The American Journal of Surgery 220 (2020) 376–380

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Predictive preoperative and intraoperative factors of anastomotic leak in gastrectomy patients

Paul Palmer, Michael Egger, Prejesh Philips, Kelly M. McMasters, Charles R. Scoggins, Robert C.G. Martin*

All Authors: University of Louisville, Division of Surgical Oncology, Hiram C Polk Jr Department of Surgery, Louisville, KY, USA

ARTICLE INFO

Article history:
Received 31 October 2019
Received in revised form
20 December 2019
Accepted 30 December 2019

Keywords:
Anastomotic leak
Gastrectomy
Complications
Gastric cancer

ABSTRACT

Background: The preoperative and intraoperative factors that could predict a higher risk of anastomotic/staple line leak for gastric cancer patients has not been accurately defined.
Methods: Patients who underwent surgery with curative intent for gastric malignancies between 2002 and 2018 were evaluated from a single prospective database.
Results: A total of 195 patients were evaluated with an overall complication rate of 40%. Anastomotic/staple line leak occurred in 13%, with 4% undergoing reoperation during the same hospitalization. Significant risk factors affecting postoperative complications (POC) were identified in the patients including number of comorbidities ($\geq$2) (HR, 5.30; 95% CI, 1.1−15.3; P = 0.037) and operation type (Total vs Distal) (HR, 2.5; CI 1.08−8.5; p = 0.048). Subset analysis of gastric adenocarcinoma patients demonstrates a five-year overall survival (OS) for patients without perioperative complications was 68%, compared with 41% for patients with POCs (p 0.001).
Conclusions: In a large single-institutional study, POCs were associated with decreased survival in patients undergoing surgery for gastric adenocarcinoma. Optimizing these patients post-operatively with limited anastomotic stress and enteral feeding tube may allow for a less complicated course.

Introduction

Previously, the impact of postoperative complications (POC) on recurrence rate and long-term outcome has been reported in esophageal or esophagogastric junction cancer.[1] Additionally, a strong correlation between POCs and poor long-term outcome has been reported for esophageal and esophagogastric junction cancer.[1] In patients with gastric cancer, there have been limited reports assessing the relationship between postoperative complications and long-term outcome. Recent studies have demonstrated that postoperative intraabdominal infectious complications adversely affect overall survival and relapse-free survival.[2] These results further emphasize that meticulous surgery and optimal post-operative management are required in order to decrease the complication rate and improve the long-term outcome of patients following curative gastrectomy.

Since an anastomotic/staple line leak following any type of gastrectomy remains one of the most severe complications that can lead to significant delays in recovery, worse short-term quality of life, and delays in initiating adjuvant chemotherapy, key predictive preoperative and intraoperative factors are essential to identify. Thus, identifying preoperative and operative factors that increase the risk for anastomotic/staple line leak are critical to understand for patient education, informed consent, operative management, and post-operative recovery. Recent preoperative nomograms have been reported and can help to accurately predict the risk of all types of perioperative mortality following gastric resections for malignancy, but no recent studies have evaluated the risk for anastomotic leak/failure and appropriate mitigation strategies.[3]

Thus, the aim of our study was to identify preoperative and intraoperative risk factors that can lead to an increased risk of anastomotic leak following all types of gastric resections, so that post-op recovery protocols can be optimized for personalized patient care.

* Corresponding author. Division of Surgical Oncology The Hiram C. Polk, Jr., MD Department of Surgery University of Louisville School of Medicine, 315 E. Broadway - #311, Louisville, KY, 40202, USA.
E-mail address: Robert.Martin@louisville.edu (R.C.G. Martin).

https://doi.org/10.1016/j.amjsurg.2019.12.030
0002-9610/

Methods

Patient eligibility criteria

This was an IRB-approved review of a prospectively maintained Gastric-Esophageal database of patients at our institution who underwent surgical resection of gastric malignancies from July 2002 to December 2018. Procedures were performed at three local hospitals associated with the University of Louisville by faculty in the Division of Surgical Oncology.

