Published in final edited form as:

Ann Surg Oncol. 2011 October ; 18(10): 2800–2807. doi:10.1245/s10434-011-1647-x.

Gastric Adenocarcinoma in Young Patients: A Population-Based Appraisal

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Abstract

BACKGROUND—Although international studies of young gastric cancer patients have mainly reported favorable survival outcomes compared to older patients, US-based experiences showed a wider spectrum of outcomes. We examined the impact of young age (under 45 years) on the presentation and survival outcomes of gastric adenocarcinoma.

METHODS—A total of 33,236 patients with gastric adenocarcinoma were identified within the 1988-2006 Surveillance Epidemiology and End Results (SEER) registry. Multivariate regression analysis of relative survival was performed to adjust for covariate effects using generalized linear models.

RESULTS—Young patients were more likely than older patients to have advanced nodal and distant metastatic disease at presentation ($p < 0.001$ for both). Unadjusted relative survival analysis demonstrated younger patients to have favorable stage-stratified survival when compared to middle-aged and older patients. These findings persisted after adjusting for covariates. After stratifying for receipt of cancer directed surgery, younger age was associated with more favorable stage-stratified relative survival.

CONCLUSIONS—This is the largest US population-based study of age-related gastric cancer outcomes. Although young patients with gastric cancer present with more advanced disease, their adjusted stage-stratified relative survival is more favorable than that of older patients. This study supports a stage-dependent treatment approach in younger populations.

INTRODUCTION

Gastric adenocarcinoma remains the second leading cause of cancer-related deaths worldwide. Although this cancer's overall incidence continues to decline in the United States, the expected numbers of new cases are projected to increase to 1 million in 2010, in part because of an increasing—and aging—world population.¹ In 2005 there were 21,860 newly diagnosed cases of – and 11,550 deaths from – gastric adenocarcinoma in the United States.²⁻⁴ Nearly half of these patients were over 70 years of age and nearly 10% were under 45 years (young group).⁵⁻¹¹

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Presented in part at the American Society of Clinical Oncology Gastrointestinal Cancer Symposium in Orlando, Florida in January, 2007 and at the Annual Meeting of The American Society of Clinical Oncology in Chicago, Illinois in June, 2007.

Although young persons are less commonly affected by gastric cancer, there has been a common perception that they have worse prognosis than older patients. Young patients become the focus of several studies from Europe and Asia, which have mainly reported favorable survival outcomes of young patients surgically treated for gastric cancer.^{12, 13} However, US-based studies have demonstrated a wide prognostic spectrum among young patients with gastric cancer.^{10, 11, 14} It has been reported that gastric adenocarcinoma exhibits a more aggressive behavior in patients under 40 years than in patients over 40 years, with median survival durations of 11 to 16 months vs. 33 months, respectively.^{10, 15} Others have reported that younger age was not associated with survival outcome (hazard ratio (HR), 1.13; 95% confidence interval [CI], 0.83 – 1.5; $p > 0.10$) when factors such as serosal or nodal involvement were considered.¹¹ Thus far, studies evaluating survival outcomes of young patients with gastric cancer in the United States remain mixed and are mostly limited to experiences from single-center and regional studies.

We hypothesized that previously observed poor outcomes among young patients with gastric cancer are due to advanced stage at presentation and that stage-stratified, co-variate adjusted survival outcomes in younger patients with gastric cancer are comparable to that of other age groups. To test our hypothesis and to better understand the clinical presentation, treatment, and prognosis of gastric adenocarcinoma in the US, we examined these factors in young gastric adenocarcinoma patients using a large U.S. population-based tumor registry.

METHODS

Data source

Data from the Surveillance End Results and Epidemiology (SEER) Program of the National Cancer Institute (released in 2009) were utilized for this study.¹⁶ SEER, a population-based cancer registry, collects cancer incidence and survival data from 17 regional population-based registries covering approximately 26% of the US population. Since 1988, SEER registries have collected data on patient demographics, primary tumor sites, tumor morphology, and American Joint Committee on Cancer (AJCC) stage at diagnosis, first course of treatment (if surgery and/or radiation), and vital status upon follow-up. When the first course of treatment includes both radiation and surgical therapy, the sequence of administration is reported. SEER also reports the status of regional lymph nodes, including total number of recovered and total number involved with metastatic disease. We did not evaluate variables for which SEER does not collect data, such as comorbidities, resection margin status, short-term operative outcomes, and systemic chemotherapy.

