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Original Article

Internal Medicine Section

Clinico-epidemiological Profile of Incidentally Detected Gastrointestinal Neuroendocrine Tumours on Gastrointestinal Endoscopy: A Retrospective Study

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ABSTRACT

Introduction: Neuroendocrine tumours (NETs) are rare tumours, with the Gastrointestinal (GI) tract and the lung as the most common sites with indolent course. Endoscopists play a pivotal role in the diagnosis of GI-NETS because the majority of patients with NETs are asymptomatic and NETs are discovered during screening examinations. Since GI-NETs are less common than other cancers, their natural history, diagnosis, and treatment may not be completely understood.

Aim: To estimate the prevalence and to characterize the clinical, endoscopic, and histological features of incidentally detected GI NETs in nodular/polypoidal/ulcerated lesions on GI endoscopy.

Materials and Methods: This record-based retrospective study was conducted at the Department of Medical Gastroenterology of a tertiary care facility. The data belonged to the period between January 2018 to December 2020. Data belonged to the patients that underwent Oesophago- gastro duodenoscopy (OGD)/ Colonoscopy and were found to have nodular/ polypoidal lesions. Records on serum chromogranin, serum gastrin and radiological tests such as Ultrasonography(USG) or Computed Tomography (CT) scan were recorded. The histopathological with immunohistochemistry staining report was used to diagnose NETs. Continuous variables were analysed for normality by the Kolmogorov Smirnov test.

Results: A total of 59 eligible patients were studied. The prevalence of GI NET tumours in 2018 was 17 (0. 32%), 19 (0. 33%) in 2019, and 23 (0. 41%) in 2020 with an overall rate of 59 (0. 36%) for all the three years. Total male participants were 35 (59.32%), and the mean age of the patients was 56.13 ±12.44 years. Majority had abdominal pain (32, 54.24%) and 35(59.32%) had tumours in the duodenum, 15 (25.42 %) in the stomach. The most common site was duodenum 35 (59.32%). As per World Health Organisation (WHO) NET, most tumours were Grade I (50, 45.76%). Majority of tumours had Synaptophysin (57, 96.61%), Chromogranin (49, 83.05%), and a Ki67 (Kiel-clone no.67) index≤ 2 (49, 83.05%), while 27 (84. 75 %) tumours were of size of <1 cm.

Conclusion: GI-NETs are uncommon, and their biology, histopathology, and clinical behavior are distinct. Typically, they are slow-growing tumours, but their growth rate can fluctuate depending on the location, size, and grade of the tumour.

Keywords: Chromogranin, Carcinoid tumours, Immunohistochemistry, Ki-67, Synaptophysin, Vimentin

INTRODUCTION

Neuroendocrine tumours (NET) are uncommon tumours that can develop virtually anywhere in the body. The incidence of NETs is 2.5% to 5% per 100,000 people annual [1]. As neuroendocrine cells are spread throughout the body, various organs, including the central nervous system, respiratory tract, larynx, gastrointestinal (GI) tract, thyroid, skin, breast, and urogenital system, have been described as having NET.

NETs are heterogeneous neoplasms developing from diverse cells scattered throughout numerous organs and tissues that share a neuroendocrine character. Since the introduction of the term "karzinoid" by Oberndorfer at the turn of the twentieth century, NETs have been recognised as biologically distinct from conventional carcinomas [2,3]. The 2010 WHO classification system classifies all NETs as neoplasms with malignant potential and recommends the acronym NEN for the term Neuroendocrine Neoplasia [3]. Neuroendocrine Tumours (NETs) are uncommon tumours comprising 2% of all malignancies, with the digestive tract and lungs being the most common site [4,5].

Although the occurrence of malignant digestive (MD) NETs is on the rise, they are still an uncommon form of cancer, accounting for only 1% of digestive cancers [6]. The majority of MD-NETs are well-differentiated. Poorly differentiated MD-NET carcinomas account for an average of 20% of cases [7]. The stage at diagnosis and prognosis of patients with MD-NETs in the general community are significantly worse than what is typically reported in limited hospital case series. The prognosis varies based on the differentiation, anatomical location, and histological subtype of the tumour. Independent of other prognostic markers, there are considerable disparities in MD-NET survival rates among the European nations. 2000-2012 Surveillance, Epidemiology, and End Results (SEER) registry showed the highest incidence of GI-NET to be 3.56 per 100000 population [8]. The prevalence also increased from 0. 006% in 1993 to 0. 048% in 2012 [6]. New therapy alternatives appear to be the most effective method for enhancing prognosis, as early diagnosis is challenging [9].

