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Interaction of Postoperative Morbidity and Receipt of Adjuvant Therapy on Long-Term Survival After Resection for Gastric Adenocarcinoma: Results From the U.S. Gastric Cancer Collaborative

Linda X. Jin, MD[1], Dominic E. Sanford, MD, MPHS[1], Malcolm Hart Squires III, MD[2], Lindsey E. Moses, MD[1], Yan Yan, MD, PhD[1], George A. Poultsides, MD[3], Konstantinos I. Votanopoulos, MD[4], Sharon M. Weber, MD[5], Mark Bloomston, MD[6], Timothy M. Pawlik, MD[7], William G. Hawkins, MD[1], David C. Linehan, MD[1], Carl Schmidt, MD[6], David J. Worhunsky, MD[3], Alexandra W. Acher, MD[5], Kenneth Cardona, MD[2], Clifford S. Cho, MD[5], David A. Kooby, MD[2], Edward A. Levine, MD[4], Emily Winslow, MD[5], Neil Saunders, MD[6], Gaya Spolverato, MD[7], Graham A. Colditz, MD, PhD[1], Shishir K. Maithel, MD[2], and Ryan C. Fields, MD[1]

[1]Department of Surgery, Barnes Jewish Hospital and The Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO; [2]Division of Surgical Oncology, Department of Surgery, Winship Cancer Institute, Emory University, Atlanta, GA; [3]Department of Surgery, Stanford University Medical Center, Stanford, CA; [4]Department of Surgery, Wake Forest University, Winston-Salem, NC; [5]Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI; [6]Department of Surgery, The Ohio State University Comprehensive Cancer Center, Columbus, OH; [7]Division of Surgical Oncology, The Johns Hopkins University School of Medicine, Baltimore, MD

ABSTRACT

Background. Postoperative complications (POCs) can negatively impact survival after oncologic resection. POCs may also decrease the rate of adjuvant therapy completion. We evaluated the impact of complications on gastric cancer survival and analyzed the combined effect of complications and adjuvant therapy on survival.

Methods. We analyzed 824 patients from 7 institutions of the U.S. Gastric Cancer Collaborative who underwent curative resection for gastric adenocarcinoma between 2000 and 2012. POC were graded using the modified Clavien–Dindo system. Survival probabilities were estimated using the method of Kaplan and Meier and analyzed using multivariate Cox regression.

Results. Median follow-up was 35 months. The overall complication rate was 41 %. The 5-year overall survival (OS) and recurrence-free survival (RFS) of patients who experienced complications were 27 and 23 %, respectively, compared with 43 and 40 % in patients who did not have complications ($p < 0.0001$ for OS and RFS). On multivariate analysis, POC remained an independent predictor for decreased OS and RFS (HR 1.3, 95 % CI 1.1–1.6, $p = 0.03$ for OS; HR 1.3, 95 % CI 1.01–1.6, $p = 0.03$ for RFS). Patients who experienced POC were less likely to receive adjuvant therapy (OR 0.5, 95 % CI 0.3–0.7, $p < 0.001$). The interaction of complications and failure to receive adjuvant therapy significantly increased the hazard of death compared with patients who had neither complications nor adjuvant therapy (HR 2.3, 95 % CI 1.6–3.2, $p < 0.001$).

Conclusions. Postoperative complications adversely affect long-term outcomes after gastrectomy for gastric cancer. Not receiving adjuvant therapy in the face of POC portends an especially poor prognosis following gastrectomy for gastric cancer.

Gastric adenocarcinoma (GAC) is the second leading cause of cancer-related deaths worldwide, with more than 22,000 new cases and more than 10,000 deaths in the United States in 2014.[1,2] For patients who present with resectable disease, surgery remains the backbone of curative treatment.[3,4] However, relapse and disease-specific death are relatively common after gastrectomy alone,

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R. C. Fields, MD
e-mail: fieldsr@wudosis.wustl.edu

making adjunctive therapies an important component of treatment.[5,6] The negative impact of postoperative complications (POCs) on survival after cancer surgery has been investigated across many solid tumor types, including head and neck, colorectal, and esophageal malignancies.[7–11] In complex operations such as gastrectomy for gastric cancer, morbidity rates remain relatively high, ranging from 35 to 46 % in the Western literature.[12–14] Importantly, recent studies in other solid tumors have shown that POCs decrease the ability of patients to receive adjuvant therapy.[15,16] The effect of complications on the receipt of adjuvant therapy and the correlation with survival has not been explored in gastric cancer. The present analysis quantifies the association between POCs and long-term survival after gastrectomy for GAC from the U.S. Gastric Cancer Collaborative and explores the combined effect of complications and adjuvant therapy on survival.

