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The Yield of Staging Laparoscopy in Gastric Cancer is Affected by Racial and Ethnic Differences in Disease Presentation

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Abstract

Background—Gastric cancer is a heterogeneous disease with variable presentation between racial and ethnic groups. Staging laparoscopy (SL) detects occult metastases not visible on cross-sectional imaging and therefore improves staging. It remains unclear how differences in race and ethnicity affect disease presentation and the yield of SL.

Methods—We performed a retrospective review of a prospectively maintained database to identify patients with gastric cancer treated with curative intent at our institutions from 2008 to 2015.

Results—Hispanic patients presented at an earlier mean age (55.5 ± 11.9 years) compared with Asian (59.8 ± 13.9 years), African American (61.0 ± 10.0 years), and white patients (61.7 ± 12.5 years; $p = 0.046$) and with more locally advanced disease (clinical stage $T3/T4$ or node positive; Hispanic 87%; African American 79%; white 68%, Asian 55%; $p = 0.03$). SL identified 42 patients (34%) with occult metastatic disease. Hispanics were more likely to have a positive SL (44%) than white patients (21%; $p = 0.04$). On univariate analysis, Hispanic ethnicity, clinical $T3/T4$, positive nodal disease, signet ring cells, and poor differentiation were predictors of a positive SL. On multivariable analysis, clinical $T3/T4$, signet ring cells, and poor differentiation independently predicted radiographically occult disease.

Conclusions—Hispanic patients presented with more locally advanced disease and were more likely to have occult disease found on SL compared with white patients. Laparoscopy should be used routinely as part of the pretreatment staging evaluation for patients with locally advanced disease as it alters the management in a significant proportion of patients.

Gastric cancer is a heterogeneous disease with variable clinical presentation and disease course depending on tumor location, histology, and molecular subtype. Dramatic differences

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in gastric cancer incidence and disease outcome have been observed between Eastern and Western patients.¹ The highest incidence of gastric cancer is found in Japan, Korea, Central America, and Eastern Europe.² In the United States, gastric cancer incidence varies among racial and ethnic groups with Hispanics, African Americans, and Asians having nearly twice the rate of gastric cancer diagnoses as whites.² However, despite the significant disease burden found in minorities and the variability of the disease among different races and ethnicities, the majority of published clinical reports focus on white and Asian patients. Randomized, clinical trials that define current treatment paradigms consist primarily of homogenous populations that are underrepresented in their number of minority patients.^{3–5} Given the lack of data on these minority groups, it is unclear whether gastric cancer behaves uniformly between race and ethnicity and whether previously published data are generalizable to patients of all backgrounds.

Laparoscopy has been shown to detect occult or microscopic peritoneal disease in a variety of gastrointestinal cancers.^{6–24} Positive staging laparoscopy (SL) prevents unnecessary invasive operations that are associated with greater in-hospital mortality and prolonged length of stay.^{9,25} Multiple reports demonstrate a uniformly poor prognosis in gastric cancer patients with peritoneal disease, leading the National Comprehensive Cancer Network (NCCN) to recommend pretreatment SL for patients with clinical stage IB or higher disease.²⁶ The reported yield of SL ranges from 13 to 62.5%, likely due to different indications across studies.^{6–22} However, most reports evaluating the utility of SL did not include minorities, especially Hispanics. Given the concern for variable presentation among different races and ethnicities, it is unclear what the yield of SL is among these groups.

Our center has a high-volume, gastric cancer program with a unique patient population that is enriched in Hispanic patients. We performed a retrospective review of our patients to evaluate the yield of SL across race and ethnicity and to determine the factors associated with a positive SL in various races and ethnicities.

METHODS

We retrospectively reviewed a prospectively maintained database to identify patients with gastroesophageal junction (GEJ) and gastric adenocarcinoma treated with curative intent at the University of Texas Southwestern (UTSW) Medical Center and Parkland Hospital from 2008 to 2015. UTSW is a tertiary care center consisting of several university hospitals; Parkland Hospital is a public hospital that serves uninsured and underinsured patients residing in Dallas County. The study was approved by the UTSW institutional review board. All patients underwent high-quality computed tomography (CT) scans at our institution before surgical intervention. Patients with distant metastases, nonregional nodal disease, or ascites were excluded. Clinical *T* and *N* staging were derived from cross-sectional imaging and, when available, endoscopic ultrasound. Patients were classified by race and ethnicity (white, Hispanic, Asian, and African American).

