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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Defining Surgical Indications for Type I Gastric Carcinoid Tumor

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ABSTRACT

Background. Most gastric carcinoid tumors (GC) (type I) occur in association with achlorhydria, hypergastrinemia, atrophic gastritis and exhibit low-grade histopathology. The management of this indolent disease is controversial. The aim of this study was to evaluate endoscopic surveillance (ES) compare with surgical resection (SR) for type I GC.

Methods. Between 1985 and 2007, 65 patients with type I GC were identified. Data analysis included: demographics, biochemical and endoscopic assessment, type of operation performed, and pathologic evaluation. The primary endpoints were disease-specific survival (DSS) in both groups and recurrence-free survival (RFS) in SR patients.

Results. Median follow-up was 30 months (range 1–176 months); most patients were female (83%) with median age of 58 years (range 29–91 years). Type I GC was diagnosed by evidence of hypergastrinemia and/or positive autoimmune antibodies with histopathologic confirmation. Patients underwent ES with polypectomy ($n = 46$) or gastric resection ($n = 19$). SR was performed with larger tumor size, increased depth of invasion, and solitary tumors. Although the 5-year RFS in SR patients was 75%, the DSS in both groups was 100%. However, concomitant adenocarcinoma was identified in 4/19 resected cases; 2/4 were detected on preoperative biopsies. All cases with coexisting gastric adenocarcinoma had larger carcinoid tumors and more advanced carcinoid disease.

Conclusions. The DSS is excellent for type I GC patients treated with either ES or SR. SR should be considered with more advanced carcinoid disease given its association with an increased risk of adenocarcinoma. ES is appropriate to assess both the status of carcinoid disease and dysplasia or adenocarcinoma that can develop in association with type I GC.

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Gastric carcinoids (GC) are rare tumors, but with increasing incidence in the last few decades.[1] There are three subtypes of GC (types I–III), which arise from distinct pathophysiology, resulting in diverse clinical outcomes, and should be managed differently.[2–4] The most common form of gastric carcinoid is type I (70–80%), which is associated with autoimmune-related pernicious anemia, atrophic gastritis, and parietal cell loss. Absence of parietal cells causes loss of hydrochloric acid production, which is a negative regulator of antral G-cell gastrin production, resulting in hypergastrinemia. Elevated serum gastrin stimulates enterochromaffin-like cell (ECL) proliferation, which is thought to be the precursor lesion of type I GC.[5,6] In type II GC, (5–10%), patients have hypergastrinemia, however this does not result from parietal cell loss, as this disease is due to gastrin secreting G cell neoplasia in association with Zollinger–Ellison syndrome and/or multiple endocrine neoplasia type I (MEN1). Type III accounts for 15–20% of GC, and is a sporadic disease associated with normal gastrin levels; it has the highest rate of metastasis (>50%) and thus the worst prognosis.

Although the outcome in type I GC is favorable (<5% metastatic rate), historically many type I GC patients have been treated with surgical resection consisting of either partial or total gastrectomy.[7] Recently, there has been a trend toward annual endoscopic surveillance with biopsy and/or endoscopic resection of small carcinoid tumors, and the availability of novel pharmacological agents that inhibit ECL cell proliferation and gastrin secretion of antral G cells may provide additional noninvasive modalities in the management of the disease.[3,8–13] Clinical evaluation of

management strategies by endoscopic surveillance and surgery in type I GC has been rarely reported. Our aim was to compare the clinicopathologic features and outcomes in type I GC patients managed by endoscopic surveillance ± endoscopic resection versus surgical resection. Primary study endpoints were disease-specific survival in both groups and carcinoid recurrence-free survival following gastric resection.

METHODS

Between July 1, 1985 and December 31, 2007, patients with type I gastric carcinoid were identified from a prospectively maintained institutional database. Type I GC was diagnosed by biochemical means, including an elevated serum gastrin level (in the absence of acid blockade), anti-parietal or anti-intrinsic factor antibodies and pathological absence of parietal cells, and presence of atrophic gastritis and neuroendocrine cell hyperplasia/neoplasia with confirmation of immunoreactivity to chromogranin A.

