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Is WHO 2010 Pathological Classification a Guide for Neuroendocrine Tumors?

2010 DSÖ Patolojik Sınıfladırması Nöroendokrin Tümörler için bir Kılavuz mudur?

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ABSTRACT

Objective: The World Health Organization (WHO) suggested a classification of neuroendocrine tumors (NETs). The aim of this study was to review the relationship of mortality and morbidity and gastrointestinal NETs with the WHO 2010 classification.

Method: Patients who were admitted to our clinic and operated for gastrointestinal cancer were included in this study. The clinical characteristics, treatment, prognoses, mortality and morbidity, and the WHO 2010 classification were retrospectively reviewed.

Results: The WHO 2010 classification was used for the pathological classification. Of the total 31 patients, 16 were GEP-NET grade 1, 7 were grade 2, and 8 were grade 3. Mortality occurred in 4 patients who had multiple metastases, and therefore the operation could not be performed. These patients were grade 3 patients. Morbidity occurred in 3 patients after the operation of whom 2 were grade 2 and 1 was grade 3.

Conclusion: Although there are limitations, the WHO 2010 classification is convenient for patients with NETs.

Keywords: Gastrointestinal, neuroendocrine, pathology, tumor

ÖZ

Amaç: Dünya Sağlık Örgütü (DSÖ) nöroendokrin tümörler (NET) için bir sınıflandırma önerdi.Bu çalışmanın amacı DSÖ 2010 sınıflandırması ile tanımlanmış nöroendokrin tümörlerde mortalite ve morbidite ilişkisinin değerledirilmesidir.

Yöntem: Kliniğimize nöroendoskrin kanser nedeni ile yatırılarak ameliyat edilen hastalar bu çalışmaya dahil edildi.Klinik karakteristikler ,tedavi,prognoz,mortalite ve morbidite ve DSÖ 2010 sınıflandırması retrospektif olarak değerlendirildi.

Bulgular: Patolojik sınıflandırma için DSÖ 2010 sınıflandırması kullanıldı.Toplamda 31 hastanın 16 sı GEP-NET grade 1,7 si grade 2 ,ve 8 i grade 3 idi.Mortalite çoklu karaciğer metastazları olan ve bu yüzden ameliyat edilmeyen 4 hasada oluştu.Bu hastalar grade 3 hastalardı.Morbidite 2 si grade 2 1 i grade 3 olan toplam 3 hastada izlendi.

Sonuç: Kısıtlamaları olmasına rağmen DSÖ 2010 sınıflandırması NET li hastalarda kullanıma uygundur.

Anahtar kelimeler: Gastrointestinal, nöroendokrin, patoloji, tümör

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INTRODUCTION

Gastrointestinal neuroendocrine neoplasms (GI-NENs) arise from neuroendocrine cells, which are distributed mainly in the mucosa and submucosa of the gastrointestinal tract. Neuroendocrine tumor (NET) is a rare neoplasm of the gastrointestinal system, which constitutes 1–3% according to some reviews. This tumor type includes carcinoid tumors, neuroendocrine carcinoma (NEC), and small cell carcinoma. Due to the confusion in classification, the World Health Organization (WHO) revised the classification of NET in 2010. According to the classification, NETs are classified into three categories: NET G1 (carcinoid), NET G2, and NEC G3 (large cell or small cell type).[1] Grading is determined according to mitotic count and Ki-67 index. NET G1 is usually benign, whereas NET G2 and NEC are malignant.[2] The survival analysis for foregut NENs (gastric, duodenal, or pancreatic), according to the ENETS-WHO 2010 grading system showed that the survival rate of patients who had G3 tumors was significantly poorer than that of patients who had G1 or G2 tumors (G1 vs G3 and G2 vs G3, $p<0.01$). Similarly, the survival rate of patients who had G2 tumors was significantly poorer than that of patients who had G1 tumors (G1 vs G2, $p=0.04$).[3] In our study, we reviewed the relationship of gastrointestinal NET with mortality and morbidity according to the WHO 2010 classification.

