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Abbreviations: CI – confidence interval; DCO – death certificate only; ECF – epirubicin, cisplatin and 5-FU; GERD – gastroesophageal reflux disease; HER2 -- human epidermal growth factor receptor 2; ICBP – International Cancer Benchmarking Partnership; ICD-10 – International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-O-3 – International Classification of Diseases for Oncology, third edition; PET – positron emission tomography; ICSS – International Cancer Survival Standard; OAC – oesophageal adenocarcinoma; OSCC – oesophageal squamous cell carcinoma; SEER – Surveillance, Epidemiology and End Results Program; TNM – tumour, node, metastasis; UK – United Kingdom

Keywords: gastric cancer, oesophageal cancer, survival, stage at diagnosis, histology, epidemiology

Abstract

Objective: To provide the first international comparison of oesophageal and gastric cancer survival by stage at diagnosis and histological subtype across high-income countries with similar access to healthcare.

Methods: As part of the ICBP SURVMARK-2 project, data from 28,923 oesophageal and 25,946 gastric cancer patients diagnosed during 2012-2014 from 14 cancer registries in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the United Kingdom) were included. One and three-year age-standardised net survival were estimated by stage at diagnosis, histological subtype (oesophageal adenocarcinoma, OAC; and oesophageal squamous cell carcinoma, OSCC) and country.

Results: Oesophageal cancer survival was highest in Ireland and lowest in Canada at one (50.3% versus 41.3%, respectively) and three years (27.0% versus 19.2%) post-diagnosis. Survival from gastric cancer was highest in Australia and lowest in the UK, for both one- (55.2% versus 44.8%, respectively) and three-year survival (33.7% versus 22.3%). Most oesophageal and gastric cancer patients had regional or distant disease, with proportions ranging between 56% and 90% across countries. Stage-specific analyses showed that variation between countries was greatest for localised disease, where survival ranged between 66.6% in Australia and 83.2% in the UK for oesophageal cancer and between 75.5% in Australia and 94.3% in New Zealand for gastric cancer at one year post-diagnosis. While survival for OAC was generally higher than that for OSCC, disparities across countries were similar for both histological subtypes.

Conclusion: Survival from oesophageal and gastric cancer varies across high-income countries including within stage groups, particularly for localised disease. Disparities can partly be explained by earlier diagnosis resulting in more favourable stage distributions, and distributions of histological subtypes of oesophageal cancer across countries. Yet differences in treatment, but also in cancer registration practice and the use of different staging methods and systems, across countries may have impacted the comparisons. While primary prevention remains key, advancements in early detection research are promising and will likely allow for additional risk stratification and survival improvements in the future.

Summary Box

1. What is already known about this subject?
    - Despite small improvements in the survival from oesophageal and gastric cancer – attributable to important advances in their treatment and management – outcomes from both malignancies remain poor. Yet, differences exist in the prognosis of upper gastrointestinal cancers across countries.
    - Stage of disease at diagnosis remains the most important prognostic factor for oesophageal and gastric cancer survival. It however remains unclear to what extent stage at diagnosis and differences in the distribution of histological subtypes explain international survival disparities.
2. What are the new findings?
    - Based on high-quality population-based cancer registry data from seven high-income countries, we document important survival differences across populations.
    - International variation in survival was most pronounced for localised disease, however representing only a small subset of patients. Most patients continue to be diagnosed at an advanced stage, for which international survival disparities were less distinct.
    - While survival from OAC was generally higher than that from OSCC, disparities across countries were similar for both histological subtypes.
3. How might it impact on clinical practice in the foreseeable future?
    - This first quantification of international survival differences by stage at diagnosis provides an important evidence-base for clinicians and health policy makers to plan appropriate cancer control.
    - The findings suggest international variation in treatment and management strategies in particular for early-stage cancers between countries that warrant further investigation to generate deeper understanding of the drivers of overall survival differences.
    - In the absence of efficient and cost-effective population-based screening, primary prevention targeting well-established risk factors such as *H. pylori* infection, tobacco and alcohol consumption, tobacco smoking, body fatness and salt intake, remains key to tackling the overall burden from oesophageal and gastric cancer.

Introduction

With together more than 1.5 million new cases and over 1.3 million deaths estimated globally in 2020 [1], oesophageal and gastric cancer belong to the group of poor prognosis cancers. Both cancers are often diagnosed at a late stage when treatment options are limited, and outcomes are poor. Although important advances in the treatment and management of oesophago-gastric cancers have led to some improvements in survival over the past years, only about one in five patients survives the disease beyond five years after diagnosis. International disparities in survival from oesophageal and gastric cancer have been described [2] and considerable variation exists across high-income countries with five-year survival estimates ranging from 14.7% to 23.5% and from 20.8% to 32.8% for oesophageal and gastric cancer patients diagnosed during 2010-2014, respectively.[3]

The epidemiology of both cancers has undergone major changes over the past decades. Incidence rates of gastric cancer have continued decreasing in most parts of the world and most of this decline has been attributed to infection with *Helicobacter pylori* [4], its main causal risk factor. Trends in the incidence of oesophageal cancer are more difficult to unpick, and differ largely between the two main histological subtypes, oesophageal adenocarcinoma (OAC) and squamous cell carcinoma (OSCC). OSCC has been mainly associated with tobacco smoking and heavy alcohol consumption, but also air pollution and unhealthy diet, and represents the most common subtype globally.[5, 6, 7] OAC has been associated with obesity and gastroesophageal reflux disease (GERD) and represents roughly two thirds of oesophageal cancers in high-income countries such as the United Kingdom and the United States [6, 8, 9]

The most important prognostic factor determining oesophageal and gastric cancer survival is stage at diagnosis. Yet, as early-stage disease rarely presents any symptoms, late-stage diagnoses remain common, and so treatment options and chances of cure are limited. However, the extent to which differences in stage distributions and survival within stage groups may explain international disparities in survival of these cancers, remains unclear. The International Cancer Benchmarking Partnership (ICBP), an alliance of clinicians, policymakers, researchers, and cancer data experts, was established with the aim to enlighten on the reasons for cancer survival differences between high-income countries with similar health systems.

