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Optimal Extent of Lymphadenectomy for Gastric Adenocarcinoma: A 7-Institution Study of the U.S. Gastric Cancer Collaborative

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Abstract

Background and Objectives—The optimal extent of lymphadenectomy in the treatment of gastric adenocarcinoma is debated. We compared gastrectomy outcomes following limited (D1) or extended (D2) lymphadenectomy.

Methods—Using the multi-institutional US Gastric Cancer Collaborative database, we reviewed the morbidity, mortality, recurrence, and overall survival (OS) of patients receiving D1 or D2 lymphadenectomies.

Results—Between 2000 and 2012, 266 and 461 patients received a D1 and D2 lymphadenectomy, respectively. ASA class, mean number of comorbidities, grade, and stage were similar between groups. While major morbidity was similar ($P=0.85$), mortality was worse for those receiving a D1 lymphadenectomy (4.9% vs. 1.3%, $P=0.004$). D2 lymphadenectomy was associated with improved median OS in stage I (4.7 years for D1 vs. not reached for D2, $P=0.003$), stage II (3.6 years for D1 vs. 6.3 for D2, $P=0.42$), and stage III patients (1.3 years for D1 vs. 2.1 for D2, $P=0.01$). After adjusting for predictors of OS, D2 lymphadenectomy remained a significant predictor of improved survival (HR 1.5, 95%CI 1.1–2.0, $P=0.008$).

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Conclusions—D2 lymphadenectomy can be performed without increased risk of morbidity and mortality. Additionally, D2 lymphadenectomy is associated with improved survival especially in early stages, and should be considered for gastric adenocarcinoma patients. *J. Surg. Oncol.*

Keywords

gastric adenocarcinoma; D2 lymphadenectomy; gastrectomy

INTRODUCTION

Gastric cancer is among the five most common and most lethal cancers in both men and women worldwide [1]. However there is substantial variation in incidence across different regions with higher prevalence in Eastern countries compared to Western countries [1,2]. Although the incidence of gastric cancer in the United States is relatively low, it will be responsible for an estimated 24,590 new cancer diagnoses and approximately 10,720 deaths this year [3].

Surgery offers the only potential cure for gastric cancer, but the ideal surgical approach continues to be the subject of intense debate. Specifically, the extent of lymphadenectomy necessary to optimize survival outcomes without prohibitively increasing morbidity is controversial. An extended, or D2, lymphadenectomy is preferred over a more limited, or D1 lymphadenectomy in high volume countries like Japan and South Korea [4]. However, surgeons in Western countries have traditionally favored more conservative nodal dissections. The variation in practice patterns between high and low volume countries is partly attributed to prospective studies from the Netherlands and the United Kingdom which initially showed no difference in survival between extended and limited lymphadenectomies and worse mortality with the more extensive dissection [5,6].

With this study, we sought to characterize the current surgical approach to gastric adenocarcinoma in the United States. We also aimed to compare outcomes following gastrectomy with a D1 or D2 lymphadenectomy.

MATERIALS AND METHODS

In order to characterize patients with gastric adenocarcinoma and compare outcomes based on the extent of lymphadenectomy, we used the multi-institutional Gastric Cancer Collaborative database to design a retrospective comparative cohort study. The United States Gastric Cancer Collaborative includes patients that received surgical treatment for gastric adenocarcinoma from 2000 to 2012 at seven tertiary referral centers: Emory University, Johns Hopkins Hospital, The Ohio State University, Stanford University, Wake Forest University, Washington University in St. Louis, and the University of Wisconsin. Participating surgeons were all fellowship trained in surgical oncology in the United States. Patients with gastric cancer were identified retrospectively and their data were collected to form the database. Data obtained from the medical record included demographic, pathologic, and treatment information. The current study initially included all patients receiving a D1 or D2 lymphadenectomy. Exclusion criteria included stage IV disease, age 85 or greater, previous gastrectomy, and palliative operations. Patient demographics, disease

characteristics, and treatment modalities were reviewed. Specific outcomes analyzed included complications, morbidity, mortality, recurrence, and overall survival (OS). Institutional review board approval was obtained from each institution.

