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Review: Screening, Diagnosis and Management of Gastric Carcinoid

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Introduction

Gastric Neuroendocrine Tumors (NETs), formerly known as Gastric Carcinoids (GCs), are neoplasms derived from enterochromaffin cells of the stomach. This heterogeneous group of tumors has been historically divided into three types, best distinguished by etiology. Type I gastric carcinoids, comprising 70-80% of gastric neuroendocrine tumors, are associated with autoimmune chronic atrophic gastritis. As a result of this condition, widespread parietal cell loss leads to chronic achlorhydria, causing G cell hypersecretion of gastrin. Type II gastric carcinoids, accounting for 5-8% of gastric are associated with gastrinomas and Zollinger-Ellison Syndrome. Neoplastic G cells secrete gastrin, again resulting in hypergastrinemia. In both Types I and II gastric carcinoids, exorbitant levels of gastrin lead to hyperplasia, dysplasia and ultimately neoplastic changes in the stomach [1,2]. Type III gastric carcinoids, constituting 15-25% of gastric NETs, are sporadic in nature, without associated increases in gastrin levels. The pathophysiology of Type III gastric carcinoids remains to be elucidated [3].

Historically, gastric NETs have been classified as benign processes, given the low mortality rate associated with this disease. Overall mortality rate for Type I GC is <1%, Type II GC <10% and Type III GC <30% [1]. However, frequently underappreciated is the presence of regional spread and distant metastases at time of diagnoses, occurring in up to 30% of cases [1]. In fact, the overall 5 year survival rate for gastric NETs, regardless of type, is at best about 67%, which argues against the relative indolence of these tumors [3,4]. Thus, we cannot neglect the possibility that these neoplasms are more aggressive than traditionally described.

Furthermore, recent studies conducted by National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry, show a steady, 10-fold increase in the incidence of gastric NETs over the last 40 years, which was paralleled by similar increases in Europe and Asia [3,5-8]. In fact, of the 13,715 carcinoids recorded in this registry, gastric carcinoids accounted for 47% of all carcinoids in the gastrointestinal tract, making the stomach the most common location for gastrointestinal carcinoids [9]. Results of this study were reproduced on a smaller scale in India, which also supported gastric carcinoids as the most common gastrointestinal NET [10]. This increase in prevalence of gastric NETs has been attributed to wider availability of endoscopy, enabling higher diagnostic capability, as well as widespread use of acid suppression medication, leading to secondary hypergastrinemia and ultimately, neoplasia [5].

Despite increasing prevalence of gastric NETs, endoscopy has enabled detection of tumors at much earlier stages of progression, resulting in a 20% increase in 5 year survival rate over the last 35 years [5,11]. To capitalize on this window for intervention, we must create a uniform screening and treatment protocol to provide patients with early diagnosis, and appropriate management. The purpose of this article is to discuss screening modalities and propose a uniform treatment algorithm.

Keywords: Gastric carcinoid; Neuroendocrine tumors; Treatment; Diagnosis

Screening and Diagnosis

To date, there are no established screening guidelines for carcinoid tumor. The majority of gastric NETs are discovered incidentally during surgery or diagnostic procedures [12]. Perhaps the greatest challenge in identifying patients who warrant screening for gastric carcinoid is its clinical silence.

In the minority of patients who present with symptoms suggestive of carcinoid syndrome, including bronchospasm, diarrhea, cutaneous flushing and right-sided valvular heart disease, it is not uncommon for these symptoms to be attributed to other, more probable causes. Thus, initiating screening tests for carcinoid tumor requires a high index of suspicion.

Biochemical assays

Traditionally, biochemical assays have been the test of choice for screening of carcinoid syndrome.

Plasma Chromogranin A (CgA): Chromogranin A, a neuroendocrine peptide precursor released by neuron secretory vesicles, has been widely accepted as a screening marker for neuroendocrine tumors [12-14]. Although use of plasma CgA as a diagnostic indicator has been supported by a high sensitivity, previous literature has criticized its use due to comparatively low specificity [15]. Of interest, several recent studies examining the diagnostic value of CgA have consistently reported sensitivities and specificities averaging 86% and 75%, respectively, opposing former data [14-17].

Despite these new findings, it is important to remain aware of non-neoplastic conditions that harbor elevated CgA levels, including renal failure, inflammatory bowel disease, chronic atrophic gastritis, and use of acid suppressing agents [18].

The latter two groups are of particular interest with respect to diagnosis of gastric carcinoids, as both atrophic gastritis and chronic use of acid suppressing agents lead to hypergastrinemia and hyperplasia of G cells, ultimately resulting in dysplasia and neoplastic changes. The ability to identify these "precursor" conditions by elevated levels of CgA may dampen the specificity for gastric carcinoid; however, may also bring attention to patients at high risk for future development of the disease.