Within the ICBP SURVMARK-2 project, we aim to examine the impact of stage of disease at diagnosis and histological subtype on international survival disparities in oesophageal and gastric cancer. Using population-based data from 14 cancer registries in seven high-income countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway, and the UK), we provide estimates for overall and stage-specific net survival at one and three years post-diagnosis.

Methods

Data sources

During the ICBP SURVMARK-2 project, data for patients diagnosed with oesophageal and gastric cancer were collected from 21 population-based cancer registries in seven countries. Data submitted included information on histology, morphology, basis of diagnosis, stage at diagnosis and treatment. Quality checks were conducted on each dataset using a standard data protocol, which is described in more detail elsewhere.[3] This included screening the data for specific anomalies such as instances of negative survival duration, out-of-range dates of diagnosis and/or dates of death, availability of stage at diagnosis information and invalid vital status codes. In the current analyses, we included oesophageal and gastric cancer patients diagnosed during 2012-2014 and followed-up until 31 Dec 2015 from the 14 registries that were able to provide information on stage at diagnosis for at least 50% of the registered cases : Australia (New South Wales), Canada (Alberta, Manitoba, Newfoundland, Nova Scotia, Prince Edward Island, Saskatchewan), Ireland (2012-2013), Denmark, New Zealand (gastric cancer only), Norway and the UK (England, Wales, Northern Ireland).

Primary malignant oesophageal and gastric tumours (ICD-10: C15 and C16) were included. Histological groups were based on the International Classification of Diseases for Oncology, third edition (ICD-O-3) and defined as OACs: 8140-8141, 8143-8145, 8190-8231, 8260-8263, 8310, 8401, 8480-8490, 8550-8551, 8570-8574 and 8576; OSCCs: 8050-8078 and 8083-8084. We excluded cases diagnosed based on death certificate only (DCO) or at autopsy, below the age of 15 or above 99 years at diagnosis, with inconsistencies in stage information (e.g., incompatibility of basis of diagnosis and stage variables), and second or higher sequenced cancers diagnosed at the same site. Furthermore, we excluded gastrointestinal stromal (8936) and neuroendocrine tumours (8013, 8041-8045, 8150-8158, 8240-8247, 8249, 8574 and 9091) as defined in ICD-O-3 from all analyses as they differ in their aetiology and prognosis from other oesophageal and gastric tumours.[10] Using these criteria, 28,923 oesophageal and 25,964 gastric cancer cases were included in the survival analyses (Table 1).

Each participating cancer registry provided information on pre-treatment pathological and clinical T, N, and M, grouped TNM stage and/or SEER summary stage 2000 (SEER SS2000).[11, 12] For the purpose of stage comparisons across all seven countries, stage information was mapped to one common system by translating individual T, N, M elements to SEER Summary staging (categorized as localised, regional and distant), using a pre-defined mapping algorithm (Supplementary Table 1). While tumours of the proximal (cardia) stomach (C16.0) were staged according to the oesophageal cancer staging scheme, tumours of the

distal (non-cardia) stomach (C16.1-6, 8-9) were staged using the scheme for gastric cancer, as described in the 7th edition of TNM. [11] Details on the conversion algorithm used are described in Cabasag et al.[13] A summary flowchart of how registry-specific staging information was mapped to SEER staging is available in Supplementary Figure 1.

Ethical approval was obtained from each participating registry and from the IARC Ethics Committee (project no. 16-36).

Statistical analyses

We report estimates of net survival with accompanying 95% confidence intervals (CI), which is the probability of survival for cancer patients in a hypothetical situation where cancer is considered the only possible cause of death. This metric ensures fair survival comparisons across populations in which the chance of dying from other diseases varies. Background mortality in the general population of each jurisdiction was obtained from lifetables of all-cause death probabilities by sex, single year of age and calendar years. Net survival at one and three years post-diagnosis were obtained using Pohar Perme estimators [14] for all oesophageal and gastric cancers as well as for OAC and OSCC, by mapped SEER stage (localised, regional and distant) for all countries and grouped TNM (I, II, III, and IV) for Canada, Denmark, Ireland and the UK, where possible. Sex-specific survival for oesophageal and gastric cancer was also estimated. The cohort approach was used to compute one-year net survival estimates, and the period approach was used to estimate three-year net survival as not all cancer patients had three years of follow-up.[15] Age-standardization was carried out using the International Cancer Survival Standard (ICSS) weights.[16]

For cases with missing stage at diagnosis, stage information was imputed using the multiple imputation (*mi)* command with the following covariates: sex, age, year of diagnosis, survival time, and the Nelson-Aalen estimator of the cumulative hazard. Age was modelled as a continuous variable and polynomial functions (splines) were used to allow for the non-linear effects of time since diagnosis. Histology (OAC/OSCC/Other) was additionally added to the imputation model for analyses including all oesophageal cancers combined. A total of 30 imputations were performed and results were combined using Rubin's rules to estimate net survival and 95% confidence interval.[17]

All analyses were performed in Stata 14 (StataCorp LP, College Station, Texas, USA). Whilst in the main manuscript we report stage-specific survival estimates using imputed stage at diagnosis, we also present results based on original, non-imputed, stage categories in Supplementary tables.