METHODS

The U.S. Gastric Cancer Collaborative includes 7 academic institutions: Emory University, Johns Hopkins Hospital, Ohio State University, Stanford University, Wake Forest University, Washington University in St. Louis, and the University of Wisconsin. All patients who underwent resection of GAC via an abdominal approach between 2000 and 2012 were included ($n = 956$). Data on demographic, preoperative, intraoperative, pathologic factors, as well as postoperative therapy and outcomes, recurrence, and survival were collected retrospectively by trained research fellows. Pathology staging was assigned per American Joint Committee on Cancer (AJCC) 7th edition.[17] POCs were graded objectively using the modified Clavien–Dindo classification of surgical complications.[18] We reviewed all data from the same hospital admission for evidence of postoperative complications, as well as all readmission events related to a surgical complication within 30 days of discharge. Grade V complications resulting in death were not included. Institutional Review Board approval was obtained at each participating institution.

Exclusion criteria included noncurative resection, death within 30 days postoperatively, or incomplete follow-up data. The primary endpoints were overall survival (OS) and recurrence-free survival (RFS). Categorical variables were compared using the Fisher exact test or χ^2 test as appropriate, and continuous variables were compared using the 2-tailed t test. OS was measured from the time of resection to death or last follow-up. RFS was measured from time of resection to recurrence, death, or last follow-up. Survival probabilities were estimated using the method of Kaplan and Meier and compared using the log-rank test.[19] Prognostic factors for survival were evaluated using multivariate Cox proportional hazards regression.[20] We hypothesized that receipt of adjuvant therapy was related to POCs in a way that could significantly reduce survival. To test this hypothesis, we analyzed for interaction effects between POCs and adjuvant therapy by testing an interaction term between complications and adjuvant therapy was analyzed within the context of the multivariate Cox regression model. A p value <0.05 was considered significant. All statistical analyses were performed using STATA version 13.1 (StataCorp LP, College Station, TX).

RESULTS

Patients and Operations

We analyzed 824 patients who underwent curative surgery for GAC, did not experience 30-day mortality, and had complete follow-up data. Clinicopathologic and operative characteristics are presented in Table 1. The cohort was 44 % female, with a mean age of 65 years (standard deviation 13; range 23–94). A total of 502 patients (61 %) had at least 1 comorbid medical condition (including heart disease, hypertension, pulmonary disease, and peripheral vascular disease). Neoadjuvant chemotherapy was given to 172 patients (21 %). The majority of patients underwent either subtotal ($n = 329$, 40 %) or total gastrectomy ($n = 346$, 42 %), with the remainder undergoing distal gastrectomy ($n = 137$, 17 %), in which <50 % of the stomach was removed, or wedge resection ($n = 8$, 1 %). Most patients received a D2 lymphadenectomy ($n = 487$, 60 %), and 85 % of resections ($n = 701$) were done using an open approach.

Postoperative Morbidity

POCs occurred in 336 patients (41 %), and a total of 699 events were recorded (Table 2). The most frequent complications were postoperative anemia/bleeding, wound infection, and pneumonia. When stratified according to severity, 47 patients (13 %) had a grade I complication, 172 patients (49 %) had grade II, 74 patients (21 %) had grade III, and 56 patients (16 %) had grade IV.

Clinicopathologic and operative variables associated with POCs are shown in Table 1. Several preoperative (older age, higher ASA class, prior gastrectomy, preoperative GI bleeding), operative (more extensive resection type, concurrent hepatectomy, reconstruction type, jejunostomy tube use, peritoneal drain use, longer operative time, higher estimated blood loss, and need for perioperative transfusion), and tumor-related variables (presence of lymphovascular invasion, perineural invasion, and higher AJCC disease stage) differed significantly

TABLE 1 Clinicopathologic variables associated with complications in 824 patients after gastrectomy for gastric cancer

