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Clinicopathological findings of thirty-nine gastrointestinal neuroendocrine neoplasms

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Aim: **In this study aimed to re-evaluate the clinicopathological parameters of gastrointestinal system neuroendocrine neoplasms (GIS-NENs) that have been diagnosed in our pathology department between 2008 and 2017, and to examine survival durations.** ***Materials and Methods:*** **The study included GIS-NENs samples of 39 patients. The total number of organ biopsies, the number of NENs, age, gender, localization, diameter, mitosis, necrosis, lymhovascular invasion and perineural invasion characteristics were evaluated. The association between survival and Ki-67 index was analysed.** ***Results:*** **We identified 39 cases of GIS-NENs that had developed from the appendix, stomach, rectum, cecum, ileum, and duodenum. Thirty four cases were diagnosed with G1 (87.2%), one case with G2 (2.6%), and four cases with G3 (10.3%). One patient was diagnosed with G3 and T2 and died during the 9th month under treatment. Another patient diagnosed with G3 and T1 died during the 26th month.** ***Conclusion:*** **In the diagnosis of GIS-NENs has increased in recent years because of the widespread use to endoscopy. While endoscopic and small diameter NENs are histologically evaluated, after all sections of the tumor tissue have been examined in the largest area, the Ki-67 index score and mitotic rate should be determined based on the WHO 2010 classification criteria. According to the Cox regression result, a unit increases in the Ki-6 7 index increases the probability of death by 3.1%.**

INTRODUCTION

The estimated prevalence of neuroendocrine neoplasms (NENs) is 1 to 2 cases per 100,000 people, of which the gastrointestinal tract is most common site.[1,2] The incidence of gastrointestinal system neuroendocrine neoplasms (GIS-NENs) is around 67.5% amongst all NENs.[2] Located in the esophagus, stomach, duodenum, pancreas, ileum, jejunum, appendix, colon, and rectum, these tumors are summarized as gastroenteropancreatic NENs.[3,32] Although multiple diagnostic instruments, such as computed tomography, magnetic resonance imaging, ultrasonography, serological tests, and endoscopy, have been developed, pathological investigation is needed for diagnosis of GIS-NENs.[4]. In 2010, the World Health Organization (WHO) announced a new classification system for NENs.[4,5]. All neuroendocrine carcinomas (NECs) are G3 tumors in terms of grading.[6] This classification is made using the Ki-67 index and mitotic count in histological material.[1,7-9] In Turkey, there is limited data available on epidemiology of gastroenteropancreatic NENs. In this study was to evaluate the survival and the demographic data of GIS-NENs cases referred to our pathology department during an eleven-year period.

MATERIALS AND METHODS

Total of 39 cases were defined to be histomorphologically diagnosed with GIS-NENs in the pathology department of University Education and Research Hospital between 1st January 2008 and 1st April 2017 (Table 1). The clinical research ethics committee of the Hitit University Medical School decision number is 025 and decision date was 27th May 2016.

Patients diagnosed with mixed adenoneuroendocrine carcinoma, endocrine cell hyperplasia and neuroendocrine cell dysplasia were excluded from the study. There were no NENs arisen from the esophagus, pancreas or liver. The study was based on the first biopsy outcomes. A total of 39 (0.10%) specimens of 16 (41.0%) appendectomy, 18 (46.2%) gastric endoscopic biopsy, 1 right colectomy, 2 rectoscopic polypectomy, 1 duodenal endoscopic biopsy and 1 ileal partial resection material were examined. A total of 39 (0.10%) patients were included in the study. There were 16 (41.0%) appendectomy, 18 (46.2%) gastric endoscopic biopsy, 1 (3.1%) right colectomy, 2 (6.3%) rectoscopic polypectomy) and one (2.6 %) patial terminal ileum resection, and one (2.6 %) duodenal endoscopic biopsy cases.

