DOI: https://doi.org/10.4038/sjdem.v16i1.7565

Original Article

Pathological Characteristics of Neuroendocrine Neoplasms in Sri Lankan Settings: A Retrospective Study

Sinduja K[1], Muthukuda D. T[2], Seneviratne B[3], Pathmanathan S[4], Sumanatilleke M. R[4], Cooray S[5], Liyanarachchi K[6], Nandasena M. S[7], Pathirana A[7], Jayawickrama M. M. A[4], Dissanayake K[4], Constantine S. R[4], Gunasinghe R[8], Sivaganesh S[9], Subasinghe D[9], Chandu de Silva M. V[10], Ruwanga V. G. D[2], Buddhika P. G[2], Subasinghe C. J[11]

[1] Department of Molecular Biology and Biotechnology, Post Graduate Institute of Science, Peradeniya, Sri Lanka
[2] Sri Jayewardenepura General Hospital, Sri Lanka
[3] Department of Pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
[4] National Hospital of Sri Lanka
[5] Teaching Hospital, Kurunegala, Sri Lanka
[6] Teaching Hospital, Rathnapura, Sri Lanka
[7] Department of Surgery, Faculty of Medical Sciences, University of Sri Jayewardenepura, Sri Lanka
[8] Department of Pathology, Apeksha Hospital, Maharagama, Sri Lanka
[9] Division of HPB Surgery, Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka
[10] Department of Pathology, Faculty of Medicine, University of Colombo, Sri Lanka
[11] District General Hospital, Chilaw, Sri Lanka

Abstract

Introduction:
Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors arising from neuroendocrine cells, with increasing incidence worldwide. Limited data exist on NENs in Sri Lanka. This study describes the demographic, anatomical, and pathological characteristics of NENs in Sri Lanka and compares findings with regional and global data.

Methods:
A retrospective descriptive study was conducted using histopathology reports from seven centers in Sri Lanka from January 2017 to June 2021. A total of 151 patient records were analyzed, categorized based on the 2022 WHO classification for NENs

Results:
The sample included 77 males and 74 females, with a median age of 58 years. Primary NENs accounted for 71% of cases, with gastroenteropancreatic NENs (GEP-NENs) being the most common (75.7%). Pancreatic NENs were the most frequent (41.9%), followed by small intestinal NENs (30.9%). The liver was the most common metastatic site (36%). Immunohistochemical markers chromogranin A and synaptophysin were positive in 82.8% and 79.5% of cases, respectively. Well-differentiated tumors (Grade 1 and 2) comprised 65%, while neuroendocrine carcinomas (NECs) accounted for 35%.

Discussion:
The pathological characteristics of NENs in Sri Lanka align with global and regional data, with pancreatic and small intestinal NENs being the most common. However, regional variations emphasize the need for localized studies and tailored management approaches.

Conclusion:
This study enhances understanding of NENs in Sri Lanka, highlighting the need for improved diagnostic expertise, systematic data collection, and further research to improve patient outcomes.

Keywords: Neuroendocrine neoplasm (NEN) neuroendocrine timours (NET) pathological characteristics, Gastroenteropancreatic NEN (GEP NEN)

Correspondence email: chandrika.ucfm@gmail.com

ORCID ID: https://orcid.org/0000-0002-4454-0194

Introduction

Neuroendocrine neoplasms (NENs) are heterogeneous group of neoplasms, derived from neuroendocrine cells [1], located in different organs in the body, which produce neurotransmitters or peptides. The incidence of NENs appears to be rising globally. The indolent nature, chronicity of the disease and its prevalence carry a multitude of healthcare problems and as a result, increase the cost of healthcare. Upgrading awareness among healthcare professionals and improvement of advanced radiological imaging studies and immunohistochemical tests will be beneficial in early identification of these tumours.