	All patients $n = 824$	No complication $n = 488$ (59 %)	Complication $n = 336$ (41 %)	*P* value
Preoperative characteristics				
Female (*n*, %)	365 (44)	222 (46)	143 (43)	0.41
Age (*x*, sd)	65 (13)	64 (13)	65 (13)	0.04
Race				0.33
White	589 (72)	306 (61)	229 (67)	
Black	142 (17)	89 (18)	56 (17)	
Asian	93 (11)	62 (12)	31 (9)	
Comorbid condition	502 (61)	282 (58)	220 (65)	0.03
BMI $\geq$ 25	375 (46)	224 (46)	151 (45)	0.79
ASA class				0.01
1	12 (2)	9 (2)	3 (1)	
2	262 (33)	176 (37)	86 (27)	
3	487 (61)	270 (57)	217 (67)	
4	33 (4)	17 (4)	16 (5)	
Prior gastrectomy	51 (6)	22 (5)	29 (9)	0.02
Preoperative upper GI bleed	283 (35)	153 (32)	130 (39)	0.03
Preoperative obstructive symptoms	293 (37)	163 (34)	131 (39)	0.10
Preoperative weight loss	347 (43)	200 (42)	147 (46)	0.37
Neoadjuvant chemotherapy	172 (21)	107 (22)	65 (19)	0.38
Operative characteristics				
Resection type				<0.001
Wedge	8 (1)	8 (2)	0 (0)	
Distal (<50 % of stomach resected)	137 (17)	94 (19)	43 (13)	
Subtotal	329 (40)	214 (44)	115 (34)	
Total	346 (42)	169 (35)	177 (53)	
Nodal dissection				0.58
D0	28 (4)	20 (4)	8 (3)	
D1	297 (36)	173 (36)	124 (37)	
D2	487 (60)	288 (59)	199 (59)	
D3	11 (1)	6 (1)	5 (2)	
Other organs resected	166 (20)	88 (18)	78 (23)	0.07
Liver resection	23 (3)	8 (2)	15 (5)	0.02
MIS technique				0.05
Open	701 (85)	404 (83)	297 (88)	
Laparoscopic	58 (7)	36 (7)	22 (7)	
Lap converted to open	56 (7)	40 (8)	16 (5)	
Reconstruction type				<0.001
Billroth I	16 (2)	12 (3)	4 (1)	
Billroth II	188 (23)	125 (26)	63 (19)	
Roux-en-y esophago-jejunostomy	333 (41)	162 (33)	171 (52)	
Roux-en-y gastro-jejunostomy	251 (31)	165 (34)	86 (26)	
J-tube placed	261 (32)	132 (27)	129 (39)	0.001
Peritoneal drain placed	440 (54)	241 (49)	199 (59)	0.006
Blood transfusion	181 (22)	56 (12)	125 (37)	<0.001
Operative time (min) (*x*, sd)	249 (96)	235 (87)	267 (104)	0.0001
EBL (mL) (*x*, sd)	296 (280)	269 (268)	335 (294)	0.002

TABLE 1 continued

	All patients $n = 824$	No complication $n = 488$ (59 %)	Complication $n = 336$ (41 %)	*P* value
Pathologic characteristics				
Tumor location				0.36
Fundus	63 (8)	34 (7)	29 (9)	
Cardia	82 (10)	46 (10)	36 (11)	
Body	296 (37)	177 (37)	119 (36)	
Antrum	301 (37)	187 (39)	114 (35)	
GE junction	64 (8)	32 (7)	32 (10)	
T stage				0.04
T1	186 (23)	119 (25)	67 (20)	
T2	104 (13)	70 (15)	34 (10)	
T3	265 (33)	157 (33)	108 (33)	
T4	248 (31)	128 (27)	120 (36)	
Positive nodes	494 (60)	281 (58)	213 (64)	0.13
Poor histologic grade	552 (69)	272 (58)	204 (62)	0.38
Signet cell histology	331 (41)	196 (41)	135 (41)	0.97
Lauren type histology				
Intestinal type	362 (66)	214 (66)	148 (65)	
Diffuse type	173 (32)	101 (31)	72 (32)	
Linitis plastica	54 (7)	29 (6)	25 (8)	0.43
LVI	330 (45)	176 (42)	154 (51)	0.01
PNI	202 (33)	107 (29)	95 (39)	0.02
R0 resection	749 (91)	444 (91)	305 (91)	0.92
AJCC stage				0.01
Stage I	229 (28)	146 (30)	83 (25)	
Stage II	200 (25)	130 (27)	70 (21)	
Stage III	343 (42)	184 (38)	159 (49)	
Stage IV	39 (5)	19 (4)	20 (6)	
Postoperative characteristics				
Length of stay (days) (x, sd)	12 (10)	8 (5)	16 (13)	<0.001
Readmission	196 (24)	96 (19)	100 (30)	0.001
Adjuvant therapy	429 (56)	282 (61)	147 (47)	<0.001