SL was generally performed in patients who (1) presented with locally advanced disease (*T3/T4* or node positive), (2) did not have bleeding or obstruction requiring upfront surgery, (3) had no evidence of metastasis on imaging, and (4) were clinically fit for an operation.

Our institutional practice is to treat locally advanced patients with multimodality therapy, including perioperative chemotherapy or neoadjuvant chemoradiation depending on the location of the tumor and the patient's performance status. Laparoscopy was performed prior to the initiation of neoadjuvant chemotherapy when possible and the start of every definitive surgical resection.²⁰ A thorough inspection of all four quadrants of the abdominal cavity was performed. If suspicious lesions were found, biopsies were done. Peritoneal lavage was performed if no gross lesions were identified. SL was considered to be positive when peritoneal biopsies or cytology revealed malignancy. Patients who had a positive laparoscopy were treated with systemic therapy with plans to reassess disease burden after 6 months.

The timing of laparoscopy was classified with respect to the initiation of neoadjuvant therapy. We divided the patients into two groups: (1) those who had an SL after neoadjuvant therapy, and (2) those who had an SL before therapy, which included patients who did not receive neoadjuvant therapy. Patients who did not receive neoadjuvant therapy were those who had a positive SL and were treated with palliative systemic chemotherapy or those not fit for chemotherapy as decided by the treating medical oncologist. The location of the primary tumor was assessed by the endoscopic reports. Tumor differentiation was determined using the pathology reports from endoscopic biopsies. Tumor histology (signet vs. adenocarcinoma) was determined from the pathology reports of the endoscopic biopsies or the surgical specimens.

A χ^2 test with exact significance or Fischer's exact test was used for categorical variables. ANOVA was used for continuous, normally distributed variables and displayed as a mean with standard deviation. The Mann-Whitney *U* test was used for continuous, nonnormally distributed variables and displayed as a median and interquartile range. Forward stepwise logistic regression was used to determine independent predictive factors for a positive SL. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 21.

RESULTS

Between 2008 and 2015, 161 patients with localized GEJ or gastric adenocarcinoma were identified. Of those, 18 patients with unclassified racial and ethnic backgrounds were excluded. Clinicopathologic characteristics of the patients are listed in Table 1. There were clear racial and ethnic variations between patients with clinically resectable gastric cancer. Hispanic patients were diagnosed at a younger age (mean age 55.5 ± 11.9 years) compared with Asian (59.8 ± 13.9 years), African American (61.0 ± 10.0 years), and white patients (61.7 ± 12.5 years; $p = 0.046$). In addition, Hispanic and African American patients presented more often with locally advanced disease (Hispanic 87%; African American 79%; white 68%; Asian 55%; $p = 0.03$). Specifically, Hispanic patients were more likely to have higher *T* stage (*T3* or *T4*) disease compared with the other groups (Hispanic 86%; African American 79%; white 61%; Asian 55%; $p = 0.01$). Gastroesophageal junction tumors were more often observed in white patients (48%) compared with Hispanic (21%), African American (18%), and Asian patients (0%; $p = 0.004$). White patients underwent more

esophagogastrectomies and total gastros-tomies compared with the other races and ethnicities ($p = 0.03$), coincident with the higher incidence of GEJ tumors.

