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Surgical Intervention in Gastric Carcinoid is Associated with Improved Survival in Local and Regional Disease

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Abstract

Introduction—Gastric carcinoid is a rare entity with complex management options. This study aims to determine if surgical intervention in patients with local, regional and metastatic gastric carcinoid is associated with prolonged survival.

Materials/Methods—The California Cancer Registry (CCR) merged with the California Office of Statewide Health Planning and Development (OSHPD) was queried for patients with a diagnosis of gastric carcinoid (2000–2011). Clinicopathologic characteristics, management and outcomes were evaluated.

Results—There were 1,012 patients with a diagnosis of gastric carcinoid identified. The median age was 63 (range 18–9) and the majority of patients were women (615, 60.7%). Most patients had localized disease (644, 64%), while 9.4% (95) had regional and 13.4% (133) had distant metastases at diagnosis. The majority of patients underwent gastric surgery (56.7%, n=574 vs 43.2%, n=438). Prolonged survival was associated with gastric surgery in patients with both local (median survival not reached; p<0.0001) and regional disease (27 months with surgery vs 5 months with no surgery; p=0.0007). In patients who underwent gastrectomy and resection of hepatic metastasis, the survival approached those patients who had surgery for only regional disease (26 vs 27 mos, p=0.8721).

Conclusions—Although the biology of the disease is the most significant predictor of overall outcome, when technically feasible and where comorbidities allow, aggressive endoscopic or surgical intervention should be offered for local and loco-regional disease respectively.

Keywords

Gastric carcinoid; gastric neuroendocrine tumor

INTRODUCTION

The overall incidence of carcinoid tumors is approximately 38 per one million individuals.¹ Gastric carcinoid is a rare entity, representing less than 2% of all gastric malignancies, and only 8.7% of all gastrointestinal carcinoids.² As the use of endoscopy for surveillance and

evaluation of dyspepsia has increased, more gastric carcinoids have been discovered incidentally.³ An autopsy series previously revealed that 85% of gastric carcinoids remained undiagnosed until post-mortem analysis.³ The finding that these tumors could remain undiagnosed throughout a patient's life illustrates the scope of the clinical spectrum of gastric carcinoid, and the variability that exists in its management.

Gastric carcinoid is classified into 4 main subtypes. Type I is the most common subtype (70–80%) and is associated with atrophic gastritis, enterochromaffin-like cell (ECL) hyperplasia and hypergastrinemia.⁴ Type I usually manifests as multiple small tumors in the body and fundus of the stomach in female patients. They are often clinically asymptomatic and found at endoscopy for dyspepsia or abdominal pain.⁵ This type is associated with the best prognosis of the 4 types. In patients with multifocal, invasive or recurrent disease⁶, the management of type I gastric carcinoid often includes antrectomy which can then cause regression of ECL hyperplasia and help to prevent tumor recurrence.⁷ Depending on the size and depth of invasion of the primary tumor, this subtype can either be managed with endoscopic resection or gastric resection.

Type II gastric carcinoid is associated with multiple endocrine neoplasia type 1, and Zollinger-Ellison Syndrome. It is significantly less common than type I, presenting in less than 10% of patients with gastric carcinoid.⁸ Patients usually have multiple small tumors with intermediate malignant potential in the gastric body, fundus and antrum. This type is associated with high gastric acid production. Surgical intervention for type II gastric carcinoid usually involves limited tumor resection, similar to type I, and can often be done endoscopically. Both Type I and Type II carcinoid are associated with immunohistochemistry that is positive for Chormogranin A and a low proliferation index (Ki67<2%).⁹

Type III gastric carcinoid is more commonly seen in men. This type is sporadic and more commonly metastasizes, most often to the liver.^{6,10,11} Of the 3 types of gastric carcinoid, this subtype behaves most like gastric adenocarcinoma, with the highest propensity for lymph node metastasis. These are usually single, larger tumors (2–5 cm) with normal gastrin and gastric acid production. The proliferative index is usually >2% and these tumors are primarily chormogranin negative. Tumor related mortality is seen in 25–30% with well-differentiated tumors and in 75–87% of patient with poorly differentiated tumors.⁹ Given the high propensity for metastasis, with the worst overall prognosis and larger tumor size, this subtype often is treated with more aggressive resection, potentially including concomitant resection of hepatic disease.^{6,10–12} Type IV gastric carcinoid represents those tumors not encompassed within the other 3 categories.