METHOD

Our study was designed as a retrospective analysis. We studied patients who were admitted to the general surgery department of Ataşehir Florence Nightingale Hospital between January 2007 and February 2021 and operated for gastrointestinal cancer. All patients were operated by open or laparoscopic procedure or the tumor was removed by an endoscopic method. The pathology specimen was examined by the same pathologist.

The clinical characteristics, treatment, prognoses, mortality and morbidity, and the WHO 2010 classification were retrospectively reviewed.

RESULTS

The study included 30 patients who were admitted to the general surgery department and operated for tumor by an endoscopic method. Of these patients, 14 were females and 16 were males. The age was 53.09 (17–76) years. The tumor was found in the gastroduodenal space in 14 patients, in the pancreas in 2 patients, in the papilla in 1 patient, in the colon in 3 patients, in the appendix in 3 patients, in the sigmoid colon in 1 patient, in the jejunum in 1 patient, in the rectosigmoid junction in 1 patient, and in the rectum in 4 patients. Radical resection was performed on 18 patients, and 8 patients underwent endoscopic polypectomy. Only biopsy was performed for 4 patients, who did not undergo surgery or endoscopic resection. The WHO 2010 classification was used for the pathological classification: 15 out of the 30 patients were GEP-NET grade 1, 7 of them were grade 2, and 8 of them were grade 3 (Table 1). Mortality occurred in 4 patients who had multiple metastases and for whom the operation could not be performed. These patients were grade 3 patients (Table 2). Wound infection occurred in 3 patients after the operation. Of these, 2 were grade 2 and 1 was grade 3. There was no mortality or morbidity in 8 patients who were treated by the endoscopic method. Of these, 7 were grade 1 and 1 was grade 3.

DISCUSSION

Although there have been many classifications of NET, none of them clearly define the clinical aspects of it. In 2000, the WHO classified the endocrine tumors of the gastrointestinal tract as follows: well-differentiated endocrine tumor (carcinoid), well-differentiated endocrine carcinoid (malignant carcinoid), and poorly differentiated endocrine carcinoma (small cell carcinoma). According to the WHO 2010 classification, well-differentiated NENs are classified as G1 and G2 NETs, and poorly differentiated NENs are referred to as G3 NECs. According to this classification, G1 tumor prognosis is better than G2 and G2 is better than NEC.[4] Rindi et al.[5] investigated 102 cases of gastric NET using the WHO 2010 classification. In this review, 81 cases were NET G1, 5 were NET G2, and 16 were NEC. All NET G2 and NEC cases had metastases, and 3-year survival rates were 20% and 7%, respectively, but as expected NET G1 showed a 3-year 100% survival rate. Obtaining GI-NEN tissues by endoscopic forceps biopsy is often difficult due to their location in the deep mucosa and submucosa. Even if the biopsy is successful, the diagnosis of GI-NEN using biopsy material is sometimes difficult due to small specimen size or "crush" artifacts, which can lead to misdiagnosis.[6,7] Although biopsy and cytology are useful for the diagnosis of NETs, the accuracy of diagnosis and the evaluation of grading using these methods are limited by intratumoral heterogeneity.[8,9] Couvelard et al.[8] studied the heterogeneity of the Ki-67 index by comparing two random cores of liver metastasis from pancreatic NENs. They found a good correlation of the Ki-67 index (intraclass correlation coefficient, 0.63) between the cores. In contrast, Yang et al.[9] reported that about half of the NENs metastasizing to the liver showed intratumoral heterogeneity for Ki-67

