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ORIGINAL ARTICLE

Prognostic factors in metastatic gastric cancer: results of a population-based, retrospective cohort study in Ontario

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Abstract

Background Stage IV gastric cancer is lethal, and little population-based research on prognostic factors has been performed in low-incidence countries. Therefore, we investigated the consistency of the associations of patient, disease and healthcare system factors identified in previous population-based research to understand their generalizability to other low-incidence populations.

Methods A population-based, retrospective cohort study of patients diagnosed with Stage IV gastric cancer in Ontario between 1 April 2005 and 31 March 2008 was performed. Kaplan-Meier methodology and the log-rank test were used for bivariate analysis. Multivariate Cox proportional hazard regression was performed. Hazard ratios (HRs) and 95 % confidence intervals (CIs) are presented.

Results On multivariate analysis, patient, disease and healthcare system factors were independent predictors of survival. Increasing age per 10 years (HR 1.07; 95 % CI 1.02–1.10), a tumor located in the gastroesophageal junction (HR 1.09; 95 % CI 0.94–1.27) or middle of the stomach (HR 1.14; 95 % CI 0.97–1.35), presence of carcinomatosis (HR 1.61; 95 % CI 1.42–1.83) and a larger burden of metastatic disease (2–3 sites of metastatic disease: HR 1.17; 95 % CI 1.03–1.32; ≥4 sites: HR 1.69; 95 % CI 1.30–2.20) were associated with worse prognosis. Female gender, receipt of surgery, chemotherapy and radiotherapy and treatment from a high-volume, gastric cancer specialist were all associated with significantly better prognosis. In addition, there was evidence of significant geographic variation in survival.

Conclusion This study provides supporting evidence for patient, disease and healthcare system prognostic factors in metastatic gastric cancer. Future work investigating the

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role of emerging molecular and biologic information will need to take these established prognostic factors into consideration.

Keywords Metastatic cancer · Prognostic factor

Introduction

Gastric cancer is the fourth most commonly diagnosed cancer worldwide and the second leading cause of cancer-related mortality [1, 2]. TNM stage is the cornerstone of prognostication in gastric cancer and used to guide treatment decision-making [3, 4]. Stage IV disease ($T_{any}N_{any}M_1$) is diagnosed in 35–55 % of gastric cases in low-incidence countries such as the USA and Canada, and this preponderance of noncurative disease contributes substantially to its dismal survival rate [5, 6]. Median disease-specific survival in metastatic disease has been estimated to be approximately 10 months [3] and overall 5-year survival estimated to be 3–5 % [6, 7].

Due to the rarity of this disease and a lack of staging data, little population-based research to investigate prognosis in patients with metastatic gastric cancer in North America or Europe has been performed [8–11]. In the few studies that have been completed using large databases, tumor grade, age, sex, ethnicity/race, marital status and receipt of treatment were identified as important prognostic factors [8–11]. These studies have been limited by missing information on important variables, such as tumor location, extent of metastatic disease, comorbidities and socioeconomic status. Furthermore, the impact of physician volume is missing and diminishes our understanding of the disease and its management at the population level.

Therefore, we aimed to use a large, population-based Canadian administrative data set supplemented by individual chart review data to expand on existing knowledge in the prognosis of Stage IV gastric cancer. Demonstrating the generalizability of prognostic factors across populations is essential to providing evidence of the consistency of the associations [12]. Replication of results is a key step in prognostic factor research, one that is often underperformed [12]. In doing so, we aimed to confirm the prognostic value of disease, patient and healthcare system factors identified in previous population-based studies, while examining the value of additional prognostic factors such as the primary tumor location, burden of metastatic disease and care from a high-volume gastric cancer specialist. The purpose of this study was to determine which factors may explain worse survival to help refine prognostication and to identify any potentially modifiable factors that might be targeted to improve patient outcomes in the future.

Methods

A retrospective, population-based cohort study and chart review of gastric cancer patients in Ontario, Canada, was performed. Ontario has over 13 million inhabitants, making it the most populous province in Canada. This project received Research Ethics Board approval at Sunnybrook Health Sciences Centre and adhered to privacy and confidentiality regulations of the Institute for Clinical Evaluative Sciences (ICES). The purpose of this study was to test the generalizability of prognostic factors identified in other low-incidence, population-based databases, as well as examine the association with survival of several prognostic factors not yet explored in the literature [12].