Study Population

Using the SEER registry, we identified those patients diagnosed between January 1991 and December 2006 with adenocarcinoma of the stomach. We included patients for whom the diagnosis of gastric adenocarcinoma was their first and only cancer diagnosis. We excluded patients with SEER-defined gastroesophageal junction tumors.

Patients were categorized by age: younger than 45 years, 45 to 70 years, and older than 70 years. Our rationale for this grouping was twofold. Firstly, to remain consistent with prior studies that have generally defined younger gastric cancer patients as those below 40 or 45 years while also including a middle-aged group as a referent. Secondly, comparisons of young patients with those over age 70 years may be complicated by coexisting comorbidities associated with older age and thus may not allow for meaningful comparisons.

Patient, tumor, and treatment-related factors were compared among age groups. Tumor-related factors included the location of the primary tumor in the stomach, histologic grade, and AJCC 6th edition stage. For tumor location within the stomach, we categorized the

patients as having tumors of the proximal third (cardia C16.0 and fundus C16.1), mid third (body C16.2 and lesser curvature C16.5), distal third (antrum C16.3 and pylorus C16.4), greater curvature (C16.6), or overlapping lesions of the stomach (C16.8). Tumors were histologically categorized into low-grade (well and moderately differentiated) versus high-grade (poorly differentiated, undifferentiated, and anaplastic tumors). All cases were re-coded according to the *AJCC Cancer Staging Manual, 6th edition* criteria from the SEER extent of disease codes.¹⁷ For treatment-related factors, we included the receipt of gastric cancer-directed surgery and of adjuvant radiotherapy.

Statistical analysis

For our univariate analyses, patient demographics, tumor factors, and treatment types were compared by age groups using the chi-square test for proportions and the Student's *t* test for means. Overall survival (OS) was assessed using the Kaplan-Meier method and the log-rank test for univariate comparisons. Relative survival analysis was calculated as the ratio of the observed survival to the expected survival for the US general population individually matched for age, sex, and the year of which the age was coded. Relative survival analysis accounts for potential errors in cause-of-death information within SEER and competing causes of death and provides an approximation of cancer-specific survival.¹⁸ Expected survival for the US population was obtained from Human Mortality Database 1988-2006 (<http://www.mortality.org/> last accessed 11/06/2009).

To assess the impact of age (as a factor) on stage-stratified relative survival adjusted for covariate influences, we utilized a relative survival regression model using generalized linear models with the Poisson assumption for the observed number of deaths.¹⁹ To determine our final logistic regression models, we used forward selection and included both variables that were significant in the univariate analyses and those with clinical relevance. We considered $p < 0.05$ to be statistically significant. All statistical analyses in this report were performed using STATA10 MP software (Statacorp, College Station, TX).

RESULTS

Patient Demographics

A total of 33,236 patients with gastric adenocarcinoma were identified from the SEER tumor registry from 1988 through 2006. Of these, 2,757 (8.3%) were younger than 45 years, 16,603 (49.9%) were between 45 and 70 years, and 13,876 (41.7%) were older than 70 years (Table 1). The median patient age at diagnosis was 68 years (interquartile range [IQR], 57 to 76 years). There was a male preponderance in all three age groups. However, among the youngest and oldest groups, women comprised a greater proportion than in the middle-aged group. Although the most common racial/ethnic group in each category was white, there were higher proportions of non-Whites in younger cohorts than older ones.

Tumor-related features

Proximal gastric tumors (cardia and fundus) represented the most frequent primary tumor location in each age group of gastric cancer patients. Young patients were more likely to have tumors with higher histologic grades than were the other age groups (for all, $p < 0.001$). They were also more likely to present with higher proportions of AJCC T3, T4, N3, and M1 disease stages than were in both older age groups (for all, $P < 0.001$). The mean number of lymph nodes examined after cancer-directed surgery was higher among the youngest patients (14.5) than the middle age (13.8, $P=0.036$) or the oldest group (11.9, $P<0.001$). Moreover, the proportion of patients who had 15 or more lymph nodes examined after gastric surgery was higher among the young patients (39.4%) than the middle-aged (35.6%, $P<0.001$) or oldest patients (28.4%, $P < 0.001$).

