ABSTRACT
Objective: Neuroendocrine tumors (NETs) encompass a heterogeneous group of tumors demonstrating varied clinical behavior. The objective was to study the clinicopathologic features, grading, treatment protocols, and prognosis of gastrointestinal neuroendocrine tumor (GI-NET).
Materials and Methods: We hereby share our experience with 6 cases with GI-NETs with individual primary site.
Results: Six cases of GI-NETs were diagnosed. The primary tumors were located in stomach, duodenum, ampulla of vater, pancreas, and appendix. NETs are not peculiar to any age, but the average age varies with the location. Overall NET of stomach and appendix are slightly more common in female whereas duodenum (D-NETs) and pancreas (P-NET) are in males. Patients were asymptomatic or presented with nonspecific symptoms. Surgery was done in all NETs except P-NET and all patient received 3 – 6 cycle of adjuvant chemotherapy as cisplatin & etoposide except appendix (A-NET). Stomach, duodenum and appendix were low grade tumors whereas ampulla of vater was high grade tumor. Mean follow up was 25 months. All patient are alive except patient of D-NET who was lost to follow up.
Conclusions: GI-NETs are uncommon and heterogeneous group of tumors, with a rising incidence. Surgery is choice of treatment, however cisplatin & etoposide based chemotherapy is highly effective in adjuvant & unresectable or metastatic NET. Recently, the newer targeted agents have significant role in patients with metastatic disease and have opened up new avenues in refractory and advanced stage disease.

1. INTRODUCTION
Carcinoid tumors are Neuroendocrine tumors (NET) arising from the cells distributed throughout the endocrine system. They comprise a broad family of tumors which can affect several organs, the most common of them are arise in the gastrointestinal (GI) tract, bronchopulmonary, thymus, and pancreas. [1] Even though NETs can develop anywhere in the body, the majority (2/3) of the NET are found in the gastrointestinal tract (54.5%), with the small intestine being the most common affected (44.7%), followed by the rectum (19.8%), appendix (18.7%), colon (10.6%), and in the stomach (7.2%). [2] Other less common NETs arises in the parathyroid, thyroid, adenal, and pituitary glands.

Most neuroendocrine tumors seem to be sporadic, with unknown risk factors and approximately 15% to 20% are recognized as part of inherited genetic syndromes, including multiple endocrine neoplasia (MEN) types 1 & 2, von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis. [3]

GI-NETs arise from neural crest cells called enterochromaffin cells of Kulchitsky, situated at the base of the crypts of Lieberkuhn, from the end of the anal sphincter [4]. These cells have an ability to secrete a variety of peptide hormones causing characteristic hormonal syndromes. GI-NETs can be clinically symptomatic, i.e. 'functioning', or silent, i.e. 'non-functioning'. Symptoms are attributable to hormonal hypersecretion and usually nonspecific. Carcinoid syndrome (CS) occurs when functional carcinoid tumors metastasize to the liver or elsewhere and the vasoactive hormones secreted by metastases, such as serotonin, histamine, or tachykinins escape metabolism by the liver and reach the general circulation. CS occurs in 8% to 35% of NET patients. NETs can be benign or malignant and are able to metastasize. [5]

Survey data from the Surveillance, Epidemiology, and End Results (SEER) program demonstrated that the incidence of malignant GI-NETs is increasing [6], due to increased physician awareness and improved diagnostic modalities.

NET is often diagnosed late during its natural history resulting in advanced/metastatic disease. The preoperative classification of the NETs is important for the decision of the surgery to be performed.

The treatment of NETs requires a multidisciplinary approach. The management of localized NETs primarily involves surgical resection followed by clinical surveillance in early stage disease and adjuvant systemic therapy in advanced stage disease. However, the treatment approach for patients with unresectable and/or metastatic disease may involve a combination of surgical resection, systemic therapy, and liver-directed therapies with the goal of alleviating symptoms of peptide release and controlling tumor growth. NETs are characterized by a relatively indolent rate of growth and prognosis is better than GI carcinomas.

In the present study we share the experience of rare cases diagnosed with GI-NET and treated in a single-institute with cisplatin and etoposide.

2. MATERIAL AND METHODS
We retrospectively reviewed the records of 6 patients who were diagnosed GI-NET between January 2013 and July 2019. Medical records were analyzed for demographic characteristics (age at diagnosis, presenting signs and symptoms, and disease location). The primary tumors were located in stomach, duodenum, ampulla of vater, pancreas, and appendix. The primary tumors were located in stomach, duodenum, ampulla of vater, pancreas, and appendix. All patient received 3 – 6 cycle of adjuvant chemotherapy as cisplatin & etoposide except appendix (A-NET). Stomach, duodenum and appendix were low grade tumors whereas ampulla of vater was high grade tumor. Mean follow up was 25 months. All patient are alive except patient of D-NET who was lost to follow up.