D1 and D2 lymphadenectomies were defined similarly to two randomized European trials except that distal pancreatectomy and splenectomy were not routinely performed in patients receiving a D2 lymphadenectomy for a proximal gastric cancer [5,6]. Based on tumor location a total, subtotal or distal gastrectomy was performed. D1 dissection included perigastric lymph nodes as well as the greater and lesser omenta, and a D2 dissection included all nodes from a D1 dissection plus those along the celiac axis, common hepatic artery, splenic artery and hilum, and the root of the left gastric artery according to the Dutch trial [7]. The operating surgeon determined the extent of lymphadenectomy appropriate for each given situation and then classified the dissection as D1 or D2. Tumors were staged according to AJCC7 [8]. To simplify grading classification from the database, anything with a well-differentiated component was considered low-grade and anything with a poorly differentiated component was considered high-grade. Specimens with moderate differentiation were reclassified as intermediate grade. Completeness of resection was classified according to the R status of resection with R0 inclusive of any specimens with microscopically negative margins. R1 denoted microscopically positive margins and R2 grossly positive margins. Resections were labeled according to most involved margin status whether proximal or distal.

Descriptive statistics included frequencies with percent for nominal variables and mean with standard deviation for continuous variables. We assessed differences in demographic and surgical variables by type of nodal dissection using chi-squared tests for nominal variables and ANOVA for continuous variables. Perioperative mortality was analyzed with univariate logistic regression. Recurrence was only considered to follow an R0 resection, and differences in the extent of recurrence based on nodal dissection were evaluated with Fisher's exact test. Survival was calculated from the date of surgery to the date of death or of last known follow-up. OS was estimated using the method of Kaplan–Meir, and differences in OS by type of nodal dissection were examined using the Log Rank Test. To determine factors associated with OS, we used univariate and multivariate Cox proportional hazard regression models. Covariates with P-values less than 0.1 were selected for the multivariate model. Statistical significance was defined as $P < 0.05$ and all analyses were performed in SAS version 9.4 (Cary, NC).

RESULTS

Between 2000 and 2012, 965 patients with gastric adenocarcinoma were treated with a gastrectomy at one of the seven institutions. The study cohort included 727 patients that received either a D1 or D2 nodal dissection. D2 lymphadenectomy (n = 461, or 63.4%) was performed more commonly than a D1 lymphadenectomy (n = 266, or 36.6%) (Fig. 1). Median follow-up was 1.3 years. In general, patients receiving D1 and D2 lymphadenectomies were similar although patients receiving a D1 lymphadenectomy were slightly older than patients receiving a D2 lymphadenectomy (65.3 vs. 63.2 years, $P = 0.02$) (Table I). Importantly, gender, American Society of Anesthesiology (ASA) class, mean

number of comorbidities, grade, stage, and signet ring cell subtypes were similar between groups. Both neoadjuvant chemotherapy (10.9% for D1 vs. 27.6% for D2, $P < 0.001$) and adjuvant chemotherapy (44.9% for D1 vs. 62.2% for D2, $P < 0.001$) were more common in the D2 cohort.

Although operative time and estimated blood loss were similar between groups, the mean number of lymph nodes recovered was significantly higher following a D2 lymphadenectomy (21.5 for D2 vs. 17.1 for D1, $P < 0.001$). In spite of this difference, the frequency of lymph node metastases and the number of positive nodes did not differ between groups (Table I). Splenectomy rates were similar in patients receiving a D1 lymphadenectomy compared with a D2 lymphadenectomy (7.1% vs. 9.8%, respectively, $P = 0.23$) although pancreatectomy was more common with a D2 lymphadenectomy (2.3% with D1 vs. 6.1% with D2, $P = 0.02$). The majority of D2 lymphadenectomies (88.3%), however, spared both the spleen and pancreas.

Complications and Morbidity

Although 30-day Clavien III/IV major morbidity was similar for patients receiving D1 and D2 lymphadenectomies (15.0% vs. 14.5%, respectively, $P = 0.85$), the specific complication pattern did vary. Patients receiving a D1 lymphadenectomy were more likely to suffer from infectious complications, myocardial infarction, and pneumonia, and more likely to require reintubation or dialysis in the post-operative period. Although rates of anastomotic leaks did not differ between groups, patients receiving a D1 lymphadenectomy returned to the operating room more often than patients receiving a D2 lymphadenectomy. Gastrointestinal bleed was more common in the D2 group (Table II).