In the majority of NENs, there is no identifiable cause [2]. Ninety-five percent of NENs show sporadic genetic mutations, while five per cent of NENs are associated with an inherited disorder[3]. Depending on the anatomical location and nature of the neuroendocrine cells, they exhibit different biological characteristics and clinical presentations. NENs can originate in any part of the body where neuroendocrine cells are present. Most commonly, NENs present in the gastrointestinal tract, specifically in the stomach, large intestine, small intestine (ileum, jejunum, duodenum), appendix and pancreas. Lung, head and neck, thyroid, parathyroid, adrenals, thymus, skin, prostate, ovaries and testes are the other known primary sites of NENs.

NENs can be classified into "functional" and "non-functional" tumours. Functional NENs that produce hormones, and other substances give rise to more specific symptoms. However, non-functional NENs neither produce hormones nor release enough other substances to cause symptoms, leading to delay in diagnosis. Most of the NENs are non-functional and are usually diagnosed at a more advanced stage [4].

In 2022, the classification of neuroendocrine tumours (NENs) continued to be refined based on their origin, histological features, and molecular characteristics. The World Health Organization (WHO) classification system remained a crucial framework for categorizing NENs. This system classified NENs into well-differentiated NENs and poorly differentiated neuroendocrine carcinomas (NECs). Well-differentiated NENs were further divided into grades 1, 2 and 3 based on their mitotic rate and Ki-67 index, reflecting their proliferative activity [5]. Histological diagnosis performed on core biopsy or excised tumour is needed to confirm the diagnosis of NENs. Immunohistochemical markers like chromogranin A and synaptophysin demonstrate the phenotype of the tumours. CD56 markers and neuron-specific enolase are positive in GEP–NENs but are less specific [6].

Objectives

To describe the demographic characteristics of a patient population with Neuroendocrine neoplasms in Sri Lankan setting.

To describe the anatomical sites and pathological characteristics of Neuroendocrine neoplasms.

To correlate the pathological characteristics with regional and global data.

Materials & Methods

We conducted a retrospective study for retrieving data from January 2017 to June 2021 at each study center. We collected data from seven study centers, including the University of Sri Jayewardenepura, National Hospital Sri Lanka, Faculty of Medicine, University of Colombo, Apeksha Hospital Maharagama, Sri Jayewardenepura General Hospital, Colombo South Teaching Hospital Kalubowila and Teaching Hospital Kurunegala.

Different study centers had various methods of documentation related to medical reports. At all study centers the histology request forms were categorized according to the anatomical site. The reports were arranged based on their serial number for the laboratory reference. We retrieved NENs data from histology reports including specific biomarkers related to NENs (chromogranin, synaptophysin). Data collection was done by a postgraduate student in experimental biotechnology, who went through each request form manually and made a database with retrieved data providing code numbers to each study center for future reference. We analyzed the characteristics of these NENs with the help of the database. We used World Health Organization (WHO) 2022 GEP-NEN classification for further analysis.

Results

We evaluated histology reports belong to 151 patients excluding duplicates. These included reports of 86 resection specimens and 65 biopsy specimens. 71% (107/151) were specimens of primary NENs, while 29% (44/151) were specimens of secondary deposits. Out of 86 resection specimens, 58 were resection specimens of primary tumours, while rest were resection specimens of secondary deposits. Total sample of the patients included 77 males and 74 females. Their age ranged between 21 to 90 years with a median age of 58 years (IQR 47,68). The majority of them were found to be above 40 years (85%, N=120). Gastroenteropancreatic NENs (GEP-NENS) were the commonest (75.7%, N=81/107) among primary tumours. GEP-NENs were most frequently found in pancreas (41.9%, N=34/81), while other sites were stomach (6.1%, N=5/81), small intestine (30.9%, 25/81), appendix (7.4%, N=6/81) and colon and anal canal (13.6%, N=11/81). Other primary tumour sites were urological system (8.4%, N=9/107), head and neck (5.6%, N=6/107), Ovaries and cervix (6.5%, N=7/107) and lung (3.7%, 4/107). Commonest metastatic site of NET was liver (36%, N=16/44), while other sites of secondary deposits were, lymph node (25%, N=11/44), central nervous system (14%, N=6), lung (23%, N=10) and bone (2.2%, N=1/44).