5-Hydroxyindoleacetic Acid (5-HIAA): An alternate for biochemical screening of carcinoids is 5-HIAA, a renally excreted serotonin metabolite produced by functioning carcinoid tumors [12]. There are several challenges in evaluation of 5-HIAA levels, the most obvious of which is the requirement of a 24 hour urine collection. In addition, to obtain accurate results, patients must be counseled to avoid any PO intake that may alter the renal excretion of 5-HIAA.

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Even in the most compliant patients, measurement of 5-HIAA for evaluation of gastric carcinoid may be inaccurate, as foregut neoplasms lack the DOPA decarboxylase enzyme required for production of serotonin from its precursor. Without conversion to serotonin, levels of its urinary metabolite, 5-HIAA, will be falsely low [15].

Direct visualization

If screening tests are suggestive of carcinoid syndrome, examination of the GI system is of high importance, as ~ 68% of carcinoid tumors occur in the GI system [12].

Gastroscopy: Prudent evaluation begins with endoscopy and biopsy of gastric lesions [8,19]. Most neoplasms will present as single or multiple polyps measuring <2 cm, characteristically located in the gastric body and fundus.

While most polyps are visible to the eye, about one-fourth is intramucosal, and not readily identified on EGD [20]. Thus, a complete gastric map with biopsies of the antrum, body and fundus, followed by histological examination, should be done to confirm the presence of carcinoid tumor.

For cases in which pathology results are unclear, the tissue can be immunohistochemically stained for presence of CgA [21]. Gastric enterochromaffin cells may also be stained for neuron-specific enolase, synaptophysin, serotonin, somatostatin and gastrin [19].

Imaging

Once gastric carcinoid is confirmed by pathology, imaging can be used to locate the primary tumor, determine of the extent of disease, and guide management and treatment options [8,22].

Endoscopic Ultrasound (EUS): During the initial endoscopy, endoscopic ultrasound can be used to identify submucosal and intramucosal lesions otherwise not visible on endoscopy. In addition, EUS can provide information regarding the lesion size, layer of origin, margins and involvement of lymph nodes; thus, facilitating the process of tumor staging [1,21,23].

Although EUS provides insight to important neoplastic characteristics, accuracy of EUS alone to diagnose neoplasms remains low at about 30% [24]. Furthermore, accuracy declines as lesions move into deeper layers, compromising the correct diagnosis of aggressive, infiltrating tumors [25]. Therefore, use of EUS alone as a diagnostic tool is not indicated.

Somatostatin Receptor Scintigraphy (SRS): The first major advancement in the studies available for diagnosis of NETs was the introduction of Somatostatin Receptor Scintigraphy. This nuclear imaging study uses radiolabelled octreotide, a somatostatin analogue, to bind to the high volume of somatostatin receptors found on a majority of neuroendocrine tumor cells. Subsequent 2D imaging reveals areas with high densities of radiolabelled octreotide, localizing the presence of primary neuroendocrine tumors and metastases with 88% sensitivity and 65% specificity [21-23]. Furthermore, positive imaging results suggest that the patient is a candidate for treatment with somatostatin receptor analogues, and treatment response can be monitored with repeat SRS [21,26,27].

One caveat when using SRS is that its propensity for successful imaging depends upon adequate presence of somatostatin receptors, which fails to be the case in 20% of gastrointestinal NETs [21,23]. In addition, SRS is often negative in both early gastric carcinoids as well as advanced neoplasms that have de-differentiated [1,27]. In these cases, a high index of suspicion for gastrointestinal NETs would warrant other forms of imaging.

Somatostatin Receptor Single Photon Emission Computed Tomography (SPECT): The use of SRS as a tool for diagnostic imaging has largely transitioned to Single Photon Emission Computed Tomography. Similar to SRS, SPECT also employs the use of radiolabelled octreotide to detect neuroendocrine tumors; however, SPECT provides a 3D image, increasing sensitivity to about 90% for detection of carcinoid NETs [23,27,28]. Enhanced spatial resolution also enables identification of surrounding anatomical structures, better enabling localization of the tumors [28].

Somatostatin Receptor Positron Emission Tomography (PET): A recent trend in imaging makes use of positron emission tomography. In this imaging study, somatostatin analogues are labeled with positron-emitting radionuclides, which produce 3D images with significantly higher clarity than those obtained by SPECT.

One article, reviewing 22 studies with over 2100 subjects, found that the average sensitivity and specificity of PET for diagnosis of NETs was 93% and 96%, respectively [22].