Perioperative Mortality

Mortality was worse for those receiving a D1 lymphadenectomy ($n = 13$ or 4.9%) compared with those receiving a D2 lymphadenectomy ($n = 6$ or 1.3%), (odds ratio [OR] 3.9, 95% confidence interval [CI] 1.5–10.4, $P = 0.004$). A multivariate analysis was not performed due to the small number ($n = 19$) of deaths in the study cohort, however, other predictors of mortality on univariate analysis included age (OR 1.0, 95% CI 1.0–1.1, $P = 0.04$), cardiac disease (OR 2.7, 95% CI 1.0–7.2, $P = 0.05$), pulmonary disease (OR 5.3, 95% CI 2.0–14.3, $P = 0.001$), and smoking history (OR 2.8, 95% CI 1.0–7.6, $P = 0.05$).

Recurrence

Recurrence rates for patients receiving D1 and D2 lymphadenectomies were 25.8% and 27.0%, respectively ($P = 0.74$). Locoregional recurrence was similar between groups (7.3% for D1 vs. 8.8% for D2, $P = 0.51$) as was distant recurrence (21.0% for D1 vs. 18.4% for D2, $P = 0.42$).

Survival

Even though recurrence rates were similar, survival was better following a D2 lymphadenectomy. For patients undergoing D1 lymphadenectomy, 3- and 5-year survival rates were 48% and 34%, versus 57% and 48% following a D2 lymphadenectomy, respectively. When subdivided by stage, D2 lymphadenectomy was associated with

improved median OS in stage I (4.7 years for D1 vs. not reached for D2, $P=0.003$), stage II (3.6 years for D1 vs. 6.3 for D2, $P=0.42$), and stage III patients (1.3 years for D1 vs. 2.1 for D2, $P=0.01$) (Fig. 2). After adjusting for significant predictors of OS, which included ASA, stage, grade, margin status, neoadjuvant chemotherapy, and adjuvant radiation, D2 lymphadenectomy remained a significant predictor of improved survival when compared with D1 lymphadenectomy (HR 1.5, 95%CI 1.1–2.0, $P=0.008$) (Table III).

DISCUSSION

D2 lymphadenectomy is being performed nearly twice as often as D1 lymphadenectomies in major academic centers across United States. Although pancreatectomy was more common in the D2 group, splenectomy was not, and the vast majority of D2 lymphadenectomies preserved both the spleen and pancreas. These data suggest that a modified D2 lymphadenectomy is being performed in contrast to those described in the Dutch and British randomized controlled trials where D2 lymphadenectomies for proximal gastric cancers always included a distal pancreatectomy and splenectomy [5,9].

In the current study, D2 lymphadenectomy was not associated with increased 30-day morbidity and mortality indicating that it is being performed safely. These findings differ from the results of both the Dutch and British trials [5,6]. The most likely explanation for this difference regards the modified nature of the nodal dissections being performed in the United States. In both the Dutch and British studies, much of the morbidity and mortality were attributed to the distal pancreatectomies and splenectomies [5,6]. The variation in complication patterns and the fact that the perioperative mortality rate in patients receiving D1 dissections was actually higher in the current study probably reflects a difference in the groups getting a D1 or D2 nodal dissection. The D1 group was slightly but significantly older and contained more patients with pulmonary disease. Thus it makes sense that D1 patients were more likely to have pneumonia or the need for reintubation complicating their post-operative course. Additionally, both age and pulmonary disease were associated with higher perioperative mortality. Besides these known confounders, there may have been others that weighed into the surgeon's decision about whether to perform a limited or extended nodal dissection. Given these differences, however, it is important to note that D2 lymphadenectomy did not increase morbidity or mortality in patients undergoing gastrectomy for cancer.

