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Comparison of WHO 2000 and WHO 2010 classifications of gastroenteropancreatic neuroendocrine tumors

TUMOURS

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Original Article

ABSTRACT

Background/Aims: Grading and staging are important in gastroenteropancreatic neuroendocrine tumors for directing treatment. In this study, we evaluated the histopathological parameters of gastroenteropancreatic neuroendocrine tumors and statistically analyzed the correlations of these parameters between the World Health Organization (WHO) 2000 and 2010 classifications.

Materials and Methods: A total of 77 cases diagnosed as neuroendocrine tumors were included in the study. Cases were classified according to the WHO 2000 and WHO 2010 classification systems, and the differences and correlations between the two systems were discussed.

Results: Among the 50 cases that were diagnosed as well-differentiated neuroendocrine tumor according to WHO 2000, 45 were found to be Grade 1 and 5 were found to be Grade 2 according to the WHO 2010 classification. Among the 8 cases with well-differentiated neuroendocrine carcinoma according to WHO 2000; 5 and 3 were Grade 1 and Grade 2, respectively, according to the WHO 2010 classification. All of the 19 cases with poorly differentiated neuroendocrine carcinoma according to WHO 2000 were found to be Grade 3 according to the WHO 2010 classification. No differences were found between the classifications in the poorly differentiated group with a full correlation between the two classifications.

Conclusion: Although WHO 2000 seems to be a better classification to predict prognosis, since it is based on various parameters, such as depth of invasion, angiolymphatic invasion, and presence of metastasis, it was concluded that there was no difference between the WHO 2000 and WHO 2010 classification, which is based on only the number of mitoses and Ki-67 proliferation index.

Keywords: Neuroendocrine tumor, pathology, classification

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are epithelial tumors originating from neuroendocrine cells. They are rare tumors with an incidence of 1-2/100,000 (1). Various terminologies are used to describe them, such as carcinoid, island cell tumor, tubular carcinoid, malignant carcinoid, and atypical carcinoid tumors (2). The term carcinoid tumor was first used by Obendorfer in 1907 to define some small bowel tumors with low malignant potential that histologically resembled carcinomas but had a different clinical behavior, which was the capacity to invade but not metastasize. Mason suggested in 1928 that carcinoids should be accepted as endocrine tumors (3).

The reason for the nomenclature of neuroendocrine tumors is that these cells, like neural cells, express chromogranin A, synaptophysin, and neuron-specific enolase glycoproteins. Although they differ according to the site in which they evolve, they produce and release more than 14 identified peptide hormones and amines. They are labeled as insulinoma, gastrinoma, glucagonoma, and serotoninoma according to the hormones they release (4,5).

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Grading and staging are important in identifying the treatment. Different classification systems according to the anatomic localization have also been used in these tumors (6,7). However, the WHO 2010 classification differs from the previous classifications in that that it is based on parameters that can be used in neuroendocrine tumors developing in the entire gastrointestinal tract (8). In this study, we evaluated pathology reports, including the prognostic factors and classifications that should be included in such a report retrospectively, and statistically analyzed the correlations of these parameters with the WHO 2010 classifications.

MATERIALS AND METHODS

All gastroenteropancreatic neuroendocrine tumor cases archived since 2004 by the Department of Pathology, Gazi University Faculty of Medicine were evaluated. Seventy-seven cases diagnosed as neuroendocrine tumors were included in the study. Clinical information was obtained from medical records and hospital information systems. Histopathological evaluations were performed on archival slides, which were been prepared by fixing patient tissue specimens in 10% formaldehyde, sampling and processing, embedding in paraffin, and staining with hematoxylin-eosin (H-E). Sections were examined with a light microscope (Olympus B×50) by ×400 (40× objective lens, 10× ocular lens, 0.151 mm^2) magnification.

Archival slides were reviewed to evaluate the tumor size, presence of cytological atypia, number of mitoses, depth of invasion, presence of perineural/angiolymphatic invasion, non-ischemic tumor necrosis, and expression of neuroendocrine markers. Sections were immunohistochemically analyzed with at least two neuroendocrine markers, namely synaptophysin (Dako, Glostrup, Denmark) and chromogranin A (Neomarkers, CA, USA). The streptavidin-biotin triple indirect immunoperoxidase method was used for immunohistochemistry.

Seventy-seven GEPNET cases were classified into four groups according to the WHO 2000 criteria: well-differentiated neuroendocrine tumor, benign (WDNET-B); well-differentiated endocrine tumor, indeterminate (WDNET-I); well-differentiated neuroendocrine carcinoma (WDNEC), and poorly differentiated neuroendocrine carcinoma (PDNEC). The WHO 2000 classification was categorized and statistically evaluated in three groups: WDNETs, WDNEC, and PDNEC (Table 1) (1,8). Mitosis was evaluated by counting 10 high-power fields (HPFs). The Ki-67 proliferation index was evaluated in 500-2000 cells and grouped according to the WHO 2010 classification as well-differentiated endocrine tumor grade 1 (G1), well-differentiated endocrine tumor grade 2 (G2), and poorly differentiated endocrine carcinoma grade 3 (G3). NET and NEC grades were identified as follows: NET G1 (carcinoid), <2 mitoses/10 HPF and/or ≤2% Ki-67; NET G2, 2-20 mitoses/10 HPF and/or 3-20% Ki-67; and NEC G3 (large cell/small cell type), >20 mitoses/10 HPF and >20% Ki-67 (8).

Cases were classified according to the WHO 2000 and WHO 2010 classification systems, and the differences and correlations between the two systems were examined.