Histopathologic findings (grade, mitotic index, Ki-67 proliferation index, lymphovascular invasion, local invasion and necrosis) were re-evaluated using archive samples. The survivor patients were contacted via phone. These patients were called to our pathology department and their consents were received in terms of ethics rules. Localization and size information of the tumors were confirmed by reviewing the radiological and endoscopic findings from the hospital computer recordings, if necessary. Macroscopic sizes were obtained from the biopsy archive reports. Maximum size was recorded in multifocal tumors. Immunochemically Ki-67 (BioGenex, 1/100, San Ramon, CA), synaptophisin (Thermo Scientific, 1/100, USA), chromogranin A (CgA) (BioGenex, 1/100, San Ramon CA), CD56 (Thermo Scientific, 1/100, USA), and pancytokeratine (BioGenex, 1/100, San Ramon, CA) were studied.

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Table 1 Distribution of the rates in biopsies and cases by years

Year	Appendix		Stomach		Colorectum		Ileum / duodenum			
	The number of appendectomy (n)	NENs n (%)	The number of gastric (corpus and antrum) biopsies (n)	NENs n (%)	The number of colorectal biopsies (n)	NENs n (%)	Ileum / duodenum biopsies (n)	NENs n (%)	Total the number of biopsies n (%)	Total GIS-NENs number, percentage n (%)
2008	589	1 (0.17)	154	0	24	0	32	0	7799	1 (0.01)
2009	816	0	404	0	42	0	89	0	1351	0
2010	939	2 (0.21)	248	0	22	0	66	0	1275	2 (0.17)
2011	796	3 (0.38)	1136	0	27	0	234	0	1959	3 (0.15)
2012	738	2 (0.27)	2459	1 (0.04)	472	0	346	0	2193	3 (0.14)
2013	624	3 (0.48)	3857	4 (0.10)	632	2 (0.32)	389	0	5502	9 (0.16)
2014	410	2 (0.49)	2554	2 (0.08)	339	0	345	0	3648	4 (0.11)
2015	1543	1 (0.070)	5832	4 (0.070)	743	1 (0.14)	462	0	8580	6 (0.07)
2016-01.04.2017	1240	2 (0.16)	5308	7 (0.13)	840	0	864	2 (0.23)	8252	11 (0.13)
Total	**7695**	**16 (0.21)**	**21952**	**18 (0.082)**	**3141**	**3 (0.10)**	**2827**	**2 (0.07)**	**40559**	**39 (0.10)**

There were four appendiceal and three gastric cases under 0.5 cm. At least 40 fields could not be evaluated in these patients and, grading was carried out and Ki-67 index was measured by screening of all tumor tissue.[7] The findings ultimately re-evaluated and classified according to the WHO 2010 criteria.[4] The evaluation of variables and tests was carried out using IBM SPSS Statistics 21 software[10] and Power Analysis and Sample Size 11 2008 Statistical Software.[11]In the statistical testing, a two-sided p value ≤ 0.05 was considered statistically significant. The distributional properties of continuous variables were expressed as mean (± standard deviation, SD), continuous categorical variables were presented by frequency and percentage, and the cumulative hazard rate of survival outcome was estimated by the Nelson-Aalen method. In univariate analysis, the two-sample *t* test was used to examine the differences in the distributions of continuous variables and categorical variables within groups. The Chi-square test and Fisher's exact test (if the expected values in any of the cells of a contingency table were <5) were used for comparison of qualitative data. For testing the quantitative variables, the *t* test, analysis of variance (ANOVA), and Kruskal-Wallis tests, as well as least significant difference (LSD) test for pairwise comparison, were used. The *Cox proportional hazards* regression was used to model survival time using related covariates.

RESULTS

The number of appendix, stomach, colorectal and ileal/duodenal biopsies in 9 years was 40,559 (Table 1). In 39 (0.10%) cases, GIS-NENs were detected. Of these, 19 (48.7%) were female and 20 (51.3%) were male (Table 2). Statistically, there was no significant difference between the tumor groups in terms of gender (p>0.05). Patients were between 20- and 83-years-old (mean 50.75 ± 6.70). The mean age was 49.3 ± 18.03 in males and 52.3 ± 15.52 in females. Statistically, there was no significant difference between genders (p=0.341). Both synaptophysin and CgA were positive in 34 patients (87.2%).

