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Gastric carcinoids: Does type of surgery or tumor affect survival?

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ABSTRACT

Background: Gastric carcinoids are rare neuroendocrine tumors of the gastrointestinal tract. They are typically managed according to their etiology. However, there is little known about the impact of surgical strategy on the long-term outcomes of these patients.

Methods: All patients who underwent resection of gastric carcinoids at 8 institutions from 2000 to 2016 were analyzed retrospectively. Tumors were stratified according to subtype (I, II, III, IV) and resection type (local resection, LR or formal gastrectomy, FG). Clinicopathological parameters, recurrence-free (RFS) and overall survival (OS) were compared between groups.

Results: Of 79 patients identified with gastric carcinoids, 34 had type I lesions associated with atrophic gastritis, 4 had type II lesions associated with a gastrinoma, 37 had type III sporadic lesions, and 4 had type IV poorly-differentiated lesions. The mean age of presentation was 56 years in predominantly Caucasian (77%) and female (63%) patients. Mean tumor size was 2.4 cm and multifocal tumors were found in 24 (30%) of patients with the majority occurring in those with type I tumors. Lymph node positive tumors were seen in 15 (19%) patients and 7 (8%) had M1 disease; both most often in type IV followed by type III tumors. R0 resection was achieved in 56 (71%) patients while 15 (19%) had R1 resections and 6 (8%) R2 resections. Patients with type I and III tumors were equally likely to have a LR (50% and 43% respectively) compared to FG while those with type II and IV all had FG with one exception. Type IV tumors had the poorest RFS and OS while Type II tumors had the most favorable RFS and OS ($p < 0.04$ and $p < 0.0004$, respectively). While there was no difference in RFS in those patients undergoing FG versus LR, OS was worse in the FG group ($p < 0.017$). This trend persisted when type II and type IV groups were excluded ($p < 0.045$).

Conclusion: Gastric carcinoid treatment should be tailored to tumor type, as biologic behavior rather than resection technique is the more important factor contributing to long-term outcomes.

Introduction

Gastric carcinoids are rare tumors of the gastrointestinal tract which comprise less than 2% of gastric malignancies and under 10% of gastrointestinal neuroendocrine tumors.[1] Gastric carcinoids arise from enterochromaffin-like (ECL) cells that reside in the gastric

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mucosa. ECL cells appear histologically similar to enterochromaffin cells that reside in intestinal villi but lack the ability to synthesize serotonin.[2]

ECL cells are implicated in the neuroendocrine control of gastric acid production. They respond to gastrin release from antral G-cells by secreting histamine which in turn stimulates neighboring acid-producing parietal cells to release hydrochloric acid, thereby acidifying the stomach.[3] Negative feedback is provided by antral D-cells which respond to the acidic environment by secreting somatostatin, which acts on G-cells to downregulate gastrin.[3] In addition to stimulating histamine release, gastrin has a potent trophic effect on ECL cells and persistently elevated levels of gastrin can lead to ECL cell growth, hyperplasia and dysplasia.[4]

Gastric carcinoids comprise four distinct entities classified by clinicopathologic qualities and biologic behavior.[5,6] Type I gastric carcinoids are typically associated with hypergastrinemia and conditions that cause achlorhydria, including autoimmune atrophic gastritis, chronic acid suppression, and pernicious anemia.[7] Anti-parietal cell or anti-intrinsic factor antibodies destroy gastric parietal cells and disrupt the delicate biochemical milieu with a decrease in acid levels and concomitant increase in gastrin. The resultant ECL hyperplasia and dysplasia give rise to type 1 gastric carcinoids.[4] This subtype is thought to have the least malignant potential of all gastric carcinoids and tends to have an indolent course.[1,8,9]

Type II gastric carcinoids appear histologically similar to type I carcinoids but are associated with gastrinomas and genetic syndromes including MEN1 and Zollinger-Ellison syndrome.[10] Gastrinomas cause hypergastrinemia though autonomous gastrin secretion in the setting of normal parietal cell function, resulting in significantly increased gastric acidity and predisposition to duodenal and jejunal ulceration.[11] These carcinoids also can present as multifocal neoplasms and tend to carry a low risk of malignancy, though thought to be higher than that of type I carcinoids.[12] In contrast to type I carcinoids, endoscopic findings usually include normal to hypertophic gastric mucosa and laboratory evaluation will demonstrate hypergastrinemia and a paradoxical increase in gastrin levels in response to intravenous secretin infusion.[13] The inciting gastrinoma typically resides in Passaro's (gastrinoma) triangle bounded by the junction of the cystic and hepatic ducts, the transition from the second to third portion of the duodenum and the pancreatic neck.[14]