Sensitivity analyses

As it is possible that some cancers of the lower oesophagus may have been incorrectly recorded or misclassified as cancers of the gastric cardia (ICD10: C16.0), sensitivity analyses were performed by histological subtype including an additional 8,216 C16.0 cases in the analyses for oesophageal cancer. While we don't present separate results for histological subtypes other than OAC and OSCC – representing between 4 and 9% of all oesophageal cancer cases across countries–, we evaluated the impact of other histological types on oesophageal cancer survival by comparing estimates including all oesophageal cancer cases with those in the combined group of OAC and OSCC patients. Following a similar reasoning as for oesophageal cancer, we estimated gastric cancer survival after excluding proximal (C16.0) tumours as some of these may have originated from the lower oesophagus and therefore potentially misclassified. Owing to the large proportion of gastric cancer with overlapping or unspecified subsite (ICD-10: C16.8-9), we did not estimate survival for proximal and distal gastric cancers separately.

Patient and Public Involvement

As this work is a retrospective analysis of cancer registry data from the years 2012-2014, patients were not involved in the design and conduct of this research.

Results

Oesophageal cancer

A total of 28,923 cases of oesophageal cancer, including 8,935 cases of OSCC (30.9%) and 17,532 cases of OAC (60.6%) diagnosed during 2012-14 were included in this study (Table 1). OAC was the most common subtype in all countries and accounted for up to two thirds of all oesophageal cancer (in Canada), while OSCC represented between 26.9% (in Canada) and 44.7% (in Ireland). Mean age at diagnosis ranged between 67 and 71 years (Table 2), with OAC patients tending to be slightly younger at initial diagnosis (Supplementary Table 2). Information on stage at diagnosis was available for more than 70% of all patients, and after mapping to summary (SEER or TNM) stage, the proportion with missing stage at diagnosis ranged from 6.4% in Canada to 29.8% in Norway.

Most oesophageal cancer cases were diagnosed with either regional or distant disease in all countries, however some distinct country-specific patterns were observed (Table 2, Figure 1). While Canada and Denmark had the highest proportion of distant cases (>50%), there was a range of 38-44% in Ireland, Norway, and the UK, and lowest in Australia (31%). Localised disease was least often diagnosed in

Denmark (9%) and most often diagnosed in Australia (42%) and ranged between 12% and 25% in the remaining countries. There were similar country-specific patterns in stage distribution by histological subtype, with fewer regional, but slightly more distant disease observed for OAC when compared with OSCC, except for Denmark. The four countries that provided data on TNM stage had similar proportions of stage IV cancers but were dissimilar in the distribution of stage I-III diagnoses.

Overall net survival from oesophageal cancer was highest in Ireland and lowest in Canada at one- (50.3% versus 41.3%, respectively) and three-years (27.0% versus 19.2%) post diagnosis (Figure 2, Supplementary Table 3). Variation of stage-specific survival between countries was greatest for localised stage, ranging between 66.6% in Australia and 82.9% in Ireland and 83.2% in the UK at one year and between 43.9% in Canada and 66.1% in Ireland at three years post diagnosis. Survival differences across countries for regional and distant stage were smaller, with one-year survival for distant disease ranging between 21.8% in Australia and 27.2% in Denmark and three-year survival between 4.4% in the UK and 7.4% in Denmark. Similar observations were made for survival from the two main histological subtypes (Figures 2-3, Supplementary Tables 4-5). Survival from OAC was generally better than from OSCC, for all stages combined and for each stage. While one year survival from localised OAC ranged between 73.4% in Australia and 87.0% in the UK, this was lower and more variable for patients with localised OSCC (ranging from 53.9% in Norway to 75.7% in Ireland). These differences in the subtype-specific survival across stage groups were less pronounced for distant disease and at three years after diagnosis. Analyses by TNM stage confirmed these observations and showed that the high survival observed in Ireland was consistent across all stages and for both histological subtypes. When comparing survival estimates obtained after imputation with those of the original data i.e., including a missing stage category, survival estimates differed slightly, but overall patterns across countries were confirmed. Generally, survival estimates for patients with missing stage were between estimates for regional and distant stage (Supplementary Table 6).

Gastric cancer

Of 25,946 gastric cancer cases diagnosed in 2012-2014 approximately equal proportions of tumours occurred in the proximal, distal, and other/ unspecified parts of the stomach (Table 1). For tumours with known topography, proximal (cardia) gastric cancer represented the majority in Australia, Denmark, Ireland, and New Zealand (36-52%) whereas the opposite was observed – distal (non-cardia) tumours being the majority – in Canada, Norway and the UK (37-43%). About two thirds of all cases occurred in men and the median age at diagnosis ranged between 70 (New Zealand) and 75 years (the UK) (Tables 1-2). The completeness of information on stage at diagnosis varied substantially across countries: while more than 80% of gastric cancer cases in Australia, Canada, Denmark and Ireland could be assigned a mapped SEER

stage, only 54% of all cases had sufficient information to assign SEER stage in New Zealand (Table 2). Grouped TNM stage was available from four countries, with missing information on stage ranging between 12% (Canada) and 31% (Ireland and the UK). After imputation of missing stage at diagnosis, most cases were diagnosed with either regional (ranging from 25% to 42% of patients in New Zealand and Denmark, respectively) or distant disease (ranging from 38% to 59% of patients in Australia and New Zealand, respectively), (Table 2, Figure 1). Localised disease was least often diagnosed in Ireland (10% of all cases), Denmark and the UK (both 11%) and most often diagnosed in Australia (33%) and ranged between 16% and 20% in the remaining countries. In the four countries that provided data on grouped TNM, stage distributions were more similar, with approximately half of all gastric cancers having stage IV disease (Table 2, Figure 1).