In addition, the digestive tract is the most prevalent location for NETs [10]. The incidence of GI-NET is approximately 67.5% of all NETs [10]. The majority of these cancers progress slowly. Some are diagnosed incidentally, while a small number have disseminated disease that may manifest as metastatic disease. Frequently, histological examination fails to distinguish between a tumour's aggressive and metastatic potential. The biology of GI NETs varies, and they may manifest with various clinical symptoms such as flushing, diarrhoea, hypoglycemia, and stomach ulcers. Among the GI-NETs, the appendix, ileum, and rectum were deemed to be the most popular sites [11,12]. However, the pattern appears to have shifted in recent years. [6,13-15].

Endoscopists play a pivotal role in the diagnosis of GI-NETS because the majority of patients with NETs are asymptomatic and NETs are discovered during screening examinations. The natural

history, diagnosis, and management of patients with NETs may not be well understood by all endoscopists due to the rarity of NETs in comparison to other malignancies and gastrointestinal pathology and incidence and prevalence of GI-NETs has been changing over the years globally, not many studies are available on clinico-epidemiological features of GI-NETs in India.

Considering these facts, the objective of the present study was to determine the prevalence, clinical profile, and laboratory profile of incidentally-detected gastrointestinal neuroendocrine tumours in nodular/ polypoidal/ ulcerated lesions on GI endoscopy (OGD/ colonoscopy).

MATERIALS AND METHODS

This hospital-based retrospective study was conducted in the Department of Medical Gastroenterology in a tertiary care medical college hospital. The data belonged to the period from January 2018 to December 2020. The institutional ethics committee had approved the study (REF: CSP- MED/20/ OCT/62/108 dated 05.11.2020). The patients undergoing Oesophago-gastro duodenoscopy (OGD)/Colonoscopy for nodular/ polypoidal lesions were subjected to biopsy for histopathological examination (HPE).

Sample size calculation: The sample size was calculated using the following formula,

$n=Z^2 x\ p \times Q/d^2$

where, z=Constant 1. 96 (at 95% confidence interval), P=Proportion of patients with GI- Neuro-endocrine Tumours is 0.04% [6], with 5% allowable error, the required sample size was 61. However, considering the previous three-year hospital records, it was possible to achieve the minimum effect size. Hence all the patients fulfilling the selection criteria for the period of previous three years was considered.

Inclusion criteria: Participants aged above 18 years of either sex, with GI- NET (nodular/polypoidal lesions), histopathological & Immuno-histochemical (IHC) confirmed were included.

Exclusion criteria: Records with incomplete data were excluded from the study.

Procedure

Data Collection: Permission was obtained from the MRD (Medical Records Department) to retrieve the data of patients. Findings for serum chromogranin, serum gastrin and radiological Computer Tomography (CT) scan were also noted. NETs were graded based on proliferative index [3], and histological features as per the WHO 2010 classification as follows: [3]

- Grade 1: Well- differentiated NETs-low grade with < 2% Ki67.
- Grade 2: Well- differentiated NETs-intermediate grade with 3%to 20% Ki67.
- Grade 3: Poorly differentiated tumours, termed Neuroendocrine Carcinomas (NECs) with > 20% Ki67.

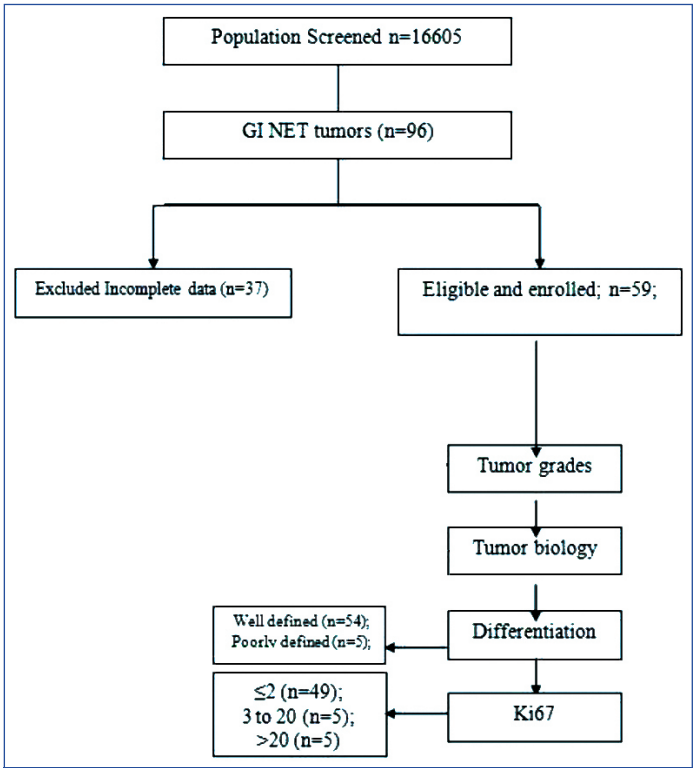
To determine the tumor biology, histopathological report was analysed for synaptophysin, chromogranin, vimentin and Insulinoma associated protein (INSM). Chromogranin A levels of <100 µg/L were regarded as normal [3].

