Comparison on Clinicopathological Features, Treatments and Prognosis between Proximal Gastric Cancer and Distal Gastric Cancer: A National Cancer Data Base Analysis

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Abstract

Background

The aim of this study was to examine the differences in clinicopathological features, treatment strategies and prognosis between patients with proximal gastric cancer (PGC) and distal gastric cancer (DGC).

Methods

Patients with gastric adenocarcinoma were identified from the National Cancer Database during the years 2004–2015. Survival analysis was performed via Kaplan-Meier and Cox proportional hazards models.

Results

A total of 97,060 patients were identified with gastric adenocarcinoma. DGC was associated with older age, more advanced tumor stage, and poorly differentiated tumors compared with PGC (all $p<0.01$). In the multivariate analysis, patients with DGC had a worse prognosis compared with those with PGC. In early and locally advanced stage, the prognosis of DGC was better compared with PGC. In distant metastasis stage, the prognosis of DGC was worse compared with PGC. Compared with patients underwent gastrectomy who received adjuvant therapy (AT) in locally advanced stage, a survival benefit was seen for DGC patients who received neoadjuvant therapy (NAT) or NAT plus AT, whereas PGC patients with locally advanced disease did not share this result ($p>0.05$).

Conclusion

PGC and DGC differed in their clinicopathologic characteristics and prognosis and heterogeneity may be due to differences in tumor biology. Tumor location should be taken into consideration when stratifying patients for optimal therapeutic strategies.

Key words: gastric cancer, clinicopathologic features, prognosis, distal gastric cancer, proximal gastric cancer

Introduction

Gastric cancer (GG) is the second leading cause of cancer-related mortality and the fourth most common cancer globally[1]. Since the 1970s, there has been a persistent trend in the increasing percentage of proximal gastric cancer (PGC) with an associated decreasing percentage of distal gastric cancer (DGC) in western countries[2-6]. Epidemiological studies proposed that PGC seems to have different etiology and biological behavior from DGC[7].

Recent reports have demonstrated that PGC and DGC exhibit different clinicopathological and biological characteristics[8, 9]. For example, Fabio et al. [10] reported PGC were associated with more advanced tumor stage and older age; Kin et al. [8] found that PGC tended to have a poorly differentiated type than DGC. Moreover, data regarding prognosis in PGC versus DGC are conflicting. Some studies have reported a significantly shorter overall survival (OS) in PGC patients[10-12], whereas others found no significant differences in prognosis of PGC and DGC[9, 13]. Katsuhiko et al[14] even demonstrated a long-term survival in patients with PGC than in those with DGC.

As such, the aim of the present study is to investigate differences in clinicopathological characteristics, treatment strategies and prognosis of PGC in comparison with DGC, using the National Cancer Data Base (NCDB). We also sought prognostic factors in relation to the location of the primary lesion to aid in the selection of optimal adjuvant treatment for patients with GC.

Patients and methods

Data source

The NCDB is a national hospital-based registry jointly sponsored by the American College of Surgeons and the American Cancer Society. It collects data from more than 1,500 Commission on Cancer-accredited facilities and captures approximately 70% of incident cancers in the United States annually. The study was reviewed by the Yale Institutional Review Board and was exempt from review as a secondary data analysis.

Study population

The study population consisted of 97,060 patients who were diagnosed with GC from the years 2004–2015. This data set was limited to patients with gastric adenocarcinoma according to International Classification of Diseases for Oncology codes C16.0 to C16.9.

Study variables

The main exposure variable was PGC/DGC. PGC was defined as tumors with the epicenter located in cardia (C16.0) or fundus (C16.1), whereas DGC was defined as lesions of the body (C16.2), antrum (C16.3) or pylorus (C16.4). Other baseline patient/tumor characteristic variables that were collected included the age group (<50, 50-64, 65-74, >=75 years), sex (male, female), race (white, black), Hispanic ethnicity (non-Hispanic, Hispanic, other), facility type(non-academic, academic), insurance (uninsured, private insurance, Medicaid, Medicare, other, unknown), median income ($) (<38,000, 38,000-47,999, 48,000-62,999, 63,000+, unknown), circle distance (miles) (less than 50, greater than 50, unknown), Carlson-Deyo score (0, 1, 2, 3), clinical and pathologic TNM categories (as defined by the American Joint Committee on Cancer staging manual),