BMI body mass index, *ASA class* American Society of Anesthesiologists classification, *J-tube* jejunostomy tube, *EBL* estimated blood loss, *LVI* lymphovascular invasion, *PNI* perineural invasion, *AJCC* American Joint Committee on Cancer, *EBL* estimated blood loss

between patients who experienced complications and those who did not. Receipt of neoadjuvant chemotherapy rates did not differ significantly between the 2 groups (22 vs. 19 %, $p = 0.38$). On multivariate logistic regression, age $\geq$60 years (OR 1.5, 95 % CI 1.1–2.1, $p = 0.02$), ASA class $\geq$3 (OR 1.2, 95 % CI 1.01–2.0, $p = 0.04$), and perioperative transfusion (OR 4.0, 95 % CI 2.7–5.8, $p < 0.001$) remained independent predictors of POCs. Notably, rate of receipt of adjuvant chemotherapy was significantly lower among patients who experienced complications (47 % compared with 61 %, $p < 0.001$).

Follow-Up and Univariate Characterization of Prognostic Factors for OS and RFS

The median follow-up period after primary resection was 35 months. The median OS was 23 months in patients who had postoperative complications compared with 45 months in those who did not, while the 5-year OS was 27 % in patients who had postoperative complications compared with 43 % in those who did not ($p < 0.0001$, Fig. 1a). Among patients who experienced complications, there were no significant differences in survival by complication grade ($p = 0.38$).

TABLE 2 Details of all complications after gastrectomy for gastric cancer in 824 patients by system

Complications	Events	% of patients
Total events	699	
Infectious		
Leak/fistula	44	5 %
Intra-abdominal abscess	15	2 %
Wound infection	71	8 %
Infectious colitis	15	2 %
SIRS/bacteremia	20	2 %
Other	5	1 %
Hematologic		
Anemia/bleeding	105	12 %
Thromboembolic	16	2 %
Other	5	1 %
Pulmonary		
Pneumonia	55	6 %
Pleural effusion	16	2 %
Respiratory distress/hypoxia	24	3 %
Respiratory failure req. reintubation	54	6 %
Other	3	0 %
Cardiovascular		
MI	9	1 %
Dysrhythmia	33	4 %
Gastrointestinal		
Ileus/SBO	37	4 %
Required TPN	34	4 %
GI bleed	23	3 %
Delayed gastric emptying	11	1 %
Renal/genitourinary		
UTI	44	5 %
Urinary retention	13	2 %
Acute renal failure	11	1 %
Neurologic		
Delirium	7	1 %
Stroke	5	1 %
Other	24	3 %

SIRS systemic inflammatory response syndrome, *MI* myocardial infarction, *SBO* small bowel obstruction, *TPN* total parenteral nutrition, *UTI* urinary tract infection

During the study period, 264 patients (32 %) developed recurrence after gastrectomy (114 patients with complications and 148 without). Of these, 79 patients (40 %) recurred with peritoneal disease only, 36 patients (18 %) recurred in the liver only, 21 patients (11 %) recurred with simultaneous involvement of the liver and peritoneum, and 17 patients (9 %) recurred with metastases in the lung. The median and 5-year RFS was 15 months and 23 %, respectively, in patients who had postoperative complications compared with 34 months and 40 %, respectively, in those who did not ($p < 0.0001$, Fig. 1b). As with OS, RFS did not correlate with complication grade. Univariate analyses of variables associated with OS and RFS are presented in Table 3.

