Understanding Survival Disparities in Gastric Cancer

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Gastric cancer is the fifth most common cancer in the world and there are significant survival disparities among patient groups. These survival disparities are complex, multifactorial, linked, and not fully elucidated. Contributing factors include, but are not limited to: race, ethnicity, sex, surgical management, receipt of multimodality therapies, birthplace and migration, molecular markers, and provision of end-of-life care. In this review, we highlight work that investigated these differences and the impact they have on survival among patients with gastric cancer.

Gastric cancer was the fifth most common cancer in 2018 with over one million new cases, 55% of which occurred in developed countries.[1,2] Mortality remains high and gastric cancer is the third leading cause of cancer-related death in the world.[1] Despite decreasing trends in incidence and death worldwide, high rates of gastric cancer remain throughout much of Asia, Eastern Europe, and Latin America.[2] The incidence in males surpasses that in females in all geographic areas.[1] Gastric cancers are generally classified as proximal and distal, or similarly cardia and non-cardia, and the prevalence of each type varies geographically, with distal cancers dominating Asian and European countries and proximal cancers steadily increasing in the Western world.[1,3]

There is an abundance of reports on the disparities related to various cancers, including gastric cancer.[4–7] The National Cancer Institute describes cancer health disparities as "differences in the incidence, prevalence, mortality, and burden of cancer and related adverse health conditions that exist among specific population groups".[8] Within cancer literature, disparities in survival are highly relevant. Morris et al. suggest that the largest survival disparities exist among patients with solid tumors, for whom appropriate and high-quality treatment is available and is an important factor in prognosis.[9] This applies to gastric cancer, where high-quality surgery and use of multimodality treatment are critical to achieve best outcomes.[10] Global trends have shown marked disparities in gastric cancer survival around the world. Five-year survival ranges from 12% in Thailand to 58% in South Korea.[11] It is important to note that South Korea has a national screening program given the high incidence of gastric cancer.[12] Males and females at least 40 years of age are eligible for screening endoscopies every 2 years.

In a meta-analysis, Markar et al. compared survival between Eastern and Western patients, pooling data from 25 randomized controlled oncologic trials and comparing chemotherapy with surgery compared to surgery alone, with adjustments for confounding variables.[13] This study showed improved 5-year survival with any treatment for gastric cancer in the East with a pooled odds ratio of 4.83. The effect remained when adjusted for age, sex, chemotherapy, tumor depth, nodal status, and gastrectomy type. With respect to potential explanations, while much of the emphasis has been put on race and ethnicity, several studies have also reported differences related to other demographic and socioeconomic factors,[14–18] stage at diagnosis, access to care,[19–21] variations in care received, genetics,[22–25] diet,[26,27] stage migration,[28–30] and *Helicobacter pylori* presence.[31] Presently, we are unable to determine the specific impact of the factors known to contribute to survival disparities, and, in addition, there may be other contributory factors that are undiscovered thus far. This review will consider a few select factors and their relationship to survival disparities in gastric cancer.

Race and ethnicity

Survival differences related to race and ethnicity are well described in the gastric cancer literature.[32–34] Using a population dataset from Los Angeles County, USA, Kim et al. showed that Asian patients had better survival compared to Whites, Hispanics, and Blacks undergoing gastrectomy in the USA.

Median survival was nearly twice as long in Asians compared to the other racial groups and the results remained robust even accounting for lymph node retrieval.[35] Interestingly, the improved survival in Asians was not equivalent across Asian ethnicities.[36] When comparing outcomes in Korean, Japanese, Chinese, Vietnamese, and Filipino surgical cohorts, Kim et al. showed that Koreans had the best survival following treatment for gastric cancer, whereas Filipinos had the worst survival. These differences persisted even when stratified by stage. In addition, Koreans had more favorable tumor features compared to the other Asian ethnicities, such as lower rates of distant and lymph node metastases, cardia tumors and signet ring cell features.[36]

Some of the survival differences between races and ethnicities may be explained by changes at the molecular level. For example, Theuer et al. demonstrated higher frequency of microsatellite instability in gastric cancers from Japanese patients compared to American patients.[37] Another publication by this group demonstrated that normal e-cadherin expression was more common in Japanese intestinal-type gastric cancer, whereas c-erbB2 expression was higher in American gastric cancers.[38] The significance of these findings and their association with survival differences, if any exists, is not fully elucidated. Work intended to improve understanding at the molecular level is in progress and may help clinicians to more appropriately select and tailor treatments and more accurately predict survival in future.