Study population

Patients were identified through the Ontario Cancer Registry (OCR), a registry of incident cancer cases in the province [13, 14]. Patients were staged according to the AJCC 7th edition [4] using radiology, pathology and clinical information collected during a primary chart review. Patients were excluded if they were younger than 18 years, older than 99 years, diagnosed with a nonadenocarcinoma cancer, had tumors in the mid to upper esophagus, were missing geographic residence information, did not have a valid Ontario Health Insurance Plan number (OHIP), were diagnosed on autopsy or death certificate only, or had nonmetastatic disease.

Data collection and sources

A comprehensive province-wide chart review (hospital charts, including radiology, endoscopy, operative and consultation notes) was performed and linked to the following administrative data sets held by ICES: OHIP, the Canadian Institute of Health Information-Discharge Abstract Database (CIHI-DAD) and the Registered Persons Database (RPDB). The chart review provided clinical disease data, such as the stage, symptoms and primary information on treatment strategies. OHIP contains physician billing claims and provided information on treatment modalities [15]. CIHI-DAD contains data on procedures for all in- and outpatient services provided at provincial institutions and provided supplemental information on the interventions provided to the cohort [15].

Outcome definition

Overall survival was the primary outcome of this study and measured using the date of death from the OCR, and death due to any cause was considered an event. Survival was measured from the date of diagnosis to death. Individuals were followed from their date of diagnosis until the end of our follow-up period (31 March 2010).Patients were censored if they did not experience the event (death) in this time period. Because there was staggered entry into the cohort (dates of diagnosis across a 2-year period), each patient had differing amounts of follow-up, with a minimum of 3 years of follow-up for all survivors. The OCR provided information on the vital status of Ontarians from the Ontario Registrar General.

Disease, patient and healthcare system prognostic factors

Information in endoscopy reports was used to define tumor location. Locations included the gastroesophageal junction (GEJ), proximal stomach, middle stomach, distal stomach, entire stomach or unknown. Results from radiology and pathology reports were used to determine the location and number of metastatic sites. The locations were categorized as follows: distant lymph node(s), carcinomatosis and/or ascites, liver, retroperitoneal, lung, bone or ovarian. Other sites of metastasis were rare and not analyzed. The number of metastatic sites was calculated as the sum of all unique distant organ locations where cancer was found. If a patient had more than one site of metastasis within an organ as categorized above, it only counted once toward the number of metastatic sites. Patients for whom an M1 diagnosis had been made, but specific sites of metastasis were not provided, were categorized as unknown.

In addition to age (modeled as a continuous variable on multivariate analysis) and sex, the following prognostic factors have been identified in the literature as being related to survival in metastatic gastric cancer: comorbidity, socioeconomic status (SES) [16], rurality [17], tumor location, location and number of metastatic sites, geographic region of residence, treatment (surgery, chemotherapy and radiotherapy) and receipt of care from a high-volume specialist. Comorbidity was measured using the Deyo modification of the Charlson score [18, 19]. In Ontario, all health services are provided by a single-payer system run by the provincial government, and healthcare planning, spending and delivery are organized into 14 Local Health Integrated Networks (LHINs) (http://www.lhins.on.ca/home.aspx). Patients were assigned to a geographic region categorized into LHINs using their postal codes. These regions were labeled 1–14. Physician billing codes were used to identify which patients had received a gastrectomy (partial or total, with or without a multivisceral resection) and chemotherapy and to define receipt of radiotherapy. Gastric cancer patient volume for each physician within each specialty (surgeon, medical oncologist, radiation oncologist) was calculated over a 7-year time period (1 April 2003–31 March 2010), and physicians were categorized into volume quartiles by specialty. Volume classifications were created such that one quarter of patients fell into each category. By our definition, a high-volume surgeon performed an average of at least 3.5 gastrectomies/year, a high-volume medical oncologist saw on average at least 6.7 gastric cancer patients/year, and a high-volume radiation oncologist saw on average at least 15.8 gastric cancer patients/year. Receipt of care or a consultation from at least one of the three high-volume specialists defined above was considered a "yes" for the high-volume consultation variable.

