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ORIGINAL ARTICLE

Gastric adenocarcinoma in young adult patients: patterns of care and survival in the United States

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Abstract

Background Evidence regarding gastric cancer patients < 40 years old is limited. This study examines young adults with gastric adenocarcinoma in the National Cancer Database to describe demographics and treatment practices, and to develop a nomogram to predict survival.

Methods The database was queried for adult patients diagnosed with gastric adenocarcinoma from 2004 to 2013. Patients were stratified into two age groups: <40 and ≥ 40 years. The database was analyzed to compare demographics, clinical characteristics, and treatments used for each group. Differences in survival were assessed using Kaplan–Meier curves and log-rank test. For adults < 40 years old, an accelerated failure time survival model was fitted for overall survival and a descriptive nomogram was constructed.

Results Of 70,084 patients included, 2615 (4%) were < 40 years old and 67,469 (96%) were ≥ 40 years. Compared to older patients, adults < 40 years old were more likely to be female (46 vs. 35%), non-white (31 vs. 23%), Hispanic (32 vs. 11%), from the northeast (36 vs. 23%), and to present with stage IV disease (59 vs. 42%) and bone metastases (36 vs. 21%; $p < 0.001$ for all). The nomogram showed clinical stage as the strongest predictor of overall survival, followed by treatment, grade, race, Charlson–Deyo comorbidity score, and sex.

Conclusions Young adults with gastric adenocarcinoma are more likely to be Hispanic, female, from the northeast, and to present with metastases. Despite these differences, clinical stage, treatment, and tumor grade are most predictive of overall survival for young adult patients.

Keywords Gastric · Young · NCDB · Adenocarcinoma

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Introduction

Gastric cancer is an aggressive malignancy that carries a poor prognosis despite treatment advances, with a 5-year survival rate of 31% [1]. Its incidence continues to decline in the United States, with a decrease of 1.7% for men and 0.8% for women annually from 1992 to 2010 [2]. However, the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute estimates that there will be 28,000 new cases and 10,960 deaths from gastric cancer in 2017. Gastric cancer typically afflicts older adults, with a median age at diagnosis of 68 years in the United States; >95% of all new cases are diagnosed in patients > 40 years of age [3].

Though young adults are less commonly affected by gastric cancer, there have been mixed reports about the prognosis of younger patients from studies around the world. Some have suggested that young patients more often have

diffuse-type and signet-ring histologies, higher stage disease, more frequent nodal involvement, and higher postoperative mortality [4–11]; and others have explored the idea of gastric cancer in the young as a different clinical entity, raising questions for the role of differential management [12, 13]. Most studies are reports from single institutions or use the Surveillance, Epidemiology, and End Results (SEER) database, which lacks detailed treatment data unless combined with data from the Medicare-linked database. The Medicare data, however, lack information on younger patients. In addition, while key trials in resectable [14–17] and metastatic [18–22] and gastric adenocarcinoma have included patients under the age of 40, they have not reported specifically on their presentation or survival. Among young adults with gastric adenocarcinoma, the geographic and ethnic distributions, receipt of treatment, and outcomes have not been fully characterized.

Young adult patients with gastric cancer face unique challenges, including biologic variation in tumors, differences in treatment effectiveness, tolerance, and adherence, issues related to fertility preservation, and psychosocial considerations associated with the early death [4, 23]. Some variation exists in the specific cutoffs used to define young adult patients, but large groups including the National Cancer Institute [24] and the Adolescent and Young Adult Oncology Progress Review Group (AYAO PRG) [25] have used age 39 as the upper limit to define young adults. In addition to studies examining gastric cancer in young adults [26, 27], survivorship studies across cancer types have similarly used 39 as the upper limit to define young adults [28, 29]. The AYAO PRG notes that patients < 40 years old have had limited improvement in survival, thus warranting further study [25].

The National Cancer Database (NCDB) is maintained as a joint project of the American College of Surgeons Commission on Cancer (CoC) and the American Cancer Society, and captures registry data that include approximately 70% of newly diagnosed cancer cases nationwide each year, compared to just 28% of all cancer cases in the SEER database [30]. The NCDB provides data on a variety of clinical and demographic patient data as well as initial management and survival. Studies examining patterns of care and survival outcomes in young patients using the NCDB have been conducted for several other areas, including lung, testicular, and breast cancer [31–33]. Here, we report our descriptive analysis of the NCDB with respect to differences across patient, tumor, and treatment characteristics between younger and older adults with gastric adenocarcinoma to elucidate factors affecting outcomes.