In 9 years, 7695 appendectomies were examined and 16 (0.21%) appendiceal NEN were identified (Table 1). Patients (F/M=6/9) with appendiceal NENs were aged between 20 and 71 years (mean ±st. deviation; 38.8±13.05) (Table 2). There were 21,952 stomach biopsies and 18 (0.082%) gastric NENs were identified (Table 1). Patients (F/M=9/9) with NEN were aged between 27 and 83 years (mean ±st. deviation; 59.9±14.60) (Table 2). A total of 3141 colorectal biopsies were examined and three (0.10%) NENs were identified (Table 1). Patients with colorectal tumors were aged between 39 and 69 years (mean ±st. deviation; 55.7±11.85). One of these was female (aged 39 years) and the other was male (aged 69 years); the cecum case was female (aged 59 years) (Table 2). There were 2827 ileal/duodenal biopsies and two (0.07%) NENs were identified (Table 1). The ileum case was 54-years-old and the duodenum case was 68-years-old. There was no statistically significant difference between tumor groups in terms of tumor size (p=0.249), mitotic count (p=0.256) or Ki67 (p=0.153). There was a significant difference between the tumor groups in terms of age (p=0.004). A significant difference was found between the appendix and stomach groups in terms of age (p<0.001). A significant difference was found between the appendix and ileum/duodenum groups in terms of age. (p=0.037). No significant difference was found between the tumor groups in terms of gender (p=0.897) (Table 2).

Thirteen appendiceal tumors were localized in the distal end, one in the one third middle section, and two in the distal and middle section. For the tumors of the appendix, the maximum diameter was 5 cm and the minimal diameter was 0.2 cm (Figure 1). The mean diameter was 1.2 cm. There was no necrosis or vascular invasion. Right hemicolectomy was performed in the tumors of 5 and 3.3 cm diameters and no residual tumors or lymph node metastasis was determined, but perineural invasion was found. There was invasion to the serosa in nine appendiceal NENs. The mean tumor dimension was 1.7 cm showing invasion to the serosa. All the cases were diagnosed as G1. Fourteen cases were stage I, one case was stage IIA and one case was stage

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Table 2 Gender, age and stage features of the NENs

Features of the NENs	Female	Male	Age (y)				Mean (age)	Stage		
			20-39	40-59	60-79	80+		Localized	Regional	Distant
Stomach n=18	9	9	3	3	11	1	59.9	16		2
Appendix n=16	7	9	11	4	1		38.8	16		
Colorectum n=3	2	1	1	1	1		55.7	2	1	
Ileum /duodenum n=2	1	1		1	1		61.0	1		1

Figure 1 Appearance of an appendiceal NEN in %10 formalin fixed tissue. Light yellow and homogenous solid mass.

Table 3 Clinical and histological features of NENs and their relationship with survival

No	Localization	Sex	Age	Tumor size (cm)	Mitotic count (/10 HPF)	Ki-67 Index (%)	Grade (WHO 2010)	TNM	Survival (month)	Recurrence or death
1	Appendix	E	20	0.2	0	≤2	1	T1a	72	Recurrence-free
2	Appendix	E	21	1	1	≤2	1	T1b	41	Recurrence-free
3	Appendix	E	30	0.3	0	≤2	1	T1a	73	Recurrence-free
4	Appendix	E	31	5	1	≤2	1	T3	19	Recurrence-free
5	Appendix	E	36	0.8	0	≤2	1	T1a	52	Recurrence-free
6	Appendix	E	37	1.5	1	≤2	1	T1b	55	Recurrence-free
7	Appendix	E	38	0.5	0	≤2	1	T1a	43	Recurrence-free
8	Appendix	E	39	1.2	1	≤2	1	T1b	33	Recurrence-free
9	Appendix	E	71	1	0	≤2	1	T1a	27.5	Recurrence-free
10	Appendix	K	29	0.9	0	≤2	1	T1a	84	Recurrence-free
11	Appendix	K	35	0.2	0	≤2	1	T1a	73	Recurrence-free
12	Appendix	K	36	3.3	1	≤2	1	T2	103	Recurrence-free
13	Appendix	K	41	0.7	0	≤2	1	T1a	82	Recurrence-free
14	Appendix	K	52	1.2	1	≤2	1	T1b	11	Recurrence-free
15	Appendix	K	57	0.8	0	≤2	1	T1a	42	Recurrence-free
16	Appendix	K	47	0.6	0	≤2	1	T1a	1	Recurrence-free
17	Cecum	K	59	6	44	>20 (90)	3	T4	39	Recurrence-free
18	Duodenum	K	68	0.9	0	≤2	1	T1	3	Recurrence-free
19	Gastric antrum	K	61	1.2	1	≤2	1	T2	36	Recurrence-free