Surgical procedures and post-operative management

Three types of gastric resections were performed, 1) sleeve/tangential gastrectomy, 2) distal gastrectomy, and 3) total gastrectomy based on histology type and extent of primary disease. All operations were performed en-bloc with lymphadenectomy when the histology required. Procedures were performed either laparoscopically or through a laparotomy. Combined multi-organ resections were carried out in patients with advanced tumors suspected of invading adjacent organs or to facilitate dissection of lymph nodes for the purpose of R0 resection.

Transfusions were recorded if they occurred perioperatively and/or within 14 days of surgery. It should be noted that our group implemented a restrictive transfusion protocol in September of 2011 in an attempt to streamline management within the practice.[4] An enhanced recovery protocol was also initiated in January 2013, with results reported previously.[5]

Data collection

Data was collected and maintained in a database with no patient identifiers. Demographic parameters, preoperative factors, perioperative factors and surgical treatments were included in evaluation. Data regarding tumor location, tumor stage, lymph node analysis, pathology stage and operative findings were recorded. Follow-up was maintained according to attending preference.

Estimated blood loss (EBL) was recorded at the end of the case primarily by the anesthesiologist after consultation with the operative surgeon. The removal of any additional visceral organs was documented, as was the introduction of any type of enteral feeding tube. Jejunostomy feeding tubes were left at the discretion of the operating surgeon and were determined on a case-by-case basis. The optimal technique for J-tube placement has been described previously.[6] Additionally, it should be noted that stapled vs. sewn anastomosis was left to the preference of the attending surgeon, with a trend toward stapled anastomosis based on more recently published data.[7]

Patient data was divided into subgroups of those who had an anastomotic/staple line leak (AL) compared with those with no anastomotic leak (NL). Anastomotic leak was defined and graded as either a radiographically or endoscopically recognized leak at a staple or suture line post-operatively. Duodenal leaks were not included in this review. Our standard diagnostic technique for anastomotic leak assessment is a non-contrast CT scan of the chest with 250 cc of oral contrast 10 min before CT scan. Standard leak assessment is performed 2–3 weeks post-procedure for patients with esophageal anastomosis on an outpatient basis, and no leak assessment for gastric anastomoses.

We have utilized a classification of the leaks based on three parameters: time of appearance after surgery, magnitude or clinical severity, and location of the leaks.[8–10] Thus, early leaks were classified as those that appeared 1–4 days after surgery; intermediate leaks those that appeared 5–9 days after surgery, and late leaks those that appeared 10 or more days after surgery. Furthermore, type I or subclinical leaks are those that appear as a localized leak, without spillage or dissemination, with few clinical manifestations, and can be managed medically. Type II leaks are those with dissemination or diffusion into the abdominal or pleural cavity, by way of an irregular pathway, with the appearance of contrast medium (methylene blue, radiological contrast) or food through any abdominal drain, with severe clinical consequences. Complications were graded using the Clavien-Dindo complication scale.[11]

Table 1
Patient demographics.

Characteristic	N = 195	%
Age (median)	65 (19–89)	
Male	132	*68*
Race		
White	140	*72*
Black	30	*15*
Asian/Pacific Islander	13	*7*
Hispanic	6	*3*
Other	6	*3*
BMI (median)	26 (19–47)	
T-stage		
Tis	1	*1*
T0	23	*12*
T1	21	*11*
T2	41	*21*
T3	94	*48*
T4	15	*8*
N-stage		
N0	86	*44*
N1	37	*19*
N2	28	*14*
N3	44	*23*
Surgery Type		
Esophagojejunostomy	113	*58*
Gastrojejunostomy	47	*24*
Wedge Gastrectomy	35	*18*
Tobacco history	68	35%
Median Pack Years	40 (10–100)	
Any Complication During Index Operation	74	38%
Grade 3 or Higher Complications	53	27%
Anastomotic Leak	25	13%
Timing of Leaks:	N = 25	
Early	1	4%
Intermediate	8	32%
Late	16	64$
Type of Leak		
Type 1	23	92%
Type 2	2	8%
Length of Stay (Median, Range)	8 (1–57)	