SL was performed in 124 patients (87%; Table 2). Hispanic patients comprised the largest proportion of the cohort (43%) compared with white (27%), African American (23%), and Asian patients (7%). The majority of patients had locally advanced disease on clinical staging with 93 patients (75%) having T3 or T4 tumors, 78 patients (63%) having radiographic nodal involvement, and 99 (79.8%) having either T3/T4 disease or positive nodal disease. Consequently, 53% of patients received neoadjuvant therapy before planned operative intervention. Of the 19 patients who did not undergo an SL, 6 patients (32%) had early-stage disease (clinical T1), and 13 (68%) had either a significant prior operation that prevented a laparoscopy or were symptomatic and required surgical intervention. The sequencing of laparoscopy and neoadjuvant chemotherapy was largely dependent on institutional referral patterns, with 40% of patients undergoing a laparoscopy after neoadjuvant therapy. There was no difference in the timing of the laparoscopy with regard to neoadjuvant therapy between the four groups ($p = 0.25$; Table 3). In addition, there was no difference in gender, age, race, ethnicity, or tumor location between patients who underwent SL before or after neoadjuvant therapy. Patients who underwent SL after treatment were more likely to have locally advanced disease. This finding is likely secondary to a selection bias due to patients with locally advanced disease being chosen to receive neoadjuvant therapy (Supplementary Table 1).

SL identified 42 patients (34%) with occult metastatic disease. Positive SL rates were 44% in Hispanic and Asian patients, 28% in African American patients, and 21% in whites ($p = 0.15$). Compared with whites, Hispanics were more likely to have a positive SL ($p = 0.04$). Subclinical gross peritoneal disease was the most common positive finding (64%), followed by positive peritoneal cytology (12%), omental disease (10%), and liver metastasis (7%). The distribution of metastatic disease was not significantly different among the groups ($p = 0.09$; Table 3). In addition, there was no statistical difference in the yield of SL before or after receiving therapy; this remained true when stratified by ethnicity (Supplementary Table 2). All patients with a positive laparoscopy were treated with systemic therapy and restaged with cross-sectional imaging. Unfortunately, all were found to have disease progression with radiographically apparent disease that precluded definitive therapy.

We attempted to identify clinical factors that predicted the discovery of metastatic disease on laparoscopy. Univariate analysis revealed that Hispanics were 2.84 times more likely to have a positive SL compared with whites ($p = 0.04$). In addition, clinical T3 or T4 (odds ratio [OR] 7.11; $p < 0.01$), positive nodal disease (OR 3.67; $p < 0.01$), signet ring cells (OR 6.43; $p < 0.01$), and poor differentiation (OR 6.61; $p < 0.01$) were associated with a positive laparoscopy. On multivariable analysis, T3 or T4 tumors (OR 6.03; 95% CI 1.49–24.40), signet ring cells (OR 5.36; 95% CI 2.11–13.64), and poor differentiation (OR 4.43; 95% CI 1.55–12.66) were independent predictors identifying occult metastatic disease on SL (Table 4).

DISCUSSION

Accurate pretreatment staging of gastric cancer is essential in guiding the use and sequence of radiation, systemic therapy, and surgical resection. While cross-sectional imaging is a critical component of staging evaluations, the sensitivity of CT scans in detecting intra-abdominal and peritoneal disease has been reported to be as low as 25%.¹² Thus, SL can be an important adjunct to cross-sectional imaging and is recommended by the NCCN for all patients with T1b or higher gastric cancer.²⁶ In our series, 34% of patients who underwent SL were found to have distant disease and avoided unnecessary laparotomy. Our series is consistent with previously published studies that reported positive findings ranging from 13% to 62.5% (Table 5).^{6–22}

There is variable utilization of laparoscopy between modern series, which is due to different inclusion criteria and application of institutional and geographic practice patterns. In Eastern-based series, screening has led to the detection of early stage cancer where neoadjuvant therapy less often is employed and laparoscopy is used selectively, as the yield is low. Indeed, most Western series show more advanced disease, where the utility of laparoscopy is more valuable. In our series, approximately 28% of the patients treated with neoadjuvant therapy were found to have occult disease on laparoscopy prior to definitive resection. While some of these patients may have had disease that progressed during treatment, others may have had occult disease at the time of diagnosis. In these cases, laparoscopy before the initiation of systemic therapy may be useful to more accurately stage patients, better guide treatment choices, and manage patient and provider expectations.