The most common immunohistochemical (IHC) biomarkers used for the confirmation of tumours were chromogranin A and synaptophysin. Chromogranin was used in 99 cases with 82.8% (N=82/99) positivity. Synaptophysin was used in 146 cases, with positivity of 79.5%, N=116/146). Other markers like CD56, CD99, E-Cadherin, vimentin, NSE, PanCK and S100, were also used for tumor confirmation. Tumour grade was mentioned in 115 reports, and out of which, 65% (N=75/115) were well differentiated tumours (G1 – 41%, G2 -50.6% and G3 – 8%), while 35% (N=40/115) were neuroendocrine carcinomas.

Clinicopathological characteristics of GEP NENs

Pancreas was the commonest primary site of GEP NENs. Pancreatic NENs (PNENs) presented at median age of 56 years (IQR 45,69) and showed female predominance (F:M ratio 1.61:1). 89.3% PNENs were well differentiated (G1 34%, G2 52%, G3 3.4%), while there were only 3 NECs (10.7%). Clinical presentation was under reported in histopathology request forms, and abdominal pain, obstructive jaundice, back pain and hypoglycemia were the recorded presentations. Six of the PNENs were recorded as insulinomas, while functional status of the other tumours was not recorded. PNENs showed 92.6% positivity for chromogranin, and 100% positivity for synaptophysin immunostaining.

Small intestinal NENs (SI NENs) were found in 25 cases with F:M ratio of 1.08:1, at median age of 61 years (IQR 51,69). 89.5% SI NENs were well differentiated including 42% grade 1 and 37% grade 2 tumours. Recorded clinical presentations were loss of appetite, loss of weight, abdominal pain and back pain. SI NENs showed 100% positivity for synaptophysin and 78.6% positivity for chromogranin. Stomach NENs presented at median age of 53 years (IQR 44.5,69) with F:M ratio of 1.5:1. 40% (N=2/5) of stomach NENs were NECs.

Appendicular NENs were found in 6 younger patients with median age of 37.5 years (IQR 20,41.75). All were well differentiated grade 1 tumours. Colon and anal canal NENs were found at older age group with median of 62 years (IQR 46,68). These were also well differentiated with 36% G1 and 45% G2 tumours.

Discussion

Neuroendocrine tumors present a significant challenge in clinical practice due to their heterogeneous presentations. This data from Sri Lanka provides specific insights into the epidemiology, pathological features, and clinical presentations of NETs in Sri Lanka and allow comparison with international data.

Epidemiology and Demographics

The epidemiological characteristics of NENs in our study show both commonalities and differences compared to other global study data. The study sample included 151 patients, with an almost equal gender distribution (77 males and 74 females) with a median age of 58 years. This profile is consistent with global statistics, which shows that NENs are usually detected in middle-aged to older persons (median age at diagnosis: 58–64 years). Studies from Sweden and the US show virtually identical gender ratios and comparable age distributions [7,8], however some studies point to a somewhat greater incidence in females [9,10]. A study based in United Kingdom yielded data indicating that the median age of diagnosis was approximately 60 years, with a slightly higher prevalence in females [11].

When considering the Asian data, in India, the median age of diagnosis is around 55-60 years, with a slight male predominance [12,13]. In studies from some other Asian countries such as Taiwan and China also show similar results with an age at diagnosis around mid-fifties with slight male predominance [14,15]. This illustrates that our data aligns with global and regional data.

Primary Tumor Sites

Gastroenteropancreatic neuroendocrine tumors (GEP-NENs) were the most common primary tumors in our sample, accounting for 75.7% of cases. Prevalence of GEP-NENs in our study mirrors the global trend, where it represents the major proportion of all NENs, around 60% to 70% of all NENs [16]. In the UK, a population-based cohort study revealed that more than half of all NENs diagnosed were GEP-NENs [3], while data from Spain using their national cancer registry also indicated a substantial percentage in their NENs were GEP-NENs. [17]. In China, GEP-NENs accounted for 69.2% of cases, with the pancreas, stomach, and rectum being frequent sites of origin [15]. Similarly, Indian studies show a high prevalence of GEP-NENs, particularly in the pancreas and small intestine. [18,19]