number of nodes examined (0-15 nodes, >15 nodes), number of nodes positive (0 nodes, 1-2 nodes, 3-6 nodes, 7-15 nodes, 16 or more nodes), scope of regional lymph node surgery (whether or not to underwent lymphadenectomy) (no, yes), and tumor grade (well, moderately, poorly, undifferentiated/anaplastic,). Characteristics of surgical treatment variables included type of gastrectomy (gastrectomy-partial, near-total/total gastrectomy, gastrectomy with esophagus, gastrectomy with other organs, gastrectomy (NOS), no surgery), and surgical margin (R0, R1, R2). Short-term outcome variables in secondary analyses included the following: surgical inpatient stay (days) (0-5, 6-7, 8-11, >=12, unknown), 30-day unplanned readmission (no unplanned readmission, unplanned readmission, unknown). OS served as the primary endpoint of the study, and follow-up time was calculated based on the month.

Statistical analyses

All analysis was done using SAS software v9.3 (SAS Institute, Inc., Cary, NC). Categorical variables were compared using Chi-square test while continuous variables were compared using student T-test. Kaplan–Meier and log-rand test was used to examine OS by GC subtype and treatment type. Cox-regression survival analysis was used to identify predictors of OS. The proportionality assumption of the cox-regression was checked by including a time-varying covariate, an interaction between the covariate and the event time. Hazard ratio (HR) and 95% confidence interval (CI) were used to measure the risk of death. A p-value less than 0.05 was considered statistically significant and all tests were two-sided.

Results

Patient characteristics

Patient characteristics at time of diagnosis were summarized in supplementary Table 1. Of the 97,060 GC patients, 60,513 (62.3%) were PGC and 36,547 (37.7%) were DGC. Patients diagnosed with GC had a mean age of 67.66 years with majority of them being male (68.95 %), white (80.31 %), and non-Hispanic (91.55 %). Compared to patients with DGC, patients with PGC were more likely to be younger (66.68 ± 12.45 years vs 69.28 ± 14.20, $p < 0.01$), male (77.46% vs.54.85%, $p<0.01$), and white (89.95% vs.64.34%, $p<0.01$). Patients with PGC were also more likely to have private insurance, higher income, traveled a longer distance to hospitals, and be treated in academic hospitals compared to patients with DGC. Patients with PGC had lower Carlson scores, clinical and pathological TNM categories and the number of lymph nodes being examined and positive compared to patients with DGC. In terms of surgical treatment, PGC patients were less likely to have surgical treatment (36.61% vs. 51.97%, $p < 0.01$) compared to DGC patients. Among surgically treated patients, a higher proportion of PGC patients received R0 resection, stayed longer in the hospital, and had no unplanned 30-day readmission compared to DGC patients.

Survival Outcomes

Kaplan-Meier survival estimates for GC in different stages were shown in Figure 1A. The median survival time of patients with GC were 98.53 months in early stage, 29.7 months in locally advanced stage and 6.21 months in distant metastasis stage ($p<0.01$)(Table S1). PGC patients in early stage had a significantly shorter survival

compared with DGC patients (p<0.01) (Figure 1B) with a median survival time of 91.83 months and 106.55 months respectively (supplementary Table S2). There were no significant differences (p=0.97) in OS between the two groups in locally advanced stage (Figure 1C). For patients with distant metastases, the PGC group had a longer survival compared with the DGC group (p<0.01) (Figure 1D) with a median survival time of 13.85 months and 12.24 months respectively (supplementary Table S2).

Figure 1E and 1F showed the survival curves for PGC and DGC patients in locally advanced stage underwent gastrectomy according to different adjuvant therapy. Among locally advanced proximal gastric cancer (LAPGC) patients underwent gastrectomy, the median survival time were 20.63 months, 37.36 months, 32.13 months, and 37.16 months in gastrectomy alone group, neoadjuvant therapy (NAT) group, adjuvant therapy (AT) group, and NAT plus AT group, respectively (supplementary Table S3). Among locally advanced distal gastric cancer (LADGC) patients underwent gastrectomy, the median survival time were 21.36 months in gastrectomy alone group, 64.3 months in NAT group, 38.9 months in AT group, and 56.31 months in NAT plus AT group (supplementary Table S3).

Prognostic Factors

In multivariate analysis, DGC (HR, 1.07; 95% CI, 1.05–1.10; p<0.01), local advanced stage (HR, 2.32; 95%, CI 2.21–2.43; p<0.01), and distant metastatic stage (HR, 5.03;95% CI, 4.76–5.31; p<0.01) were significant predictors for poor survival in GC patients (Table 2). Compared to PGC, DGC was associated with improved survival in early stage (HR, 0.82; 95% CI, 0.74–0.91; p<0.01) and local advance stage (HR, 0.94;

95% CI,0.90–0.97; $p<0.05$), while DGC was associated with poor survival in distant metastatic stage (HR, 1.19; 95% CI,1.16–1.23; $p<0.01$) (Table 3).