Sex

Sex may also be a contributing factor in survival disparities. Global data demonstrates that gastric cancer is more common in males;[1] however, Kim et al. showed that female sex may be an adverse feature in advanced gastric cancer.[39] In their retrospective analysis comprising 4,700 consecutive patients undergoing gastrectomy in a high-volume center in Korea, the authors found that female patients were more likely to be younger, have signet ring carcinoma, undifferentiated/diffuse histology and poorer survival than men, in patients under 45 years of age. They went on to study the effect of estrogen as a potential contributing factor and found that there were differences in staining of estrogen receptor (ER)-beta between the two groups, with males exhibiting a higher expression. Wang et al. demonstrated decreased expression of ER-beta in advanced gastric adenocarcinoma and suggested that ER-beta affects cell proliferation through interactions with other proteins.[40] This may potentially contribute to survival differences through effects on cell proliferation; however, this hypothesis requires further investigation.

Clinical management

Management of gastric cancer mandates a well-coordinated multidisciplinary approach. This was emphasized by Coburn et al. who developed a consensus statement on necessary processes in the management of gastric cancer.[41] Given the medical and surgical complexity and involvement of many healthcare providers, potential for variability in care is significant. Areas of variability include, but are not limited to, surgical technique, including extent of lymph node dissection (LND), and the utilization of pre-operative and adjuvant therapies as outlined below.

Lymph node dissection

Extent of LND has long been the subject of great debate in the world of gastric cancer surgery. More extensive LND in Eastern patients was shown to be associated with improved survival in a variety of early publications.[42,43] As a result, D2 LND was the standard of care in Eastern countries long before the benefits were recognized in the West. The 15-year results of the Dutch study, which compared D1 versus D2 LND, showed significantly improved local control and gastric cancer mortality in the D2 arm.[44] Dissection of lymph nodes beyond the D2 borders does not result in further improvements in survival and, in fact, contributes to increased surgery-related complications.[45] Therefore, the D2 lymphadenectomy standard of care in the East is now being adopted in the West.[46]

The phenomenon of stage migration may also be a contributing factor to survival disparities, as with larger lymph node harvest there is improved staging accuracy and survival predictions.[28] Known as the Will Rogers phenomenon, there may be migration (or up-staging) of disease into more advanced stages as a result of lymph node disease identification during more extensive dissection. In such cases, evidence of a more advanced disease stage would have remained undiscovered with less extensive dissection. Thus, the more radical LND in the East may contribute to reported survival differences.[29,30,47,48]

There is also evidence to suggest that survival continues to improve with increasing nodal harvest. Smith et al. used Surveillance, Epidemiology and End Results (SEER) data and demonstrated superior survival with increased number of lymph nodes examined.[49] The cohort consisted of patients with gastric cancer treated between 1973 and 2000 with surgery only, as multimodality therapy was not routinely offered to patients during that period. Amongst this cohort, stage subgroups were identified and sorted for number of lymph nodes examined. Interestingly, as the number of lymph nodes retrieved and examined increased, the median group survival improved for all stages examined. Improvement in survival ranged from 6 to 11% for each 10 additional lymph nodes examined.

Despite the critical nature of harvesting lymph nodes in gastric cancer surgery, there is variability in lymph node retrieval in multiple countries. In Canada, Mahar et al. reviewed patients with stage 1–3 gastric cancer diagnosed between 2005 and 2008, and showed that removal of fewer than 15 lymph nodes varied from 42 to 74% between regional centers in Ontario.[50] In the USA, Al-Refaie et al. showed that lymph node retrieval varied with race and ethnicity, as Asian race predicted a 50% reduction in risk of inadequate lymphadenectomy in patients diagnosed with gastric cancer between 1998 and 2005.[51] In the Netherlands, removal of at least 10 lymph nodes increased from 49 to 58% between 2008 and 2010 in high-volume hospitals.[52] While this is encouraging, it also means that many patients received inadequate lymphadenectomy by current standards.

Although increased extent of LND (up to D2 lymphadenectomy) improves survival outcomes, there is evidence that the survival benefit associated with retrieving more lymph nodes may not be equal amongst all racial and ethnic groups. For example, using SEER data, Nelson et al. showed that lymph node number impacted survival for White patients but not Korean-American patients undergoing curative intent gastrectomy in the USA.[53] The groups were divided into 1–15 and 16+ lymph nodes retrieved, and while greater extent of LND improved survival outcomes for White patients, this was not the case for Korean-American patients. It is possible that Korean Americans have more favorable tumor features and disease biology which may potentially reduce the benefit from extended LND.