While the prevalence percentages and prevalent forms of GEP-NENs differ throughout studies, certain recurring trends show up. The most often reported type of GEP-NENs, pancreatic NENs (PNENs), accounts for about 30–40% of all GEP-NENs. Small intestinal NENs (SI-NENs), particularly those originating in the ileum, also constitute a significant portion, ranging from 20% to 30%. Rectal NENs typically comprise 15% to 20% of GEP-NENs, whereas stomach NENs are less common, accounting for 5% to 10% of cases and appendiceal and colonic NENs typically contribute between 5% and 7% of GEP-NENs [18,20,21].

Pancreatic NENs (PNENs) were the most common GEP-NENs in our study, accounting for 41.9% of cases. This finding aligned with the majority of the studies globally. These tumors presented at a median age of 56 years and showed a female predominance (F ratio 1.61:1), which contrasts with some global data indicating a male predominance [7]. Majority of PNENs were well-differentiated (89.3%) which indicate a generally favorable prognosis for these tumours in general.

Small Intestinal NENs (SI NENs) accounted for 30.9% of GEP-NENs in our study, with a nearly equal gender distribution and a median age of 61 years which aligns with global data, where SI NENs are commonly diagnosed in older adults and exhibit a balanced gender ratio. [9,11].

In our analysis, **stomach NENs** made up 6.1% of GEP-NENs; with a female predominance and presented with a median age of 53 years. It is noteworthy that 40% of stomach NENs had neuroendocrine carcinomas (NECs), as these aggressive tumours are not as commonly documented in some areas. Data from around the world, including China, show how the prevalence of stomach NECs varies [7,9,14], which could be a result of variations in healthcare infrastructure and diagnostic procedures. Studies from India also show a decreased prevalence of stomach NECs, with a major contributing factor being variations in reporting and diagnostic criteria [18].

In our Sri Lankan data, **appendicular NENs** were accounting for 7.4% of the cases, and those were discovered in younger individuals, with a median age was 37.5 years. Those were all grade 1 well-differentiated tumours. Conversely, older persons had a higher frequency of colonic and anal canal NENs (13.6%), with a notable number of well-differentiated

cases. These results are consistent with worldwide data, which show that colonic NENs are more common in older populations, while appendiceal NENs are frequently detected in younger individuals with an excellent prognosis [16].

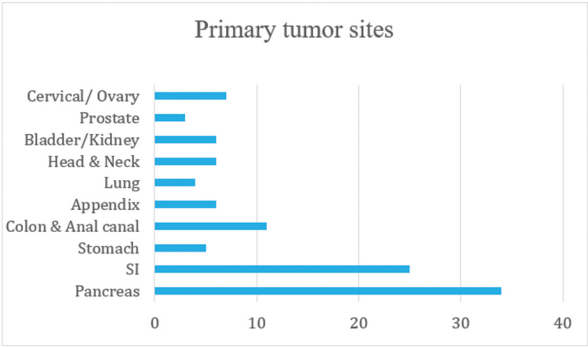

Figure 1: Primary tumour sites

Metastatic Sites

According to our data liver is the most common site (36%) in metastatic NENs, followed by lymph nodes (25%), the lungs (23%), the central nervous system (14%), and bone (2.2%). This distribution of metastatic sites is consistent with data from throughout the world. This pattern is in line with results from the studies in Asia and other regions of the world. [7,9,13]. Number of bone metastases was low in our sample, compared to other sites, possibly because bone is less commonly biopsied or resected.