Variable selection

Groups were compared along characteristics including demographic, perioperative, and outcome variables. Perioperative variables included operation type, receipt of perioperative antibiotics, operative time, receipt of DVT chemoprophylaxis, and perioperative blood transfusion. Preoperative Charlson Comorbidity index (CCI) was also incorporated for evaluation.[12] Outcome variables included length of intensive care unit stay (ICU LOS), number of days requiring mechanical ventilation, overall length of stay (LOS), incidence and severity of complications, readmission, and overall cost of care.

Statistical analysis

Univariate analysis was performed using two-sided student's t-test for continuous variables and Chi-square test for categorical variables. Multivariable analysis was performed using logistic regression analysis. Statistical analyses were performed using JMP

Table 2
Univariate analysis.

Univariate Variables	Total, n (%) (N = 195)	AL, n (%) (n = 25)	AL, n (%) (n = 170)	*p* value
Age, yrs				0.43
<70		9	125	
≥70		16	45	
Sex				0.63
Male	132	18	102	
Female	63	7	68	
Race				0.14
White	140	18	122	
Black	30	4	26	
Asian/Pacific Islander	13	2	11	
Hispanic	6	1	5	
Other	6	0	6	
BMI				0.2
<35	152	20	132	
≥35	43	5	38	
T-Stage				0.002
Tis	1	0	1	
T0	23	1	22	
T1	21	0	21	
T2	41	4	37	
T3	94	20	74	
T4	15	0	15	
	195	25	170	
N-stage				0.003
N0	86	5	81	
N1	37	4	33	
N2	28	5	23	
N3	44	11	33	
	195	25	170	
Surgery type				
Esophagojejunostomy	113	20	93	0.015
Gastrojejunostomy	47	5	42	0.82
Wedge Gastrectomy	35	0	35	NS
Totals	195	25	170	
EBL				
<399	156	15	141	0.014
400-800	34	10	24	0.004
>801	5	0	5	0.489
Blood Transfusion				<0.001
Received	38	12	26	
Did Not Receive	157	13	144	
ICU Stay				
Yes	62	15	47	0.001
CCI				
<5		4	128	
≥5	104	21	42	0.014
Tobacco History				
Positive	73	10	62	0.8
Negative	122	15	108	
Complications				<0.0001
Pulmonary	20	8	12	
Cardiac	19	8	11	
Infectious	17	7	10	
Other	22	2	20	
Any complications	78	25	53	
Positive Margin	3	0	3	NS
Neoadjuvant Chemotherapy	170	4	19	0.50
Length of Hospital Stay		21 (5–57)	7[2–14]	<0.0001
Clavien-Dindo Complication Scale				
0	63%			
1		1	3	ns
2		0	21	ns
3		19	24	0.001
4		3	3	0.001
5		2	2	0.001
Totals		25	53	
Jejunostomy tube yes	78	8	70	0.48
Anastomosis type				0.47
Stapled		8	66	
Sewn		4	21	
Past Medical History				NS
Diabetes		17	13	
Tobacco		37	34	
GERD		16	23	

Table 2 (*continued*)

Univariate Variables	Total, n (%) (N = 195)	AL, n (%) (n = 25)	AL, n (%) (n = 170)	*p* value
Tumor Site				0.65
GEJ		27	73	
Prox 1/3		19	81	
Mid 1/3		10	90	
Distal 1/3		4	96	
Albumin Level				0.53
<3.3		100		
≥3.3		14	86	

2019.

Results

A total of 195 patients were evaluated with an overall complication rate of 40%.