Statistical analysis

Median survival was calculated using Kaplan-Meier methods [20]. Bivariate and multivariate survival analyses were performed using Cox-proportional hazards methods to produce a hazard ratio. Hazard ratios and their 95 % confidence intervals provided an estimate of the relative rate of death between two comparator groups. Values >1 indicate an increased rate of death, and values <1 indicate a decreased rate of death. Backward selection modeling was used to explore whether or not a priori prognostic factors selected from the literature describing survival for metastatic gastric cancer patients in low-incidence countries were independent predictors of survival in our data set, using a cutoff p value of 0.05 to determine which predictors stayed in the model. The assumptions of proportional hazards were assessed by including a time-dependent variable in the model for each covariate [21]. All analyses were performed using SAS 9.2, copyright 2008 (Cary, NC, USA). Cell sizes containing <6 patients were suppressed because of the privacy and confidentiality regulations of ICES and the Ontario Privacy Commissioner.

Results

In Ontario, 2,516 patients had a registered diagnosis of gastric cancer during the study period. Figure 1 provides an overview of the cohort selection process. Table 1 provides a description of the final cohort of 1,433 patients (57 %) with metastatic disease. Median survival for the cohort was 6.2 months (Table 2) and is shown in Fig. 2. Bivariate relationships between all disease, patient and healthcare

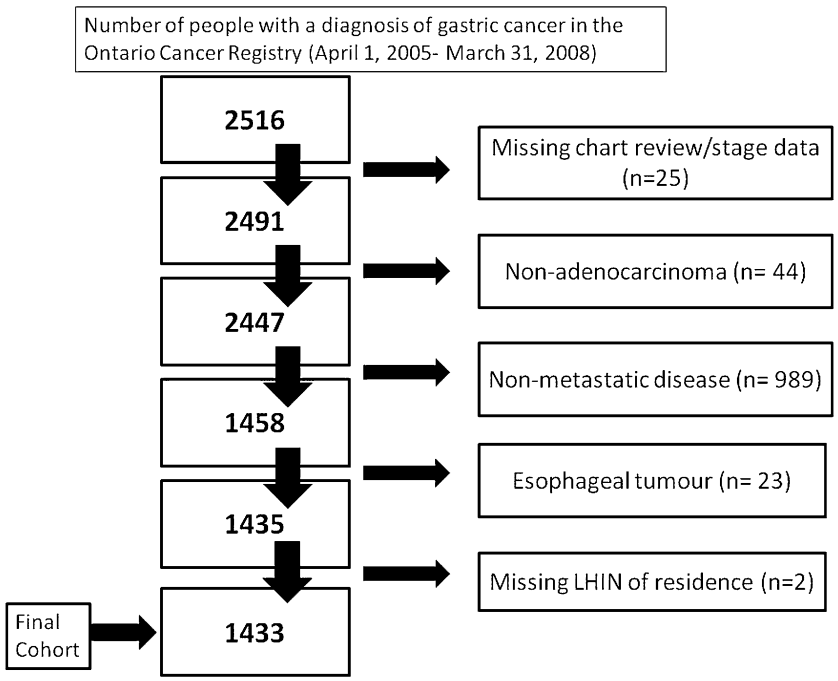


Fig. 1 Cohort selection process

system factors and survival were statistically significant, with the exception of the presence of ovarian or distant lymph node metastases, comorbidities, and median household income (Table 3). Strong associations with an increased rate of death were also documented for older age (HR 1.47; 95 % CI 1.30–1.67), tumors of the entire stomach (HR 1.41; 95 % CI 1.15–1.71), a large number of organs involved with distant disease (HR 2.12; 95 % CI 1.65–2.71), and the presence of carcinomatosis or ascites (HR 1.48; 95 % CI 1.33–1.66). The strongest predictors of survival on bivariate analysis were related to the healthcare system. Receipt of a gastrectomy was associated with a nearly 60 % reduction in rate of death (HR 0.42; 95 % CI 0.37–0.47); receipt of chemotherapy was associated with a 46 % reduced rate of death (HR 0.54; 95 % CI 0.49–0.61) and radiotherapy with a 37 % reduced rate of death (HR 0.58 95 % CI 0.51–0.65). A significantly increased rate of death was also noted in 1 of the 14 LHINs (HR 2.12; 95 % CI 1.43–3.11). Consultation with or treatment from a high-volume gastric cancer specialist was associated with an almost 40 % reduction in rate of death (HR 0.61; 95 % CI 0.54–0.68).