Types of Treatment

Overall, there were significant age-related differences in rates of gastric cancer-directed surgery likely reflecting both age and stage related effects. However, among those who did undergo cancer-directed surgery, increasing age was significantly associated with decreasing use of adjuvant radiation therapy (for all comparisons, $P < 0.0001$).

Relative Survival Outcomes

On univariate survival analysis, relative survival outcomes were significantly more favorable among the young cohort when compared to either the middle-aged and oldest cohorts. These observations remained true for all stage strata (Figure 1 through 4). The observed findings on unadjusted relative survival persisted after adjustment (for sex, race, marital status, primary tumor location, tumor grade, use of radiation, undergoing cancer-directed surgery, and number of lymph nodes examined) in the stage-stratified relative survival regression analysis, demonstrating that the association between younger age and better overall survival outcome was true (Table 2). We next evaluated only those patients who underwent cancer-directed surgery and noted that the favorable effect of young on improved survival outcomes persisted (Table 2).

DISCUSSION

Our population-based analysis demonstrated that young patients with gastric adenocarcinoma, when compared to older aged cohorts, are more likely to present with advanced or metastatic disease. However, after stratifying for stage at presentation, the young patients have survival outcomes that are more favorable than their older counterparts. To our knowledge, the present study is the largest contemporary population-based analysis in the United States examining the presentation, treatment, and survival outcomes for young patients with gastric adenocarcinoma and one of the first to demonstrate improved survival among young patients.

Our findings regarding the nature of the cancer at presentation are consistent with prior reports of gastric adenocarcinoma in young patients. Young patients (less than 40 years) in a Southern California cancer registry were more likely to have tumors with advanced grade and signet ring cell histology than were older patients (more than 40 years). Furthermore, young patients have been observed to have higher rates of advanced nodal and distant metastatic disease (either at the time of diagnosis or upon surgical exploration).^{6-8, 14} However, there have been conflicting reports regarding survival outcomes of gastric cancer among young patients.^{10, 15} A number of studies have reported that young patients have generally worse survival outcomes, suggesting more aggressive disease biology, while others have observed no age related effects.^{10, 20, 21} Most studies have been generally limited by small numbers of patients, inclusion of historical patients, lack of comparison to similar control groups, and limited ability to account for disease specific survival. In our analysis we showed that young age was actually associated with improved survival after stratification by stage at presentation and adjustment for covariate effects. As relative survival analysis has been shown to be a good approximation of disease-free survival, our findings suggest that stage at presentation is the most important predictor of outcome and that the improved survival among the young patients likely results from a greater ability to tolerate cancer-directed therapies.

Our finding of more advanced gastric cancer in the young cohort, consistent with other studies, has been attributed to several factors. First, the incidence of gastric cancer is lower among younger cohorts. Given the overlap of its presenting features with other common benign conditions (e.g., gastroesophageal reflux disease), gastric cancer in young persons

may intuitively not be considered at the time of presentation. Second, gastric cancer has a declining incidence in the United States and generally more advanced features than in Asia, where it is more common. Therefore, there has been little incentive to establish surveillance endoscopy programs to identify patients at an earlier stage. As our understanding of the molecular biology of gastric cancer continues to evolve, as in diffuse gastric cancer, a subset of persons at higher risk may be identified. Early identification of this subset of persons may decrease the proportion of disease diagnosed at locally advanced or metastatic stages, especially in younger persons.

Our study has limitations inherent to the dataset and changes to the AJCC staging system. There were some cases for which incomplete information did not allow for complete AJCC stage assignment such as in cases where no cancer-directed surgery was performed. However given the large number of patients within the study cohort, in order to reduce the potential effect of bias due to lower rates of cancer-directed surgery in the oldest cohorts, the stage-stratified analyses were performed using data from those patients with complete staging information. We also considered the changes to the AJCC 7th edition and applied them to our primary analysis but this did not affect our findings that younger patients presented with more advanced disease but with more favorable outcomes than their stage-matched older cohorts (data not shown). Our study did exclude patients with Siewart type III gastroesophageal junction tumors which are currently coded as esophageal cancers within SEER²², thus eliminating the confounding of its treatment and prognosis. Secondly, the time frame of the current study overlaps with the natural evolution of the AJCC staging system for gastric cancer. It is possible that the current analysis cannot account for the unmeasured variations in practice for gastric cancer care in previous years. Thirdly, the SEER registry does not report data on comorbidities, which may affect subsequent treatment and survival. This analysis is also subject to age related selection bias. We therefore examined covariate adjusted relative survival to measure the excess mortality in the gastric cancer patients relative to the general population. This method adjusts for differences in observed survival that may be attributed to competing causes of death, thereby avoiding the pitfalls of potential errors in cause of death information on cancer-specific survival outcomes, a particularly relevant issue when considering age-related outcomes.²³