Materials and methods

Patient selection

The Institutional Review Board at our institution deemed analysis of the NCDB Participant User File to have exempt status. Adults initially diagnosed between 2004 and 2013 with International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) topographical codes C16.0-C16.6, C16.8, or C16.9 were defined as having gastric cancer. Patients were identified ICD-O-3 morphological codes for adenocarcinoma histology; other histologies were excluded. Only patients with invasive gastric adenocarcinoma without prior history of malignancy were included. Patients with cancers originating at other sites (e.g., gastroesophageal junction) and extending into the stomach were excluded. Patients with missing clinical staging, treatment, follow-up, or vital status information were excluded. Inclusion and exclusion criteria are summarized in the CONSORT diagram in Fig. 1.

Data elements

Adult patients were divided into two age groups: < 40 years (young adult) and ≥ 40 years. The rationale for young adult group was to remain consistent with the National Cancer Institute definition and with the previous studies examining considerations uniquely related to survivorship in young adults. Baseline patient characteristics were compared across age groups. Surgery was defined as any surgical procedure, including local excision/ablation, gastrectomy, or surgical procedure not otherwise specified. Radiation treatment was defined as any external beam radiation administered to the esophagus, stomach, abdominal site not otherwise specified, and/or lymph nodes. Chemotherapy was defined as any type and number of agents as part of the first treatment course. Patients were divided into several treatment groups: surgery only, chemotherapy alone, surgery + chemotherapy, surgery + chemotherapy + radiation, chemotherapy + radiation, no treatment, and other. Any sequence or timing of these combinations was considered in these mutually exclusive groups (see Table 1).

Statistical analysis

Chi-squared tests were used to compare baseline characteristics between the two age groups. Least-squares regression was used to identify a potential trend towards a changing proportion of young adult patients over time. Survival analysis was performed using the Kaplan–Meier method and log-rank test. A descriptive nomogram was constructed using the

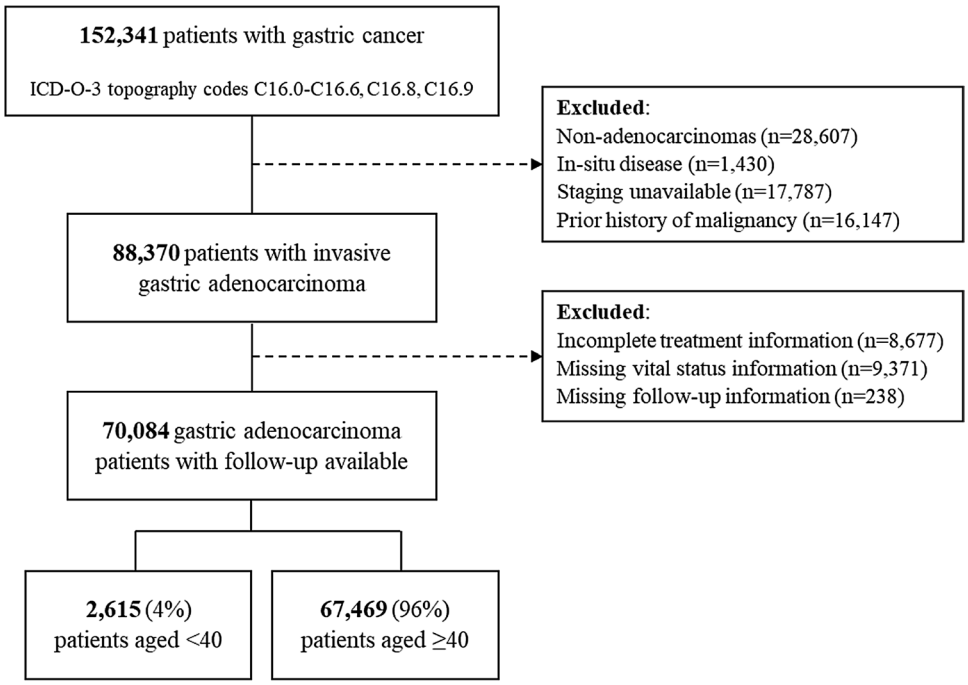

Fig. 1 CONSORT diagram of inclusion criteria and age category

rms package (https://cran.r-project.org/web/packages/rms/rms.pdf). An accelerated failure time survival model was fitted and the overall survival time was assumed to follow a Weibull distribution. All covariates for which > 80% of data were available were selected based on clinical and/or statistical significance. Included covariates were sex, race, Charlson–Deyo Comorbidity score, grade, treatment, and clinical stage. All covariates were treated as discrete variables. All statistical analyses were performed using Stata Version 13.0 (StataCorp, College Station, TX, USA) or R statistical software version 3.4.3 (R Development Core Team, 2017). Hypothesis testing was two-sided and a p value of ≤ 0.05 was used to indicate significance for all comparisons with Bonferroni corrections applied for multiple comparison.