Net survival from gastric cancer was highest in Australia –55.2% and 33.7% at one- and three-years post-diagnosis, respectively, – and lowest in the UK (44.8% and 22.3%, respectively) (Figure 2, Supplementary Table 7). Overall, patterns across countries were similar for one- and three-year survival; however, differences became apparent when comparing stage-specific estimated survival. Variation in survival estimates between countries was greatest for patients diagnosed with localised disease, ranging from 94.3% in New Zealand to 75.5% in Australia at one year and from 86.5% in New Zealand to 59.9% in the UK at three years post diagnosis. Differences in survival across countries for regional and distant stage were smaller, with survival from distant disease highest in Ireland and lowest in the UK at both one- and three-years post diagnosis, ranging from 26.6% to 20.7% at one year and from 8.0% to 3.8% at three years post-diagnosis. Analyses by TNM stage group confirmed these observations, while showing slightly more variation in estimated survival within stage groups, including stage III and IV disease (Figure 3, Supplementary Table 7). When comparing stage-specific survival estimates obtained after multiple imputation with those using the original, non-imputed data, i.e., including missing stage as a separate category, we found that estimates differed only slightly and overall patterns across countries remained the same as those observed using imputed stages (Supplementary Table 8). Cases with missing information on stage at diagnosis had a comparatively poor prognosis, with corresponding estimated survival falling between that for patients with regional and distant stage.

In sensitivity analyses, we added cardia gastric cancers to the oesophageal group and showed that while survival estimates changed marginally (increasing in most cases), overall survival patterns across countries remained the same (Supplementary Table 9, Supplementary Figures 2-3). Small differences in survival estimates were also found when comparing all oesophageal cancer patients with the combined group of OSCC and OAC patients (Supplementary Figures 4-5). In secondary analyses for gastric cancer, we additionally examined the impact of proximal gastric cancers by excluding them from the analyses. This

yielded slightly lower estimated net survival at one-year post diagnosis. Excluding proximal tumours only had a marginal impact on estimated three-year survival and on overall patterns across countries (Supplementary Table 10, Supplementary Figures 6-7). Finally, while only small survival differences were observed between male and female gastric cancer patients, females with oesophageal cancer had better survival than their male counterparts (Supplementary Figures 8-9).

Discussion

Survival from oesophageal and gastric cancer continues to vary substantially across high-income countries, including within stage and histological sub-groups. Based on high-quality data from seven countries, we highlighted important international differences in stage distributions across countries with up to 90% of patients (ranging from 67% in Australia to 90% in Ireland for oesophageal and from 58% in Australia to 91% in Denmark for gastric cancers) presenting with either regional or distant spread of the tumour at the time of diagnosis. We found that while survival for patients with distant disease varied little across countries, differences in survival were most pronounced for localised disease, where survival ranged widely for both cancers. High proportions of late-stage disease across all jurisdictions suggests greater efforts in earlier diagnosis and staging work-up of upper gastrointestinal cancer may be warranted internationally.

To our knowledge we are the first to describe international survival differences by stage at diagnosis for oesophageal and gastric cancer patients. Recent studies from the US [18, 19] and Norway [20] which presented survival at five years post-diagnosis, noted overall improvements in survival for all stages in the absence of notable changes in stage distributions over time. As many as 51% of oesophageal cancer cases and 59% of all gastric cancer cases were diagnosed with distant disease. Therefore, there is an urgent need for tools enabling early diagnosis including novel biomarkers and less invasive screening methods for oesophageal cancer, such as inflatable balloons and sponges.[21, 22] The more recent trial of the 'cytosponge' has developed a less invasive, and rapid screening test for oesophageal cancer, specifically OAC.[23] The use of this screening method varies internationally, and does not align with the time period studied, but our study highlights the need to consider the adoption and implementation of approaches like the 'cytosponge', particularly in high-incidence populations with high proportions of late stage presentations. For gastric cancer, at present, population-based screening programs have only proven cost-efficient in high-risk populations such as Japan or Republic of? Korea where incidence rates of gastric cancer are among the highest in the world.[24, 25] The larger proportions of patients with localised disease in Australia, Canada and Norway could be due to higher awareness of patients with precursors of OAC (such as gastro-oesophageal reflux disease or Barrett's oesophagus), which could equally originate or be

misclassified as cancers of the proximal stomach.[26, 27] OAC today represents the most common type of oesophageal cancer in all included countries, pointing towards an increasing incidence of cancers of the oesophago-gastric junction.[28]

The survival advantage observed for OAC compared with OSCC, particularly for those with localised or regional disease, could partly be due to differences in the aetiology of these two groups. Patients with OSCC may have additional comorbidities related to smoking (a major risk factor for this sub-type) which could play a part in their treatment options and poorer survival.[29] The higher survival observed for Ireland could potentially be explained by lower proportions of distant disease (40% of cases) and higher survival for localised and regional disease compared to other countries due to improvements in the treatment protocols including neo-adjuvant therapy for resectable, localised cases. Survival is higher for patients with locally advanced disease when chemoradiotherapy followed by surgery is administered compared with surgery alone, for both OAC and OSCC.[30] It should however, be noted that this study covered a period where neoadjuvant chemoradiotherapy had not yet been fully adopted in all jurisdictions for lower oesophageal adenocarcinoma, as it preceded publication of the CROSS study in 2015.[31] Furthermore, endoscopic Barrett's oesophagus screening and surveillance in high-risk individuals could have contributed to earlier detection of OAC, and, in combination with minimally invasive techniques in the management of localized OAC, to better outcomes when compared with OSCC.[32]

