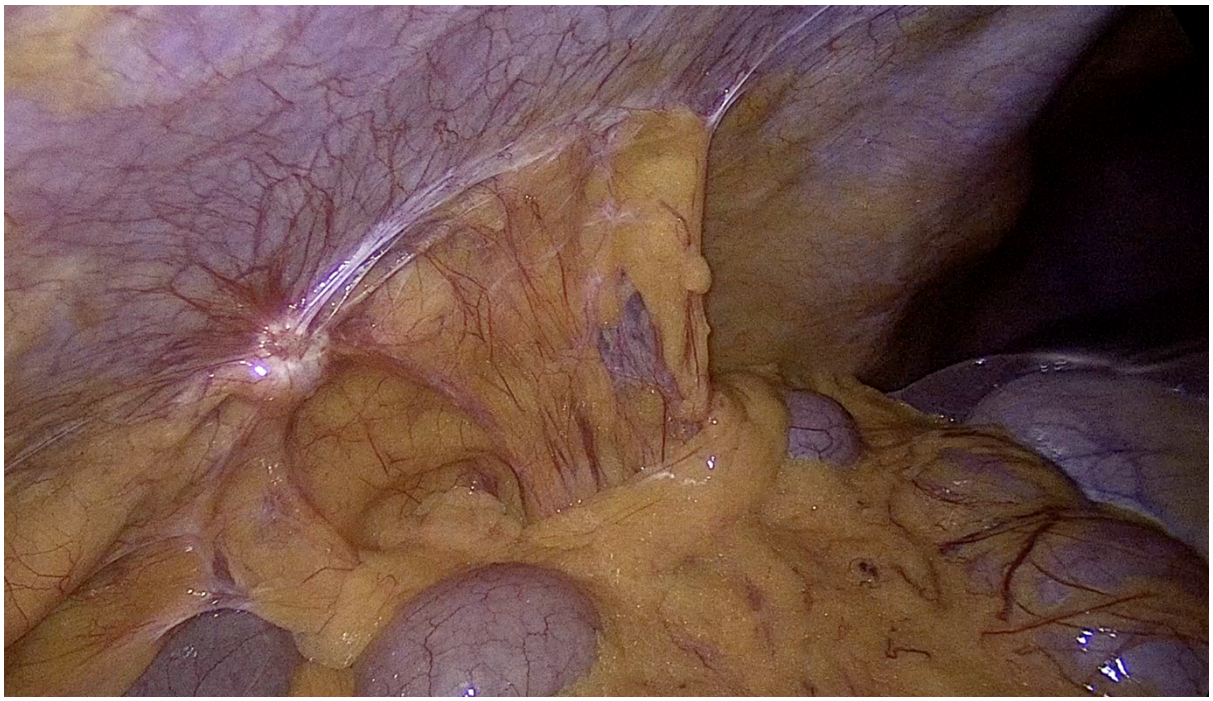
Unmet needs and unanswered questions

Significant progress has been made in diagnostic pathways and perioperative management of localised gastric cancer over the past two decades. Conversely, therapeutic strategies and outcomes in advanced and metastatic gastric cancer have changed little. Even in patients with potentially curable disease and treated with the gold standard of perioperative chemotherapy and gastrectomy, rates of recurrence remain stubbornly high and prognosis difficult to predict. The peritoneum is typically the most common site of recurrence (Figure 1.1). Historical studies have suggested that over the longer

term, up to 40% of patients treated with gastrectomy subsequently developed peritoneal recurrence in follow-up[17]. This figure may have improved in the current era of perioperative chemotherapy. NOGCA data showed a 3-year survival rate of 62.7% following curative surgery, although this figure included both gastric and oesophageal cancers[14]; data on recurrence is outside the remit of NOGCA. A Dutch retrospective multicentre study of 408 patients treated with gastrectomy and perioperative chemotherapy found post-gastrectomy recurrence in 36.8% of their cohort over a median follow-up of 27.8 months[18].

Figure 1.1: Peritoneal metastasis of gastric cancer

(Photo credit: Prof B. Kumar; photo taken with written consent for research purposes signed by patient prior to procedure.)



Outcomes of treatment in advanced and metastatic gastric cancer remain disappointing. Even with systemic chemotherapy, patients with metastatic gastric cancer typically do not survive beyond a few months[19]. This situation stands in contrast to colorectal and gynaecological cancers, where novel and aggressive approaches to metastatic disease have been incorporated into recent guidelines. Previous trials have largely failed to demonstrate consistent benefit with novel treatment strategies in metastatic gastric cancer or struggled to recruit sufficient participants. Although intrinsic tumour characteristics may partly account for disappointing trial outcomes, the realities of small patient numbers and finite resources available for trials in Western patients with advanced gastric cancer are likely to have contributed to a limited evidence base that is insufficient to guide optimal patient selection for novel therapeutic strategies.

The main unmet needs are therefore: (1) effective therapeutic strategies for patients with advanced and metastatic gastric cancer; (2) effective tools to predict the risk of cancer recurrence in surgical patients and targeted treatment strategies to reduce this risk; and (3) patient-centred tools that can inform meaningful conversations between care providers and patients about the relative risks and benefits of different treatment options and thereby enable shared decision-making and personalised care plans.

Related to the above, the main unanswered questions are: (1) whether baseline patient and disease characteristics can be used to predict both prognosis and potential treatment benefit, so as to enable personalised treatment decisions; (2) whether subsets of patients who will stand to benefit the most from novel therapeutic strategies can be identified and targeted for future clinical trials; and (3) what outcomes, other than survival, are important to patients with gastric cancer and represent meaningful endpoints for future studies.

AIMS OF THIS THESIS

Overarching aims

The overarching aims of this thesis are:

(1) To describe current outcomes in patients with gastric adenocarcinoma (including Siewert III gastro-oesophageal junction adenocarcinoma) in the United Kingdom;
(2) To identify patient and disease factors associated with poor outcomes in this under-researched population; and
(3) To highlight unmet needs that may serve as meaningful endpoints in future trials as well as subgroups of patients who might stand to benefit from novel therapeutic modalities.

This thesis initially intended to explore non-survival outcomes such as quality of life and treatment-related morbidity. The ultimate goal was to design a patient-centred tool for individualised comparisons of clinical benefit versus treatment-associated burden and risk. However, this was not possible given the dual constraints of ethical approval and available resources. Ethical approval was limited to the creation of a database from existing clinical records and did not allow for prospective data collection. Furthermore, only acute hospital records were available for research purposes, whereas the vast majority of data relating to morbidity and quality of life are in the domains of primary care and palliative care.

Summary of chapters

Chapter 2 introduces a cohort of patients with gastric adenocarcinoma treated at a tertiary referral centre in the East of England between 2011 and 2021, describes this cohort in terms of baseline patient and disease characteristics, presents overall survival outcomes, and presents a multivariable predictive model of survival at 1 year following diagnosis.

Chapter 3 focuses on older patients and patients with a poor performance status, evaluating the benefits of gastrectomy with curative intent and chemotherapy with palliative intent in these groups of patients.

Chapter 4 explores outcomes in patients undergoing surgical resection with curative intent, with a view to identifying disease and treatment characteristics associated with recurrence and poor survival.

Chapter 5 focuses on patients with linitis plastica, a particularly aggressive phenotype of gastric cancer that is rarely amenable to surgical resection and often associated with disseminated disease. A systematic review on the outcomes of surgical resection of linitis plastica with or without neoadjuvant chemotherapy is presented, as an exploration of whether more aggressive treatment strategies may lead to better outcomes in patients with diffuse cancers associated with a high risk of peritoneal metastasis.

Chapter 6 explores the characteristics and outcomes of patients with peritoneal metastasis of gastric cancer (PMGC) and seeks to identify prognostic predictors in this ‘forgotten’ population.

Chapter 7 discusses how findings in the previous chapters relate to the overarching aims and the extent to which this thesis succeeds in meeting its aims. The current evidence base for novel therapeutic modalities is reviewed and suggestions are made for future research.

CHAPTER 2- Characteristics and survival of a United Kingdom-based cohort of patients with gastric adenocarcinoma: a retrospective cohort study.

ABSTRACT

Background. Outcomes of gastric adenocarcinoma are poorly characterised in the UK population. Predictive models derived from historical cohorts or Asian cohorts may not be relevant to patients being newly diagnosed with gastric cancer in the UK or Western Europe. Compared to existing models, a model derived from a more recent UK-based cohort can better account for current disease and treatment patterns in the UK, provide patients and clinicians with a more accurate estimate of their prognosis, and more effectively highlight unmet needs for future research.

Objectives. For a population of patients with gastric cancer in the UK, we sought to: (1) characterise this population in terms of disease phenotype and fitness for intervention; (2) estimate overall survival; (3) estimate the frequencies of cancer-related complications; (4) evaluate the associations between baseline demographic, clinical, radiological and histological characteristics and overall survival; and (5) construct and evaluate the performance of a multivariable predictive model of survival at 1 year following cancer diagnosis.

Methods. This was a single-centre retrospective cohort study of all patients diagnosed with gastric adenocarcinoma between 2011 and 2021. Demographic, clinical, radiological and histological data were obtained from acute hospital care records. Descriptive statistics were compiled to characterise the cohort in terms of disease stage, disease phenotype, performance status and treatment received. Kaplan-Meier survival curves estimated overall survival with respect to disease stage, performance status and decade of age at diagnosis. Cox proportional hazards regression was used to identify independent predictors of overall survival. A predictive model was constructed using logistic regression to estimate associations between the outcome of survival at 1 year and baseline demographic, clinical, radiological and histological characteristics as well as treatment received. Model discrimination was assessed by means of Receiver Operating Characteristic (ROC) analysis. Calibration was evaluated with a calibration belt and by applying the Hosmer-Lemeshow test.

Results. 540 patients were included in the analysis. Median overall survival was 302 days (interquartile range 86-750 days) over a median follow-up of 7.44 years. Median age of the cohort was 77.44 years (IQR 70.62-83.24). Patients with recorded Eastern Cooperative Oncology Group (ECOG) performance

statuses of 0, 1, 2, 3 and 4 accounted for 28.1%, 34.3%, 18.1%, 13.5% and 0.7% of the cohort respectively. 46.1% of the cohort had AJCC Stage IV disease (metastatic disease) at the time of initial cancer diagnosis. Resection of the primary tumour (gastrectomy or endoscopic mucosal resection) was performed in 155 patients (28.7%). Patients undergoing curative resection were younger on average (median age 74.5 vs 78.9, $p<0.0001$) and significantly less likely to have an ECOG performance status of ≥2 (7.4% vs 45.1%, $p<0.0001$) compared to patients treated with palliative intent. In multivariable Cox proportional hazards regression, only performance status, cancer stage, resection of primary tumour and treatment with chemotherapy were found to be independent predictors of median overall survival. The same variables were identified as independent predictors of survival at 1 year in a logistic regression model. At a 50% predicted probability cutoff, the model's sensitivity was 68.44%, specificity 88.26%, positive predictive value 84.15% and negative predictive value 75.43%. The c-statistic for this prediction model was 0.88. Linitis plastica, signet ring cell cancer, pre-existing cardiovascular disease and cancer diagnosis following an emergency presentation were not found to be independent predictors of median overall survival or overall survival at 1 year. Smoking status and Lauren histological classification were not included in multivariable analysis due to large amounts of missing data.

Conclusions. Poor survival outcomes reflect the high proportion of Stage IV cancers, high median age of the cohort, and low proportion of patients undergoing treatment with curative intent. The predictive model derived from this cohort supports the general assumptions that guide management decisions in the UK. The prognostic predictive value of performance status far outweighs that of chronological age. The present model compares favourably to existing models in terms of its discriminatory ability and calibration but external validation is required. The study was disadvantaged by a relatively small sample size thereby restricting the number of parameters that could be included in multivariable analysis and precluding the assessment of outcomes other than overall survival.

INTRODUCTION

Clinical Problem

Beyond rudimentary survival data, the natural history of gastric cancer in the UK is poorly defined. Although national survival figures are freely available in publications from the Office for National Statistics[20] and Cancer Research UK, these publications provide only limited insight into the interplay between patient, disease and treatment characteristics in determining survival. To date, no published study has attempted to design a predictive model for medium to long-term survival specific to gastric adenocarcinoma in the UK population. Existing UK-based prognostic models for patients with gastric cancer have been derived from cohorts including both gastric and oesophageal malignancies [12,21,22] and focus primarily on short-term postoperative outcomes [21,22]. It is unclear whether predictive models derived in East Asian gastric cancer cohorts are applicable to the UK gastric cancer population.

Risk factors for poor outcomes explored in previous studies

Existing literature, including previous modelling studies, were consulted to identify putative prognostic predictive factors for assessment. Patient characteristics typically included in existing predictive models of survival are: age at diagnosis[12,21,23], sex[21,23], performance status[12,21], nutritional status[12] and pre-existing comorbidities[21]. Disease characteristics include tumour location[21], histology[21,23], overall American Joint Committee on Cancer (AJCC) disease stage, and individual 'tumour' (N), 'node' (N) and 'metastasis' (M) staging categories [21,23]. Survival following primary tumour resection, in most cases restricted to procedures performed with curative intent, remains the main focus of most predictive models[24].

Other characteristics that have been implicated as prognostic factors include: smoking status[25], Lauren 'diffuse' type cancers[25], signet ring cell histology[26], linitis plastica[27,28], and cancer diagnosis following an emergency presentation[15,29]. In a study of patients with signet ring cell cancers, linitis plastica, lymphatic involvement and tumour invasion through the serosa were identified as independent risk factors for peritoneal recurrence after surgery[30]. Linitis plastica is generally considered a more aggressive disease phenotype with more diffuse involvement and a greater propensity for local invasion and peritoneal spread. It is also often more difficult to diagnose, requiring deeper and/or repeated endoscopic biopsies which may lead to delayed diagnosis[31]. Previous UK-based single-centre studies, performed in 2004[15] and 2012[29], have shown that emergency presentation is a significant and independent predictor of poor survival [11,12].

Existing predictive models and their limitations

Unsurprisingly, given the higher incidence of gastric cancer in East Asia, the majority of models predicting survival in gastric cancer have derived from East Asian cohorts. A systematic review and meta-analysis performed by van de Boorn and colleagues in 2018 identified 22 studies describing the creation of novel prediction models in patients with gastric cancer, of which 14 were performed in East Asian countries, 5 in the United States (including a Chinese study using data from an American cancer registry), 2 in Europe (including a joint USA-Dutch cohort), and 2 in Iran[24]. The meta-analysis calculated an average c-index (a measure of discriminatory ability) of 0.75 across all upper-gastrointestinal predictive models. The majority of modelling studies did not include a formal statistical analysis of calibration (goodness of fit).

Models derived from non-European or historical cohorts are of questionable relevance with respect to patients being newly diagnosed with gastric cancer in the UK. Gastric cancer has been described as "a heterogenous disease with diverse histological characteristics (phenotypes) and genotypes"[31]. Epidemiological, phenotypic and molecular differences have been noted between gastric cancers in East Asia and gastric cancers in Western Europe. The highest incidences of gastric adenocarcinoma are observed in Eastern Asia and Eastern Europe, and the lowest incidences in Northern Europe and North America [25]. Environmental rather than genetic factors are likely to underpin differences in incidence. Whereas first-generation immigrants retain the risk rate of their native country, the incidence of gastric cancer among their descendants tends to mirror that of the general population in their new environment[25]. Cancers classified as 'diffuse' under the Lauren classification system and tumours located in the proximal stomach account for a higher proportion of gastric cancers in western countries compared with gastric cancers in East Asia[32]. Meanwhile, an analysis of over 1600 gastric cancer specimens has revealed distinct differences in gene signatures relating to T-cell function between Asian and non-Asian gastric cancers[33].

Predictive models derived from cohorts with large numbers of early-stage tumours may be less applicable in countries such as the United Kingdom where most gastric cancers are diagnosed at an advanced stage. Japan and South Korea, both advanced economies with high incidences of gastric cancer, have introduced national screening programmes involving the use of barium radiography and endoscopy[2,34]. A greater proportion of tumours in Japan and South Korea therefore tend to be diagnosed at earlier stages, leading to improved survival outcomes in those countries. As of 2017, 5-year overall survival rates of patients with gastric cancer had exceeded 50% in Japan and South Korea, compared to 25-30% internationally[34]. Unfortunately, screening programmes are difficult to justify

on either clinical or economic grounds in the United Kingdom and other western countries, where gastric cancer is only found in 1-2% of patients with dyspepsia undergoing endoscopic evaluation [25].

Furthermore, treatment algorithms differ slightly between countries. Gastrectomy with 'D2 lymphadenectomy' – involving the removal of lymph nodes along the common hepatic artery, splenic artery and coeliac axis as well as perigastric lymph nodes – is now the international standard of care[16]. Historically, however, a more-limited 'D1' gastrectomy was the norm in many Western centres [31] and findings from previous studies performed in Western cohorts may reflect this practice. Meanwhile, whereas adjuvant chemotherapy is the standard of care in East Asian centres, stronger evidence in favour of neoadjuvant chemotherapy in western trials has led to its widespread adoption in Western European and North American centres [9,16].

Finally, older predictive models, even those derived from Western cohorts may have been made obsolete by shifting disease patterns, improved diagnostic pathways and changes to management algorithms. A marked increase in the incidence of cardia and gastro-oesophageal junction cancers has been observed, particularly in the West but also in endemic countries. This is likely a consequence of a decline in the prevalence of conventional risk factors for distal gastric cancers such as *Helicobacter pylori* infection and poor food preservation techniques, coupled with a worldwide rise in obesity rates[31]. Intestinal-type tumours have declined in prevalence whilst diffuse-type tumours, which are less strongly linked with environmental factors and are associated with a worse prognosis, have remained stable or increased in frequency[25,35]. Standardised referral guidelines (the 'two-week wait' pathway) were introduced in the UK 2000 and updated in 2005 (NICE CG27) and again in 2015 (NICE NG12)[36]. The effect of improved referral pathways can be seen in the decreasing proportion of patients diagnosed with gastric cancer following an emergency presentation, quoted at 39% in a 2004 UK study compared to 14.4% in another UK study performed only 8 years later although a recent report from the National Oesophago-Gastric Cancer Audit suggests that this trend may have plateaued or possibly worsened again[14,15,29]. Meanwhile, the criteria determining eligibility for surgical resection have been tightened in light of evidence showing little benefit to operating on patients with positive peritoneal cytology[19]. Up-to-date observational data is therefore needed, reflecting the UK gastric cancer population and taking recent advances into account which would in turn allow clinicians to make more informed decisions about treatment and prognosis.

Further unmet needs

Most existing predictive models are chiefly concerned with survival following curative resection. In models where the primary outcome is overall survival calculated from the time of resection, treatment has "largely been completed at the point of resection" [24]. Predictions using such models merely

serve to provide patients and physicians with an estimate of prognosis and cannot be used to guide clinical decisions at the time of cancer diagnosis. None of the models included in van de Boorn and colleagues' meta-analysis attempted to weigh up the risks against the benefits of treatment, and none attempted to predict health-related quality of life despite widespread recognition of its importance [24].

Rationale

There is a clear unmet need for an up-to-date predictive model of survival in British patients with gastric cancer. Indeed, predictive models are more important than ever before given the increasing numbers of frail and co-morbid patients diagnosed with gastric cancer. A model derived from a more recent UK-based cohort can better account for current disease patterns in the UK, better guide treatment decisions, and provide patients with a more accurate estimate of their prognosis compared to historical models or models derived in East Asian countries. National cancer registries and national hospital admission statistics are available in the UK. However, data from these sources either do not offer the same level of detail relating to treatment decisions and outcomes or are not made freely available for research purposes.

Ideally, a new model would also assess quality of life alongside survival and provide an estimate of treatment-associated risks alongside benefits. However, the current study's potential to address these gaps in the literature is constrained by the available data, resources and ethical approval. In the absence of routinely collected data on health-related quality of life, this study sought to analyse disease-related complications as a surrogate measure of quality of life.

AIMS AND OBJECTIVES

This study aims to (1) characterise and describe the natural history of a United Kingdom-based cohort of patients with gastric adenocarcinoma, and (2) to develop a multivariable predictive model for survival in British patients with gastric adenocarcinoma.

The objectives for the first aim are:

1. To estimate the prevalence of operable vs inoperable disease and aggressive phenotypes, namely linitis plastica and signet ring cell cancers, amongst patients with gastric adenocarcinoma in the UK.

2. To estimate the fitness of patients with gastric adenocarcinoma in the UK for current and emerging treatment modalities as well as clinical trials of novel therapeutic strategies.
3. To estimate the overall survival of patients with gastric adenocarcinoma in the UK, both in aggregate and stratified by baseline characteristics and treatment modalities.
4. To estimate the frequency of cancer-related complications – namely ascites, gastrointestinal tract perforation, gastrointestinal tract obstruction and ascites requiring drainage – as surrogate measures of quality of life, and their associations with baseline patient, disease and treatment characteristics.

The objectives for the second aim are:

5. To estimate and examine the associations of baseline patient-related (i.e. demographic) and disease-related (i.e. clinical, radiological and histo-cytological) characteristics with overall survival in British patients with gastric adenocarcinoma.
6. To construct and evaluate the performance of a predictive model for overall survival at 1 year following diagnosis. Given funding and feasibility constraints, this is limited to a derivation study. Depending on the performance of the derived model as well as future funding and collaboration, external validation is intended at a later date.

The above objectives are designed with the intention of identifying unmet needs of patients with gastric adenocarcinoma in the UK. It is intended that findings from this study will guide the direction of subsequent chapters of this thesis and suggest themes for future research focusing on patients with poor prognostic features who may stand to benefit from emerging and novel therapeutic strategies.

METHODS

Study Design and Setting

This is a single-centre, hospital-based cohort study involving a retrospective analysis of prospectively collected data. The cohort comprised all patients with a formal diagnosis of gastric adenocarcinoma, including Siewert III gastro-oesophageal junction adenocarcinomas, at the Norfolk and Norwich University Hospital NHS Foundation Trust (NNUH), Norwich, United Kingdom between February 2011 and June 2021. Subjects were identified through the Somerset Care Register (SCR), which records the dates of diagnosis and death, patient demographics and treatment decisions made at oesophagogastric (OG) multidisciplinary team (MDT) meetings. Eligibility for inclusion was confirmed through a manual inspection of clinic letters, endoscopy reports and histology reports. The remaining

data (as listed under 'outcomes', 'exposures' and 'covariates' below) were retrieved from electronic health records. This study was performed under existing ethical approval for compilation and analysis of a research database incorporating routinely collected data relating to patients with upper gastro-intestinal tract cancers at the Norfolk and Norwich University Hospital (NHS Health Research Authority research ethics committee proportionate review: REC Reference 20/EM/0193; favourable outcome on 11 August 2020).

Study Population

Inclusion criteria are as follows:

i. Adult patients aged 18 years or above.
ii. Histo-cytological and/or radiological diagnosis of gastric adenocarcinoma, including Siewert III adenocarcinomas of the gastro-oesophageal junction.
iii. Date of diagnosis, as recorded on the Somerset Care Register, between 1 February 2011 and 30 June 2021 (inclusive).

Exclusion criteria are as follows:

i. Patients with incomplete or inaccessible electronic health records which precluded ascertainment of inclusion criteria and/or collection of core clinical, radiological and treatment-related data. In practice, this excluded all patients referred to the multidisciplinary team at the Norfolk & Norwich University Hospital but managed primarily at district general hospitals other than the James Paget University Hospital, Great Yarmouth.
ii. Patients with recurrence of previously resected gastric cancer diagnosed before February 2011.
iii. Histological subtypes of gastric neoplasms other than adenocarcinoma, e.g. neuroendocrine tumours, gastro-intestinal stromal tumours, gastric lymphomas, etc.

Outcomes

The primary outcomes for each of the study objectives are as follows:

- Objective 1: Number and proportion (expressed as a percentage) of patients with the pre-defined characteristics.
- Objective 2: Eastern Cooperative Oncology Group (ECOG) performance status at baseline.
- Objectives 3, 4 and 5: Overall survival, defined as survival from the date of cancer diagnosis (as recorded on the Somerset Cancer Register) to death from any cause.

Secondary outcome measures are:

- Disease-related complications resulting in hospital admission or occurring in the course of hospital admission, namely: gastro-intestinal tract perforation, intestinal obstruction, ascites, biliary obstruction, pleural effusion and urinary tract obstruction secondary to cancer.

Predictive modelling with respect to disease-related complications was originally planned, but numbers of events were too low and documented frequencies likely underestimated the true prevalence of complications (see Results). Data collection was limited to acute hospital health records due to ethical approval and feasibility constraints. Complications managed in primary and palliative care settings are therefore not reflected in the study data.

Case Ascertainment and Clinical Measurements

A medical gastroenterologist reviewed each set of electronic health records to ascertain eligibility for inclusion and to confirm the types of treatment delivered to each patient. All data recorded in the study database strictly reflect information available in existing electronic health records. In cases where information regarding an exposure or covariate was not explicitly stated in health records, this was recorded as 'missing' and not included in subsequent analysis. No attempts were made to derive data for missing variables by means of extrapolation from related clinical information (e.g., estimating performance status from narrative descriptions of a patient in clinic letters, or Lauren's histological classification from histology reports which do not explicitly provide this classification).

Exposures

The following variables were assessed for their association with overall survival:

Patient-related baseline characteristics:

- Age (continuous variable: years)
- Sex (binary variable)
- Smoking status at the time of diagnosis (binary variable)
- ECOG performance status (categorical variable: 0-4)
- Cardiovascular disease (binary variable)

Disease-related baseline characteristics:

- Involvement of the gastro-oesophageal junction (binary variable: gastric or Siewert III)
- Diagnosis following an emergency presentation (binary variable), defined as gastro-intestinal bleeding, obstruction or perforation

- American Joint Committee on Cancer (AJCC) overall stage (categorical variable: I-IV)
- Linitis plastica phenotype (binary variable)
- Signet ring cell histology (binary variable)
- Presence of peritoneal metastasis at cancer diagnosis (categorical variable)

The following baseline characteristics were also identified from electronic health records but excluded *a priori* from predictive modelling (Objective 5):

- AJCC/UICC TNM staging: T stage (categorical: 1-4) and N stage (categorical: 0-3).
- 'Ever smoker' status (categorical variable).
- Presence of extraperitoneal solid-organ metastasis at cancer diagnosis (categorical variable).
- Previous gastric surgery for benign pathology (categorical variable)
- Lauren histological classification (binary variable: intestinal or diffuse)

Decisions to exclude exposures from predictive modelling were made *a priori* on the basis of sample size calculations (see Methods: Sample Size Calculation). These decisions are justified by the increased risks of model overfitting and optimism associated with the inclusion of too many parameters within the constraints of a fixed cohort size (n=540) [37]. The Lauren histological classification was excluded from predictive modelling due to inconsistent reporting and lack of pathologist input into study design and data interpretation (see Results: Clinical Characteristics).

Covariates

Treatment with surgical resection of the primary tumour (regardless of intent or extent) and treatment with chemotherapy (neoadjuvant, adjuvant or palliative) were recorded as plausible confounding factors and also to enable stratification of survival outcomes as well as subgroup analysis in subsequent chapters.

Statistical Analysis

Descriptive data were reported in terms of frequencies and proportions for categorical variables, means with 95% confidence intervals for continuous variables following a normal distribution, and medians with interquartile ranges for non-normally-distributed continuous variables (objectives 1-2).

Associations between categorical independent variables and categorical dependent variables were evaluated using the Chi-square test (for binary independent variables) or logistic regression (for multi-level independent variables) as appropriate. Associations between continuous independent variables and categorical dependent variables were evaluated using Student's t-test or the Mann-Whitney U-

test when normality was rejected. Statistical significance was defined as a p-value equal to or less than 0.05.

Median overall survival was estimated using Kaplan Meier methodology (objective 3). The effects of baseline patient or disease characteristics on overall survival were evaluated by plotting Kaplan Meier survival curves and calculating hazard ratios using Cox proportional regression (objective 4). A Cox proportional hazards model incorporating treatment with primary tumour resection or chemotherapy as covariates was constructed to identify baseline characteristics that may be independently predictive of mortality.

Associations between baseline patient or disease characteristics and overall survival at 1 year were estimated by a logistic regression model (objective 5). Performance of the predictive model was evaluated as described below.

All statistical analyses were performed using STATA Version 17.0 MP (StataCorp, College Station, Texas, USA).

Development of predictive models and evaluation of their performance

A multivariable logistic regression model to predict overall survival as constructed by means of stepwise selection. Variables with a significance level of ≤0.25 in univariate analysis were entered into the multivariable model. A significance level of 0.05 determined elimination from the final model. The predictive model was intended to capture baseline characteristics that are routinely recorded in outpatient clinic appointments or reported in standard radiological, endoscopic and histo-cytological investigations that inform treatment decisions made at MDT meetings.

Discrimination of the model, referring to its ability to distinguish individuals with the outcome (1-year survival) versus those without, was measured using the concordance statistic (c-statistic) – equal to the area under the receiver operating characteristic (ROC) curve [38]. Calibration of the derived model was evaluated by means of a calibration belt as per the methodology described by Nattino et al and generated using their calibration belt Stata package[39,40]. Further assessment of calibration was performed using the Hosmer-Lemeshow test, a chi-square test of the difference in the proportion of patients with the outcome versus the proportion expected to develop the outcome.

Internal validation was performed with bootstrap resampling to assess model optimism, a decrease in model performance when applied to a different sample. 500 random subsets were drawn from the original dataset, of which one subset was used for derivation and compared 499 times against the remaining subsets by means of a chi-square test.

Determination of an appropriate survival time point for predictive modelling

An appropriate overall survival time point was determined for the predictive model through a process of reverse sample size calculation with respect to national survival figures, the number of expected parameters in the model, and a fixed sample size of 540 patients. The minimum number of expected parameters was 15, on the basis of baseline and exposure data collected and taking two multi-level categorical variables into account (ECOG performance status and AJCC staging). Office of National Statistics data for cancer in England between 2015-2019 showed a median survival of less than a year in patients with gastric cancer: 46.3% of patients survived to one year from cancer diagnosis, and 31.3% of patients survived to two years[20].

Risks of model overfitting and optimism are increased when the sample size is too small or the number of parameters is too large. Given the retrospective nature of this study and constraints of data availability and ethical approval, the total sample size of this cohort was fixed at 540, with the number of cases available for a complete case analysis likely to be substantially lower due to missing data. Ensuring the sample size was adequate to avoid overfitting and optimism could only be achieved by choosing an appropriate outcome and/or reducing the number of parameters. As previously described, a number of baseline characteristics were excluded *a priori* from predictive modelling to reduce the number of parameters to as close to 15 as possible.

Sample size calculations, detailed below, suggested that the sample size of 540 patients was adequate for a predictive model of 1-year overall survival with 15 parameters but underpowered for a predictive model of 2-year overall survival.

Sample Size Calculation: 1-year overall survival

Sample size calculations for the predictive model of 1-year overall survival were performed using the methods described by Riley et al[37] and the associated *pmsampsize* Stata package. The number of outcome 'events', defined as survival at 1 year from cancer diagnosis, was anticipated to be 46.3% of the cohort on the basis of national statistics for cancer survival in England between 2015-2019 [20]. The anticipated model performance, expressed as R-squared (R_{cs}^2), was estimated as 0.225. This was calculated using the formula $R_{cs}^2 = R^2_{Nagelkerke} \times max(R_{cs}^2)$. $max(R_{cs}^2)$ denotes the maximum possible value for R_{cs}^2, corresponding to 0.75 for the anticipated outcome proportion. In the absence of existing data, $R^2_{Nagelkerke}$ defaulted to 0.3 as a 'compromise' suggested by Baeza-Delgado et al when 'direct' measures (denoting direct relationships between predictors and outcomes) are absent from the model but some information on the processes involved is included[41].

Assuming an outcome proportion of 46.3% and R_{cs}^2 of 0.225, the minimum sample sizes required to avoid model overfitting and optimism are 557 with 16 parameters and 522 with 15 parameters. Candidate parameters were therefore reduced *a priori* to a number as close to 15 as possible by excluding certain baseline characteristics with either a degree of likely overlap with other baseline characteristics (e.g. TNM staging vs overall AJCC stage) or low anticipated rates of exposure (e.g. previous gastric surgery for benign pathology).

Sample Size Calculation: 2-year overall survival

The number of outcome 'events' – defined as survival at 2 years from cancer diagnosis – was anticipated to be 31.3% of the cohort on the basis of national statistics for cancer survival in England between 2015-2019 [20]. Using the same methodology as described above, the anticipated model performance, expressed as R-squared (R_{cs}^2), was estimated as 0.213. This was calculated using the formula $R_{cs}^2 = R^2_{Nagelkerke} \times max(R_{cs}^2)$. $max(R_{cs}^2)$ denotes the maximum possible value for R_{cs}^2, corresponding to 0.71 for the anticipated outcome proportion. Assuming an outcome proportion of 31.3% and R_{cs}^2 of 0.213, the minimum sample size required to avoid model overfitting and optimism is 556 with 15 parameters. A sample size of 540 patients is therefore underpowered for a model of overall survival at 2 years in British patients with gastric cancer.

Dealing With Missing Data

Missing data is an often-unavoidable challenge encountered in the retrospective analysis of patient care records. In clinical trials, the data required for analysis are pre-defined and prospectively collected, usually with the aid of tools to ensure consistency. In routine clinical practice, however, data collection may be haphazard, omitted if felt to be irrelevant, and even when collected, poorly documented or recorded in an unsystematic manner.

The three mechanisms of missing data encountered in research are: 'missing completely at random', 'missing at random' and 'missing not at random'[42]. In reality, it is not always possible to fully define the mechanism of missing data and most datasets contain a mix of all three types[43]. An effort must nonetheless be made to describe the most likely mechanism as this determines statistical handling of missing data. Inappropriate treatment of missing data may lead to biased or inaccurate estimates of treatment effect, loss of statistical power and unnecessary complexity of statistical methodology[44].

A gradual transition from paper-based to electronic records is still ongoing at the sites where this research was conducted. Baseline characteristics such as smoking status, performance status and comorbidities are not consistently entered into the Somerset Cancer Register for every patient. This

information is often found buried in clinic letters or even handwritten notes scanned onto unwieldy archives which are not amenable to a digital search and must be manually trawled. It is entirely conceivable that data may have been lost during the scanning process or not captured for reasons as trivial as illegible handwriting. Although such omissions may be assumed to be random, the possibility of systematic error (e.g. due to assessment or treatment by certain clinicians) cannot be excluded.

Variables with the highest proportions of missing data were smoking status, disease staging and performance status. As detailed in the following section, data were found to be 'missing not at random'. This was determined by testing for associations between 'missing data' for a given variable and values of other pre-specified baseline characteristics as predictors of 'missing data' using the Chi-square, Mann-Whitney U or Student's t-test as appropriate.[45] All missing variables were significantly correlated with older age at diagnosis and poor performance status. However, it was not possible to measure and account for all factors which may explain the missing data, an important criterion that distinguishes 'missing at random' from 'missing not at random'[43]. Aside from missing performance status values (associated with older age and therefore likely to be worse compared to values for patients with a recorded performance status), the probable 'direction' of most missing data cannot be deduced from their associations. In other words, there is "extra information associated with the missing data that cannot be recovered by utilising the relationships observed in the data" as described by Papageorgiou and colleagues in their definition of 'missing not at random'[44].

Strategies for handling missing data include complete case analysis, single imputation, multiple imputation and, historically, the use of dummy variables[43]. Complete case analysis excludes cases with missing data for any variables relevant to the analysis, and is the default approach for many statistical packages including STATA. Shortcomings include the loss of statistical power and precision as well as the possibility of bias in mechanisms other than 'missing completely at random'[43]. Single imputation involves replacing missing data with a single value "thought to best represent the mechanism of the missing data" and is therefore an inappropriate strategy when the reasons for missing data are not entirely clear[44]. The dummy variable technique has been mostly discredited as it can lead to errors and has been shown to generate biased estimates even in situations of data missing completely at random[43,46]. Multiple imputation attempts to overcome these limitations by generating multiple values for each data point through a process of random sampling from the predictive distribution of the observed data[44]. These values are initially stored in multiple datasets, with analyses performed on each dataset separately and subsequently combined into single estimates of effect[43]. Most statisticians now recommend multiple imputation as the strategy of choice for 'missing at random' situations[42–44].

Unfortunately, none of these methods produce unbiased estimates in 'missing not at random' situations[44]. In a simulation study involving 5000 simulated data sets, Mukaka and colleagues demonstrated that both multiple imputation and complete case analysis yielded invalid inferences in 'missing not at random' scenarios[45]. Indeed, multiple imputation was shown to over-estimate effect size and led to positive bias away from the null hypothesis[45]. Multiple imputation therefore offers little or no statistical advantage over complete case analysis when data is 'missing not at random'.

With these considerations, a conscious decision was made to perform statistical analysis on a complete-case-analysis basis to avoid unnecessary statistical complexity. The shortcomings of this strategy, including the loss of power, potential for bias and limited generalisability of results, must not be overlooked. Given the loss of power, complete case analysis is perhaps more likely to lead to bias in favour of the null hypothesis. This is arguably a less risky proposition compared to the positive bias away from the null hypothesis associated with multiple imputation in Mukaka and colleagues' simulations of 'missing not at random' scenarios[45].

RESULTS

Study Participants

625 patients with 'gastric' neoplasms and 573 patients with 'lower oesophageal' neoplasms involving the gastro-oesophageal junction were identified from the Somerset Care Register. All patients had been discussed at multidisciplinary team (MDT) meetings held at the Norfolk & Norwich University Hospital (NNUH) between February 2011 and June 2021. Of the patients with gastric neoplasms, 4 patients were excluded due to a date of original cancer diagnosis before February 2011, 96 patients were excluded due to non-adenocarcinoma pathology, and 122 patients were excluded due to incomplete or inaccessible health records (including all patients treated at a hospital other than the NNUH or James Paget's University Hospital). Of the patients with 'lower oesophageal' neoplasms, 305 patients with Siewert I or Siewert II adenocarcinomas or non-adenocarcinoma pathologies were excluded, 2 patients were excluded due to a date of original cancer diagnosis before February 2011, and 129 patients were excluded due to incomplete or inaccessible health records.

A total of 540 patients were included in the analysis cohort, including 403 patients (74.6%) with non-cardia gastric adenocarcinomas and 137 patients (25.4%) with Siewert III adenocarcinomas of the gastro-oesophageal junction. The date of last follow-up was 30 June 2023, two years from the end of the time period for inclusion into the cohort. The median follow-up from the date of diagnosis was 2717 days (7.44 years).

Clinical Characteristics

Baseline characteristics of study participants are summarised in Table 2.1. The median age was 77.44 years (interquartile range 70.62-83.24). There was a male preponderance: 377 patients (69.8%) were men and 163 patients (30.2%) were women.

211 patients (39.1%) underwent staging laparoscopy. A further 314 patients (58.1%) had cross-sectional imaging performed at the time of diagnosis, enabling the presence of distant metastases to be determined. 15 patients did not undergo any staging investigations due to clinical judgement.

Metastatic disease (stage 'M1') was identified at initial staging in 249 patients (46.1%). 140 patients (25.9%) were found to have peritoneal metastasis, including positive-cytology-only disease, and 133 (24.6%) had extraperitoneal solid organ metastasis. Patients with metastatic disease at initial staging were less likely to have been diagnosed following an emergency presentation (relative risk [RR] 0.64, 95% confidence interval [CI] 0.46-0.88, p=0.0017) and more likely to have a linitis plastica phenotype (RR 1.67, 95% CI 1.40-2.01, p<0.0001). There were no significant associations between metastatic disease and age at diagnosis, smoking status, sex, gastro-oesophageal junction involvement (Siewert III cancers) or signet ring cell histology.

Signet ring cell histology was reported in 143 patients (26.5%). Patients with signet ring cell cancers were slightly but statistically significantly younger on average (median [IQR] 75.8 years [65.8-82.4] vs 78.0 years [71.0-83.3], p=0.04), and more likely to have linitis plastica (RR 2.12, 95% CI 1.58-2.84, p<0.0001). Signet ring cell cancers were not significantly associated with sex, metastatic disease at initial staging, smoking status or diagnosis following an emergency presentation.

Table 2.1: Baseline patient and disease characteristics

	Total (n=540)	Cases with missing/unknown values
Age (median, IQR)	77.4 (70.6-83.2)	-
Gender (n, %)		-
Male	377 (69.8%)	-
Female	163 (30.2%)	-
GOJ involvement, Siewert III (n,%)	137 (25.4%)	-
Cardiovascular Disease (n, %)	156 (28.9%)	-
Previous myocardial infarction	57 (10.6%)	-
Emergency Presentation (n, %)	86 (15.9%)	-
ECOG Performance Status (n, %)		28 (5.2%)
0	152 (28.1%)	-
1	185 (34.3%)	-
2	98 (18.1%)	-
3	73 (13.5%)	-
4	4 (0.7%)	-
Smoking History (n, %)		159 (29.4%)
Current smokers	65 (12.0%)	-
Ex- smokers	187 (34.6%)	-
Never smoked	129 (23.9%)	-
AJCC Cancer Stage (n,%)		43 (8.0%)
I	39 (7.2%)	-
II	109 (20.2%)	-
III	100 (18.5%)	-
IV	249 (46.1%)	-
T stage (n,%)		102 (18.9%)
T_1	21 (3.9%)	-
T_2	36 (6.7%)	-
T_3	232 (43.0%)	-
T_4	149 (27.6%)	-
N stage (n,%)		91 (16.6%)
N_0	129 (23.9%)	-
N_1	103 (19.1%)	-
N_2	101 (18.7%)	-
N_3	116 (21.5%)	-
M stage (n,%)		16 (3.0%)
M_0	275 (50.9%)	-
M_1	249 (46.1%)	-
Peritoneal metastasis (n,%)	140 (25.9%)	15 (2.8%)
Extraperitoneal solid organ metastasis	133 (24.6%)	15 (2.8%)
Linitis Plastica (n,%)	63 (11.7%)	-
Signet ring cell histology (n, %)	143 (26.5%)	20 (3.7%)
Status at end of follow-Up (n,%)		-
Alive	62 (11.5%)	-
Dead	478 (88.5%)	-

Linitis plastica was described in 63 patients (11.5%). Patients with linitis plastica were more likely to be female (RR 1.85, 95% CI 1.17-2.94, p=0.0087), exhibit signet ring cell histology (RR 2.82, 95% CI 1.76-4.50, p<0.0001) and have metastatic disease at initial staging (RR 3.11, 95% CI 1.80-5.35, p<0.0001), particularly peritoneal metastasis (RR 4.35, 95% CI 2.71-6.99, p<0.0001) but not extra-peritoneal solid organ metastasis. Indeed, peritoneal disease was identified in 60.3% of patients with linitis plastica at initial staging. There were no significant associations between linitis plastica and age at diagnosis, smoking status or diagnosis following an emergency presentation.