Results

Patient population

A total of 70,084 patients meeting inclusion criteria were identified, of which 2615 (4%) were aged < 40 and 67,469 (96%) were aged ≥ 40. The median proportion of young adults over time was 3.7% (range 3.7–4.0%); no trend for proportion of young adults over time was noted on linear regression ($p = 0.655$). Baseline patient characteristics are presented in Table 1. Young adults were more likely than adults aged ≥ 40 to be female, non-white, Hispanic, residing in a metropolitan area, treated in a northeastern US state, or treated at a facility in the top decile of gastric cancer patient volume. They were also more likely to present with more advanced, distal tumors with poor risk features, have a Charlson–Deyo comorbidity score of 0, and have either Medicaid, private, or no insurance. Among patients with stage IV disease, young adults were more likely to present with distant organ ± lymph node metastases as compared to older patients. Young adults were also significantly more likely to present with bone metastases as compared to older patients. Young adults with Stage IV disease were equally likely as adults ≥ 40 years old (20 vs. 21%, p = 0.664) to have organ metastases in 2 + sites.

Treatment differences

Stage-specific treatments separated by age group are shown in Fig. 2. Despite higher stage disease, younger patients were more likely to receive treatment than adults ≥ 40 years (87 vs. 81%, $p < 0.001$). For stage I disease, fewer young adult patients received surgery alone as compared to older patients (47 vs. 58%, $p < 0.001$). For stage II disease, young adults more commonly received surgery + chemotherapy + radiotherapy (RT) than older patients (51 vs. 34%, $p < 0.001$). For stage III patients, young adults also more commonly received surgery + chemotherapy + RT as compared to older patients (48 vs. 34%, $p < 0.001$). For stage IV disease, young adults were more likely than older patients (55 vs. 38%, $p < 0.001$) to receive chemotherapy alone. Among stage IV disease patients, a similar proportion of patients received multimodal treatment (21 vs. 19%, $p = 0.02$).

Table 1 Patient characteristics

Attribute	Patient age < 40 (n = 2,615)		Patient age ≥ 40 (n = 67,469)		p value
	n	%	n	%	
Median age at diagnosis, years (IQR)	35 (31–37)		67 (58–77)		< 0.001
Sex (n = 70,084)					
Male	1,425	54	43,942	65	< 0.001
Female	1,190	46	23,527	35	
Race (n = 69,325)					
White	1,785	69	51,146	76	< 0.001
Black	455	18	10,265	15	
Asian/Pacific Islander	238	9	4,412	7	
Other	101	4	923	1	
Ethnicity (n = 65,541)					
Non-hispanic	1,702	68	56,408	89	< 0.001
Hispanic	793	32	6,638	11	
Region (n = 70,081)					
Northeast	937	36	15,592	23	< 0.001
Midwest	472	18	24,379	36	
South	770	29	16,583	25	
West	433	17	10,915	16	
Facility type (n = 70,081)					
Community cancer program	235	9	7,509	11	< 0.001
Comprehensive cancer program	1,099	42	28,013	42	
Academic/research program	1,009	39	26,854	40	
Integrated network cancer program	269	10	5,004	7	
Other	0	0	89	0	
Facility setting (n = 67,042)					
Metropolitan	2,210	89	55,257	86	< 0.001
Urban	248	10	8,290	13	
Rural	27	1	1,010	2	
Facility volume (n = 70,084)					
Top decile	1,144	44	24,724	37	< 0.001
Charlson–Deyo comorbidity score (n = 70,084)					
0	2299	88	46,689	69	< 0.001
1	276	11	15,101	22	
2	40	2	5,679	8	
Insurance payer (n = 68,216)					
Private	1,394	56	22,601	34	< 0.001
Medicaid	584	23	4829	7	
Medicare	79	3	34,509	53	
Other government	32	1	742	1	
None	404	16	3042	5	
Chemotherapy only	952	36	12,591	19	
Surgery + chemotherapy	375	14	6895	10	
Surgery + chemotherapy + RT	496	19	10,940	16	
Chemotherapy + RT	142	5	5242	8	
No treatment	347	13	12,838	19	
Other treatment combinations	31	1	1791	3	
Median follow-up, months (IQR) (n = 70,084)	11 (5–25)	12 (4–30)	< 0.001		
Primary tumor location (n = 70,084)					
Proximal third	722	28	27,380	41	< 0.001
Middle third	405	15	9534	14	