On multivariate analysis, age, sex, tumor location, presence of carcinomatosis or ascites, number of organs involved with metastatic disease, treatment strategy, geographic region of residence and consultation with a high-volume specialist all remained independent predictors of survival (Table 4). The effects of all prognostic factors were reduced when the other variables were included in the model. Increased age was significantly associated with an increased rate of death of 7 % for every 10 years (HR 1.07; 95 % CI 1.02–1.10). Individuals with a tumor located in the gastroesophageal junction (HR 1.09; 95 % CI 0.94–1.27) or the middle stomach (HR 1.14; 95 % CI 0.97–1.35) were also at a significantly increased rate of death. The presence of carcinomatosis remained a strong prognostic factor, after controlling for all other factors, and was associated with a 60 % increased rate of death (HR 1.61; 95 % CI 1.42–1.83). In addition, the more organs involved with metastatic disease, the greater was the rate of death. Patients with four or more anatomic sites involved with metastatic disease had a significantly higher rate of death than patients with only one site (HR 1.69; 95 % CI 1.30–2.20).

Compared to men, women had a 19 % reduced rate of death (HR 0.82; 95 % CI 0.73–0.92). Patients with tumors located in the proximal stomach had a significantly decreased rate of death compared to patients with a tumor located in the distal stomach (HR 0.83; 95 % CI 0.68–1.02). The five healthcare system prognostic factors remained the strongest prognostic factors in metastatic gastric cancer. Receipt of gastrectomy was associated with an almost 60 % reduction in rate of death (HR 0.43; 95 % CI 0.38–0.49), receipt of chemotherapy was associated with a 45 % reduction in rate of death (HR 0.56; 95 % CI 0.49–0.64), and receipt of radiotherapy was associated with a 20 % reduction in rate of death (HR 0.77; 95 % CI 0.68–0.88). While these results support an association between treatment strategies and survival, they do not confirm causation and must be interpreted with caution, given that the selection of patients for treatment is unclear. Understanding which patients are appropriate to select for which combination of treatment and palliation to incur

Table 1 Description of the cohort ($n = 1433$)

Variable	Number of patients (%)
Patient characteristics	
Age (mean)	67.5 years (range 20–97)
Gender	
Male	934 (65)
Charlson score	
0	1,279 (89)
1	82 (6)
≥2	71 (5)
Median income	
Lowest income	296 (21)
Quintile 2	329 (23)
Quintile 3	284 (20)
Quintile 4	268 (19)
Highest income	255 (18)
Rurality	
Urban	1,274 (89)
Disease characteristics	
Tumor location	
Gastroesophageal junction	390 (27)
Proximal stomach	139 (10)
Middle stomach	229 (16)
Distal stomach	476 (33)
Entire stomach	134 (9)
Unknown	65 (5)
Burden of metastatic disease	
1	700 (49)
2–3	435 (30)
≥4	179 (12)
Unknown	53 (4)
Location of metastasis	
Carcinomatosis or ascites	880 (61)
Distant lymph nodes	714 (50)
Liver	423 (29)
Lung	137 (10)
Retroperitoneum	104 (7)
Bone	92 (6)
Ovary	32 (2)
Abdominal wall	31 (2)
Brain	<6
Prostate	<6
Healthcare system characteristics	
High-volume gastric cancer specialist consultation	477 (33)
Gastrectomy	527 (37)
Chemotherapy	615 (43)
Radiotherapy	398 (28)
Local health integration network (LHIN)	
1	81 (6)
2	79 (5)
3	77 (5)
4	167 (12)
5	72 (5)
6	122 (9)
7	151 (11)
8	211 (15)
9	152 (11)
10	53 (4)
11	127 (9)
12	41 (3)
13	78 (5)
14	22 (2)

optimal benefits is necessary before the survival impact of these treatment modalities can be concluded. The effect of specialist volume was greatly reduced on multivariate analysis. This may signify that high-volume specialists see a different case mix of patients, and controlling for their characteristics in addition to treatment provided explains the majority of the provider impact on outcomes for patients with metastatic disease. Heterogeneity in rate of death for metastatic gastric cancer patients existed across the province, even after controlling for different treatment and patient characteristics that may have explained differences in survival, and it remained a significant prognostic factor.

