Title

Attrition during neoadjuvant chemotherapy for gastric adenocarcinoma is associated with decreased survival: A United States Safety-Net Collaborative analysis

Journal

Journal of Surgical Oncology, 124(8)

ISSN

8756-0437

Authors

Kronenfeld, Joshua P
Collier, Amber L
Turgeon, Michael K
et al.

Publication Date

2021-12-01

DOI

10.1002/jso.26638

Peer reviewed

HHS Public Access

Author manuscript

J Surg Oncol. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

J Surg Oncol. 2021 December ; 124(8): 1317–1328. doi:10.1002/jso.26638.

Attrition During Neoadjuvant Chemotherapy for Gastric Adenocarcinoma is Associated with Decreased Survival: A United States Safety-Net Collaborative Analysis

Joshua P. Kronenfeld, MD[1], **Amber L. Collier, MD**[1], **Michael K. Turgeon, MD**[2], **Michelle Ju, MD**[3], **Rodrigo Alterio, MD**[3], **Annie Wang, MD**[4], **Manuel Fernandez, MD**[5], **Matthew R. Porembka, MD**[3], **Harry Richter, MD**[5], **Ann Y. Lee, MD**[4], **Maria C. Russell, MD**[2], **Nipun B. Merchant, MD**[1], **Ajay V. Maker, MD**[6], **Jashodeep Datta, MD**[1]

[1.]Division of Surgical Oncology, Department of Surgery, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

[2.]Winship Cancer Institute, Division of Surgical Oncology, Department of Surgery, Emory University, Atlanta, GA

[3.]Division of Surgical Oncology, Department of Surgery, University of Texas Southwestern Medical School, Dallas, TX

[4.]Division of Surgical Oncology, Department of Surgery, NYU Langone Health, New York, NY

[5.]Division of Surgical Oncology, Department of Surgery, University of Illinois College of Medicine, Chicago, IL

[6.]Division of Surgical Oncology, Department of Surgery, University of California San Francisco, San Francisco, CA

Abstract

Background: Neoadjuvant chemotherapy (NAC) is standard management for localized gastric cancer (GC). Attrition during NAC due to treatment-related toxicity or functional-decline is considered a surrogate for worse biologic outcomes; however, data supporting this paradigm are lacking. We investigated factors predicting attrition and its association with overall survival (OS) in GC.

Methods: Patients with non-metastatic GC initiating NAC were identified from the US Safety-Net Collaborative (2012–14). Patient/treatment-related characteristics were compared between attrition/non-attrition cohorts. Cox-models determined factors associated with OS.

Results: Of 116 patients initiating NAC, attrition during prescribed NAC occurred in 24%. No differences were observed in performance status, comorbidities, treatment at safety-net hospital, or clinicopathologic factors between cohorts. Despite absence of distinguishing factors, attrition was associated with worse OS (median 11 vs. 37 months;P=0.01) and was an independent

Corresponding Author: Jashodeep Datta, MD, Division of Surgical Oncology | Department of Surgery, University of Miami Miller School of Medicine, Sylvester Comprehensive Cancer Center, 1120 NW 14th Street | Suite 410, Miami, FL 33136, Phone: (305)-243-4902, Fax: (305) 243-4907, jash.datta@med.miami.edu.

Disclosures: None

predictor of mortality (HR 4.7;95%CI:1.5–15.2;P=0.02). Fewer patients with attrition underwent curative-intent surgery (39% vs. 89%;P<0.001). Even in patients undergoing surgical exploration (n=89), NAC attrition remained an independent predictor of worse OS (HR 50.8;95%CI:3.6–717.8;P=0.004) despite similar receipt of adjuvant chemotherapy.

Conclusions: Attrition during NAC for non-metastatic GC is independently associated with worse OS, even in patients undergoing surgery. Attrition during NAC may reflect unfavorable tumor biology not captured by conventional staging metrics.

Keywords

gastric cancer; neoadjuvant therapy; completion of therapy

INTRODUCTION

Gastric adenocarcinoma (GC) is the 6th most common global cancer diagnosis and is responsible for more than 11,000 deaths annually in the United States (US) [1–3]. While the incidence has been steadily declining in recent years, GC continues to carry a poor prognosis with a five-year survival of only 25–30% [4, 5]. This grim prognosis is largely due to presentation at advanced stages, with only 10–20% of patients presenting with localized disease amenable to curative-intent resection [6, 7]. In patients with localized GC, a multimodality treatment approach, comprising chemotherapy and complete surgical resection, offers the best chance of improving survival [8, 9].

In contemporary practice, chemotherapy is delivered in the perioperative setting for patients with localized GC, and National Comprehensive Cancer Network guidelines recommend neoadjuvant chemotherapy (NAC) followed by surgical resection as the preferred treatment sequencing for patients with ≥T1b and/or node-positive cancers [10–13]. A major advantage of neoadjuvant treatment sequencing is the increased ability to deliver multimodality therapy in patients eligible for resection. Several randomized controlled trials have demonstrated that up to 50% of patients are unable to receive or complete adjuvant chemotherapy following gastrectomy, underscoring the importance of a neoadjuvant approach [14, 15]. Moreover, another putative advantage of neoadjuvant treatment sequencing—in patients whose disease does not progress distantly during induction therapy—is the biologic and physiologic selection of patients who might “benefit” from surgery. As such, attrition during NAC due to treatment-related toxicity or functional decline may be considered a surrogate for worse biologic outcomes; however, data supporting this paradigm are lacking.

In the present study, utilizing the US Safety-Net Collaborative (USSNC) database comprising five safety-net hospitals (SNH) and their affiliated tertiary referral academic centers, we sought to identify risk factors for attrition during prescribed NAC, and association between attrition and survival. Moreover, given data suggesting that socioeconomically disadvantaged patients treated at a single safety-net hospital were less likely to complete prescribed NAC compared with those treated at its academic center counterpart, we sought to investigate this question in this multi-institutional cohort [16].

MATERIALS & METHODS

Data Source

The USSNC database was utilized, which incorporates data from five academic institutions and their affiliated SNH, for this study. The US Department of Health and Human Services defines a SNH as one where providers organize and deliver a significant level of both healthcare and other health-related services to the uninsured, Medicaid, and other vulnerable populations [17]. Hospitals included in this consortium are the University of Miami Hospital and Jackson Memorial Hospital (Miami, FL), New York University Langone Health and Bellevue Hospital (New York, NY), Emory University Hospital and Grady Health System (Atlanta, GA), University of Texas Southwestern Medical Center and Parkland Memorial Hospital (Dallas, TX) and University of Illinois Hospital and Hospital of Cook County (Chicago, IL). Institutional review board approval for this study was obtained at each investigative site, and only de-identified data was shared across the consortium.