Conclusions: GI-NETs are uncommon and heterogeneous group of tumors, with a rising incidence. Surgery is choice of treatment, however cisplatin & etoposide based chemotherapy is highly effective in adjuvant & unresectable or metastatic NET. Recently, the newer targeted agents have significant role in patients with metastatic disease and have opened up new avenues in refractory and advanced stage disease.

ORIGINAL RESEARCH PAPER
GASTROINTESTINAL NEUROENDOCRINE TUMOR: A SINGLE INSTITUTION EXPERIENCE OF RARE CASES

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symptoms, serum chromogranin A and 5-HIAA), surgical findings (surgical procedure, residual tumor tissue), and the adjuvant chemotherapy prescribed, clinical outcome at follow-up, date of recurrence, date of the last medical examination, and the date of death. Staging was done as per TNM classification [7]. Histological grading was done according to WHO as Grade 1 - well-differentiated, Grade 2 - moderately differentiated, and Grade 3 - poorly differentiated tumors.

Four patients underwent surgery followed by chemotherapy. We have given inj. Etoposide 100mg/M² and inj. Cisplatin 20mg/M² (day 1-5) with G-csf support every 3 weekly. Response to chemotherapy and surgery was evaluated by computed tomography or USG according to World Health Organization (WHO) criteria and tumor markers. Pelvic and abdominal USG, chest X-ray and tumor markers were repeated after every third and the sixth treatment courses.

The recurrence was defined based on serum chromogranin A, 5-hydroxyindole acetic acid (5-HIAA) or imaging findings. This study has limited number of cases, therefore PFS and OS is calculated for individual cases.

3. RESULT AND DISCUSSION

NETs are rare and heterogeneous tumors with great variations in their biology, behavior, and treatment. [8] The incidence in different locations roughly parallels the frequency with which the kulchitsky cells are found. NETs are not peculiar to any age, but the average age varies with the location. The tumors of stomach, occur at age ranges from 25 - 89 years with the average age being 62. Whereas in appendix the disease occurs at younger age mostly 2° to 4° decade. Overall NET of stomach and appendix are slightly more common in female whereas duodenum NETs (D-NETs) and P-NET are slightly more common in males. The average age of all patients in our study was in accordance with the literature.

However most of NETs are non-functioning or asymptomatic and are diagnosed incidentally during an unrelated procedure. The clinical manifestations are depending on the site of involvement, the presence of the metastasis especially to liver and the carcinoid syndrome. When symptomatology occurs they are usually present with abdominal pain, vomiting, decreased appetite and dyspepsia associated with significant weight loss.

Clinico-pathologic characterization of gastric carcinoid neoplasm is of three subtypes. [9] Type I gastric carcinoids (approximately 80-85 %) are small benign tumors associated with chronic atrophic gastritis and chronic hypergastrinemia. Type II account for 5 - 6 % of all G-NETs. It may be large and polyoid, associated with MEN I and Zollinger and Ellison syndrome (ZES). Lymph node metastasis may be seen. Type III representing approximately 10%-15% of all G-NETs. They are usually large, solitary and unassociated with hypergastrinemic states. These tumors are highly proliferative and are more likely to be invasive with distant metastases. Approximately 10-30% of type II G-NETs and 50 % of type III G-NET have tendency to metastasize at presentation [10]. In our case gastric NET WHO grade I without nodal metastasis had polypoidal growth in upper body and fundus of stomach which was operated with total gastrectomy. However it was not associated with MEN I and ZES.

D-NETs comprise 1-3% of primary duodenal tumors, 11% of small intestinal NETs, and 5- 8% of all GI-NETs [11,12]. D-NETs encompass a heterogeneous group of neoplasms ranging from nonfunctional tumors to gastrinoma, somatostatinoma, gangliocytic paragangliomas and tumor arising in the ampulla of vater. Majority of D-NETs are limited to the mucosa or the submucosa [13], metastases to the lymph nodes (40%-60%) and liver (less than 10%) are known to occur[14-16], while ampullary tumors metastasize to regional lymph nodes. Most D-NETs are located in the first or second part of the duodenum [17], with 20% of them occurring in the periampullary region. Despite the detection of various gastrointestinal hormones in D-NETs, 90% of the tumors are non-functional [17], and 75 % are smaller than 2 cm. The majority of D-NETs are, therefore, incidentally detected on esophagogastroduodenoscopy (EGD). Symptoms related to ZES are present in 10% patients with D-NETs, while carcinoid syndrome is reported in only 3% [18]. We have encountered 2 patients of D-NET. In one patient the tumor was located at the first part of duodenum with peptic stricture and in second patient, the tumor found to be arising in ampulla of Vater. Duodenectomy and pancreatoduodenectomy was done respectively in these two patients.