Patient management included the following: Routine endoscopic surveillance was performed annually with biopsies and pathologic review. Carcinoid lesions were removed by endoscopic resection if feasible. Patients were considered for surgical resection if there was: (a) evolution (increasing size) of persistent or dominant carcinoid lesion(s), (b) inability to undergo annual endoscopic surveillance or (c) features concerning for gastric adenocarcinoma, including high-grade glandular dysplasia on pathologic review. In contrast to other centers, multicentric disease was not routinely incorporated into surgical decision-making.[7,9,14] Subtotal or total gastrectomy with lymphadenectomy was performed in selected patients with adverse features. Surgical resection for type I GC ranged from limited gastric resection of carcinoid lesions and antrectomy with removal of concerning carcinoid tumors (Table 2) to total or subtotal gastrectomy.

Data analysis included: patient demographics, serum gastrin levels, endoscopic and pathologic evaluation, type of operation performed, and patterns of recurrence. The primary endpoints were disease-specific survival (DSS) in both groups and recurrence-free survival (RFS) in those surgically resected. DSS and RFS were calculated using the Kaplan–Meier method.

RESULTS

Patient Demographics and Treatment

Over the 22-year study period, 65 patients with type I GC were identified. The majority of patients ($n = 46$, 71%) were treated with endoscopic surveillance ± endoscopic polypectomy (ES), and 19 patients were treated with surgical resection (SR). The median age at presentation was 58 years (range 29–91 years) for all patients, which did not vary between treatment groups (Table 1, $P = 0.26$). There was a higher proportion of females in both groups (Table 1; polypectomy: 85%, resection: 79%; $P = 0.76$). The median (range) follow-up was 25 (1–157) months in the ES group, which was statistically significantly different compared with the surgical resection group, in which it was 60 (1–173) months (Table 1, $P = 0.02$). Hypergastrinemia was documented in 40/42 (95%) patients tested, and anti-parietal cell or anti-intrinsic factor antibodies confirmed the diagnosis of type I GC in 12/14 (86%) patients examined. A background of atrophic gastritis was evident in all gastric biopsy specimens.

TABLE 1 Type I gastric carcinoid clinicopathologic features by treatment group

	ES ($n = 46$)	SR ($n = 19$)	*P*-value
Age, years, median (range)	59 (44–91)	58 (29–72)	0.26
Female (%)	85	79	0.76
Follow-up, months, median (range)	25 (1–157)	60 (1–176)	0.02
Size, median (cm)	0.5 ± 0.1	1.3 ± 0.3	0.01
Invasion beyond submucosa	0/46	3/19	0.02
Solitary lesions (%)	9	42	<0.001

ES endoscopic surveillance ± endoscopic resection, *SR* surgical resection, see Table 2

Pathologic Features of Type I GC by Treatment Group

Patients with surgical resection had a shorter duration of endoscopic surveillance prior to operation compared with the endoscopic surveillance group (surgical resection group median preoperative polypectomy duration: 2 months, range 0–26 months versus polypectomy group: 25 months, range 1–157 months; $P < 0.0001$). The median number of surveillance endoscopies with biopsy in the non-surgically resected group was 3.0 (range 1–9), with a median of 2.0 (range 0–6) carcinoid positive biopsies on pathologic review per patient.

Compared with other studies, the identification of multiple tumors was not itself an indication for resection, as 91% patients with endoscopic surveillance had >2 documented tumors.[7,9,14] However, those patients with larger dominant lesions that persisted or were not amenable to endoscopic resection underwent surgery (Table 1). Specifically, patients with surgical resection had larger lesions (Table 1; resection: median 1.3 ± 0.3 cm, polypectomy: 0.5 ± 0.1 cm; *P*-value 0.01), with 37% in the surgical group having lesions that were >1.0 cm compared with 4%