Patient Selection

Patients between the ages of 18 and 90 diagnosed with GC between 2012 and 2014 were identified in the USSNC database (n=378). International Classification of Diseases 9th edition codes were used to determine a diagnosis of GC, and presence of GC was confirmed through review of the medical record, imaging, and pathology. Specifically, patients with *non-metastatic* clinical stage I-III patients selected for NAC were included in this study. To provide “intention-to-treat” data, stage I-III GC patients initiating NAC were accrued *regardless* of completion of surgical exploration. Patients were excluded if NAC was not delivered, if information about the regimen was not available, if patients required emergent operative intervention for bleeding/obstruction, or if patients progressed to stage IV disease during NAC (Figure 1). Patients with progression of disease were excluded to prevent obvious confounding of planned survival analyses. The American Joint Committee on Cancer (AJCC) 8th edition was utilized to determine clinical and pathologic stage [18, 19].

Variables and Outcomes

We accrued the following categories of variables for this study: sociodemographic (age, gender, race, ethnicity, citizenship, proportion below the poverty level), healthcare access (treatment facility [academic vs. SNH], health insurance, presence of a primary care physician, and presence of a cancer care navigator), diagnostic information (screening laboratory findings, radiologic tumor size, and stage at diagnosis), neoadjuvant therapy details (time to chemotherapy, number of chemotherapy cycles, and receipt of radiation therapy), surgical intervention (whether surgery performed and extent of gastrectomy), pathologic data (pathologic tumor size, tumor differentiation, presence of lymphovascular invasion or perineural invasion, signet ring features), postoperative complication data, and adjuvant therapy details (chemotherapy given [yes/no], number of chemotherapy cycles, and receipt of radiation therapy).

Attrition was defined as the inability to complete the prescribed number of NAC cycles, as determined at the inception of treatment by the medical oncologist, and as documented in the medical record. Pertinent to the central question, reasons for attrition during NAC were

identified from chart review and codified as decline in Eastern Cooperative Group (ECOG) performance status, chemotherapy-related toxicity, or multifactorial etiology. Attrition from a multifactorial etiology was selected when a dominant cause of attrition could not be ascertained from the medical record, and encompassed a combination of performance status decline, treatment-related toxicity, patient/provider preference, and healthcare access issues, precluding completion of prescribed NAC. Overall survival (OS) was defined as months from diagnosis of GC to death or last date of follow-up.

Statistical Analysis

Sociodemographics and clinical characteristics were compared between patients who completed prescribed NAC and those that experienced attrition during neoadjuvant therapy. Variables were assessed by means of Mann-Whitney U test, chi-squared, or Fisher exact test as appropriate. Binary logistic regression was performed to identify predictors of attrition during NAC. Sociodemographic and healthcare access variables (age, gender, race, ethnicity, insurance and presence of a primary care physician and cancer care navigator) were included in this regression as they have been shown to impact treatment adherence in cancer [20–22]. A Cox proportional hazards regression model of OS was constructed controlling for age, gender, race, ethnicity, insurance status, poverty level, treatment facility, stage at presentation, presence of primary care physician, presence of a cancer care navigator, attrition during NAC, and receipt of surgery. Median OS was analyzed and stratified by attrition during or completion of NAC.

A subgroup analysis was performed for only patients who underwent surgical exploration, and an additional Cox proportional hazards regression model was utilized to identify predictors of OS in this subset of patients (included patients who were explored but not resected). All P values were deemed statistically significant at $P<0.05$ (two-sided). Statistical analysis was performed using SPSS version 26 (IBM Corporation, Armonk, NY, copyright 2019) [23].

RESULTS

Sociodemographics and Health Information

Of 116 patients who met inclusion criteria (Figure 1), median age of the cohort was 62 (interquartile range [IQR] 53–69), 75 (65%) were male, majority (58%) were white or non-Hispanic ethnicity (65%), and 20 (18%) lived in a zip code with greater than 25% of the population below the poverty level.

A majority of patients (n=62, 53%) were treated at academic centers, and 54 (47%) were treated at SNHs. Patients had varying health insurance coverage, although 24 (21%) were uninsured and 5 (4%) were insured only through hospital-based insurance. Most patient had a primary care physician (72, 70%) and a cancer care navigator (n=62, 64%).

A majority of patients (n=88, 76%) completed prescribed NAC, but 28 (24%) suffered attrition during intended NAC regimens (Table 1). Patients treated at SNHs were not statistically more likely to suffer attrition compared with those treated at academic counterparts, although there was a trend toward higher attrition in SNHs (32% vs. 18%,

P=0.09). While there was no difference between attrition and non-attrition cohorts in rates of guidance from a cancer care navigator or presence of a designated primary care physician, attrition patients were more likely to be uninsured (29% vs. 18%, P=0.07), although this comparison did not meet statistical significance.

Diagnostic and Treatment Information

Clinical staging parameters, radiographic tumor size, and pre-treatment tumor markers were similar between attrition and non-attrition cohorts. Moreover, there was no difference in time to initiation of NAC from diagnosis (42 [attrition] vs. 47 [non-attrition] days) between cohorts (Table 1). Not surprisingly, patients who suffered attrition during NAC were less likely to undergo surgical exploration (39% vs. 89%, P<0.001).

Predictors of Attrition During Prescribed NAC

On binary logistic regression controlling for age, gender, race, ethnicity, insurance and presence of a primary care physician and cancer care navigator, insurance status was an independent predictor of attrition during NAC. Uninsured patients (OR 10.66, 95% CI: 1.38–82.30, P=0.02) and those with hospital-based insurance (OR 44.84, 95% CI: 2.67–752.44, P=0.01) were more likely to have attrition on NAC (Table 2).

Subgroup Analysis of Patients Undergoing Surgery

A subgroup analysis was performed in the subset of 89 patients who underwent surgical exploration regardless of whether they completed prescribed NAC. Not surprisingly, the majority of explored patients (88%) completed NAC, but 11 (12%) actually underwent surgery despite suffering attrition during prescribed NAC. Median age was 62 (IQR: 53–67), and 58 (65%) were male (Table 3). There were no differences between the two surgically explored groups with respect to health insurance coverage, treatment at a SNH hospital, diagnostic stage, or extent of gastrectomy.

Survival Analyses

Median follow-up for the overall cohort was 30.6 (IQR: 12.8–62.7) months, and 52 (45%) were alive at the end of the follow-up period. A Cox proportional hazard regression analysis was then performed to examine the independent contribution of attrition during prescribed NAC on OS, while controlling for age, gender, race, ethnicity, insurance status, poverty level, treatment facility, stage at presentation, presence of primary care physician, presence of a cancer care navigator, and receipt of surgery (Table 4a). Attrition during NAC (HR 4.7, 95% CI: 1.5–15.2, P=0.01) was independently associated with worse OS (Figure 2a). In addition to attrition during NAC, other covariates independently associated with OS were treatment at a SNH (HR 4.0, 95% CI: 1.1–14.1, P=0.03), Asian race (HR 0.1, 95% CI: 0.0–0.4, P=0.001), and surgical exploration (HR: 0.2, 95% CI: 0.1–0.5, P=0.002).