Treatment

Although our understanding of gastric carcinoids has increased in recent years, treatment protocols for gastric carcinoids remain largely disputed [29]. Management of gastric carcinoid begins with an analysis of tumor behavior, size, and spread [21]. These categories are best represented by the 2010 WHO grade classification for gastric carcinoids, based on differentiation, and proliferative activity, determined by mitotic count and Ki-67 index [8,21].

Grade 1

Grade 1 carcinoids are comprised of well-differentiated, slowly proliferative neoplasms [11]. Typically, type I and II gastric carcinoids fall into this category. Both type I and II GCs tend to be small (<1.5-2.0 cm) and contained, with metastases occurring in less than 2% of cases [11,30]. In fact, several studies support normal life expectancy in age-corrected patients with type I GC managed by close surveillance [8,31]. The apparent benignity of these lesions has contributed to a controversial propensity for conservative management, a practice that largely lacks evidence-based support.

Grade 2

Grade 2 carcinoids encompass neoplasms with moderate differentiation [11]. Type III gastric carcinoids are characteristic of grade 2 neoplasms. These NETs are larger, with rates of metastases approaching 50% [8,32]. The aggressiveness of these tumors is demonstrated by the relatively low 5 year survival rate, ranging from less than 10-50% depending on extent of metastases [32-35]. Treatment typically involves surgical intervention.

Grade 3

The Grade 3 carcinoids include all poorly differentiated neoplasms [11]. The prognosis for this group is dismal, even with surgical intervention and/ or chemotherapy.

Conservative management

Conservative management in the form of endoscopic surveillance with, or without, resection is the widely exercised and favored treatment modality of type 1 GCs [8,29,36,37]. However, a comprehensive literature review shows scant supporting, evidence-based data that is lacking in statistical power. Results of two studies including 8 and 11 patients with type 1 GCs followed by endoscopic surveillance over the course of 11 and 12 years, respectively, found that tumors remained

stable in size despite an increase in the number of lesions [31,38]. To our knowledge, the largest study following type 1 GC with endoscopic surveillance included 88 patients [39]. In all 3 reports, tumors remained < 10 mm, the critical value above which a more aggressive evaluation is warranted, and showed no evidence of metastases. Although these preliminary studies suggest that conservative management may be appropriate for Type 1 GCs, additional prospective studies with larger sample sizes must be analyzed before definitive recommendations can be made.

Resection

Resection is considered in select patients with Grade 1 carcinoid, and majority of Grade 2 and 3 neoplasms.

Endoscopic resection

The preferred treatment in patients with low-moderately proliferative gastric carcinoids without invasion past the muscularis propria is endoscopic resection [11].

Resection in patients with grade 1 carcinoid is largely debated. Although these lesions are typically benign and treated with conservative management and surveillance, one can argue that patients with gastric carcinoid secondary to chronic atrophic gastritis remain at risk for development of adenocarcinoma, with conversion rate of up to 10% per year; therefore, warranting resection of any and all polyps [36,37,40].

However, when compared to the 4 year survival rate of patients with type 1 carcinoid that had all polyps removed conservative management falls short by only 3 percent.

Likelihood of malignant progression in grade 1 carcinoid increases with size and number; hence, some studies suggest resection of neoplasms measuring greater than 1.0 cm, or clustered in groups of 6 or more polyps [1,8,30].

Regardless of grade, endoscopic resection may be successfully executed in intraepithelial neoplasms < 2 cm, and in submucosal tumors < 1 cm in size [41,42].

Endoscopic resection can be performed by endoscopic polypectomy, mucosal dissection or submucosal dissection [11]. Use of polypectomy has declined, as grasping forceps have been found to cause tissue damage, obscuring tumor margins [41]. Recent literature supports use of submucosal dissection, which secures en bloc resections at higher rates than mucosal resection, or polypectomy [41]. In fact, one study found that the curative resection rate of gastrointestinal carcinoid tumors removed by submucosal endoscopic resection was 98% [41].

The effectiveness of endoscopic resection is limited by the high recurrence rate of gastric carcinoid polyps. One study found tumor recurrence rates to be as high as 64%, and occurring as early as 8 months after endoscopic resection. Even after these recurrences were removed, 67% of patients experienced polyp growth yet again [29].

Hence, even with high curative resection rates achieved by endoscopic submucosal dissection, patients should continue to receive regular screening.

Surgical resection

Surgical resection becomes the treatment of choice in Grade 1 gastric carcinoids in cases of large tumor size (greater than 2 cm), tumor recurrence or positive margins after endoscopic removal, or if tumor invades into or beyond the muscular wall [1,8,11,22,29,43,44].