Tablo 1. Çalışma parametrelerinin iki grup arasında karşılaştırılması

WHO grade	Place	Pathology	Ki67 %	HPF mitosis	Sinaptofizin	Kromagnanin	Operation	Tumor
G1	Pancreas	Well dif net	3	2–3	++	++	Whipple	4cm
G1	Stomach	Well dif net	8	2–3	+	+	Stomach wedge rezection	2cm
G1	Stomach	Well dif net	4	0	++	+	Total gastrectomy	2mm
G1	Stomach	Well dif net	1	1	++	+	DSG+RYGJ	8mm
G1	Stomach	Well dif net	1	1	+++	+	Total gastrectomy	3cm
G1	Apandicitis	Well dif net	1	2	+	+++	Lap apendectomy	1mm
G1	Apandicitis	Well dif net	1	2	+++	+++	Lap apendectomy	5mm
G1	Pankreas	Pank net	1	2	+	+++	Whipple	1 cm
G1	Apandist	Appendix karsinoid	1	2	+	++	Lap apendectomy	6mm
G1	Colon	Karsinoid tm	1	2	++	++	Subtotal colectomy	3cm
G1	Duodenum	Papillar net	1	1	+	++	Papillar biopsy with ERCP	3 mm
G1	Sigmoid	Grade 1 net	2	0–1	+++	–	Polipectomy	5mm
G1	Stomach	Grade 1	1	0	+	++	Endoscopic biopsy	1 mm
G1	Stomach	Well dif net	1	1	+	++	Polipectomy	5 mm
G1	Stomach	Well dif net	1–2	0–1	+	+	Polipectomy	1 cm
G1	Stomach	Well dif net	1	0–1	+	–	Polipectomy	5 mm
G1	Rectum	Well dif net	2	1	+++	–	Polipectomy	3 mm
G1	Rectum	Well dif net	2	1	+++	–	Polipectomy	3 mm
G1	Rectum	Well dif net	2	1	+++	–	Polipectomy	2mm
G1	Duodenum	Well dif net	2	0–1	+++	+++	Doudenal resection	15 mm
G1	Stomach	Well dif net	1	0–1	+++	+++	Biopsy	5 mm
G2	Sigmoid	Poor dif net	4	2–3	+	–	Sig rez	5 mm
G2	Jejunum	Poor dif net	1	2	+	+	Jujunum rez	4 cm
G2	Jejunum	Poor dif net	1–2	2–3	+	–	Jujunum rez	3.6 cm
G2	Sigmoid	Poor dif net	50	10	+++	–	Polipectomy	5 mm
G2	Stomach	Net	30	10	–	+	Hemigastrektomi+b2gj	5 cm
G2	Stomach	Poor dif net	2	2	+	++	EMR	5 mm
G3	Ileum-colon	Poor dif net	30	+	+++	+	Resection	10×8×8 cm
G3	Stomach	Karsinoid	25	0–1	+	+++	Polipectomy	5 mm
G3	Duodenum	Poor dif net	1	2–3	+	+	Rez	15 mm

WHO: World Health Organization; HPF: High power field; DSG+RYGJ: Distal subtotal gastrectomy+Roux en Y gasrojejunostomy; ERCP: Endoscopic retrograde cholangiopancreatograhy; EMR: Endoscopic mucosal resection

grading (G1 vs G2) on whole-slide subsections. Furthermore, if biopsy or cytology samples are small, they might not contain adequate numbers of tumor cells for the determination of the Ki-67 index and mitotic count.

Different classifications of the tumors in the gastrointestinal system are available. Scherübl et al.[10] classified gastric NETs into three groups: type 1 NET is related to chronic atrophic gastritis, type 2 NETs is multiple mucosal or submucosal small tumor (mm), and type 3 is a solitary polypoid tumor. Most type 3 NETs are more aggressive than type 1 and type 2 NETs. Type 3 NETs are arranged in a solid, trabecular pattern and occasionally have a high proliferation rate. Type 3 NETs often invade deeply, display lymphatic and vascular invasion, and are associated with local and/or distant metastases.