In subgroup analysis of patients undergoing exploration, median follow-up was 37.5 (IQR: 18.0–71.2) months, and 49 patients (55%) were alive at the end of the follow-up period. Even in this cohort, Cox regression analysis (Table 4b) revealed that attrition on NAC was an independent predictor of decreased overall survival (HR 50.8, 95% CI: 3.6–717.8, P=0.004)

(Figure 2b). Having a cancer care navigator (HR 0.1, 95% CI: 0.0–0.6, P=0.01) was an independent predictor of improved OS in this cohort.

DISCUSSION

While attrition during NAC in patients with localized gastric cancer has been considered biologically ominous, this study demonstrates—for the first time to our knowledge—that attrition during NAC due to treatment-related toxicity, physiologic decline, or healthcare access considerations is an independent predictor of worse survival. Even in the subgroup of patients who underwent surgical exploration, regardless of whether they completed prescribed NAC or suffered attrition, attrition during NAC remained a significant predictor of worse survival after controlling for potential confounders. These data not only provide preliminary insight into a widely held belief that attrition during NAC may in part reflect unfavorable tumor biology not captured by conventional diagnostic metrics, but also suggest that application of this treatment sequencing may serve as a selection tool to identify those with unfavorable biologic or physiologic fitness who may not benefit from surgical exploration.

While attrition during NAC may be unavoidable in many cases, it is possible that certain etiologies for attrition may be potentially modifiable. For instance, in patients developing treatment-related toxicity, efforts to modify or attenuate chemotherapy dosing/schedules, provide aggressive supportive care, or being nimble with switching chemotherapy regimens (e.g., FLOT to FOLFOX) may be worthwhile [13, 24]. In patients suffering attrition due to functional or performance status decline, enrollment in pre-habilitation programs that provide physical therapy, mental or psychosocial health resources, and nutritional support may be beneficial [25, 26]. Finally, socioeconomic barriers—such as lack of insurance access identified in this study—may hinder patients significantly during neoadjuvant treatment. Other barriers for GC patients during neoadjuvant therapy may include the inability to pay for required treatment, difficulty in scheduling appointments due to decreased health literacy, challenges in keeping scheduled appointments due to work or family-related responsibilities, and other challenges faced by vulnerable populations [21, 27, 28]. While acknowledging that these factors are challenging to address, early identification of vulnerable populations at risk for attrition may allow targeted interception strategies to mitigate its deleterious consequences.

One potential solution to the obstacles in mitigating attrition identified in this study is the positive impact of a cancer care navigator during NAC. Our Cox regression model in the subgroup of surgically explored patients revealed that having a cancer care navigator was an independent predictor of improved survival. As such, social workers and cancer care navigators may be able to assist at-risk patients by identifying systemic barriers to care delivery, working to alleviate these challenges, and helping patients maneuver through the healthcare system [7]. The favorable impact of such navigators on survival in the surgically explored—but not overall—cohort in this study likely reflects the disproportionate magnitude of care-related logistics (e.g., clinic appointments, preoperative evaluations, postoperative follow-up, etc.) necessary in patients completing all components of multimodality therapy. Further investigation into the true impact of cancer care navigators

in GC management is needed in subsequent studies. Finally, although access to a cancer care navigator was not significantly different between patients treated at SNHs or academic centers, only two-thirds of patients had documented interactions with such a navigator. Taken together, these data reveal that while such disparities in healthcare access may impact outcomes in GC patients selected for NAC, they also present opportunities for targeted interventions that could facilitate completion of NAC and improve survival in this disease.

The fact that attrition during NAC for non-metastatic GC is independently associated with worse survival even in patients who underwent curative-intent surgical exploration and received adjuvant therapy, suggest that attrition may in part reflect unmeasured biologic aggressiveness occult on contemporary diagnostic modalities. Potential avenues for translational investigation into these hypothesis-generating data may be assessment of systemic inflammatory metrics (e.g., neutrophil-to-lymphocyte ratio), multi-dimensional peripheral immunophenotyping, circulating tumor cells or tumor DNA, or cancer-related cachexia in patients initiating NAC [29–32]. Moreover, deciphering correlations between attrition and molecular subtypes in GC may reveal novel therapeutic opportunities for a molecularly focused treatment strategy in patients at risk for attrition. In this regard as well, the neoadjuvant therapy paradigm represents an ideal platform to conduct these translational investigations to augment our understanding of the genotype-phenotype chasm in gastric cancer.

Limitations of this study warrant discussion. First, a study of this nature is limited by its retrospective design in that unmeasured factors may have influenced treatment sequencing and medical decision-making. Moreover, records for patients who received NAC at outside facilities were not available. Second, this study in high-volume cancer centers, including safety-net hospitals and tertiary care academic centers, may not be generalizable to GC patients treated nationally. For example, the disproportionate favorable survival outcomes noted in the non-attrition and surgically explored cohorts, compared to historic cohorts in the literature, may reflect the highly specialized multidisciplinary care these patients receive at high-volume centers that may not be available at other hospital systems. Third, the statistical analyses herein, particularly in the surgically explored cohort, were underpowered to detect crucial differences due to small sample size. Moreover, it is possible that patients suffering attrition during NAC had inherently unfavorable biology or increased frailty not sufficiently captured by accrued variables. As such, results of this study should be validated in larger multi-institutional datasets with granular data where a propensity-score matched analysis could be performed to limit confounding. Finally, the etiology of attrition was multifactorial in 17 patients. While these patients had a combination of treatment-related toxicities, functional decline, healthcare access issues, or elective termination of NAC due to provider and/or patient preference, the singular driver of attrition was not identifiable due to the retrospective nature of the data collection. Prospective studies may allow for a more detailed qualification of its etiology and would offer a more comprehensive understanding of attrition during NAC.

CONCLUSION

Attrition during NAC is an independent predictor of decreased survival in patients with localized GC, even in patients who underwent surgical exploration despite suffering attrition during prescribed NAC. In addition to functional decline and treatment-related toxicity, one of the important contributors to attrition identified in this study leveraging data from five SNHs was the increased risk faced by patients without health insurance or with hospital-based insurance. While efforts to provide equitable care to vulnerable GC patients may mitigate attrition, additional unmeasured biologic factors dictating tumor aggressiveness may also play a key role in promoting attrition during NAC. Further research is needed to quantify and qualify the impact of these factors to improve contemporary outcomes in this lethal malignancy.

ACKNOWLEDGEMENTS:

This research was supported in part by a T32 training grant in surgical oncology from the National Cancer Institute, National Institute of Health under award T32CA211034.

Funding:

Joshua Kronenfeld – NIH/NCI T32CA211034

DATA AVAILABILITY:

The data used in this study are available on request from the corresponding author, and are not publicly available due to privacy/ethical restrictions.