There has been limited research on minority gastric cancer patients, as most studies examining the utility of laparoscopy focus on white and Asian patients (Table 5). One study that did report ethnicity distribution had Hispanics accounting for only 4% of their patient population.²⁵ Because gastric cancer biology varies across race and ethnicity, we hypothesized that the yield of SL may be different between the groups.²⁷ This study observed that the yield of SL in gastric cancer is variable between racial and ethnic groups secondary to differences in disease presentation and tumor biology. The diagnostic yield of laparoscopy to detect occult diseases was significantly higher in Hispanic (44%) compared with white patients (21%, $p = 0.04$). This is likely explained by Hispanic patients in our cohort presenting with more advanced disease, which is consistent with population-based and single-institution reports.^{1,28} On multivariate analysis, only clinical T3 or T4, signet ring cell, and poor differentiation were independent predictors of positive laparoscopy, confirming that disease biology is the primary driver of occult metastatic disease and that Hispanic ethnicity is a surrogate marker of worse disease biology.

Additionally, our results suggest there are intrinsic disparities among racial and ethnic groups with gastric cancer. Most notably, Hispanic patients presented at a significantly younger age and were more likely to have advanced disease with occult metastases compared with white patients. In addition, Hispanic patients presented with more distal disease than their white counterparts. Although these findings have been reported in population-based and single-institution studies, the basis of this disparity is not well understood and is likely multifactorial, involving environmental, socioeconomic, and

biologic factors.^{1,28} Hispanic patients are less likely to have health insurance, which may result in poor access to care, delays in diagnosis, and advanced presentation.²⁹ Studies in other cancers have shown that uninsured patients have decreased treatment utilization, a higher incidence of advanced disease, and worse survival.³⁰ In addition to socioeconomic factors, differences in tumor biology also contribute to observed racial and ethnic disparities. Hispanic patients present with diffuse-type and signet ring tumors more often than white patients.^{1,28} Diffuse gastric cancer is genetically different than intestinal-type cancer and is known to have abnormal cell–cell adhesion, which may explain the propensity for peritoneal spread.³¹ In fact, signet ring cell has been shown to be a strong predictor of peritoneal metastasis, a finding that was replicated in our study.²⁸

The demographics of patients with gastric cancer in the United States are shifting. Although the overall incidence is decreasing in the United States, the incidence of gastric cancer among young Hispanic men has been steadily increasing. Surprisingly, young Hispanic men also present more frequently with stage IV disease.³² Gastric cancer is comprised of distinct disease subtypes based on tumor location and ethnicity. Gastroesophageal junction and proximal cancers are almost exclusively a disease of non-Hispanic white men, whereas distal gastric cancer is more commonly found in minorities.²⁷ With the rapidly growing Hispanic population in the United States, understanding the basis of the disparity will be increasingly important. Additional studies are necessary to help identify the biologic basis of the disparity and to develop personalized therapies that are applicable to all patients.

This retrospective study had certain limitations. First, there was selection bias associated with a single-institution study, our unique hospital demographic, and the decision to use laparoscopy. Second, the majority of patients who presented with locally advanced disease were staged using axial imaging, which is of modest utility for determining the clinical stage of the disease in gastric cancer and may result in misclassification of the disease stage.^{33–35} However, we chose to use clinical stage in our analysis over pathologic stage, because we wanted to determine the clinical utility of SL in the pretreatment setting. Finally, a significant proportion of patients (40%) had laparoscopy after systemic therapy, which can downstage the patient's disease and lead to an underestimation of the utility of laparoscopy. Despite these limitations, our study confirmed the importance of laparoscopy in gastric cancer staging in patients at high risk for peritoneal metastasis, such as Hispanics.

CONCLUSIONS

Laparoscopy is essential to accurately stage patients with gastric cancer. Patients with locally advanced disease, poor differentiation, or signet ring cells are especially at high risk for occult peritoneal disease and would benefit the most from SL. Whereas ethnicity was not an independent predictor of detecting occult peritoneal disease, Hispanic patients present at a younger age with more advanced disease. It is unclear why Hispanic patients present in this fashion, but the utility of laparoscopy in this cohort was clear. Given the low risk of laparoscopy and its ability to directly affect patient management, laparoscopy should be routinely used early in the treatment algorithm of gastric cancer across all races and ethnicities to establish whether to use intent-to-cure therapy or palliative treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Patient characteristics stratified by race/ethnicity