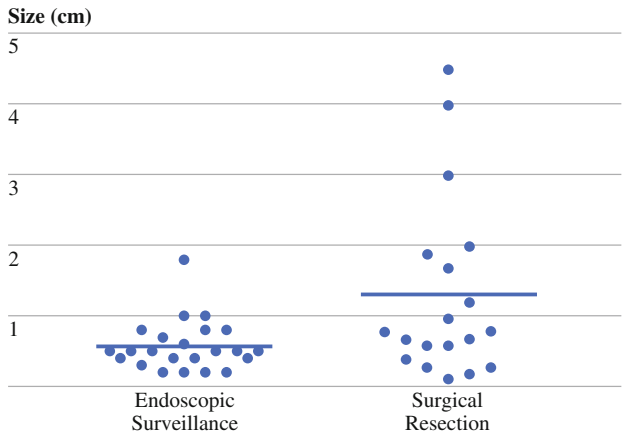

FIG. 1 Scattered plot of tumor size (mean at horizontal bar) in ES and SR of type I gastric carcinoid tumor

of polypectomy patients (Fig. 1). Deeper lesions were also evident in the surgical group as invasion beyond submucosa was seen in 3/19 patients versus in 0/46 surveillance patients (Table 1, $P = 0.01$). Although routine use of endoscopic ultrasound was not performed early in this study, which may have underestimated the depth of unresected carcinoids, a recent report from our institution demonstrated that endoscopic ultrasound only has a 57% concordance rate when used as a preoperative staging tool to assess tumor stage compared with final pathology.[15]

Management of Type I GC

During the study period, 21% of type I GC patients were surgically resected from 2000 to 2007, compared with 41% in 1993 to 1999 and 43% from 1985 to 1992. The type of surgery performed included: partial gastric resection to remove solitary or dominant larger carcinoid tumor(s) ($n = 7$), antrectomy to resect gastrin-producing G-cells ($n = 6$), and subtotal or near-total gastrectomy ($n = 6$) primarily due to concerns on preoperative biopsy of advanced carcinoid disease and/or gastric adenocarcinoma (Table 2). No major operative complications were identified. Three patients required further operative intervention for persistent carcinoid disease ($n = 2$) or recurrence of adenocarcinoma ($n = 1$). A fourth patient underwent endoscopic resection of residual carcinoid disease 4 years after antrectomy, despite a normal postoperative gastrin level. Overall, serum gastrin levels returned to the normal range in 3/3 antrectomy patients tested. One patient who underwent a gastric resection had persistent elevation of postoperative gastrin (initial solitary tumor of 1.9 cm with 1/12 lymph nodes positive for carcinoid disease), however no gross residual disease was found with additional surgery (Table 2). Another patient with persistent carcinoid disease after partial resection underwent subtotal gastrectomy as a postoperative stricture precluded adequate endoscopic surveillance and low-grade glandular dysplasia was also seen preoperatively. This patient had a T1N0 gastric adenocarcinoma with 1/12 nodes positive for carcinoid on final pathology (Table 3), underscoring the importance of continued endoscopic follow-up in these patients.

TABLE 3 Pathologic features associated with type I gastric carcinoid and concomitant adenocarcinoma in surgically resected patients

Adenocarcinoma on final pathology	No ($n = 15$)	Yes ($n = 4$)	*P*-value
Adenocarcinoma on preoperative biopsy	0	2	–
Median size of largest carcinoid tumor (cm)	1.0 ± 0.3	2.7 ± 0.9	0.02
Nodal involvement	0	1/4 adenocarcinoma 2/4 carcinoid	

Concurrent Adenocarcinoma and Carcinoid

Concomitant gastric adenocarcinoma was seen in 4/19 patients resected (Table 3). Preoperative biopsy was diagnostic in 2/4 patients, and a third biopsy showed epithelial dysplasia as discussed above. All patients with adenocarcinoma underwent a subtotal gastrectomy as their definitive surgical treatment. Lymph node involvement by carcinoid tumor occurred in two patients. One of these patients had preoperative biopsy with epithelial dysplasia alone as previously discussed and is disease free at 1 year. The second patient, who initially underwent a subtotal gastrectomy for a 4-cm carcinoid, had 1/12 lymph nodes positive for carcinoid, developed adenocarcinoma 4.3 years later in the gastric remnant, underwent completion gastrectomy (T4N3 disease), and has recurred. The patient with lymph nodes positive for adenocarcinoma (6/38) had a 1.2-cm carcinoid tumor and a preoperative diagnosis of adenocarcinoma, and