Pre-operative therapy

Disparities in treatment are also apparent with the use of pre-operative chemotherapy. Using the National Cancer Database, Ikoma et al. showed that the use of pre-operative chemotherapy increased during the study period in patients with resectable disease from 34% in 2006 to 65% in 2014, with higher use in cardia compared to non-cardia cancers.[54] However, socioeconomic and demographics factors were associated with reduced use of this modality. For example, ethnicity other than non-Hispanic White, low education level, and no insurance were associated with less frequent use of pre-operative chemotherapy, robust even with propensity score matching. In the surgery alone group, there were survival differences between the racial groups, with the best survival in non-Hispanic Whites. However, in those who underwent pre-operative chemotherapy and surgery, the survival differences between the groups disappeared. Thus, pre-operative chemotherapy may ameliorate survival differences amongst racial groups. The impact may be more significant in systems without universal healthcare coverage where access to appropriate care is limited because of financial constraints.

Adjuvant therapy

Adjuvant therapies (chemotherapy or chemoradiation) in gastric cancer have been shown to improve survival outcomes and thus have become standards of care, with utilization depending somewhat on geographical region.[55–57] Al-Refaie et al. examined factors associated with lack of receipt of adjuvant chemoradiation for those with at least Stage 1B gastric cancer.[51] The National Cancer Database was queried and the study examined 106,000 patients, of which 72% were White. In this cohort, 50% of patients underwent gastrectomy. Of the patients who were deemed to be eligible for multimodality therapy, fewer than 30% ultimately received it. African Americans and Hispanics were less likely to receive adjuvant chemoradiation, although this effect was confounded by insurance status. Other factors associated with lack of receipt of adjuvant therapy included advanced age, female sex and diagnosis before 2002. Most importantly, lack of chemoradiation was associated with poorer survival in the entire cohort.

Internationally, there is also significant variability in the utilization of adjuvant therapy. In Ontario, Canada, significant variation in the receipt of chemotherapy and radiotherapy between regional centers was noted in patients with resectable gastric cancer.[50] Receipt of chemotherapy varied from 33 to 58% and radiotherapy usage varied from 20 to 56% in regional centers. Despite the development of national guidelines in the Netherlands, there was significant inter-hospital variation in administration of adjuvant chemoradiotherapy even after case-mix adjustment.[52]

Age

A significant proportion of cancer-related deaths occur in patients >65 years of age. Disparities in cancer treatment in the elderly have been well documented in the literature[58] and also exist in gastric cancer. Using the SEER database, Dudeja et al. explored a cohort of patients 65 years and older diagnosed between 1998 and 2006 and determined whether these patients received guideline recommended care for resectable gastric cancer.[59] While 61% of gastric cancer operations occurred in those at least 65 years of age, only 31% of this group received adequate lymphadenectomy and 24% received adjuvant chemoradiation. In comparison to the youngest cohort of patients, aged 65–69, the rates of adequate lymphadenectomy and adjuvant chemoradiation decreased significantly

with increased age. While not specifically studied, this may occur because of issues related to comorbidities, frailty, decreased life expectancy and clinician perceptions.[58–60]

Conditional survival

Prior investigations on racial disparities have examined overall survival from time of diagnosis or surgical intervention; however, traditional survival estimates may become less accurate if patients survive beyond a certain period. This is where prognosis may be more accurately described using conditional survival, a statistical concept that reflects how changing hazard rates over time impact a patient's prognosis. Luyimbazi et al. examined conditional survival in gastric cancer in Asians, Blacks, and Whites.[61] The overall 5-year survival rates were highest for Asians at 43% and lower for Blacks and Whites at about 30%. However, when survival was examined in yearly increments, the racial disparities diminished as time went on. More specifically, each year beyond diagnosis there was an increase in the relative conditional survival in all the racial groups, such that by year 5 there were no significant survival differences between the three groups. One potential explanation for this would be that a greater proportion of patients with worse disease in the White and Black groups may have suffered early mortality and therefore only those with better prognosis survived. Similar results were obtained even in patients with stage 1A disease. These findings suggest that the initial survival disparities associated with race and ethnicity tend to diminish the longer patients survive beyond initial treatment.

Birthplace and migration

There is limited information on the effect of birthplace and migration on gastric cancer outcomes. Kirchoff et al. used SEER data to examine the effect of birthplace on survival in patients who underwent curative-intent surgery for gastric cancer.[62] The study consisted of data from 10,089 American patients of whom the majority were non-Asian. The Asian cohort was further divided into those born in the USA and those that were not. These were quite different cohorts clinicopathologically. Using tumor location as an example, Asians born outside of the USA had a higher percentage (42.8%) of distal tumors compared to Asians born in the USA (32.5%, p<0.001) and non-Asians (27.8%, p<0.001). There were also differences in tumor stage; Asians born outside of the USA had a higher percentage of stage 1A tumors (22.6%) compared to non-Asians (17.2%, p<0.001). There were notable differences in survival between the groups; Asians born outside the USA demonstrated the best 5-year survival rates at 51%, with a median survival of 61 months, compared to other groups whose 5-year survival ranged from 26–38%, with a median survival range of 18–32 months. Furthermore, multivariable analysis showed that factors associated with better survival included removal of greater than 15 lymph nodes and Asian ethnicity born outside of the USA. The reason for the survival difference in Asians based on birthplace suggests a probable key role of environmental factors. Thus, as Asians migrate to the USA (or elsewhere), the tumor characteristics change, and survival differences may become less pronounced.