Table 1 (continued)

Attribute	Patient age < 40 (n = 2,615)		Patient age ≥ 40 (n = 67,469)		p value
	n	%	n	%	
Distal third	518	20	13,002	19	
Greater curvature	122	5	2185	3	
Overlapping lesions or NOS	848	32	15,368	23	
Histologic subtype (n = 21,241)					
Signet-ring cell carcinoma	1094	42	13,012	65	< 0.001
Intestinal	67	3	4968	25	
Diffuse	150	6	1950	10	
Clinical stage (n = 70,084)					
Stage 0 or Stage I	302	12	15,362	23	< 0.001
Stage II	268	10	10,064	15	
Stage III	490	19	13,891	21	
Stage IV	1,555	59	28,152	42	
Metastatic involvement (n = 26,787)					
Distant lymph nodes	124	9	2969	12	< 0.001
Distant organs	956	67	16,342	64	
Distant lymph nodes + organs	258	18	4130	16	
Distant metastasis, NOS	83	6	1925	8	
Metastatic organ involvement (n = 5,857)					
Bone	51	21	578	10	< 0.001
Brain	7	3	55	1	
Liver	104	43	3276	58	
Lung	29	12	495	9	
2 sites	40	17	1045	19	
3 + sites	9	4	168	3	
Grade (n = 59,780)					
1	42	2	2751	5	< 0.001
2	291	13	16,562	29	
3	1805	82	37,174	65	
4	69	3	1086	2	
Pathologic T-stage (n = 40,431)					
T0	8	1	309	1	< 0.001
T1	238	15	10,289	26	
T2	208	13	7187	18	
T3	383	24	9646	25	
T4	729	57	11,434	29	
N0	386	16	13,948	23	< 0.001
N1	343	15	10,587	17	
N2	245	10	5346	9	
N3	184	8	3646	6	
NX	1199	51	27,631	45	
Surgery only	272	10	17,172	25	< 0.001
Chemotherapy only	952	36	12,591	19	
Surgery + chemotherapy	375	14	6895	10	
Surgery + chemotherapy + RT	496	19	10,940	16	
Chemotherapy + RT	142	5	5242	8	
No treatment	347	13	12,838	19	
Other treatment combinations	31	1	1791	3	
Median follow-up, months (IQR) (n = 70,084)	11 (5–25)	12 (4–30)	< 0.001		

IQR interquartile range, *NOS* not otherwise specified, *RT* radiotherapy

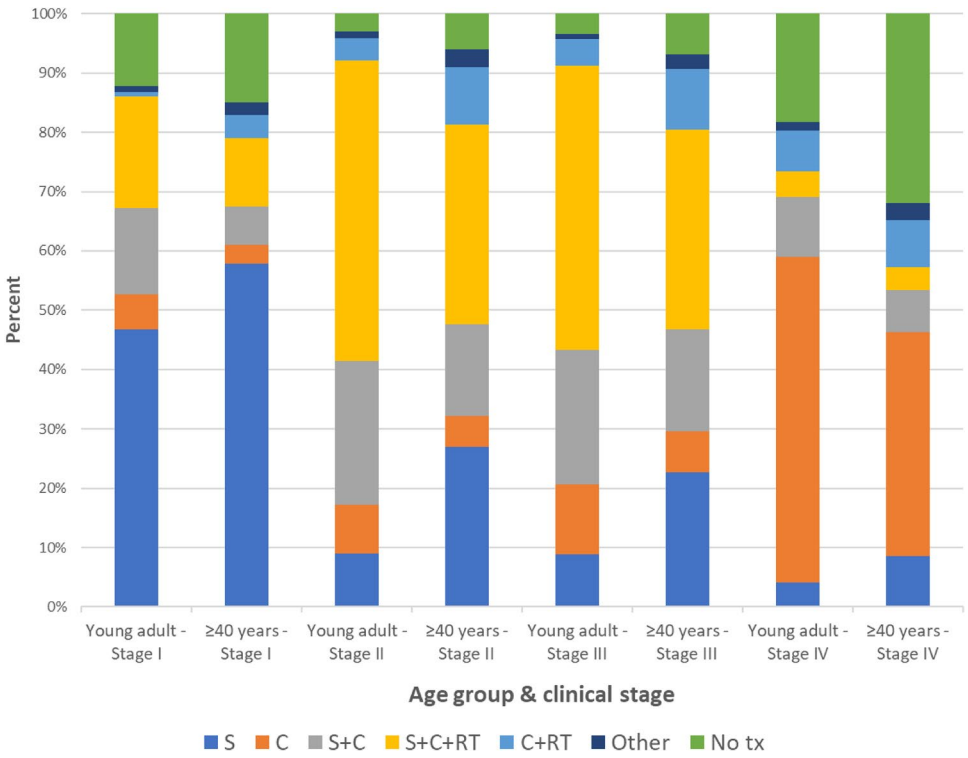

Fig. 2 Stage-specific treatment across age strata. *S* surgery, *C* chemotherapy, *RT* radiotherapy, *tx* treatment