Type III gastric carcinoids are sporadic lesions that frequently present with a larger size and deeper level of invasion compared to type I and II carcinoids.[15] ELC hyperplasia is typically absent and serum gastrin levels are normal.[16] Type III gastric carcinoids tend to have a poorer prognosis secondary to more frequent findings of angioinvasion, lymphatic invasion, and metastases.[17] Type IV gastric carcinoids are large, poorly-differentiated lesions and tend to be the most aggressive type of carcinoid and associated with the worst prognosis.[18]

The optimal resection strategy for these various lesions is unknown. Although endoscopic management is thought to be sufficient for some patients with type I gastric carcinoids, indications for surgical management are debated with some groups advocating for formal gastrectomy in patients with poor prognostic features.[19] Additionally some groups perform antrectomy for patients with multifocal or invasive type I gastric carcinoids, as removal of antral G-cells can lead to normal serum gastrin levels and regression of carcinoids; however, in some patients ECL cells may become autonomous or an insufficient number of G-cells are removed.[20] As a result, in some patients, a subtotal or total gastrectomy may be recommended.[20] Surgical management of type II lesions generally entails both resection of the offending gastrinoma as well as either endoscopic or surgical resection of the type II gastric carcinoid.[21] Type III and type IV lesions are generally treated with formal gastrectomy with lymphadenectomy as well as extirpation of any resectable metastatic disease.[22]

Resection remains the primary treatment for gastric carcinoids; however, the role that a specific surgical strategy plays on long-term outcomes including recurrence and survival is unknown-that role.

Methods

The US Neuroendocrine Tumor Study Group (US-NETSG) is an ongoing collaboration between 8 institutions: Virginia Mason Medical Center, Emory University, The Ohio State University, Stanford University, Vanderbilt University, University of Michigan, University of Wisconsin, and Washington University in St. Louis. Each institution obtained Institutional Review Board approval and retrospectively reviewed all patients who underwent resection of gastrointestinal neuroendocrine tumors from 2000 to 2016 using a standard template.

All patients with gastric neuroendocrine tumors who underwent endoscopic or surgical resection of a primary tumor were included. Each institution collected demographic, perioperative, and pathologic data from the electronic medical record. Staging was performed according to the American Committee on Cancer (AJCC) 7th edition guidelines. Patients were stratified according to gastric carcinoid type and by type of resection. The formal gastrectomy group was defined as patients who underwent distal gastrectomy, subtotal gastrectomy, or total gastrectomy. The local resection group comprised patients who underwent endoscopic resection or surgical wedge resection.

Type I carcinoids were defined by presence of atrophic gastritis, hypergastremia, and/or ECL hyperplasia. Type II carcinoids required presence of gastrinoma. Type III carcinoids were sporadic in the absence of atrophic gastritis and hypergastrinemia. Type IV carcinoids were poorly differentiated tumors.

Survival and recurrence data were collected from the electronic medical record, the Social Security Death Index, and publicly available obituaries. Statistical analysis was conducted using MEDCALC software. Chi-squared analysis was used to compare categorical variables while continuous variables were compared with student's t-test. Survival analysis was performed using recurrence-free survival (RFS) and overall survival (OS) as the primary outcomes. RFS was measured from time of resection to recurrence, death, or last follow-up in patients who had macroscopically negative (R0 or R1) final resection margins. OS was measured from the time of resection to death or last follow-up. Kaplan-Meier survival plots for RFS and OS were constructed to compare patients according to carcinoid type as well as to surgery type. A p-value <0.05 was considered statistically significant.

Results

Of 2182 patients included in the US-NETSG database, 79 underwent resection of a gastric neuroendocrine tumor. Table 1 details demographic data for this cohort. Sixty-five percent of patients were female ($n = 50$) and 77% were Caucasian ($n = 61$). Average age was 56.6 ($\pm$10.6) years and average BMI was 31.1 ($\pm$7.3). Of the 79 patients with gastric carcinoid tumors, 34 had type I lesions associated with atrophic gastritis, 4 had type II lesions associated with a gastrinoma, 37 had type III sporadic lesions, and 4 had type IV poorly-differentiated lesions. Table 2 outlines the pathologic and surgical data for the various tumor types.

