Original research

International variation in oesophageal and gastric cancer survival 2012–2014: differences by histological subtype and stage at diagnosis (an ICBP SURVMARK-2 population-based study)

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ABSTRACT

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To cite: Arnold M, Morgan E, Bardot A, et al. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/ gutjnl-2021-325266 **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 28923 patients with oesophageal cancer and 25946 patients with gastric cancer diagnosed during 2012-2014 from 14 cancer registries in seven countries (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the UK) were included. 1-year and 3-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 1 (50.3% vs 41.3%, respectively) and 3 years (27.0% vs 19.2%) postdiagnosis. Survival from gastric cancer was highest in Australia and lowest in the UK, for both 1-year (55.2% vs 44.8%, respectively) and 3-year survival (33.7% vs 22.3%). Most patients with oesophageal and gastric cancer 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 1-year postdiagnosis. 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, and 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

Significance of this study

What is already known on 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.

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 oesophageal adenocarcinoma was generally higher than that from oesophageal squamous cell carcinoma, disparities across countries were similar for both histological subtypes.

research are promising and will likely allow for additional risk stratification and survival improvements in the future.

INTRODUCTION

With together more than 1.5 million new cases and over 1.3 million deaths estimated globally in





Significance of this study

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 populationbased screening, primary prevention targeting wellestablished risk factors such as *Helicobacter 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.

2020,¹ oesophageal and gastric cancers 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 5 years after diagnosis. International disparities in survival from oesophageal and gastric cancer have been described² and considerable variation exists across high-income countries with 5-year survival estimates ranging from 14.7% to 23.5% and from 20.8% to 32.8% for patients diagnosed with oesophageal and gastric cancer 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 and also air pollution and unhealthy diet and represents the most common subtype globally.^{5–7} OAC has been associated with obesity and gastro-oesophageal reflux disease (GERD) and represents roughly two thirds of oesophageal cancers in high-income countries such as the UK and the USA.⁶⁸⁹

The most important prognostic factor determining oesophageal and gastric cancer survival is stage at diagnosis. Yet, as earlystage 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 1-year and 3-year postdiagnosis.

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. Ouality 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 patients with oesophageal and gastric cancer diagnosed during 2012-2014 and followed-up until 31 December 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 or at autopsy, below the age of 15 or above 99 years at diagnosis, with inconsistencies in stage information (eg, 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, 28923 oesophageal and 25964 gastric cancer cases were included in the survival analyses (table 1).

Each participating cancer registry provided information on pretreatment pathological and clinical T, N and M, grouped TNM stage and/or Surveillance, Epidemiology and End Results Program (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 (categorised as localised, regional and distant), using a predefined mapping algorithm (online supplemental 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 by Cabasag et al.13 A summary flowchart of how registry-specific staging information was mapped to SEER staging is available in online supplemental figure 1.

Table 1 Character	istics of patients	s with oesophag	eal and gastric c	ancer diagnos	ed during 2012–	2014		
				Oesopl	nageal cancer			
	Australia*	Canada**	Denmark	Ireland†	New Zealand	Norway	UK‡	Total
Number of patients diagnosed during 2012–2014	1424	1328	1582	769		797	24037	29937
Total exclusions								
Diagnosed based on 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§	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**	-	-	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	1365 (95.9%)	1290 (97.1%)	1522 (96.2%)	741 (96.4%)		761 (95.5%)	23244 (96.7%)	28923 (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%)	6845 (29.4%)	8935 (30.9%)
Adenocarcinoma	745 (54.6%)	847 (65.7%)	816 (53.6%)	359 (48.4%)		446 (58.6%)	14319 (61.6%)	17532 (60.6%)
Other	99 (7.3%)	96 (7.4%)	63 (4.1%)	51 (6.9%)		67 (8.8%)	2080 (8.9%)	2456 (8.5%)
				Gas	tric cancer			
Number of patients diagnosed during 2012–2014	2078	1929	1636	1096	1145	1416	18933	28233
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§	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**	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	1890 (91.0%)	1737 (90.0%)	1472 (90.0%)	1007 (91.9%)	1078 (94.1%)	1287 (90.9%)	17 493 (92.4%)	25964 (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%)	5326 (30.4%)	8608 (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%)	6413 (36.7%)	9430 (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%)	5754 (32.9%)	7926 (30.5%)

*Australia registries included: New South Wales.

†Ireland (2012-2013).

‡UK registries included: England, Northern Ireland and Wales.