Overall survival

Five-year overall survival across all stages for adults aged < 40 and those aged ≥ 40 was 21.1% [95% confidence interval (CI), 19.2–23.0%] and 22.1% (95% CI, 21.8–22.5%), respectively. Five-year stage-specific survival by age group is shown in Fig. 3. For young patients with stage I disease, median survival was not reached at last follow-up. Median survival for younger patients with stage II, III, and IV disease was 43.9 [95% confidence interval (CI), 34.7–66.5], 25.7 (95% CI, 21.7–31.0), and 7.9 (95% CI, 7.5–8.5) months, respectively. For adults > 40 years, the median survival for stage I, II, III, and IV disease was 61.5 (95% CI, 58.7–64.3), 29.9 (95% CI, 28.8–31.1), 16.9 (95% CI, 16.6–17.3), and 5.7 (95% CI, 5.6–5.8) months. On univariate log-rank analysis, young adults had significantly better 5-year OS than older patients for stages II, III, and IV disease ($p < 0.001$). When comparing stage IV patients receiving multimodal therapy on log-rank analysis, young adults showed no difference as compared to older patients ($p = 0.56$).

Nomogram for young adult patients

The nomogram identified clinical stage as the largest contributor to overall survival, followed by treatment, grade, race, Charlson–Deyo comorbidity score, and sex. Each category within these variables was assigned a score on the point scale. The 5-year overall survival probability can be determined by computing the sum of scores, locating it on the total point scale, and drawing a straight line down on the survival scale (Fig. 4). The corresponding accelerated failure time model data is reported in Table 2.

Discussion

This hospital-based analysis capturing 70% of all cancers diagnosed in the United States demonstrated that young adult patients with gastric adenocarcinoma are more likely to present with metastatic, high-grade disease. To our knowledge, this study is one of the first to look specifically at young adult patients in the era of modern trials after 2004 in localized and metastatic disease that have shaped gastric cancer treatment. The existing literature in this area is largely limited to older retrospective studies with small sample sizes, univariate analysis, significant confounding, and lack of comparison to older patients. A small number of larger analyses have been conducted but have limited or no data from the last 10 years [4, 10, 34].

Several findings regarding patient presentation in this hospital-based analysis are consistent with past reports, including higher rates of female sex, non-white race, signet-ring or diffuse histology, advanced clinical stage disease, higher grade, advanced T-stage, and nodal involvement [4–13]. Among young adult patients, findings that have not been previously reported including a larger proportion of patients treated in metropolitan areas, in the northeast, at facilities in the top decile of gastric cancer patient volume,