STATISTICAL ANALYSIS

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analysed using statistical software Statistical Package for Social Sciences (SPSS) version 20.0. Continuous variables were analysed for normality by the Kolmogorov Smirnov test. The data was expressed in terms of mean± standard deviation (SD) for the data that followed normal distribution and the data which followed skewed distribution was expressed as median and interquartile range (IQR). The prevalence of the GI NET tumours was expressed in terms of percentage.

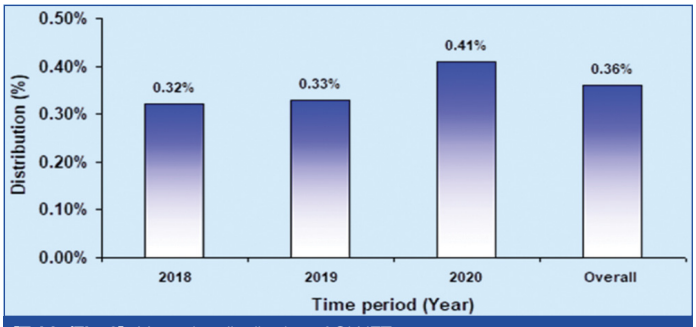
RESULTS

A total of 16605 patients were subjected to GI endoscopy/ colposcopy for various reasons during the study period, from which 96 were diagnosed to have GI NET. Of them 37 patients' records were incomplete and inconclusive. Therefore, the total study participants included in the final analysis were 59 [Table/Fig-1].



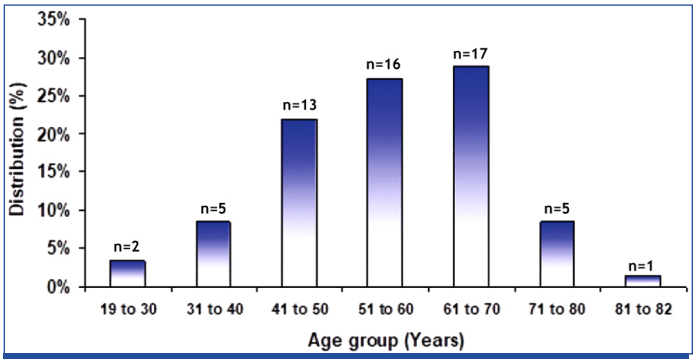
[Table/Fig-1]: Patient distribution-Screening, tumour grading and biology.

[Table/Fig-2] shows the year-based prevalence of patients diagnosed with GI NET Tumours, the overall prevalence of GI NET Tumours was 0.36% for the period of three years. Third year showed highest prevalence (0.41%).



[Table/Fig-2]: Year wise distribution of GI NETs.

There were 35 (59.32%) males and 24 (40.68%) females. The mean age was 56.13±12.44 years. Further, 28.81% of the patients were aged between 61 to 70 years and 1.39% were aged 81 to 82 years as shown in [Table/Fig-3].



[Table/Fig-3]: Distribution of tumours according to the age of the study participants.

[Table/Fig-4] shows the distribution of tumours as per grade and location. Majority off the NETs were grade I 50 (84.7%), and duodenum was the most common location, 33 (66%). Similarly, in tumour biology synaptophysin, 57 (96.6%) is majority and in Ki67 Index ≤2 was found majority.