The majority of patients were symptomatic at presentation ($n = 60$, 75.9%) with dyspepsia and abdominal pain being the most common presenting symptoms ($n = 35$ and $n = 32$, respectively),

Table 1
Demographic characteristics of patients with gastric carcinoids.

Baseline Variable	n (%)
Age (years), mean, ± STD	56.5 ± 10.6
Male	29 (36.7)
BMI, mean, ± STD	31.1 ± 7.3
Race	
White	61 (77.2)
Black	16 (20.3)
Other	2 (2.5)
Functional Status	
Independent	60 (96.8)
Partially Dependent	2 (3.2)
Smoking History	7 (8.9)
Diabetic	26 (32.9)
Any Presenting Symptom	60 (75.9)
Pain	32 (40.5)
Nausea/Vomiting	13 (16.5)
Dyspepsia	35 (44.3)
	30 on antacids
GI Obstruction	1 (1.3)
GI Bleed	16 (20.3)

frequently in combination. The remainder were incidental findings on imaging or on upper endoscopy. Mean tumor size for all gastric carcinoids was 2.4 cm (0.10–19.0 cm) and multifocal tumors were found in 30% (n = 24) of patients. Multifocal tumors were most common in type I tumors, occurring in 44% (n = 15) of type 1 tumors. Type III tumors had a higher percentage of T2 and T3 tumors (37.8% and 10.8%, respectively) compared to other tumor types. Lymph node positive tumors were seen in 19% (n = 15) patients and 8% (n = 7) had M1 disease, most commonly in type III tumors, occurring in 24.3% and 13.5% of patients with type III tumors, respectively.

Thirty-four patients underwent LR with 25 of those undergoing endoscopic resection. The remaining 9 patients in the LR group underwent wedge gastrectomy, including 2 robotic, 2 open, and 5 laparoscopic operations. Included in the LR group were 17 type 1 tumors, including 16 endoscopic resections and 1 wedge resection, 1 type II tumor treated with endoscopic resection, and 16 type III tumors, with 8 endoscopic resections and 8 wedge resections. There were no type IV tumors in the LR group.

The FG group comprised 45 patients with 10 undergoing distal gastrectomy, 24 undergoing subtotal gastrectomy, and 11 patients undergoing a total gastrectomy. Five patients in the FG underwent concomitant liver resection for metastatic disease to the liver. Of the 45 FG patients, 38 underwent open operations, 5 underwent laparoscopic operations, 1 had a laparoscopic hand-assisted operation, and one had a laparoscopic converted to open operation. Included in the FG group were 17 type I tumors, 3 type II tumors, 21 type III tumors, and all 4 type IV tumors.

Blood loss was significantly higher in the FG group compared to LR (385 ± 600 cc vs 25 ± 57 cc, p = 0.001) but operative time was significantly longer (233 ± 114 min vs 110 ± 112 min, p = 0.002) in the FG group compared to the LR group. Perioperative complications occurred in 14 patients, with an overall complication rate of 17.7%. Surgical complications occurred with greater frequency in the FG group compared to the LR group (12 patients, 26.7% vs 2 patients, 5.8%, RR 4.64 95%CI 1.11–19.3, p = 0.04) (See Table 3). All patients were discharged to home with the exception of one FG patient that was discharged to a rehabilitation facility. Length of stay was significantly longer in the FG group (7.9 ± 5.4 days vs 1.9 ± 4.6 days, p = 0.002). Readmission rate was significantly higher in the FG group with 9 readmissions within 30 days and an additional readmission within 90 days of surgery compared to 1 readmission within 30 days in the LR group (RR 7.56, 95% CI 1.02–56.2, p = 0.05).

R0 resection was achieved in 56 (71%) patients while 15 (19%) had R1 resections and 6 (8%) R2 resections. The majority of R1 resections occurred in type I tumors (n = 10) while R2 resections only occurred in type III (n = 4) and type IV (n = 2) tumors. Of the R1 resections, 9 occurred in the LR group and 6 were in the FG group. Of the 6 R2 resections, 2 were in the LR group and 4 were in the FG group. Of the 4 patients with R2 resections in the FG group, 2 patients had R2 resections of their liver metastases that had been resected at the same time as the gastric carcinoids.