The survival following gastrectomy for those getting D2 lymphadenectomies was longer, even after adjusting for other significant predictors of survival. In East Asia, D2 gastrectomy has long been the standard operation for patients with advanced gastric cancer with 5-year survival rates ranging between 61% and 71% [10]. In spite of initially finding no survival difference based on nodal dissection, a 15-year follow-up study of the Dutch trial found that patients receiving a D1 lymphadenectomy were significantly more likely to die from gastric cancer than those receiving a D2 lymphadenectomy (48% for D1 vs. 37% for D2, $P=0.01$) [7]. In contrast, long-term follow-up of the British trial found no difference in survival between D1 and D2 groups although they suggest the increased mortality associated with pancreatectomy and splenectomy may have precluded them from identifying a survival benefit from an extended nodal dissection [9]. The Italian Gastric Cancer Study Group

published their experience with pancreas-preserving D2 dissections for gastric cancer reporting 5-year OS of 55% with major morbidity and mortality comparable to that reported in other western studies [11,12].

It was observed that gastric cancer stages I and II demonstrated markedly improved survival outcomes after a D2 lymphadenectomy over their D1 counterparts. This observation challenges the argument that for early stages of disease a more limited D1 lymphadenectomy is equally effective as a D2 dissection. This survival benefit associated with a D2 dissection, is probably multifactorial. Patients receiving a D2 dissection may have benefited from a more complete resection. Another contributing factor to the observed improved survival might be stage migration. With a more complete lymphadenectomy, it can be expected that more occult nodal disease was identified upstaging patients from where they would have been classified following a D1 lymphadenectomy. Besides just shifting survival curves from this migration, the decrease in understaged gastric cancer patients in the D2 cohort may have facilitated the appropriate channeling to multimodality treatment further impacting the observed survival difference. Interestingly, patients receiving a D2 lymphadenectomy were more likely to be staged with endoscopic ultrasound preoperatively. This may have weighed into the surgeon's decision of whether to perform a D1 or D2 lymphadenectomy and potentially skewed the D2 group to having more extensive disease than the D1 group. However, the rate of nodal metastases and final pathologic staging did not differ between groups suggesting that endoscopic ultrasound probably did not introduce much bias based on extent of disease. This may be partially due to the poor correlation of endoscopic ultrasound and final pathology for T and N stage [13].

Even though patients receiving a D2 lymphadenectomy experienced longer survival than those receiving a D1 lymphadenectomy, recurrence rates were similar. This may be due to the difficulty in capturing accurate recurrence data given that many of these patients are referred for surgical therapy but receive chemotherapy and occasionally surveillance closer to home. A prior investigation reported similar recurrence rates regardless of the extent of lymphadenectomy specifically in node negative gastric cancer patients, and suggested that understaging may have played a role in this observation [14]. Understaging in this cohort could have occurred when a D1 lymphadenectomy or a D2 lymphadenectomy with an inadequate node harvest was performed.

While this study represents the largest multicenter review evaluating the optimal extent of lymphadenectomy for gastric cancer in the US, it has several limitations. Even though it is a large study, some subanalyses were not possible due to a lack of sufficient numbers. Specifically, we were unable to perform a multivariate analysis to identify independent predictors of mortality given that only 19 people in the entire cohort suffered mortality. Another limitation common to retrospective studies is that selection bias based on the desired operative approach, surgeon experience, patient comorbidities or other factors may have played a role in determining which lymphadenectomy to perform in each individual patient. For instance, more patients in the D2 group were treated with chemotherapy. While this might impact survival it could also indicate worse disease. Neoadjuvant chemotherapy was associated with worse survival, but this association likely reflects more advanced disease in those being referred for chemotherapy. Lastly, the presented outcomes may not be

generalizable to surgeons or institutions that do not regularly perform D2 nodal dissections, which is an important consideration given that most gastrectomies in the US are performed at low volume centers [15].

CONCLUSIONS

In conclusion, academic institutions in the United States are performing more D2 nodal dissections than D1 nodal dissections during gastrectomy for gastric adenocarcinoma. A D2 lymphadenectomy can be performed safely without increasing morbidity or perioperative mortality, and this technique is associated with improved survival for patients with gastric adenocarcinoma, especially when their disease is treated at an early stage.

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SYNOPSIS

This multi-institutional study explores outcomes following gastrectomy for gastric cancer based on the extent of lymphadenectomy using the US Gastric Cancer Collaborative. An extended (D2) lymphadenectomy is safe and associated with improved survival.

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Fig. 1.
Cohort inclusion and exclusion diagram.

Fig. 2.
Survival based on extent of lymphadenectomy for patients with Stages I–III gastric adenocarcinoma.