In PGC patients with local advanced stage underwent gastrectomy (Table 4), NAT (HR,0.80; 95%, CI 0.75–0.85; $p<0.01$), AT (HR,0.79; 95%, CI 0.73–0.85; $p<0.01$), and NAT plus AT (HR, 0.79; 95%, CI 0.72–0.87; $p<0.01$) were all independent predictors of better OS, and no differences in survival between different adjuvant therapies were observed ($p>0.05$). In DGC patients with local advanced stage underwent gastrectomy (Table 4), subjects with NAT (HR, 0.62; 95%, CI 0.54–0.70; $p<0.01$), AT (HR, 0.72; 95%, CI 0.68–0.77; $p<0.01$), and NAT plus AT (HR, 0.61; 95%, CI 0.53–0.71; $p<0.01$) had lower HRs than those underwent gastrectomy alone, and no differences in survival between NAT and NAT plus AT, but better survival of NAT or NAT plus AT than AT were observed.

After stratification by detailed adjuvant therapy, preoperative chemotherapy only (CT) (HR, 0.79; 95%, CI 0.71–0.87; $p<0.01$), postoperative CT (HR, 0.84; 95%, CI 0.75–0.93; $p<0.01$), pre- and post-operative CT (HR, 0.70; 95%, CI 0.60–0.82; $p<0.01$), preoperative CT plus radiotherapy (RT) (HR, 0.80; 95%, CI 0.75–0.85; $p<0.01$), preoperative CT plus RT and postoperative CT (HR, 0.79; 95%, CI 0.69–0.91; $p<0.01$), postoperative CT plus RT (HR, 0.75; 95%, CI 0.70–0.82; $p<0.01$), and preoperative CT and postoperative CT plus RT (HR, 0.73; 95%, CI 0.57–0.94; $p<0.01$) were associated with improved survival in LAPGC patients underwent gastrectomy (Table 5). Preoperative CT (HR, 0.57; 95%, CI 0.50–0.66; $p<0.01$), postoperative CT (HR, 0.82; 95%, CI 0.75–0.90; $p<0.01$), pre- and post-operative CT (HR, 0.50; 95%, CI 0.41–0.61; $p<0.01$), postoperative CT plus RT (HR, 0.67; 95%, CI 0.62–0.72; $p<0.01$), and

postoperative CT plus RT (HR, 0.67; 95%, CI 0.62–0.72; $p<0.01$) were associated with improved survival in LADGC patients underwent gastrectomy (Table 5). Prognosis for patients treated with pre- and post-operative CT was significant better than for patients treated with other therapies in LAPGC and LADGC patients underwent gastrectomy.

Discussion

Our study demonstrated that PGC was more common in younger patients similar to reports by Jun et al[15]. In contrast, several single institutional studies have shown PGC patients were older than DGC patients[4, 6, 9]. Other single institutional studies, however, have reported no association between age and tumor location[13, 16]. Analysis of different institutional databases has resulted in varying reports regarding the association between age at diagnosis and tumor location, primarily due to the limited sample size and non-representative samples.

PGC has very often been found to be inversely related to socioeconomic status (SES)[17, 18], whereas Linda et al. [19] shown that SES was not a statistically significant risk factor. Our study indicated that patients in PGC group had higher SES status reflected by higher income and private insurance. It could be due to a higher proportion of PGC patients in our study were white population. Whites were more likely to have high SES in America[20, 21].

Studies investigated prognosis of PGC and DGC have reported conflicting results with a majority of studies reporting a poorer survival in PGC[8, 10, 12, 15], one study reporting a worse prognosis in DGC patients[14], and two studies observing no significant differences[9, 13]. The reported variations of prognosis between PGC and DGC might be related to differences in stage and differentiated histology in different studies[8, 15]. Furthermore, several studies examining proximal gastric cancers included esophageal cancer in their analyses further confounding differences. While our study supported a better survival of PGC compared to DGC in overall population, we found that PGC patients in early stage or locally advanced stage had a worse prognosis compared with

DGC patients in similar stage, whereas PGC patients with distant metastasis had better prognosis than DGC with distant metastasis. Although the reason for the observed difference in survival between PGC and DGC by stage is currently unclear, we speculate that the differences in tumor biology and anatomy between PGC and DGC play a role. The intraabdominal part of the cardia and fundus are not fully covered by visceral peritoneum perhaps making early PGC more prone to infiltrate the serosa and more inclined to peritoneal metastasis compared with early DGC[16]. GC with distant metastases is uniformly incurable and treated primarily with CT. Therefore, a possible reason for this result is that the response to CT differs between PGC and DGC. Katsuhiko et al.[14] reported that patients with PGC in distant metastasis stage had a significantly better response to CT than those with DGC.