Patients with type I and III tumors were equally likely to have a LR (50% and 43%, respectively) compared to FG while those with type II and IV all had FG with the exception of one patient with a type II tumor that was resected endoscopically. Type IV tumors had

Table 3
Clavien-Dindo classification of surgical complications.

Complication Grade	Number of patients	% of patients
I	2	2.5%
II	6	7.6%
IIIa	2	2.5%
IIIb	2	2.5%
IV	2	2.5%
Total	14	17.7%

Table 2
Clinicopathologic characteristics of patients with gastric carcinoids.

Clinical Factor	Type 1 (n = 34)	Type 2 (n = 4)	Type 3 (n = 37)	Type 4 (n = 4)
Symptomatic	24	3	29	4
Size (cm)	1.5	2.4	2.8	2.6
Multifocal	15	2	7	0
T Stage				
T1	15	2	12	0
T2	8	1	14	1
T3	0	0	4	1
T4	1	0	0	1
Nodal Disease	2	1	9	3
M1 Disease	1	0	5	1
Endoscopic Resection	16	1	8	0
Wedge Resection	1	0	8	0
Distal Gastrectomy	4	1	5	0
Subtotal Gastrectomy	11	2	9	2
Total Gastrectomy	2	0	7	2
R0 Resection	24	3	27	2
R1 Resection	10	1	4	0
R2 Resection	0	0	4	2

the poorest RFS and OS while type II tumors had the most favorable RFS and OS ($p < 0.04$ and $p < 0.0004$, respectively). There was no difference in RFS in those patients undergoing FG versus LR; however, OS was worse in the FG group ($p < 0.017$). This trend persisted when type II and type IV groups were excluded ($p < 0.045$) (Fig. 1).

Four patients were treated with adjuvant chemotherapy, including 3 type IV gastric carcinoids and one type III gastric carcinoid. One of the type IV carcinoid patients treated with adjuvant chemotherapy was also treated with octreotide.

Discussion

The biologic behavior of gastric carcinoids remained elusive until advanced immunohistochemical techniques and electron microscopy led to the discovery of multiple subtypes.[17,23] Rhindi et al. went on to demonstrate that ECL cells were precursors to type I and type II gastric carcinoids with type II tumors harboring a genetic predisposition to ECL cell transformation to type 2 carcinoids. Additionally, their findings of higher rates of atypia, mitoses per field, deeper invasion into the gastric wall and angioinvasion couple with higher rates of metastases highlighted the broad spectrum of biologic behavior and natural history of the various subtypes.[17]

The discovery that gastric carcinoids represent a rare but diverse clinical entity led to interest in elucidating the optimal management strategy for each tumor type. Our findings of high rate of multifocality (44.1%) coupled with rates of locoregional lymph node involvement (5.8%) and distant metastases (2.9%) in type I tumors are consistent with previous studies.[24,25] Given the documented high rate of recurrence and low disease-associated mortality, a range of management strategies have been adopted in the pursuit of a care plan that appropriately weighs the oncologic benefits and treatment morbidities.[24,25] For type I tumors, Gladdy et al. reported a range of appropriate management strategies for these tumors ranging from endoscopic surveillance and medical management for small multifocal lesions to assess tumor progression and regression as well as glandular dysplasia of surrounding gastric mucosa to surgical resection for larger (>1.0 cm) tumors and/or findings of dysplasia which may herald an adenocarcinoma. They also highlighted the complex surgical decision making when considering wedge resection versus antrectomy. Although antrectomy frequently results in carcinoid regression and normalization of serum gastrin levels, incomplete resection of G-cells can lead to autonomously functioning ECL cells.

In contrast to type I carcinoids, type III carcinoids are typically present with larger tumor sizes and higher incidence of locoregional nodal involvement and distant metastases 24.3% and 13.5%, respectively in our series. Given their more aggressive behavior and risk for disease-related mortality, there is a general consensus that these tumors should be treated surgically with aggressive resection including gastrectomy and lymphadenectomy.[24] Despite these recommendations, there is a paucity of literature that discusses the ideal management strategy for the full spectrum of gastric carcinoids.