TABLE 2 Surgical treatment and recurrence in type I gastric carcinoid

Initial surgical procedure	No. of patients	No. of patients with recurrent disease (pathology)	Further intervention (pathology)
Partial resection (corpus)	7	2 (carcinoid)	STG (adenocarcinoma) ANT (no tumor)
Antrectomy (ANT)	6	1 (carcinoid)	ER (carcinoid)
STG/TG	6	1 (adenocarcinoma)	TG (adenocarcinoma)

STG subtotal gastrectomy, *ER* endoscopic resection, *TG* completion/total gastrectomy

is disease free at 5 years. The fourth patient with concomitant adenocarcinoma was not diagnosed preoperatively, underwent subtotal gastrectomy for a 1-cm carcinoid tumor, and had an incidentally found early gastric adenocarcinoma (T1N0) and is disease free at 8 years. We found a larger median size of carcinoid to be associated with concomitant adenocarcinoma (Table 3; 2.7 ± 0.9 cm versus 1.0 ± 0.3 cm; *P*-value 0.02).

Disease-Specific (DSS) and Carcinoid-Specific Recurrence-Free Survival (RFS) in Endoscopic Surveillance and in Surgical Resection of Type I GC patients

The 5-year disease-specific survival for both endoscopic and surgical management was 100% in our institution, which is consistent with previous reports (Table 4). The carcinoid-specific recurrence-free survival at 5 years was 75%.

DISCUSSION

The incidence of type I gastric carcinoid is increasing as it currently represents 2% of all gastric malignancies (previously 0.5%) and 9% of all gastrointestinal carcinoids.[16,17] In this study, we report the largest single-institution experience of type I GC ($n = 65$, Table 4), along with comparison with other significant series (>15 patients) to date.[3,7,9,14,18] As most patients have been treated with gastrectomy in the past, and although our retrospective study reflects changing practice patterns over a 22-year period, we sought to define *surgical guidelines* for this indolent disease, since the rarity of this disease precludes randomized assessment.

Natural History of Type I GC

Type I gastric carcinoid is frequently associated with autoimmune gastritis that predominates in females as seen in this study (Table 1). The initially published reports of type I GC are limited as they do not stratify patients by subtype or define how patients were managed.[3,19,20] More recent studies provide data on both subtype of gastric carcinoid and treatment.[7,9,14,18] It is essential that both detailed pathologic information about the resected carcinoid tumors and any follow-up data with recurrence are presented in order to be able to evaluate the efficacy of treatment strategies. It is clear however, that the disease-specific survival in type I GC is excellent and approaches ~100% (Table 4). The incidence of surgical intervention ranged from 29% (present study) to 56%, and most series had a minimum 5-year mean follow-up (Table 4).

The presence of lymph node metastasis with carcinoid disease was seen in 3/19 patients in our study, and 10/99 of patients surgically resected from our and other patient series combined (Table 4). Overall, there were no type I GC-specific deaths documented in patients with lymph node metastasis; however, at least one patient (current study) has recurrent disease. The incidence of lymph node metastasis is ~10% in the literature.[21] However, this is likely an underestimate as it is difficult to know what occult disease may have not been detected by limited gastric resections. Although Borsch et al. found that metastasis were the most important predictor of outcome by multivariate analysis [hazard ratio (HR) 22.42, 95% confidence interval (CI) 1.2–418.70, $P = 0.037$], the overall crude survival rate was not different from population controls as they observed a single carcinoid-related death due to liver metastasis.[7] Therefore, lymph node metastasis may signify

TABLE 4 Treatment and outcome in type I gastric carcinoid

Study (institution)	No. of type 1 GC patients	No. of patients treated with SR	Mean follow-up (months)	Incidence of carcinoid mets in SR patients	DSS
Present (MSKCC)	65	19	42	3/19	100%
Borch[a] (24 institutions)	51	22	95	4/22	98% (5-year OS, w/o mets) 75% (5-year OS, w/mets)
Dakin (Cornell)	18	10	NR	NR	NR
Jordan (Baylor)	18	10	72	3/10	100%
Schindl (Vienna)	16	7	70	0/7	100%
Rindi (four institutions)	152	NR	53	2/41	100%