The locally advanced stages are treated with multiple therapies[22]. Our study revealed a better prognosis for LAPGC and LADGC patients given additional therapy (NAT, AT, or NAT plus AT) as compared to gastrectomy alone. It is worth notice that NAT seems a useful treatment option for LADGC patients underwent gastrectomy with or without AT, whereas addition of NAT does not have any beneficial effect on survival in LAPGC patients underwent gastrectomy with AT. NAT is expected to improve the resection rate and long-term follow-up results by reducing the size of the primary lesion and controlling lymph node metastasis and micrometastasis[23]. Although PGC had a significantly better response to CT than DGC[14], various factors, such as stomach anatomy, different lymphatic metastasis path, and technical difficulties during surgery, could be potential explanation for the weak effect of NAT on PGC patients. During the past several years, there has been increasing awareness of the documented benefits from NAT in patients

with localized gastric cancer. However, few studies are available concerning the survival outcomes of specific adjuvant therapy between PGC and DGC.

Postoperative CT is delivered with an intention to reduce recurrence by controlling residual tumor cells following curative resection. Recent advances in postoperative CT have achieved considerable tumor regression in many cases of gastric cancer[24]. Our results support that postoperative CT was associated with improved survival in LAPGC and LADGC patients. Although the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial has established Level 1 evidence for the perioperative CT[25], the addition of preoperative chemotherapy did not show any benefit in the trial by the European Organization for Research and Treatment of Cancer[26]. In our study, preoperative CT with or without postoperative CT showed OS benefit for PGC and DGC patients with locally advanced stage underwent gastrectomy. We also observed a significant OS benefit in favor of additional CT plus RT (preoperative CT plus RT, preoperative CT plus RT and postoperative CT, postoperative CT plus RT, and preoperative CT and postoperative CT plus RT) in LAPGC patients underwent gastrectomy, whereas only postoperative CT plus RT showed OS benefit in LADGC patients. While the underlying reasons remain unclear, these results warrant further investigation and highlight the importance of potential differences in response to adjuvant therapy between LAPGC and LADGC patients.

This study has several limitations that are typical to any large, retrospective database study. These include unidentified confounding factors, missing data, and potential coding errors. Additionally, the only available survival information is overall survival, which hampered the study to investigate relapse or disease-specific survival. The NCDB also

does not provide information about completeness of adjuvant therapy. Despite these limitations, the NCDB provides a large sample size, making this study the largest study to date investigating the differences between PGC and DGC. It collects data from more than 1,500 Commission on Cancer-accredited facilities in the United States.

In summary, the study revealed that DGC was associated with older age, poorly differentiated histology, and advanced pTNM stage. Although PGC was associated with better prognosis compared to DGC, this observed better prognosis was only pronounced in patients with distant metastasis. PGC patients in early stage or locally advanced stage had a worse prognosis compared with DGC patients. A survival benefit was seen for LADGC patients underwent gastrectomy who received NAT or NAT plus AT compared with those who received AT only, whereas LAPGC patients did not share this result. Prognosis of LAPGC and LADGC varied by different forms of neoadjuvant and/or adjuvant therapy, and pre- and post-operative CT might be a recommended adjuvant treatment strategy for LAPGC and LAPGC. Although these findings in our study warrant further investigation to understand the underlying mechanisms, primary tumor location should be carefully considered when deciding treatment strategies.

Abbreviations

PGC: Proximal gastric cancer; DCG: Distal gastric cancer; AT: Adjuvant therapy; NAT: Neoadjuvant therapy; GC: Gastric cancer; OS: Overall survival; NCDB: National Cancer Data Base; HR: Hazard ratio; CL: Confidence interval; LAPGC: Locally advanced proximal gastric cancer; LADGC: Locally advanced distal gastric cancer; CT: Chemotherapy; RT: radiotherapy.