Majority of the tumours were <1 cm in size, of which 50% belonged to grade I. Majority of the grade III tumours were of size >2 cm. Majority of grade 1 tumours were type 1, 10 (90.91%), among grade 3 tumours 50% were type 2 and 50% were type 3 as shown in [Table/Fig-5].

[Table/Fig-6] shows the clinical presentation based on the location of GI-NET. Abdominal pain was noted in 45(71%) of the patients with tumours on duodenum, 73 (33%) of the gastric tumours and 40% of the tumours in right colon.

Descriptive characterstics	Right colon. N (%)	Left colon N (%)	Duodenum N (%)	Oesophagus N (%)	Gastric N (%)
Grading					
• Grade I (n=50)	2 (4)	4 (8)	33 (66)	0	11 (18.64)
• Grade II (n=4)	0	1 (25)	1 (25)	0	2 (50)
• Grade III (n=5)	1 (20)	0 (0)	1 (25)	1 (20)	2 (40)
Tumor biology					
• Synaptophysin (n=57)	3 (5.26)	4 (7.02)	35 (61.4)	1 (1.75)	14 (24.56)
• Chromogranin (n=49)	0	4 (8.16)	30 (61.22)	1 (2.04)	14 (28.57)
• Vimentin (n=25)	0	2 (8)	15 (60)	1 (4)	7 (28)
• INSM (n=4)	0	1 (25)	2 (50)	0	1 (25)
Location of the lesion and Ki67 index					
• <2 (n=49)	2 (4.08)	4 (8.16)	32 (65.31)	0	11 (22.45)
• 3 to 20 (n=5)	0	1 (20)	2 (40)	0	2 (40)
• >20 (n=5)	1 (20)	0	1 (20)	1 (20)	2 (40)
Chromogranin A levels					
• <100 (n=23)	0	2 (40)	13 (37.14)	0	8 (53.33)
• >100 (n=36)	3 (100)	3 (60)	22 (62.86)	1 (100)	7 (46.67)

[Table/Fig-4]: Descriptive characteristics of the GI- NET (Total N=59).

	Grade I (50) N (%)	Grade II (4) N (%)	Grade III (5) N (%)
Size of the tumour (cm)			
<1 (n=27)	25 (50)	1 (25)	1 (20)
1 to 2 (n=24)	22 (44)	1 (25)	1 (20)
>2 (n=8)	3 (6)	2 (50)	3 (60)
Type of tumours			
Type 1	10 (90.91)	2 (100)	0 (0)
Type 2	0 (0)	0 (0)	1 (50)
Type 3	1 (9.09)	0 (0)	1 (50)

[Table/Fig-5]: Distribution of size and type based on grades of tumour.

Clinical signs and symptoms	Duodenum (n=35)	Gastric (n=15)	Left colon (n=5)	Right colon (n=3)	Oesophagus (n=1)
Abdominal pain	16 (45.71)	11 (73.33)	2 (40)	3 (100)	0
GI bleeding	0	2 (13.33)	2 (40)	0	1 (0)
Diarrhoea	0	2 (13.33)	1 (20)	0	0
Vomiting	1 (2.86)	1 (6.67)	0	0	0
Jaundice	0	1 (6.67)	0	0	0
Loss of appetite	3 (8.57)	2 (13.33)	0	0	0
Loss of weight	1 (2.86)	0	0	0	0
Fever	0	1 (6.67)	0	0	0
Others	5 (14.29)	6 (40)	3 (60)	1 (33.33)	0

[Table/Fig-6]: Clinical presentation based on the location of the GI NET*
*Multiple responses

DISCUSSION

Neuroendocrine Tumours (NETs) are heterogeneous neoplasms arising from different cells distributed in many organs and tissues that share a common neuroendocrine phenotype [16]. NETs have been recognized as biologically different from classical carcinomas since the first description. NETs constitute only 0.5% of all malignant conditions and 2% of all malignant tumours of the GI. [17,18] However, there is still a lack of adequate information on epidemiology, endoscopic as well as histopathological characteristics of NETs detected on GI endoscopy. Scherübl H et al., reported a study evaluated epidemiological data of Gastroentero-Pancreatic (GEP)-NET from the former East German National Cancer Registry (DDR Krebsregister, 1976-1988) and its successor, the Joint Cancer Registry (GKR, 1998-2006) and reported crude incidence rate of GEP-NET (per year and 100. 000 population) rose from 0.45 in 1976 to 2(53%) in 2006 which was very high compared to the present study (0.41%) [18]. This variation may be due to the study setting. The present study was from a single center whereas the other was from the national cancer registry.