Lauren histological classification was excluded from predictive modelling due to inconsistent histology reporting. The Lauren histological classification was either ambiguous or absent in 61% of available histopathology reports. In certain cases, alternative classification systems (such as the World Health Organisation classification: papillary, tubular, mucinous, etc.) were used, which do not correspond consistently to the Lauren classification[47,48].

Performance Status, Treatment Characteristics and Fitness for Intervention

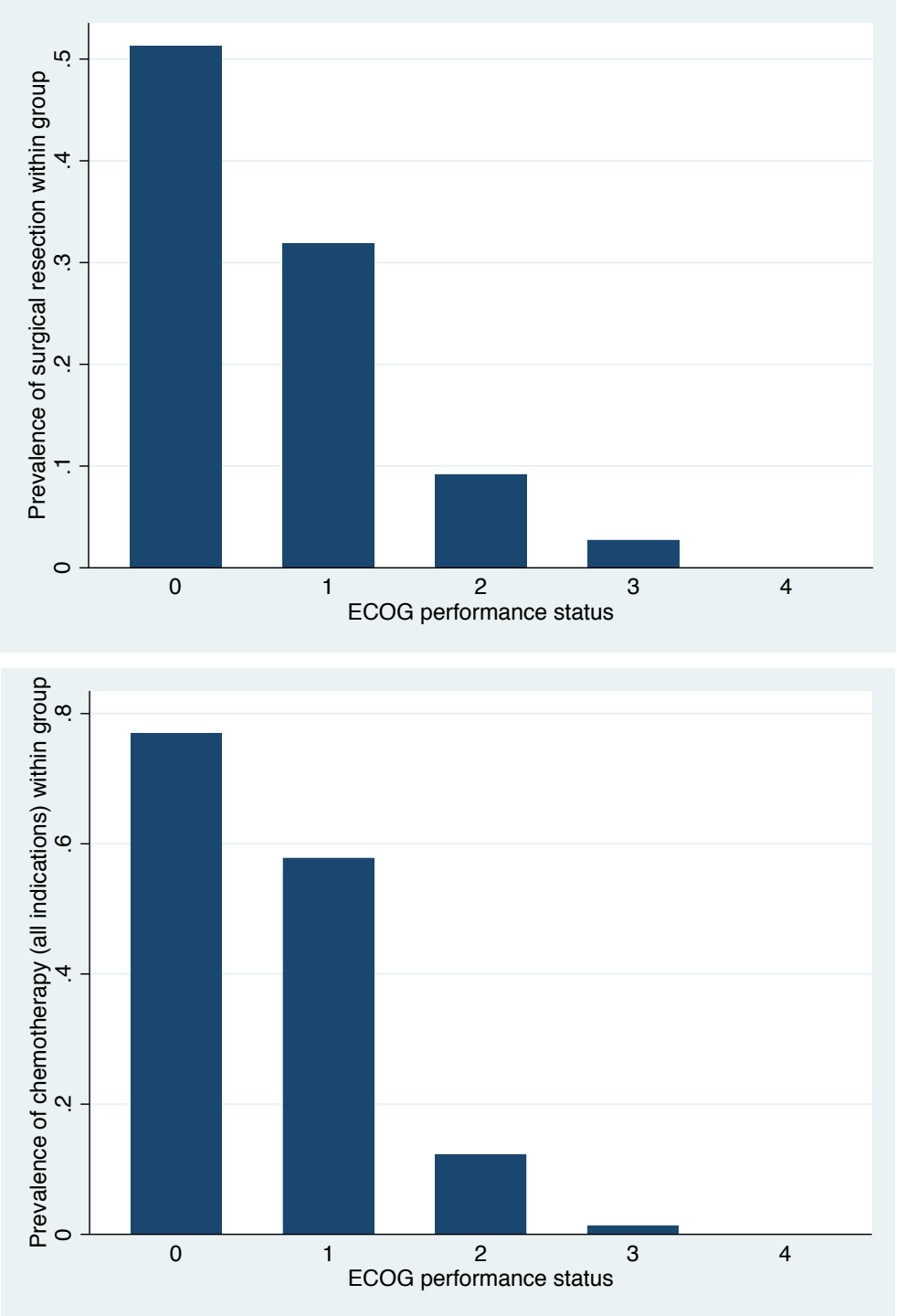
Patients with ECOG performance statuses 0 and 1 accounted for 28.1% and 34.3% of the cohort respectively, together comprising 62.4% of the cohort. Performance statuses 2, 3 and 4 accounted for 18.1%, 13.5% and 0.7% of the cohort respectively, together comprising 32.3% of the cohort. No performance status was recorded for 5.2% of patients (n=28) in the cohort. Examining the proportion of patients at each performance status undergoing surgical resection or chemotherapy (for any indication), a clear 'cut-off' between performance statuses of 1 and 2 becomes apparent [Figure 2.1]. This observation would suggest that patients with a performance status ≥2 are perceived as being unfit for intervention.

Resection of the primary tumour was performed in 155 patients (28.7%), including 150 patients (27.8%) undergoing surgical resection and a further 5 patients (0.9%) undergoing endoscopic mucosal resection alone without subsequent surgical resection. Patients undergoing surgical resection were younger on average (median age 74.5 vs 78.9, $p<0.0001$) and significantly less likely to have an ECOG performance status of ≥2 (7.4% vs 45.1%, $p<0.0001$) compared to patients treated with palliative intent.

Chemotherapy was administered to a total of 240 patients (44.4%) for all indications, i.e., neoadjuvant, adjuvant and palliative chemotherapy. 75 patients (13.9%, or 50% of patients undergoing surgical resection) received neoadjuvant chemotherapy prior to surgical resection. Patients treated with chemotherapy for any indication were, on average, 10.5 years younger than patients not receiving chemotherapy (median age at diagnosis 82.1 vs 71.6; $p<0.0001$). Only 5.5% of patients treated with chemotherapy for any indication had an ECOG performance status ≥2, compared to 58.9% of patients not receiving chemotherapy ($p<0.0001$).

92 patients (17.0%) were treated with radiotherapy for any indication, 108 patients (20.0%) underwent endoscopic stenting and 128 patients (23.7%) were treated with best supportive care alone or died before any intervention could be performed.

Figure 2.1: Proportion of patients at each ECOG performance status undergoing surgical resection or chemotherapy (for any indication)



Patterns of Missing Data

Baseline demographic and treatment characteristics were not consistently reported in electronic health records. Notably, smoking status was not recorded for 159 patients (29.4%) and ECOG performance status was missing from the records of 28 patients (5.2%). Numbers of cases with missing

variables differ for each individual component of TNM staging and the overall AJCC stage. This was due a combination of uncertainty in staging (typically recorded as 'x') and incomplete documentation in medical records.

Data were found to be 'missing not at random'. All missing variables were significantly correlated with age and poor performance status. Patients aged over 80 at cancer diagnosis were significantly more likely to have no recorded ECOG performance status (RR 1.59, p=0.017), no recorded smoking status (RR 1.45, p=0.0007), no recorded overall AJCC stage (RR 2.13, p<0.0001), no information recorded regarding the presence of metastatic disease (RR 2.29, p=0.0001), and no histology (RR 1.56, p=0.05). Absence of staging was positively correlated with worse ECOG performance status on logistic regression. An ECOG performance status ≥2 was significantly associated with no recorded smoking status (RR 1.37, p=0.014), no information recorded regarding metastatic disease (RR 3.05, p<0.0001) and no histology (RR 2.28, p=0.0005).

The patterns identified suggest that documentation of baseline demographic and treatment characteristics may be less consistent in situations where treatment is not felt to be appropriate – for example, in particularly old or frail patients. Indeed, management with best supportive care only was strongly associated with all missing variables (p<0.0001). This is perhaps unsurprising: patients for whom intervention is deemed inappropriate are not routinely reviewed in surgical or oncological outpatient clinics and their baseline characteristics are therefore not entered into electronic health records.

The main implication of data 'missing not at random' is that multiple imputation offers little advantage over complete case analysis in such a scenario and may even over-estimate effect size[45]. All data analysis was therefore performed on a complete-case basis. It must be acknowledged, however, that complete case analysis is also likely to yield invalid inferences with non-random missing data and the findings here must therefore be cautiously interpreted with this caveat in mind.

Cancer-Related Complications

Gastrointestinal tract perforation were documented in 19 patients (3.5%), intestinal obstruction in 36 patients (6.7%), ascites requiring drainage in 32 patients (5.9%), biliary obstruction in 23 patients (4.3%) and malignant pleural effusion in 13 patients (2.4%). These figures are likely to be underestimates due to a combination of cases managed palliatively in the community and collection of data from electronic health records which may not fully reflect events occurring during inpatient episodes which were historically documented on paper-based notes.

Gastrointestinal tract perforation was significantly associated with linitis plastica (RR 2.70, 95% CI 1.01-7.25, p=0.04). Intestinal obstruction was significantly associated with linitis plastica (RR 2.52, 95% CI 1.24-5.12, p=0.01), signet ring cell cancer (RR 1.88, 95% CI 1.00-3.55, p=0.049) peritoneal disease at the time of cancer diagnosis (RR 1.96, 95% CI 1.04-3.70, p=0.04) and treatment with chemotherapy (RR 2.50, 95%CI 1.28-4.89, p=0.006).

These findings are difficult to interpret given the low event numbers. It is clearly apparent, even without formal power calculations, that the present cohort is grossly underpowered to allow for any statistical modelling with respect to complications other than death as outcome measures. Furthermore, the data presented here are likely to significantly underestimate the true rates of disease-related complications. An age at diagnosis of over 80 years was inversely associated with all complications. This observation suggests that a large number of complications in older patients are not documented in hospital records, perhaps because older patients are more likely to be treated with palliative intent in the community.

As data relating to disease complications derived from the present cohort are likely to be both incomplete and unreliable, they unfortunately cannot be used to inform power calculations for future studies.

Overall Survival: Baseline Characteristics Associated with All-Cause Mortality

62 patients (11.5%) were alive at the end of follow-up, across a median follow-up period of 7.44 years. Overall survival was defined as survival from the date of cancer diagnosis as documented on MDT records to death from any cause. Median overall survival was 302 days (IQR 86-750 days) across the whole cohort, 172 days (IQR 58-373 days) in patients treated with palliative intent, and 3.92 years (IQR 1.67-9.64 years) in patients undergoing resection of the primary tumour with curative intent (gastrectomy and endoscopic mucosal resection).

The following exposures were associated with worse overall survival (all-cause mortality) in univariate analysis [Table 2.2]: increasing age, lower ECOG performance status, cardiovascular disease, more advanced AJCC cancer stage, linitis plastica and peritoneal disease at cancer diagnosis. Resection (surgical or endoscopic) of the primary lesion and treatment with chemotherapy were both associated with improved survival. There were no significant associations between survival and sex, smoking status, gastro-oesophageal junction involvement, diagnosis following an emergency presentation or signet ring cell histology.

Table 2.2: Univariate associations between baseline demographic, clinical and treatment characteristics and all-cause mortality.

Characteristic	Hazard Ratio (95% CI)	p-value
Age per year	1.02 (1.01–1.03)	**<0.001**
Sex (male)	0.92 (0.76–1.12)	0.411
Current smoker at diagnosis	0.87 (0.65–1.16)	0.342
ECOG Performance Status (relative to PS 0)		
Performance Status 1	1.50 (1.18–1.91)	**0.001**
Performance Status 2	2.85 (2.16–3.75)	**<0.001**
Performance Status 3	4.49 (3.33–6.07)	**<0.001**
Performance Status 4	15.59 (5.69–42.72)	**<0.001**
Cardiovascular disease	1.25 (1.03–1.52)	**0.026**
OGJ involvement, i.e., Siewert III	0.89 (0.72–1.10)	0.282
Emergency presentation & diagnosis	1.16 (0.91–1.47)	0.232
AJCC Cancer Stage (relative to Stage I)		
Stage II	1.33 (0.85–2.09)	0.213
Stage III	2.28 (1.46–3.57)	**<0.001**
Stage IV (Metastatic Disease)	6.98 (4.55–10.71)	**<0.001**
Linitis Plastica	2.05 (1.56–2.68)	**<0.001**
Signet Ring Cell Histology	1.14 (0.93–1.40)	0.220
Peritoneal Involvement at Cancer Diagnosis	2.59 (2.10–3.20)	**<0.001**
Surgical/Endoscopic Resection of Primary	0.17 (0.13-0.21)	**<0.001**
Chemotherapy Treatment, All Indications	0.55 (0.45–0.66)	**<0.001**

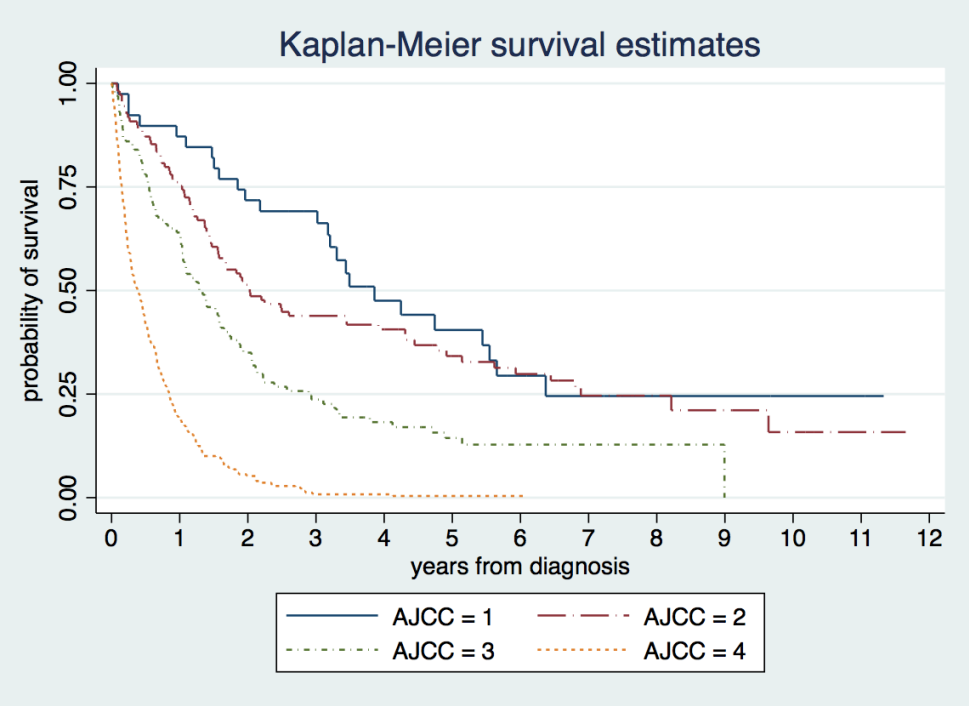
Note: All characteristics associated with a p-value <0.05 (highlighted in bold) were included in multivariable analysis.

Each increment in AJCC cancer stage was associated with an approximate halving of median overall survival from diagnosis and doubling of mortality hazard [Figure 2.2]. Whereas patients with stage 1 and stage 2 cancers could expect to live for several years, patients with metastatic disease at diagnosis (stage 4) had a median overall survival of less than 5 months. Each increment in ECOG performance status was associated with a similar increase in mortality hazard [Figure 2.3]. Only patients with a performance status of 0 had a median overall survival of over one year. Given the correlation described earlier between a lower performance status and a higher probability of receiving chemotherapy or undergoing surgical resection [Figure 2.1], multivariable analysis is required to elucidate whether these observed differences in overall survival reflect the prognostic significance of performance status or treatment effects.

Interestingly, the relationship between age at diagnosis and overall survival was not entirely linear. When age at diagnosis was stratified by decade, patients aged 60 years or under at diagnosis had a shorter median overall survival (309 days; IQR 138-667) compared to patients aged between 61 and 80. Indeed, compared to patients aged between 61-70 years, an age at diagnosis of 60 years or

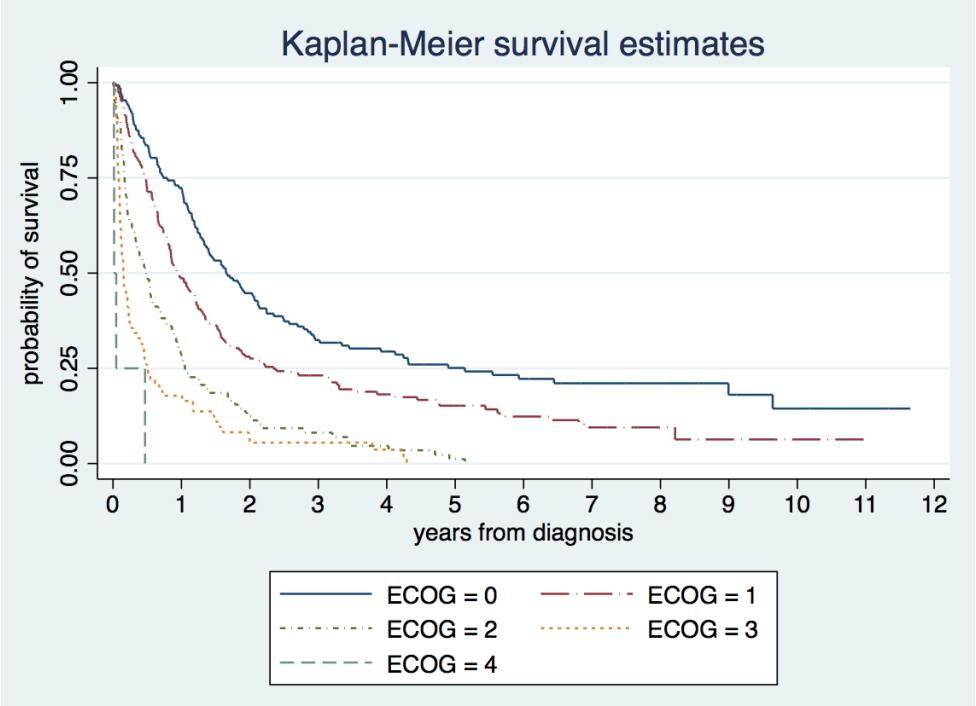
younger was associated with a mortality hazard ratio of 1.74 (95%CI 1.18-2.56; p=0.006). Median overall survival decreased with each decade in patients aged 61 and above [Figure 2.4].

Figure 2.2: Kaplan-Meier survival curves stratified by overall AJCC cancer stage.



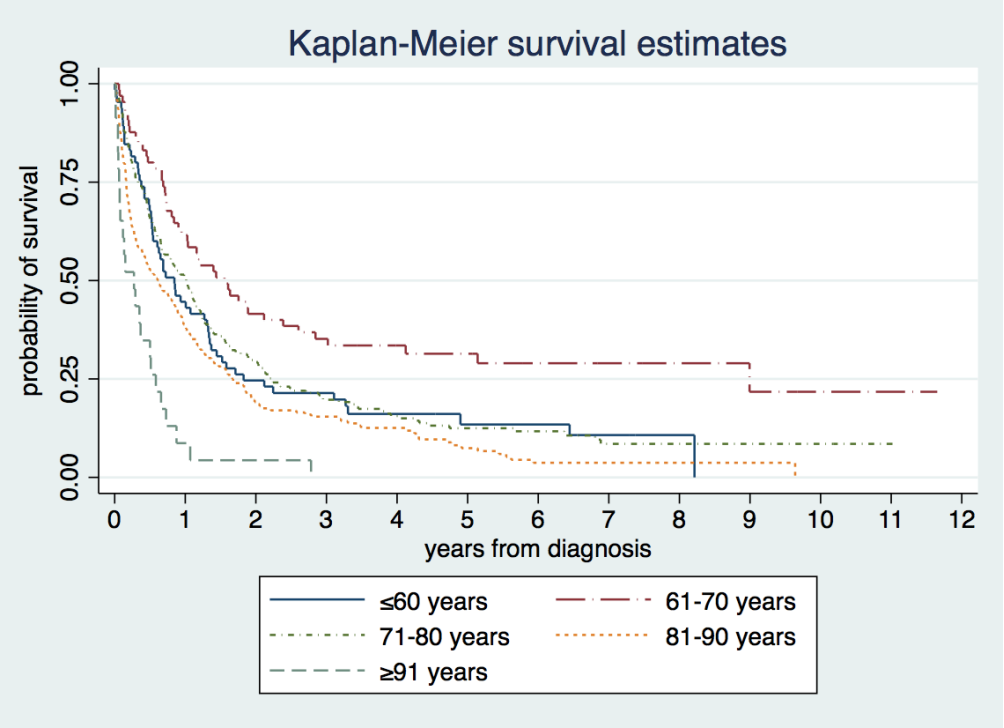
AJCC Cancer Stage	Median Overall Survival	Interquartile Range
Stage I (n=39)	1409 days	268–1878
Stage II (n=109)	741 days	167–857
Stage III (n=100)	470 days	62–384
Stage IV (n=249)	143 days	31–183
Stage unrecorded (n=43)	*183 days*	*43–468*

Figure 2.3: Kaplan-Meier survival curves stratified by ECOG performance status.



ECOG Performance Status	Median Overall Survival	Interquartile Range
PS 0 (n=152)	603 days	268–1878
PS 1 (n=185)	341 days	167–857
PS 2 (n=98)	176 days	62–384
PS 3 (n=73)	55 days	31–183
PS 4 (n=4)	6 days	5–17
PS unrecorded (n=28)	*53 days*	*18–202*

Figure 2.4: Kaplan-Meier survival curves stratified by decade of age at diagnosis.



Age At Diagnosis (Stratified by Decade)	Median Overall Survival	Interquartile Range
≤60 years (n=65)	309 days	138–667
61-70 years (n=65)	568 days	251–3285
71-80 years (n=198)	370 days	121–812
81-90 years (n=189)	222 days	60–609
≥91 years (n=23)	100 days	23–213

In multivariable analysis [Table 2.3] the only retained variables independently associated with worse overall survival (all-cause mortality) were lower ECOG performance status and more advanced AJCC cancer stage. Even when adjusted for the treatment effects of primary tumour resection and chemotherapy, performance status and cancer stage remained strong predictors of overall survival. Among the other baseline characteristics entered into the multivariable model, linitis plastica and peritoneal involvement at diagnosis were not independent of metastatic disease (stage 4) as predictors of overall survival, whilst cardiovascular comorbidity was strongly associated with poor performance status.

Table 2.3: Multivariable associations between demographic, clinical and treatment characteristics and all-cause mortality – Cox proportional hazards regression model.

Characteristic	Hazard Ratio (95% CI)	z	p-value
ECOG Performance Status (relative to PS 0)			
Performance Status 1	1.30 (1.01–1.68)	2.06	0.039
Performance Status 2	1.74 (1.22–2.46)	3.09	0.002
Performance Status 3	2.77 (1.87–4.10)	5.08	<0.001
Performance Status 4	94.16 (23.98–369.80)	6.51	<0.001
AJCC Cancer Stage (relative to Stage I)			
Stage II	1.66 (1.05–2.62)	2.15	0.032
Stage III	2.19 (1.37–3.52)	3.27	0.001
Stage IV (Metastatic Disease)	5.13 (3.12–8.43)	6.45	<0.001
Surgical/Endoscopic resection of primary	0.39 (0.28–0.55)	-5.40	<0.001
Chemotherapy Treatment, All Indications	0.60 (0.47–0.77)	-4.00	<0.001
$\chi 2 = 373.64$, $p<0.001$			
Model developed in a total of 475 patients on a complete case analysis basis.			

Predictive model for survival at 1 year

Overall survival at 1 year was chosen as the endpoint for a predictive model on the basis of power calculations detailed in 'Methods' and the median overall survival of 302 days in this cohort.

Univariate analysis [Table 2.4] identified four variables as significant predictors ($p<0.05$) of mortality within 1 year of cancer diagnosis: advancing age, declining ECOG performance status, higher overall AJCC cancer stage and linitis plastica. Conversely, resection (surgical or endoscopic) of the primary tumour and treatment with chemotherapy were significantly associated with survival at 1 year. Other variables meeting the predefined criteria for inclusion in the multivariable model ($p<0.250$) were female gender and pre-existing cardiovascular disease, both of which exhibited a trend towards worse prognosis.

A documented 'current smoker' status at the time of diagnosis was paradoxically correlated with survival at 1 year. This is almost certainly a result of confounding as older patients, patients with a lower performance status and patients treated with best supportive care alone were all significantly less likely to have a recorded smoking status. Smoking status was therefore not assessed for inclusion in the multivariable model despite meeting the predefined criteria.

The multivariable analysis [Table 2.5], performed on a 'complete case' basis, included 457 patients. Following stepwise elimination, the following variables emerged as independent predictors of survival at one year following diagnosis: ECOG performance status, overall AJCC cancer stage, resection of the primary tumour and treatment with chemotherapy. Each increment in performance status and AJCC cancer stages III and IV were associated with significant reductions in the odds of survival at one year. After adjustment for performance status and cancer stage, resection of primary tumour was

associated with 6.5-fold improved odds of survival at one year whilst chemotherapy treatment (for any indication) was associated with 2-fold improved odds.

Table 2.4: Univariate analysis of baseline parameters predictive of survival at 1 year following cancer diagnosis.

	Alive at 1 year (n=244)	**Not alive at 1 year (n=296)**	**Odds Ratio for Survival at 1 year (95% CI)**	**p-value**
Age (median, IQR)	75.5 (68.5–81.0)	79.2 (72.0–84.7)	0.98 (0.96-0.99)	**0.002**
Gender (n,%)				
Male	178 (73%)	199 (67%)	1.00	**-**
Female	66 (27%)	97 (33%)	0.76 (0.52–1.10)	**0.149**
Smoking status (n,%)				
Smoker at diagnosis	41 (17%)	24 (8%)	1.89 (1.09–3.28)	**0.023**[1]
Ex-smoker/never smoked	150 (61%)	166 (56%)	1.00	
ECOG performance status (n,%)				
PS 0	110 (45%)	42 (14%)	1.00	**-**
PS 1	90 (37%)	95 (32%)	0.36 (0.23–0.57)	**<0.001**
PS 2	28 (11%)	70 (24%)	0.15 (0.09–0.27)	**<0.001**
PS 3	13 (5%)	60 (20%)	0.08 (0.04–0.17)	**<0.001**
PS 4	0 (0%)	4 (1%)	0.00	**-**
Cardiovascular disease (n,%)				
Yes	64 (26%)	92 (31%)	0.79 (0.54–1.15)	**0.216**
No	180 (74%)	204 (69%)	1.00	-
GOJ involvement (n,%)				
Yes (Siewert III)	67 (27%)	70 (24%)	1.22 (0.83–1.80)	0.312
No	177 (73%)	226 (76%)	1.00	-
Emergency first presentation (n,%)				
Yes	37 (15%)	54 (18%)	0.80 (0.51–1.27)	0.342
No	207 (85%)	242 (82%)	1.00	-
AJCC cancer stage (n,%)				
Stage I	34 (14%)	5 (2%)	1.00	**-**
Stage II	82 (34%)	27 (9%)	0.45 (0.16–1.26)	**0.127**
Stage III	64 (26%)	36 (12%)	0.26 (0.09–0.73)	**0.010**
Stage IV	48 (20%)	201 (68%)	0.04 (0.01–0.09)	**<0.001**
Linitis plastica (n,%)				
Yes	14 (6%)	49 (17%)	0.31 (0.16–0.57)	**<0.001**
No	230 (94%)	247 (83%)	1.00	**-**
Signet ring cell cancer (n,%)				
Yes	61 (25%)	82 (28%)	0.81 (0.55–1.20)	0.299
No	180 (74%)	197 (67%)	1.00	**-**
Resection of primary (n,%)				
Yes	142 (58%)	13 (4%)	30.31 (16.44–55.85)	**<0.001**
No	102 (42%)	283 (96%)	1.00	-
Chemotherapy treatment (n,%)				
Yes (all indications)	142 (58%)	98 (33%)	2.81 (1.98–4.00)	**<0.001**
No	102 (42%)	198 (67%)	1.00	-

[1]Smoking status excluded from multivariable analysis due to very high rates of missing data and potential for confounding (significant association between old age/poor performance status and no smoking status recorded).

Table 2.5: Multivariable predictive model for survival at 1 year following cancer diagnosis – logistic regression model.

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status (relative to PS 0)			
Performance Status 1	0.39 (0.22–0.72)	-3.05	0.002
Performance Status 2	0.29 (0.12–0.65)	-2.96	0.003
Performance Status 3	0.11 (0.04–0.35)	-3.80	<0.001
AJCC cancer stage (relative to Stage I)			
Stage II	0.31 (0.09–1.14)	-1.76	0.078
Stage III	0.23 (0.06–0.84)	-2.23	0.026
Stage IV (Metastatic Disease)	0.06 (0.15–0.21)	-4.31	<0.001
Surgical/endoscopic resection of primary	6.47 (3.02–13.90)	4.79	<0.001
Chemotherapy treatment, All Indications	2.07 (1.11–)	2.30	<0.001

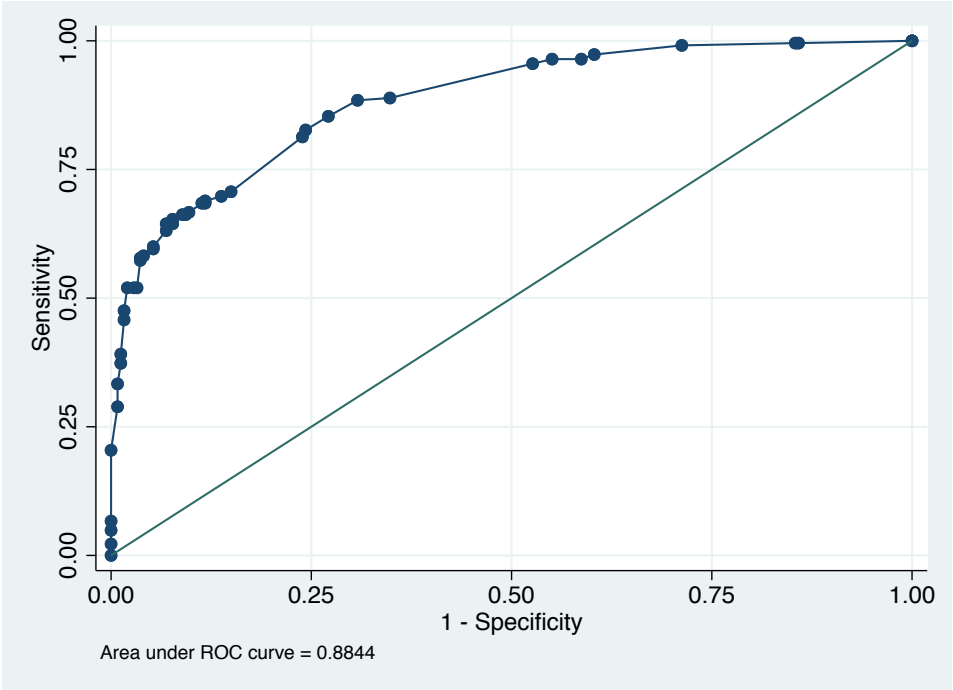
$\chi 2 = 255.85$, $p<0.001$

Model developed in a total of 472 patients on a complete case analysis basis. 3 Patients with an ECOG performance status of 4 were excluded as this characteristic predicted death within 1 year perfectly.

Model Discrimination

The discriminatory ability (c-statistic) of this model, as defined based on the area under the receiver operating curve, was estimated at 0.8844 (95% CI 0.86-0.91) [Figure 2.5]. At a 50% predicted probability cutoff, sensitivity of the model was 68.44%, specificity 88.26%, positive predictive value 84.15% and negative predictive value 75.43%.

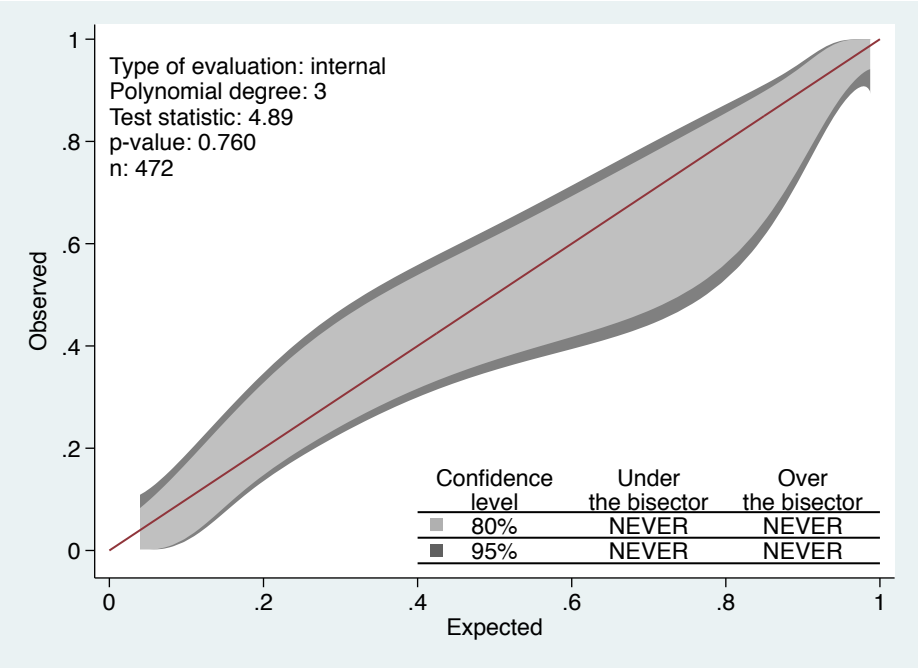
Figure 2.5: Receiver Operator Curve (ROC) analysis for the predictive model of survival at 1 year



Model Calibration

Calibration was assessed graphically by means of a calibration belt and statistically through the Hosmer-Lemeshow test. The calibration belt, as per the methodology described by Nattino et al and generated using their *calibrationbelt* Stata package, plots the relationship between the model's fit probabilities and the observed proportions of the response [Figure 2.6][39,40]. The calibration belt test statistic of 4.89 and associated p-value of 0.760 are in keeping with good calibration (i.e., the 'null hypothesis' of good calibration is not rejected). Further calibration assessment using the Hosmer-Lemeshow test indicates adequate goodness of fit with a chi-square statistic of 13.22 and p-value of 0.104 (the null hypothesis being that proportions predicted from the model are equal to the observed proportions).

Figure 2.6: Calibration belt for the predictive model of survival at 1 year



Internal validation

In the absence of an external dataset for validation, bootstrapping was performed with 500 replications to assess model fit. The analysis indicated a low level of sampling bias and low probability of model optimism ($p<0.0001$) [Table 2.6].

Table 2.6: Bias estimation and correction, using bootstrap resampling technique

	Observed Odds Ratio	Bias	Bias-corrected 95% CI	p-value
ECOG Performance sstatus (relative to PS 0)				
Performance Status 1	0.39	-0.013	0.21–0.73	0.003
Performance Status 2	0.29	-0.033	0.12–0.67	0.004
Performance Status 3	0.11	-0.110	0.03–0.46	0.002
AJCC cancer stage (relative to Stage I)				
Stage 2	0.31	-0.092	0.07–1.31	0.112
Stage 3	0.23	-0.146	0.05–0.97	0.045
Stage 4 (Metastatic Disease*)	0.06	-0.156	0.01–0.26	<0.001
Resection of primary	6.47	0.077	2.74–15.28	<0.001
Chemotherapy, All Indications	2.07	0.030	1.08–3.97	0.028

Case Example

Using this model, a patient with stage III gastric adenocarcinoma and an ECOG performance status of 1 has a 1-year overall survival probability of 79% (95% CI 65–93%) with resection alone and 89% (95% CI 81–97%) with both resection and chemotherapy. These probabilities are 73% (95% CI 55–91%) and 85% (72%–99%) respectively in a patient with a performance status of 2.

A patient with stage IV gastric adenocarcinoma (metastatic disease) and an ECOG performance status of 0 has a 1-year survival probability of 27% (95% CI 12–40%) without chemotherapy and 43% (95% CI 31–55%) with chemotherapy. These probabilities are 9% (95% CI 4–15%) and 18% (95% CI 6–29%) respectively in a patient with a performance status of 2. These figures must be balanced against any potential effects of treatment on quality of life.

DISCUSSION

General Observations

Patients with gastric cancer in the United Kingdom are an under-studied population, partly owing to the relatively low prevalence of gastric cancer in the UK compared to Eastern Asia and Eastern Europe. The present retrospective cohort study is based on a sample broadly representative of the UK population and Western European clinical practice. Although a sample size of 540 may be considered relatively small for a cohort study, the numbers reflect the incidence of gastric cancer in the UK and the data provide valuable insight into the interplay between patient, disease and treatment characteristics and their effects on outcomes in an under-studied population.

Survival figures reflect the poor prognosis of patients with gastric cancer in a Western setting: only 11.5% of included patients were alive at the end of follow-up, with a median follow-up period of 7.44 years. The vast majority of patients (71%) were not deemed eligible for, or declined curative

treatment. This is partly due to gastric cancer being predominantly a disease of older adults in the present cohort (median age 77) and partly because most cancers were diagnosed at a relatively advanced stage: 18.5% of tumours were stage III and 46.1% were stage IV at diagnosis. These figures are likely to be underestimates of the actual proportion of advanced cancers. Overall AJCC stage was not recorded or could not be determined for 8% of patients. 18.9% and 16.6% of the cohort had an indeterminate (or unrecorded) 'T' and 'N' stage respectively. The gap between the number of patients without an overall AJCC stage and patients without full TNM staging is accounted for by the fact that metastatic disease automatically confers an overall stage of IV.

Although the existing literature already includes modelling studies in patient with gastric cancer, the majority of these studies were performed in East Asian populations and focused mainly on survival following curative resection[24]. Findings in Asian studies may not be applicable to Western populations. Large randomised trials in East Asia have demonstrated survival rates 30-40% higher than in comparable Western trials[32]. Biological differences have been documented between Asian and Western gastric cancer populations, including higher frequencies of signet ring histology and proximal involvement in Western populations[31–33]. Furthermore, national screening programmes in Japan and South Korea have improved detection rates of early gastric cancers – in contrast to the UK, where national screening is neither clinically nor economically justifiable and most gastric cancers are still diagnosed at an advanced stage.

Main Findings

Across the entire cohort, independent predictors of all-cause mortality in both multivariable analysis of overall survival and a model of survival at 1 year were: poorer ECOG performance status, advanced AJCC cancer stage, no resection of primary, and no chemotherapy (for any indication). Despite its apparent simplicity, the derived model's discriminatory ability (c-statistic = 0.88) compares favourably to those of existing prediction models for patients with upper gastrointestinal cancers (average pooled c-statistic of 0.75 in van de Boorn and colleagues' meta-analysis[24]).

These findings are consistent with the general assumptions that guide management decisions relating to patients with gastric cancer in the UK. Whilst unlikely to change current clinical practice, the derived model remains useful in terms of providing estimates of prognosis tailored to patients' functional status and disease stage, and facilitating discussions of whether or not treatment is likely to be in a patient's best interests. The estimates provided by this model must nonetheless be weighed up against treatment complications and the effects of treatment on quality of life, which this study was unable to assess.

It is interesting to note the baseline patient and disease characteristics which were not shown to represent independent predictors of survival in multivariable analysis. Although age at diagnosis (evaluated as a continuous independent variable) and linitis plastica were both significantly associated with poor survival in univariate analysis, they failed to emerge as independent predictors in multivariable analysis. It is now accepted that chronological age is a poor predictor of treatment response compared to functional age[49]. The findings from the present study would support this assertion. Even though increasing age corresponds with increasing mortality, the association between age at diagnosis and overall survival is considerably weakened once performance status is taken into account.

Furthermore, there was a trend towards worse survival in younger patients under the age of 60, although this did not reach statistical significance. Patients aged 18-60 at diagnosis appeared to have outcomes almost as poor as those aged 70-90. Compared to patients aged over 60, patients aged 60 and under were more likely to have T4 tumours (RR 1.40, p=0.008) and peritoneal disease (RR 1.69, p=0.004) at diagnosis. A significantly higher proportion of patients ≤60 years were recorded as being current smokers at the time of cancer diagnosis compared to patients >60 years (RR 3.01, p<0.0001), although interpretation of this figure is complicated by the high number of patients with no recorded smoking status. It may be postulated that the poorer outcomes seen in younger patients are due to a combination of lifestyle risk factors and possibly a more aggressive disease phenotype. In a historical South Korean cohort of 3362 patients enrolled between 2000 and 2005, younger patients with gastric cancer, aged 45 years or younger, were found to have a higher proportion of poorly differentiated tumours, signet ring cell histology and linitis plastica[50]. On the other hand, a smaller Mexican cohort study of patients treated between 1988 and 1994 did not identify any significant clinico-pathological differences between older and younger patients, aged ≥70 years and <40 years respectively[51]. In the present cohort, there is no significant difference between the incidence of linitis plastica in patients aged ≤60 years and patients aged >60 years, but this observation may be a factor of the relatively small number of patients with linitis (n=62, of whom 10 were aged ≤60 years at diagnosis). Signet ring cell pathology was more common in patients aged ≤60 years (RR 1.65, p=0.03) but was not associated with worse survival in this cohort.

Contrary to expectations, linitis plastica was not an independent predictor of mortality even though patients with linitis suffered from significantly poorer survival (HR2.05, p<0.001). This could be explained by the extremely strong associations between linitis plastica and advanced cancers (Stage IV; RR 1.67, p<0.0001) and particularly between linitis plastica and peritoneal disease (RR 2.78, p<0.0001). No existing predictive model of survival includes linitis plastica as a predictive factor, but

historical case series have consistently demonstrated poorer outcomes in patients with linitis plastica[52,53]. The findings from the current cohort suggest that the poor survival outcomes associated with linitis plastica appear to be a consequence of its tendency to metastasise to the peritoneum. It should be emphasised, however, that this study is underpowered to determine whether a diagnosis of linitis plastica in itself confers prognostic value independent of disease stage or peritoneal metastasis. Linitis plastica will be explored further in Chapter 5.

Comparison to previous models

Existing prognostic models for patients with gastric cancer, as listed in Boorn et al's meta-analysis, are primarily concerned with outcomes following curative resection. However, the majority of patients with gastric cancers in the UK present with advanced or metastatic disease. The most notable model derived from a western population is the Memorial Sloan Kettering nomogram published in 2003, which attempts to predict postoperative disease-specific survival based on clinical characteristics of 1039 patients undergoing R0 resection at a major American tertiary referral centre [54]. Independent prognostic factors in this model were: male sex, age at diagnosis (each decade under 60 or above 70), proximal tumours particularly those involving the gastro-oesophageal junction, Lauren diffuse tumours, tumour size, tumour depth and number of positive nodes.