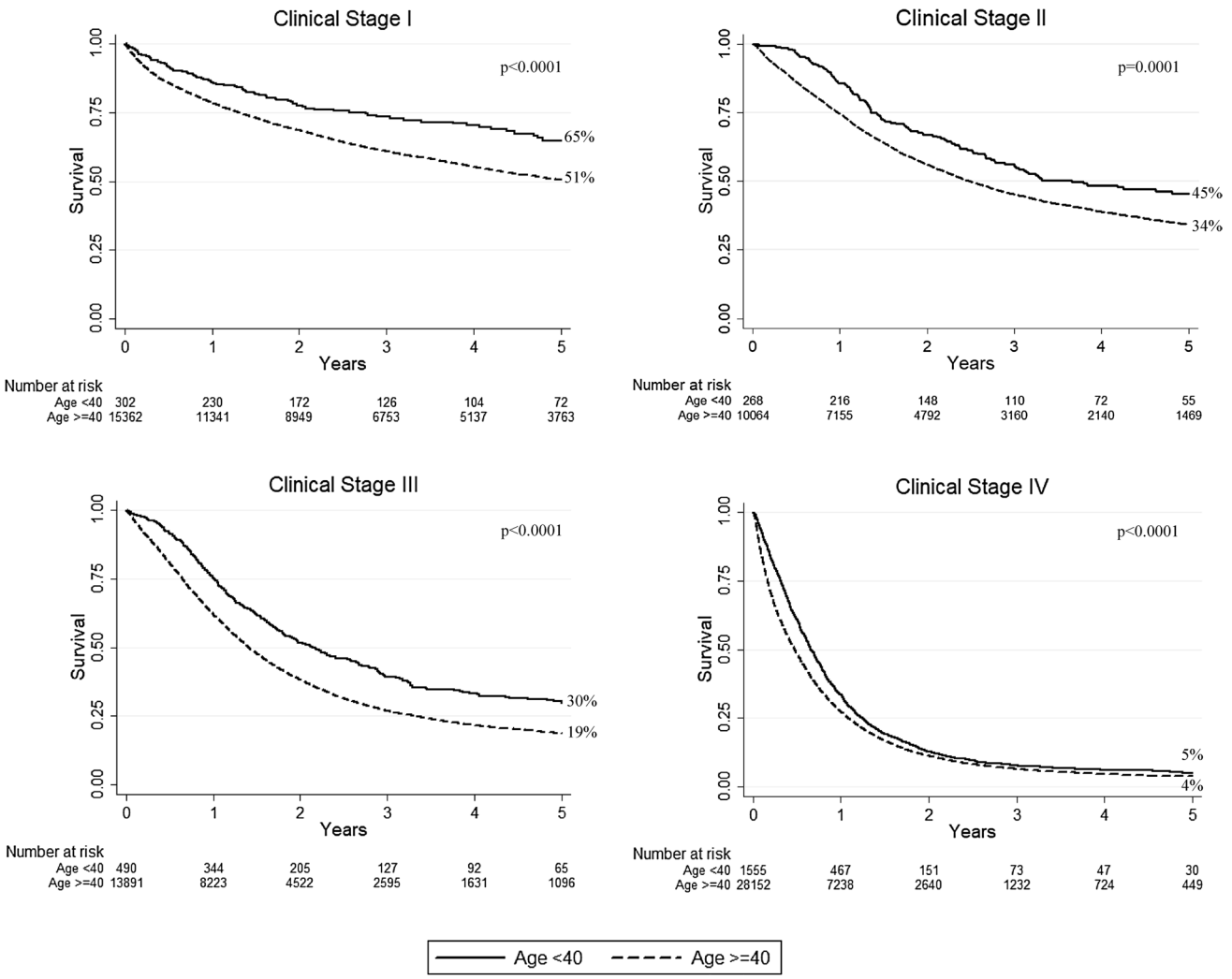

Fig. 3 Kaplan–Meier curves displaying 5-year overall survival for each age group, separated by clinical stage. Estimates for 5-year overall survival and log-rank survival comparisons are noted on each graph. Significance was assessed at the 0.05 level

and with private, Medicaid, or no insurance and higher frequency of bone metastases. To date, there is no clear explanation for the larger proportion of young adult females with gastric cancer, though some studies have hypothesized that hormonal factors such as a higher percentage of estrogen receptor-positive cells may be responsible [34–36]. A higher frequency of bone metastases in young adult patients may also be explained by estrogen receptor positivity, which has been shown to be associated with osseous metastasis in tumors at other sites [37, 38]. Markers of more advanced, aggressive disease in young adults have been reported by several series. While the NCDB does not capture patient history prior to the initial presentation, other series have reported shorter symptom duration, delays in diagnosis, and hereditary factors may be responsible for presentation with advanced disease [6, 12, 34, 39]. Despite an overall decrease in the incidence of gastric cancer in the United States, the proportion of young adults with gastric cancer in this analysis has remained around 4% with no obvious trend between 2004 and 2013.

Young adults as a group displayed similar survival, with a 5-year OS of 21% as compared to 22% for older patients, possibly due to a greater percentage of young patients presenting with metastatic, high-grade disease. Among stage IV patients, young adults were more likely to present with organ involvement, suggestive of a potentially greater burden of disease. When stage-specific survival was examined, young adults appeared to do as well as or better than older patients.