SR surgical resection, *DSS* disease-specific survival, *OS* overall survival, *NR* not reported, *mets* metastatic disease in either lymph nodes or liver, *NR* not reported

[a] DSS not reported

progressive disease; however, nodal involvement has not been directly related to carcinoid-specific death.[22]

Management of Type I GC: Endoscopy Surveillance Versus Surgical Resection

Despite a better understating of type I gastric carcinoid pathobiology at the cellular and molecular level in in vitro and in vivo models, given the rarity of the disease the application of molecular diagnostic modalities has been limited to the research level.[23–25] Nevertheless, it is important to emphasize that prospective clinical validation of molecular markers will likely provide the necessary data to better stratify patient care based on specific prognostic and therapeutic biomarkers. Until then, the current indications for surgery in type I GC patients are size (suggested range: >1.0 cm to >2.0 cm), multiple lesions (suggested range: >3 to >5 lesions), recurrent disease, and/or evidence of serosa or locoregional (lymph node) involvement.[7,9,14,18,26] A recent study by Borch et al. found that neither size >1.0 cm, depth of tumor infiltration, nor multicentric disease correlated with outcome.[7] However, this is likely a reflection of the excellent prognosis in type I GC. Greater than 37% of patients undergoing gastric resection had a tumor >1.0 cm versus 4% in those managed with endoscopic surveillance, with median tumor size 0.5 ± 0.1 cm in the endoscopic surveillance versus 1.3 ± 0.3 cm in the surgical resection group (Table 1, $P = 0.01$, Fig. 1). Patients with coexisting adenocarcinoma also had much larger GC tumors (Table 3; adenocarcinoma: 2.7 ± 0.9 cm versus no adenocarcinoma: 1.0 ± 0.3 cm, $P = 0.02$). Before more definitive molecular diagnostic strategies have been fully developed, tumor size is useful in assessing the stage of the tumor and we agree with a threshold of >1.0 cm to consider patients for surgical resection among other factors discussed below.

Multiplicity of disease has traditionally been used as a factor in surgical decision-making.[7,9,14,26] However, since type I GC by definition is *multifocal* ECL hyperplasia/neoplasia, the number of lesions alone has not been used to guide our patient care as over 91% of patients undergoing endoscopic surveillance had >2 lesions present at time of endoscopy (Table 1). We surgically resected dominant (>1.0 cm) solitary lesions due to concerns of autonomous growth and coexistent adenocarcinoma (Table 1: 42% solitary lesions in surgical resection versus 9% in endoscopic surveillance, $P < 0.001$, and Table 3: presence of adenocarcinoma in 4/19 SR patients). Thus, we perform endoscopic surveillance of multifocal type I GC to document tumor progression/regression and, in conjunction with careful pathologic review of gastric mucosa for glandular dysplasia, use these features, along with size >1.0 cm, to guide when surgical resection may be appropriate and, if so, what the optimal extent of surgery should be.

The optimal surgical procedure had been debated in type I GC.[26] Earlier studies support the use of antrectomy as the initial and hopefully definitive surgical procedure in type I GC.[7,14,18,27] The rationale for antrectomy is the removal of most/all gastrin-producing G-cells, which should decrease the proliferative stimulus to ECL cells and thus mitigate type I GC formation.[28] To date the results of 41 antrectomies (our study, $n = 6$) have been reported for the treatment of type I GC, with most centers documenting postoperative normalization of serum gastrin.[7,9,18,29,30] Regression of GC occurred in over 85% of patients with a mean follow-up of 4–5 years, while salvage of recurrent GC by endoscopic resection was performed in one patient (current study), surgical resection in four patients, while in one patient the treatment plan not specified.[18] However, there are two main reasons why antrectomy may not be successful in type I GC. Firstly, if an inadequate antrectomy is performed which requires removal of the antrum, distal stomach, and duodenal cap, then postoperative hypergastrinemia may persist. Secondly, once the growth of ECL cells becomes autonomous and gastrin-independent growth or if another endocrine factor is the mitogen propagating ECL hyperplasia, than GC will persist/recur.[31] Since determining these factors preoperatively is difficult, deciding to perform a partial gastrectomy is a challenging clinical decision. In addition it is important to emphasize that an accurate pathological assessment of subtypes of gastric carcinoid tumor is crucial in disease management; while most type I carcinoid tumors can be managed by endoscopic surveillance, surgery still plays an important role in sporadic type III gastric carcinoid tumor and type I carcinoid tumor with the risk of developing adenocarcinoma.