Primary pancreatic NET (P-NETs) accounts for 3.6% of all NETs [19] and represent about 1-2% of all pancreatic neoplasms [20]. More than 50 % of functional P-NETs located in the tail except gastrinoma which is located in head of pancreas. Patients with functional P-NETs are usually presents with symptoms, such as typical Whipple triad, refractory peptic ulcer, migratory erythema, intractable diarrheas, hypokalemia and Cushing syndrome. About 30-50 % of P-NETs are non-functioning and 60-90% patients develop malignancy [21,22].

Nonfunctional P-NETs are diagnosed incidentally or with symptoms secondary to mass effect or liver metastasis with a higher incidence of metastases compared to functional P-NETs. There is a correlation between tumor size and malignancy in nonfunctioning P-NETs [23]. Characteristically, nonfunctioning P-NETs are large, and 80% to 85% of them having liver metastases at the time of diagnosis [24]. The incidence of metastasis in primary pancreatic carcinoid was about 72% and about 20% of patients presented with carcinoid syndrome [25]. Our patients present with nonfunctional P-NET located at head & body region with liver metastasis.

Appendiceal carcinoids are present as either asymptomatic or acute appendicitis, which is diagnosed incidentally post appendicectomy. Therefore preoperative diagnosis of A-NETs is difficult. A-NETs also present as recurrent episodes of abdominal pain due to partial obstruction of the appendiceal lumen. A-NET can lead to a carcinoid syndrome characterized by flushing, bronchoconstriction, diarrheas, and heart disease occurs in less than 10% of cases. Appendiceal carcinoid behaves as benign tumors. Certain lesions metastasizes, primarily by lymphatic route and hepatic metastases are rare. Most frequent site of occurrence is the tip of appendix (60-75%), followed by body (20%) and base (5%) [26]. In the present patient, the tumor was located at the tip of the appendix and the patient experienced recurrent right lower abdominal pain. This location, as well as their small size and presentation at earlier ages may explain their indolent course and good prognosis.

Carcinoid syndrome occurs in 8- 35% of patients, when the disease metastasize to the liver because the vasoactive peptides escape the filtering action of the liver. These tumors secrete various substances like serotonin, histamine and prostaglandins and comprises of flushing, pellagra, wheezing, abdominal pain, diarrhea, bronchospasm and carcinoid heart disease [27]. GI-NET presents at the diagnosis with advanced/metastatic disease in a high proportion of cases (43.2%). Metastases are frequent from a midgt primary tumor and rare from appendiceal carcinoid.

The diagnosis of GI-NETs is based on clinical symptoms, hormone levels, radiological and nuclear imaging, and histological confirmation. Computed tomography and MRI are gold-standard imaging tests to assess the tumor burden and are important to rule out regional involvement and distant metastases [28]. UGI endoscopy, Colonoscopy, DOTA-NOC
chemotherapy in patients with advanced P-NETs. It is highly sensitive method for diagnosis and preoperative evaluation.

Somatostatin Receptor Imaging (SRI) using Indium-111, Somatostatin Receptor scintigraphy (SRS), and Positron Emission Tomography (PET) using Gallium-68 with somatostatin analogues (octreotide) are used in patients where curative resection has not been achieved or when there is suspicion of metastasis. Gallium-68 labeled octreotide PET/CT is more accurate than octreoscan [30,31].

Immunohistochemical staining is positive for synaptophysin, chromogranin A, neuron-specific enolase, and CD59. Serum tumor marker chromogranin A, 5-HIAA and synaptophysin are essential for diagnosis, monitoring response to treatment and follow-up. 5-HIAA levels in a 24 hour urine sample can be measured. When metastatic lesions are present, chromogranin A is more sensitive than 5-HIAA [32].

Tumor stage is the most important prognostic factor. Some additional factors like mitotic count, Ki-67 proliferation index, Chromogranin A level, gastrin level in stomach, plasma serotonin level and plasma or urinary 5-HIAA level are recommended.

Treatment and prognosis depends on the size, stage, grade, location, resectability and distant metastasis. However their behavior does not seem to correlate absolutely with tumor grade.