The Memorial Sloan Kettering nomogram was validated by Ashfaq and colleagues in 2015 using the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Database[55]. Patients diagnosed with gastric adenocarcinoma between 1988 and 2012 and receiving surgery with curative intent. Results of the validation study demonstrated actual disease-specific survival 7-15% lower than that predicted by the nomogram. The authors suggested that this discrepancy is likely due to the nomogram's derivation from patients at a high volume specialist centre whereas the SEER Database included patients treated in the community. Whilst the median age of the derivation cohort was not reported in the original Memorial Sloan Kettering study, the median age of the SEER validation cohort was 70 years, younger on average than patients undergoing surgery in the present cohort (median 74.5 years).

Three UK-based models were included in Boorn et al's meta-analysis, all of which combined gastric and oesophageal cancers. Deans and colleagues' 2007 model was derived from 220 patients with newly-diagnosed gastric or oesophageal cancer between March 2002 and June 2004 in the Edinburgh region[12]. Although this was a predominantly oesophageal cohort (gastric cancers accounted for 35.9% of the cohort), it bore some resemblance to the present study: all cancers diagnosed within a specified period were included regardless of stage or operability, and death within 12 and 24 months were defined as the primary endpoints. Advanced clinical stage, reduced performance score, weight

loss exceeding 2.75% per month and serum CRP > 5mg/L were identified as independent prognostic indicators in multivariable analysis. The median age of the Edinburgh cohort was 71 years and median overall survival was 13 months, in comparison to a median age of 77.44 years and median overall survival of 10 months in our study cohort. Two other UK-based models, O-POSSUM[22] and Fischer 2016 [13], evaluated predictive factors for short-term outcomes, namely postoperative mortality and anastomotic leakage rates following oesophagogastric cancer resections. In both models, gastric tumours constituted a minority of the derivation cohort.

Prominent Japanese models of overall survival in patients with gastric cancer include those published by Han et al in 2012 [56] and Hirabayashi et al in 2014 [57]. Independent predictive variables in common between the two studies were: age over 60 at the time of operation, male sex, proximal tumours, depth of invasion and number of metastatic lymph nodes.

The current study therefore presents the only survival model derived from a western population that is both specific to gastric cancer and includes both surgical and non-surgical candidates. As a consequence of its inclusion of non-surgical candidates, surgical-histological characteristics such as depth of invasion or number of involved lymph nodes could not be included in this model. Disease stage and poor performance status were common predictive factors of poor prognosis across all studies. Notably, in contrast to previous models, the current model did not identify age as an independent adverse predictive factor when performance status was also taken into account. Furthermore, whereas involvement of the gastro-oesophageal junction was highlighted as a predictor of poor prognosis in both American and Japanese models, this was not the case in the present study in either univariate or multivariable analysis. It is unclear whether this difference is due to population and disease factors or advances in treatment such as the use of perioperative chemotherapy in standard European practice. No previous model included linitis plastica as a prognostic predictor.

The present cohort stands out from previous derivation and validation cohorts in having a noticeably higher median age of participants. This reflects the demographics of the local area: 24.4% of Norfolk's population was aged 65 and over in 2021, compared to 18.4% of the population of England as a whole[58]. It could therefore be considered a more favourable cohort for studying disease outcomes and treatment effects in older and frailer patients, which will be the focus of the following chapter. The cohort also differs from American cohorts in the relative homogeneity of the study population: 90% of Norfolk's population was born in the UK[58], a figure that is likely even higher in older age groups. As this study did not collect data on race and ethnicity, precise figures cannot be provided for the study cohort. The author's experience suggests, however, that individuals from minority ethnic backgrounds constitute an extremely small proportion of patients referred to the OG MDT. Although

there are strong arguments to be made in favour of cohorts drawn from more diverse populations, the current study fills a niche by focusing on a population that has heretofore been underrepresented in the literature on gastric cancer.

Strengths

Despite the identification of relatively few independent predictive factors, the present predictive model of survival in gastric cancer is by no means inferior to previous models in terms of either performance or methodology. With a c-statistic of 0.88, its discriminatory ability and calibration compare favourably with those of previous models[24]. Model calibration was formally assessed with the Hosmer-Lemeshow test and presented visually by means of a calibration belt, whereas only a minority of studies in the meta-analysis performed a formal calibration analysis. The present model includes all patients diagnosed with gastric cancer in a single tertiary OG centre and overall survival is measured from the point of diagnosis. This stands in contrast to a "focus on prediction of survival after curative resection" in most previous models, which has been criticised as being "of limited value for treatment decisions"[24].

Sample size calculations were performed *a priori* in order to prevent model overfitting and optimism. Predictor variables were specified on the basis of existing literature, and parameters were limited in number in accordance with sample size calculations.

As a 'real-world' consecutive series of patients in a predominantly suburban and rural setting, the study cohort may be considered broadly representative of gastric cancer in the British population outside of major metropolitan areas and reflects the ageing of the general population. A further advantage of this cohort is the very low rate of loss to follow-up (n=4; 0.7%, all due to moving out of area). Possible reasons for this phenomenon include the character of the region as a retirement destination, lack of competing healthcare providers, and the concentration of oncology services in regional centres of excellence under the British model of public healthcare. The clinical journey from cancer diagnosis to death could therefore, in theory, be traced for nearly all patients in this cohort.

Limitations

As with most existing predictive models, the sole focus is overall survival at the expense of other meaningful outcomes such as quality of life. This limitation is an unavoidable consequence of retrospective study methodology, small sample size, and restrictions on data available for research purposes under existing ethical approval.

Given the retrospective cohort nature of this study, it is difficult to separate the effects of baseline patient and disease characteristics from those of treatment decisions on disease outcomes. Reflecting clinical practice in the 'real world', treatment decisions may have been biased by preconceived assumptions regarding potential to benefit or tolerability. A model derived from a real-world cohort inevitably inherits and may even propagate these biases. A retrospective cohort study must also address the problem of missing data. In the present case, data were missing 'not at random', with older patients and patients with a worse ECOG performance status less likely to have full staging, histology or smoking status recorded.

A sample of 540 patients is relatively small for a retrospective cohort study. This sample size constrained the number of parameters that could be assessed for inclusion in the predictive model. Furthermore, the study may have been insufficiently powered to detect small but potentially significant effects of baseline characteristics, or differences in the rates of relatively uncommon outcomes such as perforation (n=19). Sample sizes of certain subgroups, such as patients with linitis plastica undergoing surgery (n=3), were insufficient to allow for meaningful analysis.

Finally, ethical approval for this study only covered care records from an acute hospital trust. Primary care and palliative care records were unavailable for research purposes. As a result, non-survival outcomes such as symptoms, quality of life and disease-related complications could not be reliably assessed. The vast majority of cancer-related symptoms and complications are managed in the community. Most patients with gastric cancer choose to die at home or in a hospice setting. Disease and treatment complications severe enough to warrant acute hospital admission represent only the 'tip of the iceberg'. Finally, patient-reported symptoms are not systematically recorded in outpatient clinic letters and quality of life data is not routinely collected, further limiting the value of acute hospital records in evaluating non-mortality outcomes.

Implications for clinical practice

The predictive model presented here may assist in communicating prognostic estimates to patients, enabling better-informed shared decision making between patients and clinicians. Furthermore, a number of observations can be made from this model which carry implications for treatment decisions and future research. First, the prognostic predictive value of performance status far outweighs that of chronological age. The current model was derived from a considerably older cohort than those investigated in previous studies, and therefore included a large number of older patients who nonetheless retained a good performance status. It could be argued that older but relatively fit patients, even those with advanced disease, should be considered for emerging modalities of

treatment, such as targeted therapies or hyperthermic intraperitoneal chemotherapy (HIPEC), which may lead to improvements in survival and quality of life. Second, the prognostic value of aggressive disease phenotypes, namely linitis plastica and signet ring cell carcinoma, does not appear to be independent of disease stage. It may be hypothesised that treatment is of similar efficacy in linitis plastica compared to non-linitis gastric adenocarcinomas of equivalent stage, and curative therapy may therefore have a role in selected cases of linitis plastica. As the present cohort is underpowered to test such a hypothesis, this will be explored by means of a systematic review in a later chapter. Finally, the surprisingly poor outcomes observed in younger patients suggest a potential need for more aggressive treatment in this patient group.

Conclusion

Gastric cancer in the UK is typically diagnosed at an advanced stage and is associated with a poor prognosis. An up-to-date predictive model reflecting current European clinical practice and the UK gastric cancer population is particularly important at a time where older, frailer and more co-morbid patients are increasingly being diagnosed with gastric cancer. Disease stage, performance status, resection of primary tumour and treatment with chemotherapy emerged as the only independent predictors of both median overall survival and overall survival at 1 year. The predictive model for 1 year survival compares favourably to existing models in terms of discrimination and calibration and represents the first such model derived from a gastric-cancer-specific cohort based in the United Kingdom. The study remains underpowered and available data are insufficient to assess additional predictive parameters or outcomes other than overall survival, such as quality of life. Ethical approval and additional resources (including funding) must be sought for expansion of the derivation cohort, access to records from palliative care and primary care services, and external validation of the predictive model in a separate validation cohort.

CHAPTER 3- Gastric adenocarcinoma outcomes with surgery and chemotherapy in older patients and patients with poor performance status.

ABSTRACT

Background. The average age of patients diagnosed with gastric cancer continues to rise. The limited research evidence available to guide treatment decisions in older and frail patients has not kept pace with the increasing focus on healthy ageing and patient-centred decision making. There remains considerable uncertainty surrounding the merits of surgery and chemotherapy in older and frail patients with gastric cancer. As frailty scores are not internationally standardised and were rarely used in routine clinical settings until recently, performance status remains part of the global language of oncology and a key component of research datasets despite its shortcomings. The present study attempted to evaluate the benefits and risks associated with gastrectomy and palliative chemotherapy in a UK-based real-world cohort of patients aged over 80 or with a performance status ≥2.

Objectives. This retrospective observational study sought to: (1) compare overall survival between patients aged ≤80 and >80 undergoing gastrectomy with curative intent; (2) evaluate the survival benefit associated with gastrectomy in patients aged >80 and in patients with an ECOG performance score of 2-3; (3) compare rates of surgical complications in patients aged ≤80 vs >80 and in patients with a performance score of 0-1 vs 2-3; and (4) evaluate the survival benefit associated with palliative chemotherapy in cases where gastrectomy was deemed inappropriate in patients aged >80 and in patients with an ECOG performance score of 2-3.

Methods. This single-centre retrospective cohort study evaluated patients with gastric cancer aged ≥80 years and patients with an ECOG performance status ≥2 at diagnosis. Baseline patient and disease characteristics, treatments received, adverse events and dates of death were obtained from acute hospital care records. The primary outcome measure was overall survival at 2 years in the surgical cohort and overall survival at 1 year in the non-surgical cohort. Propensity score methodology was used to adjust for confounding. Covariates were included in the propensity score if they were significantly associated with the primary outcome of interest. Trimming was performed to restrict analysis to the area of overlapping propensity scores, followed by inverse probability of treatment weighting by the propensity score to compare outcomes between patients in intervention and non-intervention groups.

Results. Overall survival following gastrectomy with curative intent was not significantly different between patients aged ≤80 and patients aged >80 at diagnosis (median overall survival 4.32 years vs 3.31 years; p=0.159). Applying trimming and inverse probability of treatment weighting by the propensity score to adjust for confounding factors, gastrectomy was shown to be associated with significantly improved odds of survival at 2 years in patients aged over 80 at diagnosis without metastatic disease (OR 6.26, p=0.046), but not in patients with a performance status of 2-4 and no metastatic disease (OR 1.79, p=0.624). Although chemotherapy was associated with a trend towards improved survival in patients aged over 80 managed with palliative intent, this did not achieve statistical significance (OR 3.38, p=0.081). Rates of Clavien-Dindo grade ≥3 surgical complications were comparable between patients aged ≤80 and >80, and between patients with a performance status of 0-1 and 2-3. The small sample sizes and inability of performance status 2 to distinguish between frail and non-frail patients should be taken into account when interpreting these findings.

Conclusions. There is a clear case for surgical resection in older patients with operable disease and adequate performance status. Conversely, the balance of risks is not necessarily in favour of intervention in patients with a poor performance status. This study was limited by the absence of frailty-related data, unavailability of primary care and palliative care data, and the small number of patients meeting the eligibility criteria receiving palliative chemotherapy. A shift in research goals towards patient-centred outcome measures and a greater focus on frailty will be required to generate meaningful research findings with the potential to transform the care of older and frail patients with gastric cancer.

INTRODUCTION

Clinical problem

With life expectancy increasing throughout the world, gastric cancer is rapidly becoming a disease of the elderly. Half of all deaths from gastro-oesophageal cancer in western populations are in people aged over 75 years [10]. Even in developing countries, the peak incidence of gastric cancer is now in the 70-80 age group [59]. Coupled with increasing life expectancy, there is an ever increasing emphasis on healthy ageing and active retirement. Shifting attitudes towards ageing have resulted in a paradigm change in the management of older patients diagnosed with cancer. Age itself no longer represents a barrier to treatment, whilst the concept of frailty has become more important than ever.

Unfortunately, there is minimal evidence to guide management decisions in older or frailer patients with gastric cancer. As in other conditions, research participants tend to be younger than the average patient with gastric cancer. In both the landmark MAGIC and FLOT4 trials of perioperative chemotherapy for gastro-oesophageal cancers, the median age of participants was 62 years although neither trial specifically excluded older patients [9,60]. Subgroup analysis of older and frailer patients was not incorporated into the design of either study. Previous predictive models of survival in western patients with gastric cancer, including non-surgical patients, were derived from cohorts with a median age of approximately 70 years (see Chapter 2 Discussion). By contrast, the median age of the cohort evaluated in Chapter 2 was 77 years at the time of cancer diagnosis.

In the previous chapter, performance status but not age was identified as an independent predictor of poor survival in patients with gastric cancer. Similar to performance status, frailty is strongly associated with poorer overall survival [61]. Several mechanisms contributing to poor survival in frail patients with cancer have been described, including lower treatment tolerability, higher rates of treatment toxicity and higher risks of postoperative complications, as well as reduced physiological reserve to withstand disease-related insults [61,62]. The present cohort, given its high median age, may seem ideal for exploring the effects of treatment on outcomes and morbidity in older and frailer patients. In reality, treatment decisions in the real world are invariably linked to baseline patient characteristics. Stürmer described frailty as “a powerful confounder that is difficult to measure and can either increase or decrease the likelihood of treatment” [63]. In gastric cancer, older and frailer patients are more likely to be directed towards palliative management strategies. In addition to confounding, real-world retrospective studies in these patient groups are limited by relatively small numbers of patients receiving surgery or chemotherapy, resulting in insufficient power to answer questions regarding treatment benefit. At the same time, weighing up clinical efficacy against quality

of life, treatment tolerability and risk is key to determining whether a treatment strategy is in the best interests of patients with shorter baseline life expectancies.

Performance status and frailty

Performance status and frailty overlap in their scope but are not identical. Performance status is part of the 'global language' of oncologists [62], routinely recorded in both individual patient records and cancer databases, and included in standard datasets used for cancer research. By contrast, the concept of frailty has only recently come into vogue. In 2011, a survey of British gastro-intestinal oncologists revealed that objective frailty assessments were not used at all to guide treatment decisions in the UK [10].

Performance status is a global assessment of the patient's level of physical function and ability to self-care [64]. First formulated by Karnofsky and Burchenal in 1949, the original Karnosfky performance score was later developed into the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale. Much of its value lies in its simplicity as a 6-point scale. Universally understood by clinicians worldwide, performance status is characterised by a low degree of inter-observer variability and has proven its worth in prognostication and triaging patients to treatment strategies [65]. Previous studies have demonstrated that performance status is closely aligned with chemotherapy risk-to-benefit profiles and patient preferences regarding treatment, as well as facilitating prognostication in palliative care settings [62].

The simplicity of performance status comes at a price. Performance status is a unidimensional measure. Unlike frailty scores, it does not take into account the non-physical domains of nutrition, multimorbidity and cognition which play important roles in determining prognosis. Notably, performance status does not differentiate between organ dysfunction and musculoskeletal symptoms as the cause of poor performance [62]. A common criticism of the ECOG Performance Status Scale is its lack of precision at performance status 2, defined as "ambulatory and capable of all selfcare but unable to carry out any work activities". Performance status 2 is often a crucial decision point but brackets together a disparate collection of patients including some with mild musculoskeletal ailments but normal organ function and others with significant systemic morbidity [62].

By contrast, frailty scores are variably defined but commonly include multiple domains including physical activity, nutrition and/or weight loss, cognition, comorbidity, polypharmacy and socioenvironmental characteristics [59,66]. Frailty as a concept has been described as "a continuous age-related accumulation of deficits" evaluated from the perspective of the whole patient[59]. It can be conceptualised as a cumulative decline in multiple physiological systems resulting in an impaired

ability to recover to a previous functional baseline [62]. Unfortunately, little standardisation exists for frailty scores, making it difficult to combine or compare frailty-related outcomes across studies. A scoping review of the effect of frailty on outcomes of gastrectomy for gastric cancer listed a total of 9 frailty assessment tools used across 15 studies [59]. As yet, there is no consensus on the most effective screening tool for frailty in cancer patients [61].

The findings discussed in Chapter 2 are consistent with the historical experience of clinicians and researchers over the past 70 years: performance status is widely recognised for being strongly associated with overall survival [65]. A reasonable question to ask is whether this association represents a self-fulling prophecy in which patients with worse performance status are directed away from life-prolonging treatment and therefore suffer from poorer outcomes. It could be argued that too much emphasis is currently placed on performance status, with numerous study protocols, treatment guidelines and funding decisions using performance status as the sole criterion of patient 'fitness' [62]. Clinical trials have either excluded patients with poor performance status outright, or used performance status to stratify survival outcomes but not treatment toxicity [62]. Frailty, on the other hand, is seen as a condition that can be mitigated and optimised. Although frailty assessments are invariably more cumbersome than the 'snap judgement' nature of performance status, the processes involved are designed to identify aspects in which mitigatory measures such as nutritional supplementation or guided exercise might be beneficial in reducing adverse treatment outcomes [59,66].

Existing evidence for chemotherapy and surgery in frail and older patients

Participants in chemotherapy trials tend to be younger than the median age of patients diagnosed with gastric cancer in real-world settings. In a Cochrane review of chemotherapy for advanced gastric cancer, median ages of participants ranged from 56 to 67 years in studies comparing chemotherapy and best supportive care, and from 55 to 70 years in head-to-head comparisons of chemotherapy regimens [67]. In general, chemotherapy was found to extend overall survival by approximately 6.7 months compared to best supportive care alone in patients with advanced gastric cancer. Combination chemotherapy further extended survival slightly by approximately one month [67]. The intrinsic value assigned to these additional months of life naturally differs from patient to patient, and must be carefully considered in frailer and older patients with a limited quality of life at baseline and increased susceptibility to treatment side effects.

The UK-based GO2 phase III trial is the largest clinical trial so far that specifically sought to evaluate chemotherapy regimens in older and frail patients with advanced gastro-oesophageal cancer [10]. GO2 was preceded by 321GO, a randomised feasibility trial which compared a three-drug (epirubicin,

oxaliplatin, capecitabine), two-drug (oxaliplatin and capecitabine) and one-drug (capecitabine) regimen and found that the two-drug regimen achieved the best balance between benefit and tolerability [68]. GO2 itself was divided into two randomisation pathways: CHEMO-INTENSITY (n=514), which compared 3 dosing intensity levels of oxaliplatin/capecitabine, and CHEMO-BSC (n=45) which compared the least intense dosing level of oxaliplatin/capecitabine against best supportive care. As the key eligibility criterion, all included patients were considered unsuitable by their oncologists for full-dose standard combination chemotherapy.

Within the current research context, the GO2 trial arguably established a new gold standard for clinical trials involving older and frail patients with gastric cancer. Many of its core features could serve as a foundation for future studies in this patient group. Endpoints of the GO2 trial included not only conventional survival outcomes such as progression-free survival and overall survival but also the novel 'overall treatment utility' measure developed in the FOCUS2 trial as a combination of clinical efficacy, tolerability, quality of life and the patient's own assessment of treatment value and acceptability [69]. A baseline frailty assessment was performed, assessing impairment in nine domains. Quality of life was evaluated after consent but before randomisation with the EORTC Elderly Minimum Data Set.

Key findings from GO2 CHEMO-INTENSITY were non-inferior performance-free survival and better overall treatment utility associated with the lowest-intensity regimen of oxaliplatin/capecitabine compared to more intense regimens. GO2 CHEMO-BSC, meanwhile, found non-significant trends towards longer overall survival (median 6.1 vs 3.0 months), improved quality of life and reduced fatigue with lowest-intensity oxaliplatin/capecitabine compared to best supportive care alone.[10]

Evidence relating to surgical outcomes in older or frail patients is mostly derived from retrospectively analysed data. A recent scoping review of gastrectomy outcomes in frail patients highlighted significant associations between frailty and postoperative complications, mortality, length of hospital stay, quality of life and discharge to a non-home destination [59]. Quantitative synthesis of data was not possible due to considerable heterogeneity in the frailty assessment tools used, translating to wide variations in the incidence rates of frailty between studies [59]. In a cohort study of Korean parents aged >65 undergoing gastrectomy, a multidimensional frailty score of >5 was associated with higher 1-year mortality on univariate analysis but not on multivariable analysis incorporating pathological stage, tumour location and type of gastrectomy amongst other disease and treatment characteristics [70].

In 2022, Lee and colleagues published a US-based case-control study comparing propensity-score-matched 'frailty-present' and 'frailty-absent' groups with respect to various endpoints following

gastrectomy [66]. Participants were drawn from the 2011-2017 National Inpatient Sample and frailty was defined according to the Johns Hopkins Adjusted Clinical Groups (ACG) criteria. After propensity score matching, frailty was associated with higher mortality (6.83 vs 3.50%, OR 2.02, p<0.001), length of stay (16.7 vs 12.0 days, p<0.001), costs of treatment, and complications including wound complications, infections and respiratory failure.

Rationale

Notwithstanding the significant inroads made by the GO2 trial, there remains a large element of uncertainty surrounding the merits of surgery and chemotherapy in older and frail patients with gastric cancer. Ultimately, decisions concerning a patient's 'best interests' will vary from individual to individual, both in terms of personal preferences and personalised risk. However, the clinical evidence needed to guide such treatment decisions is currently lacking. More refined tools are needed to stratify treatment-associated risk and quantify expected benefit.

The present study attempted to evaluate the benefits and risks associated with treatment in a UK-based cohort of patients aged over 80 or with a performance status ≥2. Propensity score methodology was used to counteract the effects of confounding. Although an imperfect workaround, the propensity score serves as a 'balancing score' and thereby attempts to mimic a randomised controlled trial by accounting for baseline covariates that may represent potential confounders [71]. Unlike conventional multivariable modelling (as used in Chapter 2), propensity score methods separate modelling from estimation of treatment effects [71]. The methodology used here combines inverse probability of treatment weighting by the propensity score with propensity score trimming (as described by Stürmer and colleagues) to reduce bias due to unmeasured confounders [63]. Although limited by retrospective methodology, sample size and absence of frailty assessment, it is hoped that the findings generated by this study will provide impetus and generate meaningful research questions for future projects.

AIMS AND OBJECTIVES

This chapter aims to answer the following questions:

1. Is gastrectomy performed with curative intent associated with a survival benefit in older patients (>80 years) or patients with poor performance status (ECOG PS≥2) with clinically resectable gastric and Siewert III adenocarcinomas?

2. Is gastrectomy associated with a greater degree of morbidity in older patients (>80 years) or patients with poor performance status (ECOG PS≥2) compared to younger and fitter patients?
3. Does palliative chemotherapy confer a survival benefit in older patients (>80 years) or patients with poor performance status (ECOG PS≥2) in whom surgery is deemed inappropriate?

The objectives for the first aim are:

1. To compare overall survival in patients aged over 80 years versus patients aged 80 years or younger at diagnosis undergoing gastrectomy with curative intent.
2. To compare overall survival associated with curative-intent versus palliative treatment in patients aged over 80 years at diagnosis, using propensity score methodology to adjust for differences in baseline characteristics between patients treated with these contrasting strategies.
3. To compare overall survival associated with curative-intent versus palliative treatment in patients with an ECOG performance status of 2 or 3 at diagnosis, using propensity score methodology to adjust for differences in baseline characteristics between patients treated with these contrasting strategies.

The objectives for the second aim are:

4. To compare rates of surgical complications classed as Clavien-Dindo grade 3 or more between patients aged over 80 years versus patients ≤ 80 years at diagnosis.
5. To compare rates of surgical complications classed as Grade 3 or more on the Clavien-Dindo classification and post-operative length of stay between patients with an ECOG performance status of 0-1 versus patients with an ECOG performance status of 2-3 at diagnosis.

The objective for the third aim is:

6. To compare overall survival associated with palliative chemotherapy versus best supportive care alone in patients aged over 80 years at diagnosis and in patients with an ECOG performance status of 2 or 3, using propensity score methodology to adjust for differences in baseline characteristics between patients treated with these contrasting strategies.

METHODS

Study design, setting and study population

Cases included in this study were drawn from the cohort used for the predictive model described in Chapter 2. This was a single-centre cohort comprising all patients with a formal diagnosis of gastric

adenocarcinoma, including Siewert III gastro-oesophageal junction adenocarcinoma, at the Norfolk and Norwich University Hospital (NNUH) between February 2011 and June 2021. The process by which patients were identified for inclusion is detailed in Chapter 2, and this study is covered by the same ethical approval.

The following groups of patients were of interest in this study:

- Patients aged over 80 years at the point of diagnosis with gastric cancer;
- Patients with a Eastern Cooperative Oncology Group (ECOG) performance status of 2-4 at baseline.

Outcomes

The primary outcome measures for each of the study objectives are as follows:

- Objective 1: Overall survival, defined as survival from the date of cancer diagnosis as recorded on the Somerset Cancer Register to death from any cause.
- Objectives 2-3: Overall survival at 2 years. This time point was chosen for comparisons of outcomes in patients treated with curative intent versus patients treated with palliative intent as it represents a 'middle ground' between expected survival in the two patient groups. As estimated using Kaplan-Meier methodology in Chapter 2, median overall survival was 3.92 in patients undergoing surgery and 302 days (0.83 years) across all patients in the cohort regardless of treatment modality.
- Objectives 6: Overall survival at 1 year. This time point was selected on the basis of a median overall survival of 302 days across the entire cohort, as estimated using Kaplan-Meier methodology in Chapter 2.
- Outcomes 4-5: Surgical complications classified as Clavien-Dindo Grade 3 or more.

Case ascertainment and clinical measurements

As described in Chapter 2, a medical gastroenterologist reviewed each set of electronic health records to ascertain eligibility for inclusion and collate data for entry into the database. For the purposes of this study, the relevant variables requiring a manual trawl of health records were: ECOG performance status, treatment(s) administered, surgical complications, and post-operative length of stay. ECOG performance status was obtained verbatim from clinic letters. In cases where performance status was not explicitly reported, no attempts were made at extrapolation. The last date of data collection, on which the vital status of all included patients was ascertained, was 30 June 2023. This therefore represents the date of last follow-up.

Exposures and covariates

Exposures and covariates for which data were collected are listed in Chapter 2. These were incorporated into propensity score analysis as described below.

Statistical analysis

Descriptive data were reported in terms of frequencies and proportions for categorical values, means with 95% confidence intervals for continuous variables following a normal distribution, and medians with interquartile ranges for non-normally-distributed continuous variables.

Overall survival was estimated using Kaplan-Meier methodology.

Differences between groups (e.g. age at diagnosis ≤80 years vs >80 years, or a performance status of 0-1 vs 2-4) were evaluated by means of the Chi-square test for binary variables, logistic regression for multilevel categorical variables, Student's t-test for continuous variables following an independent distribution, and the Mann-Whitney U-test for non-normally distributed continuous variables.

All statistical analyses were performed using STATA Version 17.0 MP (StataCorp, College Station, Texas, USA).

Propensity scoring

Propensity score methodology was used to adjust for confounding by baseline patient and disease characteristics that may influence decisions regarding treatment, and thereby to enable valid comparisons of outcomes between intervention and non-intervention groups. The propensity score is defined as the probability of receiving treatment given a set of baseline characteristics [71]. Covariates for inclusion in the propensity score model were identified from the exposures and confounders listed in Chapter 2. Logistic regression was used to explore associations between covariates and outcomes. Covariates were included if they were measured at baseline and significantly associated with the primary outcome of interest (1-year or 2-year overall survival), as recommended by Brookhart and colleagues [72].

The propensity score was estimated by fitting a logistic model with the treatment in question as the 'outcome' and the selected covariates as explanatory variables, followed by the Stata command *'predict ps'*. Areas of propensity score overlap between treatment groups were evaluated graphically by means of a histogram and two-way density plot. 'Trimming' was performed as described by Stürmer and colleagues [63] to restrict analysis to the area of overlapping propensity scores. The following

Stata commands, adapted from Dr John Tazare's lectures at the London School of Hygiene & Tropical Medicine, were used for this purpose [73]:

Identifying minimum and maximum propensity scores in the group not receiving treatment:

- *summ ps if trt==0*
- *local min0 = r(min)*
- *local max0 = r(max)*

Identifying minimum and maximum propensity scores in the treatment group:

- *summ ps if trt==1*
- *local min1 = r(min)*
- *local max1 = r(max)*

Dropping patients with propensity scores in non-overlapping areas:

- *local overlapMin = max(`min1', `min0')*
- *local overlapMax = min(`max1', `max0')*
- *drop if ps < `overlapMin' | ps > `overlapMax'*

Finally, inverse probability of treatment weighting by the propensity score was used to compare outcomes between patients in the two groups. Variables containing the weights for each patient were generated using the Stata commands *'gen weight = 1/ps if trt==1' and 'replace weight = 1/(1-ps) if trt==0'*, where *trt* refers to the treatment variable under evaluation. Weights were then incorporated into a logistic regression model: *'logistic outcome i.trt [pweight=weight]'*, where *outcome* is the primary outcome variable and *trt* is the treatment variable under evaluation.

RESULTS

Study participants and clinical characteristics

For the purposes of this chapter, 'older' patients were defined those aged over 80 years at cancer diagnosis and 'resectable disease' was defined as localised cancer without evidence of metastatic disease on staging investigations.

212 patients aged over 80 years at diagnosis were identified from the database, representing 39.3% of the cohort. Within this group, 91 patients (42.9%) were found to have metastatic disease on staging

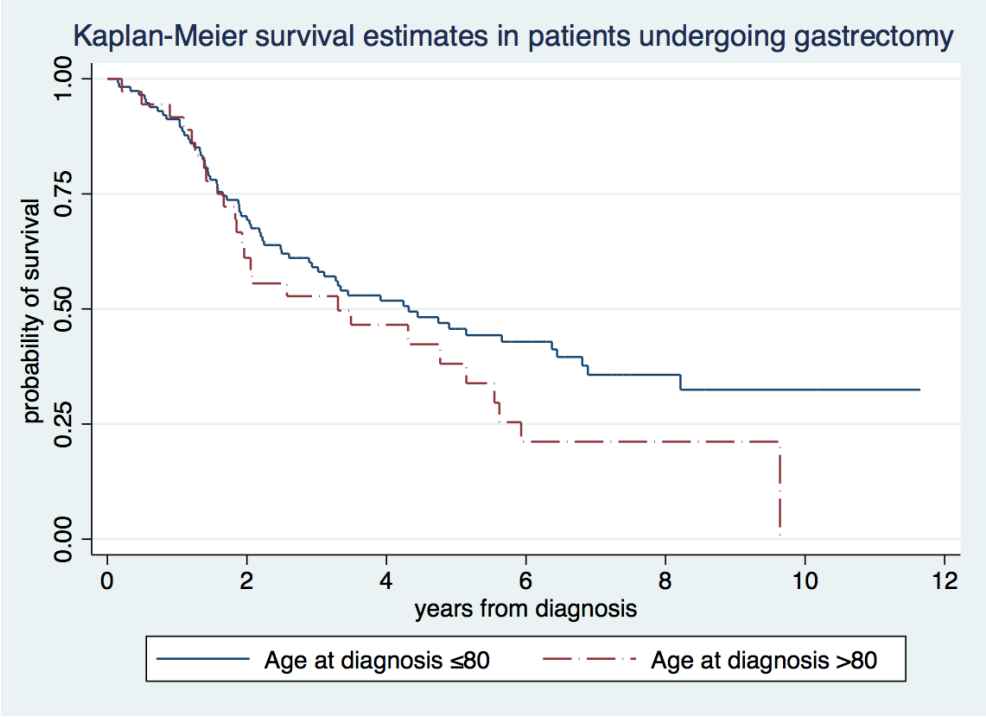
investigations including imaging and/or laparoscopy whilst 107 (50.5%) had no overt metastases. 14 patients (6.6%) did not undergo staging investigations.

175 patients with an ECOG performance status of 2-4 at diagnosis were identified, representing 32.4% of the cohort. Within this group, 84 patients (48.0%) were found to have metastatic disease on staging whilst 79 (45.1%) had no overt metastases. 12 patients (6.9%) did not undergo staging investigations.

Outcomes of surgery in older patients compared to younger patients

Of the 150 patients in the cohort who underwent surgical resection with curative intent, 114 (76%) were aged 80 years or under and 36 (24%) were aged over 80 years at diagnosis. Amongst patients treated with curative intent, median overall survival was 4.32 years (IQR 1.65–no upper bound) in patients aged ≤80 and 3.31 years (IQR 1.58–5.93 years) in patients aged >80 as estimated by Kaplan-Meier methodology [Figure 3.1]. The difference in overall survival between patients aged ≤80 and patients aged >80 treated with curative intent did not reach statistical significance (HR 1.39, 95%CI 0.88–2.19; p=0.159).

Figure 3.1: Survival curves in patients undergoing surgical resection with curative intent, stratified by age ≤80 or >80 years at diagnosis



Age At Diagnosis	Median Overall Survival	Interquartile Range
≤80 years (n=114)	4.32 years	1.65–no upper bound
>80 years (n=36)	3.31 years	1.58–5.93

Outcomes of surgery compared to palliative management for resectable disease in older patients

107 patients over the age of 80 did not have overt metastatic disease on initial staging. Within this subgroup, 36 patients (33.6%) underwent gastrectomy and 71 (66.3%) were treated with palliative intent. Median overall survival was 3.31 years (IQR 1.58–5.93) in patients undergoing gastrectomy and 0.65 years (IQR 0.17–1.24) in patients treated with palliative intent [Figure 3.2]. Patients undergoing gastrectomy were significantly less likely to have an ECOG performance status ≥2 (15.8% vs 68.6%; RR 0.19; p<0.0001) and less likely to have linitis plastica (0% vs 13.7%; p=0.015) compared to their peers who were treated non-operatively. Patients undergoing gastrectomy were marginally but statistically significantly younger (median age at diagnosis 83.0 years vs 84.8 years; p=0.005). There were no significant differences in the proportions of patients with T4 tumours, or in sex or smoking status.

Baseline characteristics were selected for inclusion into a propensity score model by evaluating their associations with overall survival at 2 years across all patients without overt metastases, regardless of age or treatment modality. The following baseline characteristics were significantly associated with overall survival of less than 2 years in univariate analysis: diagnosis following an emergency presentation (p=0.026), overall AJCC stage 2 or above (p=0.023), tumour (T) stage ≥3 (p=0.013), ECOG performance status ≥2 (p<0.001), and linitis plastica (p=0.041). The following characteristics were not associated with 2-year overall survival: sex, involvement of the gastro-intestinal junction, nodal (N) stage, smoking status, and presence of signet ring cells.

A propensity score model with respect to curative resection was generated with overall AJCC stage, T-stage, ECOG performance status, emergency presentation and linitis plastica as covariates and 2-year overall survival as the endpoint [Table 3.1]. After trimming, 56 patients aged over 80 and without overt metastatic disease were included in the final analysis: 23 treated operatively with curative intent and 33 treated non-operatively with palliative intent. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 2 years was 6.26 (95%CI 1.04-37.82; p=0.046) with curative gastrectomy compared to palliative management in elderly patients without metastatic disease.

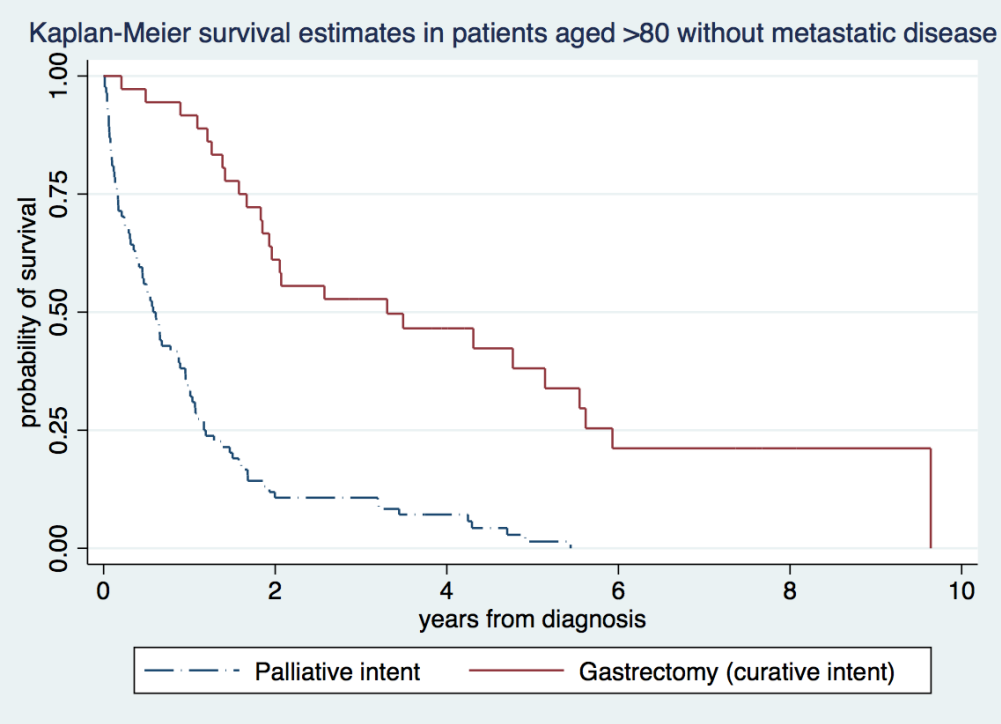
Table 3.1: Logistic regression model producing propensity score with respect to curative resection (probability of receiving gastrectomy with curative intent, analysed across entire cohort)

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status (relative to PS 0)			
Performance Status 1	0.295 (0.135–0.646)	-3.05	0.002
Performance Status 2	0.030 (0.009–0.096)	-5.92	<0.001
AJCC cancer stage (relative to Stage I)			
Stage II	0.469 (0.063–3.489)	-0.74	0.459
Stage III	0.198 (0.022–1.795)	-1.44	0.150
Acute presentation	1.155 (0.447–2.988)	0.30	0.766
Linitis plastica	0.304 (0.043–2.134)	-1.20	0.231

$\chi 2 = 70.43$, $p<0.0001$

Model developed in a total of 201 patients on a complete case analysis basis. STATA excluded patients with ECOG PS 3 and 4 and AJCC stage IV from the model as these characteristics 'perfectly predicted' non-operative management.

Figure 3.2: Survival curves in patients aged >80 at diagnosis without overt metastatic disease at cancer diagnosis, stratified by curative gastrectomy vs treatment with palliative intent.



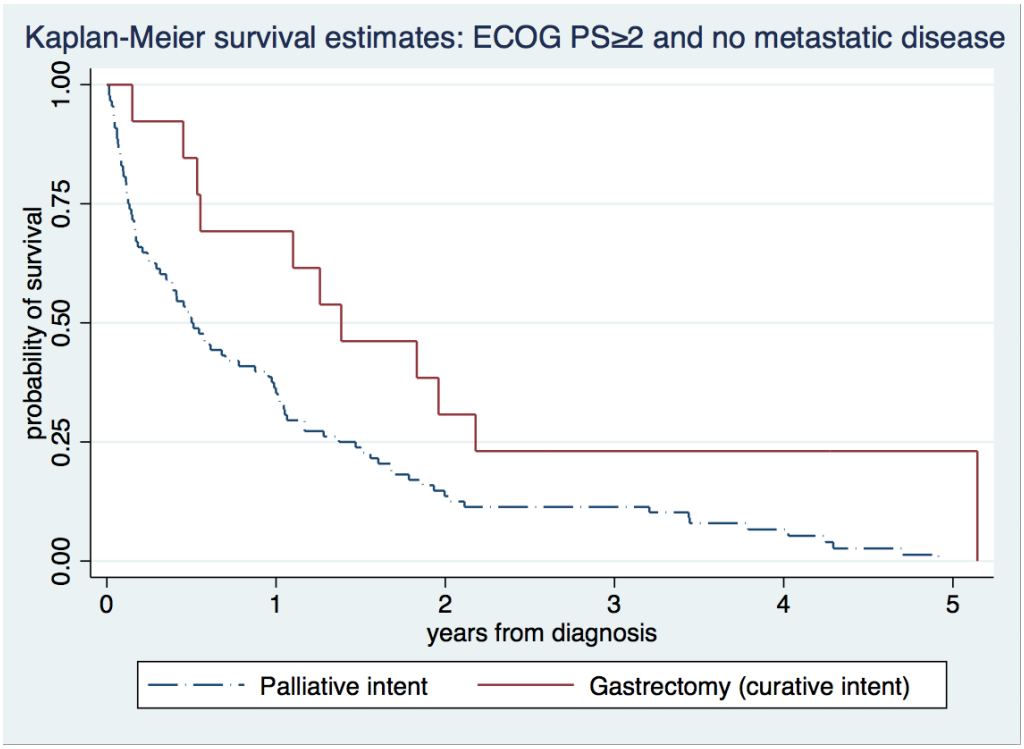
Treatment	Median Overall Survival	Interquartile Range
Gastrectomy, curative intent (n=36)	3.31 years	1.58–5.93
Palliative intent (n=71)	0.65 years	0.17–1.24

Outcomes of surgery compared to non-operative treatment for resectable disease in patients with performance status ≥2

79 patients with an ECOG performance status of 2-4 did not have overt metastatic disease on initial staging. This figure does not include patients who did not have a documented performance status or for whom no form of staging investigation was performed. Within this subgroup, 11 patients (13.9%) underwent gastrectomy and 68 were treated with palliative intent (86.1%). Median overall survival was 1.26 years (IQR 0.53-2.18) in patients undergoing gastrectomy and 0.70 years (IQR 0.16-1.68) in patients treated with palliative intent [Figure 3.3]. Patients undergoing gastrectomy were significantly younger (median age at diagnosis 77.1 years vs 81.5 years; p=0.006). There were no significant differences in the proportions of patients with T4 tumours or linitis plastica, or in sex or smoking status.