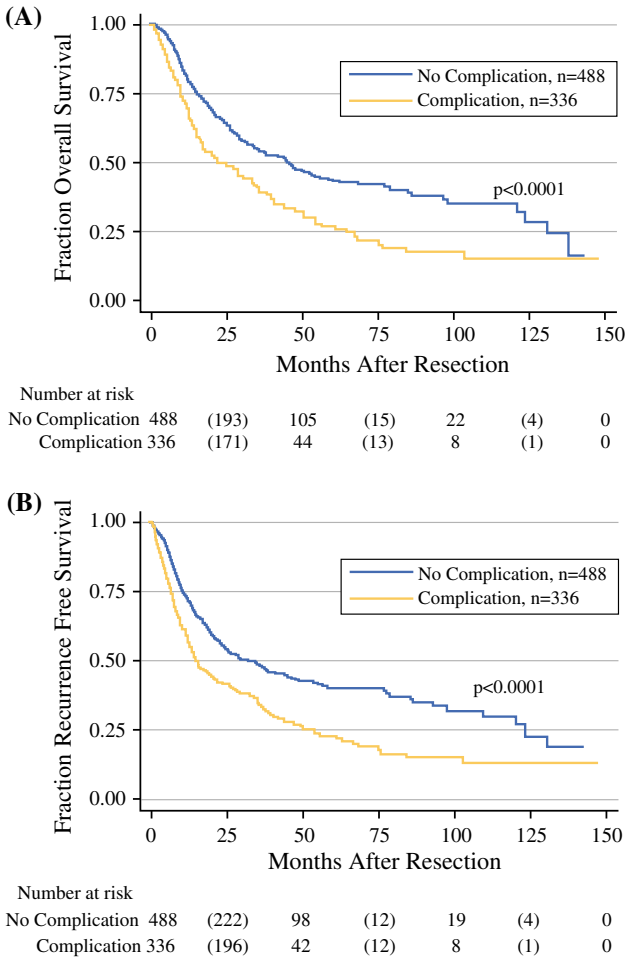

FIG. 1 **a** Kaplan–Meier estimates of OS for 824 patients who did and did not have postoperative complications. **b** Kaplan–Meier estimates of RFS for 824 patients who did and did not have postoperative complications. Note: Failure events are reported in parentheses in between at-risk time points shown

Relationship Between Complications and Adjuvant Therapy

On initial multivariate Cox regression of OS and RFS, postoperative complications, age, Asian race, AJCC stage, total gastrectomy, perioperative transfusion, and neoadjuvant chemotherapy emerged as independent predictors of both OS and RFS (Table 4). The presence of postoperative complications had an independently negative impact on both OS (HR 1.3, 95 % CI 1.1–1.6, $p = 0.03$) and RFS (HR 1.3, 95 % CI 1.01–1.6, $p = 0.03$).

TABLE 3 Univariate analysis of variables associated with OS and RFS in 824 patients after gastrectomy for gastric cancer

	n	Overall survival		Recurrence-free survival	
		Median survival (months)	*p* value	Median survival (months)	*p* value
Complication	336	23	<0.0001	15	<0.0001
No complication	488	45		34	
Preoperative variables					
Age ≥60	538	33	0.16	23	0.1
Age <60	288	38		29	
Race					
White	591	29	0.001	20	0.0003
Black	142	44		29	
Asian	93	70		36	
Male	461	36	0.58	26	0.540
Female	365	33		22	
Comorbid condition					
Yes	503	43	0.14	23	0.16
No	323	30		26	
BMI ≥25	376	44	0.08	27	0.1
BMI<25	450	33		22	
ASA class ≥3	552	29	0.005	22	0.007
ASA class <3	274	45		36	
Neoadjuvant therapy					
Yes	172	23	0.01	13	0.0001
No	653	37		29	
Tumor-related variables					
Tumor size ≥4 cm	440	24	<0.0001	15	<0.0001
Tumor size <4 cm	386	47		38	
Lymph node positive disease					
Yes	494	68	<0.0001	15	<0.0001
No	326	23		63	
Poor histologic grade					
Yes	552	29	0.08	20	0.03
No	242	39		35	
PNI					
Yes	202	15	<0.0001	11	<0.0001
No	624	45		35	
LVI					
Yes	330	19	<0.0001	13	<0.0001
No	396	67		49	
Signet ring histology					
Yes	331	27	0.01	21	0.01
No	472	40		29	
R0 resection					
Yes	750	15	<0.0001	13	<0.0001
No	76	38		27	
AJCC stage 3/4	396	17	<0.0001	14	<0.0001
AJCC stage 1/2	430	68		63	
Operative and postoperative variables					
Total gastrectomy					
Yes	346	21	<0.0001	15	<0.0001

TABLE 3 continued

	n	Overall survival		Recurrence-free survival	
		Median survival (months)	*p* value	Median survival (months)	*p* value
No	480	45		36	
Other organs resected					
Yes	166	15	<0.0001	12	<0.0001
No	659	44		29	
Roux-en-Y esophago-jejunostomy					
Yes	333	22	<0.0001	24	<0.0001
No	493	45		36	
Perioperative transfusion					
Yes	181	15	<0.0001	11	<0.0001
No	637	41		33	
OR time ≥250 min	240	28	0.09	240	0.08
OR time <250 min	328	43		328	