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Authors' contributions

Xiang Wang: Conceptualization, methodology, writing original draft, visualization, project administration, and writing-review and editing. **Fangfang Liu:** Conceptualization, methodology, software, validation, formal analysis, investigation, data, curation, and writing–review and editing. **Yumin Li:** Conceptualization, methodology, investigation, resources, supervision, and writing–review and editing. **Song Tang:** Writing–review and editing. **Yawei Zhang:** Writing–review and editing. **Yingtai Chen:** Conceptualization, methodology, investigation, resources, supervision, project administration, funding acquisition, and writing–review and editing. **Sajid A. Khan:** Conceptualization, methodology, investigation, resources, supervision, project administration, funding acquisition, and writing–review and editing.

Competing Interests

The authors have declared no conflicts of interest.

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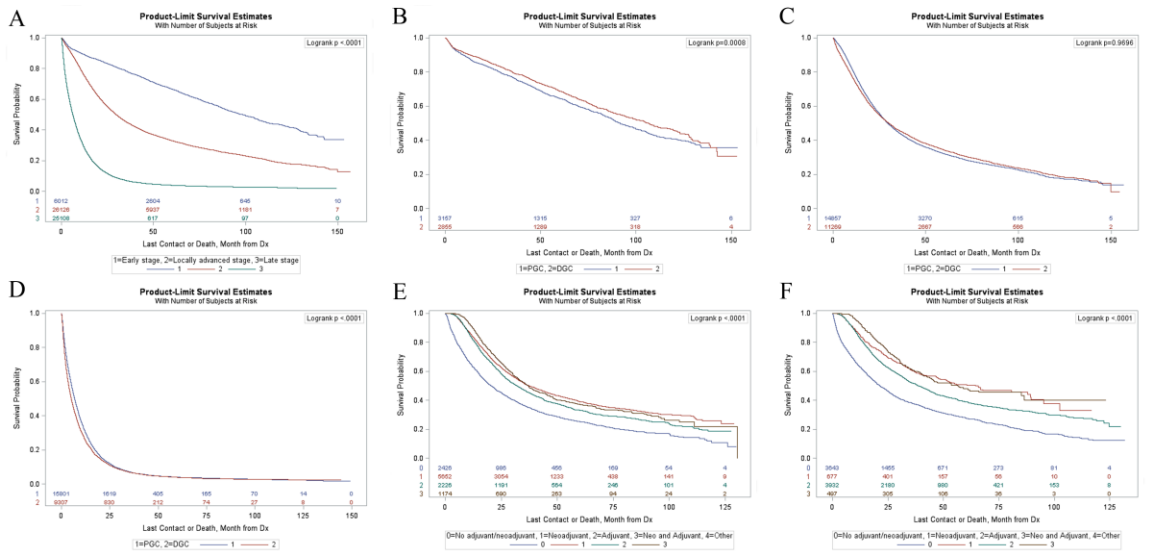

Figure 1. (A) Kaplan-Meier survival analyses of all patients with different stages. (B) Kaplan-Meier survival analyses of PGC group and DGC group in early stage. (C) Kaplan-Meier survival analyses of PGC group and DGC group in locally advanced stage. (D) Kaplan-Meier survival analyses of PGC group and DGC group in distant metastasis stage. (E) Kaplan-Meier survival analyses of LAPGC with gastrectomy stratified according to different adjuvant therapy. (F) Kaplan-Meier survival analyses of LADGC with gastrectomy stratified according to different adjuvant therapy.