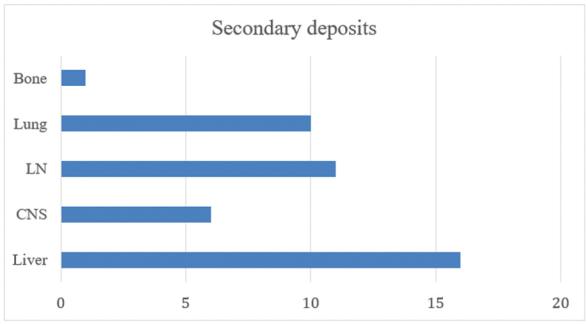

Figure 2: Metastatic sites

Diagnostic Markers and Tumor Grading

The key markers used in immunohistochemical analysis in our study were synaptophysin and chromogranin A, with positive rates of 79.5% and 82.8%, respectively. These indicators are widely accepted as standard for determining whether a tumour is neuroendocrine [16]. Even though immunohistochemical expression of neuroendocrine indicators, such as Synaptophysin and Chromogranin A, can be performed in Sri Lanka, those are not freely available. Other markers used in diagnosis of NENs include vimentin, NSE, PanCK, CD56, CD99, E-Cadherin, and S100. Future development in molecular profiling will enable more accurate understanding of the biology of tumours and possible targets for treatment. When combined with conventional histological evaluations, these molecular insights can improve the precision of diagnosis and prognosis for patients with NENs.

According to tumour grading, 65% of the samples in our study were well-differentiated, grade 1 and grade 2 tumours. NECs made up only 35%. These results are in line with worldwide trends. [7,8,11,15], where well-differentiated NETs are more prevalent and have a better prognosis than NECs.

Clinical Presentation

Neuroendocrine tumours (NETs) primarily manifest with vague symptoms, which can cause diagnostic delays. In our cohort of patients also, abdominal pain, obstructive jaundice, back pain, loss of appetite and loss of weight were the common presenting symptoms. These symptoms align with worldwide data, which show that NENs often appear with nonspecific, nebulous symptoms that might be mistaken for other gastrointestinal or systemic disorders [18,23,24]. The therapy and prognosis are frequently complicated by late-stage diagnoses that arise from these vague clinical symptoms.

The underreporting of symptoms in histopathology request forms is a main draw back in analyzing the symptomatology in our cohort of patients, hence it is difficult to compare our data with the excising data.

Limitations and strengths

Data were collected exclusively from histopathology reports, without correlation with imaging or clinical records. This limits the ability to assess tumor burden, disease staging, and potential multifocality. As a retrospective study, missing data and reporting inconsistencies could introduce bias. The study did not evaluate treatment outcomes or survival data, limiting its implications for prognosis and management.

This is the first multi-center study providing a comprehensive overview of NENs in Sri Lanka, covering diverse patient populations. The findings align with global trends, reinforcing the validity of results while also highlighting regional variations in anatomical distribution. The use of WHO 2022 classification ensures standardization and comparability with international studies. The study establishes a foundation for prospective research incorporating imaging, clinical data, and long-term patient outcomes.

Conclusion

This retrospective study demonstrated that the pathological characteristics of NENs in Sri Lanka are generally consistent with worldwide data. International trends are observed in the demographic as well as in the pathological aspects, such as tumour grading and metastatic patterns. Regional variations in pathological characteristics, however, emphasize how crucial it is to conduct local research to customize treatment and diagnostic approaches. To ensure worldwide standards are met and Sri Lankan NEN management is optimized, more studies and national data collection will be necessary.