UV univariate, *MV* multivariate, *HR* hazard ratio, *BMI* body mass index, *ASA class* American Society of Anesthesiologists classification, *PNI* perineural invasion, *LVI* lymphovascular invasion, *R0* resection with negative margin, *AJCC* American Joint Committee on Cancer

TABLE 4 Multivariate Cox regression of factors associated with OS and RFS in 824 patients after gastrectomy for gastric cancer

Variable	Overall survival			Recurrence-free survival		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Complication	1.3	1.1–1.6	0.03	1.3	1.01–1.6	0.03
Age (continuous)	1.01	1.006–1.03	0.001	1.01	1.006–1.02	0.001
ASA class ≥3	1.1	0.9–1.4	0.39	1.1	0.9–1.4	0.33
Race						
White			Reference			Reference
Black	1.0	0.7–1.3	0.72	0.9	0.7–1.2	0.64
Asian	0.6	0.4–0.9	0.01	0.6	0.4–0.9	0.006
AJCC stage						
I			Reference			Reference
II	1.6	1.1–2.3	0.02	1.8	1.3–2.6	0.001
III	2.8	1.8–4.2	<0.001	3.4	2.3–5.2	<0.001
IV	6.7	4.1–11.1	<0.001	7.8	4.8–12.8	<0.001
Total gastrectomy	1.4	1.1–1.7	0.002	1.3	1.1–1.6	0.005
Poor histologic grade	0.9	0.7–1.2	0.63	1	0.8–1.3	0.89
Transfusion	1.7	1.3–2.1	<0.001	1.6	1.3–2.0	<0.001
Neoadjuvant therapy	1.5	1.1–1.9	0.01	1.8	1.4–2.6	<0.001
Signet ring histology	1.2	1.0–1.6	0.10	1.1	0.9–1.4	0.35
BMI ≥25	0.9	0.7–1.1	0.41	0.9	0.7–1.1	0.38
R0 resection	0.8	0.6–1.1	0.25	0.9	0.7–1.3	0.58
Tumor size ≥4 cm	1.2	1.0–1.5	0.09	1.1	0.9–1.4	0.24
Lymph node positive disease	1.1	0.8–1.6	0.43	1.1	0.8–1.4	0.75

ASA class American Society of Anesthesiologists classification, *AJCC* American Joint Committee on Cancer, *BMI* body mass index

We hypothesized a priori that experiencing postoperative complications might affect the receipt of adjuvant therapy in a way that significantly influences survival. Univariate analysis confirmed a statistically and clinically significant disparity in the rates of adjuvant therapy between patients with complications and those without (Table 2). Furthermore, on multivariate analysis of factors predictive of receipt of adjuvant therapy in this cohort, POCs remained a significant negative predictor (OR 0.5, 95 % CI 0.3–0.7, $p < 0.001$), when adjusting for age,

TABLE 5 Multivariate Cox regression of factors associated with OS and RFS taking into account the interaction between complications and adjuvant therapy in 824 patients after gastrectomy for gastric cancer

Variable	Overall survival			Recurrence-free survival		
	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Complication/adjuvant therapy						
No complication and no adjuvant therapy			Reference			Reference
No complication but adjuvant therapy	0.6	0.4–0.8	0.01	0.7	0.5–0.99	0.04
Complication but no adjuvant therapy	2.3	1.6–3.2	<0.001	1.7	1.2–2.3	0.001
Complication and adjuvant therapy	0.7	0.5–0.9	0.03	0.8	0.6–1.2	0.283
Age (continuous)	1.01	0.99–1.01	0.18	1.01	0.99–1.01	0.05
ASA class ≥3	1.1	0.9–1.4	0.29	1.1	0.9–1.4	0.39
Race			Reference			Reference
White						
Black	0.9	0.6–1.1	0.28	0.9	0.7–1.1	0.29
Asian	0.6	0.6–0.9	0.01	0.6	0.4–0.8	0.004
AJCC stage						
I			Reference			Reference
II	2.2	1.4–3.3	<0.001	2.2	1.5–3.2	<0.001
III	3.8	2.4–5.9	<0.001	4.1	2.6–6.4	<0.001
IV	9.4	5.5–15.7	<0.001	9.6	5.8–16.0	<0.001
Total gastrectomy	1.3	1.1–1.7	0.01	1.3	1.1–1.6	0.02
Poor histologic grade	0.9	0.7–1.2	0.61	1.0	0.7–1.4	0.81
Transfusion	1.6	1.2–2.0	0.001	1.5	1.2–2.0	0.001
Neoadjuvant therapy	1.5	1.1–2.0	0.01	1.9	1.5–2.5	<0.001
Signet ring histology	1.2	0.9–1.5	0.24	1.1	0.8–1.4	0.61
BMI ≥25	0.9	0.8–1.1	0.41	0.9	0.8–1.1	0.48
R0 resection	0.8	0.6–1.1	0.25	0.9	0.7–1.3	0.63
Tumor size ≥4 cm	1.2	1.0–1.5	0.11	1.2	0.9–1.5	0.16
Lymph node positive disease	1.3	0.9–1.8	0.16	1.1	0.8–1.6	0.41