Higher survival observed within stage groups of gastric cancer, in particular those diagnosed with early and regional disease, is potentially attributable to varying treatment and management of patients across countries as well as possible differences in the prevalence of comorbidities, e.g., obesity. Since the publication of the MAGIC trial in 2006, reporting survival benefits for patients receiving perioperative chemotherapy consisting of epirubicin, cisplatin and 5-FU (ECF), (neo)adjuvant chemotherapy became an important element in the treatment of stage I-III gastric cancer.[33] To-date, first-line treatment for gastric cancer includes surgery for early-stage disease and multimodal approaches for locally advanced and metastatic disease. These include surgery followed by chemoradiation, or chemotherapy before and after surgery for locally advanced disease and chemotherapy, immunotherapy (in particular anti-HER2-therapies), or chemoradiation and supportive care for patients with metastatic disease. Treatment approaches might differ across countries, leading to discrepancies in surgical techniques, different types of adjuvant therapy and treatment sequence.[34] This is particularly evident in the elderly, when gastric cancer is most common and often coupled with comorbidity and frailty, where evidence for optimal treatment strategies is limited. According to previous evidence, treatment differences exist across North European countries for patients with stages II and III resectable gastric cancer aged 70 years or older.[35]

Moreover, centralisation of treatment for oesophago-gastric cancer might contribute to the observed survival differences across countries. Several European countries, including the UK, Ireland, the Netherlands, Norway, Denmark, and New South Wales in Australia have implemented centralisation of oesophago-gastric cancer treatment, which has led to improved survival and reduced post-operative mortality in some settings. [36, 37, 38, 39] This could partly explain the consistently high survival within all stage groups in Ireland, where effects of centralisation of stomach cancer services (started in 2007) were found to be strongest for surgical treatment and higher survival was observed for patients treated in one of the eight specialist centres, compared with other public hospitals.[39] It may still be too early to observe the full effects of these recent changes in organisation of cancer services on outcomes in other countries, but initial evaluations are promising. It should also be noted that this study period covered a transition period in New South Wales where centralisation was in the process of implementation. Lower post-operative mortality rates observed in high-volume hospitals in England may furthermore support the centralisation of oesophageal and gastric cancer surgical services and may partly explain survival differences across countries after resection.[40] More robust in-depth studies exploring the impact of centralisation of services and cancer outcomes internationally are warranted to further understand this relationship.

In addition to the factors outlined above, several other factors may explain better or worse survival in a population or sub-population. The introduction of screening programs and prophylactic gastrectomies targeting high-risk individuals may have led to an increased identification at early stage and therefore better survival e.g., in New Zealand. More biological factors have also been reported, for example, germline CDH1 mutations have been found to contribute to the high frequency of early-onset diffuse gastric cancer cases in the Māori population of New Zealand, who carry a disproportionate burden from this cancer.[41, 42] Finally, previous studies have documented survival advantages in women when compared with men, pointing towards sex as an independent prognostic factor.[43, 44] We confirmed this observation for oesophageal cancer, but only marginal differences in gastric cancer survival by sex.

The data used for this study were provided by high-quality cancer registries from countries with similar access to healthcare. We ensured the highest possible data quality and comparability at all stages of data collection and harmonization using a predefined protocol. All results were validated and interpreted with the input of local experts, including registry experts, epidemiologists, and clinicians from each country. Despite these precautions, a few limitations should be noted. First, notwithstanding marked improvements over the past decade, information on stage at diagnosis for both oesophageal and gastric cancer is still often missing or incomplete in cancer registry records. Out of 21 cancer registries participating in the ICBP-SURVMARK2 study, only 14 were able to provide sufficient data on stage at diagnosis. Moreover, patients

with missing stage information tended to be older at diagnosis (Table 2) and therefore less likely to have undergone invasive diagnostic procedures and radical treatment. However, cases with missing stage did not exclusively represent those with the worst outcomes, given that their survival was often closer to that for patients diagnosed with regional rather than distant disease. By imputing missing stage at diagnosis separately for each country and by incorporating important measures of survival time, we included the main determinants of stage to inform stage distributions and to mitigate differential missingness patterns across countries. We showed that both approaches (with and without imputation) led to very similar estimates of stage-specific survival.

Second, when merging information from different staging systems, misclassification may occur, potentially confounding stage distributions and survival estimates. We tried to mitigate this by carefully comparing the different classification systems and involving staging experts and clinicians in the conversion to one common system. While stage information was not converted for the Australian data as it was provided in the SEER format, the stage distribution for New South Wales differed markedly from other countries, with a very large proportion of cases diagnosed with localised (42% for oesophageal and 33% for gastric cancers) and relatively small proportions with regional (27% and 29%, respectively) and distant disease (31% and 38% respectively). Coupled with the relatively low survival from localised oesophageal cancer in New South Wales, this group likely contains a mixture of localised and regional disease, which we were not able to examine further as there was no additional information on stage or treatment. Similar observations were made for Norway. This clearly illustrates the limits of stage-specific analyses and the comparability of results in this study, which should be interpreted with caution, especially for New South Wales. We are also aware of varying staging modalities across jurisdictions. The access to more specialised staging modalities such as positron emission tomography (PET) scans, are variable between and even within jurisdictions and may influence the patient's final stage staging.[45] While, for the purpose of comparison, we used the SEER system to compare stage-specific survival estimates across countries, it should be noted that TNM remains the preferred staging classification, as it reflects patients' groupings in clinical settings. The utilisation of a recently developed and simplified set of TNM rules, called essential TNM, might facilitate the collection of stage information and improve international stage comparisons in the future.[46]