As previously described, a propensity score model with respect to curative resection was generated with overall AJCC stage, T-stage, ECOG performance status, emergency presentation and linitis plastica as covariates and 2-year overall survival as the endpoint. After trimming, 34 patients with a performance status of 2-4 and no overt metastatic disease were included in the final analysis: 5 treated operatively with curative intent and 29 treated non-operatively with palliative intent. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 2 years was 1.79 (95%CI 0.17-18.51; p=0.624) with curative gastrectomy compared to palliative management in patients with a performance status ≥2 and no metastatic disease. Gastrectomy was therefore not associated with a significant survival benefit in this patient group.

Figure 3.3: Survival curves in patients with ECOG performance status ≥2 and no overt metastatic disease at cancer diagnosis, stratified by curative gastrectomy vs treatment with palliative intent.



Treatment	Median Overall Survival	Interquartile Range
Gastrectomy, curative intent (n=11)	1.26 years	0.53–2.18
Palliative intent (n=68)	0.70 years	0.16–1.68

Operative morbidity

Compared to patients aged ≤80 years, patients aged >80 years undergoing gastrectomy with curative intent did not have a higher rate of surgical complications classified as Clavien-Dindo grade 3 or above (10.3% vs 11.2%; p=0.87).

Compared to patients with an ECOG performance status of 0-1, patients with a performance status of 2-4 undergoing gastrectomy with curative intent did not have a higher rate of surgical complications classified as Clavien-Dindo grade 3 or above (6.3% vs 8.8%; p=0.73).

Older patients managed with palliative intent

176 patients aged over 80 years at diagnosis were managed with palliative intent, including 91 patients with overt metastatic disease at initial staging, 71 patients without overt metastatic disease and 14 patients who did not undergo staging investigations. Reasons for palliative management of potentially operable disease were not included in the dataset. However, clinic letters indicated that typical

reasons were frailty, comorbidity, patient choice and local invasion. Patients aged ≥80 years with metastatic disease on staging investigations demonstrated considerably worse overall survival than those without metastatic disease (median 73 days vs 236 days; HR 1.93 [95%CI: 1.39-2.67]; p<0.001).

Palliative chemotherapy in older patients

Of the 176 patients aged over 80 years managed palliatively, only 18 (10.2%) were treated with palliative chemotherapy, all of whom had an ECOG performance status of 0 (n=6) or 1 (n=12). Patients undergoing chemotherapy had a median OS of 302 days (IQR 222–602) compared to 87 days (IQR 37–314) in patients managed with best supportive care. This difference is not statistically significant in multivariable analysis incorporating ECOG performance status. We therefore cannot ascertain whether improved survival in older patients undergoing chemotherapy is due to the effects of treatment or their superior baseline performance status.

Baseline characteristics associated with overall survival at 1 year were selected for inclusion into a propensity score model with respect to treatment with chemotherapy [Table 3.2]. These variables were previously identified in Chapter 2 (see Table 2.2) and are as follows: ECOG performance status, cardiovascular disease, overall AJCC cancer stage, linitis plastica, and peritoneal disease. After trimming, 48 patients aged >80 at diagnosis and managed with palliative intent were included in the final analysis: 17 receiving chemotherapy and 31 receiving best supportive care. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 1 year was 3.38 (95%CI 0.86-13.24; p=0.081) with chemotherapy compared to best supportive care. Despite a trend towards better survival following palliative chemotherapy, this did not achieve statistical significance in patients aged over 80.

Table 3.2: Logistic regression model producing propensity score with respect to chemotherapy (probability of receiving chemotherapy for any indication, analysed across entire cohort)

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status (relative to PS 0)			
Performance Status 1	0.417 (0.247–0.703)	-3.28	0.001
Performance Status 2	0.042 (0.193–0.091)	-7.99	<0.001
Performance Status 3	0.004 (0.0004–0.028)	-5.34	<0.001
AJCC cancer stage (relative to Stage I)			
Stage II	2.116 (0.829–5.403)	1.57	0.459
Stage III	4.031 (1.536–10.577)	2.83	0.150
Stage IV	3.912 (1.458–10.496)	2.71	0.150
Peritoneal disease at initial staging	1.155 (0.447–2.988)	0.30	0.766
Linitis plastica	0.304 (0.043–2.134)	-1.20	0.231

$\chi 2$ = = 204.07, p<0.0001

Model developed in a total of 472 patients on a complete case analysis basis. STATA automatically excluded ECOG PS 4 from the model as this characteristic 'perfectly predicted' management without chemotherapy, i.e. best supportive care alone.

From the clinical records available for our research purposes, only one chemotherapy-related adverse event graded CTCAE 3 or higher was recorded in this patient group.

Patients with performance status ≥2 managed with palliative intent

164 patients with an ECOG performance status ≥2 were managed with palliative intent, including 84 patients with overt metastatic disease at initial staging, 68 patients without overt metastatic disease and 12 patients who did not undergo initial staging. These numbers do not include patients for whom no performance status was recorded. Within this subgroup, patients with metastatic disease on staging investigations demonstrated considerably worse overall survival than those without (median 58 days vs 199 days; HR 2.85 [95%CI 1.98-4.11]; p<0.001).

Palliative chemotherapy in patients with poor performance status (ECOG ≥2)

Of the 164 patients with an ECOG performance status ≥2 managed palliatively, only 11 (6.7%) underwent palliative chemotherapy. Overall median survival in patients undergoing chemotherapy was 199 days (IQR 120–315), compared to 77 days (IQR 37–285) in patients not undergoing chemotherapy (HR 0.84, 95%CI 0.45–1.55; p=0.57). Given the poor prognosis in both groups and low number of patients receiving chemotherapy, further statistical analysis is unlikely to be meaningful.

From the clinical records available for our research purposes, no chemotherapy-related adverse events graded CTCAE 3 or higher were recorded in this patient group.

Summary of key findings

Overall survival following gastrectomy with curative intent was not significantly different between patients aged ≤80 and patients aged >80 at diagnosis. Propensity score trimming and inverse probability of treatment weighting by the propensity score were performed to improve balance between treatment groups with differing baseline characteristics. Using these methods, gastrectomy was shown to be associated with significantly improved odds of survival at 2 years in patients aged over 80 at diagnosis without metastatic disease, but not in patients with a performance status of 2-4 and no metastatic disease [Table 3.3]. Although chemotherapy was associated with a trend towards improved survival in patients aged over 80 managed with palliative intent, this did not achieve statistical significance. The small sample sizes involved in the above analyses should be taken into account when interpreting these findings.

Table 3.3: Summary of odds ratios associated with treatment in selected patient groups following propensity score trimming and inverse probability of treatment weighting by the propensity score

Patient group and comparison	Outcome	Odds ratio	95% CI	*p*-value
Age > 80 (any performance status), no metastatic disease: *gastrectomy vs no gastrectomy*	2 year OS	6.26	1.07–37.82	0.046
ECOG ≥2 (any age), no metastatic disease: *gastrectomy vs no gastrectomy*	2 year OS	1.79	0.17–18.51	0.624
Age > 80 (any performance status) treated with palliative intent: *chemotherapy vs best supportive care*	1 year OS	3.38	0.86–13.24	0.081

DISCUSSION

General Observations

Treatment decisions involving older and frail patients are often challenging. In an era of evidence-based medicine and patient-centred care, the lack of data relating to older and frailer patients presents a major obstacle to shared decision making involving these groups of patients. Earlier chapters have established that patients aged over 80 years and patients with an ECOG performance status ≥2 suffer from worse survival outcomes. Although these observation are hardly surprising, they raise two important questions. First, is treatment of any benefit in patients whose baseline characteristics predispose them to poorer outcomes? Second, are the poorer outcomes in these patient groups attributable mostly to their unfavourable baseline characteristics or to the fact that they are less likely to be offered treatment? The results discussed in this chapter suggest that surgical resection for operable disease does indeed confer a significant survival benefit in older patients although not in patients with a performance status ≥2, whilst no conclusions can be drawn from the available data regarding the role of palliative chemotherapy in these patient groups.

Main Findings

There is a clear case for surgical resection in older patients with operable disease and adequate performance status. In patients over the age of 80 years without metastatic disease on staging investigations, surgical resection was associated with significantly better outcomes even when propensity scoring methodology was used to reduce imbalances between intervention and non-intervention groups. Literature from the past decade is generally supportive of offering curative treatment to fit elderly patients, with broad agreement that chronological age alone is not a

justification for withholding treatment [74]. A Korean case-control study published in 2016 reported significantly higher overall 3- and 5-year survival rates following surgical resection compared to conservative treatment (73.7% and 58.8% vs 29.8% and 0% respectively) “when analysis was confined to resectable elderly (defined as age > 80 years) patients with a favourable performance”.[75]

Equally importantly, the frequency of serious post-operative complications in the current cohort was no higher in patients aged over 80 compared to those aged 80 and under. A Japanese single-institution cohort study covering a similar time period also demonstrated no differences in surgical outcomes, rates of anastomotic leakage, pancreatic fistula or respiratory complications in patients aged ≥80 years compared to patients aged 70-79 yeas [76]. Similar findings were reported in older studies from Italy [77,78] and the United States [79]. Conversely, a Taiwanese study published in 2000 showed higher rates of surgical complications in patients aged > 74 years, but these findings may be reflective of less stringent selection criteria for surgery in the 1990s [80]. This aspect of the patient’s experience of curative surgery should be discussed alongside survival outcomes in conversations with older people regarding potential management options.

The case for surgical resection is less robust in patients with poor performance status. Data from this cohort lend themselves to a weak recommendation in favour of surgical resection for patients with an ECOG performance status of 2-3. Only 13 patients in the cohort with an ECOG performance status ≥2 underwent gastrectomy. Compared to patients with a performance status of 0-1, rates of serious peri-operative complications were no higher in patients with a performance status of 2-3. This last observation is unexpected and likely the result of small sample size and/or the imprecise nature of performance status 2 which has been criticised as “lacking in granularity” due to its inability to distinguish between levels of frailty [62]. Strong associations between frailty and post-operative morbidity were described in both Tan and colleagues’ scoping review and Lee and colleagues’ propensity-score-matched case-control study, discussed earlier in this chapter.

Palliative chemotherapy was offered to very small numbers of non-surgical patients over the age of 80 (n=18) and patients with a performance status ≥2 (n=11). As these numbers were too small, and the sizes of the chemotherapy and best supportive care arms too imbalanced, no meaningful conclusions could be drawn from this data. With this caveat, the analysis suggested a non-significant trend towards improved survival in non-surgical patients aged over 80 treated with palliative chemotherapy compared to best supportive care.

Strengths and limitations

The current study's strengths are its use of propensity score methodology and the relatively large number of older patients for a single-centre cohort of gastric cancer patients in a western country. Limitations include the potential of confounding by baseline characteristics including those not accounted for in the data collected, incomplete cancer-specific mortality data, and a lack of data relating to treatment-associated complications and quality of life.

In the 'real world' setting of a retrospective cohort study, disentangling the effects of treatment from those of baseline characteristics can be challenging. Multivariable analysis is one way of addressing this problem, but provides less-than-satisfactory results in a context where treatment decisions closely reflect baseline characteristics. One approach is to perform more complete subgroup analyses by including all patients in each analysis and adding treatment-subgroup interaction terms. Such an approach could have been used, for example, to compare odds ratios of survival associated with gastrectomy in patients aged over 80 vs patients aged 80 and below, and in patients with an ECOG performance status $\geqslant$2 vs 0-1. However, such analyses would have limited statistical power. The problem of confounding and lack of statistical power are further magnified by the imbalance in numbers between treatment and non-treatment arms. Other baseline characteristics and potential confounders may not have been accounted for in the analysis, either due to their omission from the predefined data collection template or incomplete documentation in medical records. In this study, propensity score methodology was used to counteract the effects of confounding. In addition to inverse probability of treatment weighting, trimming by the propensity score was applied as a further safeguard against bias due to unmeasured confounders.

Survival figures in this study relate to all-cause mortality. Data for cancer-specific mortality were incomplete: causes of death were not always recorded in acute hospital records, whilst primary care and palliative care records were not available for research purposes. A majority of patients, accounting for 75% of patient deaths across the entire cohort, were palliated at home, in a hospice or nursing home. From a research perspective, this is particularly problematic for interpretation of survival outcomes in older and frailer patients, many of whom are likely to have died from causes other than cancer. It could be argued that the lack of reliable cancer-specific mortality data obscures the associations between disease, treatment and survival figures, making it difficult to extrapolate from the data to advise individual patients regarding their treatment options. Conversely, a case may be made in favour of using all-cause mortality figures on the basis that regardless of any anti-cancer effects, treatment may not be in a patient's best interests if it adversely impacts quality of life in situations where death is likely to occur as a result of non-cancer causes.

Given the importance of quality of life, it is regrettable that the present study was unable to adequately address this aspect of patients' experiences with cancer. As only medical records from an acute hospital trust were available for research purposes, data regarding patients' symptoms and complications were incomplete and haphazard. This limitation applies equally to disease-related and treatment-related complications. Adverse events graded 1-2 were intentionally omitted from the present analysis as these are predominantly managed in the community. Only one CTCAE grade 3 chemotherapy-related adverse event was recorded in patients aged over 80 receiving palliative chemotherapy, and none were recorded in patients with a performance status ≥2 receiving palliative chemotherapy. This is undoubtedly a gross underestimate of the treatment burden. The rate of grade 3-4 febrile neutropenia, for example, was as high as 9.3% in a clinical trial arm treated with ECF, whilst 10.2% of patients experienced grade 3-4 nausea or vomiting [11]. A Japanese retrospective study of patients with advanced gastric cancer treated with oral chemotherapy, meanwhile, identified significantly higher rates of grade 3-4 haematological toxicity, anorexia, and nausea and vomiting in patients with performance status 2 compared to patients with performance status 0-1 [81].

Finally, the concept of performance status itself, having served clinicians and researchers well for 70 years, may have outlived its usefulness as a meaningful determinant of prognosis. The ECOG performance status does not adequately cover the domains of multimorbidity, cognition or nutrition, and fails to reflect changes in patients' conditions [82]. Criticisms have also been directed at the imprecision of performance status 2 which often represents a critical decision point. For these reasons, recent guidance from the International Society of Geriatric Oncology recommends a Comprehensive Geriatric Assessment in older cancer patients, but considerations of time and efficiency have led to other surrogate measures being used as well as a continued dependence on performance status [83,84].

Implications for treatment

Findings from this cohort are in keeping with those of previous Asian studies suggesting that older but fitter patients with operable disease benefit from surgical resection and should be offered this chance of cure. It is increasingly recognised that chronological age alone is not a reason to deny patients potentially curative treatment [74]. The results discussed above appear to support this argument. Reassuringly, the data also indicate that older but fit patients are indeed routinely offered surgical resection at our centre and do not suffer from a particularly high rate of complications.

Although the argument for surgical resection in patients with poor performance status is less conclusive, a case may be made for 'prehabilitation' to address any concerns identified through a comprehensive frailty assessment prior to intervention [85]. From a physiological point of view, it is

unsurprising that frail patients suffer from poor outcomes following invasive intervention. Protein and energy insufficiency result in impaired wound healing, increased risk of infection and respiratory complications from diaphragmatic dysfunction [66]. Impaired mobility prevents adequate postoperative rehabilitation, leading to a vicious circle of increasing debility, recurrent falls and recurrent hospital admissions. Addressing these factors would therefore seem a sensible approach to optimising post-operative outcomes.

In view of the limitations discussed above, no definite recommendations regarding palliative chemotherapy in older and frailer patients can be drawn from this study. However, the survival benefit associated with palliative chemotherapy appears to be considerably less pronounced in patients with an ECOG performance status ≥2. Any survival benefit may potentially fail to outweigh the adverse effects of drug toxicity on quality of life, an outcome that the present study was unable to adequately evaluate. The GO2 trial highlighted the potential advantages of using frailty or geriatric assessments as tools to tailor treatment strategies to the individual patient. Previous research in elderly patients with lung cancer had demonstrated the value of integrating a comprehensive geriatric assessment into cancer decision making [86]. GO2 also introduced the idea that treatment strategies need not be 'all or nothing' decisions but may be adjusted to achieve the best balance between benefit and tolerability [10].

Suggestions for future research

The main unanswered questions are how treatment strategies can be targeted to individual patients to optimise the risk-benefit profile, and what role frailty scores might play in determining the best treatment for an individual patient. Randomised controlled trials are the ideal study design to answer these questions. Historically, older and frailer patients were often excluded from randomised controlled trials due to either ethical considerations or mistaken assumptions about the treatment preferences of these patient groups. GO2 demonstrated that such a trial is not only possible but also very welcome in this under-researched population. Novel outcome measures such as Overall Treatment Utility may serve as more meaningful trial endpoints that balance clinical efficacy with tolerability, quality of life and perceived benefit from the patient's point of view.

Observational studies will nonetheless continue to play an important role in the evidence base. The logistical difficulties of recruiting older and frail patients into clinical trials are not to be underestimated. Trial recruitment in the setting of advanced gastric cancer is further limited by life expectancies measured in months. A few key lessons can be learnt from the limitations of the present study to help design future meaningful observational studies. First, the importance of ensuring

adequate sample size cannot be understated. Second, high-quality data relating to quality of life, symptoms, disease complications and treatment-related adverse events are of particular importance in patient populations where survival benefits are small and burdens of treatment considerable. Third, the direction of travel in the care of older patients is clearly in favour of measuring and addressing clinical frailty. Future research involving older and frail patients should therefore include validated frailty scores in their 'standard data set' as a matter of routine.

Much of the required data is either not routinely collected in current clinical practice, or absent from clinical records held in acute hospitals and only to be found in primary care and palliative care. It is eminently clear that any study hoping to accurately reflect the full experiences of elderly and frail patients with gastric cancer will require multi-centre and multi-disciplinary collaborations between acute care, primary care and palliative care providers. Needless to say, sufficient funding and sufficient ethical approval will need to be secured.

Conclusion

There is a clear imperative for research strategies to reflect a shifting paradigm for the management of older and frail patients with gastric cancer. The present analysis demonstrates that age itself is not necessarily an adverse prognostic factor. Older but fit patients can and do benefit from surgery and potentially other aggressive management strategies. Findings from previous retrospective studies also support this conclusion. Conversely, the balance of risks is not always in favour of intervention in frail patients and patients with a poor performance status. Given that few patients with an ECOG performance status ≥2 underwent gastrectomy or chemotherapy, the cohort analysed here was underpowered to generate recommendations regarding treatment in this patient group. Furthermore, the use of performance status as a means of prognostication and stratification is increasingly being challenged: a performance status of 2 often fails to discriminate between frail and non-frail patients. As the typical population of patients with gastric cancer continues to advance in age, more refined tools will be required to enable personalised treatment decisions that take both clinical efficacy and patient-centred outcomes into account. Future clinical trials and observational studies will need sufficient resources and multi-disciplinary as well as multi-centre collaborations to answer research questions that are relevant to older and frail patients.

CHAPTER 4- Outcomes in patients with surgically resectable gastric adenocarcinoma.

ABSTRACT

Background. Only a minority of patients diagnosed with gastric adenocarcinoma in the UK have surgically resectable disease. Even in surgical candidates, long-term survival remains poor. Previous UK-based predictive models of outcomes in patients undergoing gastrectomy have focused on short-term postoperative outcomes but do not provide long-term insight. This chapter sets out to clarify the natural history linking baseline characteristics, outcomes of curative treatment, disease recurrence and death. It is hoped that the findings will inform potential therapeutic strategies for novel adjuvant treatment modalities.

Objectives. This retrospective observational study sought to: (1) characterise a UK-based cohort of patients with gastric and Siewert III gastro-oesophageal junction adenocarcinomas undergoing gastrectomy with curative intent; (2) compare outcomes between patients undergoing gastrectomy on an emergency versus elective basis; (3) compare outcomes between patients receiving neoadjuvant chemotherapy versus upfront surgery; and (4-5) identify characteristics predicting poor survival and disease recurrence. Overall survival, defined as survival from cancer diagnosis to death from any cause, was the primary outcome measure.

Methods. Patients diagnosed with gastric adenocarcinoma (including Siewert III gastro-oesophageal junction cancer) between 2011-2021 and treated with gastrectomy with curative intent at the Norfolk and Norwich University Hospital were included. In addition to baseline patient and disease characteristics, data relating to postoperative pathological findings and disease recurrence were obtained from electronic health records. Multivariable Cox proportional regression was used to evaluate the prognostic predictive value of baseline characteristics and postoperative pathological findings. Propensity score methodology, as previously described, was used to adjust for confounding in comparisons between emergency and elective surgery groups, and between neoadjuvant chemotherapy and upfront surgery groups.

Results. Median overall survival was 4.24 years in patients treated with gastrectomy. Involvement of the gastro-oesophageal junction was not an adverse prognostic factor in this cohort. Patients undergoing emergency gastrectomy demonstrated significantly worse overall survival (1.65 years vs 4.74 years; $p<0.001$) whilst patients receiving neoadjuvant chemotherapy demonstrated significantly

better overall survival (5.14 years vs 2.60 years; p=0.014). However, these trends were no longer statistically significant after weighting by the propensity score. Emergency surgery and upfront surgery without neoadjuvant chemotherapy were significantly associated with both positive resection margins (RR 6.89 and 4.0 respectively) and nodal involvement (RR 6.89 and 4.0 respectively) on postoperative pathological staging. In multivariable analysis, performance status ≥2 and nodal involvement were the strongest predictors of poor survival. The peritoneum was the most common site of recurrence, and peritoneal recurrence was significantly associated with emergency surgery (RR 2.0) and nodal involvement (RR 3.98).

Conclusions. Performance status and lymph node involvement emerged as the strongest predictors of survival in patients with gastric cancer undergoing curative-intent gastrectomy. Associations between emergency surgery, upfront surgery without chemotherapy, positive resection margins, nodal involvement and early mortality suggest a chain of adverse prognostic factors connecting suboptimal preoperative optimisation with poor prognosis. Key limitations of this study are its small sample size and lack of data from primary care and palliative care.

INTRODUCTION

To recapitulate, the overarching aims of this thesis are to describe current outcomes in UK-based patients with gastric adenocarcinoma and to identify unmet needs in this population that may serve as meaningful endpoints for future trials. In Chapter 2, a predictive model for survival in patients with gastric cancer was described. This model was derived from a cohort that included all patients diagnosed with gastric adenocarcinoma within a tertiary centre's referral area over a ten-year period, regardless of disease extent or treatment modality.

Patients undergoing gastrectomy accounted for a minority (27.8%) of this cohort. Surgical resection represents the only treatment modality for gastric cancer considered to be curative at present. Given the aims of the thesis, treatment outcomes in patients treated with curative intent are separately explored and analysed here. This chapter sets out to clarify the natural history linking baseline characteristics, outcomes of curative treatment, disease recurrence and death. It is hoped that the findings will inform potential therapeutic strategies for novel adjuvant treatment modalities as well as aid clinical decision-making.

Current characteristics and short-term outcomes in patients undergoing gastrectomy in the United Kingdom

The National Oesophago-Gastric Cancer Audit (NOGCA) published its State of the Nation Report in January 2024[14]. Demographics and treatment outcomes of patients with diagnosed with oesophagogastric cancer in England and Wales between 2020 and 2022 were audited. Treatment with curative intent was planned in 31.7% of patients with gastric cancer, including Siewert III adenocarcinomas of the gastro-oesophageal junction. 20.8% of patients with gastric cancer in the NOGCA cohort were diagnosed following an initial emergency presentation. Curative treatment was less commonly performed in older patients and patients living in more deprived areas, even after adjustment for clinical stage, tumour site, comorbidities, performance status and sex. Positive longitudinal margins were found in 9.8% of gastrectomy specimens. Rates of overall survival were 85.3% at 1 year post-gastrectomy and 62.7% at 3 years post-gastrectomy. These survival figures were calculated from the time of operation, which differs from the definition of overall survival used in this thesis (cancer diagnosis to death of any cause).

Predictive factors of survival outcomes following surgery

Two UK-based prognostic models for patients undergoing gastrectomy were identified in van de Boorn and colleagues' 2018 meta-analysis of predictive models in gastric cancer[13,24,87]. Both modelled only short-term post-operative outcomes. The O-POSSUM model was published in 2004 and predicted short-term post-operative mortality, defined as death during the same hospital admission as upper gastrointestinal surgery[87]. This model was based on a scoring system which combined measures of operative severity with pre-operative physiological parameters including age, vital signs and findings on basic investigations such as blood tests and electrocardiogram. Given the high postoperative mortality rate of 12% observed in the derivation cohort, this model is likely to be of limited relevance to present-day patients with surgically resectable gastric cancer. For comparison, the 2024 NOGCA State of the Nation Report reported 30-day mortality and 90-day mortality rates of 1.5% and 2.9% respectively in UK patients undergoing curative oesophagogastric cancer surgery in 2020-2022[14].

Fischer and colleagues' 2016 model was derived from data submitted to NOGCA between 2011 and 2013[13]. 30-day and 90-day mortality rates were 2.3% and 4.4% respectively during this period. Positive predictive factors for short-term postoperative mortality in multivariable analysis were: comorbidity count, an ECOG performance status ≥2, American Society of Anaesthesiologists (ASA) fitness grade ≥II and nodal stage N3. Conversely, the size and extent of the primary tumour (i.e. T-stage) and involvement of the gastro-oesophageal junction had no bearing on short-term outcomes. Neither Fischer's model nor O-POSSUM investigated cancer recurrence or long-term survival.

Most models of long-term survival following gastrectomy were derived from Asian cohorts. Hirabayashi and colleagues' model, although published in 2014, used retrospective data from Japanese patients with locally advanced, serosa-negative gastric cancer undergoing gastrectomy between 2001 and 2003[57]. Factors predictive of overall survival at 5 years were: age at operation, gender, tumour size, proximal (including gastro-oesophageal junction) involvement, macroscopic type, histological type, subserosal involvement and number of positive lymph nodes. Han and colleagues' Korean model, published in 2012, identified a very similar set of predictive factors[56].

Emergency presentation and emergency surgery

Studies in East Asia and the United Kingdom have demonstrated a poorer overall prognosis in patients with an emergency initial presentation of gastric cancer[2,15,29]. Emergency presentations include gastric outlet or intestinal obstruction, perforation and severe bleeding requiring urgent intervention. Improving survival figures internationally are in no small part due to advances in screening, diagnosis and referral pathways[88]. In Japan, where a national screening programme is in place, fewer than 1%

of gastric cancer diagnoses are made following an emergency presentation with perforation or acute bleeding[2]. In the United Kingdom, the proportion of gastric cancer diagnoses made following an initial emergency presentation declined from around 40% in the 1990s and early 2000s to around 20% in the past decade[15,29,89]. Unfortunately, the NOGCA State of the Nation Report suggests that the progress made prior to 2010 may have plateaued in recent years: 20.8% of patients with gastric cancer in 2020-2022 were diagnosed following an emergency admission[14].

Markar and colleagues analysed England-wide Hospital Episode Statistics (HES) between 1997 and 2012, reporting worse 5-year survival in patients diagnosed with gastric cancer following an emergency presentation compared to elective presentations (15.1% vs. 26.6%; HR 1.19; 95%CI 1.05-1.22)[89]. Interestingly, they also found that emergency initial presentation was associated with a higher rate of disease recurrence in the liver (7% vs. 4.8%, $p<0.001$) but not with peritoneal recurrence. The proportion of emergency presentations in this study was 39.6% across oesophageal and gastric cancers combined, reflecting the historical period.

In a single-centre study by Vasas and colleagues in 2012 which included 291 surgical patients with gastric cancer, 14.4% of cases were diagnosed following an initial emergency presentation[29]. Modes of emergency presentation were in keeping with present-day expectations: obstruction (59.6%), upper gastrointestinal bleeding (35.7%) and perforation (4.8%), unlike earlier studies where 'emergency' presentations included abdominal pain and vomiting[15]. Emergency diagnoses were more often made at later disease stages: 45% of the emergency group had stage IV disease at diagnosis compared to 25% of the elective group ($p<0.005$). Three-year survival was 14.3% in the emergency group compared to 32.5% in the elective group ($p<0.006$). Even after adjusting for disease stage, the authors found that emergency presentation was associated with a worse prognosis.

To our knowledge, the prognostic implications of emergency surgery, as opposed to emergency presentation, have not been previously evaluated in a UK-based cohort.

Multimodality treatment

Perioperative chemotherapy combined with radical gastrectomy and D2 lymphadenectomy is now the standard of care in Western Europe for all resectable gastric cancers except stage IA tumours[16]. D1 resection, involving removal of the perigastric lymph nodes plus nodes along the left gastric artery, was formerly the norm in Western Europe. Historical observational studies performed in western cohorts are likely to reflect this practice. Studies in Asian centres demonstrated superior outcomes following D2 resection, which entails resection of additional lymph nodes along the common hepatic artery, splenic artery and coeliac axis[16]. European trials of D2 versus D1 resection have painted a

somewhat more mixed picture, showing no initial survival advantage and slightly higher postoperative mortality but fewer locoregional recurrences and fewer gastric cancer-related deaths in the long term with D2 resection[19]. Regardless, consensus opinion and the two most recent iterations of European Society for Medical Oncology (ESMO) guidelines for gastric cancer now recommend D2 gastrectomy in specialised, high volume centres for medically fit patients in western countries[16,19].

The MAGIC and FLOT4 trials of perioperative chemotherapy will be discussed in further detail in the following chapter. In summary, the MAGIC trial demonstrated improved overall survival and disease-free survival at 5 years with a perioperative regimen of epirubicin, cisplatin and fluorouracil (ECF) compared to upfront gastrectomy[9]. The FLOT4 trial demonstrated superior survival outcomes with a perioperative regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT4) compared to ECF without a significant difference in toxicity[60]. The benefits of neoadjuvant chemotherapy have not been replicated in Asian trials and adjuvant chemotherapy continues to be the norm in most East Asian centres[90].

Rationale

With population-level data available from national databases and numerous predictive models already in existence, an obvious question is why yet another single-centre retrospective study is needed. Research in western patients with gastric cancer continues to lag behind research in Asian patients. Previous prognostic studies performed in the UK have focused primarily on short-term postoperative outcomes, whilst identification of adverse prognostic features is beyond the remit of NOGCA. Predictive models derived from Asian cohorts are of uncertain relevance to western patients with gastric cancer, considering differences in tumour biology and standards of care.

Radical gastrectomy with D2 lymphadenectomy was the standard of care in the current surgical cohort. Suitability for perioperative chemotherapy was assessed on a case-by-case basis, with ECF as the preferred regimen until 2019 and FLOT from 2019 onwards. Management strategies in the current cohort therefore reflect current European guidelines, which is not the case in Asian cohorts or historical western cohorts. Unlike previous UK-based studies, this chapter will focus primarily on long-term survival and cancer recurrence.

AIMS AND OBJECTIVES

The aims of this chapter are to characterise a cohort of patients undergoing curative resection for gastric adenocarcinoma and to identify characteristics that predict poor long-term outcomes in a UK-based setting that reflects current European standards of care. The findings are intended to clarify the natural history linking adverse prognostic features with adverse outcomes, and thereby to highlight high-risk patient subgroups as well as therapeutic targets that should represent the focus of future clinical trials.

Specific objectives are as follows:

1. To characterise a UK-based cohort of patients undergoing gastrectomy for gastric and Siewert III gastro-oesophageal junction adenocarcinoma, in terms of baseline patient and disease characteristics, postoperative histological findings, surgical complications and overall survival.
2. To compare outcomes between patients undergoing gastrectomy on an emergency versus elective basis, using propensity score methodology to adjust for differences in baseline characteristics between patients in the two groups.
3. To compare outcomes between patients receiving neoadjuvant chemotherapy versus upfront surgery, using propensity score methodology to adjust for differences in baseline characteristics between patients treated with these contrasting strategies.
4. To identify characteristics that predict poor survival following gastrectomy.
5. To identify characteristics that predict disease recurrence following gastrectomy.

METHODS

Study design, setting and study population

Cases for inclusion were identified from the cohort used for the predictive model described in Chapter 2. This was a single-centre cohort comprising all patients with a formal diagnosis of gastric adenocarcinoma, including Siewert III gastro-oesophageal junction adenocarcinoma, at the Norfolk and Norwich University Hospital (NNUH) between February 2011 and June 2021. The process by which patients were identified for inclusion in the cohort is detailed in Chapter 2, and this study is covered by the same ethical approval.

The study discussed in this chapter included all patients in the cohort undergoing gastrectomy. The two main sub-groups were: patients undergoing elective gastrectomy with curative intent and patients undergoing emergency gastrectomy (often under circumstances where it is difficult to fully

establish ‘curability’ prior to surgery). Patients treated with endoscopic mucosal resection were excluded from the analysis unless they subsequently underwent gastrectomy.

Outcomes

The primary outcome measures for each of the study objectives are as follows:

- Objective 1-4: Overall survival, defined as survival from the date of cancer diagnosis as recorded on the Somerset Cancer Register to death from any cause.
- Objectives 5: Recurrence of gastric adenocarcinoma at any site, treated as a binary outcome.

Secondary outcome measures for Objectives 1-2 are:

- R0 resection, i.e. free of microscopic tumour involvement at longitudinal resection margins.
- Lymph node involvement by cancer on resected specimens.
- Peri-operative complications graded III or above on the Clavien-Dindo Scale.
- Postoperative length of stay.

Case ascertainment and clinical measurements

As described in Chapter 2, a medical gastroenterologist reviewed each set of electronic health records to ascertain eligibility for inclusion and collated data for entry into the database. The last date of data collection, on which the vital status of all included patients was re-ascertained, was 30 June 2023. This therefore represents the date of last follow-up.

Exposures and covariates

In addition to the baseline characteristics detailed in Chapter 2, the following data relating to surgical outcomes were obtained from electronic health records:

- Completeness of resection with respect to longitudinal resection margins (residual tumour ‘R’ classification);
- Number of lymph nodes involved;
- ypTNM staging based on histopathological examination of surgical specimens;
- Peri-operative complications defined as Clavien-Dindo grade III or higher;
- Postoperative length of stay;
- Cancer recurrence, and location and date of recurrence.

Statistical analysis

Descriptive data (objective 1) were reported in terms of frequencies and proportions for categorical values, means with 95% confidence intervals for continuous variables following a normal distribution, and medians with interquartile ranges for non-normally-distributed continuous variables.

Differences between groups (objectives 2-3) were evaluated using the Chi-square test for binary variables, logistic regression for multilevel categorical variables, Student's t-test for continuous variables following an independent distribution, and the Mann-Whitney U-test for non-normally distributed continuous variables. The same statistical tests were used to evaluate for associations with cancer recurrence (objective 5). Statistical significance was defined as a p-value equal to or less than 0.05.

Overall survival was estimated using Kaplan-Meier methodology (objectives 2-4). Associations between baseline characteristics, treatment characteristics or surgical outcomes and overall survival were evaluated using Cox proportional regression models (objective 4). Formal predictive modelling was not performed as the sample size was inadequate for modelling according to the power calculations detailed in Chapter 2. Whereas the surgical cohort included only 150 patients, a sample size of 522 was deemed necessary for a predictive model involving 15 parameters for survival at 1 year, with even larger sample sizes required for survival at more distant time points.

Propensity score methods were used to adjust for confounding factors that may predispose patients towards treatment with neoadjuvant chemotherapy or upfront surgery and also influence survival (objective 3). These methods are described in detail in chapter 3 and combine trimming with inverse probability of treatment weighting by the propensity score. Overall survival at a time point approximating median survival across all surgical patients was chosen as the endpoint for comparisons between neoadjuvant chemotherapy and upfront surgery groups.

All statistical analyses were performed using STATA Version 17.0 MP (StataCorp, College Station, Texas, USA).

RESULTS

Study participants and clinical characteristics

150 patients underwent gastrectomy (19 emergency and 131 elective procedures) for gastric and gastro-oesophageal adenocarcinoma between February 2011 and June 2021. The median age of patients undergoing surgery was 74.9 years (IQR 70.0–80.0). Median follow-up from the date of

diagnosis was 7.19 years (IQR 4.79–9.72). Baseline patient, disease and treatment characteristics of patients undergoing surgery are summarised in Table 4.1 below.

Table 4.1: Baseline patient and disease characteristics

	Total (n=150)	**Cases with missing/unknown values**
Age (median, IQR)	74.5 (65.6-79.6)	-
Gender (n, %)		-
Male	109 (72.7%)	-
Female	41 (27.3%)	-
GOJ involvement, Siewert III (n,%)	40 (26.7%)	-
Cardiovascular Disease (n, %)	35 (23.3%)	-
Previous myocardial infarction	15 (10.0%)	-
Emergency Presentation (n, %)	30 (20.0%)	-
ECOG Performance Status (n, %)		2 (1.3%)
0	78 (52.0%)	-
1	59 (39.3%)	-
2	9 (6.0%)	-
3	2 (1.3%)	-
4	0 (0%)	-
Smoking History (n, %)		29 (19.3%)
Current smokers	25 (16.7%)	-
Ex- smokers	59 (39.3%)	-
Never smoked	37 (24.7%)	-
AJCC Cancer Stage (n,%)		2 (1.3%)
I	26 (17.3%)	-
II	73 (48.7%)	-
III	48 (32.0%)	
IV	1 (0.7%)	-
T stage (n,%)		24 (16.0%)*
T_1	12 (8.0%)	-
T_2	22 (14.7%)	-
T_3	75 (50.0%)	-
T_4	17 (11.3%)	-
N stage (n,%)		16 (16.6%)*
N_0	60 (40.0%)	-
N_1	40 (26.7%)	-
N_2	30 (20.0%)	-
N_3	4 (2.7%)	-
Linitis Plastica (n,%)	3 (2.0%)	-
Signet ring cell histology (n, %)	45 (30.0%)	-
Neoadjuvant chemotherapy (n, %)	75 (50.0%)	-
Surgery setting (n, %)		
Emergency surgery	19 (12.7%)	-
Elective surgery	131 (87.3%)	-
Status at end of follow-Up (n,%)		-
Alive	59 (39.3%)	-
Dead	91 (60.7%)	-

** Missing/unknown values include patients staged as Tx or Nx.*

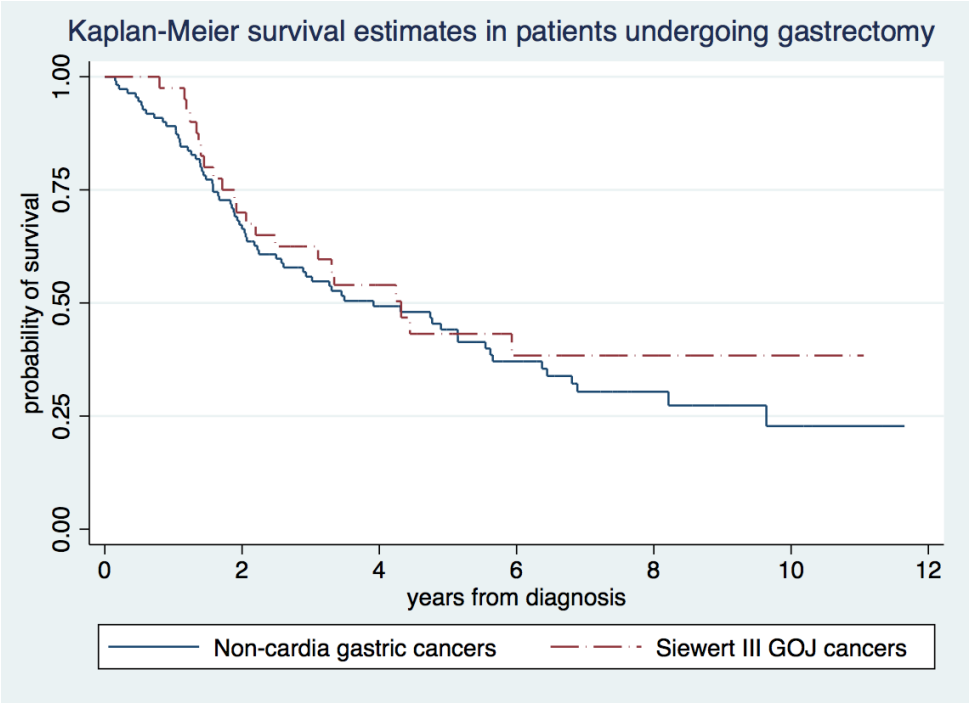
Overall survival

Using Kaplan-Meier survival curves, median overall survival across the surgical cohort was estimated at 4.24 years (IQR 1.65 – no upper bound). Estimated median overall survival in patients with non-cardia gastric adenocarcinomas was 3.92 years (IQR 1.58–9.64) compared to 4.32 years (IQR 1.71 – no

upper bound) in patients with Siewert III adenocarcinomas [Figure 4.1]. This difference was not statistically significant (p=0.497) although it stands in contrast to previous models reporting worse outcomes in patients with tumours involving the GOJ. Median overall survival in patients undergoing emergency gastrectomy was 1.65 years (IQR 0.60–2.60) compared to 4.74 years (IQR 1.89 – no upper bound) in patients undergoing elective gastrectomy (HR 2.84, p<0.001) [Figure 4.2]. Patients receiving neoadjuvant chemotherapy had a median overall survival of 5.14 years (IQR 1.92 – no upper bound) compared to 2.60 years (IQR 1.42–6.37) in patients receiving upfront surgery (HR 0.59, p=0.014) [Figure 4.3].

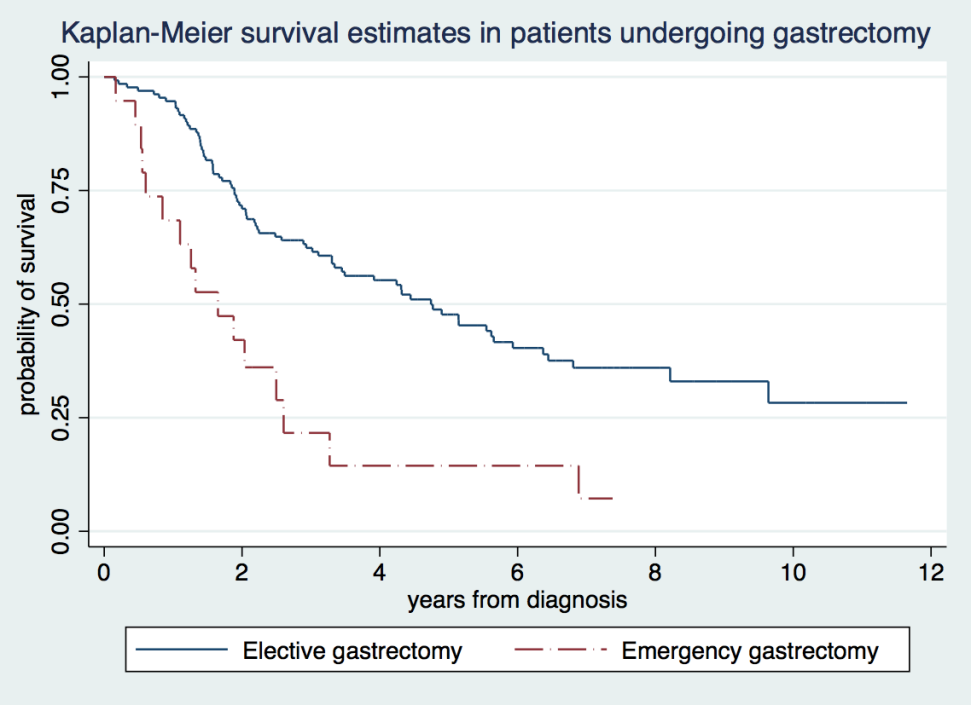
Over a median follow-up period of 7.19 years, 39.3% (n=59) of the surgical cohort was alive at the end of follow-up. Cancer recurrence was documented in 38% (n=57) of the cohort.