AL occurred in 13% of our patients, with 4% undergoing reoperation during the same hospitalization (Table 1). Not surprisingly we did not see any resection line leaks for patients under wedge type of resection, thus demonstrating that with good surgical technique and good stapler choice that a leak in these types of patients should be close to a never event. The majority of the leaks occurred in patients undergoing esophagogastric anastomosis (20 out of 25 AL; 80%), with the rest of the AL being at the gastrojejunostomy anastomosis. Because of this distribution we will separate these two operations for AL evaluation. The timing and type of leak were also consistent across both operations, with most being late leaks and type 1 in severity. This was consistent with esophageal anastomosis (Timing 16 late, with 14 type 1 and 2 patients type 2). All of the gastrojejunostomy leaks occur early or in the intermediate timing and were all type 1 in severity).

Anastomotic leak for esophageal anastomosis

On univariate analysis we found preoperative and operative factors of higher T-stage, N-stage, and need for blood transfusions were significantly associated with anastomotic leak ($p < 0.001$) (Table 2). ICU stay post-operatively was also associated with anastomotic leaks ($p = 0.001$). Preexisting factors that were not significant included race, age, gender, BMI, tobacco history, NSAID use and history of GERD. Multivariate analysis did not identify any independent risk factors for anastomotic leak. However, we were able to identify that CCI >5 & EBL 400–800 were significant as predictors of postoperative complications on multivariate analysis.

Anastomotic leak for gastrojejunostomy anastomosis

In a specific review of the five patients with AL, all had neoadjuvant/induction based chemotherapy for over 5 months, median albumin of 3.2 (2.6–3.5), and recent weight loss of a median of 11% (range 9%–15%) during chemotherapy. None of these factors were significant, but were the pre-operative markers in these patients when compared to the other gastrojejunostomy patients.

Predictors of outcomes of post-opertive complications

Significant risk factors affecting postoperative complications were identified in the patients, including number of comorbidities (≥2) (HR, 5.30; 95% CI, 1.1–15.3; P = 0.037), operation type (Total vs Distal) (HR, 2.5; CI 1.08–8.5; p = 0.048).

Outcomes of post operative complications for gastric adenocarcinoma

Five-year overall survival (OS) for patients without perioperative complications was 68%, compared with 41% for patients with POCs (p 0.001), when matched for pre-operative stage, pathologic stage, and extent of adjuvant chemotherapy. Disease-free survival (DFS) at five years was 53% for patients without POCs, compared to 36% in patients with POCs (p 0.002). Patients without POCs were significantly more likely to receive adjuvant therapy (89% vs 57%; p 0.001).

Discussion

In total, 195 patients were evaluated with an overall complication rate of 40% and an anastomotic leak rate of 13%, with 4% undergoing reoperation during the same hospitalization. These rates are in line with the previously published literature of 2–13%.[13–16]

The primary aim of our study was to identify risk factors for anastomotic leak in gastrectomy patients. While we were able to find univariate factors, ultimately no risk factors for anastomotic leak were determined on multivariate analysis.

However, through multivariate analysis, we were able to identify risk factors for overall complications. On further analysis of patients who had POC compared with non-complicated patients, we found that POC had a significant impact on OS, DFS and decreased likelihood that those patients would ultimately receive adjuvant chemotherapy.

Frailty, as determined by the Charlson Comorbidity Index (CCI), was extremely useful in determining which patients were more likely to have complications. Similar results have been published by Hsu et al. on 164 elderly patients that showed higher CCI patients to have worse mortality and morbidity in gastrectomy.[17] Thus preoperative calculation and awareness of these high risk patients is critical in the informed consent process and in the managing patients expectations for immediate and delayed (30–90 day) complications.[18] A clear understanding of the patients psychosocial risk factors, which have been found to be directly related to a patiens ability to cope with unexplained post-operative events and complications is critical to long term recovery of these patients.[19]

We also found EBL to be predictive of POC, with EBL 400–800 cc having a multivariate significance. Hayashi et al. also found that high EBL was more likely to occur in patients with POC.[20]

Regarding longer term outcomes for these patients, our findings of decreased OS & DFS correlate with similar studies, as do our reports of the rates of patients ultimately receiving adjuvant chemotherapy. Tokunaga et al. studied 764 patients with curative gastrectomies and found intraoperative complications to have significance in predicting 5-year overall survival (HR 2.448; CI 1.47–4.06) and relapse-free-survival (HR 2.219; 1.33–3.41). This was comparable to our study that found higher rates of complications associated with decreased 5-year OS (49% vs. 74%, p = 0.001) and disease-free-survival (46% vs. 58%, p = 0.002).