References

1. Sandvik OM, Søreide K, Gudlaugsson E, Kvaløy JT, Søreide JA. Epidemiology and classification of gastroenteropancreatic neuroendocrine neoplasms using current coding criteria. *Br J Surg.* 2016;**103**(3):226-232. doi:10.1002/bjs.10034
2. Scherübl H, Streller B, Stabenow R, et al. Clinically detected gastroenteropancreatic neuroendocrine tumors are on the rise: epidemiological changes in Germany. *World J Gastroenterol.* 2013;**19**(47):9012-9019. doi:10.3748/wjg.v19.i47.9012
3. Genus TSE, Bouvier C, Wong KF, et al. Impact of neuroendocrine morphology on cancer outcomes and stage at diagnosis: a UK nationwide cohort study 2013-2015. *Br J Cancer.* 2019;**121**(11):966-972. doi:10.1038/s41416-019-0606-3
4. WM, Tan SH, Tan DMY, et al. Clinicopathologic Characteristics and Survival of Patients with Gastroenteropancreatic Neuroendocrine Neoplasm in a Multi-Ethnic Asian Institution. *Neuroendocrinology.* 2019;**108**(4):265-277. doi:10.1159/000495140
5. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol.* 2022;**33**(1):115-154. doi:10.1007/s12022-022-09708-2
6. Hirabayashi K, Zamboni G, Nishi T, Tanaka A, Kajiwara H, Nakamura N. Histopathology of gastrointestinal neuroendocrine neoplasms. *Front Oncol.* 2013 Jan 22;**3**:2. doi: 10.3389/fonc.2013.00002. PMID: 23346552; PMCID: PMC3551285.
7. Dasari A, Shen C, Halperin D, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients with Neuroendocrine Tumors in the United States. *JAMA Oncol.* 2017;**3**(10):1335-1342. doi:10.1001/jamaoncol.2017.0589.
8. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;**26**(18):3063-3072. doi:10.1200/JCO.2007.15.4377.
9. Hallet J, Law CHL, Cukier M, et al. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. *Cancer.* 2015;**121**(4):589-597. doi:10.1002/cncr.29099.
10. Oberg K, Knigge U, Kwekkeboom D, Perren A, and the ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2012;**23**(Suppl 7)
11. Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am.* 2011;**40**(1):1-18, vii. doi:10.1016/j.ecl.2010.12.005.
12. Uppin MS, Uppin SG, Sunil CS, Hui M, Paul TR, Bheerappa N. Clinicopathologic study of neuroendocrine tumors of gastroenteropancreatic tract: a single institutional experience. *J Gastrointest Oncol.* 2017 Feb;**8**(1):139-147. doi: 10.21037/jgo.2016.12.08. PMID: 28280618; PMCID: PMC5334039.
13. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology.* 2020;**76**(2):182-188.
14. Tsai HJ, Wu CC, Tsai CR, Lin SF, Chen LT, Chang JS. The epidemiology of neuroendocrine tumors in Taiwan: a nation-wide cancer registry-based study. *PLoS One.* 2013 Apr 22;**8**(4):e62487. doi: 10.1371/journal.pone.0062487. PMID: 23614051; PMCID: PMC3632554.
15. Zhang P, Li J, Liu B, et al. Clinicopathological characteristics and prognosis of gastroenteropancreatic neuroendocrine neoplasms: a multi-center retrospective study in China. *Sci Rep.* 2020;**10**(1):16300. doi:10.1038/s41598-020-73215-5.
16. Pape UF, Niederle B, Costa F, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms of the appendix and goblet cell carcinoids. *Neuroendocrinology.* 2012;**95**(2):135-156.
17. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognosis of patients with gastroenteropancreatic neuroendocrine tumors: results from the National Cancer Registry of Spain. *Endocrine.* 2010;**41**(3):627-637.
18. Menon P, Arun I, Varma V, et al. Gastroenteropancreatic Neuroendocrine Tumors: An Institutional Experience with Critical Appraisal of Literature. *J Oncol.* 2021;2021:6612341. doi:10.1155/2021/6612341.
19. Rao S, Bhaskar M, Kotian CM, et al. Gastroenteropancreatic neuroendocrine tumors: A retrospective study of clinicopathological features and treatment outcomes from a tertiary care center in India. *J Gastrointest Oncol.* 2021;**12**(5):2043-2052. doi:10.21037/jgo-21-265
20. Frilling A, Åkerström G, Falconi M, Pavel M, Ramos J, Kidd M, Modlin IM. Neuroendocrine tumor disease: an evolving landscape. *Endocr Relat Cancer*. 2012;**19**(5). doi:10.1530/ERC-12-0024.
21. Itanet Database Project, 2023; Endocrine, 2023.
22. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* 2008;**9**(1):61-72.
23. Caplin ME, Baudin E, Ferolla P, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. *Ann Oncol.* 2015;**26**(8):1604-1620.
24. Ito T, Lee L, Jensen RT. Carcinoid-syndrome: recent advances, current status and controversies. *Curr Opin Endocrinol Diabetes Obes.* 2010;**17**(1):50-59. doi:10.1097/MED.0b013e328334f61d.