Third, the prognostic staging of oesophageal and gastric cancer should ideally take into account both the topographic location and the histological type of the tumour. Proximal gastric cancers as well as cancers of the diffuse Lauren type histology [47] have a worse prognosis when compared with distal (non-cardia) and intestinal types.[20, 48] Given the large proportion of gastric cancers with unknown anatomic subsite, representing up to one third of all cases, we were unable to analyse survival by subsite. Furthermore, since

the 7th edition of the TNM classification of malignant tumours[11], cancers of the oesophago-gastric junction (C16.0) that extend into the oesophagus are staged using the oesophageal scheme as they are considered the same clinical entity. As junctional cancers are sometimes difficult to classify and registration practices might differ across countries, in sensitivity analyses we estimated survival for cancers of the oesophagus including cancers of the oesophago-gastric junction and gastric cancer excluding these junctional cancers. While survival estimates changed slightly, patterns and differences across countries remained, suggesting that the differential misclassification of junctional cancers can only marginally add to the explanation of survival disparities between countries. Fourth, while treatment data were part of the data request of this project, only few registries were able to provide this information, often only for a small subset of patients. We were therefore unable to evaluate the impact of treatment on international survival differences in this study. Finally, while all efforts were made to reach the highest possible degree of data comparability, other differences in registration practice may have affected our results. These limitations should be considered when interpreting the results, including uncontrolled confounding.

In conclusion, disparities in oesophageal and gastric cancer survival across high-income countries were observed, most notably for localised disease. This suggests international variation in treatment and management strategies between countries and warrants further investigation of these procedures and protocols to generate deeper understanding of the drivers of overall survival differences. Most cases of both malignancies continue to be diagnosed at an advanced stage across all countries suggesting greater efforts are universally required to improve early diagnosis. In the absence of efficient and cost-effective population-based screening, primary prevention targeting well-established risk factors such as *H. pylori* infection, tobacco and alcohol consumption, tobacco smoking, body fatness and salt intake, remains key to tackling the overall burden from oesophageal and gastric cancer. Considering important limitations related to the comparability of staging systems and methods, stage-specific comparisons should be interpreted with caution. Evidently, the improved collection and standardisation of staging data, and the accrual of additional variables such as treatment and co-morbidities are critical steps in developing a complete understanding of the underlying mechanisms that explain international differences in cancer survival.

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Contributorship statement

Study concept and design: MA, IS. Data analysis: MA, AB, MJR. Data collection and interpretation: EM, JF, AL, BM, OB, PD, RRW, NSJ, AG, GE, MPA, GP, PW, SV, SK, AVR, CL, SH, NM, DOC, TM, ME, JZ, DWH, DR, FB. Drafting the manuscript: MA, EM, IS. Critical revision of the manuscript for important intellectual content: all authors.

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Table 1. Characteristics of patients with oesophageal and gastric cancer diagnosed during 2012-2014

	Oesophageal cancer							
	Australia[°]	Canada[†]	Denmark	Ireland[¶]	New Zealand	Norway	United Kingdom[‡]	Total
Number of patients diagnosed during 2012-2014	1,424	1,328	1,582	769		797	24,037	29,937
Total exclusions								
Diagnosed based on death certificate only (DCO) or autopsy	34 (2.4%)	9 (0.7%)	2 (0.1%)	5 (0.7%)		13 (1.6%)	309 (1.3%)	372 (1.2%)
Quality control[Δ]	4 (0.3%)	-	-	-		-	-	4 (0.0%)
Age <15 or >99 years	1 (0.1%)	1 (0.1%)	-	1 (0.1%)		-	17 (0.1%)	20 (0.1%)
Second or higher order cancers at the same site	2 (0.1%)	-	3 (0.2%)	3 (0.4%)		1 (0.1%)	15 (0.1%)	24 (0.1%)
Cases with inconsistencies in stage information[*]	-	-	5 (0.3%)	2 (0.3%)		-	50 (0.2%)	57 (0.2%)
GIST[Ŧ]	-	-	4 (0.3%)	1 (0.1%)		3 (0.4%)	10 (0.0%)	18 (0.1%)
Neuroendocrine tumours[§]	18 (1.3%)	28 (2.1%)	46 (2.9%)	16 (2.1%)		19 (2.4%)	392 (1.6%)	519 (1.7%)
Total cases eligible for survival analysis	1,365 (95.9%)	1,290 (97.1%)	1,522 (96.2%)	741 (96.4%)		761 (95.5%)	23,244 (96.7%)	28,923 (96.6%)
% Males	68.1%	78.5%	73.7%	65.3%		75.3%	67.9%	68.8%
Histological subtype								
Squamous Cell Carcinoma	521 (38.2%)	347 (26.9%)	643 (42.2%)	331 (44.7%)		248 (32.6%)	6,845 (29.4%)	8,935 (30.9%)
Adenocarcinoma	745 (54.6%)	847 (65.7%)	816 (53.6%)	359 (48.4%)		446 (58.6%)	14,319 (61.6%)	17,532 (60.6%)
Other	99 (7.3%)	96 (7.4%)	63 (4.1%)	51 (6.9%)		67 (8.8%)	2,080 (8.9%)	2,456 (8.5%)