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20	Gastric antrum	E	68	1	4	2-20 (10)	2	T1	15	Recurrence-free
21	Gastric corpus	E	36	0.7	0	≤2	1	T1	19	3. and 40. month, there is recurrence
22	Gastric corpus	E	48	1.2	0	≤2	1	T2	11.5	Recurrence-free
23	Gastric corpus	E	66	0.8	0	≤2	1	T1	11.5	Recurrence-free
24	Gastric corpus	E	67	1	1	≤2	1	T1	41	1. month, there is recurrence
25	Gastric corpus	K	27	0.9	1	≤2	1	T1	34	3. and 7. month, there is recurrence
26	Gastric corpus	K	62	0.8	0	≤2	1	T1	2	13. month, there is recurrence
27	Gastric corpus	K	68	1.5	1	≤2	1	T2	20	Recurrence-free
28	Gastric corpus	K	73	0.3	0	≤2	1	T1	38	Recurrence-free
29	Gastric corpus	K	79	0.8	0	≤2	1	T1	21	3. month, there is recurrence
30	Gastric corpus	E	57	0.5	0	≤2	1	T1	2	Recurrence-free
31	Gastric corpus	E	63	0.7	0	≤2	1	T1	8	Recurrence-free
32	Gastric corpus	K	38	1.4	0	≤2	1	T1	7	Recurrence-free
33	Gastric corpus	K	65	0.4	0	≤2	1	T1	9	Recurrence-free
34	Gastric corpus	E	61	1	28	>20 (40)	3	T1	46.5	Recurrence-free
35	Gastric corpus	E	83	1.5	24	>20 (70)	3	T2	9	dead in 9th month
36	Gastric corpus	K	57	0.8	26	>20 (60)	3	T1	26	died in 26th month
37	İleum	E	54	2	2	≤2	1	T3	3	Recurrence-free
38	Rectum	E	60	0.9	0	≤2	1	T1	24	Recurrence-free
39	Rectum	K	39	1.5	1	≤2	1	T1	44	Recurrence-free

IIB.[9,10] None of the cases displayed metastasis. The patients have been surviving without disease for a mean of 48.5± months (Table 3).

For gastric cases, the mean age was 59.9± years. There were 16 cases in the corpus and two cases in the antrum. Four (28.6%) gastric lesions were multicentric. The maximum diameter was 1.5 cm and the mean diameter was 0.9± cm. Fourteen cases were diagnosed with G1. Of these, one relapsed on the first month, one on the 3rd and 40th months, one on the 3rd and 7th months and one on the 3rd months. The patients who developed recurrence on the 3rd and 40th months was evaluated in an outer center and, in the last biopsy examination, their Ki-67 index was reported as 10 and the mean number of mitoses was reported as 8 in 50 HPF. One case was diagnosed with G2 and three cases with G3. Fourteen patients were stage T1 and four patients were stage T2 that they were the surgical margin negative in endoscopic mucosal resection (EMR). One patient was diagnosed with G3 whose surgical margin was positive and total gastrectomy was performed. This patient was diagnosed as NEC G3 and T2 and died under treatment during the 9th month. In this case, there were metastases in three lymph nodes and liver. Another patient, who's surgical margin was negative, EMR was diagnosed with G3 and T1 and died during the 26th month. There were metastases to the liver in this case. Blood gastrin and serotonin levels were within normal limits. Another patient with G3 and T1 is still alive (for 46.5 months), whose surgical margin was negative for EMR (Table 3). None of the other patients developed metastasis. There was atrophic gastritis in 11 of these cases. The duodenum NEN was 0.9 cm in diameter and was diagnosed as G1. The tumor was limited to the submucosa and mucosa but its basal surgery margin was positive. The EMR was performed again and the tumor was not observed at the surgical margin. Also, the blood gastrin level was within normal limits.