Figure 4.1: Survival curves in patients undergoing gastrectomy stratified by cancer involvement of the gastro-oesophageal junction



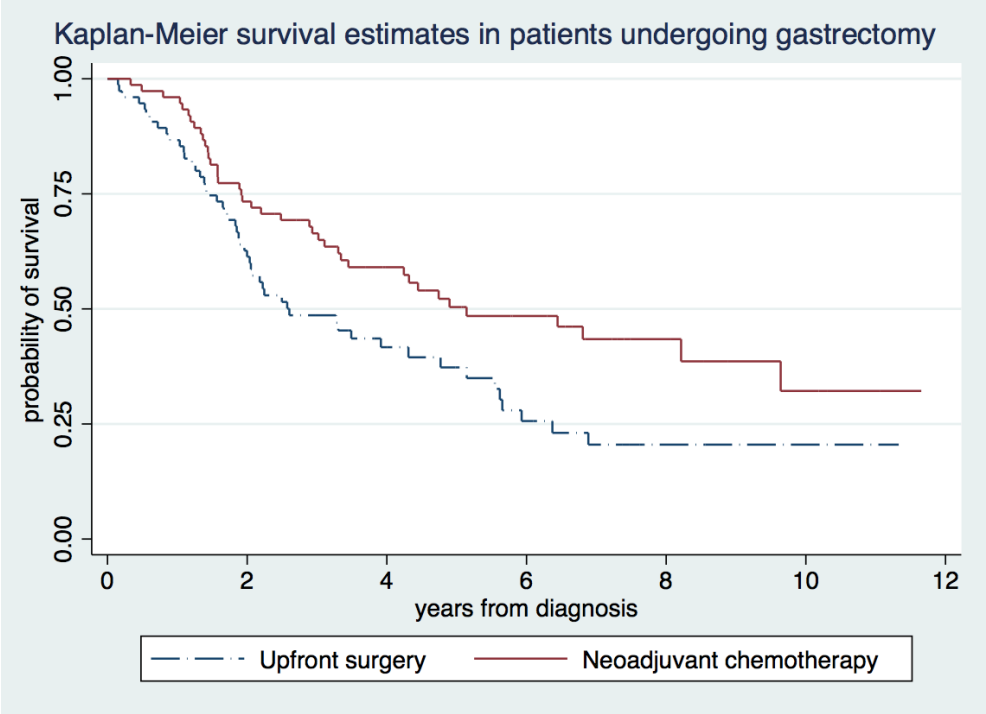
Group	Median Overall Survival	Interquartile Range
Non-cardia gastric cancers (n=110)	3.92 years	1.58–9.64
Siewert III cancers (n=40)	4.32 years	1.71–no upper bound

Figure 4.2: Survival curves in patients undergoing gastrectomy stratified by elective vs emergency surgery



Group	Median Overall Survival	Interquartile Range
Elective gastrectomy (n=131)	4.74 years	1.89–no upper bound
Emergency gastrectomy (n=19)	1.65 years	0.60–2.60

Figure 4.3: Survival curves in patients undergoing gastrectomy stratified by neoadjuvant chemotherapy vs upfront surgery



Group	Median Overall Survival	Interquartile Range
Neoadjuvant chemotherapy (n=75)	5.14 years	1.92–no upper bound
Upfront surgery (n=75)	1.65 years	1.92–5.14

Outcomes of surgery and histological findings

Negative longitudinal resection margins (R0 resection) were achieved in 93.3% of all gastrectomies: 96.2% of elective gastrectomies vs 73.7% of emergency gastrectomies, and 97.3% of patients treated with neoadjuvant chemotherapy vs 89.3% of patients treated with upfront surgery. Without accounting for confounding factors, the risk ratios for positive resection margins were 6.89 with emergency surgery (95%CI 2.20–21.62; p=0.0002) and 4.0 (95%CI 0.88–18.22; p=0.0495) with upfront surgery.

Postoperative pathological TNM (ypTNM) staging is summarised in Table 4.2. Nodal involvement was observed in 94.7% of emergency gastrectomy specimens compared to 53.9% of elective gastrectomy specimens (RR 1.76, 95%CI 1.45–2.13; p=0.0007), and 68.9% of specimens from patients receiving upfront surgery compared to 49.3% of specimens from patients receiving neoadjuvant chemotherapy (RR 1.42, 95%CI 1.07–1.88; p=0.013).

Table 4.2: Postoperative pathological staging (ypTNM).

	Total (n=150)	Cases with missing/unknown values
Longitudinal resection margins (n, %)		
R0 resection	140 (93.3%)	-
R1 resection	10 (6.7%)	-
ypT stage (n,%)		3 (2.0%)*
T_0	6 (4.0%)	
T_1	22 (14.7%)	-
T_2	22 (14.7%)	-
T_3	58 (38.7%)	-
T_4	39 (26.0%)	-
ypN stage (n,%)		3 (2.0%)*
N_0	60 (40.0%)	-
N_1 (1-2 nodes involved)	28 (18.7%)	-
N_2 (3-6 nodes involved)	33 (22.0%)	-
N_3 (≥7 nodes involved)	26 (17.3%)	-
ypM stage (n,%)		3 (2.0%)*
M_0	140 (93.3%)	-
M_1	7 (4.7%)	-

** Missing/unknown values include patients staged as Tx, Nx or Mx.*

Peri-operative complications, postoperative mortality and postoperative length of stay

16 patients (10.7%) experienced complications graded III or higher on the Clavien-Dindo classification. Of these, 11 patients experienced grade III complications (requiring surgical, endoscopic or radiological intervention), 2 patients experienced grade IV complications (life-threatening) and 3 patients experienced grade V complications (death), yielding a peri-operative mortality rate of 2%. There were 7 cases of postoperative anastomotic leak (4.7%). No individual patient, disease or treatment characteristic was significantly associated with a higher rate of peri-operative complications, perhaps due to insufficient sample size.

The 30-day postoperative mortality rate was 2.7%, comprising 4 patients. Causes of death for these patients were as follows: one case of perforated conduit resulting in peritonitis, one case of postoperative pneumonia and acute coronary syndrome requiring critical care, one case of sudden and unexplained death at home following an uneventful discharge, and one case where the cause of death could not be established from medical records available for research purposes. The 90-day postoperative mortality rate was 3.33%, comprising 5 patients. In addition to the aforementioned cases, one patient died after readmission with a duodenal stump leak and necrotising pancreatitis following emergency gastrectomy.

Median postoperative length of stay was 7 days (IQR 5–9) across all patients. Emergency gastrectomy was associated with a longer postoperative length of stay compared to elective gastrectomy: 10 days (IQR 7–12) vs 7 days (IQR 5–9); p=0.0022.

Predictive factors for overall survival

Univariate analyses of associations between patient, disease, treatment, pathological and postoperative characteristics and all-cause mortality are summarised in Table 4.3.

Table 4.3: Univariate associations with all-cause mortality.

Characteristic	Hazard Ratio (95% CI)	p-value
Age per year	1.02 (1.00–1.04)	0.064
Sex (male)	1.04 (0.65–1.66)	0.411
Current smoker at diagnosis	1.35 (0.77–2.36)	0.293
ECOG Performance Status (relative to PS 0)		
Performance Status 1	1.15 (0.74–1.79)	0.538
Performance Status 2	3.46 (1.61–7.43)	**0.001**
Performance Status 3	101.36 (16.39–626.98)	**<0.001**
Cardiovascular disease	1.39 (0.88–2.21)	0.158
OGJ involvement, i.e., Siewert III	0.85 (0.52–1.37)	0.497
Emergency presentation & diagnosis	1.93 (1.19–3.14)	**0.008**
Clinical AJCC stage (relative to Stage I)		
Stage II	1.23 (0.66–2.29)	0.522
Stage III	2.32 (1.22–4.39)	**0.010**
Stage IV (Metastatic Disease)	8.83 (1.12–69.80)	**0.039**
Linitis plastica	1.73 (0.54–5.47)	0.354
Signet ring cell histology	1.57 (1.01–2.44)	**0.044**
Neoadjuvant chemotherapy	0.59 (0.39–0.90)	**0.014**
Emergency gastrectomy	2.84 (1.64–4.91)	**<0.001**
R1 resection (longitudinal margins involved)	3.43 (1.63–7.19)	**0.001**
Pathological T-stage (relative to ypT_0)		
ypT_1	1.94 (0.23–16.09)	0.541
ypT_2	5.13 (0.67–39.28)	0.116
ypT_3	7.15 (0.98–52.17)	0.053
ypT_4	13.00 (1.77–95.68)	**0.012**
Pathological N-stage (relative to ypN_0)		
ypN_1	2.66 (1.43–4.96)	**0.002**
ypN_2	3.61 (2.03–6.43)	**<0.001**
ypN_3	6.34 (3.44–11.67)	**<0.001**
Clavien Dindo grade ≥3 complications	1.34 (0.69–2.60)	0.385
Postoperative length of stay ≥10 days	1.39 (0.87–2.22)	0.164

Note: All characteristics associated with a P-value <0.05 (highlighted in bold) were included in multivariable analysis.

Variables significantly associated with all-cause mortality in univariate analysis were incorporated into a multivariable Cox regression model. In multivariable analysis, only performance status and nodal involvement on resected specimens remained significant independent predictors of all-cause mortality [Table 4.4] .

Table 4.4: Multivariable analysis of associations with all-cause mortality – Cox proportional hazards regression model

Characteristic	Hazard Ratio (95% CI)	z	p-value
ECOG Performance Status (relative to PS 0)			
Performance Status 1	1.01 (0.61–1.66)	0.02	0.982
Performance Status 2	3.02 (1.28–7.12)	2.52	**0.012**
Performance Status 3	88.99 (11.72–676.02)	4.34	**<0.001**
Emergency presentation	1.50 (0.77–2.93)	1.19	0.236
Clinical AJCC stage (relative to Stage I)			
Stage II	0.88 (0.43–1.78)	-0.36	0.718
Stage III	0.81 (0.36–1.80)	-0.52	0.606
Stage IV (Metastatic Disease)	1.04 (0.79–13.54)	0.03	0.980
Signet ring cell histology	0.94 (0.55–1.60)	-0.23	0.816
Neoadjuvant chemotherapy	1.02 (0.60–1.72)	0.06	0.954
Emergency gastrectomy	1.38 (0.61–3.14)	0.77	0.439
R1 resection (longitudinal margins involved)	2.09 (0.79–5.53)	1.48	0.138
Pathological N-stage (relative to ypN_0)			
ypN_1	2.29 (1.13–4.66)	2.30	**0.021**
ypN_2	2.69 (1.31–5.54)	2.69	**0.007**
ypN_3	6.78 (3.24–14.22)	5.07	**<0.001**

$\chi 2 = 63.57$, $p<0.0001$
Model developed in a total of 143 patients on a complete case analysis basis.

Effects of emergency surgery and neoadjuvant chemotherapy on overall survival following weighting by the propensity score

Propensity score models with respect to emergency surgery [Table 4.5] and neoadjuvant chemotherapy [Table 4.6] were generated with ECOG performance status, emergency presentation, overall clinical AJCC stage and signet ring cell histology as covariates and 4-year overall survival as the endpoint. Although there remained trends towards worse survival in the emergency surgery group and improved survival in the neoadjuvant chemotherapy group, these did not achieve statistical significance after weighting by the propensity score was applied.

Table 4.5: Logistic regression model producing propensity score with respect to emergency surgery (probability of receiving emergency surgery amongst patients undergoing curative-intent gastrectomy)

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status ≥2	7.813 (0.894–68.284)	1.86	0.063
AJCC cancer stage (relative to Stage I)			
Stage II	0.777 (0.190–3.180)	-0.35	0.726
Stage III	*See notes below*	-	
Signet ring cell histology	1.045 (0.255–4.278)	0.06	0.951
Acute presentation	31.62 (7.258–137.67)	4.60	<0.001

$\chi 2 = 42.30$, $p<0.0001$
Model developed in a total of 120 patients on a complete case analysis basis. AJCC stage III was colinear with AJCC stage II.

Table 4.6: Logistic regression model producing propensity score with respect to neoadjuvant chemotherapy (probability of receiving emergency surgery amongst patients undergoing curative-intent gastrectomy)

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status (relative to PS 0)			
Performance Status 1	0.390 (0.182–0.841)	-2.40	0.016
AJCC cancer stage (relative to Stage I)			
Stage II	2.095 (0.735–5.969)	1.38	0.166
Stage III	3.109 (0.961–10.055)	1.89	0.058
Signet ring cell histology	0.647 (0.277–1.510)	-1.01	0.313
Acute presentation	0.157 (0.050–0.494)	-3.16	0.002

$\chi 2 = 27.15$, p=0.0001
Model developed in a total of 134 patients on a complete case analysis basis. STATA automatically excluded ECOG PS≥2 from the model as this characteristic 'perfectly predicted' absence of neoadjuvant chemotherapy.

In the emergency surgery propensity score model, 115 patients were included in the analysis after trimming: 13 patients undergoing emergency gastrectomy and 102 patients undergoing elective gastrectomy. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 4 years was 0.45 (95%CI 0.50-4.12; p=0.483) in patients undergoing emergency surgery compared to patients undergoing elective surgery.

In the neoadjuvant chemotherapy propensity score model, 121 patients were included in the analysis after trimming: 73 patients treated with neoadjuvant chemotherapy and 48 patients receiving upfront surgery. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 4 years was 1.88 (95%CI 0.84–4.22; p=0.127) with neoadjuvant chemotherapy compared to upfront surgery.

Disease recurrence

Out of 150 patients undergoing gastrectomy, 57 (38%) had documented evidence of disease recurrence. The most common site of recurrence was the peritoneum, which was involved in 68.4% of recurrence cases. In patients with documented evidence of recurrence, the median duration from surgery to cancer recurrence, as documented in medical records and/or confirmed on radiology and histology reports, was 1.15 years (IQR 0.62–1.75). These figures do not take into account patients who were not investigated for cancer recurrence due to reasons of clinical judgement or personal preference, or patients who died before investigations could be performed.

Peritoneal recurrence was significantly associated with emergency surgery (risk ratio 2.07, 95% CI 1.17–3.65; p=0.02), cancer diagnosis following emergency hospital presentation (RR 2.0, 95%CI 1.17–3.41; p=0.016) and nodal involvement on pathological staging (RR 3.98, 95%CI 1.78 – 8.93; p=0.0001). No significant associations were identified between peritoneal recurrence and serosal involvement,

linitis plastica or R1 resection, perhaps due to low numbers of patients exhibiting these high-risk characteristics within the surgical cohort.

Summary of key findings

Median overall survival was 4.24 years in patients treated with gastrectomy. Involvement of the gastro-oesophageal junction was not an adverse prognostic factor in this cohort. Patients undergoing emergency gastrectomy demonstrated significantly worse overall survival (1.65 years vs 4.74 years; p<0.001) whilst patients receiving neoadjuvant chemotherapy demonstrated significantly better overall survival (5.14 years vs 2.60 years; p=0.014). However, these trends no longer achieved statistical significance after weighting by the propensity score. Emergency surgery and upfront surgery without neoadjuvant chemotherapy were significantly associated with both positive resection margins (RR 6.89 and 4.0 respectively) and nodal involvement (RR 6.89 and 4.0 respectively) on postoperative pathological staging. In multivariable analysis, performance status ≥2 and nodal involvement were the strongest predictors of poor survival. The peritoneum was the most common site of recurrence, and peritoneal recurrence was significantly associated with emergency surgery (RR 2.0) and nodal involvement (RR 3.98).

DISCUSSION

General Observations

This was a single-centre cohort of 150 patients who underwent surgical resection with curative intent for gastric adenocarcinomas. Reflecting the tendency towards late diagnosis of gastric cancer in western populations, this group constituted a minority of patients diagnosed with gastric cancer during the 10-year period covered by this retrospective study.

Gastrectomy, with or without perioperative chemotherapy, is the only treatment modality considered potentially curative for all but the earliest gastric cancers. Given the significant morbidity associated with such a major operation and high rates of cancer recurrence, patient selection is understandably crucial. It therefore comes as no surprise that the surgical cohort was significantly younger (p=0.0001), albeit by only 4 years on average, and significantly less likely to have an ECOG performance status of 2 or above (p<0.0001) compared to patients with gastric cancer treated non-operatively at the same centre.

Median overall survival was 4.24 years. Although this figure may appear worse than expected in a ‘curatively treated’ cohort, it should be noted that it reflects all-cause mortality from both cancer-

related and cancer-unrelated deaths. The median age at diagnosis of patients (71.6% of whom are men) undergoing gastrectomy in this cohort is 74.5 years in a country where life expectancy at birth for males was 79 years in 2018-2020[91]. The proportion of patients in the surgical cohort with documented disease recurrence (38%) was noticeably lower than the proportion of patients who had died by the end of follow-up (60.7%). The temptation to attribute the residual deaths to cancer-unrelated causes, however, must be tempered with the caveat that some patients with no documented recurrence may in fact have developed recurrent disease without undergoing confirmatory investigations.

Main Findings

In keeping with expectations, emergency surgery and upfront surgery without neoadjuvant chemotherapy were strongly associated with poor survival in unadjusted survival analysis. These trends were no longer significant after weighting by the propensity score was applied, perhaps due to insufficient power.

There is high-quality evidence in favour of perioperative chemotherapy for European patients with oesophagogastric cancers and this is now the standard of care in Western Europe[16]. The MAGIC and FNCLCC/FFCD 9703.3 trials established that perioperative chemotherapy is both well tolerated and leads to improved overall and progression-free survival in this patient population[9,92].

Previous literature from both Western and East Asian centres have consistently shown poorer outcomes following emergency presentation or emergency surgery[2,29]. Possible reasons include the absence of a window of opportunity for pre-operative optimisation or neoadjuvant chemotherapy. It is also plausible that high-risk disease characteristics such as a greater propensity for local invasion and peritoneal seeding may be associated with emergency presentations. Within the present cohort, serosa-positive tumours were significantly associated with emergency presentations (RR 2.8, 95%CI 1.03-7.64, p=0.05) but not with emergency surgery, presumably because a high proportion of such tumours were inoperable.

Of all baseline characteristics, performance status was the best predictor of survival. There was a clear cut-off in survival outcomes between ECOG performance statuses of 1 and 2. As discussed in chapter 3, the association between performance status and survival outcomes is well established although it is often difficult to separate baseline life expectancy from the effects of disease and its treatment. Amongst postoperative outcome measures, nodal involvement on pathological staging was the strongest predictor of poor overall survival as well as peritoneal recurrence. Given that emergency surgery and upfront surgery were both strongly associated with nodal involvement, this suggests a

likely chain of events linking suboptimal pre-operative optimisation to residual microscopic disease, peritoneal recurrence and finally death. Hyperthermic intraperitoneal chemotherapy (HIPEC) may play a potential role in breaking this chain of events. It would seem sensible to pilot HIPEC in patients exhibiting high-risk characteristics for postoperative cancer recurrence, such as patients requiring emergency gastrectomy, even in the absence of macroscopic peritoneal disease.

In contrast to the findings of Asian retrospective studies and predictive models, involvement of the gastro-oesophageal junction was not an adverse prognostic factor. This was not merely an instance of an association failing to reach statistical significance. Comparison of the survival curves of Siewert III and pure gastric cancers in the current cohort makes it apparent that the prognosis of tumours involving the gastro-oesophageal junction is at least as good as that of pure gastric adenocarcinomas.

Strengths and limitations

This study provides an up-to-date snapshot of outcomes following gastrectomy in a western setting that reflects an ageing population as well as recent advances in both cancer diagnosis and treatment. The establishment of referral guidelines and pathways in the UK have led to a considerable drop in the proportion of gastric cancers diagnosed following an emergency presentation from around 40% in the 1990s and early 2000s to fewer than 20% in the past decade. Meanwhile, the newer FLOT regimen of perioperative chemotherapy has demonstrated its potential to markedly improve survival outcomes in a clinical trial setting, and is now the standard of care at our centre. Conversely, the ageing of patients with gastric cancer has brought a new set of challenges which were discussed in the previous chapter. Compared to older UK-based studies and studies from East Asia, findings from the current cohort could therefore serve as a more appropriate point of reference for future UK-based trials.

Key limitations of this study are its small sample size and restrictions on data available for research purposes. Small sample size precluded formal predictive modelling and severely diminished the value of multivariable analysis in eliciting small but meaningful associations. When propensity score methods were applied to mitigate the effects of confounding, even the association between neoadjuvant chemotherapy and improved survival became statistically insignificant. This is likely the effect of insufficient sample size as high-quality evidence from clinical trials have demonstrated the benefits of neoadjuvant chemotherapy in western patients with gastric cancer. Equally, the cohort was too small to allow for meaningful multivariable analysis, much less predictive modelling, with respect to risk factors for surgical complications or disease recurrence.

Data regarding causes of death and patient morbidity were incomplete without access to primary care or palliative care records. Patient records in primary care and palliative care (which is provided by a different NHS trust) are separately maintained from acute hospital care records. Ethical approval and access permissions were limited to acute hospital records. The specific issues encountered here relate to recording of non-fatal outcomes rather than exclusion of patients. All cancer diagnoses in the Norfolk and Waveney area are discussed and registered at the NNUH. Dates of death regardless of location are recorded in hospital-based electronic records. However, healthcare in the area is organised such that low-grade symptoms and best supportive care are often managed in primary or palliative care settings without involving the acute hospital team. This is especially so towards the end of life, as many patients choose to die at home and avoid hospital admission. When death occurs in the community, the cause of death is not published in hospital-based records. Whereas death may be assumed to be cancer-related in patients treated with palliative intent, this is not necessarily the case in post-surgical patients.

As a consequence, disease-specific survival and disease-related morbidity could not be evaluated as endpoints. Hospital admissions for cancer-related complications and terminal disease are likely to represent merely 'the tip of the iceberg' and causes of death in the community could not be ascertained. Furthermore, acute hospital records alone are inadequate for obtaining a complete picture of both disease- and treatment-related morbidity as well as quality of life. In an era of increasing emphasis on patient-centred outcomes and shared decision making, evaluation of clinical efficacy should ideally be accompanied by an exploration of treatment tolerability and quality of life. Unfortunately this was not possible in the current study given the constraints described.

Implications for treatment and future research

The implications of this study's findings for clinical practice and future research are as follows:

First, the prognostic factors identified in this study simultaneously validated and challenged the 'received wisdom' from the past 20 years of research and clinical experience. As expected, elective gastrectomy and neoadjuvant chemotherapy were associated with better survival. Findings on multivariable analysis reinforced the idea, explored in the two previous chapters, that performance status is a considerably better predictor of survival than age and patients should not be denied potentially curative treatment on the basis of chronological age alone. Conversely, in marked contrast to Asian predictive models, involvement of the gastro-oesophageal junction was clearly not an adverse prognostic factor. It is unclear whether this discrepancy is attributable to demographic differences between Asian and European cancer populations or to the particular expertise of the unit in oesophagogastric cancer surgery. Regardless, the findings indicate that involvement of the gastro-

oesophageal junction need not be a cause for concern in western patients, provided that the necessary surgical expertise is available.

Second, in view of the limitations discussed above and the shift towards a more patient-centred approach to cancer care, future research in gastric cancer surgery should ideally involve multicentre and multidisciplinary collaborations including input from primary care and palliative care. Such a collaboration is necessary to secure the sample sizes and data necessary to enable the construction of predictive models for not only survival but also treatment complications and cancer recurrence. These models could then be used to balance clinical efficacy against tolerability and quality of life, so as to inform shared decision making between clinicians and patients.

Third, the findings highlighted a chain of adverse prognostic factors, linking together suboptimal preoperative optimisation (including emergency surgery and upfront surgery without neoadjuvant chemotherapy), nodal involvement and peritoneal recurrence. Breaking this chain of events is a worthwhile goal for future treatment strategies. Hyperthermic intraperitoneal chemotherapy (HIPEC) and other novel adjuvant treatment modalities should be trialled in patients for whom neoadjuvant chemotherapy is impossible or undesirable. It may be hypothesised that HIPEC could reduce rates of peritoneal recurrence in patients undergoing emergency gastrectomy without conferring significant additional risk. HIPEC will be discussed further in Chapter 6.

Conclusion

The survival outcomes presented in this chapter reflect the ageing of patients being diagnosed with gastric cancer in the UK as well as recent advances in cancer referral pathways and perioperative chemotherapy. Although overall survival may appear unimpressive for a cohort of surgical patients, these figures must be considered in the context of a median age of 75 at diagnosis and a life expectancy of 79 years in British males. Performance status and nodal involvement emerged as the strongest predictors of survival in surgical candidates with gastric cancer. Associations between emergency surgery, upfront surgery without chemotherapy, positive resection margins, nodal involvement and early mortality suggest a chain of adverse prognostic factors connecting suboptimal perioperative optimisation with poor prognosis. Novel adjuvant treatment modalities such as hyperthermic intraperitoneal chemotherapy may potentially play a role in breaking this chain of events.

CHAPTER 5- A systematic review of outcomes following surgical resection of gastric linitis plastica with or without neoadjuvant chemotherapy.

(Note: All tables are presented at the end of this chapter.)

ABSTRACT

Background. Linitis plastica is a variant of gastric adenocarcinoma characterised by diffuse submucosal infiltration and thickening of the stomach wall. Linitis plastica is associated with a poor prognosis and high risk of peritoneal metastasis or recurrence, even in curatively-treated patients with localised disease. Compared to other subtypes of gastric adenocarcinoma, there is a relative lack of evidence to guide treatment decisions in patients with linitis plastica. Perioperative chemotherapy has now been established as the standard of care in Europe for patients with surgically resectable gastric cancer. It is unclear, however, whether neoadjuvant chemotherapy prior to surgical resection leads to better survival outcomes in the specific context of linitis plastica given the condition's propensity for peritoneal recurrence.

Objectives. This systematic review sought to describe outcomes of neoadjuvant chemotherapy followed by surgical resection in patients with non-metastatic linitis plastica, and to evaluate whether such a strategy leads to improved outcomes compared with upfront surgery in this patient group.

Methods. Human studies published after the year 2000 assessing overall survival in patients with non-metastatic gastric linitis plastica treated with neoadjuvant systemic chemotherapy followed by surgical resection were included in this systematic review. The primary outcome measure was overall survival. Secondary outcome measures were R0 resection rate, chemotherapy-associated adverse events and quality of life. Studies were identified from Ovid Medline and Embase using a pre-determined search strategy and assessed according to pre-defined inclusion and exclusion criteria. Randomised controlled trials were evaluated according to the revised Cochrane Collaboration Risk of Bias tool (RoB 2), whilst the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of non-randomised trials and retrospective studies. Data extracted from the included studies were collated into 'summary of study and baseline patient characteristics' and 'summary of outcomes' tables. Where patterns are identified or heterogeneity is marked, the underlying reasons for these observations were explored. Meta-analysis was intended and appropriate methodology for this was pre-specified, but did not prove possible due to the small number of comparative studies and considerable

heterogeneity between studies in terms of patient and treatment characteristics as well as outcome measures.

Results. Nine studies were included, comprising two randomised controlled trials, three single-arm phase II clinical trials and four retrospective cohort studies. Five studies, including the two randomised controlled trials, included a comparison group receiving upfront surgery without neoadjuvant chemotherapy. Methodological quality was generally mediocre. The JCOG0501 phase III clinical trial was the only high-quality study with a low risk of bias and balanced baseline characteristics between intervention and control groups. In addition to wide variations between studies in baseline characteristics including the proportion of patients with serosa-positive disease, various different chemotherapy regimens were used and overall survival was defined in several different ways, precluding meaningful quantitative data synthesis. Accepting these limitations, no significant difference in overall survival between patients treated with neoadjuvant chemotherapy versus upfront surgery could be demonstrated. The pooled R0 resection rate in patients undergoing neoadjuvant chemotherapy and surgery was 77.9% across the four studies that reported this outcome. None of the included studies evaluated quality of life and no conclusions could be drawn regarding chemotherapy-related adverse events due to wide disparities in the reported rates of events.

Conclusions. The existing evidence base is insufficient to answer the primary research question of whether neoadjuvant chemotherapy followed by surgical resection leads to improved outcomes in patients with curatively-treated linitis plastica compared to upfront surgery. This systematic review highlights a clear need for definitive trial evidence to guide management decisions in patients with potentially resectable linitis plastica. The different behaviours of Asian and western gastric cancer populations should be taken into account, as gastric cancer trials to date suggest that neoadjuvant chemotherapy is likely to confer a greater benefit in western patients than in Asian patients.

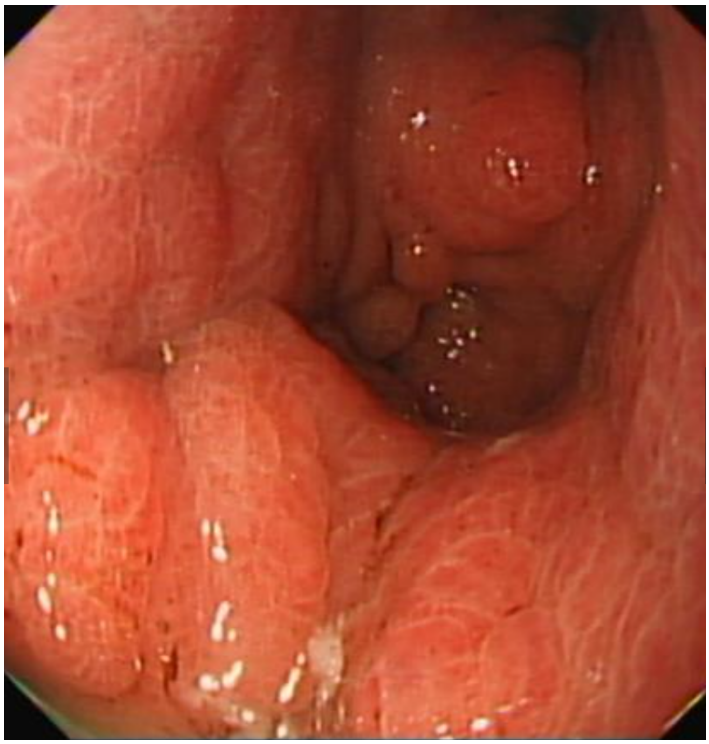
INTRODUCTION

Linitis plastica and associated conditions

'Linitis plastica' refers to a variant of gastric adenocarcinoma characterised by diffuse submucosal infiltration and thickening of the stomach wall with fibrous scar-like tissue [Figure 5.1] [93,94]. First described by William Brinton in 1859, it typically involves the entire stomach, producing the classic 'leather bottle' appearance [93]. Pathologically, cancer-stroma interactions involving cancer cells, cancer-associated fibroblasts and their milieu result in the excessive production of fibrous tissue, submucosal stromal proliferation and hypertrophy of the underlying muscle layer [93]. Whereas the global incidence of gastric cancer in general has declined in recent years, the incidence of diffuse gastric cancer including linitis plastica continues to rise [94].

Figure 5.1: Endoscopic appearance of gastric linitis plastica

(Photo taken by author with written consent for research purposes signed by patient prior to procedure.)



The precise definition of linitis plastica remains contentious. Papers reporting outcomes in patients with linitis plastica have employed various definitions based on macroscopic or histological criteria or both [94]. Diagnostic scoring systems have been proposed [95,96], but these are not consistently applied across studies or routinely used in clinical practice.

Other, similar classification systems further add to the confusion. In the Borrmann classification system commonly used in East Asia, 'type IV' gastric cancers are diffuse and infiltrative with unclear

margins. The term ‘scirrhous gastric cancer’, encountered frequently in Japanese studies, refers to a process ‘in which cancer cells trigger a stromal reaction involving mature and immature fibrosis’ [93]. Although the definitions of linitis plastica, Borrmann type IV gastric cancers and scirrhous gastric cancers are not identical, there is a high degree of overlap in practice. All three share common features of diffuse infiltration, stromal fibrosis and a thickened gastric wall, and are associated with a high risk of peritoneal recurrence following surgery [93,97,98]. These terms are often used interchangeably in studies [53,99].

Even more so than gastric cancer in general, linitis plastica (including related conditions) is typically associated with diagnosis at an advanced stage and poor prognosis. Whether curative treatment is appropriate in linitis plastica remains a topic of debate. Previous retrospective analyses have shown poor outcomes even following attempted surgical resection, often due to a combination of difficulty in achieving optimal resections and a high rate of disease recurrence particularly in the peritoneum [27,98,99]. Some authors, particularly in past decades, have suggested that linitis plastica is not a surgical disease and patients with linitis plastica should be offered primary chemotherapy rather than surgery even in the absence of other adverse characteristics [100]. In Japan, where outcomes of gastric cancer are significantly better than in the western world, the 5-year survival rate of surgically resected Borrmann type IV cancers is 21.4%, compared with 46.7-63.7% for other types of advanced gastric cancer [98].

In Chapter 2, a retrospective analysis of 540 consecutive patients with gastric cancer in the East of England was presented and predictive model for 1-year survival was derived. Of the 63 patients in the cohort with documented linitis plastica, only 3 patients (5%) underwent surgical resection. Two of these cases were in fact emergency operations following acute presentations with gastric outlet obstruction. The remaining 60 patients with linitis plastica were managed from the outset with palliative intent. Relative to the whole cohort, linitis plastica was strongly associated with metastatic disease at initial staging ($p<0.0001$) and the presence of signet ring cells ($p<0.0001$). Indeed, peritoneal disease was identified in 60.3% of patients with linitis plastica at initial staging. Patients with linitis plastica were also more likely to experience disease complications requiring hospital admission, namely perforation and bowel obstruction.

Surprisingly, linitis plastica was not identified as an independent predictor of mortality in multivariable models adjusting for disease stage, peritoneal involvement, performance status and treatment received. This raises two clinical questions: First, does a diagnosis of linitis plastica confer an adverse prognostic value in itself, or are the worse outcomes seen purely a product of the associations between linitis plastica and advanced disease stage and/or peritoneal involvement? Second, could

treatment with curative intent lead to similar outcomes in linitis plastica compared to non-linitis gastric adenocarcinomas of equivalent stage? Unfortunately, our study cohort was underpowered to answer these questions.

No studies, to our knowledge, have performed a head-on comparison of curative versus palliative treatment in randomised or matched samples of patients with linitis plastica. On the other hand, the outcomes of treatment in linitis vs non-linitis gastric cancers have been explored in the existing literature, and several studies have investigated various curative treatment regimes in patients with linitis plastica.

Research to date and unanswered questions in the management of linitis plastica

Historical cases series have invariably demonstrated poorer outcomes in patients with gastric linitis plastica compared to patients with non-linitis gastric cancers. Conversely, studies have also shown that, where possible, optimal resections with negative microscopic margins (R0) could lead to improved outcomes in a small but potentially significant proportion of patients with linitis plastica. [52,53,101]

Pedrazzani and colleagues analysed 102 patients with linitis plastica across four Italian centres from 1990 to 2007, with linitis plastica defined as diffuse gastric cancer causing thickening and stiffening of at least one-third of the gastric circumference. 60 of these patients (59%) underwent surgical resection, reflecting the practice of an era in which staging laparoscopy was not routinely performed and neoadjuvant treatment was not offered. Only 28 of these resections were potentially curative (R0) whereas 20 were explicitly palliative in nature (R2) and 12 were 'R1' with microscopic residual margins. Despite the predilection for aggressive surgical intervention in this historical cohort, median survival remained only 5.7 months. Even in patients undergoing R0 resections, median overall survival was only 15.8 months. Cancer recurrence was documented in 36 of the 40 patients (90%) who received an R0 or R1 gastrectomy and was predominantly related to peritoneal seeding. [27]

A German single-centre series, published in 2011, evaluated outcomes in 120 patients with 'linitis plastica' undergoing total gastrectomy. Accepting a somewhat unconventional definition of linitis plastica as a locally-advanced diffuse gastric cancer with signet ring cell infiltration, median survival for the whole series was merely 8 months, although patients who received an R0 resection (n=37) had an improved median overall survival of 17 months. The authors therefore argued that gastrectomy should be offered to patients in whom R0 resection can be achieved, and listed negative lavage cytology, low Ca19-9 levels and absence of distant metastases as positive prognostic factors that could be used to identify a subset of patients who could stand to benefit from surgical resection. [102]

More recently, Ayub and colleagues performed a retrospective analysis of 896 patients with linitis plastica (identified by ICD histology codes for 'scirrhous adenocarcinoma' and 'linitis plastica') in the US National Cancer Database (NCDB) spanning from 2004 to 2017. 41.2% underwent surgical resection whilst 58% received chemotherapy for any indication. Similar to our findings in Chapter 2, disease stage, treatment with chemotherapy and treatment with surgery were independently associated with survival in multivariable Cox-regression analysis. Survival outcomes were noticeably better in this cohort compared to Pedrazzani's, with a mean overall survival of 16.9 months across all patients with linitis plastica, 17.1 months in patients receiving surgery alone, and 28.4 months in patients receiving surgery with chemotherapy and/or radiotherapy. Unsurprisingly, R0 resection was associated with the best outcome, a mean overall survival of 35.3 months. The authors noted that the proportion of patients receiving surgery decreased over time whilst proportions of patients receiving chemotherapy and radiotherapy increased. Remarkably, however, there was no significant difference in survival outcomes between the 2004-2010 and 2011-2017 time periods. Unfortunately, the database did not differentiate between chemotherapy indications and therefore could not be used to assess the benefits of neoadjuvant or adjuvant chemotherapy. [52]

Meanwhile in Japan, Fushida and colleagues retrospectively analysed the records of 119 patients with 'scirrhous' gastric cancer treated with multidisciplinary therapy at a single Japanese tertiary centre between 1990 and 2012. 'Multidisciplinary treatment' typically involved a combination of surgical resection with intraoperative intraperitoneal chemotherapy in patients without peritoneal disease, or systemic and intraperitoneal chemotherapy in patients with peritoneal metastases. Median overall survival was significantly longer in patients treated after 2000 (22.8 months vs 9.5 months). Notably, R2 resection rates were considerably higher pre-2000 (48% vs 20%). Whereas R0-1 resections were associated with a median overall survival of 29.2 months and 5-year survival rate of 31%, prognosis following R2 resection was no different from that of patients treated non-operatively. Indeed, R2 resection was the prognostic factor most strongly associated with poor survival in multivariable analysis, an observation that would support the argument that incomplete surgical resection merely contributes to morbidity without contributing to any tangible benefit. [53]

Key unanswered questions suggested by the above findings are: (1) whether neoadjuvant therapy may help to increase the probability of an R0 resection and thereby improve survival outcomes in patients with linitis plastica; (2) which modality and/or regimen of neoadjuvant therapy would lead to the best outcomes; and (3) whether certain subsets of patients (e.g. in terms of disease stage, performance status or ethnicity) with linitis plastica may stand to benefit more than others from neoadjuvant therapy.

Neoadjuvant chemotherapy in the management of resectable gastric cancer

Within a European context, perioperative chemotherapy is well established as part of standard care for resectable gastric cancer [16,19]. The seminal MAGIC trial, published in 2006, established the efficacy of a perioperative regimen of epirubicin, cisplatin and fluorouracil (ECF) compared to surgery alone, demonstrating both improved overall survival (36% vs 23%, p=0.009) and improved disease-free survival at 5 years[9]. 503 patients with gastric, junctional or lower oesophageal adenocarcinoma were recruited from 45 centres in the UK and a few other centres in Germany, the Netherlands, Brazil, Singapore and New Zealand. The French FNCLCC/FFCD 9703.3 trial also found improved 5-year overall survival with a perioperative cisplatin and fluorouracil compared with surgery alone (38% vs 24%) in patients with oesophagogastric adenocarcinoma[92].

More recently, a regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) has been developed. This evolved from a previous regimen of docetaxel, cisplatin and fluorouracil which showed promise in metastatic settings but was associated with significant toxicity. Cisplatin was therefore substituted with oxaliplatin, resulting in decreased toxicity, improved tolerability and greater efficacy in inducing response in locally advanced, resectable tumours[60]. The phase III FLOT4 trial randomised 716 patients with gastric or gastro-oesophageal junction adenocarcinoma to either perioperative FLOT or perioperative ECF. Compared to ECF, FLOT was associated with improved overall survival (median overall survival 50 months vs 35 months; p=0.012) and a similar rate of hospitalisation for chemotherapy-related toxicity (25% vs 26%) despite a different toxicity profile[60].

Evidence from Asian studies is more mixed, however. In a population where outcomes of gastric cancer are considerably better than those observed in the western world, neoadjuvant chemotherapy is seen to confer little or no additional survival benefit[32,90]. To this day, neoadjuvant chemotherapy does not constitute part of the standard treatment protocol for gastric cancer in either Japan or South Korea[90]. Nonetheless, the recent Korean PRODIGY trial demonstrated significant tumour downstaging and a small but statistically significant improvement in progression-free survival (HR 0.70, 95% CI 0.52-0.95, p=0.023) associated with neoadjuvant chemotherapy using a regimen of docetaxel, oxaliplatin and S-1 (an oral fluorouracil-based agent)[103].

The above randomised controlled trials did not distinguish between linitis plastica and non-linitis gastric cancers. Assuming that linitis plastica and non-linitis gastric cancers respond similarly to neoadjuvant chemotherapy, it can be hypothesised that neoadjuvant chemotherapy may be similarly efficacious in downstaging linitis plastica and thereby lead to higher rates of R0 resection and improved survival outcomes.

Rationale for a systematic review

To our knowledge, no published systematic review has attempted to address the question of whether neoadjuvant chemotherapy in combination with surgical resection leads to improved outcomes in patients with linitis plastica compared to upfront surgery. A systematic review synthesising the available evidence will suggest meaningful endpoints for future trials involving patients with linitis plastica and may help to guide clinical decisions for this patient group.