Our study has implications for future investigation of gastric cancer in young patients. The present study represents one of the largest population-based analyses in North America examining the presentation survival outcomes of young patients with gastric adenocarcinoma. Our results support a stage-dependent rather than age-dependent approach in the management of gastric cancer in young patients. Secondly, our study offers relevant information on the advanced patterns of gastric cancer in younger persons. These results may help to maximize the utility of diagnostic laparoscopy, peritoneal cytology, and consideration for neoadjuvant therapy protocols, thus avoiding the pitfalls of non-therapeutic laparotomy.

In conclusion, this large US population-based study showed that young patients with gastric cancer presented with more advanced disease; however, their stage-stratified relative survival was more favorable than that of older patients. This study validates previous international experiences and supports a stage-dependent treatment approach in younger populations.

Acknowledgments

We thank Maude Veech and Diane Hackett for their assistance with editing this manuscript.

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ABBREVIATIONS

US	United States
SEER	Surveillance Epidemiology and End Results
AJCC	American Joint Committee on Cancer
OS	overall survival
CSS	cancer-specific survival
OR	odds ratio
RR	risk ratio
CI	confidence interval

Demographic, Clinical, Tumor-, and Treatment-related Features in Patients with Gastric Adenocarcinoma, Stratified by Age at Diagnosis (1988–2006)

Table 1

Variables		Age Category						P-value (45-70 yrs vs. <45 yrs)	P-value (>70 yrs vs. <45 yrs)
		<45 yrs (n=2,757)		45-70 yrs (n=16,603)		>70 yrs (n=13,876)			
		No.	%	No.	%	No.	%		
AJCC stage								<.001	<.001
IA		151	5.5	1,288	7.8	1,315	9.5		
IB		209	7.6	1,774	10.7	1,868	13.5		
II		299	10.8	2,574	15.5	2,295	16.5		
IIIA		299	10.8	1,868	11.3	1,539	11.1		
IIIB		76	2.8	484	2.9	333	2.4		
IV(M0)		248	9	1,462	8.8	1,007	7.3		
IV(M1)		1,475	53.5	7,153	43.1	5,519	39.8		
Sex								<.001	0.119
Male		1,560	56.6	11,275	67.9	7,993	57.6		
Female		1,197	43.4	5,328	32.1	5,883	42.4		
Race								<.001	<.323
Non-Hispanic White		926	33.6	8,817	53.1	8,310	59.9		
Hispanic White		816	29.6	2,598	15.6	1,581	11.4		
Black		438	15.9	2,076	12.5	1,376	9.9		
Asian/Pacific islander		577	20.9	3,112	18.7	2,609	18.8		
Marital Status								<.001	<.001
Unmarried		968	35.1	3,770	22.7	1,707	12.3		
Married		1,714	62.2	12,369	74.5	11,823	85.2		
Unknown		75	2.7	464	2.8	346	2.5		
Primary Tumor Location								<.001	<.001
Proximal third		673	24.4	5,669	34.1	3,367	24.3		
Mid third		505	18.3	2,839	17.1	2,773	20		
Distal third		616	22.3	3,699	22.3	4,057	29.2		
Greater curvature		135	4.9	678	4.1	657	4.7		