The intraoperative management of these high-risk patients must take into account both the significant variables that we have presented, as well as some of the pre-surgical predictive factors, such as CCI. In particular, temporary nutrition should be considered, via either TPN or J-tube access, when planning gastrectomy for patients at high risk for complications and/or anastomotic leak. Our decision-making for J-tube placement is based on preoperative and intraoperative risk factors for complications including 1) any esophageal anastomosis, 2) preoperative prealbumin $\leq$ 14, or 3) severe pulmonary co-morbidity (defined as preoperative O2 supplementation or pulmonary function tests <70% predicted). These are temporary tubes and the decision for jejunostomy removal is based on the ability of the patient to consume at least 1800 calories a day and the ability of the patient to maintain weight for 3 weeks once enteral feeds were stopped. We have found J tubes to be effective, safe, and fairly efficient to manage these patients (In Press: Complications of Jejunostomy Feeding Tubes: A Single Center Experience, Conor H. O'Neill, MD and Robert C G Martin, II, MD PhD.) The use of TPN for these three factors above can also be utilized as a supplement/replacement to J tube feeds.

We have recently published on the safety and cost saving for an Enhanced Recovery pathway in these types of patients with a clear modification from standard ERAS protocols.[5] Clearly, patients that are at an increased risk for anastomotic complications will keep their NGT's longer and we utilize a 2–3 week NPO status to allow for more efficient discharge and optimal anastomotic healing. It has been our management for all esophageal anastomosis to have patients remain NPO for 2–3 weeks post-surgery, which means they go home for 5–10 days on NPO with all nutrition, hydration, and medications via J tube management and then come back as an outpatient for their CT chest and then office visit as described in our methods. Patients are very compliant with this when they understand preoperatively the need for this type of management.