Appropriate management can lead to cure, especially if the tumor can be fully resected, or to long-term palliation with medical treatment or cytoreductive surgery, or both, with good survival periods. For localized tumors, surgical resection should be performed. For advanced-stage disease, control of symptoms of carcinoid syndrome and prudent use of antitumor therapy are mainstay of treatment. However, in metastatic carcinoid tumors, treatment is aimed at removing the primary tumor with adequate margins even in the presence of liver metastasis. In liver-dominant disease, liver directed therapy such as microwave or radiofrequency ablation and hepatic artery embolization are suggested [33,34].

Medical treatment plays a vital role in metastatic disease or incompletely resectable disease. The systemic therapy include somatostatin analogs, interferons, chemotherapy, targeted therapy with agents such as inhibitors of the mammalian target of rapamycin (mTOR) pathway (everolimus), kinase inhibitors (sunitinib) and peptide receptor radionuclide therapy (PRRT).

In functioning P-NETs, long-acting somatostatin analogs are generally successful in the initial management. There is no clear evidence that somatostatin analogs treat nonfunctioning P-NETs, but they most likely restrain tumor growth [35,36]. Based on PROMID study results somatostatin analogs are now widely used for their antiproliferative effects in patients with advanced and metastatic midgut NETs where long-term use of octreotide is reported [37].

During the course of North American Neuroendocrine Tumor Society (NANETS) guidelines development several controversial topics were identified like, use of octreotide for tumor control in patients with advanced pancreatic NETs and indications for initiating targeted therapies or cytotoxic chemotherapy in patients with advanced P-NETs. Controversy in midgut NETs like specific recommendations for dosing of octreotide LAR in refractory carcinoid syndrome and indications for initiating octreotide for tumor control in patients with advanced carcinoid tumors.

According to the NANETS guidelines, the level of recommendation is listed as “consider” to use of everolimus in metastatic functioning NETs because there has been no sufficient evidence to recommend routine use of it [38,39]. However, chemotherapy is indicated for intermediate and high grade P-NETs. In patients with poorly differentiated P-NETs, cisplatin and etoposide or its analogs has shown a response rate of 40-70% [40-44]. Marie-Louise H. et.al. could not see any differences in response between well differentiated and poorly differentiated P-NETs or between patients with typical and atypical foregut carcinoids [45].

Moertel et al. [46] reported that cisplatin plus etoposide produced a good response rate (67%) in 18 patients with neuroendocrine carcinomas. Mitry et al. [47] obtained a response rate of 41.5% in 41 P-NET patients, with a PFS of 8.9 months and an overall survival of 15 months. Alberto B et al reported that these are also an effective therapy for patients with metastatic gastrointestinal-NETs, especially those with positive 68Ga PET/CT. Based on these results platinum with etoposide is recommended in NETs [46].

In present study, surgery was done in all NETs except P-NET where both patients presented with liver metastasis and except A-NET all patient received 3 – 6 cycle adjuvant chemotherapy as cisplatin & etoposide. Though our study is relatively small and is a retrospective chart review, it is therefore difficult to make reliable conclusions about outcomes (PFS & OS, table). However cisplatin with etoposide chemotherapy is effective in GI-NETs and it can be used in economically poor patients where cost effectiveness is concerned with use of therapy like octreotide, everolimus and other targeted therapy. Post-operative radiotherapy should be given after adjuvant chemotherapy in carcinoid stomach patients with regional lymph node metastasis, as they have a high rate of loco regional recurrence.

After so much of studies and trials like CALGB 80701, RADIANT-2 & 4, PROMID and CLARINET, it is still debatable to having a standard protocol regarding the use of targeted therapies in metastatic NET. Because of some unanswered questions, like the best targeted therapy has not been demonstrated, whether targeted therapy can replace chemotherapy, particularly in high-grade NET, is not known and optimal timing & sequence for starting molecular targeted therapy are unknown [49].

Newer modality PRRT with radio labeled somatostatin analogues 111Ytrium (Y) and 177Luetetium (Lu) delivers β radiation dose directly to the tumor cells leads to cytotoxic effects.

As widely known, GI carcinoid is a slow-growing tumor with an overall favorable prognosis, and long-term survival is possible despite advanced stages of disease as compared to GI carcinoma. However CS has a significantly worse quality of life. Therefore, early diagnosis of CS may improve quality of life.

NETs are intrinsically complex group of tumors with heterogenous presentations. Fortunately, surgical treatment in non-metastatic disease and cisplatin & etoposide chemotherapy in advanced diseases have markedly improved their prognosis. Recently, the biological targeted agents have significant role in patients with metastatic disease. Newer modalities like peptide receptor targeted therapies and radioembolization appears to be a valuable
3. Öberg K et al. The genetics of neuroendocrine tumors. Semin Oncol 2013;40:37-44.