§Includes: data inconsistencies (invalid age, missing/incomplete dates), tumours with non-malignant behaviour, tumours with invalid morphological or topographical codes.

¶Stage error or in situ flag. **Gastrointestinal stromal tumour (GIST): ICD-0-3 Morphology code 8936.

t+ICD-0-3 Morphology codes 8013, 8041–8045, 8150–8158, 8240–8247, 8249, 8574 and 9091.

DCO, death certificate only.

Statistical analyses

We report estimates of net survival with accompanying 95% CI, which is the probability of survival for patients with cancer 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 1-year and 3-year postdiagnosis were obtained using

Pohar Perme estimators¹⁴ 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 1-year net survival estimates, and the period approach was used to estimate 3-year net survival as not all patients with cancer had 3 years of follow-up.¹⁵ Age-standardisation was carried out using the International Cancer Survival Standard 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% CI.¹⁷

All analyses were performed in Stata V.14 (Stata, College Station, Texas, USA). While 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 online supplemental 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 8216 C16.0 cases in the analyses for oesophageal cancer. While we do not 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 patients with OAC and OSCC. 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 28923 cases of oesophageal cancer, including 8935 cases of OSCC (30.9%) and 17532 cases of OAC (60.6%) diagnosed during 2012–2014 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 patients with OAC tending to be slightly younger at initial diagnosis (online supplemental 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 1-year (50.3% vs 41.3%, respectively) and 3-year (27.0% vs 19.2%) postdiagnosis (figure 2, online supplemental 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 1-year and between 43.9% in Canada and 66.1% in Ireland at 3-year postdiagnosis. Survival differences across countries for regional and distant stage were smaller, with 1-year survival for distant disease ranging between 21.8% in Australia and 27.2% in Denmark and 3-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, online supplemental tables 4, 5). Survival from OAC was generally better than from OSCC, for all stages combined and for each stage. While 1-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 3 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 that is, 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 (online supplemental tables 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,

Image: state						TNM stage									Mapped SEER			
Normalizational statemetric statemetris statemetris statemetric statemetric statemetric statemetric sta				Oesophagea	al cancer			Ga	stric cancer				Oesophageal	cancer			Gastric cano	-
Image: sector index and the						%				%					%			%
Mode Mode <th< th=""><th></th><th>Stage</th><th>Number</th><th>Median age at diagnosis (P25–P75*)</th><th>Observed</th><th>After imputation</th><th>Number</th><th>Median age at diagnosis (P25–P75*)</th><th>Observed</th><th>After imputation</th><th>Stage</th><th>Number</th><th>Median age at diagnosis (P25-P75*)</th><th>Observed</th><th>After imputation Nun</th><th>Median ag at diagnos iber (P25–P75*</th><th>je is () Observed</th><th>After imputat</th></th<>		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 Nun	Median ag at diagnos iber (P25–P75*	je is () Observed	After imputat
104 104 <th>Australia†</th> <th>All patients</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th>All patients</th> <th>1365</th> <th>71 (63–79)</th> <th></th> <th>1</th> <th>90 71 (61–80)</th> <th></th> <th></th>	Australia†	All patients									All patients	1365	71 (63–79)		1	90 71 (61–80)		
1 1		Missing									Missing	239	73 (64–81)	17.5		224 74 (64–84)	11.9	
1 1		_									Localised	462	73 (66–83)	41.0	42.1	542 72 (62–81)	32.5	33.3
1 1		=									Regional	308	68 (60–77)	27.4	26.8	180 70 (60–78)	28.8	28.7
N N		=									Distant	356	67 (59–76)	31.6	31.1	544 69 (59–79)	38.7	37.9
ImageJuneConstrainedCon		≥																
10 10<	Canada‡	All patients	1290	67 (58–76)			1737	71 (61–80)			All patients	1290	67 (58–76)			37 71 (61–80)		
1 1		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	
iii		_	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
i i		=	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	185 69 (61–78)	30.5	30.3
It B G-01 C <td></td> <td>=</td> <td>278</td> <td>64 (58–73)</td> <td>24.3</td> <td>24.1</td> <td>312</td> <td>67 (57–76)</td> <td>20.5</td> <td>20.2</td> <td>Distant</td> <td>615</td> <td>64 (57–73)</td> <td>51.0</td> <td>51.0</td> <td>796 69 (59–78)</td> <td>50.1</td> <td>50.1</td>		=	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
Mom Signal Signal <td></td> <td>≥</td> <td>489</td> <td>65 (57–73)</td> <td>42.7</td> <td>43.0</td> <td>740</td> <td>70 (59–78)</td> <td>48.6</td> <td>48.3</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>		≥	489	65 (57–73)	42.7	43.0	740	70 (59–78)	48.6	48.3								
Indicational Indicatioral Indicational Indicational<	Denmark	All patients	1522	69 (62–76)			1472	70 (62–78)			All patients	1522	69 (62–76)		1	172 70 (62–78)		
i i		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 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
i i 0		=	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
N 6 6.2.7 35 36 6.1 3.2 5.1 6.1 2.2 4.1 Mayer 31 6.6.7 3 3 5.6.7 3.6 3.6.3		=	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
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GI cancer