Indeed, in our study we found that type I carcinoids were equally likely to get local resection and formal gastrectomy. Type I and type III carcinoids were equally likely to have local resection

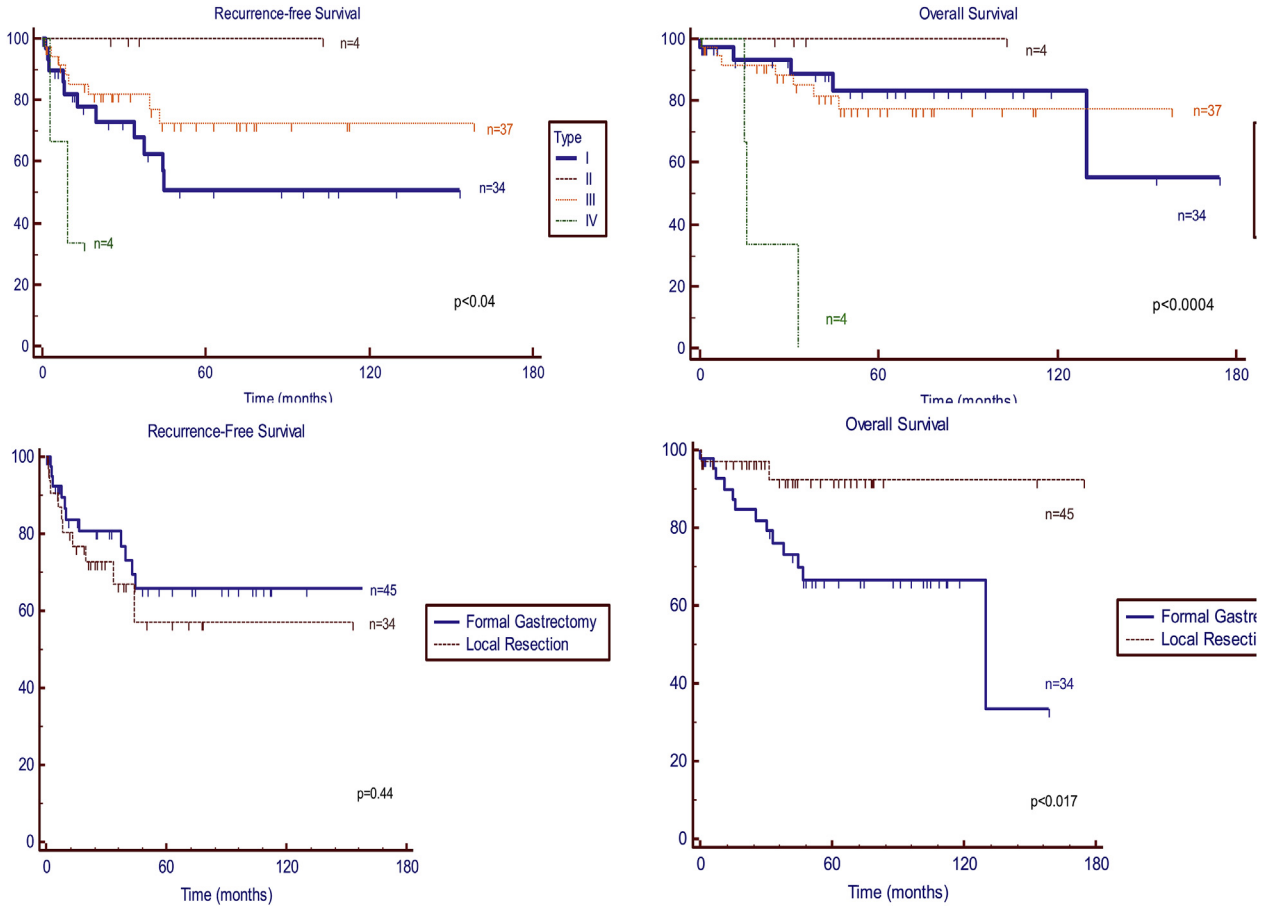

Fig. 1. Kaplan-Meier survival curves for patients with gastric carcinoids.

compared to formal gastrectomy despite the type III tumors tending to be larger and more likely to have lymphatic involvement. RFS was not affected by resection strategy; rather, RFS and OS appeared to be driven by carcinoid type with type II tumors having the most favorable RFS and OS. These findings once again support the imperative role that the tumor biology plays in outcomes.

Interestingly, the type I tumors had the second lowest survival rate following type IV tumors, despite being the least malignant subtype. This finding could be due, in part, to misclassification of tumor types. Although the database identified patients that were treated with antacid therapies, it lacks the granularity to determine whether patients were receiving proton pump inhibitors or antihistamines as well as whether proton pump inhibitors were held prior to measuring gastrin levels. This introduces the possibility that some type III tumors may have been misclassified as type I tumors based on artificially elevated gastrin levels in the setting of ongoing proton pump inhibitor therapy. Perhaps the lower survival rate was a result erroneous inclusion of type III tumors in the analysis.