Type I GC and Concomitant Adenocarcinoma

Type I GC is a well-differentiated endocrine tumor according to World Health Organization (WHO) classification.[32] In this study, we report a 21% incidence of concurrent adenocarcinoma in surgically resected, and 6% of all type I, gastric carcinoid (Table 3). In contrast, other larger series of type I GC have not reported coexisting gastric adenocarcinoma, which may be a result of study exclusion criteria not explicitly reported or due to a referral bias at our institution with more advanced disease in many patients. In this subgroup, all patients had a T1 adenocarcinoma, while three patients had lymph nodes positive for carcinoid (two) or adenocarcinoma (one) (Table 3). To date, three patients have no evidence of disease with a median follow-up of 6.3 years since initial diagnosis (range

1.3–11.3 years) and the fourth patient is alive with disease following resection of recurrent adenocarcinoma. In the limited case reports of concomitant adenocarcinoma and carcinoid of the stomach, a preoperative biopsy has been diagnostic for both tumors, which was either diagnostic or suspicious in 3/4 of our cases.[33,34]

It has been speculated that approximately 10% of all gastric carcinomas may arise from neuroendocrine carcinomas and there is a well-documented connection between atrophic gastritis of varying etiology and the development of epithelial dysplasia leading to adenocarcinoma from epidemiologic studies.[26,35,36] In situations of long-standing atrophic gastritis, hypergastrinemia and excessive cytokine and growth hormone release are inevitable, which are likely the mechanisms associated with the development of adenocarcinoma in type I gastric carcinoid.[25] However, it is unknown what duration of atrophic gastritis is associated with metaplasia/neoplastic transformation. Whether adenocarcinoma and carcinoid represent distinct or "collision" tumors or transformation of neuroendocrine cells to adenocarcinoma is of debate. Our study indicates that patients with advanced carcinoid disease, likely associated with long-standing gastric atrophy, are at risk for development of adenocarcinoma. However, due to the rarity of this condition, it is difficult to identify a universal parameter that is indicative of gastric adenocarcinoma. Thus, it is critical that clinicians managing type I GC patients continue surveillance for both the carcinoid disease and gastric mucosa dysplasia leading to potential development of adenocarcinoma.

SUMMARY: MANAGEMENT RECOMMENDATIONS

Ultimately, management of these rare tumors may be improved by defining molecular markers that can stratify patients that are at high risk of malignant transformation versus patients with indolent disease; however, since these biomarkers have not yet been validated, management of type I GC is still controversial. We propose that, once a diagnosis of type I GC has been established via documentation of hypergastrinemia, anti-parietal cell antibodies, along with pathologic evidence (atrophic gastritis and neuroendocrine hyperplasia/neoplasia), it is imperative that the clinician recognize any high-risk features seen on an endoscopic assessment and the detailed pathologic review that may herald advanced carcinoid disease or an associated gastric adenocarcinoma. If a preoperative biopsy is diagnostic for gastric adenocarcinoma, a formal oncologic gastric resection with lymphadenectomy is warranted. We recommend annual surveillance endoscopy in low-risk patients with biopsy and endoscopic resection of enlarging/suspicious carcinoid lesions as well as biopsies of adjacent atrophic gastric mucosa for the assessment of glandular dysplasia/neoplasia. If partial gastrectomy is performed for the removal of large or solitary lesions, patients require continued endoscopic surveillance to monitor for persistent/refractory carcinoid disease and/or the development of gastric adenocarcinoma, as further surgical intervention may be necessary. Therefore in our retrospective series, we identified patients who may be at higher risk for aggressive behavior of carcinoid disease or concomitant adenocarcinoma as those with enlarging or persistent solitary lesions, or with pathologic features which are suggestive of malignant glandular transformation, and would recommend considering surgical resection in this subgroup.

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