REFERENCES

1. Rawla P and Barsouk A, Epidemiology of gastric cancer: global trends, risk factors and prevention. Prz Gastroenterol, 2019. 14(1): p. 26–38. [PubMed: 30944675]
2. NIH. Cancer Stat Facts: Common Cancer Sites. 2020 03/05/2021]; Available from: https://seer.cancer.gov/statfacts/html/common.html.
3. Sung H, Ferlay J, Siegel RL, et al. , Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2021.
4. Sitarz R, Skierucha M, Mielko J, et al. , Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Manag Res, 2018. 10: p. 239–248. [PubMed: 29445300]
5. Asplund J, Kauppila JH, Mattsson F, and Lagergren J, Survival Trends in Gastric Adenocarcinoma: A Population-Based Study in Sweden. Ann Surg Oncol, 2018. 25(9): p. 2693–2702. [PubMed: 29987609]
6. NIH. Gastric Cancer Treatment (PDQ®)–Health Professional Version. 2021 03/05/2021]; Available from: https://www.cancer.gov/types/stomach/hp/stomach-treatment-pdq#_163_toc.
7. Recio-Boiles A and Babiker HM, Gastric Cancer, in StatPearls. 2021: Treasure Island (FL).
8. Datta J, McMillan MT, Ruffolo L, et al. , Multimodality Therapy Improves Survival in Resected Early Stage Gastric Cancer in the United States. Ann Surg Oncol, 2016. 23(9): p. 2936–45. [PubMed: 27090793]
9. Newton AD, Datta J, Loaiza-Bonilla A, et al. , Neoadjuvant therapy for gastric cancer: current evidence and future directions. J Gastrointest Oncol, 2015. 6(5): p. 534–43. [PubMed: 26487948]
10. NCCN. Gastric Cancer. 2021 03/05/2021]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.

11. Son T, Sun J, Choi S, et al. , Multi-institutional validation of the 8th AJCC TNM staging system for gastric cancer: Analysis of survival data from high-volume Eastern centers and the SEER database. J Surg Oncol, 2019. 120(4): p. 676–684. [PubMed: 31338834]
12. Reddavid R, Sofia S, Chiaro P, et al. , Neoadjuvant chemotherapy for gastric cancer. Is it a must or a fake? World J Gastroenterol, 2018. 24(2): p. 274–289. [PubMed: 29375213]
13. Orditura M, Galizia G, Sforza V, et al. , Treatment of gastric cancer. World J Gastroenterol, 2014. 20(7): p. 1635–49. [PubMed: 24587643]
14. Kilic L, Ordu C, Yildiz I, et al. , Current adjuvant treatment modalities for gastric cancer: From history to the future. World J Gastrointest Oncol, 2016. 8(5): p. 439–49. [PubMed: 27190583]
15. Leiting JL and Grotz TE, Advancements and challenges in treating advanced gastric cancer in the West. World J Gastrointest Oncol, 2019. 11(9): p. 652–664. [PubMed: 31558971]
16. Zaidi MY, Rappaport JM, Ethun CG, et al. , Identifying the barriers to gastric cancer care at safety-net hospitals: A novel comparison of a safety-net hospital to a neighboring quaternary referral academic center in the same healthcare system. J Surg Oncol, 2019. 119(1): p. 64–70. [PubMed: 30481370]
17. ASPE. Definition of Safety Net Hospitals. 2013 03/08/2021]; Available from: https://aspe.hhs.gov/report/environmental-scan-identify-major-research-questions-and-metrics-monitoring-effects-affordable-care-act-safety-net-hospitals/c-definition-safety-net-hospitals.
18. Marano L, D'Ignazio A, Cammillini F, et al. , Comparison between 7th and 8th edition of AJCC TNM staging system for gastric cancer: old problems and new perspectives. Transl Gastroenterol Hepatol, 2019. 4: p. 22. [PubMed: 31143843]
19. Liu JY, Peng CW, Yang XJ, et al. , The prognosis role of AJCC/UICC 8(th) edition staging system in gastric cancer, a retrospective analysis. Am J Transl Res, 2018. 10(1): p. 292–303. [PubMed: 29423014]
20. Sutton AL, Salgado TM, He J, et al. , Sociodemographic, clinical, psychosocial, and healthcare-related factors associated with beliefs about adjuvant endocrine therapy among breast cancer survivors. Support Care Cancer, 2020. 28(9): p. 4147–4154. [PubMed: 31897782]
21. Kronenfeld JP, Graves K, Penedo FJ, and Yanez B, Overcoming Disparities in Cancer: A Need for Meaningful Reform for Hispanic and Latino Cancer Survivors. Oncologist, 2021.
22. Penedo FJ, Oswald LB, Kronenfeld JP, et al. , The increasing value of eHealth in the delivery of patient-centred cancer care. Lancet Oncol, 2020. 21(5): p. e240–e251. [PubMed: 32359500]
23. IBM. IBM SPSS Statistics 26. 2020 03/08/2021]; Available from: https://www.ibm.com/support/pages/downloading-ibm-spss-statistics-26.
24. Liu M, Hu G, Wang Y, et al. , Comparison of FOLFOX and DOF regimens as first-line treatment in East Asian patients with advanced gastric cancer. Onco Targets Ther, 2018. 11: p. 375–381. [PubMed: 29398919]
25. O'Neill L, Moran J, Guinan EM, et al. , Physical decline and its implications in the management of oesophageal and gastric cancer: a systematic review. J Cancer Surviv, 2018. 12(4): p. 601–618. [PubMed: 29796931]
26. Rosania R, Chiapponi C, Malfertheiner P, and Venerito M, Nutrition in Patients with Gastric Cancer: An Update. Gastrointest Tumors, 2016. 2(4): p. 178–87. [PubMed: 27403412]
27. Kronenfeld JP, Ryon EL, Goldberg D, et al. , Survival inequity in vulnerable populations with early-stage hepatocellular carcinoma: a United States safety-net collaborative analysis. HPB (Oxford), 2020.
28. Kronenfeld JP, Ryon EL, Goldberg D, et al. , Disparities in Presentation at Time of Hepatocellular Carcinoma Diagnosis: A United States Safety-Net Collaborative Study. Ann Surg Oncol, 2020.
29. Zhou Y, Wei Q, Fan J, et al. , Prognostic role of the neutrophil-to-lymphocyte ratio in pancreatic cancer: A meta-analysis containing 8252 patients. Clin Chim Acta, 2018. 479: p. 181–189. [PubMed: 29407690]
30. Giakoustidis A, Neofytou K, Costa Neves M, et al. , Identifying the role of neutrophil-to-lymphocyte ratio and platelets-to-lymphocyte ratio as prognostic markers in patients undergoing resection of pancreatic ductal adenocarcinoma. Ann Hepatobiliary Pancreat Surg, 2018. 22(3): p. 197–207. [PubMed: 30215041]