	Gastric cancer							
	Australia[°]	Canada[†]	Denmark	Ireland[¶]	New Zealand	Norway	United Kingdom[‡]	Total
Number of patients diagnosed during 2012-2014	2,078	1,929	1,636	1,096	1,145	1,416	18,933	28,233
Total exclusions								
Diagnosed based on death certificate only (DCO) or autopsy	36 (1.7%)	12 (0.6%)	5 (0.3%)	9 (0.8%)	7 (0.6%)	23 (1.6%)	358 (1.9%)	450 (1.6%)
Quality control[Δ]	2 (0.1%)	3 (0.2%)	-	-	-	-	-	5 (0.0%)
Age <15 or >99 years	1 (0.0%)	1 (0.1%)	-	-	1 (0.1%)	2 (0.1%)	14 (0.1%)	19 (0.1%)
Second or higher order cancers at the same site	6 (0.3%)	7 (0.4%)	2 (0.1%)	4 (0.4%)	-	3 (0.2%)	47 (0.2%)	69 (0.2%)
Cases with inconsistencies in stage information[*]	-	1 (0.1%)	7 (0.4%)	3 (0.3%)	-	1 (0.1%)	41 (0.2%)	53 (0.2%)
GIST[Ŧ]	61 (2.9%)	57 (3.0%)	107 (6.5%)	18 (1.6%)	30 (2.6%)	47 (3.3%)	387 (2.0%)	707 (2.5%)
Neuroendocrine tumours[§]	82 (3.9%)	111 (5.8%)	43 (2.6%)	55 (5.0%)	29 (2.5%)	53 (3.7%)	593 (3.1%)	966 (3.4%)
Total cases eligible for survival analysis	1,890 (91.0%)	1,737 (90.0%)	1,472 (90.0%)	1,007 (91.9%)	1,078 (94.1%)	1,287 (90.9%)	17,493 (92.4%)	25,964 (92.0%)
% Males	66.8%	67.4%	68.0%	65.3%	63.8%	63.7%	66.3%	66.3%
Subsite								
Proximal (cardia, C16.0)	690 (36.5%)	612 (35.2%)	764 (51.9%)	423 (42.0%)	392 (36.4%)	401 (31.2%)	5,326 (30.4%)	8,608 (33.2%)
Distal (non-cardia, C16.1-6)	633 (33.5%)	746 (42.9%)	389 (26.4%)	339 (33.7%)	352 (32.7%)	558 (43.4%)	6,413 (36.7%)	9,430 (36.3%)
Other/Unspecified (C16.8-9)	567 (30.0%)	379 (21.8%)	319 (21.7%)	245 (24.3%)	334 (31.0%)	328 (25.5%)	5,754 (32.9%)	7,926 (30.5%)

‡ United Kingdom registries included: England, Northern Ireland and Wales

° Australia registries included: New South Wales

¶ Ireland (2012-2013)

Δ Includes: data inconsistencies (invalid age, missing/incomplete dates), tumors with non-malignant behavior, tumors with invalid morphological or topographical codes

* Stage error or in situ flag

Ŧ Gastrointestinal stromal tumour (GIST): ICD-O-3 Morphology code 8936

§ ICD-O-3 Morphology codes 8013, 8041-8045, 8150-8158, 8240-8247, 8249, 8574 and 9091

Table 2. Number of patients with oesophageal and gastric cancer diagnosed during 2012-2014 according to country and stage at diagnosis (TNM and SEER Summary Stage 2000), before and after imputation