Tablo 2. Patients mortality and morbidity ratio

	Morbidity n (%)	Mortality n (%)
G1 (21 patients)	2 (9.4)	1 (4.7)
G2 (6 patients)	1 (16.6)	2 (33.4)
G3 (3 patients)	1 (33.4)	1 (33.4)

Wang et al.[11] showed that the pancreas is the principal site of GEP-NENs. However, many studies in the literature detected that the rectum is the most frequent site of the GEP-NENs, followed by the stomach and duodenum, whereas the jejunum/ileum accounts for less than 2% of the tumor cases. In our study, 15 tumors were in the midgut and 13 were in the hindgut. Therefore, different procedures are followed for the treatment of tumors. For example, the rectal NET was resected by an endoscopic method and the pancreatic NET was operated by Whipple procedure.[12] NENs can also be classified into functional and nonfunctional tumors based on the presence or absence of symptoms associated with the overproduction of hormones.[13] No information about the mortality and morbidity rate of the two groups is given in the WHO 2010 classification. In our study, we compared the mortality and morbidity rate of the two groups and found no difference between them. The study also demonstrated that the majority of the nonfunctional NENs usually presented with nonspecific symptoms, which may lead to a misdiagnosis of the tumor as irritable bowel syndrome or digestive adenocarcinoma. Among the many therapeutic options for NENs, surgery is the treatment of choice. Endoscopy is a useful choice for rectal carcinoma. Many types of operation are available to remove the tumor and improve the survival rate. The extent of surgical resection depends on the tumor size and origin, and approximately 75.9% of the patients underwent radical surgery. Our study showed that although WHO 2010 classification has some limitations, it is convenient to follow as a guide.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul University of Health Sciences Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 2022.01.06, Date: 04/08/2021).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. WHO classification of tumors of the digestive system. 4th ed. Lyon: International Agency for Research on Cancer; 2010.
2. Solcia E, Capella C, Klöppel G, Heitz PU, Sobin LH, Rosia J. Endocrine tumors of the gastrointestinal tract. In: Solcia E, Klöppel G, Sobin LH, editors. Histological typing of endocrine tumors. 2nd ed. Heidelberg, New York: Springer Verlag; 2000. p.61–4.
3. Pape UF, Jann H, Müller-Nordhorn J, Bockelbrink A, Berndt U, Willich SN, et al. Prognostic relevance of a novel TNM classification system for upper gastroenteropancreatic neuroendocrine tumors. Cancer 2008;113:256–65.
4. Endo S, Dousei T, Yoshikawa Y, Hatanaka N, Taniyama K, Yamauchi A, et al. Gastric neuroendocrine tumors in our institutions according to the WHO 2010 classification. Int Surg 2012;97:335–9.
5. Rindi G, Azzoni C, La Rosa S, Klersy C, Paolotti D, Rappel S, et al. ECL cell tumor and poorly differentiated endocrine carcinoma of the stomach: Prognostic evaluation by pathological analysis. Gastroenterology 1999;116:532–42.
6. Hoda SA, Hajdu SI. Small cell carcinoma of the esophagus. Cytology and immunohistology in four cases. Acta Cytol 1992;36:113–20.
7. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract :A review. J Clin Oncol 2004;22:2730–9.
8. Couvelard A, Deschamps L, Ravaud P, Baron G, Sauvanet A, Hentic O, et al. Heterogeneity of tumor prognostic markers: A reproducibility study applied to liver metastases of pancreatic endocrine tumors. Mod Pathol 2009;22:273–81.
9. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: Implications for prognostic stratification. Am J Surg Pathol 2011;35:853–60.
10. Scherübl H, Jensen RT, Cadiot G, Stölzel U, Klöppel G. Management of early gastrointestinal neuroendocrine neoplasms. World J Gastrointest Endosc 2011;3:133–9.
11. Wang YH, Lin Y, Xue L, Wang JH, Chen MH, Chen J. Relationship between clinical characteristics and survival of gastroenteropancreatic neuroendocrine neoplasms: A single-institution analysis (1995-2012) in South China. BMC Endocr Disord 2012;12:30.
12. Hirabayashi K, Zamboni G, Nishi T, Tanaka A, Kajiwara H, Nakamura N. Histopathology of gastrointestinal neuroendocrine neoplasms. Front Oncol 2013;3:2.
13. Klimstra DS, Modlin IR, Adsay NV, Chetty R, Deshpande V, Gönen M, et al. Pathology reporting of neuroendocrine tumors: Application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol 2010;34:300–13.