AIMS AND OBJECTIVES

The aims of this systematic review are as follows:

1. *To describe outcomes in patients with non-metastatic linitis plastica receiving neoadjuvant chemotherapy followed by curative-intent surgical resection, including survival, R0 resection rates, treatment-associated adverse events and quality of life.*
2. *To evaluate whether neoadjuvant chemotherapy followed by surgical resection results in improved outcomes in patients with non-metastatic linitis plastica compared to upfront surgery.*

METHODS

Eligibility criteria

Human studies published after the year 2000 assessing overall survival in patients with gastric linitis plastica treated with systemic chemotherapy followed by surgical resection were included in this systematic review.

Inclusion criteria were as follows:

Population and target condition

Adult patients with gastric linitis plastica, ‘scirrhous’ gastric adenocarcinoma or ‘Borrmann type IV’ gastric adenocarcinoma without distant metastasis.

Intervention of interest

Systemic chemotherapy administered in a neoadjuvant setting, as a precursor to surgical resection performed with curative intent.

Predefined outcomes of interest

Overall survival must be assessed and reported specifically for patients with linitis plastica treated with neoadjuvant chemotherapy, as this represents the primary outcome measure of the systematic review.

Types of studies

Included studies can be any of the following types, with or without a comparator group:

- Retrospective cohort studies (single-centre, multi-centre and registry)
- Prospective registry studies
- Phase II trials
- Phase III and other randomised controlled trials

Exclusion criteria are as follows:

- Non-human and basic science studies
- Case reports and small case series (fewer than 10 patients)
- Dose-finding (i.e. Phase I) trials
- Studies primarily evaluating treatment given with palliative intent
- Studies published in a language other than English
- Studies published before the year 2000

The scarcity of data on treatment outcomes in patients with linitis plastica, and the even smaller number of comparative studies in this patient group, justify the inclusion of studies with only a single treatment arm. Their inclusion will contribute towards the first aim by providing additional data for descriptive outcomes. This will help paint a more complete picture of outcomes in non-metastatic linitis plastica treated with surgery and neoadjuvant chemotherapy, and provide a baseline for future comparison.

Limiting the systematic review to studies published after the year 2000 is justified on the basis that treatment outcomes prior to that date are unlikely to be relevant to current clinical practice. Today's patients with gastric cancer are a different population from their counterparts in the 1990s and earlier, owing to improvements in diagnostic pathways, widespread treatment of *Helicobacter pylori* and cancer screening (in East Asia). A Japanese retrospective cohort study of outcomes in scirrhous gastric cancers demonstrated a considerable difference in median survival between pre-2000 patients (9.5 months) and post-2000 patients (22.8 months). [53]

Outcomes, prioritisation and measures of effect

Primary outcome measure:

Overall survival from initial diagnosis of cancer

Secondary outcome measures:

- R0 resection
- Chemotherapy-associated complications and adverse events (defined by the Common Terminology Criteria for Adverse Events)
- Quality of life, as defined by validated scoring systems

Wherever possible, results were used from an 'intention to treat' analysis. For example, patients listed for surgery who were subsequently found to have metastatic deposits on laparotomy and hence did not undergo surgical resection would still be included in any analysis of outcomes.

Study authors were contacted by email in cases where reports mostly met inclusion criteria but outcome measures were not specifically reported for patients with linitis plastica (or equivalent conditions) and/or separately reported for patients receiving neoadjuvant chemotherapy vs upfront surgery. Two studies were included on this basis after receipt of the requested information from study authors. Unfortunately, no reply was received from the authors of a further five studies who were contacted for additional information. Data obtained via email correspondence are clearly marked as such.

Measures of effect:

Overall survival was preferentially expressed in terms of median and interquartile range, as survival data are rarely normally distributed. For comparative studies, outcomes for each arm and associated effect measures were recorded. Per protocol, the original intention was to calculate hazard ratios for survival outcomes, risk ratios (relative risks) for other dichotomous outcomes and weighted mean differences for continuous outcomes in order to enable quantitative data synthesis in the form of a meta-analysis.

Information sources

Ovid Medline and Embase were searched using the following search strategy:

1. linitis.af,hw,kw
2. scirrhous.af,hw,kw
3. Borrmann type IV.af,hw,kw
4. Borrmann type 4.af,hw,kw
5. or/1-4
6. (gastric or stomach or upper gastrointestinal or UGI or UGIT).ab,hw,kw,ti
7. 5 and 6
8. limit 7 to yr="2000 -Current"
9. remove duplicates from 8

Reference lists from all studies identified through the search strategy and meeting inclusion criteria were also manually trawled to identify other potentially relevant studies. Previous systematic reviews/meta-analyses relevant to patients with gastric linitis plastica or neoadjuvant chemotherapy in gastric cancer, and results from major clinical trials of neoadjuvant chemotherapy in gastric cancer were examined to identify additional studies that could potentially fulfil the inclusion criteria.

Data extraction

Two authors (AM, TT) independently executed the search strategy, sifted titles and abstracts, and identify studies meeting the inclusion criteria described below. Non-human studies, basic science studies, case reports and small case series, reviews, non-English studies and studies published before 2000 were excluded at the 'titles and abstracts' stage.

All post-2000 human studies reporting on outcomes of interest in patients with linitis plastica were obtained as full-text articles and read in full. Studies not reporting the primary outcome measure of overall survival in patients with linitis plastica and studies in which neoadjuvant chemotherapy did not constitute part of the treatment protocol were excluded at this point.

In the event of a disagreement between the two authors, an opinion from a third author (RL) would have been sought and an attempt would be made to resolve the disagreement through discussion.

A standardised data collection form was used with fields for study characteristics and baseline data as well as predefined outcome measures (see Appendix). Two authors (AM, RL) independently completed the relevant data fields for each included study. In the event of any discrepancies between data collected by the two authors, attempts were made to resolve the disagreement through discussion. If an agreement could not be reached, a third author (TT) would arbitrate to resolve the disagreement; in any event, this did not prove necessary.

The following information relating to study characteristics and baseline patient data were extracted from each included publication. The purpose of collecting this data was for assessing inter-study heterogeneity and guiding decisions on whether pooling data for meta-analysis would be appropriate.

Study design and characteristics:

- Number of study arms, and (if applicable) treatment received by comparator group
- Study type: e.g. retrospective cohort study; prospective non-randomised study; randomised controlled trial.
- Interventions received by study participants in addition to neoadjuvant chemotherapy and gastrectomy.
- Single-centre vs multi-centre (including national registries)
- Means of patient selection and (if applicable) randomisation or allocation to study arms
- Primary outcome measure of study (if predefined)

Baseline patient characteristics, selection and follow-up:

- Number of patients (and if more than one arm, number of patients in each arm)
- Age (median [IQR] or mean [SD] as appropriate)
- Means of patient selection/recruitment
- Inclusion and exclusion criteria
- Length of follow-up

In studies with more than one arm, baseline patient characteristics were be noted for each arm. Where data was missing or incomplete, original study authors were contacted via email to request this information.

Assessment of methodological quality and risk of bias of individual studies

Risk of bias/methodological quality assessments were performed independently by two authors (AM, RL). As per Cochrane Collaboration guidelines, disagreements were be resolved through discussion.

Randomised studies

Risk of bias in randomised studies were assessed using the revised Cochrane Collaboration Risk of Bias tool (RoB 2), which includes the following five domains: randomisation, deviations from intended

interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Assessment of each of these five domains contribute towards an overall risk-of-bias judgement.

Non-randomised studies (cohort and case-control studies) and single-arm studies (case series)

The internal validity of non-randomised comparative studies was appraised according to the Newcastle-Ottawa Scale. For single-arm studies, Lawley and colleagues' adaptation of the Newcastle-Ottawa Scale (NOS) was used [104].

Data synthesis

Qualitative presentation of results

Data extracted from the included studies were collated into 'summary of study and baseline patient characteristics' and 'summary of outcomes' tables. Where patterns are identified or heterogeneity is marked, the underlying reasons for these observations were explored.

All studies were included regardless of level of evidence or risk of bias. However, an assessment of each study's methodological quality is separately presented.

Quantitative synthesis of data

The protocol for this systematic review provided for meta-analysis to be performed where appropriate, as defined by the following conditions:

- More than one study assessing identically defined outcomes in an 'intervention' group receiving neoadjuvant chemotherapy and gastrectomy against a 'control' group receiving upfront surgery.
- Minimal clinical heterogeneity observed between pooled studies in terms of patient baseline characteristics and treatment protocols (e.g. use of neoadjuvant and adjuvant treatment modalities).

As per standard meta-analysis methodology, outcomes would be calculated using random-effects models. Where significant statistical heterogeneity exists, only results from the random-effects model would be reported. The Cochrane Q value and I^2 inconsistency would be used to determine statistical heterogeneity. p-values of <0.05 would be considered statistically significant.

Evaluation of meta-biases

Reporting bias was qualitatively evaluated by identifying whether outcome measures were pre-defined, ascertaining that trial protocols were published prior to trial initiation, and examining the presentation of results for any evidence of selective reporting. Generalisability of findings was

assessed by examining the inclusion and exclusion criteria of individual studies. Per the review protocol, Egger's test would have been performed for a meta-analysis including at least 10 studies, This would assess for small study effects including publication bias.

RESULTS

Study selection

After removing duplicates, 1051 studies were identified from Ovid MEDLINE and Embase using the search protocol. After screening of titles and abstracts, 78 reports were sought for full-text review. 7 studies met the eligibility criteria and were included. The authors of a further 7 studies were emailed for additional data; from these studies, 2 were included after the receipt of favourable replies with the requested data. A total of 9 studies were therefore included in the systematic review.

Study characteristics

The 9 included studies comprised two randomised controlled trials [105,106] (including one Phase III clinical trial[105]), three single-arm phase II clinical trials [107–109], and four retrospective cohort studies [110–113] [Table 5.1]. A total of 754 patients with linitis plastica were included in the 9 studies. 352 patients received neoadjuvant chemotherapy followed by gastrectomy whilst 402 patients received upfront surgery. Five studies, comprising two randomised controlled trials [105,106]and three retrospective cohort studies [110,112,113], included both patients receiving neoadjuvant chemotherapy followed by surgery and patients receiving upfront surgery, allowing for direct (but not necessarily balanced) comparisons between the two groups. Two single-arm phase II trials of neoadjuvant chemotherapy compared their outcomes against a 'historical cohort' of patients treated with upfront surgery [107,108]. The remaining two studies, one retrospective and one phase II trial, only evaluated outcomes in patients receiving neoadjuvant chemotherapy. All except one study originated from East Asian centres, with the exception being a small case series from the UK[112].

Patient and disease characteristics

Baseline patient and disease characteristics are summarised in Table 5.1. The median age of participants ranged from 53 years in a Chinese randomised controlled trial[106] to 70 years in a UK retrospective cohort study[112]. There was a trend towards younger ages in prospective trials (median/mean ages of 53, 54, 55, 56 and 62/64) compared to retrospective studies (median/mean ages of 60, 62, 68/69 and 70).

Only one study used the definition of 'linitis plastica', adopting a 'pragmatic approach' to identifying patients with this condition which included cases where the term was used verbatim in radiology or endoscopy reports as well as cases where endoscopic or radiological findings suggested a diffusely abnormal mucosa, poor distension, or diffuse thickening in more than one contiguous area of the stomach[112]. Five studies, two from Japan and three from China, used a definition of 'Borrmann type IV', i.e. diffusely infiltrative tumours with unclear margins [105,106,109,110,113]. A further three studies, all from Japan, used a definition of 'scirrhous gastric cancer' [107,108,111].

Tumour staging was reported by seven out of nine studies, but with inconsistent forms of data presentation which made direct comparisons between studies difficult (Table […]). Unsurprisingly, given the nature of linitis plastica and related conditions, patients with an overall cancer stage of III or IV accounted for a majority of participants (63-100%) in all four studies where this metric was reported. Conversely, the proportion of patients with serosa-positive (T4) disease (reported in 5 studies) varied widely, ranging from as little as 2% and 4% in the two arms of a recent Japanese phase III trial [105] to as high as 100% in a Chinese phase II trial [109]. In the same two trials, the proportions of patients with N3 disease (7 or more nearby lymph nodes affected) were 0% and 58% respectively.

Treatment characteristics

Treatment characteristics are summarised in Table 5.2. Neoadjuvant chemotherapy regimens were standardised in 6 studies: two randomised controlled trials (including one phase III trial), three phase II trials and one retrospective cohort study. Four of these studies incorporated oral S-1, a fluorouracil-based combination medication which is not used in European or North American practice, into their chemotherapy regimens [105,107,109,111]. Platinum-based agents (e.g. cisplatin, oxaliplatin) were also commonly administered. Two multicentre retrospective cohort studies did not describe the chemotherapy regimens used, likely due to either heterogeneity or incomplete records [110,112]. One retrospective cohort study described the use of various chemotherapy regimens at a single centre [113].

Total or subtotal gastrectomy with D2 lymphadenectomy was the standard curative operation in 8 studies. In two studies, palliative surgery was offered to patients who initially met the inclusion criteria for study participation but were later found to have metastatic disease. One retrospective cohort study, from the UK, did not provide details of surgical resections performed[112]. Adjuvant chemotherapy was administered pro-protocol in three prospective trials and as part of standard care in three retrospective cohort studies. One trial specified that adjuvant chemotherapy was not given, whilst another two studies – one prospective and one retrospective – did not describe the use of

adjuvant therapy. All prospective trials used an 'intention-to-treat' approach for analysing data and reporting results. Five studies reported a median follow-up time, ranging from 1.85 to 6 years.

Assessment of methodological quality

Randomised controlled trials: risk of bias assessment

Risk of bias in the two randomised controlled trials was assessed according to the Revised Cochrane Risk-of-Bias Tool for Randomised Trials (RoB 2) with respect to the outcome measure of overall survival [Table 5.3]. The Japanese JCOG0501 phase III clinical trial scored well in all domains, leading to an overall assessment of low risk of bias. The single-centre randomised controlled trial reported in Sun 2011 carried a high risk of bias due to insufficient detail regarding the randomisation process, a significant imbalance between the proportion of patients in the two arms undergoing curative (as opposed to palliative) resection, the lack of a pre-specified primary outcome measure, and absence of information regarding important non-protocol interventions.

Single-arm phase II clinical trials

In the absence of a validated quality assessment tool for single-arm trials, an adaptation of the Newcastle-Ottawa Scale was used for this purpose [Table 5.4]. All three single-arm phase II clinical trials performed identically, receiving total scores of 5 stars (out of 9). In all cases, the number of stars that could be awarded was limited by definition, given the lack of a valid control group or use of a non-matched 'historical cohort' as a comparator. No stars were therefore awarded in the 'comparability' domain. In the 'selection' domain, all three trials automatically scored 2 stars out of 4 for 'ascertainment of exposure' and 'outcome of interest not present at start' (given death as the outcome of interest) whilst falling short on representativeness of the exposed cohort. Assessment of outcomes and follow-up were adequate in all cases, hence a score of 3 stars out of 3 in the 'exposure' domain.

Retrospective cohort studies

Retrospective cohort studies were assessed according to the Newcastle-Ottawa Scale for cohort studies [Table 5.4]. Three retrospective studies included both patients treated with neoadjuvant chemotherapy followed by surgical resection and patients undergoing upfront surgery, whilst one study only included patients receiving neoadjuvant chemotherapy and therefore lacked a comparison group. However, even in studies with a valid comparison group, the two groups were poorly comparable in terms of disease stage and other baseline characteristics. All four studies therefore received zero stars in the 'comparability' domain. Two studies, Thompson 2017 and Xu 2023, were

awarded the full number of stars in 'selection' and 'exposure' domains[112,113]. One study, Fujita 2021, was awarded 2 stars out of 4 in the 'selection' domain as participants were given neoadjuvant chemotherapy either at the discretion of their clinicians or by virtue of being enrolled in a clinical trial[110]. Another study, Kunisaki 2015, was awarded 2 stars out of 3 in the 'exposure' domain due to a short median follow-up period[111]. These scores are by and large the result of real-world circumstances rather than any failings on the part of the studies' authors, but nonetheless affect the validity and applicability of any conclusions that can be drawn from the results.

Survival outcomes associated with neoadjuvant chemotherapy followed by gastrectomy vs upfront gastrectomy

Survival outcomes are summarised in Table 5.5.

Reporting of survival outcomes

Definitions of 'overall survival' and reporting of survival outcomes were inconsistent across the included studies. 'Overall survival' was defined in various ways including diagnosis to death (1 study), trial enrolment to death (1 study), randomisation to death (1 study), initial treatment to death (1 study), initiation of chemotherapy to death (2 studies) and surgical resection to death (1 study), and not defined in two studies.

Five studies reported median overall survival in patients treated with neoadjuvant chemotherapy followed by surgery; three of these studies also reported median overall survival in patients treated with upfront surgery. Interquartile ranges were provided for only one study, with this information obtained via e-mail. The other four studies reporting median overall survival either provided a 95% confidence interval for the median, an overall range or neither. One study (Kinoshita 2009) did not report median overall survival but included Kaplan-Meier survival curves from which median overall survival figures could be visually estimated for both neoadjuvant chemotherapy and upfront surgery groups. One study provided a mean overall survival figure (without a confidence interval) whilst another study provided neither a median nor mean overall survival but reported rates of 5-year overall survival and thereby met the inclusion criteria for this systematic review. Four studies reported rates of overall survival at 2 years and two studies reported rates of overall survival at 5 years.

Median overall survival following neoadjuvant chemotherapy and surgical resection ranged from 16.4 months in a Japanese phase II trial published in 2001 and 16.5 months in a Chinese randomised controlled trial published in 2011, to 39.3 months (95% CI 28.5-57.4) in the recent Japanese JCOG0501 phase III trial.

Effects of neoadjuvant chemotherapy on median overall survival

No study convincingly demonstrated a significant difference in overall survival between patients treated with neoadjuvant chemotherapy versus upfront surgery.

The largest apparent trend towards a survival benefit associated with neoadjuvant chemotherapy was seen in Thompson and colleagues' UK-based retrospective series, with a median overall survival of 24.8 months (95% CI 8.0-41.6) in the neoadjuvant chemotherapy group versus 9.9 months (95% CI 0-25.0) in the upfront surgery group [Table 5.5c]. The small sample size of this series (n=17; neoadjuvant 7, upfront 10), however, resulted in overlapping confidence intervals. Furthermore, within the context of standard clinical practice in the UK, it is unlikely the two groups of patients were comparable in terms of baseline patient and disease characteristics (this information was not provided in the report)[112].

Conversely, on the whole, neoadjuvant chemotherapy did not appear to improve survival outcomes of Asian patients with Borrmann type IV or scirrhous gastric cancers. Two randomised controlled trials have been performed to address this clinical question, both in East Asian populations. A recent high-quality Japanese phase III clinical trial demonstrated a median overall survival of 39.3 months (95%CI 28.5-57.4) in patients with Borrmann type IV cancers who were randomised to neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy, compared to 40.8 months (95%CI 29.0-52.5) in patients randomised to standard treatment with surgery and adjuvant chemotherapy. 5-year survival rates in the two groups were 37.6% and 36.1% respectively. Although a Chinese randomised controlled trial showed a considerably higher rate of overall survival at 2 years in patients given neoadjuvant chemotherapy compared to those receiving upfront surgery (31 vs 15.4%), this study suffered from a high risk of bias[106]. Notably, the proportion of patients undergoing curative resection differed considerably between the two study arms (51.7% vs 30.8%). Most of the remaining patients were treated with palliative surgery, which is not standard practice for gastric cancer in either Western Europe or Japan and not supported by existing evidence[27,53].

Two Japanese single-arm phase II trials demonstrated similar rates of 2-year overall survival in patients treated with neoadjuvant chemotherapy compared to 'historical controls' treated with upfront surgery [Table 5.5b] . Data from a recent Japanese retrospective cohort study which analysed 288 patients with Borrmann type IV cancers in fact showed a trend towards shorter median overall survival in patients receiving neoadjuvant chemotherapy compared to those treated with upfront surgery (32.4 months [IQR 19.8-56.4] vs 37.9 months [IQR 18.1-88.4]).

Meta-analysis

Regrettably, meta-analysis could not be performed due to considerable heterogeneity between studies in terms of patient and treatment characteristics, definitions of outcome measures, and the reporting of these outcome measures. It would be both inappropriate and meaningless to combine data from studies where serosa positive disease accounted for 3% or 100% of participants, or studies involving various different regimens of chemotherapy. Six different definitions of overall survival were present across nine studies. In a condition where survival is measured in months, these differing definitions are very likely to affect the comparability of results. Finally, the various different ways in which overall survival was reported (median and interquartile range, median and range, median and confidence interval, survival curves only, survival at 2 years, survival at 5 years, etc.) made quantitative synthesis of data impossible.

R0 resection

Data relating to R0 resection, where margins are microscopically free of tumour, are detailed in Table 5.6. In four studies, R0 resection rates in patients with linitis plastica were clearly reported. Across these four studies, R0 resection was achieved in 67 patients out of a total of 82 patients with linitis plastica treated with neoadjuvant chemotherapy followed by gastrectomy with curative intent. The 'pooled' R0 resection rate from these four studies was therefore 77.9%. Intention-to-treat analysis in two phase II trials, including patients who did not proceed to surgery or underwent palliative surgery, yielded R0 resection rates of 65% and 66.7% (pooled rate: 66.1%).

Only one of these four studies provided R0 resection data for patients with linitis undergoing upfront surgery. Here, the R0 resection rate associated with neoadjuvant chemotherapy compared unfavourably to upfront surgery (78.9% vs 88.0%) but the retrospective nature of this study and the significantly higher proportion of patients in the neoadjuvant arm with N3 disease (47.4% vs 12%) should be taken into account[113].

Two additional studies provided data relating to R0 or 'curative' resections but are not included in the table. The JCOG0501 phase III trial reported R0 resection rates of 70.9% in its neoadjuvant arm and 67.1% in its upfront surgery arm per 'intention to treat' analysis. R0 resection rates in patients who actually underwent gastrectomy were 80.6% in the neoadjuvant arm and 72.1% in the upfront surgery arm. However, both Borrmann type IV cancers and large type III cancers were included in this data which is therefore not specific for linitis plastica. The JCOG0002 phase II trial reported 'curative resection' rates of 80.8% in patients with scirrhous gastric cancer treated with neoadjuvant chemotherapy compared to 90.3% in 'historical controls' receiving upfront surgery, but it is unclear whether these figures were derived from 'intention to treat' analysis or patients undergoing gastrectomy with curative intent.

Adverse events associated with chemotherapy

Five studies – one phase III trial, three phase II trials and one retrospective cohort study – reported rates of chemotherapy-associated adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) [Table 5.7]. Rates of CTCAE grade ≥3 neutropenia varied widely between studies from 1.8% to 70%, likely owing to a combination of baseline patient and treatment characteristics as well as intensity of monitoring. Pooling data to generate an aggregate figure would therefore be inappropriate. Two studies listed the total number of patients experiencing CTCAE grade ≥3 adverse events of any type, with rates of 5.5% and 19.4%.

Quality of life

Quality of life was not evaluated by or reported in any of the included studies.

DISCUSSION

General Observations

This systematic review attempted to evaluate the evidence for neoadjuvant chemotherapy in the context of linitis plastica deemed to be surgically resectable. Nine studies were included, eight of which were conducted in East Asian centres. The overall quality of evidence was low, with only one high-quality phase III randomised controlled trial amongst the nine included studies. Another randomised controlled trial was associated with a high overall risk of bias. The remaining studies consisted of single-arm phase II clinical trials or retrospective cohort studies where patients receiving neoadjuvant chemotherapy and upfront surgery were not balanced in terms of baseline characteristics.

Significant heterogeneity between the studies in terms of patient populations, treatment regimens, and measurement and reporting of outcome measures precluded meaningful meta-analysis. Even without attempting quantitative data synthesis, it is apparent that the existing evidence base is insufficient to support clinical decisions regarding the use of neoadjuvant chemotherapy in linitis plastica.

Main Findings

Findings from this systematic review must be interpreted taking the considerable heterogeneity between studies, overall low quality of evidence and predominantly Asian study populations into account. Where comparisons against upfront surgery were performed, no study conclusively

demonstrated a survival benefit associated with neoadjuvant chemotherapy in the setting of resectable linitis plastica. The single high-quality phase III clinical trial of neoadjuvant chemotherapy for patients with linitis plastica found no difference in median overall survival or 5-year overall survival rate compared to standard care in Japan (39.3 vs 40.8 months).

Median overall survival in the included studies ranged from 16.4 months in the oldest study to 39.3 months in the most recent trial. By comparison, the FLOT4 trial reported a median overall survival of 50 months in European patients randomised to neoadjuvant FLOT and curative surgery[60]. The poor survival outcomes described here for linitis plastica are all the more striking when considering that the data relate predominantly to Asian patients. Historically, large randomised controlled trials involving Asian patients with gastric cancer have demonstrated survival rates 30-40% higher compared to trials in the West.[32]

Amongst the four studies reporting this metric, the pooled R0 resection rate was 77.9% in patients with linitis plastica undergoing neoadjuvant chemotherapy followed by surgery with curative intent. Similar rates of R0 resection were reported in the JCOG0501 phase III trial which included both Borrmann type IV and large type III tumours. Reflecting the invasive nature of linitis plastica, these results compare unfavourably to the 90.2% rate of negative longitudinal margins following gastrectomy reported in the United Kingdom National Oesophago-Gastric Cancer Audit.[114]

The preponderance of East Asian studies in this systematic review should be highlighted as most of the evidence to date supporting the use of neoadjuvant chemotherapy in gastric cancer has come from European studies. The only western study in this systematic review did in fact show a trend towards improved survival in patients receiving neoadjuvant chemotherapy. However, it was underpowered to show a significant difference and outcomes were likely to have been confounded by baseline patient and disease characteristics which affected treatment decisions. An American database study which did not meet the inclusion criteria for this systematic review also suggested a non-significant trend towards better outcomes following neoadjuvant chemotherapy in linitis plastica, associated with a hazard ratio of 1.67 (95% CI 0.65-0.88) [99]. Conversely, East Asian clinical guidelines and trials have not supported the use of neoadjuvant chemotherapy for gastric cancer in general. The standard of care in Japan remains D2 gastrectomy followed by adjuvant chemotherapy for locally advanced gastric cancer.[98]

Limitations

This systematic review was limited by the generally low quality of evidence, considerable heterogeneity between studies and small number of comparative studies, which ultimately precluded

meta-analysis. Marked heterogeneity between studies was present not only in terms of baseline patient, disease and treatment characteristics but also in the selection and reporting of outcome measures. Even without accounting for the heterogeneity described, the very small number of comparative studies limited the potential for meta-analysis. Among the nine included studies, there was only a single high-quality prospective study where treatment arms were comparable with respect to baseline characteristics.

Given these limitations, the present systematic review was unable to answer the primary research question of whether neoadjuvant chemotherapy followed by surgical resection leads to improved outcomes in patients with curatively-treated linitis plastica compared to upfront surgery. Although the findings at face value do not appear to suggest a treatment benefit, the absence of a truly valid comparison group in eight out of nine studies must be taken into account.

Comparison with previous studies on neoadjuvant chemotherapy for gastric cancer

To our knowledge, no other systematic review has specifically focused on patients with linitis plastica. This is unsurprising, given the paucity of evidence relating to this patient population. However, exploring previous systematic reviews of neoadjuvant chemotherapy for patients with gastric cancer in general may help to put the above findings in perspective.

The European MAGIC and FLOT4 trials, which have been discussed earlier, led to the establishment of perioperative chemotherapy as the standard of care for surgically resectable gastric cancer across Europe. Perhaps due to the relatively lower incidence of gastric cancer in Western Europe, both of these trials recruited patients with gastro-oesophageal junction cancers (including Siewert I and II tumours centred on the oesophagus and gastro-oesophageal junction respectively) in addition to patients with gastric cancers. Only 44% of the patients in each arm of the FLOT4 trial had purely gastric cancers[60]. Outcomes were not separately reported for patients with gastric and junctional cancers in either trial.

Systematic reviews and meta-analyses of the international evidence have generated more equivocal results which do not conclusively support the use of neoadjuvant chemotherapy for gastric cancer. The greater weighting of Asian studies is likely to represent an important factor, as in the current systematic review.

Xu and colleagues' 2014 meta-analysis included nine 'high-quality' randomised controlled trials published between 1995 and 2010 evaluating the outcomes of neoadjuvant chemotherapy followed by surgery versus surgery alone for gastric carcinoma[115]. Although noting the potential of neoadjuvant chemotherapy to downstage tumours and improve rates of R0 resection, this meta-

analysis did not identify a long-term survival benefit associated with neoadjuvant chemotherapy. Of the nine included trials, six were performed in East Asian centres whilst two were performed in Western Europe and one in Eastern Europe. The MAGIC trial was not amongst these, as its inclusion of gastro-oesophageal junctional tumours fell into the exclusion criteria for this meta-analysis. As remains true today, standards of care differed between regions at the time of this review's publication. Notably, although D2 lymphadenectomy was already widely performed in Japan and South Korea, it did not yet constitute a routine part of gastrectomy in other countries.

A more recent systematic review by Lim and colleagues, published in 2023, was also limited to trials for purely gastric cancers[116]. Once again, no significant differences were observed between patients receiving neoadjuvant chemotherapy and patients receiving upfront surgery in terms of overall survival or progression-free survival. Similar to the present systematic review, considerable heterogeneity was observed in the definitions and reporting of survival outcomes. This limited the potential for meta-analysis, which could not be performed for overall survival following neoadjuvant chemotherapy and surgery versus surgery alone. A meta-analysis combining the 3-year rates of disease-free survival, progression-free survival and event-free survival across four studies evaluating perioperative versus adjuvant chemotherapy did not find a significant difference in outcomes.

Conversely, Coccolini and colleagues' 2018 systematic review and meta-analysis included trials involving patients with both gastric and junctional cancers[117]. Their analysis did in fact identify small but significant reductions in the risk of mortality at 3 years (RR 0.81, 95%CI 0.74-0.89, p<0.0001) and 5 years (RR 0.88, 95%CI 0.83-0.93, p<0.0001) in patients receiving neoadjuvant chemotherapy followed by surgery compared to patients receiving surgery alone. Rates of treatment-related morbidity or perioperative mortality were comparable between the groups.

The Korean PRODIGY trial is first Asian study finding in favour of perioperative chemotherapy for gastric cancer[103]. Publishing its final survival outcomes in 2023, the PRODIGY trial demonstrated significant tumour downstaging and a small but statistically significant improvement in progression-free survival (HR 0.70, 95% CI 0.52-0.95, p=0.023) associated with neoadjuvant chemotherapy using a regimen of docetaxel, oxaliplatin and S-1 (an oral fluorouracil-based agent)[103]. Rates of progression-free survival at 3 years were 66.3% (95%CI 59.6-72.1%) and 60.2% (95%CI 53.6-66.3%) in the neoadjuvant chemotherapy and upfront surgery arms respectively. Lim and colleagues postulated that the more favourable outcomes associated with neoadjuvant chemotherapy seen in the PRODIGY trial may be attributable in part to its inclusion of earlier-stage disease whereas other Asian trials of neoadjuvant chemotherapy have mostly focused on more advanced disease.[116]

In summary, the evidence for neoadjuvant chemotherapy in the setting of curative gastric cancer remains ambiguous, likely differs according to patient population and disease extent, and in the European setting, has largely been derived from studies including patients with both gastric and gastro-oesophageal junction cancers. Given the degree of uncertainty surrounding the benefits of neoadjuvant chemotherapy even for gastric cancer as a whole, the lack of evidence to support its use in the context of linitis plastica should perhaps come as little surprise.

Implications for clinical practice and future directions

Notwithstanding its limitations, this systematic review has highlighted a clear need for definitive trial evidence to guide management decisions in patients with potentially resectable linitis plastica. A randomised controlled trial of perioperative chemotherapy and surgery versus surgery alone in western patients with linitis plastica, mirroring the MAGIC trial, would represent the gold standard. The existing evidence base, which primarily relates to non-linitis gastric cancers, suggests that outcomes seen in Asian patients cannot necessarily be extrapolated to Western patients and vice-versa. The low numbers of patients with potentially resectable linitis plastica may pose a challenge for trial recruitment, and multicentre or even multinational collaboration will be required for such a trial.

At least on a theoretical level, intraperitoneal therapy holds great promise for linitis plastica. Of all subtypes of gastric cancer, linitis plastica has the greatest tendency to metastasise to the peritoneal cavity and is therefore least likely to be amenable to curative treatment. Even in Japan, where gastric cancer tends to be diagnosed at an earlier stage, most cases of linitis plastica have already metastasised to the peritoneum by the time of diagnosis. In Fushida and colleagues' single-centre cohort of 119 Japanese patients with scirrhous gastric cancer, the prevalence of peritoneal disease was 61.3%[53]. The same figure of 61.3% was found in patients with linitis plastica identified from our UK-based cohort. Intraperitoneal chemotherapy could potentially be used as a strategy for converting inoperable metastatic disease to operable localised disease, although the extensive stromal fibrosis that characterises the peritoneal spread of linitis plastica may represent a barrier to drug delivery[53]. Patients with positive peritoneal cytology but no macroscopic peritoneal disease are a population of particular interest for this treatment indication. Alternatively, intraperitoneal chemotherapy could play a role in reducing the risk of peritoneal recurrence following curative gastrectomy for non-metastatic linitis plastica.

The Japanese phase III PHOENIX-GC2 trial is currently recruiting and will assess the efficacy of intraperitoneal paclitaxel plus systemic chemotherapy versus standard systemic chemotherapy in Borrmann type IV gastric cancers without overt metastatic disease. The primary endpoint is disease-

free survival at 3 years. Patients with positive peritoneal cytology will be eligible for inclusion, although treatment regimens differ between patients with negative and positive cytology. Only patients with positive peritoneal cytology will receive neoadjuvant chemotherapy whereas patients with negative cytology will receive adjuvant chemotherapy during and following radical gastrectomy. Patients in both categories will be randomised to either intraperitoneal plus intravenous chemotherapy or intravenous chemotherapy; all patients will also receive oral S-1 as this represents the standard of care in Japan.[98]

Conclusion

The existing evidence base is insufficient to answer the primary research question of whether neoadjuvant chemotherapy followed by surgical resection leads to improved outcomes in patients with curatively-treated linitis plastica compared to upfront surgery. This systematic review highlights a clear need for definitive trial evidence to guide management decisions in patients with potentially resectable linitis plastica. Although the recent JCOG0501 phase III trial showed that neoadjuvant chemotherapy did not improve outcomes in Japanese patients with Borrmann type IV gastric cancers, the different behaviours of Asian and western gastric cancer populations must be taken into account. Looking to the future, intraperitoneal chemotherapy appears to be a promising strategy for both downstaging linitis plastica with limited peritoneal disease and reducing the risk of peritoneal recurrence following curative resection of non-metastatic linitis plastica. A Japanese phase III trial of intraperitoneal chemotherapy for Borrmann type IV cancers is currently recruiting, but a large western multicentre trial involving patients with linitis plastica remains lacking and is desperately needed.

Table 5.1: Summary of included studies: study and patient characteristics

Author & year (ref)	*Study type*	*Specific cancer definition*	*Country and study period*	*Number of patients with LP or equivalent*	*Age distribution (years)*	*Gender, M/F*	*AJCC stage ≥III (%)*	*cT4 (%)*	*cN3 (%)*
Fujita 2021*	Retrospective cohort (multicentre)	Borrmann type IV	Japan, 2005-2015	Total: 288 NA: 63 SU: 225	*Median (IQR):* Laparoscopic group 69 (62-76) Open group 68 (57-76)	Overall: 58/42%	-	*T3-4* Overall: 92.4%	*'N+'* Overall: 69.4%
Iwasaki 2021, Terashima 2019 (JCOG0501)	Phase III randomised controlled trial (multicentre)	Borrmann type IV	Japan, 2005-2013	Total: 187 NA: 96 SU: 91	*Median (range)[1]:* NA 64 (30-75) SU 62 (28-75)	NA: 58/42%[1] SU: 60/40%[1]	NA: 64.2%[1] SU: 63.1%[1]	NA: 4%[1] SU: 2%[1]	NA: 0%[1] SU: 0%[1]
Kinoshita 2009 (JCOG0002)	Phase II single-arm trial (multicentre)	Scirrhous gastric cancer involving > ½ stomach	Japan, 2001-2003	NA: 55 *(SU historical controls: 241)*	*Mean (range):* NA 56 (31-70)	NA: 47/53%	-	NA: 9.6%[2]	-
Kunisaki 2015	Retrospective cohort (single centre)	Scirrhous gastric cancer	Japan, 2004-2012	NA: 27	*Median (range):* NA 62 (35-79)	NA: 48.1/51.9%	NA: 66.6%	NA: 74.1%	*N1-N3* NA: 51.9%
Sun 2011	Randomised controlled trial (single centre)	Borrmann type IV	China, 2008-2010	Total: 55 NA: 29 SU: 26	*Mean (range):* Overall 52.6 (33-72)	Overall: 67.3/32.7%	-	-	-
Takahashi 2001	Phase II single-arm trial (single centre)	Scirrhous gastric cancer	Japan, 1994-1997	NA: 20 *(SU historical controls: 371)*	*Median (range):* NA 54 (38-67)	NA: 55/45%	-	-	-
Thompson 2017	Retrospective cohort (multicentre)	Linitis plastica	UK, 2006-2010	Total operable: 17 NA: 7 SU: 10	*Mean (SD)*: Overall 69.6 (13.6)	Overall: 50/50%	-	Overall: 29%	Overall: 41%
Xiang 2020	Phase II single-arm trial (single centre)	Borrmann type IV	China, 2016-2018	NA: 36	*Median (IQR):* NA 55 (29-72)	NA: 52.8/47.2%	NA: 100%	NA: 100%	NA: 58.3%

Xu 2023	Retrospective cohort (single centre)	Borrmann type IV	China, 2009-2018	Total: 69 NA: 19 SU: 50	*Median (range):* Overall 60 (26-80) NA 60 (46-73) SU 61 (26-80)	Overall: 58/42% NA: 47/53% SU: 62/38%	Overall: 94.2% NA: 100% SU: 92%	-	Overall: 21.7% NA: 47.4% SU: 12%

** Including additional data received via email*

[1] Including both Borrmann type III and type IV cancers

[2] Out of 52 patients undergoing laparotomy (of the remainder, 2 refused consent and 1 was found to have pulmonary metastases)

NA = neoadjuvant chemotherapy; SU = upfront surgery; IQR = interquartile range; SD = standard deviation

Table 5.2: Summary of included studies: study and treatment characteristics

Author & year (ref)	*Study type*	*Specific cancer definition*	*Country and study period*	*Neoadjuvant chemotherapy regimen*	*Type of surgery*	*Adjuvant therapy*	*Primary outcome measure*	*Length of follow-up*
Fujita 2021*	Retrospective cohort (multicentre)	Borrmann type IV	Japan, 2005-2015	Not reported	Open (n=226) or laparoscopic (n=62) gastrectomy and D2 lymphadenectomy	Adjuvant chemotherapy (S-1)	Overall survival	Per protocol: 5 years
Iwasaki 2021, Terashima 2019 (JCOG0501)	Phase III randomised controlled trial (multicentre)	Borrmann type IV	Japan, 2005-2013	**S-1/cisplatin (SP)**: 2 cycles of 4 weeks each; oral S-1 twice daily for three weeks, IV cisplatin on day 8 of each course	Total or distal gastrectomy with D2/3 lymphadenectomy	Adjuvant chemotherapy (S-1)	Overall survival	Median: 4.5 years
Kinoshita 2009 (JCOG0002)	Phase II single-arm trial (multicentre)	Scirrhous gastric cancer involving > ½ stomach	Japan, 2001-2003	**S-1**: 2 cycles of 4 weeks' oral administration and 2 weeks' withdrawal	Total gastrectomy (n=36) with D1 (n=1) or D2/D3 (n=35) lymphadenectomy; palliative resection of main tumour (n=10)	None	2-year survival rate	(Range: 2-4 years)
Kunisaki 2015	Retrospective cohort (single centre)	Scirrhous gastric cancer	Japan, 2004-2012	**S-1/cisplatin (SP)**: 2 cycles of 3 weeks' treatment (oral S-1 twice daily, IV cisplatin on day 8) separated by 2-week rest period	Total gastrectomy and D1 (n=5), D2 (n=17) or D3 (n=5) lymphadenectomy; splenectomy (n=11)	Adjuvant chemotherapy (S-1)	Not predefined	Median: 2 years (range: 0.9-10.1)
Sun 2011	Randomised controlled trial (single centre)	Borrmann type IV	China, 2008-2010	**Docetaxel/cisplatin/ 5-fluorouracil/ leucovorin**: 3 cycles of treatment at 3-week intervals; intravenous administration	Radical total gastrectomy (n=23) or palliative resection (n=21) or non-resectional palliative surgery (n=11)	Adjuvant chemotherapy (NA group 3 cycles; SU group 6 cycles)	Not predefined	(Range 1-3 years)
Takahashi 2001	Phase II single-arm trial (single centre)	Scirrhous gastric cancer	Japan, 1994-1997	**Methotrexate/5-fluorouracil/leucovorin/ docetaxel**: 2 cycles at 4-week intervals;	Total gastrectomy with D2 lymphadenectomy	Not specified	2-year survival rate	Median: 4.9 years

				intravenous administration				
Thompson 2017	Retrospective cohort (multicentre)	Linitis plastica	UK, 2006-2010	Not reported	Gastric resection (various types)	Not specified	Overall survival	(Range: 3.5-7.5 years)
Xiang 2020	Phase II single-arm trial (single centre)	Borrmann type IV	China, 2016-2018	**Etoposide/oxaliplatin/ epirubicin/S-I**: 3 cycles of 3 weeks; intra-arterial etoposide, oxaliplatin and epirubicin on day 1; oral S-1 twice daily on days 1-14	Gastrectomy and radical lymphadenectomy	Adjuvant chemotherapy (S-1 and oxaliplatin)	Overall survival	'Average': 1.85 years (range: 0.5-3.4 years)
Xu 2023	Retrospective cohort (single centre)	Borrmann type IV	China, 2009-2018	Various regimes (EOX, SOX, DOX, FLOT, etc.)	Gastrectomy with D2 lymphadenectomy	Adjuvant chemotherapy	Overall survival	Median: 6 years (range: 3.7-10.1 years)

Table 5.3: Included studies (randomised controlled trials): risk of bias assessment – RoB2

Author & year (ref)	*Randomisation*	*Assignment to interventions*	*Adhering to interventions*	*Missing outcome data*	*Measurement of the outcome*	*Selection of the reported result*	*Overall risk of bias*
Iwasaki 2021 (JCOG0501)	Low	Low	Low	Low	Low	Low	Low
Sun 2011	High	Some concerns	High	Low	Low	Some concerns	High

Table 5.4: Included studies (non-randomised and single-arm): quality assessment – Newcastle-Ottawa Scale

Author & year (ref)	*Representativeness of exposed cohort*	*Selection of non-exposed cohort*	*Ascertainment of exposure*	*Outcome of interest not present at start*	*Comparability with respect to disease stage*	*Comparability with respect to other baseline characteristics*	*Assessment of outcomes*	*Length of follow-up*	*Adequacy of follow-up*	*Total score/9*
Fujita 2021	0	0	1	1	0	0	1	1	1	5
Kinoshita 2009 (JCOG0002)	0	0	1	1	0	0	1	1	1	5
Kunisaki 2015	1	N/A	1	1	N/A	N/A	1	0	1	5
Takahashi 2001	0	0	1	1	N/A	N/A	1	1	1	5
Thompson 2017	1	1	1	1	0	0	1	1	1	7
Xiang 2020	0	0	1	1	N/A	N/A	1	1	1	5
Xu 2023	1	1	1	1	0	0	1	1	1	7

Table 5.5: Summary of included studies: survival outcomes in patients with linitis plastica (or comparable conditions)

(a) Prospective trials: randomised controlled trials

Author & year (ref)	*n=*		*OS definition*	*Median OS*		*HR (95% CI) for mortality*	*2yr OS (%)*		*5yr OS (%)*		*R0 resection (%)*	
	NA	*SU*		*NA*	*SU*		*NA*	*SU*	*NA*	*SU*	*NA*	*SU*
Iwasaki 2021, Terashima 2019 (JCOG0501)	96	91	Randomisation to death	39.3 months (95%CI 28.5-57.4)[a]	40.8 months (95%CI 29.0-52.5)[a]	0.960 (0.678-1.360)[a]	-	-	37.6%[a]	36.1%[a]	-	-
Sun 2011	29	26	Not defined	16.5 months (range 8.7-46.9)[b]	12.8 months (range 6.4-40.2)[b]	-	31%[b]	15.4%[b]	-	-	-	-

[a] *Including additional data received via email.*

[b] *Patients with intra-abdominal metastases not excluded*

OS = overall survival; NA = neoadjuvant chemotherapy; SU = upfront surgery; HR = hazard ratio= CI = confidence interval

(b] Prospective trials: single-arm phase II trials

Author & year (ref)	*n=*		*OS definition*	*Median OS*		*HR (95% CI) for mortality*	*2yr OS (%)*		*5yr OS (%)*		*R0 resection (%)*	
	NA	*SU*		*NA*	*SU*		*NA*	*SU*	*NA*	*SU*	*NA*	*SU*
Kinoshita 2009 (JCOG0002)	55	241[c]	Initiation of chemotherapy to death	~27.5 months[d]	~23.5 months[c,d]	-	59%	45%[c]	-	-	80.8%	90.3%[c]
Takahashi 2001	20	371[c]	Initiation of chemotherapy to death	16.4 months	-	-	25%	27%[c]	-	-	65%	-
Xiang 2020	36	-	Enrolment to death	27.1 months (95%CI 22.24-31.97)	-	-	48.5%	-	-	-	66.7%	-

[c] *"Historical controls" with comparable lesions, treated at the same institution.*

[d] *Visual estimate from survival curves*

OS = overall survival; NA = neoadjuvant chemotherapy; SU = upfront surgery; HR = hazard ratio= CI = confidence interval

(c) Retrospective studies

Author & year (ref)	*n=*		*OS definition*	*Median OS*		*HR (95% CI) for mortality*	*2yr OS (%)*		*5yr OS (%)*		*R0 resection (%)*	
	NA	*SU*		*NA*	*SU*		*NA*	*SU*	*NA*	*SU*	*NA*	*SU*
Fujita 2021[a]	63	225	Initial treatment to death	32.4 months (IQR 19.8-56.4)[a]	37.9 months (IQR 18.1-88.4)[a]	-	-	-	-	-	-	-
Kunisaki 2015	27	-	Not defined	Mean: 32.4 months	-	-	-	-	27.1%	-	55.6%	-
Thompson 2017	7	10	Resection to death	24.8 months (95%CI 8.0-41.6)	9.9 months (95%CI 0-25.0)	-	-	-	-	-	-	-

Xu 2023	19	50	Diagnosis to death	-	-	-			15.8%	24.8%	78.9%	88.0%

[a] *Including additional data received via email.*

OS = overall survival; NA = neoadjuvant chemotherapy; SU = upfront surgery; HR = hazard ratio= CI = confidence interval

Table 5.6: R0 resection rates in patients with linitis plastica (or comparable condition)

Author & year (ref)	*Study type*	*NA group: total patients (ITT)*	*NA patients: resection with curative intent*	*NA patients: R0 resection margins*	*NA patients: R0 resection rate (ITT)*	*NA patients: R0 resection rate (curative intent)*	*SU patients: R0 resection rate*
Takahashi 2001	Phase II trial	20	18	13	65.0%	72.2%	-
Xiang 2020	Phase II trial	36	27	24	66.7%	88.9%	-
Kunisaki 2015	Retrospective	-	22[a]	15	-	68.2%[a]	-
Xu 2023	Retrospective	-	19	15	-	78.9%	88.0%
Pooled (trials: ITT)	-	*56*	-	*37*	*66.1%*	-	-
Pooled (all)	-	-	*86*	*67*	-	*77.9%*	-

[a] Figures exclude patients with peritoneal dissemination or positive cytology, who were included in the authors' analysis but are not candidates for surgery with curative intent by definition.