	TNM stage									Mapped SEER								
	Oesophageal cancer			%		Gastric cancer		%		Oesophageal cancer			%		Gastric cancer		%	
	Stage	Number	Median age at diagnosis (P25-P75¥)	Observed	After imputation	Number	Median age at diagnosis (P25-P75¥)	Observed	After imputation	Stage	Number	Median age at diagnosis (P25-P75¥)	Observed	After imputation	Number	Median age at diagnosis (P25-P75¥)	Observed	After imputation
Australia°	All patients									All patients	1,365	71 (63-79)			1,890	71 (61-80)		
	Missing									Missing	239	73 (64-81)	17.5		224	74 (64-84)	11.9	
	I									Localised	462	73 (66-83)	41.0	42.1	542	72 (62-81)	32.5	33.3
	II									Regional	308	68 (60-77)	27.4	26.8	480	70 (60-78)	28.8	28.7
	III									Distant	356	67 (59-76)	31.6	31.1	644	69 (59-79)	38.7	37.9
	IV																	
Canada†	All patients	1,290	67 (58-76)			1,737	71 (61-80)			All patients	1,290	67 (58-76)			1,737	71 (61-80)		
	Missing	146	72 (64-85)	11.3		213	81 (70-88)	12.3		Missing	83	76 (66-86)	6.4		148	84 (74-88)	8.5	
	I	192	70 (61-78)	16.8	16.9	265	74 (64-82)	17.4	18.0	Localised	230	70 (61-78)	19.1	19.1	308	74 (64-81)	19.4	19.6
	II	185	67 (60-75)	16.2	16.1	207	71 (63-78)	13.6	13.6	Regional	362	67 (59-75)	30.0	29.9	485	69 (61-78)	30.5	30.3
	III	278	64 (58-73)	24.3	24.1	312	67 (57-76)	20.5	20.2	Distant	615	64 (57-73)	51.0	51.0	796	69 (59-78)	50.1	50.1
	IV	489	65 (57-73)	42.7	43.0	740	70 (59-78)	48.6	48.3									
Denmark	All patients	1,522	69 (62-76)			1,472	70 (62-78)			All patients	1,522	69 (62-76)			1,472	70 (62-78)		
	Missing	313	74 (66-83)	20.6		300	76 (68-84)	20.4		Missing	256	76 (67-83)	16.8		246	76 (68-84)	16.7	
	I	101	67 (60-73)	8.4	7.9	125	68 (61-76)	10.7	10.2	Localised	117	67 (60-74)	9.2	9.1	134	69 (62-77)	10.9	10.8
	II	159	67 (61-74)	13.2	13.1	174	71 (63-79)	14.8	14.7	Regional	509	67 (60-73)	40.2	39.5	513	69 (61-78)	41.8	41.5
	III	483	67 (60-73)	40.0	39.5	342	68 (60-76)	29.2	28.9	Distant	640	68 (62-74)	50.6	51.4	579	68 (61-76)	47.2	47.7
	IV	466	68 (62-74)	38.5	39.6	531	68 (61-76)	45.3	46.1									
Ireland¶	All patients	741	70 (62-78)			1,007	72 (62-79)			All patients	741	70 (62-78)			1,007	72 (62-79)		
	Missing	255	75 (66-83)	34.4		312	73 (63-82)	31.0		Missing	181	77 (66-84)	24.4		198	75 (68-83)	19.7	
	I	34	64 (57-69)	7.0	7.0	62	73 (65-81)	8.9	11.2	Localised	78	67 (60-76)	13.9	14.0	71	75 (65-82)	8.8	10.2
	II	116	69 (63-76)	23.9	24.2	61	73 (64-77)	8.8	10.0	Regional	245	69 (62-76)	43.8	45.7	302	71 (61-77)	37.3	38.0
	III	138	67 (61-75)	28.4	29.9	143	71 (63-78)	20.6	20.1	Distant	237	69 (60-76)	42.3	40.3	436	70 (61-78)	53.9	51.8
	IV	198	69 (60-76)	40.7	38.8	429	69 (61-78)	61.7	58.7									
New Zealand	All patients									All patients					1,078	70 (59-79)		
	Missing									Missing					498	73 (63-81)	46.2	
	I									Localised					83	70 (48-77)	14.3	16.0
	II									Regional					116	70 (60-77)	20.0	24.8
	III									Distant					381	66 (57-77)	65.7	59.2
	IV																	
Norway	All patients									All patients	761	69 (62-78)			1,287	72 (62-80)		
	Missing									Missing	227	73 (66-81)	29.8		274	76 (66-84)	21.3	
	I									Localised	130	70 (64-78)	24.3	25.0	219	74 (63-82)	21.6	21.6
	II									Regional	201	67 (60-75)	37.6	37.4	386	71 (62-79)	38.1	38.1
	III									Distant	203	67 (60-75)	38.0	37.7	408	69 (60-78)	40.3	40.3
	IV																	
United Kingdom‡	All patients	23,244	71 (63-80)			17,493	75 (66-82)			All patients	23,244	71 (63-80)			17,493	75 (66-82)		
	Missing	6,593	77 (67-84)	28.4		5,479	79 (70-85)	31.3		Missing	6,211	77 (67-84)	26.7		5,255	79 (70-85)	30.0	
	I	1,965	70 (63-78)	11.8	11.4	1,412	75 (67-81)	11.8	11.1	Localised	2,197	71 (64-78)	12.9	12.3	1,413	75 (67-81)	11.5	10.9
	II	2,756	71 (63-79)	16.6	16.3	2,216	74 (66-81)	18.4	18.0	Regional	7,624	70 (63-78)	44.8	43.5	4,973	74 (65-80)	40.6	39.2
	III	6,186	69 (62-77)	37.2	36.0	2,896	72 (64-79)	24.1	22.9	Distant	7,212	70 (62-78)	42.3	44.2	5,852	73 (64-80)	47.8	49.9
	IV	5,744	70 (62-78)	34.5	36.4	5,490	73 (64-80)	45.7	48.0									

† Canadian provinces included: Alberta, Manitoba, Newfoundland, Nova Scotia, Prince Edward Island and Saskatchewan
‡ United Kingdom registries included: England, Northern Ireland and Wales
° Australia registries included: New South Wales
¶ Ireland (2012-2013)
¥ 25th-75th percentiles

FIGURE LEGENDS

Figure 1. Distribution of (imputed) stage at diagnosis by cancer site, histological subtype, country and staging system, 2012-2014

OAC= oesophageal adenocarcinoma ; OSCC = oesophageal squamous cell carcinoma

Figure 2. Age-standardised one- (top panel) and three-year (bottom panel) net survival from oesophageal and gastric cancer by (imputed) SEER stage, country and histological subtype, 2012-2014

† Canadian provinces included: Alberta, Manitoba, Newfoundland, Nova Scotia, Prince Edward Island and Saskatchewan
‡ United Kingdom registries included: England, Northern Ireland and Wales
º Australia registries included: New South Wales
¶ Ireland (2012-2013)
OAC= oesophageal adenocarcinoma ; OSCC = oesophageal squamous cell carcinoma

Figure 3. Age-standardised one- and three-year net survival from oesophageal and gastric cancer by (imputed) TNM stage, country and histological subtype, 2012-2014

† Canadian provinces included: Alberta, Manitoba, Newfoundland, Nova Scotia, Prince Edward Island and Saskatchewan
‡ United Kingdom registries included: England, Northern Ireland and Wales
¶ Ireland (2012-2013)
OAC= oesophageal adenocarcinoma ; OSCC = oesophageal squamous cell carcinoma