The majority of the patients had a low grade tumour (grade I-50 (84.75%). On the other hand, a study by Kulkarni RS et al., from Ahmedabad, India, revealed an equal distribution of tumours with respect to grades had (32%) had Grade 1, (33%) had Grade 2, and (35%) had Grade 3 [19].

[Table/Fig-7] shows comparison of salient epidemiological features of GI- NETs in India over past few years. In the present study, the size of the tumour was < 1 cm in 27 (45.76%). 1 to 2 cms in 24 (40.67%)and > 2 cms in 8 (13.55%) of the patients. However, this observation could not be compared with previous studies as the others have not analysed the size of the tumour [20].

In the present study, more than half of the patients 32/59 (54.23%) presented with abdominal pain being the common presentation, followed by various non-specific presentations (27.12%). These observations were comparable with the findings in a study by Amarapurkar DN et al., [20]. However, owing to the small subset of tumours on left and right colon as well as esophagus site specific symptoms require further validation [20].

A study from India by Hegde V et al., analyzing cases of gastric carcinoid has also shown rising incidence of gastric NETs as compared to the past [21]. The same was partially true in the present study as majority of the patients (61.02%) had chromogranin A levels of ≥ 100 µg/L. Also, the mean and median chromogranin A levels were elevated (308. 23±546. 53 and 148 (IQR 274. 00µg/ L). The most often used biomarker to gauge the severity of illness and track therapy response is serum chromogranin A, which is elevated in both functional and non-functional neuroendocrine tumours just as the present study. It is clear that the clinical prevalence of NETs in the population of India differs from that of Western nations. In order to provide present study patients with the best care possible, it is necessary to raise knowledge about the symptoms, diagnostic techniques, and Indian NET standards. To more clearly describe the epidemiology and clinical features of this rare condition, more multi-institutional investigations are needed.

Limitation(s)

This was the first study from South India to focus on the epidemiology of GI NETs, including prevalence rates, clinical features, and histological aspects. Despite of the novelty, link between various clinical aspects and biological measures could not be determined because of the smaller subset of patients with age group, severe grades, and diverse locales.

CONCLUSION(S)

The GI NET tumours are becoming more common, more likely to affect men, and are identified in their sixth decade of life. Although

Author and year of publication of study	Study setting	Period of study	Common Location	Common grade	Common presenting symptom	No. of GI-NET cases
Present Study	Single Centre	2018 to 2020	Duodenum (59.32%)	Grade 1 (84.75%)	Abdominal pain (54.2%)	59
Amarapurkar DN et al., (2010) [20]	Single center	2000 to 2007	Stomach (30.2%)	Grade 1 (33.7%)	Abdominal pain (50%)	74
AP-NETs registry (2017) [22]	Multicentric	2001 to 2005	Pancreas (37.8%)	Grade 1 (67.5%)	Abdominal pain (42.4%) followed by Flushing (20.1%)	37
AP-NETs registry (2017) [22]	Multicentric	2006 to 2010	Pancreas (48.5%)	Grade 1 (80.1%)		136
AP-NETs registry (2017) [22]	Multicentric	2011 to 2016	Pancreas (40.5%)	Grade 1 (85.8%)		234
Kulkarni RS et al., (2019) [19]	Regional cancer center	2014 to 2016	Pancreas (35%)	Grade 3 (35%)	Abdominal pain (63.8%)	97
Uppin M et al., (2017) [23]	Single center	2012 to 2015	Duodenum (22.5%)	Grade 1 (35%)	Abdominal pain (37.5%)	40

[Table/Fig-7]: Comparison of salient epidemiological features of GI-NETs (studies from India).

abdominal discomfort is still a crucial clinical feature, patients with GI NET tumours are more likely to come with vague symptoms, and only a small percentage may have a history of hypertension or diabetes. The most frequent location for tumours is the duodenum, followed by the stomach. Type 1 stomach tumours are the most frequent type. Although gastric tumours appear to be more common with grade II and III tumours, duodenal tumours are probably the most common site of tumour in grade I tumours. On endoscopy, the GI NET tumours are likely to show up as polyps and ulcerative lesions. These tumours are clearly characterized, and histological examination reveals the presence of synaptophysin, chromogranin, vimentin, and Ki-67, although INSM is only weakly present.