NA = neoadjuvant chemotherapy; SU = upfront surgery; ITT = intention to treat

Notes:

- Kinoshita 2009 (JCOG0002): 'Curative resection' rates were reported; 80.8% in patients with linitis plastica treated with neoadjuvant chemotherapy and 90.3% in 'historical controls' receiving upfront surgery. However, it is unclear whether these figures were from 'intention to treat' or 'per protocol' analysis, and actual patient numbers with R0 or R1 resections were not provided.
- Iwasaki 2021/Terashima 2019 (JCOG0501): Rates of R0 resection were reported but relate to all patients enrolled in the trial, including patients with both Borrmann type IV and large type III cancers, and are therefore not specific to linitis plastica. Per 'intention to treat' analysis, R0 resection rates were 70.9% in the neoadjuvant group and 67.1% in the upfront surgery group. In patients actually undergoing gastrectomy, R0 resection rates were 80.6% in the neoadjuvant group and 72.1% in the upfront surgery group.

Table 5.7: Chemotherapy-related adverse events in patients receiving neoadjuvant chemotherapy (CTCAE grade ≥3)

Author & year (ref)	*Study type*	*Neoadjuvant chemotherapy regimen*	*Total patients experiencing grade ≥3 events*	*Grade ≥3 neutropenia*	*Grade ≥3 febrile neutropenia*
Iwasaki 2021, Terashima 2019 (JCOG0501)	Phase III RCT	S-1/cisplatin	-	32/93 (34.4%)	1/93 (1.1%)
Kinoshita 2009	Phase II trial	S-1	3/55 (5.5%)	1/55 (1.8%)	-
Takahashi 2001	Phase II trial	Methotrexate/5-FU/ leucovorin/docetaxel	-	14/20 (70%)	-

Xiang 2020	Phase II trial	Etoposide/oxaliplatin/ epirubicin/S-1	7/36 (19.4%)	1/36 (2.8%)	-
Kunisaki 2015	Retrospective	S-1/cisplatin	-	2/27 (7.4%)	-

CHAPTER 6- Outcomes in patients with peritoneal metastasis of gastric cancer

ABSTRACT

Background. The peritoneum is the second most common site of synchronous metastasis from gastric cancer and the most common site of recurrence. Prognosis in peritoneal disease has historically been poor, with median survival ranging from 2.2 to 8.8 months and typically no survival at 5 years. Patients with peritoneal metastasis of gastric cancer (PMGC) are a 'forgotten' population, with very few western studies on the natural history or treatment outcomes of patients with PMGC. Standard management options are currently limited to systemic chemotherapy, palliative interventions such as radiotherapy and stenting, and best supportive care. Up-to-date observational data reflecting the UK gastric cancer population and current clinical practice are required to highlight unmet needs and inform future trials of novel therapeutic strategies in this 'forgotten' population.

Objectives. This chapter aims to characterise a representative sample of UK-based patients with peritoneal metastasis of gastric cancer (PMGC) by: (1) describing baseline demographic and disease characteristics in this patient group and identifying characteristics associated with PMGC compared to gastric cancer without peritoneal involvement; (2) identifying prognostic predictors and evaluating the effect of palliative chemotherapy on survival; (3) comparing rates of disease-related and treatment-related complications between patients with PMGC and non-surgical patients with gastric cancer not involving the peritoneum. It is hoped that the findings will highlight unmet needs of this patient population and help to determine the suitability of novel therapeutic strategies for patients with PMGC.

Methods. Patients with gastric adenocarcinoma (including Siewert III gastro-oesophageal junction cancer) treated at or referred to the Norfolk and Norwich University Hospital between 2011 and 2021 were included. For the purposes of the present analysis, PMGC was defined as synchronous peritoneal metastasis found on staging investigations performed at the time of cancer diagnosis. In addition to baseline characteristics and survival, data relating to hospital admissions and secondary-care interventions for predefined disease-related complications were obtained from electronic health records. Cox proportional regression was used to evaluate the prognostic predictive value of baseline characteristics. Propensity score methodology, as previously described, was used to adjust for

confounding in comparisons between patients treated with palliative chemotherapy versus best supportive care.

Results. Median overall survival in patients with PMGC was 164 days (IQR 61–310). PMGC was significantly associated with linitis plastica (RR 4.35, 95%CI 2.71–6.99; p<0.0001) and the presence of signet ring cells (RR 1.76, 95%CI 1.34–2.32; p=0.0001). 51.4% of patients with PMGC were treated with palliative chemotherapy; compared to patients with PMGC not receiving chemotherapy, these patients were significantly younger, by a decade on average. Median survival was 276 days in patients receiving palliative chemotherapy and 71 days in patients not receiving chemotherapy. Following trimming and inverse probability of treatment weighting by the propensity score, palliative chemotherapy was associated with an odds ratio for 1-year overall survival of 10.49 (p=0.002). When patients aged >80 years were excluded, applying the same adjustments based on the propensity score resulted in a smaller odds ratio for 1-year survival of 4.25 which was no longer statistically significant (p=0.186). In non-surgical patients, PMGC was associated with a higher aggregate frequency of disease-related complications necessitating hospital admission or secondary-care intervention (RR 2.12, p<0.001).

Conclusions. Survival in patients with PMGC is poor regardless of treatment offered or baseline patient characteristics. Although palliative chemotherapy improves survival, this survival benefit is typically measured in months. Identification of adverse prognostic factors in a UK-based population with PMGC is difficult due to a combination of low patient numbers and relatively small absolute differences in survival between patients with the best outcomes and worst outcomes. PMGC was associated with a higher rate of disease-related complications requiring hospital admission or secondary-care intervention. However, numbers of such events in the current dataset are likely to underestimate the true degree of morbidity. Multicentre and perhaps multinational studies with engagement from researchers working in primary and palliative care settings are necessary to fully map the natural history of PMGC.

INTRODUCTION

Peritoneal metastasis of gastric cancer (PMGC): a 'forgotten' group of cancer patients

The peritoneum is the second most common site of synchronous metastasis from gastric cancer, after the liver, and the most common site of recurrence[118,119]. The quoted incidence of peritoneal disease at diagnosis of gastric cancer ranges from 5 to 30% depending on the population under investigation and staging modalities used[120]. In addition, approximately 5% of patients who are initially deemed to be eligible for curative treatment are subsequently found to have positive peritoneal cytology for cancer cells[121]; this group of patients is considered to have peritoneal metastases under current guidelines[19]. Among patients receiving nominally curative therapy, up to 40% subsequently develop peritoneal recurrence in follow-up[17].

Prognosis in peritoneal disease has historically been poor, with median survival figures ranging from 2.2 to 8.8 months and typically no survival at 5 years[122]. Treatment is invariably palliative in nature and hampered by poor penetration of cytotoxic agents into the abdominal cavity. Current treatment options include systemic chemotherapy, best supportive care, and interventions with palliative intent such as stenting or bypass surgery for obstruction and radiotherapy for bleeding. Unfortunately, outcomes are uniformly disappointing in this patient group regardless of treatment modality.

Patients with PMGC remain very much a 'forgotten' population. As of 2021, there were no UK-based studies on the natural history or treatment outcomes of patients with PMGC. The paucity of gastric cancer research in the West comes with serious human consequences. Whereas the 5-year survival of all patients with gastric cancer in East Asia is in the region of 40-60%, the equivalent figure in Europe is only 24.5%[5]. Furthermore, literature searches on PMGC generate little more than survival data. Within a research paradigm that focuses almost exclusively on survival outcomes, understanding of the lived experiences and complications experienced by these patients is negligible.

There are therefore two 'unmet needs': first, an unmet need for research involving this patient group, particularly studies focusing on non-survival endpoints; and second, an unmet need for novel therapies to improve not only survival but also quality of life in patients with this condition.

Mechanisms of peritoneal spread

The conventional understanding of peritoneal metastasis can be framed in terms of Stephen Paget's 'seed and soil' hypothesis[5]. Within this framework, cancer cells are the 'seeds' and fertile sites for metastasis represent the 'soil'. Tumours are thought to metastasise through a sequence of cell migration, adhesion, invasion and proliferation. According to this model, cancer cells invade through the serosal layer, 'seed'

through the abdominal cavity, adhere to the peritoneum and invade through the basement membrane. This is followed by a process of proliferation which is characterised by epithelial-mesenchymal transition and angiogenesis. Competing theories describe cancer spread to the peritoneum via haematogenous or lymphatic routes[5].

Current standard of care for patients with PMGC

Systemic chemotherapy is the current standard of care for patients with locally advanced and/or metastatic gastric cancer, including cytology-only peritoneal disease without macroscopic deposits. Typical regimes are doublet combinations of platinum and a fluoropyrimidine, and triplet combinations of platinum, fluoropyrimidines and anthracyclines[19]. Comparisons between chemotherapy regimes are outside the scope of this thesis, but systemic chemotherapy is generally associated with improved survival outcomes compared to best supportive care alone in patients with adequate organ function and performance status[19]. The efficacy of systemic chemotherapy in PMGC is limited by the poor blood supply to the peritoneal surface and hence poor penetration of cytotoxic agents into tumour nodules[123], coupled with systemic toxicity at high doses.

Resectional surgery is not generally recommended in the setting of PMGC, except in experimental contexts and for a small number of patients deemed operable following an exceptional response to systemic chemotherapy[16,19].

Survival outcomes from previous studies in western populations

PMGC is characterised by poor survival, even with optimal treatment. In a large population-based study from Eindhoven, The Netherlands, median overall survival (OS) was only 4 months in patients with PMGC across a 16-year period from 1995 to 2011[118]. In patients with isolated PMGC, median OS was 4.6 months (95% confidence interval 4.0-5.2 months) compared to 14 months in patients without metastatic disease[118]. A contemporary observational study from a single tertiary centre in the United States (Memorial Sloan-Kettering Cancer Center, New York; 1993-2009) reported a median disease-specific survival (DSS) of 0.8 years (from initial laparoscopy to death) in patients with macroscopically visible peritoneal disease (n=198) and 1.3 years in patients with positive peritoneal washings for cancer cells but no visible peritoneal deposits (n=93)[119].

Conventional therapy typically extends survival by merely a few months. In the Eindhoven Cancer Registry, median OS of patients with PMGC undergoing chemotherapy was 8 months (95%CI 6.8-9.3 months)[118]. Historically, patients with cytology-only or limited peritoneal disease underwent resectional surgery at certain centres. A number of these patients were included in both the

Eindhoven Cancer Registry and the Memorial Sloan-Kettering study. In Eindhoven, median OS of patients with isolated peritoneal metastases undergoing resection of the primary cancer was 9.9 months (95%CI 7.7-11.9), not significantly longer compared to patients treated with chemotherapy[118]. At the Memorial Sloan-Kettering, 29 patients with cytology-only disease underwent immediate gastrectomy (i.e. without neoadjuvant chemotherapy) before a change of protocol in 2005; median DSS for these patients was 1.1 years (range 0.3-5.9 years) from initial laparoscopy, versus a median DSS of 1.3 years for all patients with cytology-only disease across the entire study period[119]. Unsurprisingly, most current guidelines do not recommend surgery for patients with PMGC except with palliative intent for bowel obstruction.

Identifying risk factors for PMGC and prognostic predictive factors may help to target novel therapies towards appropriate patient groups. Primary tumour characteristics associated with peritoneal metastases include advanced T-stage (Eindhoven Cancer Registry: OR 2.9; 95%CI 2.1-4.0), signet ring cell histology (OR 1.7; 95%CI 1.4-2.2) and linitis plastica phenotype (OR 2.0; 95%CI 1.5-2.8)[118]. No demographic characteristics were found to be independent prognostic predictors when subjected to multivariable analysis in the Memorial Sloan-Kettering study.

Patients with positive peritoneal cytology for cancer cells who subsequently convert to negative cytology after chemotherapy experience significantly better survival compared to patients who remained positive (median DSS 2.5 years vs 1.4 years in the Memorial Sloan-Kettering study; p=0.0003)[119]. This principle forms the basis of ‘conversion therapy’, where treatment is given with the intention of converting unresectable disease into a potentially resectable state. Interestingly, in the same study, gastrectomy did not improve outcomes in patients who had converted from positive to negative peritoneal cytology. This observation must be interpreted cautiously given the small numbers of patients in this subset (27 in total, of whom 20 underwent gastrectomy), as well as the authors’ admission that patients whose disease improved whilst on chemotherapy tended not to be selected for resection[119].

Rationale

Notwithstanding the historical data discussed above, there remains a need for up-to-date observational data that reflects the UK gastric cancer population and current guidelines for the diagnosis and management of gastric cancer. Although the Eindhoven and Memorial Sloan-Kettering cohorts are demographically more similar to the UK gastric cancer population compared to East Asian cohorts, it is unclear whether their findings are applicable to the current UK clinical context. Clinical practice has undergone a series of changes over the past two decades. Diagnostic and referral pathways have been refined, even though the available therapeutic modalities for PMGC have seen

little change. Meanwhile, updated guidelines have narrowed the pool of patients eligible for gastrectomy: whereas patients with positive peritoneal cytology were historically considered surgical candidates in some centres, they are now classified as having metastatic ('MI') disease [P17]. Finally, changes to systemic chemotherapy regimens may have improved outcomes even in patients with metastatic disease.

AIMS AND OBJECTIVES

This chapter aims to characterise a representative sample of UK-based patients with peritoneal metastasis of gastric cancer (PMGC) so as to identify demographic, disease and treatment characteristics associated with poor outcomes. It is hoped that the findings will highlight unmet needs of this patient population in terms of morbidity and quality of life, and help to determine the suitability of novel therapeutic strategies for patients with PMGC.

Specific objectives are as follows:

1. To characterise a UK-based cohort of patients with peritoneal metastasis of gastric cancer (PMGC) in terms of baseline patient and disease characteristics.
2. To identify baseline characteristics associated with PMGC compared to gastric cancer without peritoneal disease.
3. To describe survival in patients with PMGC and to identify baseline patient and disease characteristics associated with poor survival.
4. To compare survival in patients with PMGC treated with palliative chemotherapy versus best supportive care after adjustment by the propensity score.
5. To compare rates of disease-related complications in patients with peritoneal metastasis vs patients without peritoneal metastasis, excluding patients undergoing gastrectomy with nominally curative intent.
6. To compare rates of complications related to palliative chemotherapy in patients with peritoneal metastasis vs patients without peritoneal metastasis, excluding patients undergoing gastrectomy with nominally curative intent.

METHODS

Study design, setting and study population

Cases for inclusion were identified from the cohort used for the predictive model described in Chapter 2. This cohort included all patients with a formal diagnosis of gastric or Siewert III gastro-oesophageal junction adenocarcinoma treated at or referred to the Norfolk and Norwich University Hospital between February 2011 and June 2021.

For the purposes of this chapter, PMGC was defined as synchronous peritoneal metastasis found on staging investigations performed at the time of cancer diagnosis. This definition does not include patients who subsequently developed peritoneal metastasis on disease progression or recurrence following surgery, or patients who did not undergo staging investigations. The decision to restrict analysis to synchronous peritoneal disease was intentional due to incomplete and inconsistent data on cancer recurrence across the cohort.

Outcomes

The primary outcome measures for each of the study objectives are as follows:

- Objectives 1-2: Not applicable.
- Objectives 3: Overall survival defined as survival from cancer diagnosis to death from any cause.
- Objective 4: Rate of overall survival, defined as above, at 1 year from cancer diagnosis.
- Objective 5: Aggregate rate of pre-defined disease-related complications (perforation, intestinal obstruction, biliary obstruction, urinary tract obstruction, clinically significant ascites and pleural effusion) necessitating hospital admission and/or treatment in an acute-care setting.
- Objective 6: Rate of chemotherapy-related adverse events graded 3 or above according to the Common Terminology Criteria for Adverse Events (CTCAE).

Case ascertainment and clinical measurements

As described in Chapter 2, a medical gastroenterologist reviewed each set of electronic health records to ascertain eligibility for inclusion and collated data for entry into the database. The last date of data collection, on which the vital status of all included patients was re-ascertained, was 30 June 2023. This therefore represents the date of last follow-up.

Exposures and covariates

In addition to baseline patient and disease characteristics detailed in Chapter 2 and treatment modalities received, data relating to hospital admissions (including day-case admissions) for the following predefined disease-related complications were obtained from electronic health records:

- Perforation of the gastro-intestinal tract
- Intestinal obstruction (not including gastro-oesophageal junction obstruction or gastric outlet obstruction caused by the primary tumour)
- Biliary obstruction due to compression from metastatic disease
- Urinary tract obstruction due to compression from metastatic disease
- Clinically significant malignant ascites requiring aspiration or drainage
- Clinically significant pleural effusion requiring aspiration or drainage

Statistical analysis

Descriptive data (objectives 1-2) were reported in terms of frequencies and proportions for categorical values, means with 95% confidence intervals for continuous variables following a normal distribution, and medians with interquartile ranges for non-normally-distributed continuous variables.

Differences between groups (objectives 3-6) were evaluated using the Chi-square test for binary variables, logistic regression for multilevel categorical variables, Student's t-test for continuous variables following an independent distribution, and the Mann-Whitney U-test for non-normally distributed continuous variables. Statistical significance was defined as a p-value equal to or less than 0.05.

Overall survival was estimated using Kaplan-Meier methodology (objectives 3-4). Associations between patient, disease or treatment characteristics and overall survival were evaluated using Cox proportional regression models (objective 3). Propensity score methods were used to adjust for confounding factors that may predispose patients towards treatment with palliative chemotherapy or best supportive care and also influence survival (objective 3). These methods are described in detail in chapter 3 and combine trimming with inverse probability of treatment weighting by the propensity score.

All statistical analyses were performed using STATA Version 17.0 MP (StataCorp, College Station, Texas, USA).

RESULTS

Clinical characteristics

Within a cohort of 540 patients with gastric or Siewert III gastro-oesophageal junction adenocarcinoma, 140 patients were found to have synchronous peritoneal metastasis at the time of initial staging. 385 did not have peritoneal disease at diagnosis whilst staging investigations were not performed in 15 patients. Baseline characteristics of patients with and without peritoneal disease at initial staging are compared in Table 6.1.

Table 6.1: Characteristics of patients with peritoneal metastasis vs no peritoneal metastasis at the time of gastric cancer diagnosis

	Peritoneal metastasis (n=140)	**No peritoneal metastasis (n=385)**
Age (median, IQR)	75.8 (64.7-82.3)	77.5 (71.0-83.2)
Gender (n, %)		
Male	92 (65.7%)	278 (72.2%)
Female	48 (34.3%)	107 (27.8%)
GOJ involvement, Siewert III (n,%)	31 (22.1%)	104 (27.0%)
Cardiovascular Disease (n, %)	32 (22.9%)	121 (31.4%)
Previous myocardial infarction	13 (9.3%)	43 (11.2%)
Emergency Presentation (n, %)	15 (10.7%)	72 (18.7%)
ECOG Performance Status (n, %)		
0	37 (26.4%)	115 (29.9%)
1	54 (38.6%)	131 (34.0%)
2	27 (19.3%)	66 (17.1%)
3	16 (11.4%)	51 (13.2%)
4	1 (0.7%)	3 (0.8%)
Not recorded	5 (3.6%)	19 (4.9%)
Documented smoking history (n, %)		
Documented current smokers	12 (8.6%)	53 (13.8%)
Documented ever smokers	57 (40.7%)	195 (50.6%)
Linitis Plastica (n,%)	38 (27.1%)	24 (6.2%)
Signet ring cell histology (n, %)	54 (40.9%)	87 (23.3%)
Extraperitoneal solid organ metastasis (n, %)		
Status at end of follow-Up (n,%)		
Alive	1 (0.7%)	61 (15.8%)
Dead	139 (99.3%)	324 (84.2%)

** Missing/unknown values include patients staged as Tx or Nx.*

Peritoneal disease was significantly associated with linitis plastica (RR 4.35, 95%CI 2.71–6.99; p<0.0001) and the presence of signet ring cells (RR 1.76, 95%CI 1.34–2.32; p=0.0001). Unexpectedly, patients with peritoneal metastasis were less likely to be diagnosed with gastric cancer following an emergency presentation, perhaps reflecting a more insidious disease course leading to later-stage diagnosis (RR 0.57, 95%CI 0.34–0.97; p=0.0295). There were no significant differences in age, sex, gastro-oesophageal junction involvement, previous cardiovascular disease, ECOG performance status or smoking status between patients with and without peritoneal disease.

Treatment modalities for PMGC

72 patients with PMGC (51.4%) were treated with palliative chemotherapy. Survival outcomes with respect to palliative chemotherapy are presented in the next section. Amongst patients with PMGC, patients receiving chemotherapy were significantly younger than those not receiving chemotherapy (median 71.8 vs 81.8 years, p<0.0001). Compared to patients not receiving chemotherapy, patients treated with palliative chemotherapy were less likely to have been diagnosed following an emergency presentation (RR 0.36, 95%CI 0.13–1.01; p=0.01) and less likely to have cardiovascular disease (RR 0.54, 95%CI 0.32–0.93; p=0.009). No significant differences were observed between the two groups with respect to gender, gastro-oesophageal junction involvement or frequency of extraperitoneal solid organ metastasis [Table 6.2].

Table 6.2: Characteristics of patients with peritoneal metastasis treated with palliative chemotherapy vs no chemotherapy

	Chemotherapy (n=72)	**No chemotherapy (n=68)**
Age (median, IQR)	71.8 (58.9-76.2)	81.7 (75.5-85.6)
Gender (n, %)		
Male	49 (68.1%)	43 (63.2%)
Female	23 (31.9%)	25 (36.8%)
GOJ involvement, Siewert III (n,%)	20 (27.8%)	11 (16.2%)
T-stage (n, %)		
2	11 (1.4%)	0
3	28 (38.9%)	21 (30.9%)
4	39 (54.2%)	25 (36.8%)
Not recorded	4 (5.6%)	22 (32.4%)
Cardiovascular Disease (n, %)	10 (13.9%)	22 (32.4%)
Previous myocardial infarction	3 (4.2%)	10 (14.7%)
Emergency Presentation (n, %)	3 (4.2%)	12 (17.7%)
ECOG Performance Status (n, %)		
0	28 (38.9%)	9 (13.2%)
1	38 (52.8%)	16 (23.5%)
2	6 (8.3%)	21 (30.9%)
3	0	16 (23.5%)
4	0	1 (1.5%)
Not recorded	0	5 (7.4%)
Documented smoking history (n, %)		
Documented current smokers	7 (9.7%)	5 (13.8%)
Documented ever smokers	34 (47.2%)	23 (33.8%)
Linitis Plastica (n,%)	23 (31.9%)	15 (22.1%)
Signet ring cell histology (n, %)	28 (40.0%)	26 (41.9%)
Extraperitoneal solid organ metastasis (n, %)	19 (26.4%)	21 (30.9%)

** Missing/unknown values include patients staged as Tx or Nx.*

One patient underwent emergency subtotal gastrectomy following an emergency admission with subacute small bowel obstruction, whereupon she was found to have peritoneal disease and subsequently received palliative chemotherapy (survival 484 days). In another patient, peritoneal disease was identified during elective gastrectomy (survival 392 days). The same patient was subsequently treated with palliative chemotherapy and also underwent palliative bypass surgery for

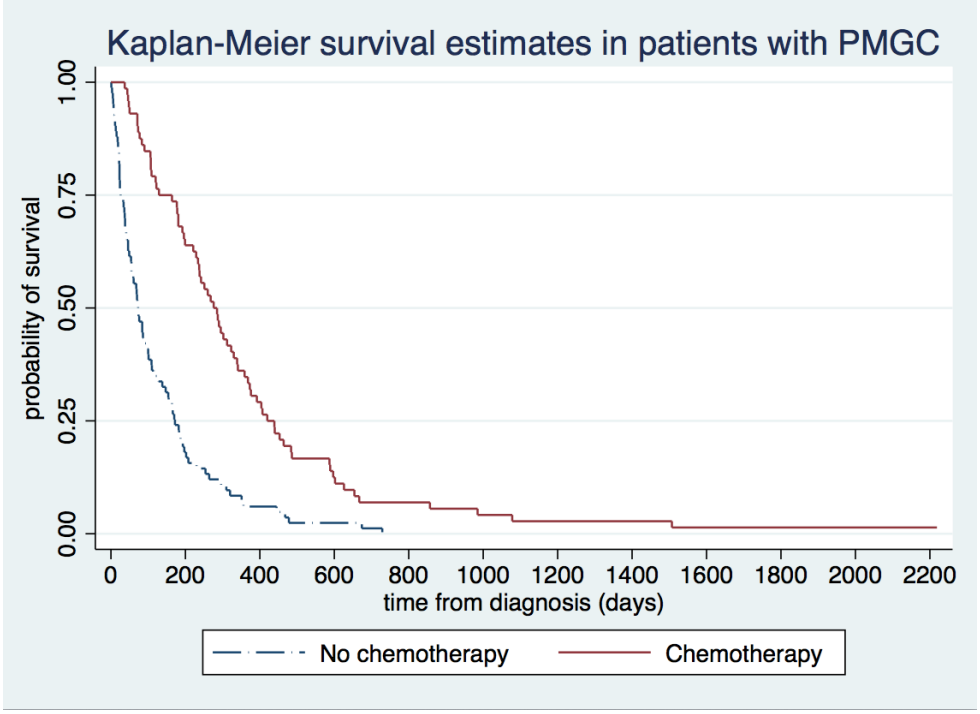
caecal perforation. Three patients underwent palliative gastrojejunostomy (survival 166, 264, 674 days), none of whom received palliative chemotherapy.

Palliative stenting was performed in 43 patients with PMGC (30.7%) whilst 19 patients (13.6%) received palliative radiotherapy.

Overall survival

Using Kaplan-Meier survival curves, median overall survival across all patients with peritoneal metastasis at the time of gastric cancer diagnosis was estimated at 164 days (IQR 61–310). Estimated median overall survival in patients treated with chemotherapy was 276 days (IQR 129–420) compared to 71 days (IQR 33–164) in patients who did not receive chemotherapy (unadjusted HR 0.31; 95%CI 0.22–0.45; p=0.001) [Figure 6.1]. Median overall survival was similar in patients with Siewert III cancers (164 days; IQR 70–368) and patients with non-cardia gastric cancers (166 days; IQR 55–310).

Figure 6.1: Survival curves in patients with PMGC stratified by treatment with palliative chemotherapy



	Median Overall Survival	Interquartile Range
Palliative chemotherapy (n=72)	276 days	129–420
No chemotherapy (n=68)	71 days	33–164

Predictive factors for overall survival

Associations between patient, disease, treatment, pathological and postoperative characteristics and all-cause mortality in univariate analysis are summarised in Table 6.3. Perhaps due to small sample size, only performance status and treatment with palliative chemotherapy were identified as predictive factors for overall survival.

Table 6.3: Univariate associations with all-cause mortality in patients with PMGC.

Characteristic	Hazard Ratio (95% CI)	p-value
Age per year	1.01 (0.99–1.02)	0.273
Age >80 years at diagnosis	1.34 (0.95–1.90)	0.100
Sex (female)	1.25 (0.88–1.78)	0.214
Current smoker at diagnosis	0.71 (0.38–1.30)	0.264
ECOG Performance Status (relative to PS 0)		
Performance Status 1	1.20 (0.79–1.84)	0.394
Performance Status 2	4.16 (2.39–7.24)	**<0.001**
Performance Status 3	10.46 (5.43–20.14)	**<0.001**
Performance Status 4	189.73 (16.56–2174.30)	**<0.001**
Cardiovascular disease	1.41 (0.94–2.10)	0.093
OGJ involvement, i.e., Siewert III	1.04 (0.69–1.55)	0.856
Diagnosis following emergency admission	1.59 (0.92–2.75)	0.094
T_4 relative to T_3 tumours*	1.19 (0.82–1.73)	0.368
N-stage (relative to N_0)		
N_1	1.09 (0.58–2.07)	0.783
N_2	1.14 (0.58–2.22)	0.704
N_3	1.66 (0.94–2.92)	0.078
Linitis plastica	0.99 (0.68–1.44)	0.954
Signet ring cell histology	0.87 (0.61–1.23)	0.432
Palliative chemotherapy	0.31 (0.22–0.44)	**<0.001**
Extraperitoneal solid organ metastasis	1.19 (0.81–1.75)	0.367

Note: All characteristics associated with a P-value <0.05 (highlighted in bold) were included in multivariable analysis.
* T_2 tumours not analysed as n=1.

Effects of palliative chemotherapy on overall survival following weighting by the propensity score

A propensity score model [Table 6.4] with respect to palliative chemotherapy was generated with ECOG performance status (multilevel categorical variable), age (continuous variable) and diagnosis following emergency presentation as covariates, and overall survival at 1 year as the endpoint.

Table 6.4: Logistic regression model producing propensity score with respect to palliative chemotherapy in PMGC (probability of receiving palliative chemotherapy, analysed in patients with PMGC)

Characteristic	Odds Ratio (95% CI)	z	p-value
ECOG performance status (relative to PS 0)			
Performance Status 1	1.112 (0.391–3.163)	0.20	0.842
Performance Status 2	0.116 (0.032–0.412)	-3.33	0.001
Age at diagnosis (continuous variable)	0.918 (0.876–0.964)	-3.49	<0.001
Emergency presentation	0.353 (0.071–1.761)	-1.27	0.204

$\chi 2 = 48.36$, $p<0.0001$

Model developed in a total of 123 patients on a complete case analysis basis. STATA automatically excluded ECOG PS3 and PS4 from the model as these characteristics 'perfectly predicted' management without chemotherapy, i.e. best supportive care alone.

98 patients were included in the analysis after trimming by the propensity score: 71 patients receiving palliative chemotherapy and 27 patients treated with best supportive care. Even after trimming, patients receiving palliative chemotherapy remained significantly younger on average (median age 71.8 vs 79.2; p=0.003) but proportions of patients at each performance status were approximately equal between the two groups. Median overall survival after exclusion of patients in non-overlapping tails of the propensity score distribution was 285 days (IQR 129–439) in patients treated with chemotherapy and 154 days (IQR 68–230) in patients not receiving chemotherapy. When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 1 year was 10.49 (95%CI 2.44–45.13; p=0.002).

Given the significant difference in age between the two groups even after trimming, the above comparison was repeated with analysis limited to patients aged ≤80 years at diagnosis. After exclusion of patients aged >80 years followed by trimming, 71 patients remained in the analysis: 56 patients receiving palliative chemotherapy and 15 patients treated with best supportive care. Median age was 67.4 years in the palliative chemotherapy group and 69.7 years in the best supportive care group (p=0.481). When inverse probability by treatment weighting was applied, the odds ratio for overall survival at 1 year was 4.25 with chemotherapy but this did not achieve statistical significance despite a clear trend, perhaps due to insufficient power (95%CI 0.50–36.10; p=0.186).

Disease-related complications

Among patients not undergoing gastrectomy, documented rates of predefined disease-related complications necessitating hospital admission or secondary-care intervention are detailed in Table 6.5. Within this group of patients, PMGC was associated with a two-fold increase in the overall risk (RR 2.12, p<0.001) of hospital admission or secondary-care intervention relating to any of the

predefined disease-related complications. This was mostly due to significantly higher rates of intestinal obstruction (RR 3.01, p=0.007) and ascites requiring drainage (RR 5.72, p<0.001).

Table 6.5: Rates of predefined disease-related complications in patients with peritoneal metastasis of gastric cancer (PMGC) and patients without peritoneal metastasis (No PM) at the time of cancer diagnosis, excluding patients undergoing surgery with curative intent

	PMGC (n=138)	**No PM (n=237)**	**RR (95%CI)**	***p*-value**
Perforation of the GI tract	3 (2.5%)	6 (2.5%)	0.86 (0.22–3.38)	0.827
Intestinal obstruction*	14 (10.1%)	8 (3.4%)	3.01 (1.29–6.98)	**0.007**
Biliary obstruction	8 (5.8%)	10 (4.2%)	1.37 (0.56–3.40)	0.491
Urinary tract obstruction	5 (3.6%)	3 (1.3%)	2.86 (0.69–11.79)	0.128
Ascites requiring intervention	20 (14.5%)	6 (2.5%)	5.72 (2.36–13.91)	**<0.001**
Pleural effusion requiring intervention	3 (2.2%)	3 (1.3%)	1.71 (0.35–8.39)	0.499
Any complication requiring hospital admission/secondary care intervention	*42 (30.4%)*	*34 (14.4%)*	*2.12 (1.42–3.17)*	***<0.001***

** Excludes gastro-oesophageal junction obstruction or gastric outlet obstruction caused by the primary tumour.*

Excluding patients undergoing gastrectomy, patients with PMGC were younger than patients without PM (median age 76.1 vs 79.6; p=0.002) and were less likely to have an ECOG performance status ≥2 (33.1% vs 49.6%; p=0.003). Given these significant differences in baseline characteristics, the findings above could be interpreted in two ways: either patients with PMGC suffer from more disease-related morbidity despite being younger and fitter on average, or the findings may reflect a tendency of younger and fitter patients to attend hospital with disease complications whilst older and frailer patients may prefer to receive palliative treatment at home. Without access to primary care and palliative care records, it is difficult to determine which explanation is more likely to account for the findings.

Chemotherapy-related complications

Amongst patients not undergoing gastrectomy, rates of chemotherapy-related complications graded ≥3 according to the Common Terminology Criteria for Adverse Events were 2.17% in patients with PMGC and 6.75% in patients without peritoneal disease at the time of cancer diagnosis. Although these figures appear to suggest a trend towards fewer chemotherapy-related complications in patients with PMGC (RR 0.32, RR 0.10–1.09; p=0.051), they are derived from acute care records alone and likely to be gross underestimates of the true prevalence of chemotherapy-related complications. As such, no conclusions can be drawn from this observation.

Summary of key findings

Median overall survival in patients with PMGC was 164 days (IQR 61–310). PMGC was significantly associated with linitis plastica (RR 4.35, 95%CI 2.71–6.99; p<0.0001) and the presence of signet ring cells (RR 1.76, 95%CI 1.34–2.32; p=0.0001). 51.4% of patients with PMGC were treated with palliative chemotherapy; compared to patients with PMGC not receiving chemotherapy, these patients tended to be younger and were less likely to have been diagnosed following an emergency presentation.

Median survival was 276 days in patients receiving palliative chemotherapy and 71 days in patients not receiving chemotherapy. Following trimming and inverse probability of treatment weighting by the propensity score, palliative chemotherapy was associated with an odds ratio for 1-year overall survival of 10.49 (p=0.002). When patients aged >80 years were excluded, applying the same adjustments based on the propensity score resulted in a smaller odds ratio for 1-year survival of 4.25 which was no longer statistically significant (p=0.186).

In non-surgical patients, PMGC was associated with a higher aggregate frequency of disease-related complications necessitating hospital admission or secondary-care intervention (RR 2.12, p<0.001). Patients with PMGC were significantly younger and fitter than non-surgical patients without peritoneal disease and perhaps more likely to opt for intervention rather than palliation at home, which may represent a potential confounder.

DISCUSSION

General Observations

This study attempted to characterise a sample of patients with PMGC as a subset of a larger cohort of patients diagnosed with gastric and Siewert III adenocarcinomas in a UK-based setting. The underlying intentions for performing this analysis were threefold: to describe a ‘forgotten’ population of patients with limited management options, to evaluate for characteristics in this patient population that may explain poor survival other than the mere presence of peritoneal disease, and to highlight the unmet needs of this population in terms of morbidity and quality of life.

The survival outcomes described here are in line with those from historical cohort studies. As in the Eindhoven Cancer Registry and Memorial Sloan-Kettering study, linitis plastica and signet ring cells were strongly associated with PMGC, whilst no demographic characteristics were identified as predictors of survival. Palliative chemotherapy conferred a small but significant survival benefit, the value of which depends on the individual patient’s circumstances and priorities. However, efforts to

construct predictive models and to generate meaningful findings regarding disease complications and morbidity were hampered by small sample size and the absence of primary care and palliative care data.

Main Findings and Comparisons to Previous Studies

Baseline characteristics of patients with PMGC on initial staging investigations ('synchronous peritoneal disease') were broadly reflective the entire cohort. There were no obvious demographic differences distinguishing patients with PMGC from those without peritoneal disease. In terms of disease characteristics, patients with PMGC were more likely to have linitis plastica and signet ring cells, consistent with previous observational cohort studies performed in both Asian and Western settings[124].

Median overall survival was 5.3 months across all patients with PMGC on initial staging, and 9 months in patients treated with palliative chemotherapy. These figures are generally in keeping with survival outcomes seen in previous studies. A meta-analysis of the REAL-2 and ML17032 trials performed in the early 2000s (in the UK and East Asia respectively) reported a median overall survival of 9.9 months in patients treated with ECF[19,125]. The slightly worse median survival seen in the present study may be explained by the fact that this cohort was older on average: the median age of patients in this cohort offered palliative chemotherapy for PMGC was 71.8 years, compared to medians of 56 and 65 years in the REAL-2 and ML17032 trials[125]. A retrospective analysis of patients with metastatic gastric adenocarcinoma in the Taiwanese Cancer Registry Database between 2008-2015 found a median overall survival of 6.2 months across all patients and 7.0 months in patients treated with chemotherapy alone[126]. The Taiwanese figures indicate that in the context of PMGC, prognosis is equally poor in western and Asian populations despite significant differences in clinical practice. In fact, a considerable proportion (25%) of patients with metastatic cancer in the Taiwanese registry were offered surgery either alone or in combination with chemotherapy.