	No. of patients (%)				<i>p</i> value
	White	Hispanic	Asian	African American	
<i>N</i>	41 (29)	57 (40)	11 (8)	34 (24)	
Male gender	27 (66)	37 (65)	7 (64)	29 (85)	0.16
Mean age ^a (SD)	61.7 (12.5)	55.5 (11.9)	59.8 (13.9)	61.0 (10.0)	0.046
Locally advanced	28 (68)	50 (87)	6 (55)	27 (79)	0.03
T3/T4	25 (61)	49 (86)	6 (55)	27 (79)	0.01
Node positive disease	23 (56)	39 (68)	6 (55)	20 (59)	0.57
Neoadjuvant chemotherapy	19 (46)	30 (53)	3 (27)	19 (56)	0.38
Surgery type					0.03
Esophagogastrectomy	8 (20)	2 (4)	0	0	
Total gastrectomy	13 (32)	11 (19)	2 (18)	6 (18)	
Distal gastrectomy	10 (24)	17 (30)	5 (46)	18 (53)	
Others	3 (7)	1 (2)	1 (9)	2 (6)	
No operations/palliative resection	7 (17)	22 (39)	3 (27)	8 (24)	
Tumor location					0.004
GE junction	19 (48)	12 (21)	0	6 (18)	
Body/antrum	21 (52.5)	40 (70.2)	11 (100)	28 (82.4)	
Diffuse	0	5 (8.8)	0	0	
Histology					
Signet ring cell	12 (29)	22 (39)	5 (46)	6 (18)	0.14
Poorly differentiated	22 (54)	40 (70)	6 (55)	18 (53)	0.26

^aExpressed as years, not number of patients

TABLE 2

Comparison of patients who did or did not undergo staging laparoscopy

	No. of patients (%)		<i>p</i> value
	No SL	SL	
<i>N</i>	19 (13)	124 (87)	
Median age ^a (IQR)	63 (49–71)	58.5 (51–67)	0.61
Male gender	15 (79)	85 (69)	0.43
Race/ethnicity			0.25
White	8 (42)	33 (27)	
Hispanic	4 (21)	53 (43)	
Asian	2 (11)	9 (7)	
African American	5 (26)	29 (23)	
Clinical <i>T</i> stage			0.03
<i>T</i> 1	6 (32)	9 (7)	
<i>T</i> 2	2 (11)	22 (18)	
<i>T</i> 3	7 (37)	64 (52)	
<i>T</i> 4	4 (21)	29 (23)	
Clinical <i>N</i> stage			0.45
Node negative disease	9 (47)	46 (37)	
Node positive disease	10 (53)	78 (63)	
Locally advanced disease	12 (63.2)	99 (79.8)	0.14
Neoadjuvant chemotherapy	5 (26)	66 (53)	0.047
Timing of SL			
Before neoadjuvant		74 (60)	
After neoadjuvant		50 (40)	

SL staging laparoscopy, *IQR* interquartile range

^aExpressed as years, not number of patients. The age data for the “No SL” group was not normally distributed, and the Mann–Whitney U test was used to compare both groups

TABLE 3

Yield of staging laparoscopy stratified by race/ethnicity

	No. of patients (%)				<i>p</i> value
	White	Hispanic	Asian	African American	
SL (N)	33	53	9	29	
Timing					0.25
After neoadjuvant	17 (51.5)	18 (34)	2 (22.2)	13 (44.8)	
Before neoadjuvant	16 (48.5)	35 (66)	7 (77.8)	16 (55.2)	
Positive SL	7 (21)	23 (44) ^a	4 (44)	8 (28)	0.15
After neoadjuvant	5 (29.4)	6 (33.3)	1 (50)	2 (15.4)	0.10
Before neoadjuvant	2 (12.5)	17 (48.6)	3 (42.9)	6 (37.5)	0.63
Positive SL findings					0.09
Peritoneal disease	6 (86)	16 (70)	1 (25)	4 (50)	
Positive cytology	0	3 (13)	2 (50)	0	
Liver	1 (14)	0	1 (25)	1 (12)	
Omental disease	0	3 (13)	0	1 (12)	
Other	0	1 (4)	0	2 (24)	