Within each disease stage, choice of treatment differed substantially across age groups. For stage I disease, the most commonly chosen treatment for each age group was surgery only, but young adult patients were more likely to additionally receive chemotherapy or RT. Young adults with stage II and III disease were more likely to receive

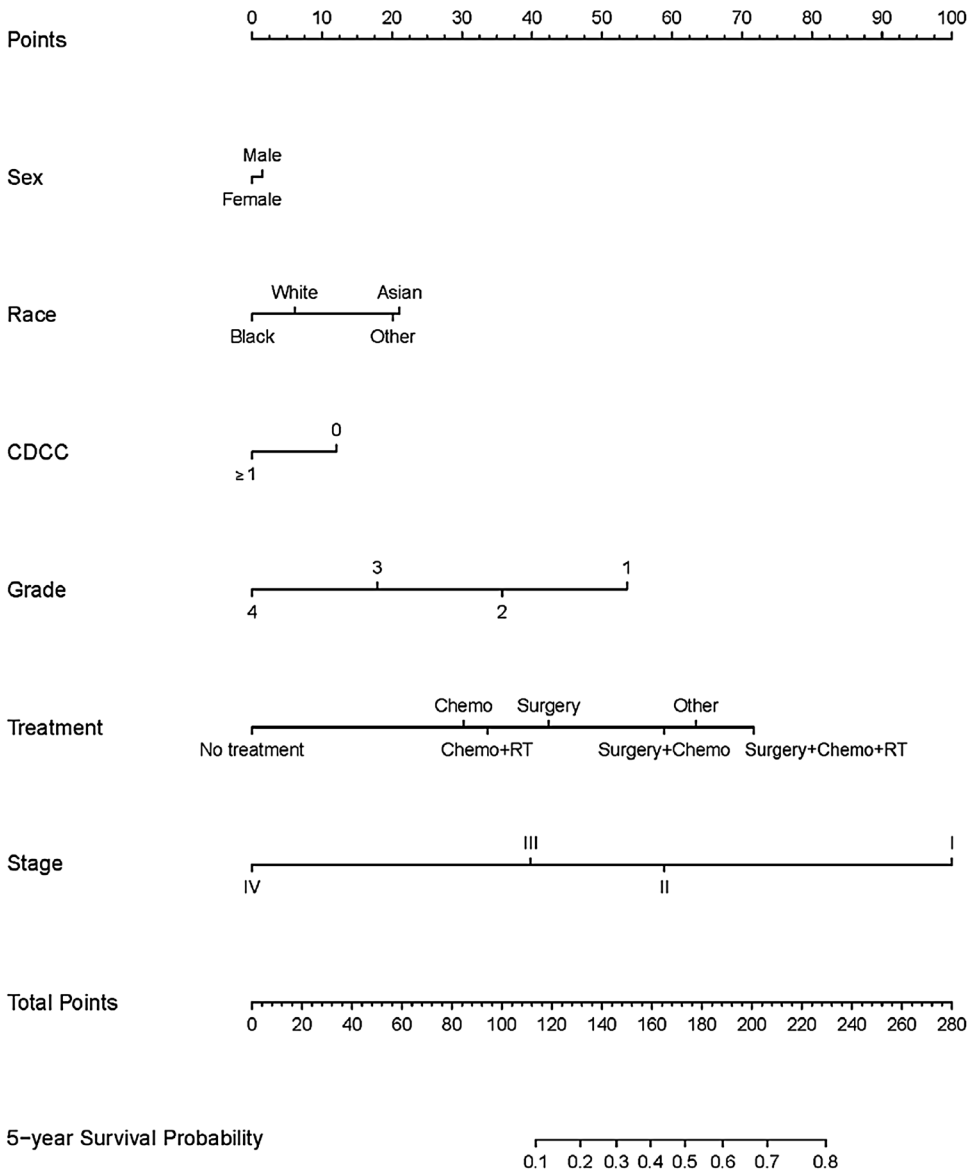

Fig. 4 Nomogram for overall survival for young adults with gastric adenocarcinoma

surgery + chemotherapy + RT than older patients. For stage IV disease, younger patients were less likely to receive no treatment than older patients. A trend towards more aggressive treatment in younger patients may reflect a perceived ability for patients to tolerate treatment given younger age and fewer comorbidities. Nonetheless, more aggressive treatment with trimodality therapy was not used more often in patients < 40 years of age, suggesting that age alone may not change physicians' perceived optimal treatment. Studies have indicated that younger patients are more likely to suffer postoperative mortality, though these data are not captured in the NCDB [5, 12]. Although staging in gastric adenocarcinoma [40] serves to guide treatment and prognosis, these results demonstrate that other factors, including age, may strongly impact how clinicians choose therapies for patients.

The nomogram for young adult patients showed stage, treatment, and grade to be most predictive of 5-year overall survival, whereas Charlson–Deyo comorbidity score, race, and sex were found to be less predictive. The demonstrated effect of treatment is consistent with other gastric cancer studies including the MAGIC trial [14], which showed improved OS for patients receiving perioperative chemotherapy, Intergroup Study 0116 [15], which showed improved OS for patients receiving adjuvant chemoradiotherapy, and RTOG 9904 [41], which showed an improved pathologic complete response rate with preoperative chemoradiation. The nomogram findings support the use of multimodality therapy in young adult patients as appropriate, particularly since these patients are more likely to present without significant comorbidities or impairment of functional status.