The terminal ileum NEN was 2 cm in diameter. Neoplasia showed invasion to the serosa. Perineural and angiolymphatic invasion was not detected, the NEN was diagnosed with G2, and there was metastases in the liver. The rectal cases were polypoid masses with 1.5 and 0.9 cm diameters (Figure 2). Both cases were G1. One was stage IA and the other was stage IB[8] (Table 3). The Ki-67 index was 90 in the cecum localized tumor, which was diagnosed with G3. There were focal necrosis, perineural invasion, and spread to the seroza. However, angiolymphatic invasion and lymph node metastasis were not found. This case was stage IIIA[8] (Table 3). Ki-67 proliferation index was between 20% and 55% in 1 case and in 3 cases larger than 55%. These cases were over 55 years old. Of 39 patients, 4 (%10.3) had a history of diabetes. None of the patients had a history of alcohol use. The number of cases with 1 mitosis in 50 high power fields (HPF) (40× /0.65, plane, Nikon, Japan) was 27 (84.4%). The gastric tumors diagnosed with G2 included four mitoses in 50 HPF. Whereas, G3 cases included 24 to 90 mitoses in 50 HPF. There was a statistically significant difference between G1and G3 cases in terms of the number of mitoses ($p<0.001$).

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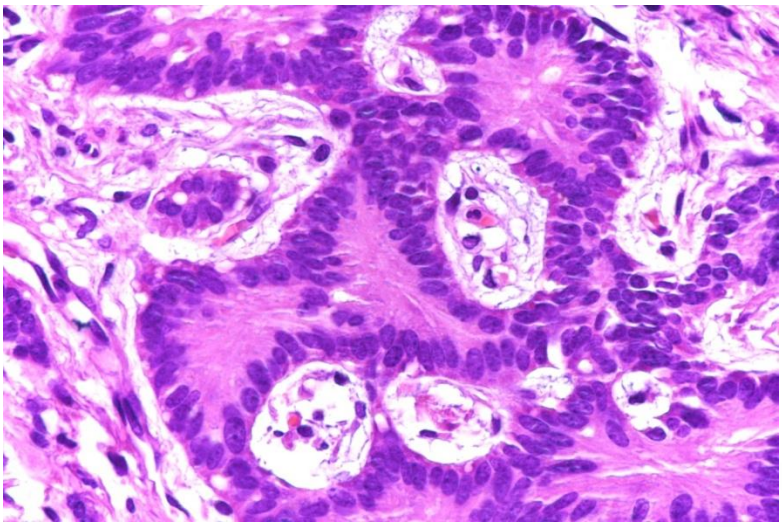

Figure 2 Tumor cells of uniform appearance with a mildly coarse granular chromatin distribution (H&E, × 600).

According to the WHO 2010[3,4]; 27 cases were classified as NEN G1, one case as NEN G2 and four cases as NEC G3.

DISCUSSION

In the GIS-NENs, the classification of WHO requires screening of at least 50 fields with higher mitotic rates at 40× magnification, while European Neuroendocrine Tumor Society (ENETs) requires screening of at least 40 fields, and counting at least 500 cells for mitotic rates.[4,7,8] In this study, at least 50 fields were screened in ten HPF for every tumor. There were four appendiceal and three gastric cases under 0.5 cm, and at least 40 fields could not be evaluated. In this study, these localizations and mean age are consistent with the literature.[3,4,8]. Several publications in the literature report a mean age about 55 years for GIS-NENs.[2,6]