Gastric carcinoid is often an indolent disease, although over 44% of patients will ultimately develop liver metastasis within their lifetime.^{10,13} The AJCC staging of gastric carcinoid⁸ classifies N0 disease as the absence of lymph nodes, and N1 disease as the presence of lymph nodes. Because of the indolent disease, and the likelihood of developing liver metastases which can progress to liver failure and ultimately patient demise, cytoreductive surgery is often advocated in addition to resection of the primary tumor.^{10–13} In this retrospective analysis of the California Cancer Registry, outcomes associated with surgical

intervention on local, regional, and metastatic (to the liver) gastric carcinoids are evaluated. We hypothesize that surgical intervention is associated with improved overall survival in patients with gastric carcinoid.

METHODS

Data Source

The California Cancer Registry (CCR) is maintained by the California Department of Public Health, within the branch of Chronic Disease Surveillance and Research. This database provides statewide cancer specific information regarding demographics, tumor characteristics, histology, cancer treatment and vital status of all patients diagnosed with cancer in the state of California (California Cancer Registry, ccrca.org). The California Office of Statewide Health Planning and Development (OSHPD) manages data regarding the state of California's healthcare outcomes and inpatient hospitalizations (<http://www.oshpd.ca.gov/AboutUs.html>). The CCR and OSHPD data sets can be merged to provide more specific information regarding inpatient and outpatient care provided to cancer patients in the state of California.

Cohort Selection

The CCR was queried for all neuroendocrine tumors corresponding to ICD-O-3 codes 8240–8247 and 8249 (carcinoid tumor) between 2000–2011. Initially all carcinoids were compiled, and the anatomic distribution was examined. Next, from that group all but those within the stomach (ICD-O-3 site code C160–C169) were eliminated. We also excluded all patients under the age of 18, all without a histologically confirmed diagnosis, all who died within 30 days of diagnosis or who were diagnosed by autopsy, and finally all patients without matching OSHPD records. This yielded a final cohort of 1,012 patients with histologically proven gastric carcinoid represented both in CCR and OSHPD.

Data Analysis

The cohort of 1,012 patients with gastric carcinoid was evaluated for demographic characteristics, number and type of tumors, incidence of lymphadenopathy, and incidence of hepatic metastasis. In order to simplify our analysis, we grouped patients with gastric carcinoid into 3 groups: local, regional (positive lymph node metastasis) and distant metastatic disease. Because cytoreductive surgery seems to achieve the best results in patients with liver metastasis without extrahepatic disease¹⁰, we focused our attention on those patients with hepatic metastasis as their only site of distant disease. The data was queried as to whether patients had undergone surgery on the primary tumor and/or resection of liver metastasis. We then focused on survival outcomes among the 3 groups of local, regional and (hepatic) metastatic disease, stratifying by surgical treatment on primary disease and/or liver metastasis. Kaplan-Meier curves were used to analyze survival rates. All analyses were performed using the Stata 13 statistical software (StataCorp, College Station, TX).

RESULTS

Anatomic Distribution of Gastrointestinal Carcinoids

The distribution of gastrointestinal carcinoids is listed in Table 1. Within the CCR, the greatest number of gastrointestinal carcinoids were seen within the colon and rectum (n=5,504, 34.3%) followed by the small intestine (19.1%, N=3,056). The third most common gastrointestinal carcinoids were pancreatic (7.4%, N=1,012). and gastric (7.4%, N=1,012). In the CCR during this time period there were 3,141 (19.6%) carcinoids that were identified as unknown and 1,618 (10.1%) that were of unknown primary. However, these are of all of the carcinoids in the CCR therefore they may include carcinoids derived from sites out of the gastrointestinal system (Table 1). If these categories were excluded, then gastric carcinoids would comprise 8.9% of all known gastrointestinal carcinoids (N=11,268).