31. Miyamoto R, Inagawa S, Sano N, et al. , The neutrophil-to-lymphocyte ratio (NLR) predicts short-term and long-term outcomes in gastric cancer patients. Eur J Surg Oncol, 2018. 44(5): p. 607–612. [PubMed: 29478743]

32. Datta M, Coussens LM, Nishikawa H, et al. , Reprogramming the Tumor Microenvironment to Improve Immunotherapy: Emerging Strategies and Combination Therapies. Am Soc Clin Oncol Educ Book, 2019. 39: p. 165–174. [PubMed: 31099649]

Synopsis:

In this study leveraging data from five safety-net hospitals and affiliated academic centers, attrition during neoadjuvant chemotherapy (NAC) is an independent predictor of decreased survival in patients with localized gastric cancer, even in those who ultimately underwent surgical exploration. In addition to functional decline and treatment-related toxicity, one of the important contributors to attrition was the increased risk faced by patients without health insurance or with hospital-based insurance. While efforts to provide equitable care to vulnerable gastric cancer patients may mitigate attrition, additional unmeasured biologic factors dictating tumor aggressiveness may also play a key role in promoting attrition during NAC.

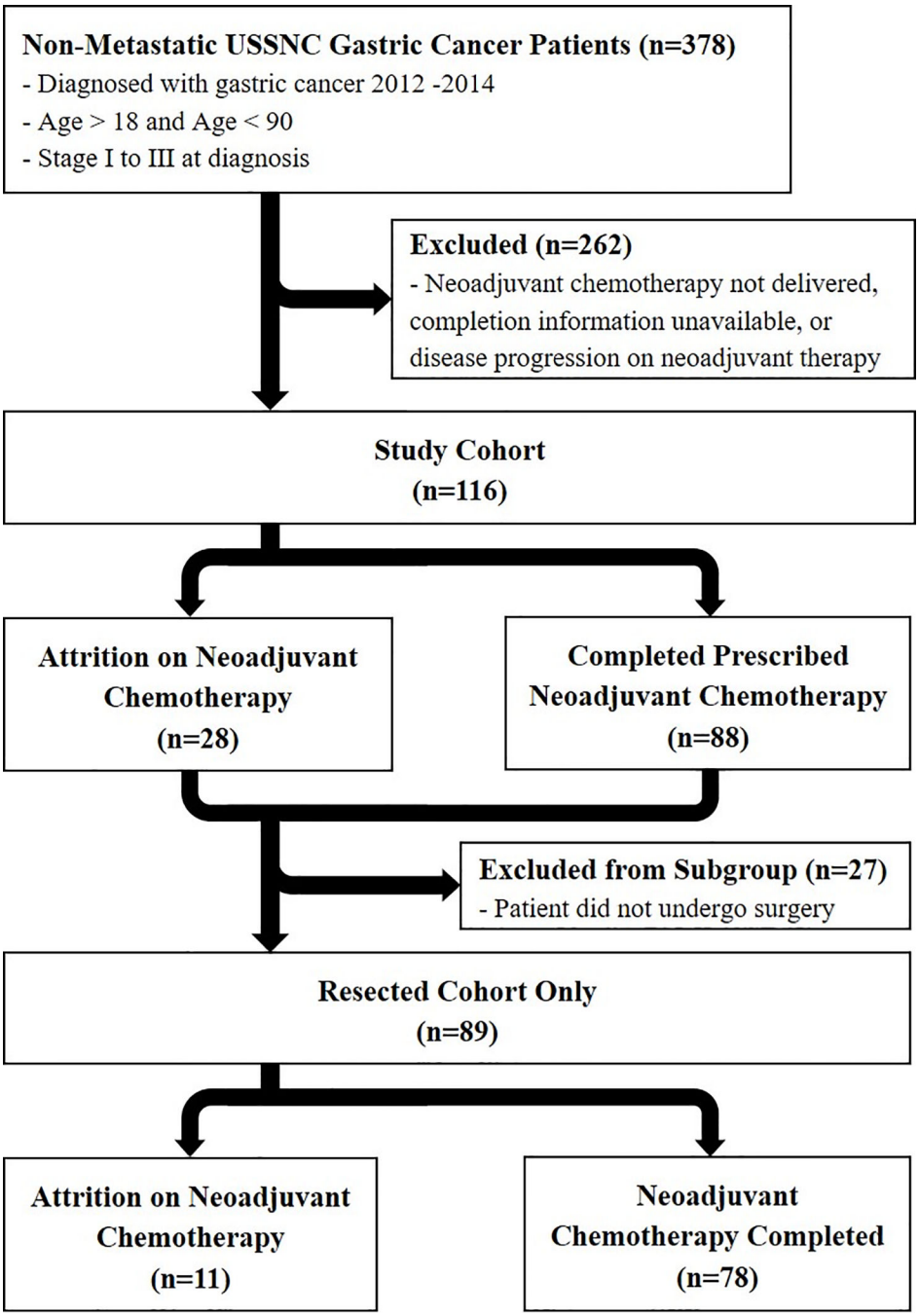
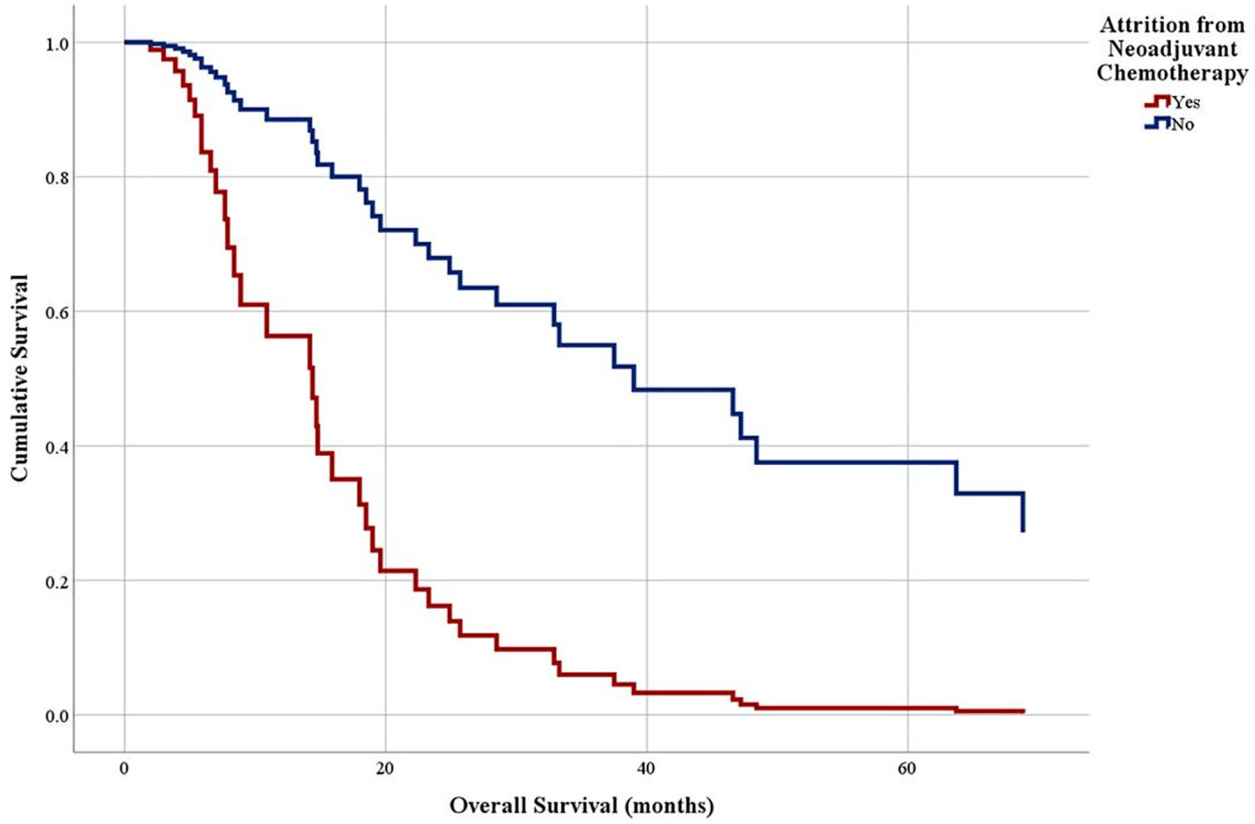