Discussion

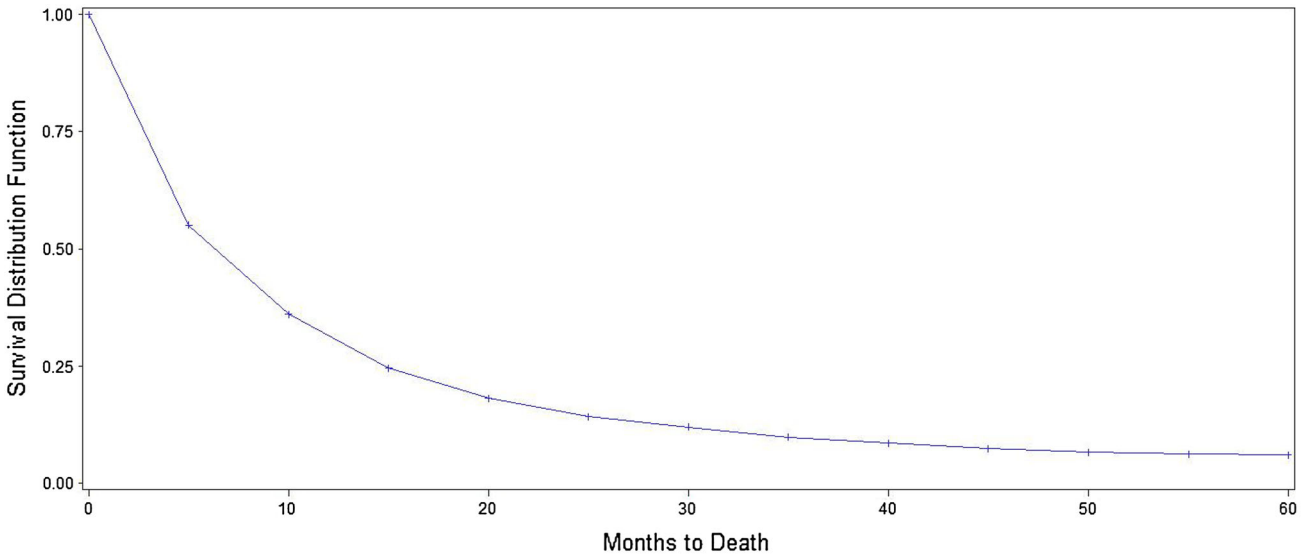
In low-incidence countries, the average oncologist will face more incurable cases of gastric cancer than curative. Our study is consistent with other Western studies, finding more than 50 % of gastric cancer cases are metastatic at diagnosis. On average, these patients have a dismal prognosis, and in our study median survival was only 6.2 months. This study supports previous findings that a number of patient, disease and healthcare system prognostic factors are associated with survival in this terminally ill population, some of which may be modifiable. Increasing age and male sex were associated with worse prognosis, and variation in rates of death were documented across tumor locations and geographic regions. In addition, the presence of carcinomatosis and/or ascites and the extent of metastatic disease were identified as significant predictors of

Table 2 Comparing survival among patient, disease and healthcare system variables (log-rank test)