Table 2 Accelerated failure time model results for young adult patients with gastric adenocarcinoma

	Estimated coefficient	95% confidence interval	*p* value	Acceleration factor
Sex (vs. male)				
Female	− 0.03	(0.87, 1.08)	0.583	0.97
Race (vs. white)				
Black	− 0.13	(0.77, 1.01)	0.066	0.88
Asian	**0.31**	**(1.11, 1.67)**	**0.003**	**1.36**
Other	0.29	(1.00, 1.79)	0.051	1.34
Charlson–Deyo comorbidity score (vs. score = 0)				
Score ≥ 1	**− 0.25**	**(0.66, 0.91)**	**0.002**	**0.78**
Grade	**− 0.37**	**(0.61, 0.78)**	**< 0.0001**	**0.69**
Treatment (vs. surgery alone)				
Chemo	**− 0.25**	**(0.61, 0.99)**	**0.038**	**0.78**
Surgery + chemo	**0.34**	**(1.10, 1.81)**	**0.008**	**1.41**
Surgery + chemo + RT	**0.60**	**(1.43, 2.34)**	**< 0.0001**	**1.83**
Chemo + RT	− 0.18	(0.62, 1.13)	0.237	0.83
No treatment	**− 0.88**	**(0.32, 0.54)**	**< 0.0001**	**0.42**
Other	0.43	(0.92, 2.60)	0.102	1.54
Clinical stage (vs. stage I)				
Stage II	**− 0.85**	**(0.31, 0.59)**	**< 0.0001**	**0.43**
Stage III	**− 1.24**	**(0.21, 0.39)**	**< 0.0001**	**0.29**
Stage IV	**− 2.07**	**(0.09, 0.17)**	**< 0.0001**	**0.13**

Acceleration factor is defined as the constant multiplicative extent to which the covariate impacts survival. Significant results at the 5% significance level are displayed in bold

RT radiotherapy. Coefficient > 0 indicates positive correlation with survival and coefficient < 0 indicates negative correlation with survival

This study has several limitations typical of large database analysis. The patient demographic attributes in the NCDB are limited; there may be confounders within the analysis that are unable to be accounted for. There is no recorded information on cancer outcomes beyond OS, including locoregional control, distant control, salvage treatment, cancer-specific survival, or quality of life. The database also lacks metrics of response to treatment, types of systemic therapy received, and molecular data. Toxicities, such as malabsorption, dumping syndrome, cytopenias, ototoxicity, and secondary malignancies, are known to have a profound impact on patients but are not recorded in the NCDB. While the age categories chosen in this study reflect divisions studied in the previous studies, they are inherently arbitrary, and there may be differences in outcomes for smaller age subgroups. Several attributes in the NCDB, such as histology, grade, and sites of metastatic involvement are incompletely coded, which also limits our analysis. Therapeutic approaches have also evolved between 2004 and 2013, the timeframe of this study; D2 surgery, pancreas and spleen preserving gastrectomy, minimally invasive surgery, perioperative chemoradiation, and targeted therapy have been increasingly offered during these years [42]. Though the NCDB offers detailed information on treatment, the impact of these changes in treatment approach cannot be granularly assessed in the present study.

Despite these limitations, this study is one of the largest hospital-based analyses in the United States examining the presentation, treatment, and outcomes of young gastric adenocarcinoma patients. While these data do not provide any information on the benefit of surveillance, there appears to be a strong advantage to the early diagnosis in younger patients. Educating primary care physicians and patients about the early signs of gastric cancer might be beneficial in reducing mortality, particularly among Asian/Pacific Islander and Hispanic patients with a family history or known genetic predisposition. Given the paucity of randomized evidence for younger patients with gastric adenocarcinoma, large database analyses like this represent the best resource to potentially answer clinical questions surrounding younger patients.

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Author contributions Study concept and design: De and Ang. Administrative support: all authors. Provision of study materials: all authors. Collection and assembly of data: all authors. Data analysis and interpretation: all authors. Manuscript writing: De. Final approval of manuscript: all authors.

Compliance with ethical standards

Conflict of interest Randall Holcombe reports personal fees from Anthem Healthcare and Merck, outside the submitted work, and also reports involvement in a colon cancer clinical trial as Chair of a Data Safety and Monitoring Committee, outside the submitted work. All other authors declare that they have no conflicts of interest.

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