SL staging laparoscopy^aCompared with whites, Hispanics had a significantly higher SL yield ($p = 0.04$)

TABLE 4

Factors associated with occult metastases found on staging laparoscopy

	Univariate analysis, OR	Wald <i>p</i> value	Multivariate analysis, OR (CI)
Age (year)	0.98	0.14	
Gender			
Female	Reference		
Male	1.22	0.62	
Ethnicity		0.15	
White	Reference		
Hispanic	2.84	0.04	
Asian	2.97	0.17	
African American	1.41	0.56	
Clinical <i>T</i> stage			
<i>T</i> 1 or <i>T</i> 2	Reference		
<i>T</i> 3 or <i>T</i> 4	7.11	<0.01	6.03 (1.49–24.40)
Clinical <i>N</i> stage			
<i>N</i> 0	Reference		
<i>N</i> +	3.67	<0.01	
Location		0.24	
GE/cardia	Reference		
Body/antrum	0.49	0.93	
Diffuse	0.80	0.82	
Signet ring cells	6.43	<0.01	5.36 (2.11–13.64)
Poor differentiation	6.61	<0.01	4.43 (1.55–12.66)

TABLE 5

Summary of previous staging laparoscopy series for patients without metastasis

Series	Country	Year	N	Indications	% SL use	% yield
Asia						
Kriplani ¹⁰	India	1991	40	Included all patients except ones with unresectable lesions or presenting with obstructive symptoms		40
Yano ¹⁵	Japan	2000	32	T3 or T4 expected to undergo curative resection		40.6
Song ⁷	Korea	2007	24	T3 or T4		62.5
				No M1 disease		
				No bleeding or obstruction		
Nakagawa ¹⁶	Japan	2007	100	T3 or T4		51.6
				Macroscopic type 4, or type 2 and type 3 with positive metastasis in regional lymph node		
Shimizu ⁶	Japan	2010	34	Curatively resectable type 4 tumors, large type 3 tumors, or extensive lymph node metastasis		29.4
Ishigami ¹⁹	Japan	2014	178	Deeper than T2		
Miki ³⁶	Japan	2015	88	Type 4 and large type 3 gastric cancer		36.3
Yamagata ¹⁸	Japan	2013	124	Type 4 or large type 3		45.9
				Extensive lymph node metastasis		
Hu ²⁰	China	2016	582	Clinical T2, T3, or T4	56.6	36.3
Europe						
D'uglio ¹⁴	Italy	1997	100	All clinical M0 patients		21
Asencio ¹³	Spain	1997	71	Patients with presumed resectable lesions		40.8
Muntean ³⁷	Romania	2009	98	Gastric cancer with no M1 disease,		37.8
				No obstruction or bleeding or perforation		
Burbidge ¹²	UK	2013	52	Potentially resectable disease	56	21.1
				Excluded T2 on EUS, M1 disease		
Mirza ²¹	UK	2015	387	GEJ and gastric cancer		17
				Potential future neoadjuvant and surgical therapy		
				Excluded M1 disease		
North America						
Burke ⁹	USA	1997	110	Candidate for possible curative resection	15	37
Sarela ⁸	USA	2006	657	Advanced gastric cancer,	41	31
				No bleeding or obstruction		

Series	Country	Year	N	Indications	% SL use	% yield
No M1 disease						
No contraindication for gastrectomy						
Karanicolas ²⁵	USA	2011	506	Patients	65 with primary gastric cancer	29.8
South America						
Santa-Maria ¹¹	Brazil	2014	32	Primary gastric adenocarcinoma, without M1 disease		22.6
Tourani ²²	Australia	2013	148	Excluded patients with M1 on CT and early T1 disease on EUS	74.3	25.6

Type 2 gastric cancer: ulcerating lesion with elevated border, type 3: ulcerating lesion with invasion of the gastric wall, type 4: diffuse infiltration *EUS* endoscopic ultrasound, *GJE*/gastroesophageal junction