Table 1. Characteristics of Gastric Adenocarcinoma by Tumor Location

Characteristic	Total (97,060)		PGC group(n=60,513)		DGC group (n=36,547)		P value
	Number	%	Number	%	Number	%	
	Mean	SD	Mean	SD	Mean	SD	
Age	67.66	13.20	66.68	12.45	69.28	14.20	<.0001
Age (y)							
<50	9037	9.31	5342	8.83	3695	10.11	
50-64	28703	29.57	19910	32.90	8793	24.06	
65-74	26594	27.40	17782	29.39	8812	24.11	
>=75	32726	33.72	17479	28.88	15247	41.72	<0.0001
Gender							
Male	66920	68.95	46873	77.46	20047	54.85	
Female	30140	31.05	13640	22.54	16500	45.15	<0.0001
Race							
White	77946	80.31	54432	89.95	23514	64.34	
Black	11431	11.78	3492	5.77	7939	21.72	
Other	7683	7.92	2589	4.28	5094	13.94	<0.0001
Hispanic ethnicity							
Non-Hispanic	84059	86.61	54135	89.46	29924	81.88	
Hispanic	7760	8.00	2949	4.87	4811	13.16	
Unknown	5241	5.40	3429	5.67	1812	4.96	<0.0001
Insurance							
Uninsured	3404	3.51	1742	2.88	1662	4.55	
Private Insurance	30982	31.92	21343	35.27	9639	26.37	
Medicaid	6259	6.45	3145	5.20	3114	8.52	
Medicare	52886	54.49	31902	52.72	20984	57.42	
Other	1265.00	1.3	943	1.56	322	0.88	
Unknown	2264	2.33	1438	2.38	826	2.26	<0.0001
Median income ($)							
<38,000	17258	17.78	9019	14.90	8239	22.54	
38,000-47,999	22216	22.89	14128	23.35	8088	22.13	
48,000-62,999	25720	26.50	16627	27.48	9093	24.88	
63,000+	30185	31.10	19750	32.64	10435	28.55	
Unknown	1681	1.73	989	1.63	692	1.89	<0.0001
Circle distance (miles)							
Less than 50	83870	86.41	50971	84.23	32899	90.02	
Greater than 50	11536	11.89	8577	14.17	2959	8.10	
Unknown	1654	1.70	965	1.59	689	1.89	<0.0001
Facility type							
Non-academic	57028	58.76	35349	58.42	21679	59.32	
Academic	37638	38.78	23913	39.52	13725	37.55	
Other	2394	2.47	1251	2.07	1143	3.13	<0.0001
Charlson score							
0	66532	68.55	42416	70.09	24116	65.99	
1	21697	22.35	13061	21.58	8636	23.63	
2	6209	6.40	3545	5.86	2664	7.29	
3	2622	2.70	1491	2.46	1131	3.09	<0.0001
Clinical T							

T0	1092	1.13	659	1.09	433	1.18	
T1	14016	14.44	8884	14.68	5132	14.04	
T2	9735	10.03	6578	10.87	3157	8.64	
T3	21472	22.12	16812	27.78	4660	12.75	
T4	7858	8.10	3915	6.47	3943	10.79	
Unknown	42887	44.19	23665	39.11	19577	53.57	<0.0001
Clinical N							
c0	36270	37.37	21864	36.13	14406	39.42	
c1	22747	23.44	17175	28.38	5572	15.25	
c2	5048	5.20	3585	5.92	1463	4.00	
c3	2284	2.35	1490	2.46	794	2.17	
Unknown	30711	31.64	16399	27.10	14312	39.16	<0.0001
Clinical M							
c0	71684	73.86	43961	72.65	27723	75.86	
c1	25376	26.14	16552	27.35	8824	24.14	<.0001
CTNM							
I	15513	15.98	9807	16.21	5706.00	15.61	
II	11262	11.60	7925	13.10	3337.00	9.13	
III	12388	12.76	9790	16.18	2598.00	7.11	
IV	26144	26.94	16826	27.81	9318.00	25.5	<.0001
Unknown	31753	32.71	16165	26.71	15588.00	42.65	
Pathologic T							
p0	2053	2.12	1650	2.73	403	1.10	
p1	10230	10.54	6049	10.00	4181	11.44	
p2	9365	9.65	4897	8.09	4468	12.23	
p3	13943	14.37	8458	13.98	5485	15.01	
p4	5102	5.26	1344	2.22	3758	10.28	
Unknown	56367	58.07	38426	63.50	18492	50.60	<0.0001
Pathologic N							
p0	18111	18.66	10693	17.67	7418	20.30	
p1	11336	11.68	6577	10.87	4759	13.02	
p2	5741	5.91	2756	4.55	2985	8.17	
p3	3918	4.04	1494	2.47	2424	6.63	
Unknown	57954	59.71	38993	64.44	18961	51.88	<0.0001
Pathologic M							
p0	89051	91.75	56140.00	92.77	32911	90.05	
p1	8009	8.25	4373.00	7.23	3636	9.95	<.0001
PTNM							
I	13959	14.38	8251.00	13.64	5708.00	15.62	
II	12957	13.35	7762.00	12.83	5195.00	14.21	
III	5306	5.47	1923.00	3.18	3383.00	9.26	
IV	8009	8.25	4373.00	7.23	3636.00	9.95	
Unknown	56829	58.55	38204.00	63.13	18625.00	50.96	<.0001
Number of nodes examined							
0-15 nodes	75162	77.44	47814	79.01	27348	74.83	
>15 nodes	17239	17.76	9392	15.52	7847	21.47	
Other	4659	4.80	3307	5.46	1352	3.70	<0.0001
Number of nodes positive							
0 nodes	18844	19.41	11108	18.36	7736	21.17	