REFERENCES

[1] Albishi AM, Mostafa AMM, Ali HM, Alhagawi YA, Bazeed MF, Hussein MRA, et al. Incidence of Gastrointestinal Neuroendocrine Tumor: Case Series, Armed Forces Hospital Southern Region, Hospital- Based Tumor Board Registry. Case Rep Oncol Med. 2020; 2020:8819392. Doi: 10.1155/2020/8819392. eCollection 2020.

[2] Oberndorfer S. Karzinoide tumoren des dünndarms. Frankfurter Zeitschrift för Pathologie. 1907;1:426-32.

[3] Nagtegaal I, Odze R, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2019;76(2):182-88.

[4] Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, G önen M, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. American Journal of Surgical Pathology. 2010;34(3):300-13.

[5] Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: A review of nomenclature, grading, and staging systems. Pancreas. 2010;39:707-12. Doi: 10.1097/MPA.0b013e3181ec124e.

[6] Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol. 2020;12(8):791-07.

[7] Anaizi A, Rizvi- Toner A, Valestin J, Schey R. Large c ell neuroendocrine carcinoma of the lung presenting as pseudoachalasia: a case report. J Med Case Reports. 2015;9(1):56.

[8] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335-42.

[9] Lepage C, Bouvier AM, Faivre J. Endocrine tumours: epidemiology of malignant digestive neuroendocrine tumours. Eur J Endocrinol. 2013;168(4):R77-83.

[10] Modlin IM, Ley KD, Kidd M. A 5-decade analysis of 13, 715 carcinoid tumours. Cancer 2003;97(4):934-59.

[11] Saha S, Hoda S, Godfrey R, Sutherland C. Raybon K. Carcinoid tumours of the gastrointestinal t ract: a 44-year experience. South Med J. 1989;82(12):1501-05.

[12] Delle Fave G, Capurso G, Milione M, Panzuto F. Endocrine tumours of the stomach. Best Pract Res Clin Gastroenterol. 2005;19(5):659-73.

[13] Burkitt MD, Pritchard DM. Review art ic le: Pathogenesis and management of gastric carcinoid tumours. Aliment Pharmacol Ther. 2006;24(9):1305-20.

[14] Zeitels J, Naunheim K, Kaplan EL, Straus F. Carcinoid tumours. a 37- year experience. Arch Surg. 1982;117(5):732-37.

[15] Oberg K. Neuroendocrine gastrointestinal t umours. Ann Onco l. 1996;7(5):453-63.

[16] Rindi G, Klimstra DS, Abedi- Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization(WHO) expert consensus proposal. Mod Pathol. 2018; 31(12):1770-86.

[17] Moertel CG. Karnofsky memorial lecture. An odyssey in the land of small tumors. J Clin Oncol. 1987;5(10):1502-22.

[18] Scherübl H, Streller B, Stabenow R, Herbst H, Höpfner M, Schwertner C, et al. Clinically detected gastroenteropancreatic neuroendocrine tumors are on the rise: epidemiological changes in Germany.World J Gastroenterol. 2013;19(47):9012-19.

[19] Kulkarni RS, Anand AS, Parikh SK, Panchal HP, Patel AA, Mehta DP, et al. Clinical and epidemiological profile of neuroendocrine tumors: An experience from a regional cancer center from Western India. South Asian J Cancer. 2019;8(3):198-02.

[20] Amarapurkar DN, Juneja MP, Patel ND, Amarapurkar AD, Amarapurkar PD. A retrospective clinico-pathological analysis of neuroendocrine tumors of the gastrointestinal t ract. Trop Gastroenterol. 2010;31(2):101-04.

[21] Hegde V, Mohandas KM, Ramadwar M, Shukla P, Mehta S. Gastric carcinoids-a changing t rend. Indian J Gastroenterol. 2003;22(6):209 -11.

[22] Palepu J, Shrikhande SV, Bhaduri D, Sh ah RC, Sirohi B, Chhabra V, et al. Trends in diagnosis of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in India: A report of multicenter data from a web- based registry. Indian J Gastroenterol. 2017;36(6):445-51.

[23] Uppin M, Uppin S, Sunil C, Hui M, Paul T,Bheerappa N, et al. Clinicopathologic study of neuroendocrine tumors of gastroenteropancreatic tract: A single institutional experience. Journal Of Gastrointestinal Oncology. 2017;8(1):139-47. Doi:10.21037/jgo.2016.12.08

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