The incidence of gastric NENs is less than 2% among gastric neoplasms[12] and these tumors are account for 8.7%-41% of all GIS-NENs.[13] In this study, the frequency of gastric NENs among all the GIS-NENs was 46.2%. In the study of Niederleet al.[3], the incidence of gastric NENs was 0.08 per 100,000. In recent studies, gastric NENs are observed more often compared than ileal and appendiceal NENs.[6] In this study, the frequency of gastric NENs is close to that of appendiceal NENs, which is similar to the findings of Özkara et al.[6] and Nikou et al.[14] Gastric NENs are observed as multifocal, small, and polypoid tumors (<10 mm) in the corpus and/or fundus[4,5] and divided into four types.[15] In this study, four of the cases were multifocal. Sixteen were corpus localized and two were antrum localized. Early identification of gastric NENs is important in patients with atrophic gastritis.[2] There was atrophic gastritis in 11 of the cases included in this study. A patient with G1 relapsed during the 40th month. Repeat EMR was performed in this patient in an outer center. The Ki-67 was higher than 2 and this patient was diagnosed as G2. Local excision, antrectomy, and gastrectomy are treatment options in the cases having a diameter smaller than 1 cm and develop recurrence.[14]A tumor diameter exceeding 1 cm is considered as a poor prognostic factor.[16] About 75% of GIS-NENs infiltrate into the submucosa. In this tumors, conventional polypectomy has difficulty achieving complete pathological resection, and the complete resection rate of EMR varies from 52.2% to 84.6%.[17] Including the statement of "high grade NEC may not be ruled out" in the pathology report of the endoscopic biopsy of primary tumor would be appropriate when defining Ki-index.[9] One case of 1.5 cm diameter diagnosed with T2 and G3 died during the 9th month and another case of 0.8 cm diameter diagnosed with G3 died during the 26th month. The other patients are currently recurrence free for durations varying between 2 and 46.5 months (mean 20.1 month). There were eight cases with tumor diameters equal to or greater than 1 cm. In the study of Ishida et al.[18] survival was reported as 66.7% in stage I, 49.3% in stage II, 64.3% in stage III , and 7.7% in stage IV patients.

In this study, 16 (0.21%) appendiceal NEN cases were identified. In the study of In't Hof et al.[19] seven (0.47%) cases of appendiceal NEN were found among 1,485 appendectomies. In the study of Akbulutet al.[20] the rate of cases diagnosed with carcinoid tumors was 0.21% (n=287) among 80,698 appendectomies. The incidence is 0.08 per 100,000 in the study of Niederleet al.[3] These rates are consistent with the findings reported here. Appendiceal NENs constitute 55% of GIS endocrine tumors.[21] In this study, this rate was found to be 41.0% and thirteen of the tumors were localized in the distal section. The most common (75%) localization site of appendiceal NENs is type region.[19,21] As stated in the study of Ruoff et al.[22] many appendiceal NENs are asymptomatic and it usually takes about 9 years for these to become symptomatic. Similarly, in this study, all appendiceal NENs were asymptomatic and detected incidentally. In prognosis, the principal factor is tumor diameter in apendiceal NETs with a cut-off value of 2 cm diameter.[23] In this study, all patients have lived without recurrence for mean 48.5 months.

Rectal NENs are observed more commonly than colonic NENs.[8] Niederleet al.[3] reported the incidence rate as 0.03 per 100,000. These NENs are seen in the rectosigmoid and descending in 20% of cases, and in the cecum and transverse colon in 8% of cases.[24] In this study, three (0.12%) NEN were identified. Two (0.080%) of these cases were rectum localized and one (0.040%) was cecum localized. Both cases were G1. These patients are still disease free and have been recurrence free for 14 and 34 months respectively. Macroscopically, rectal NENs are observed as solitary sessile or semi-pedicle tumors with protected surrounding epithelium.[25] Many rectal NENs have small diameters (<1-2 cm) and a submucosal localization.[26] Therefore, the incidence of metastasis is high in these tumors.[2] In this study, the rectal NENs were of a polypoid structure. In the study of Yamagishi et al.[27], of 20 cases with rectal NENs, the 10-year disease free survival was reported as 86.8%; while in study of Maggard et al.[28] with 1271 cases, the 5-year survival was

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reported as 87.5%. In this study, there was a case with cecum tumor that as diagnosed as NEC. This patient, who underwent right hemicolectomy, has been living recurrence free for 39 months.