1-2 nodes	8798	9.06	5284	8.73	3514	9.62	
3-6 nodes	6834	7.04	3585	5.92	3249	8.89	
7-15 nodes	5165	5.32	2236	3.70	2929	8.01	
16 or more nodes	1725	1.78	617	1.02	1108	3.03	
Other	55694	57.38	37683	62.27	18011	49.28	<0.0001
Scope of regional lymph node surgery							
No	54512	56.16	36805	60.82	17707	48.45	
Yes	41193	42.44	22759	37.61	18434	50.44	
Unknown	1355	1.40	949	1.57	406	1.11	<0.0001
Tumor grade							
Well	4345	4.48	2907	4.80	1438	3.93	
Moderately	26426	27.23	18040	29.81	8386	22.95	
Poorly	49420	50.92	28402	46.94	21018	57.51	
Undifferentiated; anaplastic	1245	1.28	705	1.17	540	1.48	
Unknown	15624	16.1	10459	17.28	5165	14.13	<0.0001
Stage							
Early stage	6619	6.82	3481	5.75	3138	8.59	
LAGC	28779	29.65	16479	27.23	12300	33.66	
Distant	28142	28.99	17777	29.38	10365	28.36	<.0001
Type of gastrectomy							
Gastrectomy-partial	18382	18.94	18382	18.94	13526	37.01	
Near-total or total gastrectomy	4098	4.22	4098	4.22	2007	5.49	
Gastrectomy with esophagus	14288	14.72	14288	14.72	1496	4.09	
Gastrectomy with other organs	3974	4.09	3974	4.09	1830	5.01	
Gastrectomy, NOS	408	0.42	408	0.42	136	0.37	
No surgery	55910	57.6	38358	63.39	17552	48.03	<.0001
Surgical Margin							
R0	36951	38.07	20969	34.65	15982	43.73	
R1	3332	3.43	1715	2.83	1617	4.42	
R2	2732	2.81	1283	2.12	1449	3.96	
Unknown	54045	55.68	36546	60.39	17499	47.88	<.0001
Surgical Inpatient stay (days)							
0-5	8368	8.62	4423	7.31	3945	10.79	
6-7	7517	7.74	3031	5.01	4486	12.27	
8-11	12534	12.91	7386	12.21	5148	14.09	
>=12	11637	11.99	7429	12.28	4208	11.51	
Unknown	57004	58.73	38244	63.2	18760	51.33	<.0001
30-day unplanned readmission							
No unplanned readmission	91354	94.12	57231	94.58	34123	93.37	
Unplanned readmission	3199	3.3	1769	2.92	1430	3.91	
Unknown	2507	2.58	1513	2.5	994	2.72	<.0001

Table 2. Multivariate analysis of GC after stratification by location and clinical stage.

			Adjusted			
			HR	95%CI		*P* Value
Prognostic Factors	Number	%		Lower	Upper	
Location						
PGC	54434	62.06	Ref			
DGC	33279	37.94	1.07	1.05	1.10	<0.01
Stage						
Early	6012	10.50	Ref			
Local advanced	26126	45.64	2.32	2.21	2.43	<0.01
Distant metastatic	25108	43.86	5.03	4.76	5.31	<0.01

Adjust for age sex race Hispanic INSURANCE CDCC YEAR_OF_DIAGNOSIS income FLOC FTYPE distance grade RX_SUMM_SCOPE_REG_LN_SUR margin stay readm.
Abbreviations: GC, gastric cancer; PGC, proximal gastric cancer; DGC distal gastric cancer; HR, hazard ratio; CI, confidence interval.

Table 3. Multivariate analysis between PGC and DGC after stratification by clinical stage

Prognostic Factors	Number	%	Adjusted HR	95%CI Lower	95%CI Upper	*P* Value
Early stage						
PGC	3157	52.51	ref			
DGC	2855	47.49	0.82	0.74	0.91	<0.01
Local advanced						
PGC	14857	56.87	ref			
DGC	11269	43.13	0.94	0.90	0.97	<0.01
Distant metastatic						
PGC	15801	62.93	ref			
DGC	9307	37.07	1.19	1.16	1.23	<0.01

Adjust for age sex race Hispanic INSURANCE CDCC YEAR_OF_DIAGNOSIS income FLOC FTYPE distance grade RX_SUMM_SCOPE_REG_LN_SUR margin stay readm
Abbreviations: PGC, proximal gastric cancer; DGC distal gastric cancer; HR, hazard ratio; CI, confidence interval.