Figure 1:
Patient selection diagram with inclusion and exclusion criteria.



No. At Risk

Yes	28	6	1	0
No	88	63	42	33

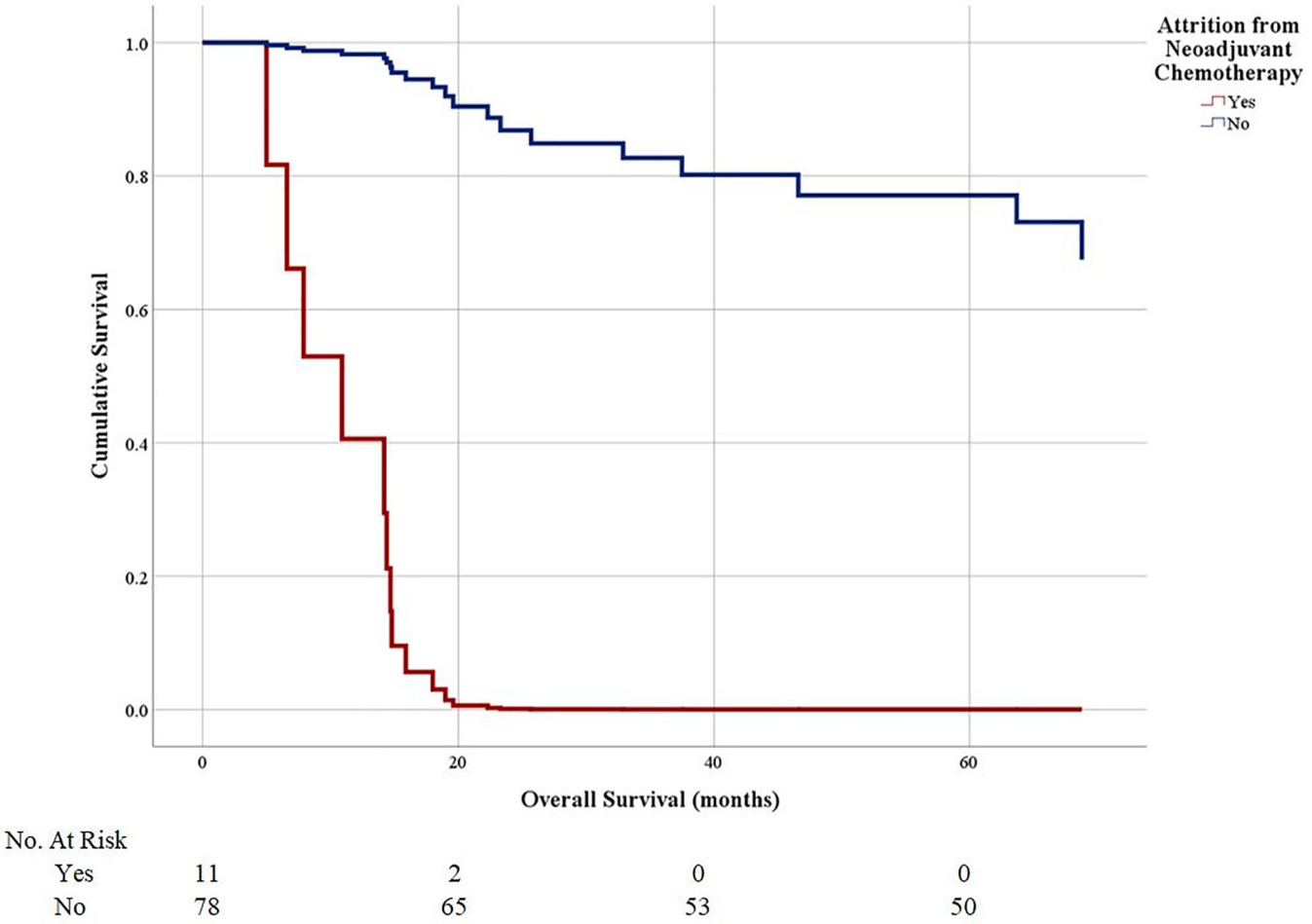


Figure 2:

(A) Overall survival stratified by attrition during neoadjuvant chemotherapy; **(B)** Overall survival stratified by attrition during neoadjuvant chemotherapy in the subgroup of patients who underwent surgical resection.

Table 1.

Sociodemographics and clinical information comparing patients who had attrition during neoadjuvant chemotherapy compared to those who completed prescribed treatment