ASA class American Society of Anesthesiologists classification, *AJCC* American Joint Committee on Cancer, *BMI* body mass index

AJCC disease stage, lymph node status, and perioperative transfusion. When stratifying receipt of adjuvant therapy by Clavien complication grade, there was a slight trend toward higher rates of adjuvant therapy use in patients with less severe complications, although this trend did not reach statistical significance ($p = 0.17$).

To quantify this effect, we explored the interaction between complications and adjuvant therapy, while controlling for the same confounding variables (Table 5). We found that the interaction was highly significant, as the presence or absence of adjuvant therapy acted as an effect modifier of complications on survival. The combination of experiencing a postoperative complication and not subsequently receiving adjuvant therapy significantly increased the hazard of death by 130 % and the hazard of recurrence by 70 % compared with patients who had neither postoperative complications nor adjuvant therapy (HR 2.3, 95 % CI 1.6–3.2 for OS; HR 1.7, 95 % CI 1.2–2.3 for RFS), even when controlling for disease stage. However, patients who received adjuvant therapy and experienced a complication did not have significantly decreased OS or RFS. Among patients who received adjuvant therapy (using no complications but adjuvant therapy as the reference cohort), the effect of complications becomes nonsignificant (HR 1.1, 95 % CI 0.8–1.5, $p = 0.41$ for OS; HR 1.2, 95 % CI 0.9–1.5, $p = 0.32$ for RFS). Additionally, when analyzing only patients with AJCC stage I disease, in which adjuvant therapy is expected to have less impact on survival, the interaction term between complications and lack of adjuvant therapy becomes nonsignificant (HR 1.3, 95 % CI 0.7–2.5, $p = 0.44$).

DISCUSSION

Across a large, modern North American cohort, postoperative morbidity had an independently negative impact on long-term oncologic outcomes after gastrectomy for gastric adenocarcinoma, similar to previous findings in

several other solid tumor types.[2,7,8,21] Importantly, we observed that complications and failure to receive adjuvant therapy interact significantly on their effect on long-term survival. Patients who experienced a postoperative complication were 50 % less likely to receive adjuvant therapy, and the combination of a postoperative complication and not receiving adjuvant therapy increased the risk of death more than 200 % compared with patients who had no complications and no adjuvant therapy.

Gastrectomy for GAC is a complex operation, and complication rates remain relatively high. Our overall complication rate of 41 % is consistent with other Western series, while Asian centers have reported rates of 10–24 %.[12–14,22–24] The inconsistency of defining and grading complications and differences between gastric cancer populations in Asia and the West make comparisons of morbidity rates difficult. In the present study, we found that risk factors including patient age, ASA class $\geq$3, and use of perioperative transfusion were independently associated with higher rates of postoperative morbidity. Similar risk factors have been previously described in surgery for gastric cancer.[13,25] Our data did not indicate that the use of preoperative chemotherapy led to increased incidence of perioperative complications, which supports previous results that neoadjuvant therapy is safe for locally advanced GAC.[26,27] Notably in our multivariate regression models of survival, receipt of neoadjuvant therapy was consistently associated with lower long-term survival, even when adjusting for pathologically poor factors such as tumor stage. A similar phenomenon has been previously reported in both retrospective gastric cancer data and metastatic colorectal cancer data. Therefore, we suspect that the worse outcomes observed in this subset of patients in our dataset represent an artifact of retrospective analysis, in which we are not fully able to adjust for the adverse pathologic features associated with being selected for preoperative chemotherapy despite adjusting for a robust number of clinicopathologic features. Despite this artifact, our data shows that with complex procedures such as gastrectomy for gastric cancer in which postoperative complications can significantly reduce the receipt of adjuvant therapy and long-term survival, the importance of neoadjuvant chemotherapy cannot be overlooked.