A gastrin-producing NEN (46%) presents as a small polypoid tumor within the submucosa and commonly occurs in the first part of the duodenum.[4] In this study, the duodenum NEN was 0.9 cm and was diagnosed as G1. The blood gastrin level was within normal limits.

In the study of Tsikitiset al.[29] rectal and appendiceal NENs have the best prognosis (with 95.6% and 90.3%), while colon and gastric NENs are stated to have a poor prognosis. In the same study, the 5-year survival was 86.2% for the small intestine, 82.7% for the stomach, and 67.4% for the colon.

In the study of Yao et al.[23], the median survival durations in patients with G1/G2 NENs who had localized, regional, and distant disease were 223, 111, and 33 months, respectively. For poorly differentiated NENs, the median survival durations in patients with localized, regional, and distant disease were 34, 14, and 5 months, respectively.[23] In our study, the mean survival rate in all cases was 32.9 months. The mean survival in appendiceal NENs was 50.7 months and, in gastric NENs, was 18.6 months. The cecal NEN case has lived for 39 months, rectal cases for 24 and 44 months, the terminal ileum NEN case for 3 months, and the duodenal NEN case is 3 months, without recurrence.

In recent years, more subclassification was needed, especially in G3 tumors due to a wide range of Ki-67 from 20% to 100%. Fazio et al.[30] proposed a general introduction of G4 NEC when Ki-67 exceeded 55%. In our study, four G3 cases were over 55 years old. In three of these cases, Ki-67 proliferation index was above 55%, and one died at 9 months and the other at 26 months. In the study of Cai W et al.[31] stated that metastatic disease developed in 30.20% of all patients with NEC, and the liver was the most common site of metastasis and comprised 74.80% of all metastatic disease. In our study, there was liver metastasis in one gastric NEC G3 and one ileal NET G2 cases. Both cases were over 50 years old.

In this study, statistical analysis could not be performed between grade and survival since we have only two deaths in our data set, but according to the statistical Cox regression analysis, a one unit increase in the Ki-67 index was found to increase probability of death by 3.7% (p=0.034). In the study of Paper et al.[1], the 2-year survival rates were reported as 100% in G1-NENs, 88.7% in G2-NENs, and 4.16% in G3-NENs, while the 5-year survival rates were 91.7% in G1-NENs, 73.4% in G2-NENs, and 27.7% in G3-NENs.

CONCLUSION

Thirty nine cases were histologically diagnosed with NEN and re-evaluated based on Ki-67 index and mitotic rate, according to the ENETS grading system and WHO classification. When appendiceal NENs were excluded, the incidence of gastric NENs was seen to increase over time. It should be remembered that tumors may be overlooked when NENs with small diameter and endoscopic biopsies are evaluated. Again, it was understood that, when endoscopic and small diameter NENs are histologically evaluated, after all sections of the tumor tissue have been taken in the largest area, the decision should be made for Ki-67 index and mitotic rate by WHO 2010 classification criteria. However, a clear reporting should be made by recording pathological findings, such as localization, tumor size, histomorphological features, tumor invasion-depth, Ki-67 index, mitotic rate, grade, and surgical margins, in order to allow conversion between these two classifications. The Ki-67 index (as a continuous variable) significantly correlated with recurrence-free, overall survival by Cox proportional hazard model [hazards ratio (HR)=1.03, P=0.034]. An increase of one unit in Ki-67 index was found to increase probability of death by 3.1%.

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Abbreviations
NENs: Neuroendocrine neoplasms
GIS-NENs: Gastrointestinal system neuroendocrine neoplasms
WHO: World Health Organization
NECs: Neuroendocrine carcinomas
HPF: High power fields (HPF)
G: Grade
CgA: Chromogranin A
SD: Standard deviation
ANOVA: Analysis of variance
LSD: Least significant difference
EMR: Endoscopic mucosal resection
ENETs: European Neuroendocrine Tumor Society

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