Variable		Overall cohort (n=116) n (%)	Attrition during Neoadjuvant Chemotherapy (n=28) n (%)	Neoadjuvant Chemotherapy Completed (n=88) n (%)	P-value
Sociodemographics					
Age (median, IQR)		62.0 (53.0–68.5)	60.2 (53.0–70.4)	62.0 (53.1–67.2)	0.816
Gender	*Female*	41 (35.3)	10 (35.7)	31 (35.2)	0.963
	Male	75 (64.7)	18 (64.3)	57 (64.8)	
Race	*Asian*	14 (13.3)	3 (10.7)	11 (14.3)	0.339
	Black	30 (28.6)	11 (39.3)	19 (24.7)	
	White	61 (58.1)	14 (50.0)	47 (61.0)	
Ethnicity	*Hispanic*	40 (34.8)	7 (25.0)	33 (37.9)	0.211
	Not Hispanic	75 (65.2)	21 (75.0)	54 (62.1)	
US Citizen		64 (83.1)	17 (77.3)	47 (85.5)	0.387
>25% of Population in Zip Below Poverty Level		20 (18.2)	4 (14.8)	16 (19.3)	0.602
ECOG Functional Status	*ECOG 0–1 (Independent)*	103 (88.8)	26 (92.9)	77 (87.5)	0.434
	ECOG 2 (Partially Dependent)	13 (11.2)	2 (7.1)	11 (12.5)	
	ECOG 3 (Totally Dependent)	0 (0.0)	0 (0.0)	0 (0.0)	
Healthcare Access					
Treatment Facility	*Academic Center*	62 (53.4)	11 (39.3)	51 (58.0)	0.085
	Safety-Net Hospital	54 (46.6)	17 (60.7)	37 (42.0)	
Health Insurance	*Government*	49 (42.2)	12 (42.9)	37 (42.0)	0.068
	Hospital Card	5 (4.3)	3 (10.7)	2 (2.3)	
	Private	38 (32.8)	5 (17.9)	33 (37.5)	
	Uninsured	24 (20.7)	8 (28.6)	16 (18.2)	
Primary Care Physician		72 (69.9)	16 (64.0)	56 (71.8)	0.460
Cancer Care Navigator		62 (63.9)	15 (60.0)	47 (65.3)	0.636
Diagnostic and Tumor Characteristics at Presentation					
CEA Level (median, IQR)		3.0 (1.4–6.3)	4.4 (2.6–16.1)	2.2 (1.2–5.1)	0.250
CA 19–9 Level (median, IQR)		9.0 (5.0–34.0)	21.0 (5.9–37.0)	8.0 (4.5–11.0)	0.226
CA 125 Level (median, IQR)		9.6 (6.0–18.4)	30.3 (10.1–51.6)	7.5 (4.5–13.7)	0.400
Radiologic Tumor Size (median, IQR)		4.5 (3.0–6.6)	4.4 (3.9–4.8)	5.0 (2.1–7.7)	0.359
Stage at Diagnosis (AJCC 8th ed.)	*I*	5 (5.3)	0 (0.0)	5 (7.1)	0.213
	II	29 (30.9)	10 (41.7)	19 (27.1)	
	III	60 (63.8)	14 (58.3)	46 (65.7)	
Neoadjuvant Therapy					
Time to Chemotherapy in Days (median, IQR)		45 (32–65)	42 (34–68)	47 (32–63)	0.501

Variable		Overall cohort (n=116) n (%)	Attrition during Neoadjuvant Chemotherapy (n=28) n (%)	Neoadjuvant Chemotherapy Completed (n=88) n (%)	P-value
Number of Chemotherapy Cycles (median, IQR)		4 (3–6)	3 (2–4)	4 (3–6)	0.440
Reason for Attrition	*Decline in Performance Status*	3 (2.6)	3 (10.7)	--	--
	Toxicity	8 (6.9)	8 (28.6)	--	
	Multifactorial[*]	17 (14.7)	17 (60.7)	--	
Radiation Therapy		3 (2.6)	1 (3.7)	2 (2.3)	0.690
Surgical Intervention					
Surgical Exploration		89 (76.7)	11 (39.3)	78 (88.6)	**<0.001**
Type of Operation	*Aborted Procedure*	7 (7.9)	2 (18.2)	5 (6.4)	0.437
	Partial Gastrectomy	27 (30.3)	4 (36.4)	23 (29.5)	
	Total Gastrectomy	51 (57.3)	5 (45.5)	46 (59.0)	
	Gastrectomy NOS[#]	4 (4.5)	0 (0.0)	4 (5.1)	

[^] Eastern Cooperative Oncology Group

[*] confirmed no metastasis

[#] Not Otherwise Specified

Table 2.

Predictors of attrition during neoadjuvant chemotherapy on binary logistic regression.

Variable		β (95% CI)	p Value
Age at Diagnosis			
	Increasing Age	1.00 (0.95–1.05)	0.974
Gender			
	Female Gender	1 [Reference]	
	Male Gender	0.55 (0.16–1.90)	0.348
Race			
	White	1 [Reference]	
	Black Race	0.97 (0.22–4.22)	0.966
	Asian	0.49 (0.07–3.52)	0.481
Ethnicity (Hispanic)			
	No	1 [Reference]	
	Yes	0.44 (0.09–2.11)	0.307
Insurance			
	Private Insurance	1 [Reference]	
	Government Insurance	4.67 (0.79–27.61)	0.089
	Hospital Card Insurance	44.84 (2.67–752.44)	**0.008**
	Uninsured	10.66 (1.38–82.30)	**0.023**
Primary Care Physician			
	No	1 [Reference]	
	Yes	1.94 (0.49–7.73)	0.349
Cancer Care Navigator			
	No	1 [Reference]	
	Yes	1.50 (0.48–4.69)	0.491

Table 3.

Sociodemographics and clinical information in the subgroup of patients who underwent surgical exploration.

Variable		Combined (n=89) n (%)	Attrition during Neoadjuvant Chemotherapy (n=11) n (%)	Neoadjuvant Chemotherapy Completed (n=78) n (%)	P-value
Sociodemographics					
Age (median, IQR)		62.0 (53.0–67.0)	59.7 (49.2–68.0)	62.0 (53.3–67.0)	0.350
Gender	*Female*	31 (34.8)	2 (18.2)	29 (37.2)	0.216
	Male	58 (65.2)	9 (81.8)	49 (62.8)	
Race	*Asian*	13 (16.5)	2 (18.2)	11 (16.2)	**0.027**
	Black	19 (24.1)	6 (54.5)	13 (19.1)	
	White	47 (59.5)	3 (27.3)	44 (64.7)	
Ethnicity	*Hispanic*	32 (36.4)	2 (18.2)	30 (30.9)	0.180
	Not Hispanic	56 (63.6)	9 (81.8)	47 (61.0)	
US Citizen		45 (81.2)	6 (75.0)	39 (83.0)	0.589
>25% of Population in Zip Below Poverty Level		17 (20.5)	2 (20.0)	15 (20.5)	0.968
Functional Status	*Independent*	77 (87.5)	10 (90.9)	67 (87.0)	0.715
	Partially Dependent	11 (12.5)	1 (9.1)	10 (13.0)	
Healthcare Access					
Treatment Facility	*Academic Center*	36 (40.4)	5 (45.5)	31 (39.7)	0.718
	Safety-Net Hospital				
Health Insurance	*Government*	40 (44.9)	7 (63.6)	33 (42.3)	0.473
	Hospital Card	2 (2.2)	0 (0.0)	2 (2.6)	
	Private	33 (37.1)	2 (18.2)	31 (39.7)	
	Uninsured	14 (15.7)	2 (18.2)	12 (15.4)	
Primary Care Physician		60 (76.9)	8 (88.9)	52 (75.4)	0.365
Cancer Care Navigator		45 (63.4)	4 (44.4)	41 (66.1)	0.207
Diagnostic and Tumor Characteristics at Presentation					
CEA Level (median, IQR)		2.3 (1.3–4.9)	4.6 (1.7–16.1)	2.2 (1.3–4.8)	.379
CA 19–9 Level (median, IQR)		8.6 (4.0–34.0)	37.0 (3.0–144.7)	8.3 (4.0–11.7)	--
CA 125 Level (median, IQR)		7.5 (4.5–13.7)	--	7.5 (4.5–13.7)	--
Radiologic Tumor Size (median, IQR)		5.0 (2.4–6.6)	4.8 (4.3–5.0)	5.0 (2.1–7.0)	0.125
Stage at Diagnosis (AJCC 8th ed.)	*I*	4 (5.7)	0 (0.0)	4 (6.7)	0.125
	II	23 (32.9)	6 (60.0)	17 (28.3)	
	III	43 (61.4)	4 (40.0)	39 (65.0)	
Neoadjuvant Therapy					
Time to Chemotherapy in Days (median, IQR)		45.5 (32.5–63.0)	38.5 (33.0–69.5)	46.5 (32.5–62.5)	0.708
Number of Chemotherapy Cycles (median, IQR)		4 (3–5)	3 (3–4)		0.472
Reason for Attrition	*Decline in Performance Status*	2 (2.2)	2 (18.2)	--	--
	Toxicity	3 (3.4)	3 (27.3)	--	