Conclusion

No modifiable risk factors for anastomotic leak prevention were identified in this study. However, we were able to identify risk factors for post-operative complications and we were able to show that patients who received POC had overall worse OS, DFS and less successful adjuvant chemotherapy.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Hirai T, Yamashita Y, Mukaida H, et al. Poor prognosis in esophageal cancer patients with postoperative complications. *Surg Today*. 1998;28(6):576–579. PubMed PMID: 9681604. Epub 1998/07/29.
2. Tokunaga M, Tanizawa Y, Bando E, et al. Poor survival rate in patients with postoperative intra-abdominal infectious complications following curative gastrectomy for gastric cancer. *Ann Surg Oncol*. 2013 May;20(5):1575–1583. PubMed PMID: 23076557. Epub 2012/10/19.
3. Dhir M, Smith LM, Ullrich F, et al. A preoperative nomogram to predict the risk of perioperative mortality following gastric resections for malignancy. *J Gastrointest Surg*. 2012 Nov;16(11):2026–2036. PubMed PMID: 22948837. Epub 2012/09/06.
4. Wehry J, Agle S, Philips P, et al. Restrictive blood transfusion protocol in malignant upper gastrointestinal and pancreatic resections patients reduces blood transfusions with no increase in patient morbidity. *Am J Surg*. 2015 Dec;210(6):1197–1205. PubMed PMID: 26602534.
5. Bhutiani N, Quinn SA, Jones JM, et al. The impact of enhanced recovery pathways on cost of care and perioperative outcomes in patients undergoing gastroesophageal and hepatopancreatobiliary surgery. *Surgery*. 2018 Oct;164(4):719–725. PubMed PMID: 30072252. Epub 2018/08/04.
6. Shumer EMRCG. Minimally invasive feeding tube and esophageal stent placement. *Minimally invasive foregut surgery for malignancy: Principles and practice*. 2015;1:183–188.
7. Rostas JW, Graffree BD, Scoggins CR, et al. Long-term outcomes after hand-sewn versus circular-stapled (25 and 29 mm) anastomotic technique after esophagogastrectomy for esophageal cancer. *J Surg Oncol*. 2018 Mar;117(3):469–472. PubMed PMID: 29044576. Epub 2017/10/19.
8. Csendes A, Diaz JC, Burdiles P, et al. Classification and treatment of anastomotic leakage after extended total gastrectomy in gastric carcinoma. *Hepato-Gastroenterology*. 1990 Dec;37(Suppl 2):174–177. PubMed PMID: 2083933. Epub 1990/12/01.
9. Csendes A, Burdiles P, Burgos AM, et al. Conservative management of anastomotic leaks after 557 open gastric bypasses. *Obes Surg*. 2005 Oct;15(9):1252–1256. PubMed PMID: 16259881. Epub 2005/11/02.
10. Csendes A. Conservative management of anastomotic leaks. *Obes Surg*. 2006 Mar;16(3):375–376. author reply 6. PubMed PMID: 16545173. Epub 2006/03/21.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004 Aug;240(2):205–213. PubMed PMID: 15273542. Pubmed Central PMCID: PMC1360123. Epub 2004/07/27.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. PubMed PMID: 3558716. Epub 1987/01/01.
13. Carboni F, Valle M, Federici O, et al. Esophagojejunal anastomosis leakage after total gastrectomy for esophagogastric junction adenocarcinoma: options of treatment. *J Gastrointest Oncol*. 2016 Aug;7(4):515–522. PubMed PMID: 27563440. Pubmed Central PMCID: PMC4963362. Epub 2016/08/27.
14. Sierzega M, Kolodziejczyk P, Kulig J, Polish Gastric Cancer Study G. Impact of anastomotic leakage on long-term survival after total gastrectomy for carcinoma of the stomach. *Br J Surg*. 2010 Jul;97(7):1035–1042. PubMed PMID: 20632269. Epub 2010/07/16.
15. Li QG, Li P, Tang D, et al. Impact of postoperative complications on long-term survival after radical resection for gastric cancer. *World J Gastroenterol*. 2013 Jul 7;19(25):4060–4065. PubMed PMID: 23840153. Pubmed Central PMCID: PMC3703195. Epub 2013/07/11.
16. Claassen YHM, Hartgrink HH, Dikken JL, et al. Surgical morbidity and mortality after neoadjuvant chemotherapy in the CRITICS gastric cancer trial. *Eur J Surg Oncol*. 2018 May;44(5):613–619. PubMed PMID: 29503129. Epub 2018/03/06.
17. Hsu JT, Liu MS, Wang F, et al. Standard radical gastrectomy in octogenarians and nonagenarians with gastric cancer: are short-term surgical results and long-term survival substantial? *J Gastrointest Surg*. 2012 Apr;16(4):728–737. PubMed PMID: 22350724. Epub 2012/02/22.
18. Shutt TA, Philips P, Scoggins CR, et al. Permanent loss of preoperative independence in elderly patients undergoing hepatectomy: key factor in the informed consent process. *J Gastrointest Surg : official journal of the Society for Surgery of the Alimentary Tract*. 2016 May;20(5):936–944. PubMed PMID: 26811246.
19. Leeds IL, Meyers PM, Enumah ZO, et al. Psychosocial risks are independently associated with cancer surgery outcomes in medically comorbid patients. *Ann Surg Oncol*. 2019 Apr;26(4):936–944. PubMed PMID: 30617868. Epub 2019/01/09.
20. Hayashi M, Yoshikawa T, Yura M, et al. Does neoadjuvant chemotherapy cancel out the negative survival impact induced by surgical complications after gastrectomy? *Gastric Cancer*. 2019 Apr 3. PubMed PMID: 30945120. Epub 2019/04/05.