Variable	Category	Median survival (months)	95 % CI	*p* value
Patient characteristics				
Age (years)	<65	8.6	7.5–9.6	<0.0001
	65–74	6.8	5.2–7.8	
	>74	4.1	3.4–4.8	
Sex	Female	6.3	5.4–7.6	0.1473
	Male	6.0	5.3–6.9	
Charlson score	0	6.4	5.8–7.2	0.0706
	1	4.2	2.4–6.0	
	≥2	5.1	2.8–7.6	
Median income	Lowest income	5.5	4.7–6.9	0.6212
	Quintile 2	6.2	5.2–7.6	
	Quintile 3	6.5	4.8–7.9	
	Quintile 4	5.9	4.8–7.4	
	Highest income	7.0	5.6–8.1	
Rurality	Rural	5.2	4.2–7.2	0.0309
	Urban	6.2	5.7–7.0	
Disease characteristics				
Tumor location	GEJ	7.0	5.6–8.2	0.0124
	Proximal	6.6	4.8–8.6	
	Middle	5.0	3.9–5.9	
	Entire	4.3	3.1–5.6	
	Distal	7.4	6.0–8.2	
	Unknown	7.6	3.4–10.8	
Number of metastatic sites	1	8.6	7.6–9.7	<0.0001
	2–3	4.8	4.3–5.3	
	≥4	3.5	2.4–4.8	
	Unknown	5.3	2.7–9.9	
Distant LN metastasis	No	6.1	5.3–7.1	0.5600
	Yes	6.2	5.3–7.2	
Carcinomatosis or ascites	No	8.8	7.7–10.0	<0.0001
	Yes	5.0	4.3–5.4	
Liver metastasis	No	7.1	6.1–7.9	<0.0001
	Yes	5.0	4.3–5.7	
Retroperitoneal metastasis	No	6.4	5.8–7.1	0.0276
	Yes	5.5	5.0–6.4	
Lung(s) metastasis	No	6.3	5.7–7.0	0.0169
	Yes	4.9	3.9–7.4	
Bone(s) metastasis	No	6.3	5.7–7.1	0.0098
	Yes	4.6	3.2–6.4	
Ovarian metastasis	No	6.0	5.5–6.8	0.5893
	Yes	10.8	5.0–15.9	
Healthcare system characteristics				
LHIN	1	6.0	3.9–9.1	0.0108
	2	5.0	3.5–8.0	
	3	6.1	3.4–8.6	
	4	7.3	5.1–8.9	
	5	9.1	5.2–13.0	
	6	6.3	4.7–8.3	
	7	5.8	4.9–7.2	
	8	5.8	4.5–7.6	
	9	7.6	5.6–10.2	
	10	5.2	2.4–6.9	
	11	6.6	4.6–10.1	
	12	3.4	2.2–4.8	
	13	6.7	4.3–8.7	
	14	4.7	2.9–18.8	
Gastrectomy	No	4.2	3.9–4.7	<0.0001
	Yes	13.3	11.0–14.8	
Chemotherapy	No	3.4	3.0–3.9	<0.0001
	Yes	11.7	10.4–12.9	
Radiotherapy	No	4.7	4.3–5.1	<0.0001
	Yes	12.0	10.5–13.4	
High-volume gastric cancer specialist consultation	No	4.3	3.9–4.7	<0.0001
	Yes	11.9	10.6–13.4	

worse prognosis. Healthcare system factors, including treatment, region of residence and consultation with a high-volume gastric cancer specialist, were strong predictors of survival after adjustment for patient- and disease-related factors.

After adjusting for patient and disease characteristics, our results supported other population-based data, leading to the conclusion that gastrectomy, chemotherapy and radiotherapy are associated with improved overall survival compared to patients not undergoing the therapy [8–11]. Although consistent, these results should be interpreted with caution. It has been well documented that treatment selection bias, or a lack of understanding of the decision-making behind receipt of a particular modality, likely confounds the association between treatment and survival [22]. Therefore, the treatment strategy a patient undergoes may be more a reflection of the patient's overall health and patient, physician and institution behaviors and preferences. We were unable to determine why some patients did not receive chemotherapy or any of the other treatment modalities. A Cochrane review has provided strong



Number at Risk						
0 months	10 months	20 months	30 months	40 months	50 months	60 months
1435	527	276	191	145	120	114

Fig. 2 Overall Kaplan-Meier curve of time from diagnosis to death (from any cause) for metastatic gastric cancer patients in Ontario

evidence of a significant survival benefit for receipt of chemotherapy in comparison with best supportive care alone [23], and ongoing randomized controlled trials are investigating the benefit of surgery in metastatic patients [24, 25]. Until these results are available, guidelines for treatment decision-making in the metastatic population will remain inconclusive as to the best management strategy [25, 26]. In the absence of these data, future work understanding the characteristics of patients who receive these therapies will provide further support to clinicians in making treatment decisions.