Demographic Results

Demographic data for this cohort of patients are listed in Table 2. Our cohort included 1,012 patients diagnosed with gastric carcinoid in the CCR database between 2000–2011. The average age at diagnosis was 63 (range 18–99). There were more female (615, 60.7%) than male patients which is consistent with previously published reports highlighting the female predominance of this disease.¹⁴ The majority of patients were Caucasian (464, 45.9%) or Hispanic (331, 32.8%). Most of the patients either had private insurance or HMO (436, 43.1%) or Medicare (385, 38%). Overall the patients were healthy, with 60% (n=609) of patients reporting no comorbidities, and 29.1% (n=294) reporting one comorbidity. (Table 2)

Disease Characteristics

Although nearly half of gastric carcinoids registered within the CCR were of unknown size (n=477, 47.1%), 32.8% (332) were less than 2 cm, 5.5% (56) were between 2 and 3 cm, 6.8% (69) were between 3 and 5 cm and 7.8% (78) were greater than 5 cm (Table 3). The majority of tumors of known size were less than 2 cm, which is consistent with type 1 or 2 carcinoids, as they are often small.

In terms of surgical intervention, 56.7% (574) patients underwent surgery at the primary site. The type of surgery included local excision/endoscopic resection (257, 25.4%), gastric wedge resection (23, 2.3%), partial gastrectomy (205, 20.3%), total gastrectomy (48, 4.7%), gastrectomy with other organ resection (37, 3.7%), and other surgery (4, 0.4%). Sixty-three percent (n=644) of disease was characterized as local, 9.4% (n=95) as regional, and 13.1% (n=133) as remote. In our cohort, the vast majority had N0 disease (88.9%, n=900). Only 3.4% (n=34) had liver metastasis. Only five of the 34 patients (14.7%) had liver resection for liver metastasis. (Table 3)

Survival Outcomes

In patients with localized disease only, surgery is associated with improved survival after adjusting for age and comorbidities (HR=0.48, 95% CI 0.37–0.62, $p<0.001$), (Figure 1A, 5 year survival for surgery and no surgery was 99.6% and 96.4% respectively, $p<0.001$). In patients with regional disease only, there was also longer survival associated with surgery (Figure 1B, 5 year survival 89.1% and 40.8%, $p<0.001$). After adjusting for age and

comorbidities the hazard ratio was 0.28 (95% CI 0.16-0.5, $p<0.001$). There were no differences in survival in patients who underwent surgery with liver metastases, however, there were too few patients in this subset to yield any meaningful conclusions.

Differences in Presentation and Management in Patients with Local and Locoregional Disease

In order to assess if there were differences at presentation or management between the node negative and node positive patients some clinicopathologic variables were reviewed (Table 4). Patients were significantly younger in the surgery group (60.4 vs 66.2 yrs; $p<0.0001$) in the localized disease group, indicating perhaps there was a bias to offer surgery to those that would otherwise require prolonged surveillance based on their age. Additionally, in patients with node negative disease, a majority with private or HMO insurance were managed with surgery ($p<0.001$). In contrast, in patients with node positive regional disease, neither age nor insurance status were different in the surgery or no surgery groups.

DISCUSSION

Our results reveal, in a cohort of 1,012 patients with gastric carcinoid, an associated survival advantage for patients who have surgical intervention for both local and regional disease. The findings of this study imply that surgical intervention has associated survival implications in what is often otherwise deemed an indolent disease.

The incidence of gastric carcinoid has increased over time, likely as a result of increased diagnosis with endoscopy.¹⁵ Additionally, there is some long-term data following patients after endoscopic resection for Type 1 gastric carcinoids. Uyguyn et al reviewed 22 patients from 1999–2012 with Type I gastric carcinoid who were initially diagnosed with hypergastrinemia, atrophic gastritis and intestinal metaplasia.¹⁶ The polyps were >1 cm in 4 patients and between 0.5 cm and 1 cm in 18 patients. All lesions were successfully resected. Recurrence was detected in 4 (18%) patients and endoscopic resection was performed again. Local or distant metastases were not observed in any patient with a median follow up of 7 years. This indicates that although recurrence is an issue in up to 20% of patients, as previously described regional and metastatic disease is rare.¹⁶