In terms of survival outcomes, an ECOG performance status of 2 or above was associated with significantly worse overall survival in the present cohort. Peritoneal metastasis appeared to confer a detrimental effect that is consistent across all age groups. Patients with PMGC were significantly younger than non-surgical patients without peritoneal disease in this cohort. This finding may be attributed to the inclusion of older patients without metastatic disease but deemed too frail for surgery in the latter group. However, the presence of peritoneal disease itself was also associated with younger age in previous cohort studies[124], suggesting that younger patients with gastric cancer may be more likely to suffer from more aggressive disease phenotypes.

As expected, palliative chemotherapy conferred an improvement in overall survival. However, the survival benefit with chemotherapy was reduced following weighting by the propensity score and particularly after patients aged >80 years were excluded to achieve a better balance between treatment and non-treatment groups. A previous Cochrane meta-analysis had demonstrated a clear survival advantage conferred by palliative chemotherapy compared to best supportive care in the setting of advanced gastric cancer[67]. The outstanding questions are whether some patient groups stand to benefit from palliative chemotherapy more than others, and whether a small survival advantage measured in months outweighs treatment-associated burden. A Japanese retrospective cohort analysis showed that use of oral chemotherapy (S-1) was in fact associated with worse survival in patients with a performance status of 2 and 'histologically or cytologically proven inoperable gastric cancer'[81]. Conversely, the GO2 trial discussed in Chapter 3 demonstrated good tolerability and improved outcomes using a less intense doublet regimen in older and frail patients[10].

Limitations

This study was limited by its small sample size and likely incomplete data resulting in underestimates of disease- and treatment-related complications. Ethical approval and access permissions only extended to medical records maintained at one acute hospital trust. Although patient numbers were enhanced by the trust's status as a regional tertiary referral centre, primary care and palliative care records were unavailable for research purposes. The study was therefore only able to produce meaningful data relating to overall survival, an endpoint which has already been covered in previous larger studies, whilst falling short of its stated aims to explore morbidity and quality of life.

This chapter set out to characterise the natural history of patients with PMGC. Given its limitations, however, we were unable to map out a complete picture of the events and disease mechanisms leading up to death. Morbidity could not be fully assessed without access to primary care and palliative care data. Complications resulting in hospital admission were used as a surrogate measure for morbidity. However, absolute numbers of these events were unexpectedly low. It is likely that the vast majority of both disease-related complications and treatment-related adverse events were in fact managed in the community. Hence, no conclusions can be drawn from this study regarding the effects of either peritoneal metastasis or its management on patients' quality of life.

Efforts to construct a predictive model of survival in patients with PMGC were primarily hindered by the small sample size of 140 patients. ECOG performance status and treatment with palliative chemotherapy were the only variables associated with survival. The dataset of this small retrospective cohort study reflects actual clinical practice in which baseline patient characteristics inevitably affect treatment decisions, investigations performed and even the availability of data in medical records.

Comparisons between groups of patients with differing baseline characteristics or patients treated with different strategies are therefore difficult and subject to confounding. Patients considered to be 'fitter' and patients with fewer comorbidities were naturally more likely to be offered chemotherapy. Even after efforts to adjust for confounding by using propensity score methods, a significant imbalance in age remained between treatment and non-treatment groups.

Finally, for practical reasons, the scope of this chapter was limited to peritoneal metastasis identified at the time of cancer diagnosis. Rates of disease progression to involve the peritoneum are impossible to measure accurately in a real-world setting where patients are not monitored for progression at fixed intervals. As investigations are only performed in cases where they are likely to alter management, it is conceivable that detected frequencies of peritoneal progression will be higher in younger and fitter patients undergoing active treatment compared to older and frailer patients on best supportive care. For this reason, the current dataset did not allow for the construction of a predictive model for peritoneal progression that could be used to target high-risk patients for pre-emptive intraperitoneal chemotherapy.

Implications for treatment and future research

Notwithstanding the limitations described, the results of this study indicate that all patients with PMGC suffer from poor outcomes regardless of their baseline characteristics, and chemotherapy is independently associated with a small but significant improvement in survival. This is not to imply that all patients should be persuaded to undergo chemotherapy. Any survival benefit must be balanced against the effects of chemotherapy on quality of life, which this study was unable to quantify. Furthermore, it should be highlighted that even after chemotherapy, median overall survival in patients with peritoneal metastasis was found to be little more than 9 months. The value attributed to these additional few months of life will be individual to each patient, and may not necessarily outweigh any additional morbidity associated with chemotherapy. Treatment decisions therefore need to be made on a case-by-case basis, with the patient's own perspective given foremost consideration.

On the basis of the results described, no definitive recommendations can be made regarding patient groups to target for intraperitoneal chemotherapy. A case might be made, however, for neoadjuvant or prophylactic administration of intraperitoneal chemotherapy to patients with linitis plastica and tumours with serosal involvement, both of which have previously been shown to confer a high risk of disease progression into the peritoneum[124]. This will be further explored in Chapter 7.

It is difficult to conceive of a randomised controlled trial in patients with PMGC within a UK-based setting. Any prospective trial design involving this population is highly unlikely to recruit a sufficient number of participants in the UK given the small absolute numbers of patients with PMGC in the UK and their extremely limited life expectancies. Large retrospective cohort studies therefore represent the only practicable study design for characterising the natural history of patients with peritoneal disease. A multicentre, multidisciplinary collaborative effort across acute care, palliative care and primary care services is necessary to ensure the requisite sample size and data. The results of such an analysis will equip clinicians and patients with the evidence required for difficult treatment decisions that give due consideration to both quality and duration of life.

At the same time, prospective studies on a national or intentional level are needed to construct a predictive model for the development of peritoneal metastasis in patients without overt peritoneal disease at cancer diagnosis. This argument derives from the observation above that follow-up investigations are not performed without a specific indication in routine clinical practice. Addressing research questions relating to disease progression would necessitate additional investigations and data collection purely for research purposes, on top of those performed in standard clinical practice. Such a study will therefore require research-specific consent and additional resources in terms of funding, manpower and equipment.

Conclusion

Survival in patients with PMGC is poor regardless of treatment offered or baseline patient characteristics. Although palliative chemotherapy improves survival, this survival benefit is typically measured in months. Identification of adverse prognostic factors in a UK-based population with PMGC is difficult due to a combination of low patient numbers and relatively small absolute differences in survival between patients with the best outcomes and worst outcomes. PMGC was associated with a higher rate of disease-related complications requiring hospital admission or secondary-care intervention. However, numbers of such events in the current dataset are likely to underestimate the true degree of morbidity. Multicentre and perhaps multinational studies with engagement from researchers working in primary and palliative care settings are necessary to fully map the natural history of PMGC. Nonetheless, there is clearly an unmet need for novel therapeutic strategies in this patient group, as well as strategies to prevent or delay the development of peritoneal disease in patients with gastric cancer. Intraperitoneal chemotherapy may help to fulfil these unmet needs in carefully selected patients, and will be discussed in greater detail in the next chapter.

CHAPTER 7- Conclusion and future directions

GENERAL DISCUSSION: KEY CONCLUSIONS AND LIMITATIONS

Overarching aims revisited

This thesis sought to describe current outcomes in patients with gastric adenocarcinoma in the United Kingdom, identify factors associated with poor outcomes, and highlight unmet needs to guide future research.

Despite recent advances in treatment, the prognosis of gastric cancer in the UK remains poor. The UK has played a leading role in oesophagogastric cancer research, including the seminal MAGIC trial of perioperative chemotherapy. However, trial cohorts are not necessarily representative of 'real-world' cancer populations. With the obvious exception of the GO2 trial, clinical trials have tended to recruit younger patients with fewer comorbidities. Much of our knowledge of gastric cancer populations is derived from East Asian studies as well as historical western models from the 1990s and early 2000s. Findings from Asian studies may not be directly applicable to western cancer populations where late-stage diagnosis is more common and prognosis tends to be poorer even following treatment with curative intent[127].

Received wisdom from previous decades has been made obsolete by epidemiological shifts and advances in treatment. The overall incidence of gastric cancer has declined thanks to widespread eradication of *Helicobacter pylori* and improved food preservation techniques. Conversely, tumours involving the gastro-oesophageal junction (GOJ) now account for a growing proportion of both oesophageal (Siewert I and II) and gastric (Siewert III) cancers due to rising rates of obesity and gastro-oesophageal reflux disease[128]. Finally, gastric cancer is increasingly a disease of the elderly, in keeping with overall population trends in the western world and East Asia.

Unsurprisingly, tailoring management strategies to the individual patient often proves challenging. Although it is clear from research evidence that newer chemotherapy regimens and novel treatment strategies improve survival, absolute survival benefit is often measured in months especially in advanced gastric cancer. Aggressive phenotypes including peritoneal carcinomatosis and linitis plastica (which is associated with peritoneal disease) generally carry a poor prognosis regardless of treatment. Older and frail patients may benefit even less from treatment and any survival advantages associated with treatment must be weighed up against treatment-associated morbidity and considered in the context of quality of life.

From the clinical landscape described here, a number of gaps in research and knowledge were identified and guided the development of the thesis:

First, an up-to-date model prognostic model of survival in western patients with gastric cancer was lacking. Existing models were mostly derived from either Asian or historical western cohorts, and chiefly concerned with postoperative survival following resection with curative intent. Chapter 2 set out to construct a predictive model for 1-year overall survival in a cohort of patients with gastric cancer at a regional centre in England, using baseline characteristics collected in routine clinical practice.

Second, limited data exist to guide treatment selection in older patients and frail patients. In Chapter 2, the cohort under investigation was found to be older compared to not only clinical trial populations but also the national average. Chapter 3 further explored treatment-associated outcomes in patients aged over 80 years and in patients with an ECOG performance status ≥2, harnessing the relatively large numbers of patients meeting these criteria by the standards of a single-centre retrospective cohort.

Third, the long-term prognosis of gastric cancer even following curative-intent treatment remains poor in western populations compared to East Asian populations. Strategies to identify patients at risk of cancer recurrence and to reduce the risk of recurrence are lacking. Chapter 4 analysed risk factors associated with recurrence in patients undergoing surgery with curative intent. Chapter 5 explored the existing evidence for the use neoadjuvant chemotherapy in patients with non-metastatic linitis plastica, a disease phenotype associated with a particularly high risk of peritoneal recurrence.

Fourth, patients with peritoneal metastasis of gastric cancer (PMGC) are very much a ‘forgotten’ population in the current body of research evidence. Chapter 6 described characteristics and outcomes in patients with PMGC within the local cohort, so as to highlight their unmet needs and guide future research in this population.

This thesis largely succeeded in its more straightforward aims of describing survival and identifying adverse prognostic factors, both in the cohort as a whole and in under-researched patient groups of interest. Unfortunately, the underlying intention of designing a patient-centred framework for individualised treatment decisions remains a distant goal. Ideally, such a framework would allow patients and clinicians to weigh up treatment-associated benefit against tolerability and adverse effects in a context where survival and quality of life are considered side-by-side. The work in this thesis was limited to retrospective data collected in routine clinical practice and stored in acute hospital care records. Due to the local organisation of healthcare, low-grade symptoms (whether disease-related or treatment-related) as well as ‘best supportive care’ are often managed in primary

care or palliative care settings. Health records from these settings were both inaccessible to researchers employed at the acute hospital and not covered by ethical approval granted for the research described herein. The main shortcomings of this thesis are therefore the absence of meaningful non-survival outcomes as well as the potential for confounding and selection bias inherent in all retrospective studies.

Outcomes of gastric cancer in the study cohort

Findings from this study cohort underscore the poor prognosis of patients with gastric cancer despite treatment in accordance with the current standards of care. Median overall survival was 302 days across the whole cohort and 4.24 years in patients undergoing gastrectomy with curative intent. With a median age of 77.44 years, patients in this cohort were older on average compared to cohorts in previous modelling studies and clinical trials as well as the national average. Characteristics and outcomes in patients treated with curative intent were largely consistent with those from the National Oesophago-Gastric Cancer Audit[114], although a direct comparison of survival is not possible due to differing outcome measures and definitions of survival. Surgery and chemotherapy were associated with improved survival across almost all patient groups; older but fit patients can and do benefit from surgery and potentially other aggressive management strategies. Conversely, the balance of risks is not always in favour of intervention in frail patients and patients with a poor performance status. In patients with peritoneal metastasis of gastric cancer, palliative chemotherapy improves survival but this survival benefit is typically measured in months and must be weighed against other patient priorities.

The thesis characterised a consecutive, unselected cohort of patients referred to the Norfolk and Norwich University Hospital oesophagogastric cancer multidisciplinary team with gastric adenocarcinoma between 2011 and 2021. This included patients with Siewert III adenocarcinomas of the gastro-oesophageal junction, who accounted for 25.4% of the cohort. A particularly notable feature of this cohort was its high median age of 77.44 years compared to the national average of 74 years in the NOGCA State of the Nation Report for 2020-2022[114]. Historical cohorts were markedly younger: the Edinburgh 2002-2004 cohort in Dean et al's prognostic model had a median age of 71 years[12]. Clinical trial participants tend to be younger still, with a median age of 62 years in both the MAGIC and FLOT4 trials[9,60]. The Norfolk area is predominantly suburban and rural. In older age groups, people from minority ethnic backgrounds account for a very small proportion of the local population. Considering these demographics, the findings discussed in this thesis are of greatest relevance to the ageing White European cancer population. They are perhaps less applicable to multiracial urban populations which also tend to be younger.

Benefits of research in the Norfolk population include very low rates of loss to follow-up as well as opportunities to observe outcomes in large numbers of older and frailer people. These qualities may be explained by Norfolk's character as a popular retirement destination and well as the concentration of regional cancer services at a single centre without competing institutions or a sizeable private sector.

Research-related challenges in this population are attributable to the organisation of services in the area coupled with the tendency for older and frailer patients to be managed with best supportive care. As previously explained, symptom control and best supportive care are largely provided in primary and palliative care settings, and associated care records were not available for research purposes. Just under a quarter of the cohort (23.7%) was treated with best supportive care alone or died before any intervention could be performed. In patients offered palliative chemotherapy, hospital care records only reflect periods of 'active treatment' and often do not cover the weeks or months leading up to death. In patients treated with curative intent, recurrence may not be documented if a patient is subsequently deemed too frail to benefit from investigation and hence not referred back to oncology services.

Dates of death regardless of location are documented in acute hospital records, allowing for analysis of overall survival. However, causes of death are not always clear and progression-free survival and recurrence-free survival could not be reliably assessed. In patients treated with palliative intent, it would perhaps be safe to assume that cancer was either directly or indirectly (e.g. via aspiration pneumonia or pulmonary embolism) the cause of death. The patchy nature of oncological follow-up in older patients is arguably of greater concern in the analysis of outcomes following surgical resection with curative intent. Median overall survival from diagnosis in patients undergoing surgery was 4.24 years. However, this figure reflects all-cause mortality in a predominantly male cohort of patients with a median age of 74.5 years at diagnosis, in a country where life expectancy for males was 79 years in 2018-2020. Postoperative cancer recurrence was treated as a dichotomous outcome. In the context of a retrospective study using data from normal clinical practice, time-to-recurrence could not be reliably compared between patients with recurrence identified on routine surveillance, patients presenting acutely with symptoms of cancer recurrence, and frailer patients who may have died following undiagnosed recurrence.

Retrospective studies are inherently subject to confounding, selection bias and immortal time bias. The first two problems can be discussed together: in the present context, most confounding stems from the fact that baseline characteristics assumed to indicate a poorer prognosis are also likely to reduce a patient's chances of being offered aggressive treatment. As a consequence, the effects of

treatment are not always easy to disentangle from those of baseline characteristics with prognostic significance. Logistic regression modelling and propensity score methodology were used to address these issues in the work described but remain imperfect workarounds.

Immortal time bias is an inevitable consequence of calculating survival from the point of diagnosis. Defining survival 'from diagnosis to death from any cause' is the only practical approach in a study comparing outcomes of different treatment modalities (or no treatment) in a real-world context. It is also the most sensible approach for predictive models which are intended to aid in decision-making at the point of diagnosis. Previous models where survival was calculated from the point of treatment have been criticised as being "of limited value for treatment decisions, as treatment has largely been completed"[24]. Although this particular criticism does not apply to the definition of survival used throughout this thesis, the issue of immortal time bias arises in its place. Simply put, the very fact that patients who undergo an intervention must survive long enough to be exposed to the intervention introduces a source of bias and may distort comparisons of survival[129].

Immortal time bias must therefore be considered when interpreting and applying the findings in this thesis. In particular, the survival benefits associated with palliative chemotherapy in PMGC (Chapter 6) and curative resection in older patients (Chapter 3), as well as the non-significant trend towards improved survival following palliative chemotherapy in older patients (Chapter 3) are likely to be of a smaller magnitude once immortal time bias is taken into account. Immortal time bias is of lesser concern in the multivariable models in Chapters 2 and 4 since treatment modalities are treated as covariates and not predictive factors in these models.

Accepting these caveats, this thesis demonstrated that older bit fit patients achieve outcomes comparable to those of their younger counterparts and stand to benefit from more aggressive treatment strategies. In Chapter 2's model of 1-year survival, age was not an independent prognostic factor after adjustment for performance status. In Chapter 3, outcomes of surgery in patients aged over 80 were non-inferior to outcomes in younger patients. Although a trend was observed towards reduced overall survival in patients aged over 80 (3.31 years vs 4.32 years), this did not reach statistical significance and reflects all-cause mortality in an elderly population. Rates of significant surgical complications classified as Clavien-Dindo grade 3 or above were no higher in older patients. Age should therefore not serve as a barrier to treatment. A case could be made for this argument to be extended to novel treatment modalities, including those under assessment in clinical trials as well as individual cases where treatment is approved on a named-patient basis.

On the other hand, performance status is clearly a significant consideration. This is readily apparent in multivariable prognostic models. Unfortunately, the number of patients with a poor performance

status undergoing active intervention was insufficient to allow for assessment of treatment-related benefit in this patient group. Furthermore, as discussed in Chapter 3, performance status is not without its drawbacks as a surrogate measure of patient frailty. Frailty scores were not in routine clinical use at the Norfolk and Norwich University Hospital between 2011 and 2021 but have gained increasing acceptance during the intervening years.

Patients with peritoneal disease suffer from poor outcomes regardless of intervention. Although palliative chemotherapy appears to confer a survival benefit even after weighting by the propensity score, this is in most cases a small number of months. Given the possibility of immortal time bias, the true survival benefit associated with palliative chemotherapy may be even smaller. This situation poses a dilemma: novel treatment strategies for PMGC are desperately needed, but survival outcomes are so poor that recruiting patients with PMGC into clinical trials would be incredibly difficult.

Due to previously discussed constraints, this thesis was unable to evaluate non-survival endpoints such as quality of life and disease-related symptoms. Except in cases where disease-related or treatment-related complications result in hospital admission or assessment in the oncology day unit, data relating to quality of life and symptoms are mostly recorded in primary care and palliative care records. This is especially so towards the end of life, as many patients choose to die at home and avoid hospital admission.

Factors associated with poor outcomes

As demonstrated by the predictive model presented in Chapter 2, poor survival outcomes in the UK gastric cancer population are largely a consequence of the high proportion of Stage IV cancers and high degree of frailty evident within this population. Treatment with curative intent is not feasible or appropriate in the majority of UK patients with gastric cancer. Chapter 6 establishes that survival in patients with peritoneal metastasis from gastric cancer (PMGC) is poor regardless of treatment offered or baseline patient characteristics. Indeed, the baseline characteristics of patients with PMGC are not significantly different from those of the gastric cancer population as a whole, and their worse prognosis appears to be directly attributable to peritoneal disease and its complications.

The model in Chapter 2, despite its simplicity, performed favourably in comparison to previous models in terms of both discriminatory ability and calibration[24]. Although it adds little to the current decision-making paradigm, a few key findings emerged from this model. As discussed earlier, age did not emerge as an independent predictor of prognosis. Furthermore, in contrast to historical models and findings from Asian studies which suggested a poorer prognosis in patients with proximal and junctional cancers, tumours involving the GOJ were not associated with a worse prognosis in the

present cohort. This observation was consistent across analyses involving the entire cohort, patients undergoing curative-intent resection and patients with PMGC. Given the increasing numbers of GOJ cancers, the absence of an adverse prognostic association in this cohort will hopefully be of some reassurance to clinicians and patients alike. Potential explanations include recent oncological advances (such as perioperative FLOT chemotherapy) which have been incorporated into standard European practice, as well as the extensive experience in managing oesophageal and GOJ neoplasms in Norwich and perhaps across the UK.

Amongst patients eligible for curative surgery, a chain of associations between emergency surgery and/or upfront surgery without chemotherapy, positive resection margins, nodal involvement and early mortality was demonstrated in Chapter 4. Poor outcomes can therefore be traced back to suboptimal preoperative optimisation. Future studies should explore the role of intraoperative strategies in reducing the risk of recurrence in patients receiving emergency surgery and patients offered upfront surgery for non-emergency reasons.

As linitis plastica is known to be a particularly aggressive phenotype, we felt it was meaningful to investigate whether more aggressive treatment strategies could lead to better outcomes for non-metastatic linitis plastica. The systematic review presented in Chapter 5 found the current evidence base insufficient to answer this question. Even in the potentially curative setting, survival in patients with linitis plastica was poor across all studies. This is even more striking considering that most studies included in the systematic review were performed in East Asia, where better outcomes are typically seen. The analysis performed in Chapter 2 suggests that peritoneal disease largely accounts for the poor prognosis of linitis plastica. Peritoneal involvement was noted in 60.3% of patients with linitis plastica, and linitis plastica was no longer an independent prognostic factor after adjustment for disease stage. As only 3 patients with linitis plastica underwent curative-intent resection (2 in an emergency setting) over the study period, treatment outcomes in linitis plastica could not be evaluated further in this cohort. However, studies in the systematic review demonstrate high rates of incomplete resection margins in surgically-treated linitis plastica. Relevant questions for future studies, ideally in a prospective setting, should therefore include strategies to improve resection margins in linitis plastica as well as the role of novel therapeutic modalities such as intraperitoneal chemotherapy and immune checkpoint inhibitors.

Overall limitations and unmet needs

The thesis was unable to achieve its underlying aim of creating a tool for patient-centred treatment decisions in gastric cancer. This remains an unmet need which no study has accomplished to date. Fundamentally, such a tool would facilitate discussions between clinicians and patients by estimating

the survival benefit associated with a particular treatment modality for an individual patient as well as the potential impact of treatment on quality of life. This 'impact' can either be positive, for example by reducing disease-related symptoms and complications, or negative as in the case of postoperative recovery and chemotherapy-related adverse events. A previous longitudinal analysis has demonstrated that recovery to baseline quality of life can take up to a year following gastrectomy[130]. Physical and psychosocial impacts of gastrectomy can persist for several years[131]. Patients are often unprepared for these effects of treatment[131]. Despite their importance to patients, quality-of-life-related outcomes are rarely explored by trials in gastric cancer.

Reasons for the lack of data on symptoms and quality of life in this thesis have been discussed. Other limitations relate to the size and demographics of the cohort. Although the cohort was of a reasonable size by the standards of a single-centre gastric cancer study in a western population, it remained underpowered for multivariable modelling with respect to non-survival outcomes. Cohort demographics reflect those of an ageing Western European population. This should be seen as a strength and not a flaw: the Western European population is relatively under-researched in the context of gastric cancer, in marked contrast to other malignancies. However, it is fair to admit that the findings described in this thesis are not necessarily generalisable on a global scale. The same criticism can be levied at most studies in gastric cancer. To date, most modelling studies and clinical trials have been confined to patients with gastric cancer in particular geographic regions and lack the scale and diversity to inform clinical practice across international borders.

Finally, the poor outcomes seen in patients with PMGC even with palliative chemotherapy demonstrate that current treatment strategies are unable to meet the needs of this 'forgotten' cancer population. Novel intraperitoneal therapeutic modalities as well as targeted immunotherapy offer a glimmer of hope. However, recruitment of patients with PMGC into clinical trials has proven challenging, perhaps due to a combination of small patient numbers, poor prognosis, uncertain treatment benefit and a misalignment of priorities between researchers and patients.

FUTURE DIRECTIONS

New therapeutic modalities and the local context

Immunotherapy (immune checkpoint inhibitors) and intraperitoneal chemotherapy are the latest developments in the management of gastric cancer. European Society for Medical Oncology (ESMO) guidelines issued in 2022 now recommend trastuzumab for human epidermal growth factor receptor 2-positive (HER2+) disease and nivolumab for programmed death-ligand 1-positive (PD-L1+) disease

in addition to standard platinum-fluoropyrimidine chemotherapy for advanced and metastatic gastric cancer[16]. The guidelines also recognise a potential role for intraperitoneal chemotherapy in carefully selected patients[16].

Screening for HER2 is routinely performed at the NNUH. Surprisingly, a positive HER2 status was recorded for only 7 patients in the database (1.3% of the cohort). The reasons behind this low number were not explored. HER2 overexpression is typically expected in around 30% of intestinal-type gastric cancers, 5% of diffuse-type cancers and 15% of mixed-type cancers[132]. Anecdotally, the proportion of patients with HER2+ tumours at a nearby tertiary referral centre is more in keeping with these expected figures, suggesting that the low number in the present cohort could not be simply explained by patient demographics. Nivolumab and PD-L1 screening were not yet part of the standard treatment pathway during the period covered in the database.

Hyperthermic intraperitoneal chemotherapy with cytoreductive surgery (CRS-HIPEC) is the only modality of intraperitoneal chemotherapy used in the UK outside of trial settings. The NNUH offers CRS-HIPEC for colorectal cancer and, as of 2022, was one of only two units in the UK where HIPEC was available for ovarian cancer. Although not part of the standard OG cancer pathway, CRS-HIPEC has been approved on a named-patient basis for at least one patient with gastric cancer at the time of writing this thesis.

A patient-centred approach of weighing up individualised benefit from treatment against tolerability and impact on quality of life should apply equally to novel treatment modalities and existing standard care. Some inroads have been made into the identification of patient subgroups likely to benefit from immunotherapy. This is not the case for intraperitoneal chemotherapy: studies have shown that some patients perform extremely well following intraperitoneal chemotherapy but overall outcomes remain disappointing. We note that recent multicentre European trials of novel treatment modalities for PMGC have struggled to recruit sufficient participants[133]. Although the reasons for this are unclear, we should acknowledge that patients' and researchers' priorities do not always align.

Immune checkpoint inhibitors

Recent drug development has focused on immune checkpoint proteins as a target for molecular therapies. Although playing an important role in health by preventing autoimmune inflammation, immune checkpoint proteins also allow cancer cells to evade immune surveillance[134]. Accompanying the development of targeted therapies, new molecular subtypes of gastric cancer have been defined alongside existing histological subtypes. The Cancer Genome Atlas (TCGA) defined four molecular subtypes of gastric cancer. The chromosomal instability (CIN) subtype is the most common,

accounting for 50% of gastric cancers and generally associated with Lauren intestinal-type histology[128]. HER2 overexpression and genomic amplification of vascular endothelial growth factor (VEGF) are commonly seen in this subtype[16,127]. The genomically stable subtype (20% of gastric cancers) is characterised by a lack of cell cohesion and mostly exhibits Lauren diffuse-type histology. The high microsatellite instability (MSI-H) subtype (22% of gastric cancers) and Epstein-Barr virus (EBV)-positive subtype (9% of gastric cancers) are associated with PD-L1 overexpression and generally respond best to immune checkpoint inhibitors[128].

2022 ESMO guidelines recommend assessing HER2 status and PD-L1 combined positive score nivolumab in patients with advanced and metastatic gastric cancer[16]. Trastuzumab is recommended in addition to platinum-fluoropyrimidine chemotherapy in patients with HER2+ tumours. Nivolumab, a programmed cell death protein 1 (PD-1) inhibitor, has demonstrated efficacy in tumours with a positive PD-L1 combined positive score. There remains some disagreement regarding an appropriate cutoff value for the PD-L1 combined positive score. Cutoffs of ≥1 and ≥5 have been used in different studies. 50-60% of gastric tumours have a combined positive score ≥1 but a higher cutoff score of ≥5 “represents a validated threshold for overall survival (OS) benefit of nivolumab given in addition to standard platinum-fluoropyrimidine chemotherapy”[16].

The ATTRACTION-2 phase III clinical trial compared nivolumab versus placebo in Japanese, Korean and Taiwanese patients with advanced gastric cancer previously treated with two or more chemotherapy regimens[135]. Nivolumab improved overall survival by approximately 1 month (median OS 5.3 months with nivolumab vs 4.1 months with placebo; HR 0.63; $p<0.0001$). Overall survival at 2 years was 11% vs 3% in nivolumab-treated patients and placebo-treated patients respectively. The CheckMate-649 trial randomised 1581 patients across 29 countries with HER2-negative unresectable gastric cancers to nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy alone in the first-line setting[136]. In patients with a PD-L1 combined positive score ≥5, median OS was 14.4 months with nivolumab plus chemotherapy compared to 11.1 months with chemotherapy alone ($p<0.001$). Median progression free survival in the same patient groups was 7.7 months vs 6.1 months ($p<0.001$). On the basis of these findings, the National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) have both updated their guidelines to include a recommendation for the use of nivolumab alongside platinum-fluoropyrimidine chemotherapy for advanced gastric cancers with a PD-L1 combined positive score ≥5[137].

As expected, the main challenges associated with immune checkpoint inhibitors are patient selection and treatment tolerability. The PD-L1 combined positive score cutoff of ≥5 remains a point of disagreement[134]. Even amongst patients meeting this criterion, some do not benefit from

nivolumab whilst others perform extremely well, surviving upwards of two years. Although recent clinical trials have presented results separately for patients exhibiting biomarkers thought to be associated with treatment response, outcomes in biomarker-negative patients are not generally reported. It therefore remains unknown whether a subset of patients who test negative for currently recognised biomarkers may respond well to immune checkpoint inhibitors[134]. Furthermore, only individual biomarkers have been explored and not composite biomarkers[134].

Nivolumab appears to be well tolerated but, as with all anticancer drugs, a certain proportion of patients receiving nivolumab experience treatment-related adverse events. In the ATTRACTION-2 trial, CTCAE grade 3 or 4 adverse events were documented in 10% of patients receiving nivolumab and 4% of patients receiving placebo. Frequently reported treatment-related adverse events were pruritis (9%), diarrhoea (7%), rash (6%) and fatigue (5%). Serious adverse events reported in 2 or more patients were interstitial lung disease (n=3), colitis, pyrexia, pneumonia and diabetic ketoacidosis (n=2 each)[135]. Across all immune checkpoint inhibitors, 35-50% of patients experience gastrointestinal side effects, with immune checkpoint inhibitor-induced colitis (IO colitis) being a particular problem[138]. However, rates of IO colitis are lower with anti-PD1 agents such as nivolumab compared to anti-CTLA4 agents (e.g. ipilimumab) which are not currently recommended for gastric adenocarcinoma[138,139].

Intraperitoneal chemotherapy

The efficacy of systemic chemotherapy in PMGC is limited by poor penetration into peritoneal deposits. Intraperitoneal administration can achieve logarithmically higher concentrations of cytotoxic agents within the peritoneal cavity whilst minimising systemic toxicity. In conjunction with cytoreductive surgery (CRS), HIPEC is the only mode of intraperitoneal chemotherapy that is administered in a curative setting. However, given its significant associated risks, CRS-HIPEC must be carefully targeted towards patients with limited peritoneal disease and good physiological reserve. Another proposed role for intraperitoneal chemotherapy is the conversion of inoperable peritoneal carcinomatosis to potentially operable disease (‘conversion therapy’). Pressurised intraperitoneal aerosolised chemotherapy (PIPAC) has been developed to fill this niche in Europe, whilst laparoscopic HIPEC has attracted more interest in the United States. Asian centres have trialled normothermic catheter-based intraperitoneal chemotherapy using taxanes as an alternative approach.

Hyperthermic intraperitoneal chemotherapy

Hyperthermia enhances drug accumulation within tumour nodules and may itself exert a direct cytotoxic effect[140]. In colorectal cancer with peritoneal carcinomatosis, HIPEC has gained wide acceptance following a seminal trial by Verwaal and colleagues in 2003 which demonstrated a median overall survival of 22.3 months with HIPEC versus 12.6 months with systemic chemotherapy[141]. This survival benefit of HIPEC for metastatic colorectal cancer was replicated in large-scale meta-analyses[142]. Similarly, in ovarian cancer there is accumulating trial evidence for a survival benefit from CRS-HIPEC versus CRS alone, increasing median survival from 33.9 months (CRS) to 45.7 months (CRS-HIPEC)[143].

The evidence for CRS-HIPEC in PMGC is less robust. Three European trials have investigated its use in this context. The German GASTRIPEC-I trial randomised adult patients with PMGC to either CRS-HIPEC with cisplatin and mitomycin or CRS alone[133]. GASTRIPEC-I was unfortunately terminated early due to slow recruitment. Intention-to-treat analysis revealed no difference in overall survival between the trial arms, but significantly improved progression-free survival in the CRS-HIPEC group (7.1 months vs 3.5 months). The Dutch PERISCOPE II trial and French GASTRICHIP trials are still in progress[144,145].

Although patient selection is clearly crucial, the precise factors that determine which patients stand to benefit most from CRS-HIPEC remain elusive. Completeness of cytoreduction and a low peritoneal carcinomatosis index (PCI) were identified as important prognostic factors in a 2016 systematic review by Chia and colleagues[146]. For patients with complete cytoreduction, median overall survival ranged from 11.2 to 43.4-months (11 studies); 5-year overall survival was 13-23% (2 studies)[146]. These figures must be balanced against the morbidity and mortality associated with CRS-HIPEC, although recent evidence suggests similar or lower risk profiles compared to other major gastrointestinal surgical procedures[147]. Some studies have suggested PCI≥7 as a threshold above which patients are unlikely to benefit from CRS-HIPEC[121,148,149].

Laparoscopic HIPEC

A few centres, notably the MD Anderson Cancer Center (Houston, Texas), have investigated laparoscopic HIPEC as a novel approach for low-volume peritoneal disease. This has the advantage of a low-morbidity procedure as an adjunct to conventional therapy, which may allow selection of patients with biologically-favourable disease responding to intraperitoneal chemotherapy for eventual curative treatment. Early reports suggest laparoscopic HIPEC is safe, well tolerated and can be performed repeatedly, with a proportion of patients demonstrating resolution of PMGC and subsequently proceeding to surgical resection[150,151]. In the MD Anderson group's latest phase II trial of laparoscopic HIPEC followed by

curative-intent gastrectomy plus CRS-HIPEC in carefully selected patients, median overall survival was 24.2 months from diagnosis with a 90-day postoperative mortality of 0%[152]. Retrospective analysis from the same centre failed to demonstrate a significant survival benefit compared to standard systemic chemotherapy[153].

Laparoscopic HIPEC has also been used in a Japanese trial published in 2017 as part of a multi-modality strategy combining neoadjuvant laparoscopic HIPEC, neoadjuvant normothermic catheter-based chemotherapy plus systemic chemotherapy, and finally CRS-HIPEC with curative intent[149]. Complete cytoreduction was achieved prior to CRS-HIPEC in 57.6% of patients treated with this strategy[149].

Pressurised intraperitoneal aerosolised chemotherapy

Pressurised intra-peritoneal aerosol chemotherapy (PIPAC) is a novel 'minimally invasive' therapeutic strategy that can be administered to patients with peritoneal carcinomatosis for whom more HIPEC would not be deemed appropriate. A pressure gradient is used to overcome high tumour interstitial pressures, resulting in increased concentrations and a more even distribution of cytotoxic agents throughout the peritoneum whilst limiting systemic toxicity[154].

A systematic review published by Alyami and colleagues in 2017 identified clinical response in the range of 50-91% and median survival of 8.4–15.4 months following PIPAC in patients with PMGC[155]. A more recent systematic review by the PIPAC-UK collaborative included a total of 15 studies that specifically reported outcomes of PIPAC in patients with PMGC: four prospective phase II trials and 11 retrospective analyses of prospectively maintained databases[154]. Median overall survival ranged from 8 to 19.1 months and rates of overall survival at 1 year from 49.8% to 77.9%[154]. Analysis of treatment response was complicated by significant heterogeneity of endpoints between studies. Overall levels of treatment toxicity were low. In three studies that assessed quality of life, PIPAC was not associated with any significant change in validated quality of life scores[154].

Some unanswered questions remain. It is not known whether earlier intervention with PIPAC as first-line treatment for PMGC might lead to better outcomes[154]. The relative advantages of bidirectional therapy with systemic chemotherapy alongside PIPAC compared to PIPAC alone are unclear, and no study thus far has been designed or powered to address this question[154]. Finally, the potential role of PIPAC in converting inoperable PMGC to potentially operable disease, perhaps has a precursor to CRS-HIPEC, has not been formally assessed[156].

Normothermic catheter-based intraperitoneal chemotherapy

A third strategy involving normothermic, normobaric catheter-based intraperitoneal chemotherapy has gained traction in East Asian centres. This strategy possesses the advantages of minimal invasiveness and repeatability. Through an access port placed subcutaneously and connected to an indwelling intraperitoneal catheter, intraperitoneal chemotherapy can be administered repeatedly in outpatient settings without the need for hospital admission or general anaesthetic[157]. In practice, this is often combined with systemic chemotherapy in a bidirectional approach. Recent Asian trials of catheter-based intraperitoneal chemotherapy have investigated the use of taxanes in this setting. The main advantage of taxanes is their longer half-life within the peritoneum and hence longer 'effective duration' of targeted cytotoxicity [158].

A recently published meta-analysis by Guchelaar and colleagues identified 13 studies of normothermic catheter-based intraperitoneal chemotherapy; all studies except one were performed in East Asian centres[157]. The median number of intraperitoneal chemotherapy cycles per patient ranged from 3 to 16 for paclitaxel and 1 to 8 for docetaxel, compared to 1–3 cycles per patient in PIPAC studies[157]. No study has assessed quality of life in patients treated with this strategy.

Two phase III randomised controlled trials have been performed: the Japanese PHOENIX-GC trial published in 2018 and a Chinese trial by Bin and colleagues published in 2022[158,159]. Median overall survival in the PHOENIX-GC trial was 17.7 months with intraperitoneal and systemic chemotherapy compared to 15.2 months with systemic chemotherapy alone (p=0.08). Although statistical superiority was not demonstrated with respect to this primary outcome measure, 3-year overall survival was substantially higher in patients receiving bidirectional chemotherapy (21.9%; 95% CI 14.9–24.9) compared to patients receiving systemic chemotherapy alone (6.0%; 95% CI 1.6–14.9)[158]. Bin and colleagues' trial, meanwhile, found a small but statistically significant improvement in survival with bidirectional chemotherapy compared to systemic chemotherapy alone (11.7 vs 10.5 months) as well as improvement in ascites control following intraperitoneal chemotherapy[159].

Comparing intraperitoneal strategies

CRS-HIPEC is only modality of intraperitoneal chemotherapy used for PMGC in the UK outside of trial settings. However, the significant morbidity and uncertain benefit associated with CRS-HIPEC restrict its use to a small number of carefully selected patients with limited peritoneal disease and good physiological reserve, and have hampered recruitment into phase III clinical trials.

Studies of laparoscopic HIPEC, PIPAC and normothermic catheter-based intraperitoneal chemotherapy have shown promise in less invasive strategies that are well tolerated and likely to improve outcomes in a group of patients for whom treatment options are otherwise limited. Although median survival figures continue to disappoint, studies have consistently shown that small but significant numbers of patients treated with these strategies achieve good outcomes with complete cytoreduction, conversion to operability and/or prolonged survival[152,158,160,161]. Patient and disease characteristics predicting a good response to intraperitoneal chemotherapy remain uncertain.

No direct comparisons of these contrasting intraperitoneal strategies have been performed. Guchelaar and colleagues' meta-analysis found a 'significantly higher' overall survival in patients treated with normothermic catheter-based intraperitoneal chemotherapy compared to patients treated with PIPAC[157]. However, differences in the populations treated with these contrasting strategies must be taken into account, with better outcomes generally observed in Asian patients.

Suggestions for future research and closing remarks

The various 'unmet needs' we have discussed can be summarised in three themes: tools for choosing the right treatment for the right patient, treatment strategies for peritoneal disease, and a greater focus on patient-centred outcomes other than survival.

More sophisticated and accurate predictive models are needed to help clinicians and patients select appropriate treatment strategies. Molecular signatures and biomarkers will likely play a part in future models, and whole genome sequencing may eventually help guide treatment selection[162]. Large multinational studies are necessary to generate the number and diversity of patients required for a universally applicable model. Ideally, both survival and non-survival-related outcomes should be modelled to paint a complete picture of both mortality and morbidity. Multidisciplinary collaborations between researchers from acute, primary and palliative care backgrounds will help to ensure that all aspects of the patient's journey are accounted for.

Clinical equipoise remains in the current treatment landscape for peritoneal metastasis of gastric cancer. There is a need for larger and more robust comparative studies before an 'optimum' management pathway for PMGC can be recommended. Trials of novel treatment modalities for PMGC have struggled to recruit sufficient participants. Although the poor survival of this patient group may play a role, we should acknowledge that patients' and researchers' priorities do not always align. Experimental treatment is associated with an additional element of uncertainty with respect to both potential risk and benefit. Scepticism towards novel treatment modalities is understandable within a

context of uncertain benefit, poor overall prognosis regardless of treatment, and high treatment-related morbidity.

Research in gastric cancer has focused almost exclusively on survival outcomes. Disease-related quality of life in this patient population is poorly described. Patients' own perceptions of their disease experience and quality of life are rarely encountered in the existing literature. In a vacuum of knowledge, we are inclined to make assumptions of our patients' experiences and priorities. There is a risk that the hypotheses we generate and outcome measures we choose may not be particularly meaningful to the intended beneficiaries of our research. Future research would benefit from greater levels of patient and public involvement. Qualitative research methodology may be one way of giving voice to patients' priorities and perceptions of their own well-being.

Although this thesis did not succeed in pushing these boundaries, foundations have been laid for future studies to build on. We have highlighted the poor outcomes in PMGC and linitis plastica. We have identified a link between suboptimal pre-operative optimisation, nodal involvement and postoperative recurrence that may serve a target for future clinical trials. More promisingly, we have also established that older bit fit patients benefit from aggressive treatment strategies, and cancers involving the gastro-oesophageal junction do not necessarily carry a worse prognosis. We hope the unmet needs highlighted in this thesis will spur the multicentre, multidisciplinary and multinational collaborations needed to revolutionise the future of gastric cancer management.

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