Two metaanalyses have investigated the prognostic role of surgeon volume in gastric cancer patients undergoing cancer-directed surgery, and both determined a consistent association between higher volume and reduced short-term mortality; the association with long-term outcomes was less clear [27, 28]. In the metastatic population, the effect of surgeon volume on outcomes was reduced. We explored the possibility that this interaction may be better represented by measuring contact (consultation or treatment) with a high-volume specialist (medical oncologist, surgeon or radiation oncologist), as their treatment is multidisciplinary, and best practice may be the nonreferral to surgery rather than the surgery itself that most impacts long-term outcomes in the metastatic population. This study identified care from a high-volume specialist as being a strongly protective factor, associated with a 15 % reduction in rate of death (95 % CI 0.75–0.98). High surgeon volume has been proposed to represent experience, training and understanding of disease management, and this depth of understanding likely applies across specialties. In the metastatic setting, volume may positively influence long-term outcomes through appropriate supplementary care (not measured in this study), management of symptoms and optimal patient selection for treatment modalities. Further investigation and refinement of our understanding of the role of specialty volume and survival in metastatic cancer are warranted and could provide an understanding of the benefits of centralization of cancer care above and beyond the traditional knowledge of operative outcomes.

This study was limited by its inability to provide an evaluation of the prognostic value of many biologic, pathologic and molecular features of the cancer. Data on such factors as histologic classification, lymphovascular invasion or perineural invasion were missing in more than 50 % of cases, reflecting the large proportion of cases who did not receive surgical management and therefore likely did not receive an in depth pathologic examination. However, given that these features are likely unknown for the majority of patients, this study provides a population-based analysis of practical prognostic factors that will likely be available for prognostication in most metastatic gastric cancer patients in low-incidence countries. In addition, information on performance status was not collected for any of the patients and would likely be a strong predictor of survival.

In the absence of reliable information on molecular, biologic and pathologic tumor factors, primary tumor location, the presence of carcinomatosis, number of metastatic sites, age, sex, geography, treatment modality and receipt of care from a high-volume specialist can be

Table 3 Bivariate analysis of overall survival using Cox proportional hazards regression

Variable	Unadjusted HR (95 % CI)	*p* value
Patient characteristics		
Age (years)		
<65	Reference	<0.0001
65–74	1.17 (1.03–1.34)	
>74	1.47 (1.29–1.67)	
Sex		
Male	Reference	0.1480
Female	0.91 (0.82–1.03)	
Charlson score		
0	Reference	0.0716
1	1.29 (1.02–1.61)	
≥2	1.12 (0.88–1.43)	
Median income		
Lowest income	Reference	0.6208
Quintile 2	0.94 (0.80–1.11)	
Quintile 3	0.87 (0.74–1.03)	
Quintile 4	0.93 (0.79–1.10)	
Highest income	0.96 (0.80–1.14)	
Rurality		
Urban	Reference	0.0313
Rural	1.20 (1.02–1.43)	
Disease characteristics		
Tumor location		
Distal stomach	Reference	0.0129
Gastroesophageal junction	1.12 (0.97–1.28)	
Proximal stomach	1.08 (0.89–1.32)	
Middle stomach	1.24 (1.05–1.46)	
Entire stomach	1.41 (1.15–1.71)	
Unknown	1.14 (0.87–1.49)	
Number of metastatic sites		
1	Reference	<0.0001
2–3	1.49 (1.33–1.67)	
≥4	2.12 (1.65–2.71)	
Unknown	1.33 (0.99–1.81)	
Distant LN metastasis		
No	Reference	0.5607
Yes	0.97 (0.87–1.08)	
Carcinomatosis or ascites		
No	Reference	<0.0001
Yes	1.48 (1.33–1.66)	
Liver metastasis		
No	Reference	0.0001
Yes	1.26 (1.12–1.42)	
Retroperitoneal metastasis		
No	Reference	0.0280
Yes	1.26 (1.03–1.55)	
Lung(s) metastasis		
No	Reference	0.0172
Yes	1.24 (1.04–1.49)	
Bone(s) metastasis		
No	Reference	0.0100
Yes	1.33 (1.07–1.65)	
Ovarian metastasis		
No	Reference	0.5900
Yes	0.91 (0.64–1.29)	
Healthcare system factors		
LHIN		
1	1.30 (0.94–1.81)	0.0130
2	1.45 (1.04–2.01)	
3	1.29 (0.92–1.80)	
4	1.10 (0.82–1.47)	
5	Reference	
6	1.32 (0.98–1.79)	
7	1.19 (0.89–1.60)	
8	1.11 (0.84–1.47)	
9	1.03 (0.77–1.39)	
10	1.34 (0.92–1.94)	
11	1.24 (0.92–1.68)	
12	2.12 (1.43–3.11)	
13	1.36 (0.98–1.90)	
14	1.09 (0.66–1.80)	
Gastrectomy		
No	Reference	<0.0001
Yes	0.42 (0.37–0.47)	
Chemotherapy		
No	Reference	<0.0001
Yes	0.54 (0.49–0.61)	
Radiotherapy		
No	Reference	<0.0001
Yes	0.63 (0.56–0.71)	
High-volume gastric cancer specialist consultation		
No	Reference	<0.0001
Yes	0.61 (0.54–0.68)	