TABLE I
Patient Characteristics

Variable	D1 (n=266)	D2 (n=461)	P-value
Age, mean (SD)	65.3 (11.3)	63.2 (12.4)	0.02
Female gender, n (%)	199 (44.7)	204 (44.3)	0.90
Race, n (%) (n=721)			0.007
White	181 (68.8)	261 (57.0)	
Black	37 (14.1)	92 (20.1)	
Other	45 (17.1)	105 (22.9)	
ASA Class, mean (SD) (n =704)	2.6 (0.6)	2.7 (0.6)	0.35
Number of comorbidities, mean (SD)	1.9 (1.6)	1.7 (1.4)	0.14
Obese, n (%) (n= 656)	56 (24.7)	82 (19.1)	0.01
Hypertension, n (%) (n=718)	134 (51.9)	225 (48.9)	0.44
Diabetes, n (%) (n=718)	51 (19.8)	84 (18.2)	0.59
Cardiac disease, n (%) (n=719)	63 (24.4)	89 (19.3)	0.11
Peripheral vascular disease, n (%) (n =715)	14 (5.5)	24 (5.2)	0.86
Pulmonary disease, n (%) (n=718)	45 (17.5)	44 (9.5)	0.002
Alcohol abuse, n (%) (n=694)	28 (11.5)	53 (11.8)	0.91
Smoker, n (%) (n= 695)	102 (41.6)	178 (39.6)	0.59
Last preoperative albumin, mean (SD) (n = 636)	3.7 (0.6)	3.7 (0.6)	0.85
Preoperative endoscopic ultrasound performed, n (%) (n=725)	55 (20.8)	134 (29.1)	0.02
Grade, n (%) (n= 700)			0.18
Low	23 (9.0)	24 (5.4)	
Intermediate	59 (23.0)	100 (22.6)	
High	175 (68.1)	319 (72.0)	
Signet ring pathology, n (%) (n= 706)	101 (38.6)	197 (44.4)	0.16
Stage (AJCC 7), n (%) (n= 717)			0.12
I-A	54 (20.5)	81 (17.8)	
I-B	27 (10.3)	45 (9.9)	
II-A	36 (13.7)	64 (14.1)	
II-B	32 (12.2)	46 (10.1)	
III-A	51 (19.4)	63 (13.9)	
III-B	34 (12.9)	85 (18.7)	
III-C	29 (11.0)	70 (15.4)	
Operative approach, n (%)			0.12
Laparoscopic	16 (6.0)	43 (9.3)	
Open	250 (94.0)	418 (90.7)	
Length of operation (min), mean (SD) (n = 502)	239 (90.1)	245 (88.9)	0.49
Estimated blood loss (ml), mean (SD) (n = 640)	279 (249)	273 (227)	0.76
Total number of lymph nodes recovered, mean (SD) (n =725)	17.1 (11.0)	21.5 (11.3)	<0.0001
Presence of lymph node metastases, n (%) (n=725)	162 (61.1)	287 (62.4)	0.74
Number of positive nodes, mean (SD)	4.3 (6.6)	4.9 (7.2)	0.23

Variable	D1 (n=266)	D2 (n=461)	P-value
Ratio of positive nodes to total nodes recovered, mean (SD) (n =725)	0.26 (0.31)	0.23 (0.28)	0.14
Neoadjuvant chemotherapy, n (%)	29 (10.9)	127 (27.6)	<0.0001
Neoadjuvant radiation, n (%) (n=591)	6 (3.6)	15 (3.6)	0.99
Adjuvant chemotherapy, n (%) (n=684)	110 (44.9)	273 (62.2)	<0.0001
Adjuvant radiation, n (%) (n=671)	80 (33.2)	167 (38.8)	0.15

ASA, American society of anesthesiologists; AJCC, American joint committee on cancer.