Molecular markers

More recently, a molecular classification of gastric cancer has generated some new insights into the disease.[22] Analysis of 295 treatment-naïve specimens of patients with gastric cancer revealed the presence of four distinct molecular subtypes (Epstein-Barr virus positive, microsatellite unstable, genomically stable, and tumors with chromosomal instability),

each with unique features. While survival differences were not observed in this initial data, more recent evidence suggests that there are differences in survival amongst the four distinct subtypes.

Molecular profiling of a cohort of patients who underwent gastrectomy for cancer in South Korea revealed that those with Epstein-Barr virus positive tumors had the best survival whereas those with genomically stable tumors had the worst survival.[63] Given that the specimens were from Korean patients only, the results cannot be generalized to other races and ethnicities, although this would be an exciting avenue to pursue. There is also a growing body of information pertaining to various genetic polymorphisms which may confer risk for worsening gastric cancer phenotype, differential responses to treatment and differences in survival.[23–25,64,65] This type of molecular information will allow for more selective testing of therapies in subgroups of patients with gastric cancer and may lead to more accurate survival predictions in the future.

Response to immunotherapy in advanced disease

With improved understanding of gastric cancer at a molecular level, there is now growing interest in the use of immunotherapies in patients with metastatic and advanced unresectable disease. The ATTRACTION-2 study assessed the efficacy and safety of nivolumab (programmed cell death protein 1 [PD-1] inhibitor) in Japanese, South Korean, and Taiwanese patients whose advanced gastric or gastroesophageal junction cancer was refractory to two or more chemotherapy regimens.[66] The authors reported that compared to placebo, nivolumab extended overall survival in this cohort. The KEYNOTE-059 study sought to assess the efficacy of pembrolizumab in patients with previously treated gastric and gastroesophageal junction cancers.[67] Patients from 17 countries (Eastern and Western) were included in the study. The authors reported an objective response rate of 12%, complete response rate of 2% and 12-month overall survival of 23% in the cohort. In sub-group analyses there were no significant differences between Whites and Asians with respect to objective response rate and overall survival. These therapies are promising options for patients and further studies are required to determine whether factors such as race and ethnicity are associated with differential responses to treatment.

End-of-life care

Disparities extend across the entire spectrum of the patient disease trajectory, including end-of-life. Our research group has examined potentially aggressive care and palliative care in patients with gastrointestinal cancer at the end-of-life. We previously reported that two-thirds of patients with gastrointestinal cancer in Ontario, Canada received some form of aggressive end-of-life care within the final 30 days of life.[68] More specifically, hospitalizations, emergency department visits, and death in hospital hovered in the 40–50% range. Less than 10% of patients received chemotherapy, had an intensive care unit (ICU) admission or death in ICU during the study period which was from 2003 to 2013.

In contrast, in the USA, there were significantly higher rates of chemotherapy in the last 2 weeks of life and ICU admissions in the last 30 days of life.[69] In a study that directly compared indicators in Ontario, Canada and the USA, there were small differences in emergency department visits at end-of-life, but striking disparities with respect to usage of chemotherapy, ICU admissions and hospitalizations.[70]

Disparities with respect to availability and access to palliative care services, were observed across multiple countries. Our group recently reported that 74% of patients with gastrointestinal cancer received at least one palliative care encounter within 2 years of death in the province of Ontario, Canada.[71] In contrast, in the USA a similar population-based study examining use of palliative care services in Medicare patients with advanced cancer reported that only 4.5% of patients had had a palliative care encounter.[72]

Discussion

The main disparity in gastric cancer pertains to differences in survival, but this is directly related to other disparities which extend across the spectrum of care including the very end of life. The disparities are large, multifactorial and linked. There are significant limitations to the existing literature, including the retrospective nature of population-based studies and the difficulty in determining the impact of each individual factor, as no single study can fully evaluate all factors.

We hope that groups will be motivated by the data to continue identifying contributory factors but more importantly, to create innovative solutions. These are complex problems, the solutions to which will require buy-in from clinicians, policy makers and government; therefore, healthcare providers, in conjunction with appropriate stakeholders, should seek out modifiable factors and discuss ways in which to narrow the survival gap between patient groups. ❑

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