Additionally, in a more recent long term follow up of a multi-institution larger series of patients with type 1 gastric carcinoid the above results were corroborated. Thomas et al reviewed the presentation, management and outcomes of 101 patients with Type 1 gastric carcinoid.¹⁷ Most patients initially had indications for endoscopy secondary to upper gastrointestinal tract symptoms or assessment of long-standing anemia. The most common medical comorbidities in this population were B12 deficiency anemia (42%), and Hashimoto's thyroiditis (37%). Pre-treatment gastrin levels but not chromogranin A levels correlated with maximum tumor diameter at endoscopy. Octreotide scan was only positive in 6/60 patients and computed tomography was only positive in 9/111 patients. In this series 20/111 patients had surgical interventions. Long term outcomes of this series were comparable to those previously reported where with a mean follow up of 76 months there were no carcinoid related mortalities reported.¹⁶ Due to the indolent nature of this disease, Gladdy et al sought to define surgical indications for Type I gastric carcinoid.¹⁸ In their

series 65 patients identified between 1985–2007 with a mean follow up of 30 months, the disease specific survival was 100% whether they had surgery or not. However adenocarcinoma was identified in 4/19 resected cases. Their recommendations are to consider surgical resection with more advanced carcinoid disease given its associated with an increased risk of adenocarcinoma.¹⁸

In 2009, Landry et al identified 1, 543 in the Surveillance Epidemiology and End Results (SEER) database between 1973–2004 with the aim of identifying clinicopathologic factors that affect survival for patients diagnosed with gastric carcinoid.¹⁹ On multivariate analysis age, depth of invasion, and size of the primary tumor were all associated with survival. Interestingly, in patients that were Stage I or II (node negative) the 5 year survival was 82 and 63% respectively. The authors did not correct for comorbidities or take into account surgical resection. In patients with regional disease (node positive), the 5-year survival was only 21%. Our study demonstrated that with regional disease only and after correcting for age and comorbidities survival can be as high as 89.1% with and 40.8% without surgery. The authors indicate that these were the survival data for patients with only 1 tumor so perhaps this population was enriched with more Type III gastric carcinoid patients. However, they do state that the survival analysis of the entire cohort (including patients with multifocal tumors in the stomach and therefore more likely Type 1 gastric carcinoid) yielded similar results.¹⁹

Patients that are not with Type I gastric carcinoid may have more advanced disease at the time of diagnosis, with hepatic metastasis as the most common distant site. Surgical resection provides the best chance at cure of the disease, and previous studies have demonstrated a survival advantage to aggressive debulking of metastatic disease¹⁰. Hellman et al.²⁰ previously demonstrated a more prolonged survival in association with resection of the primary tumor in patients with midgut carcinoid tumor who presented with both regional disease and liver metastasis (7.4 vs 4 years, $p < 0.01$). Similarly, Givi et al. revealed that resection of the primary neoplasm was associated with improved progression-free survival and overall survival in patients with abdominal carcinoid neoplasms.¹² We have demonstrated in this study that these results remained consistent when examining only gastric carcinoids. The limitation of our study is that the type of gastric carcinoid is not specified in the California Cancer Registry and this remains the limitation of any large database study with this disease. However, in compiling all gastric carcinoids and adjusting for both age and comorbidities, it appears that removal of the gastric carcinoid is associated with significant benefits. both in local and regional disease.

Historically, surgical decision making in gastric carcinoids has been largely based on subtype. Type I carcinoids are often treated with resection of the primary tumor (local excision) with consideration for concomitant antrectomy in patients with hypergastrinemia or recurrence. Our study revealed that local excision was the most common surgical intervention performed with a diagnosis of gastric carcinoid (25.4%). This likely reflects the incidence of type I carcinoids, which are the most common subtype. The second most common gastric surgery was partial gastrectomy, which may be representative of antrectomy such as for type I carcinoids, or resection of primary tumor for types II or III.