In the last decade, there has been a growing preference for surgical intervention in patients Grade 1 gastric carcinoids resulting from hypergastrinemia. These include patients with Type I and II gastric carcinoids caused by chronic atrophic gastritis and gastrinomas, respectively [29,45,46]. It is reasoned that antrectomy in patients with gastrin-responsive Type I GCs and surgical excision of gastrinomas in Type II GCs, results in definitive removal of the source of hypergastrinemia, thereby halting tumor growth and leading to regression [1,8,47].

Surgical intervention is a mainstay of treatment in cases of Grade 2 and 3 neoplasms. These gastric carcinoids are classically invasive, with high rates of metastases, hence they are managed as gastric adenocarcinomas, requiring subtotal or total gastrectomy [1,8,32,48].

Medical management

The most recent advances in treatment of gastric carcinoids involve medical management of these tumors.

Somatostatin analogues

Somatostatin receptors are present in about 80%, of gastrointestinal carcinoid tumors, allowing us to target Type I and II gastric carcinoids resulting from hypergastrinemia [1,21,49]. In patients with positive SRS, administration of somatostatin analogues, including octreotide, inhibits gastrin secretion, thereby inhibiting triggers for cell metaplasia. In addition, some studies show tumor regression, suggesting possible anti-proliferative effects of SS analogues [1,50,51]. This definitive treatment creates a potential for SS analogue biotherapy to replace antrectomy; however, many patients treated with SS analogues experienced recurrence of tumors after cessation of therapy [8]. The current recommendation is to continue treatment without intention of termination [52].

Peptide Receptor Radionuclide Therapy (PRRT)

By capitalizing on presence of somatostatin receptors on gastric carcinoids, PRRT linking radioactive somatostatin analogues to radioactive isotopes can enable radiation therapy targeted to these tumor cells. Although this treatment modality is promising, only 20% of gastric carcinoids show response to therapy [1,21,53].

Gastrin receptor inhibition

Gastrin receptors have become the focus of much attention in treatment of Type I and II carcinoids. Several modalities for inhibition of the gastrin receptor have been employed, including gastrin receptor antagonists (YF476) and gastrin antibodies. Similar to SS analogue biotherapy, inhibition of gastrin receptors results in cessation of hypergastrinemia [1,8].

Of note, researches have formulated a vaccine which induces strong cellular immunity against the gastrin subunit G17, responsible for stimulating hyperplasia of ECL cells and leading to neoplastic changes. Initial trials have shown an early increase in G17 production, representing an attempt to stimulate HCl secretion in response to a drop in level of gastrin; however, this is followed by a sharp decrease in ECL hyperplasia, with subsequent regression or disappearance of carcinoid tumor cells by ~2 years [8,30].

Chemotherapy

The majority of gastric carcinoids are slowly proliferative, rendering chemotherapy ineffective. For this reason, indications for chemotherapy are limited to particularly malignant tumors with high Ki-67 values [8]. Even in these cases, response rates are less than 30% for multi-agent

chemo [21]. Therefore, before initiation of chemotherapy, a risk-benefit analysis is warranted.

Conclusion

With the increasing incidence of gastric carcinoid tumors, and evidence undermining the historical benignity of these tumors, it is of due importance to review the most recent literature regarding screening, diagnosis and treatment.

With respect to screening, CgA remains the most sensitive biochemical marker, largely eliminating the role of 5-HIAA. Patients who screen positive should undergo gastroscopy with biopsy for definitive diagnosis. EUS may be used to aide in visualization of submucosal or intramucosal lesions.

Should biopsy confirm the presence of carcinoid tumor, imaging will be required to identify the primary tumor and extent spread. In this regard, the use of SPECT has largely replaced SRS. Recent studies suggest that PET provides 3D images with even greater clarity, increasing the sensitivity and specificity for carcinoid tumor detection.

Treatment of gastric carcinoid tumors is best related to the grade of the tumor. Grade 1 GCs may be managed conservatively with endoscopic surveillance. Submucosal endoscopic resection of polyps should be offered to patients with chronic atrophic gastritis, or in the presence of neoplasms greater than 1.0 cm in size or grouped in clusters of 6 or more. Surgical resection is warranted in cases involving recurrent tumors, tumors with positive margins after resection, tumors invading the muscular layer, and all Grade 2 and 3 gastric carcinoid tumors.

Several methods for augmenting treatment of gastric carcinoids are supported. Gastrin receptor antagonists along with somatostatin receptor analogues can be used to inhibit gastric secretion and facilitate tumor regression. Somatostatin analogues also enable targeted radiation therapy using PRRT.

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