TABLE II

Complications in Patients Undergoing D1 and D2 Lymphadenectomy

Complication	D1 (n=266)	D2 (n =461)	P-value
Infectious complication, n (%) (n=625)	68 (34.3)	111 (26.0)	0.03
Surgical site wound infection, n (%) (n=594)	23 (13.4)	39 (9.2)	0.14
Deep intra-abdominal infection, n (%) (n=598)	17 (9.8)	29 (6.8)	0.21
Myocardial infarction, n (%) (n =587)	7 (4.2)	4 (1.0)	0.009
Cerebrovascular accident, n (%) (n=584)	3 (1.8)	2 (0.5)	0.11
Reintubation, n (%) (n=602)	29 (16.4)	27 (6.4)	0.0001
Pneumonia, n (%) (n=594)	20 (11.7)	28 (6.6)	0.04
Pulmonary embolism, n (%) (n= 586)	3 (1.8)	4 (1.0)	0.38
Deep vein thrombosis, n (%) (n=585)	1 (0.6)	6 (1.4)	0.42
Renal failure requiring dialysis, n (%) (n = 585)	6 (3.7)	3 (0.7)	0.009
Reoperation, n (%) (n=597)	24 (13.9)	32 (7.6)	0.02
Anastomotic leak, n (%) (n =599)	14 (8.0)	21 (5.0)	0.15
Gastrointestinal bleed, n (%) (n = 584)	2 (1.2)	21 (5.0)	0.04
Readmission, n (%) (n=723)	61 (23.2)	95 (20.7)	0.42

TABLE III

Univariate and Multivariate Survival Analyses in Patients Undergoing Gastrectomy for Gastric Adenocarcinoma

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	<i>P</i>	Hazard Ratio (95% confidence interval)	<i>P</i>
Age	1.0 (1.0 – 1.0)	0.07	1.0 (1.0 – 1.0)	0.33
Gender (male vs. female)	1.0 (0.8 – 1.2)	0.71		
Race				
White	Ref		Ref	
Black	0.9 (0.6 – 1.2)	0.48	0.9 (0.6 – 1.4)	0.71
Other	0.44 (0.3 – 0.6)	<0.0001	0.5 (0.3 – 0.7)	0.001
ASA Class	1.3 (1.1 – 1.6)	0.01	1.0 (0.8 – 1.4)	0.87
Number of comorbidities	1.1 (1.0 – 1.2)	0.07	1.0 (0.9 – 1.2)	0.62
Obese	1.1 (0.8 – 1.5)	0.48		
Hypertension	1.1 (0.8 – 1.4)	0.60		
Diabetes	0.8 (0.6 – 1.2)	0.29		
Cardiac disease	1.5 (1.2 – 2.0)	0.002	1.0 (0.7 – 1.6)	0.89
Peripheral vascular disease	1.0 (0.6 – 1.7)	0.99		
Pulmonary disease	1.7 (1.2 – 2.3)	0.002	1.6 (1.0 – 2.5)	0.04
Alcohol abuse	1.2 (0.8 – 1.7)	0.36		
Smoker	1.2 (0.9 – 1.5)	0.15		
Last preoperative albumin	0.6 (0.5 – 0.8)	<0.0001	0.8 (0.6 – 1.0)	0.04
Grade				
Low	Ref		Ref	
Intermediate	2.3 (1.2 – 4.3)	0.01	1.1 (0.5 – 2.3)	0.77
High	2.3 (1.2 – 4.2)	0.008	1.1 (0.6 – 2.3)	0.74
Stage by AJCC7				
I	Ref		Ref	
II	1.6 (1.1 – 2.4)	0.02	2.7 (1.6 – 4.5)	<0.001
III	3.4 (2.4 – 4.7)	<0.0001	5.3 (3.3 – 8.4)	<0.001
Lymphadenectomy (D1 vs. D2)	1.4 (1.1 – 1.8)	0.005	1.5 (1.1 – 2.0)	0.008
Margin status (R0 vs. R1)	0.6 (0.4 – 0.8)	0.002	0.8 (0.5 – 1.3)	0.36
Neoadjuvant chemotherapy	1.6 (1.2 – 2.1)	0.002	1.5 (1.0 – 2.1)	0.05
Neoadjuvant radiation	1.8 (0.9 – 3.6)	0.11		
Adjuvant chemotherapy	0.9 (0.7 – 1.1)	0.34		
Adjuvant radiation	0.6 (0.5 – 0.8)	0.002	0.4 (0.3 – 0.6)	<0.001

ASA, American society of anesthesiologists; AJCC, American joint committee on cancer.