Even in the context of a large population series, the incidence of hepatic metastases was low and those subsequently subjected to resection were also few. Therefore, conclusions based on these numbers are limited in scope and applicability. However, the authors do believe that as in other neuroendocrine tumors of the GI tract, when feasible and safe, liver directed therapy including surgical debulking is reasonable. A previous multi-institutional study examined hepatic resection as compared to ablation and ablation with resection in patients with hepatic neuroendocrine tumor metastasis.¹⁰ Although this study included all neuroendocrine subtypes, carcinoids were the most common at 53%. Liver-directed therapy demonstrated a correlation to prolonged survival regardless of whether patients underwent resection or ablation, however the patients did have a high rate of recurrence.

Limitations

A significant limitation of our study is inherent in the reliance on retrospectively analyzed data in the CCR and OSHPD. There is therefore a significant omitted variable bias. We have attempted to control for patient age and comorbidities as influential factors as that may contribute to the decision to offer surgery for local and locoregional disease. This data is a reflection of practitioner judgment in combination with assessment of outcomes and this is an inherent limitation of all retrospective studies. Our data is strengthened, however, by the inclusion of both the CCR and OSHPD as data sources, as it allowed analysis of all inpatient hospital records, especially given the relative rarity of gastric carcinoids. We also recognize an inherent limitation in our study in that we were unable to fully characterize each of the gastric carcinoids by type. We used size data when available and the presence of lymph node or liver metastasis to approximate which type of gastric carcinoids was represented, but are aware that given that carcinoids are approached differently based on the subtype, our results are difficult to translate into clinical practice. Similarly, it was difficult to characterize multifocality of the tumors as a surrogate for type of carcinoid, given that this data was only available in the CCR after 2006. Lastly, there is the limitation in not knowing what additional liver directed therapies patients with liver metastasis may have had. In our study of 1,012 gastric carcinoids and the association of surgical intervention with outcome, we demonstrate a significant survival advantage associated with surgical intervention in patients with local and locoregional disease after correction for age and comorbidities.

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Figure 1.**Figure 1A.** Kaplan-Meier Survival Estimate for Surgery in Local Disease**Figure 1B.** Kaplan-Meier Survival Estimate for Surgery in Regional Disease

TABLE 1

Anatomic Distribution of Gastrointestinal Carcinoids Captured in CCR

Anatomic Site	N (%) (N=16,027)
Esophageal	58 (0.3%)
Gastric	1,194 (7.4%)
Small Intestine	3,056 (19.1%)
Colorectal	5,504 (34.3%)
Liver	117 (0.7%)
Gallbladder	66 (0.4%)
Other Biliary	79 (0.5%)
Pancreas	1,194 (7.4%)
Other	3,141 (19.6%)
Unknown Primary	1,618 (10.1%)

TABLE 2

Patient Demographics and Clinical Characteristics (N=1,012)

Characteristic	N (%)
Age at diagnosis	63 years (range 18–99)
Sex	
Male	397 (39.3%)
Female	615 (60.7%)
Race	
Caucasian	464 (45.8%)
Hispanic	331 (32.7%)
African-American	87 (8.6%)
Asian/Pacific Islander	76 (7.5%)
Other	54 (5.3%)
Insurance Status	
Private/HMO	436 (43.1%)
Medicare	385 (38.0%)
Medicaid/Indigent	170 (16.8%)
Unknown	12 (1.19%)
VA/Federal	9 (0.9%)
Comorbidities	
None	609 (60.2%)
1	294 (29.1%)
2+	109 (10.8%)

TABLE 3

Disease Characteristics (N=1,012)