HR hazard ratio, *CI* confidence interval

considered significant prognostic factors. The consistent identification of these prognostic factors across data sets allows for generalizable prognostication in low-incidence countries. Understanding the added value of molecular and biologic prognostic factors in metastatic gastric cancer in personalizing prognosis and treatment decision-making will require adjustment for these established characteristics. The next steps in precision medicine for metastatic

Table 4 Multivariate analysis of overall survival using Cox proportional hazards regression

Variable	Overall survival	*p* value
	Adjusted HR[a] (95 % CI)	
Patient characteristics		
Age (per 10 years)	1.07 (1.02–1.10)	0.0036
Sex		
Male	1.00 (reference)	0.0008
Female	0.82 (0.73–0.92)	
Disease characteristics		
Tumor location		
Distal	1.00 (reference)	0.0275
Gastroesophageal junction	1.09 (0.94–1.27)	
Proximal	0.83 (0.68–1.02)	
Middle	1.14 (0.97–1.35)	
Entire	0.99 (0.81–1.23)	
Unknown	0.80 (0.60–1.05)	
Presence of carcinomatosis or ascites		
No	1.00 (reference)	<0.0001
Yes	1.61 (1.42–1.83)	
Number of metastatic sites		
1	1.00 (reference)	0.0007
2–3	1.17 (1.03–1.32)	
≥4	1.69 (1.30–2.20)	
Unknown	1.13 (0.82–1.55)	
Healthcare system factors		
Gastrectomy		
No	1.00 (reference)	<0.0001
Yes	0.43 (0.38–0.49)	
Chemotherapy		
No	1.00 (reference)	<0.0001
Yes	0.56 (0.49–0.64)	
Radiotherapy		
No	1.00 (reference)	0.0001
Yes	0.77 (0.68–0.88)	
High-volume gastric cancer specialist		
No	1.00 (reference)	0.0206
Yes	0.85 (0.75–0.98)	
Local health integration network		
1	1.03 (0.74–1.45)	0.0073
2	1.35 (0.97–1.89)	
3	1.10 (0.79–1.55)	
4	1.03 (0.77–1.38)	
5	1.00 (reference)	
6	1.02 (0.75–1.39)	
7	0.88 (0.65–1.18)	
8	0.92 (0.69–1.22)	
9	0.77 (0.58–1.04)	
10	0.96 (0.66–1.41)	
11	0.93 (0.69–1.26)	
12	1.53 (1.03–2.28)	
13	1.16 (0.83–1.63)	
14	0.96 (0.58–1.60)	

[a] Adjusted for all other variables in the model

gastric cancer should include the development of a prognostic tool to estimate individualized survival probabilities, incorporating both standard, established prognostic factors and emerging information.

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