Variable		Combined (n=89) n (%)	Attrition during Neoadjuvant Chemotherapy (n=11) n (%)	Neoadjuvant Chemotherapy Completed (n=78) n (%)	P-value
	Multifactorial	6 (6.7)	6 (54.5)	--	
Radiation Therapy		1 (1.1)	0 (0.0)	1 (1.3)	0.704
Surgical Exploration					
Type of Operation	*Aborted Procedure*	7 (7.9)	2 (18.2)	5 (6.4)	0.437
	Partial Gastrectomy	27 (30.3)	4 (36.4)	23 (29.5)	
	Total Gastrectomy	51 (57.3)	5 (45.5)	46 (59.0)	
	Gastrectomy NOS	4 (4.5)	0 (0.0)	4 (5.1)	
Pathologic Data					
Pathologic Tumor Size (median, IQR)		4.4 (2.4–7.0)	3.8 (1.3–4.7)	4.4 (2.4–7.5)	0.707
Tumor Differentiation/Grade	*Well-Differentiated*	1 (1.2)	0 (0.0)	1 (1.3)	0.899
	Moderately Differentiated	23 (26.7)	2 (20.0)	21 (27.6)	
	Poorly Differentiated	61 (70.9)	8 (80.0)	53 (69.7)	
Lymphovascular Invasion		44 (56.4)	5 (55.6)	39 (56.5)	0.956
Perineural Invasion		40 (52.6)	6 (66.7)	34 (50.7)	0.369
Signet Ring		38 (46.9)	4 (44.4)	34 (47.2)	0.875
Postoperative Complications		38 (45.2)	4 (40.0)	34 (45.9)	0.723
Adjuvant Therapy					
Chemotherapy		50 (80.6)	5 (83.3)	45 (80.4)	0.861
Number of Chemotherapy Cycles (median, IQR)		3 (0–5)	2 (0–3)	3 (0–6)	0.704
Radiation Therapy		0 (0.0)	0 (0.0)	0 (0.0)	--

[#] Not Otherwise Specified

Table 4a.

Multivariable Cox proportional hazards regression model of overall survival.

Variable		HR (95% CI)	P-value
Age at Diagnosis			
	Increasing Age	0.99 (0.95–1.03)	0.624
Gender			
	Female Gender	1 [Reference]	
	Male Gender	0.81 (0.36–1.80)	0.600
Race			
	White	1 [Reference]	
	Black Race	0.30 (0.09–1.03)	0.056
	Asian	0.09 (0.02–0.38)	**0.001**
Ethnicity (Hispanic)			
	No	1 [Reference]	
	Yes	0.63 (0.23–1.73)	0.373
Insurance			
	Private Insurance	1 [Reference]	
	Government Insurance	0.40 (0.10–1.58)	0.193
	Hospital Card Insurance	0.02 (0.01–0.36)	**0.008**
	Uninsured	0.57 (0.10–3.21)	0.524
>25% of Population Below Poverty			
	No	1 [Reference]	
	Yes	0.34 (0.04–3.24)	0.349
Treatment at Safety-Net Hospital			
	No	1 [Reference]	
	Yes	3.98 (1.12–14.18)	**0.033**
Stage at Diagnosis			
	Stage I Disease	1 [Reference]	
	Stage II Disease	1.92 (0.26–14.37)	0.524
	Stage III Disease	4.57 (0.67–31.28)	0.122
Primary Care Physician			
	No	1 [Reference]	
	Yes	2.12 (0.87–5.17)	0.097
Cancer Care Navigator			
	No	1 [Reference]	
	Yes	1.30 (0.59–2.92)	0.508
Attrition during Neoadjuvant Chemotherapy			
	No	1 [Reference]	
	Yes	4.71 (1.46–15.22)	**0.010**
Surgical Exploration			
	No	1 [Reference]	
	Yes	0.16 (0.05–0.49)	**0.002**

Table 4b.

Multivariable Cox proportional hazards regression model of overall survival in subgroup of patients undergoing surgical exploration.

Variable		HR (95% CI)	P-value
Age at Diagnosis			
	Increasing Age	1.01 (0.94–10.8)	0.762
Gender			
	Female Gender	1 [Reference]	
	Male Gender	0.30 (0.06–1.45)	0.135
Race			
	White	1 [Reference]	
	Black Race	0.14 (0.01–1.45)	0.098
	Asian	0.07 (0.01–0.73)	**0.037**
Ethnicity (Hispanic)			
	No	1 [Reference]	
	Yes	0.43 (0.08–2.24)	0.318
Insurance			
	Private Insurance	1 [Reference]	
	Government Insurance	0.07 (0.01–0.73)	**0.026**
	Hospital Card Insurance	--	--
	Uninsured	0.67 (0.07–6.37)	0.724
>25% of Population Below Poverty			
	No	1 [Reference]	
	Yes	0.34 (0.03–3.77)	0.382
Treatment at Safety-Net Hospital			
	No	1 [Reference]	
	Yes	4.29 (0.46–40.00)	0.201
Stage at Diagnosis			
	Stage I Disease	1 [Reference]	
	Stage II Disease	0.17 (0.01–3.54)	0.250
	Stage III Disease	1.61 (0.10–26.13)	0.736
Primary Care Physician			
	No	1 [Reference]	
	Yes	3.38 (0.62–18.41)	0.159
Cancer Care Navigator			
	No	1 [Reference]	
	Yes	0.12 (0.02–0.62)	**0.012**
Attrition during Neoadjuvant Chemotherapy			
	No	1 [Reference]	
	Yes	50.81 (3.60–717.77)	**0.004**