Table 4. Multivariate analysis of LAPGC and LADGC patients underwent gastrectomy after stratification by different adjuvant therapies.

	PGC						DGC					
			HR	95%CI		*P* value			HR	95%CI		*P* Value
Prognostic Factors	Number	%		Lower	Upper		Number	%		Lower	Upper	
Therapy												
No NAT/AT	2426	21.14	Ref				3643	41.64	Ref			
NAT	5652	49.24	0.80	0.75	0.85	<0.01	677	7.74	0.61	0.54	0.70	<0.01
AT	2226	19.39	0.79	0.73	0.85	<0.01	3932	44.94	0.72	0.68	0.77	<0.01
NAT plus AT	1174	10.23	0.79	0.72	0.87	<0.01	497	5.68	0.61	0.53	0.71	<0.01
No NAT/AT			1.25	1.17	1.33	<0.01			1.62	1.43	1.84	<0.01
NAT			Ref						Ref			
AT			0.99	0.92	1.05	0.67			1.62	1.43	1.84	0.02
NAT plus AT			0.10	0.91	1.08	0.82			0.99	0.83	1.19	0.92
No NAT/AT			1.27	1.18	1.36	<0.01			1.39	1.31	1.48	<0.01
NAT			1.01	0.95	1.08	0.67			0.86	0.76	0.97	0,02
AT			Ref						Ref			
NAT plus AT			1.00	0.91	1.10	0.93			0.85	0.73	0.98	0.03
No NAT/AT			1.26	1.15	1.39	<0.01			1.64	1.41	1.9	<0.01
NAT			1.01	0.93	1.1	0.82			1.01	0.84	1.21	0.92
AT			0.10	0.91	1.09	0.93			1.18	1.02	1.36	0.03
NAT plus AT			ref						ref			

Adjust for age sex race Hispanic INSURANCE CDCC YEAR_OF_DIAGNOSIS income FLOC FTYPE distance grade RX_SUMM_SCOPE_REG_LN_SUR margin stay readm.

Abbreviations: LAPGC, locally advanced proximal gastric cancer; LADGC, locally advanced distal gastric cancer; HR, hazard ratio; NAT, neoadjuvant therapy; AT, adjuvant therapy.

Table 5. Multivariate analysis of LAPGC and LADGC patients underwent gastrectomy after stratification by different detailed adjuvant therapies.

	PGC						DGC					
	Number	%	HR	95%CI		*P* value	Number	%	HR	95%CI		*P* Value
Prognostic Factors				Lower	Upper					Lower	Upper	
Therapy												
No CT/RT	2426	21.22	ref				3643	41.64	ref			
Pre-op CT only	888	7.77	0.79	0.71	0.87	<0.01	580	6.63	0.57	0.50	0.66	<0.01
Post-op CT only	669	5.85	0.84	0.75	0.93	<0.01	1103	12.61	0.82	0.75	0.90	<0.01
Pre and post operative CT only	355	3.10	0.70	0.60	0.82	<0.01	312	3.57	0.50	0.41	0.61	<0.01
Pre-op RT only	35	0.31	0.94	0.62	1.41	0.75	3	0.03	1.06	0.26	4.27	0.93
Pre-op CT plus RT	4729	41.36	0.80	0.75	0.85	<0.01	94	1.07	0.85	0.65	1.11	0.23
Pre-op RT and post-op CT	68	0.59	0.88	0.65	1.19	0.41	6	0.07	0.38	0.09	1.51	0.17
Pre-op RT plus CT and post-op CT	438	3.83	0.79	0.69	0.91	<0.01	20	0.23	0.57	0.29	1.15	0.12
Post-op RT only	78	0.68	1.07	0.83	1.38	0.61	115	1.31	1.05	0.85	1.31	0.65
Pre-op CT and post-op RT	153	1.34	0.82	0.66	1.01	0.06	71	0.81	0.79	0.57	1.10	0.16
Post-op CT plus RT	1479	12.93	0.75	0.70	0.82	<0.01	2714	31.02	0.67	0.62	0.72	<0.01
Pre-op CT and post-op RT plus CT	117	1.02	0.73	0.57	0.94	0.01	87	0.99	0.82	0.62	1.08	0.16

Abbreviations: LAPGC, locally advanced proximal gastric cancer; LADGC, locally advanced distal gastric cancer; HR, hazard ratio; CT, chemotherapy; RT, radiotherapy; Pre-op, preoperative; Post-op, postoperative.