Disease Characteristic	N (%)
Tumor Size	
2 cm	332 (32.8%)
2–3 cm	56 (5.5%)
3–5 cm	69 (6.8%)
5 cm	78 (7.7%)
Unknown	477 (47.1%)
Multifocal disease	N=501 *only available after 2006
No	416 (83%)
Not ascertained	46 (9.1%)
Yes	39 (7.7%)
Surgery at Primary Site	
No	438 (43.3%)
Yes	574 (56.7%)
Type of Surgery Received	
None	438 (43.3%)
Local excision/endoscopic resection	257 (25.4%)
Gastric wedge resection	23 (2.3%)
Gastrectomy+other organ resection	37 (3.7%)
Partial gastrectomy	205 (20.3%)
Total gastrectomy	48 (4.7%)
Other	4 (0.4%)
Extent of disease	
Localized	644 (64%)
Regional	95 (9.4%)
Metastatic	133 (13.4%)
Unknown	140 (13.8%)
Positive Lymph Nodes	
No	900 (88.9%)
Yes	112 (11.1%)
Liver Metastasis Present	
No	978 (96.6%)
Yes	34 (3.4%)
Liver Resection for Metastatic Disease	
No	N=34
No	29 (85.3%)
Yes	5 (14.7%)

TABLE 4

Clinicopathologic and Treatment Characteristics in Patients with Local and Locoregional Disease

Node Status	Variable	Surgery	No Surgery	P value
Node Negative LOCALISED DISEASE	Age, mean (sd)	60.4 (14.2)	66.2 (14.2)	<0.0001
	Gender			0.507
	Male	189 (60.8%)	122 (39.2%)	
	Female	328 (58.5%)	233 (41.5%)	
	Race			0.821
	White	246 (61.2%)	156 (38.8%)	
	Black	40 (54.8%)	33 (45.2%)	
	Hispanic	169 (58.5%)	120 (41.5%)	
	Asian/Pac. Isl.	34 (58.6%)	24 (41.4%)	
	Other	28 (56.0%)	22 (44.0%)	
	Comorbidity			0.296
	0	311 (60.9%)	200 (39.1%)	
	1	145 (55.3%)	117 (44.7%)	
	2	61 (61.6%)	38 (38.4%)	
Node Positive LOCOREGIONAL DISEASE	Insurance			0.001
	Private	187 (66.3%)	95 (33.7%)	
	HMO	90 (66.7%)	45 (33.3%)	
	Medicare	163 (51.4%)	154 (48.6%)	
	Medicaid	57 (56.4%)	44 (43.6%)	
	Other	20 (54.0%)	17 (46.0%)	
	Tumor Size (cm)			<0.0001
	< 1 cm	161 (73.5%)	58 (26.5%)	
	1 to < 2 cm	75 (80.6%)	18 (19.4%)	
	2 to <3 cm	34 (77.3%)	10 (22.7%)	
	3 to < 5 cm	22 (59.5%)	15 (40.5%)	
	5 cm	19 (55.9%)	15 (44.1%)	
	Unknown	206 (46.3%)	239 (53.7%)	
	Age, mean (sd)	63.7 (14.2)	60.6 (20.4)	0.4684
	Gender			0.084
	Male	47 (78.3%)	13 (21.7%)	
	Female	25 (62.5%)	15 (37.5%)	
	Race			0.642
	White	32 (74.4%)	11 (25.6%)	
	Black	6 (66.7%)	3 (33.3%)	
	Hispanic	21(67.7%)	10 (32.3%)	

Node Status	Variable	Surgery	No Surgery	P value
	Asian/Pac. Isl.	11(84.6%)	2(15.4%)	
	Other	2(50.0%)	2 (50.0%)	
	Comorbidity			0.348
	0	43 (67.2%)	21 (32.8%)	
	1	19 (79.2%)	5 (20.8%)	
	2	10 (83.3%)	2 (16.7%)	
	Insurance			0.861
	Private	28 (75.7%)	9(24.3%)	
	HMO	11 (64.7%)	6 (35.3%)	
	Medicare	23 (74.2%)	8 (25.8%)	
	Medicaid	9 (69.2%)	4 (30.8%)	
	Other	1 (50.0%)	1 (50.0%)	
	Tumor Size (cm)			<0.0001
	< 1 cm	7 (87.5%)	1 (12.5%)	
	1 to < 2 cm	9 (90.0%)	1 (10.0%)	
	2 to <3 cm	7 (77.8%)	2 (22.2%)	
	3 to < 5 cm	20(90.9%)	2 (90.1%)	
	5 cm	22 (73.3%)	8 (26.7%)	
	Unknown	7 (33.3%)	28 (66.7%)	