Because our cohort was evaluated and managed at major academic centers with neuroendocrine expertise, we postulate that gastrin levels were measured in the absence of proton pump inhibitor therapy and that a very small minority of carcinoids were misclassified. Our overall breakdown of type I and type III carcinoids are consistent with the current literature, providing additional reassurance that if misclassification occurred, it was infrequent.[15,17,25]

An alternate explanation for the lower survival rate in type I carcinoids is that these patients were dying of unrelated causes at a fairly high rate. Because type 1 carcinoids are at high risk of recurrence, even with FG, this finding suggests that surgical resection should be reserved for special cases of type 1 carcinoids, as patients with type 1 carcinoid are much more likely to die of causes.

Strategies for type IV carcinoids, the poorly differentiated subtype, are quite limited with few groups specifically addressing their management. In our study, this group had the highest rates of nodal involvement (75%) and distant metastases (25%). This group had the worst OS and RFS despite all undergoing FG. The role for FG, regional lymphadenecomy, and tumor debulking is unclear, as outcomes were poorer compared to the other subtypes despite the more aggressive surgical approaches. It is possible that these patients, like others with high-grade neuroendocrine tumors, may benefit from systemic chemotherapy as opposed to upfront surgery.

Using a large multi-institutional database, this study found that formal gastrectomy was the more commonly employed surgical approach overall, but that long-term outcomes including RFS and OS were similar regardless of surgical strategy. Although there was no difference in RFS between patients who underwent FG versus LR, OS was worse in the FG group. Patients who underwent formal gastrectomy had higher morbidity with longer operating time, greater blood loss, and higher incidence of complications. Additionally, patients who underwent formal gastrectomy had longer length of stays and higher rates of readmission. It is possible that the gastrectomy-associated morbidity with the more aggressive surgical strategies contributed to the worse OS in the FG group. In the setting of similar RFS and OS, these findings suggest that the more limited surgical approach may offer similar survival outcomes while providing a more favorable complication and morbidity profile.

In a cohort study of over 1000 patients with gastric carcinoids from the California Cancer Registry, Callahan et al. found that in a surgery provided a survival advantage for patients who had local and regional disease.[15] Although they were unable to stratify tumors by subtype due to the absence of this field in the registry, they did attempt to use tumor size, presence of locoregional lymph node and distant metastasis, and multifocality to approximate tumor subtypes. Additionally, they controlled for age and comorbidities as those factors may contribute to clinical decisions making and surgical planning. In addition to finding that gastric surgery was associated with improved overall survival, they found that patients with hepatic metastases who underwent both gastrectomy and debulking had similar survival to patients who underwent gastrectomy and resection of locoregional disease; however, they were unable to identify a surrogate marker for tumor subtype and determine the effect of extent of surgery on survival outcomes.

In our study, R0 resections were achieved in the majority of patients with the highest number of R1 resections occurring in type I carcinoids and R2 resections occurring only in type III and type IV carcinoids. Despite having a higher proportion of microscopic positive margins and therefore a higher risk for locoregional recurrence, the type I carcinoids had favorable long-term survival curves, suggesting again that biologic behavior plays a pivotal role in long-term outcomes.

This study is limited by the inclusion of only resected gastric carcinoids as well as by a relatively small sample size despite the multi-institutional dataset from 8 tertiary academic centers. This is a reflection of the rarity of gastric carcinoids. While it does include patients from all geographic regions of the United States, the retrospective multi-institutional design does introduce difficulty in capturing disease-specific survival as well as a lack of standardization of the evaluation and management decisions of patients with gastric carcinoids. Finally, the dataset does not provide the intent of the clinical decision making that took place to determine each patient's resection strategy. We suspect that the operating surgeonsconsidered a variety of factors, including carcinoid type and regional lymph node involvement, in their selection of a surgical strategy which may have introduced some treatment bias into our study.

In conclusion, management strategies for gastric carcinoids span endoscopic surveillance, medical management, endoscopic resection, surgical wedge resection and formal gastrectomy. In agreement with the current body of literature, our findings confirm the paramount importance of identifying gastric carcinoid subtype prior to adopting a management strategy. Further studies will help to determine which patients will benefit from more aggressive surgical strategies.

Conflicts of interest

The authors have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2018.12.057.

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