Variables	Age Category						P-value (45-70 yrs vs. <45 yrs)	P-value (>70 yrs vs. <45 yrs)
	<45 yrs (n=2,757)		45-70 yrs (n=16,603)		>70 yrs (n=13,876)			
	No.	%	No.	%	No.	%		
Overlapping lesions of stomach	349	12.7	1,541	9.3	1,287	9.3		
Other NOS	479	17.4	2,177	13.1	1,735	12.5		
Grade							<.001	<.001
Low	366	13.3	4,080	24.6	4,388	31.6		
High	1,978	71.7	10,498	63.2	8,144	58.7		
Unknown	413	15	2,025	12.2	1,344	9.7		
T-stage*							<.001	<.001
T1	241	14.3	1,953	17.2	1,816	18.9		
T2	661	39.2	5,079	44.6	4,483	46.7		
T3	331	19.6	1,980	17.4	1,607	16.8		
T4	324	19.2	1,679	14.8	1,217	12.7		
TX	131	7.8	692	6.1	469	4.9		
N-stage							<.001	<.001
N0	425	15.4	3,400	20.5	3,557	25.6		
N1	648	23.5	4,567	27.5	3,910	28.2		
N2	362	13.1	2,111	12.7	1,478	10.7		
N3	155	5.6	787	4.7	487	3.5		
NX	1,167	42.3	5,738	34.6	4,444	32		
M-stage							<.001	<.001
M0	1,282	46.5	9,450	56.9	8,357	60.2		
M1	1,475	53.5	7,153	43.1	5,519	39.8		
Undergoing Cancer-directed Surgery							0.002	<.001
No	1,483	44.4	8,768	41.4	10,859	49.7		
Yes	1,855	55.5	12,336	58.3	10,945	50.1		
Unknown	4	0.1	59	0.3	38	0.2		
Number of Lymph Nodes Examined**							<.001	<.001
0	101	6.1	325	3	256	2.7		

Variables	Age Category						P-value (45-70 yrs vs. <45 yrs)	P-value (>70 yrs vs. <45 yrs)
	<45 yrs (n=2,757)		45-70 yrs (n=16,603)		>70 yrs (n=13,876)			
	No.	%	No.	%	No.	%		
1-14	818	49.5	6,291	57.5	6,185	64.8		
15-90	651	39.4	3,897	35.6	2,715	28.4		
Unknown/NA	81	4.9	425	3.9	389	4.1		
Use of Radiotherapy**							<.001	<.001
No	992	60.1	7,244	66.2	8,192	85.8		
Yes	617	37.4	3,477	31.8	1,210	12.7		
Unknown	42	2.5	217	2	143	1.5		

* M1 cases excluded.

** Among patients who underwent cancer-directed surgery.

Abbreviations: AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

Table 2

Stage-Stratified Adjusted Relative Survival*

AJCC stage	All Patients		Following Cancer Directed Surgery	
	Age Group	Hazard Ratio	P value	Hazard Ratio
Overall	< 45 years	1		1
	45-70 years	1.12(1.07-1.17)	<.001	1.11(1.04-1.19)
	> 70 years	1.32(1.26-1.38)	<.001	1.39(1.29-1.48)
IA (n=2,754)	< 45 years	1		1
	45-70 years	1.83(0.99-3.36)	0.05	1.68(0.99-3.36)
	> 70 years	3.27(1.75-6.09)	<.001	3.11(1.75-6.09)
IB (n=3,851)	< 45 years	1		1
	45-70 years	1.61(1.22-2.12)	0.001	1.58(1.20-2.10)
	> 70 years	2.05(1.54-2.72)	<.001	1.96(1.46-2.62)
II (n=5,168)	< 45 years	1		1
	45-70 years	1.19(1.00-1.41)	0.040	1.19(1.00-1.41)
	> 70 years	1.56(1.31-1.86)	<.001	1.55(1.30-1.85)
IIIA (n=3,706)	< 45 years	1		1
	45-70 years	1.24(1.06-1.44)	0.006	1.25(1.07-1.45)
	> 70 years	1.47(1.25-1.73)	<.001	1.48(1.25-1.74)
IIIB (n=893)	< 45 years	1		1
	45-70 years	1.23(0.90-1.68)	0.187	1.24(0.90-1.69)
	> 70 years	1.81(1.31-2.51)	<.001	1.82(1.31-2.52)
IV, M0 (n=2,717)	< 45 years	1		1
	45-70 years	1.27(1.08-1.49)	0.003	1.29(1.09-1.53)
	> 70 years	1.70(1.43-2.01)	<.001	1.73(1.45-2.07)
IV, M1 (n=14,147)	< 45 years	1		1
	45-70 years	1.22(1.15-1.30)	<.001	1.10(0.97-1.25)
				0.106

		All Patients		Following Cancer Directed Surgery	
AJCC stage	Age Group	Hazard Ratio	P value	Hazard Ratio	P value
	> 70 years	1.70(1.59-1.81)	<.001	1.41(1.23-1.61)	<.001

* model adjusted for sex, race, marital status, primary tumor location, tumor grade, use of radiation, undergoing cancer-directed surgery, and number of lymph nodes examined. Excluded cases with unknown surgery or radiation status.

Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence intervals.