The evidence supporting the negative impact of postoperative morbidity on long-term prognosis after solid tumor resection is mounting. Because we did not include patients with perioperative mortalities, the difference in long-term survival between patients who had complications and those who did not reflects a long-term effect by which postoperative morbidity may decrease long-term survival. Ito et al. studied more than 1000 patients undergoing resection of colorectal liver metastases at Memorial Sloan Kettering Cancer Center and found that patients who experienced complications had a significantly decreased disease-specific survival and disease-free survival at 5 years.[21] Similar findings have also been reported in esophageal cancer, colorectal cancer, and head and neck cancers.[7–9,11] Kubota et al. recently reported that in nearly 1400 patients from Japan, complications after oncologic gastrectomy resulted in a significant hazard ratio of 1.9 for both overall survival and disease-specific survival.[28]

Despite numerous reports across cancer types linking postoperative morbidity to decreased survival, the causative mechanism remains to be elucidated. The hypothesis most often discussed is that a prolonged inflammatory state present in patients who experience complications leads to greater degree of host immunosuppression, which may allow residual micrometastatic tumor cells to proliferate, causing disease recurrence.[29–31] This hypothesis is strongly supported by the related immunosuppressive effect of perioperative blood transfusions, and the correlation of blood transfusion with earlier cancer recurrence, an effect that is also significant in our own dataset.[32,33] Indeed, Kubota et al. showed definitively that gastric cancer patients who experienced a postoperative complication had an increased and prolonged inflammatory state as measured by daily changes in white blood cell count, peak body temperature, and C-reactive protein.[28] Though these associations are both strong and suggestive, the causal mechanism between complications, inflammation, and disease progression deserves further elucidation.

This study is the first to investigate effect of decreased receipt of adjuvant therapy in patients with postoperative complications and outcomes of long-term survival. Two recent analyses using ACS-NSQIP data showed that in both pancreatic cancer and stage III colon cancer, the occurrence of postoperative complications was associated with decreased use of or delayed initiation of adjuvant therapy.[15,16] We found a similar effect in our dataset. Given this association, we explored the interaction of complications and failure to receive adjuvant therapy on long-term oncologic outcomes. We observed a significant interaction effect between complications and failure to receive adjuvant therapy that strongly decreased overall survival and recurrence-free survival. These results help quantify a logical clinical conclusion that patients who experience a complication may have worse long-term outcomes in part from a failure to receive adjuvant therapy.

Interestingly, Kubota and colleagues discussed their own exploration of adjuvant therapy as a potential mechanism connecting complications and survival. In their single-institution dataset of nearly 1400 patients undergoing resection for GAC, there were no significant differences in receipt of adjuvant therapy between patients who did and did not have complications.[28] Therefore, they conclude that adjuvant therapy is not likely to explain the

survival difference observed. A few key differences should be noted between these 2 studies. In Kubota et al., the overall complication rate was 15 %, which was significantly lower than our own rate of 41 %.[28] Nearly 50 % of the patients in their analysis underwent fully laparoscopic resections, compared with the 7 % in our cohort. Lastly, nearly two-thirds of the patients in their analysis had stage I disease, while the majority of patients in our analysis had stage II or III disease and would have been more likely to be eligible for adjuvant therapy.[28] Therefore, both the higher rate of postoperative complications and the greater proportion of patients eligible for adjuvant therapy in our dataset make the failure to receive such therapy more likely to have a significant impact on survival. The inconsistent results between these 2 well-powered studies help emphasize the fundamental differences between the Eastern and Western experiences with GAC treatment.

This study is limited as a retrospective analysis; therefore we are limited in assuming causality in the relationships we observe. However, our results are consistent with the clinical hypothesis specified a priori, and our findings are significant in that they are the first to quantify the interaction between complications and adjuvant therapy and their effect on long-term survival in gastric cancer.

In conclusion, this study demonstrates a strong negative impact of postoperative morbidity on long-term outcomes after gastrectomy for gastric cancer. A significant interaction was observed between complications and failure to receive adjuvant therapy, and this interaction had a strong negative impact on survival. Further efforts aimed at reducing complications may enhance long-term oncologic outcomes in patients with gastric cancer and should have a specific focus on minimizing morbidity to increase rates of adjuvant therapy completion in postoperative patients.

DISCLOSURE None.

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