Table 2 C	ontinued															
				TNM stage									Mapped SEER			
		Oesophage	al cancer			Gas	tric cancer				Oesophageal c	ancer			Gastric cancer	
				%				%					%			%
	Stage Numl	Median age at diagnosi: ber (P25–P75*)	s 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
	III 618	36 69 (62–77)	37.2	36.0	2896	72 (64–79)	24.1	22.9	Distant	7212	70 (62–78)	42.3	44.2 5852	73 (64–80)	47.8	49.9
	IV 57 ₄	44 70 (62–78)	34.5	36.4	5490	73 (64–80)	45.7	48.0								
*25th–75th percentile †Australia registries in ‡Canadian provinces ii §Ireland (2012–2013).	s. cluded: New South Wales. icluded: Alberta, Manitoba, Ne	wfoundland, Nova Scol	tia, Prince Edward Islanc	l and Saskatchewan.												

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).

Netsurvival from gastric cancer was highest in Australia—55.2% and 33.7% at 1-year and 3-year postdiagnosis, respectively-and lowest in the UK (44.8% and 22.3%, respectively) (figure 2, online supplemental table 7). Overall, patterns across countries were similar for 1-year and 3-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 1 year and from 86.5% in New Zealand to 59.9% in the UK at 3-year postdiagnosis. 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 1-year and 3-year postdiagnosis, ranging from 26.6% to 20.7% at 1-year and from 8.0% to 3.8% at 3-year postdiagnosis. 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, online supplemental table 7). When comparing stage-specific survival estimates obtained after multiple imputation with those using the original, nonimputed data, that is, 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 (online supplemental 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 (online supplemental table 9, online supplemental figures 2, 3). Small differences in survival estimates were also found when comparing all patients with oesophageal cancer with the combined group of patients with OSCC and OAC (online supplemental 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 1-year postdiagnosis. Excluding proximal tumours only had a marginal impact on estimated 3-year survival and on overall patterns across countries (online supplemental table 10, online supplemental figures 6, 7). Finally, while only small survival differences were observed between male and female patients with gastric cancer, females with oesophageal cancer had better survival than their male counterparts (online supplemental figures 8, 9).

DISCUSSION

registries included: England, Northern Ireland and Wales

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Survival from oesophageal and gastric cancer continues to vary substantially across high-income countries, including within stage and histological subgroups. 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



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.

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 patients with oesophageal and gastric cancer. Recent studies from the USA¹⁸¹⁹ and Norway²⁰ which presented survival at 5-year postdiagnosis, 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 programmes have only proven costefficient 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 GERD 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 subtype) 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 with 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 OAC, as it preceded publication of the CROSS study in 2015.³¹ Furthermore, endoscopic Barrett's oesophagus screening and surveillance in highrisk individuals could have contributed to earlier detection of OAC, and, in combination with minimally invasive techniques in the management of localised 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, for example, 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, (neo)adjuvant









New Zealand (NZL)

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Country

Norway (NOR)

Figure 2 Age-standardised 1-year (top panel) and 3-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; ‡ Australian registries included: New South Wales; [§]Ireland (2012-2013).









3-year net survival (%)

Oesophageal Cancer

Stage II

÷

Stage III

•

Stage IV

Stage

All stages

100

80

60

40

20 0







Figure 3 Age-standardised 1-year and 3-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; ‡ Australian registries included: New South Wales; [§]Ireland (2012-2013).

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 oesophagogastric cancer treatment, which has led to improved survival and reduced postoperative mortality in some settings.^{36–39} 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 postoperative 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 subpopulation. The introduction of screening programmes and prophylactic gastrectomies targeting high-risk individuals may have led to an increased identification at early stage and therefore better survival, for example, 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 harmonisation 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 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 histology⁴⁷ 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 populationbased 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 comorbidities are critical steps in developing a complete understanding of the underlying mechanisms that explain international differences in cancer survival.

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GI cancer

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