Statistical analysis

McNemar's chi-square test was used to check for any significant difference between the WHO classifications. Consistency and correlation were also evaluated. For the measurement of consistency and correlation of the two classifications, the kappa and Kendall's tau-b values were determined. SPSS v10.0 (SPSS, Chicago, IL, USA) was used for database setup and statistical analyses.

RESULTS

Among the 77 cases, 33 were females (42.9%) and 44 were males (57.1%). The female/male ratio was 3:4. The mean age was 50.84 years with a range of 14-80 years. There were resection materials in 39 cases and endoscopic biopsies in 38. The localization of the tumors was as follows: 46 in the stomach, 9 in the small bowel, 7 in the appendix, 5 in the colon, and 10 in the pancreas (Table 2).

The size of the tumors and depth of invasion were evaluated in the resection materials. The number of cases with a tumor diameter of ≤1 cm, 1-2 cm, and >2 cm were 15 (38.5%), 5 (12.8%), and 19 (24.7%), respectively. Invasion was limited to the mucosa and sub-mucosa in 8 stomach tumors and 1 small bowel tumor. Invasion into the muscularis propria or beyond was identified in 8 stomach tumors, 1 esophageal tumor, 2 colon tumors, and 3 small bowel cases. Meso-appendix invasion was present in 4 cases. Six cases were limited to the pancreas. Three cases with pancreatic tumors with local invasion or metastasis were identified.

Metastasis was present in 20 (26%) cases (evaluated as lymph node metastasis and distant metastasis), and angiolymphatic invasion was present in 25 (32.5%) cases. Non-ischemic tumor necrosis was present in 20 (26%) cases, perineural invasion was present in 15 (19.5%) cases, and atypia was observed in 25 (32.5%) cases (Table 3).

According to the WHO 2000 classification, there were 50 (64.9%) cases of WDNET, 8 cases (10.4%) of WDNEC, and 19 (24.7%) cases of PDNEC. In the PDNEC group, 7 cases had metastasized.

As a result of the evaluation, 50 cases had <2 mitoses/10 HPF (64.9%), 23 cases had 2-20 2 mitoses/10 HPF (29.9%), and 4 cases had >20 mitoses (5.2%). There were 48 cases with a proliferation index of ≤2% Ki-67 (62.3%), 11 cases with 3-20% Ki-

Table 1. The comparison of the diagnostic parameters according to WHO 2000 and 2010 recommendations in five sites of the GI tract

Diagnoses based on WHO 2000	Stomach		Duodenum-Jejenum		Appendix		Ileum, colon, rectum		Pancreas	
	2000	2010	2000	2010	2000	2010	2000	2010	2000	2010
WDNET	Benign: M or SM, AI: (-) <1 cm	G1	Benign: M or SM, AI: (-) <1 cm	G1	Benign: confined to appendiceal wall AI: (-) 2 cm	G1	Benign: M or SM, AI: (-), <1 cm in size (ileum) or 2 cm colon and rectum	G1	Benign: Confined to the pancreas, <2 cm in diameter, <2 mitoses per 10 HPF, <%2 Ki67-positive cells, AI: (-), PN: (-)	G1
	Benign or low-grade malignant (UMP): M or SM, AI: (-) or (+) 1-2 cm		Benign or low grade malignant (UMP): M or SM, AI: (-) or (+) 1 cm		Benign or low-grade malignant (UMP): invading the mesoappendix, AI: (+) >2 cm		Benign or low-grade malignant (UMP): M or SM, AI: (+) or <1 cm in size (ileum) or 2 cm colon and rectum		Uncertain behavior: Confined to the pancreas and one or more of the following features: >2 cm in diameter, >2 mitoses per 10 HPF, >%2 Ki67- positive cells, AI: (+), PN: (+)	
WDNEC	MP and beyond or Metastases (+) >2 cm	G2	MP and beyond or Metastases (+) >2 cm	G2	Infiltrating deep in the mesoappendix Metastases or >2.5 cm	G2	MP and beyond or Metastases (+)	G2	Gross local invasion and/or metastases (+)	G2
PDNEC		G3		G3		G3		G3		G3

WDNET: well-differentiated endocrine tumor; WDNEC: well-differentiated neuroendocrine carcinoma; PDNEC: poorly differentiated neuroendocrine carcinoma; UMP: uncertain malignant potential; (-): Absent; (+): Present; G1, 2, and 3: Grade 1, 2, and 3; HPF: high-power fields

In each box, the first feature is the depth of invasion. M: mucosa; SM: submucosa; MP: muscularis propria

- The second one is the presence or absence of angioinvasion (AI).
- The presence or absence of perinöral invazion (PN).
- The numeric parameters implicate the size of the tumor.

Table 2. Demographic data of the study group

Average age	50.84
Gender	
Male, n (%)	44 (57.1%)
Female, n (%)	33 (42.9%)
Material	
Resection	39 (50.6%)
Endoscopy	38 (49.4%)
Tumor localizations	
Stomach	46
Duodenum	9
Colon	5
Appendix	7
Pancreas	10

67 (14.3%), and 18 cases with >20% Ki-67 (23.4%). According to the WHO 2010 classification, 50 cases were found to be G1 (64.9%), 8 cases were found to be G2 (10.4%), and 19 cases were found to be G3 (24.7%). The number of cases with WDNET and WDNEC according to the WHO 2000 classification and the number of cases with G1 and G2 according to the WHO 2010 classification were equal, although the cases were different. In our series of 77 cases, 10 of them were categorized differently according to the WHO 2000 and 2010 classifications. Among the 50 cases that were diagnosed as well-differentiated endocrine tumor according to WHO 2000, 45 were found to be Grade 1 and 5 were found to be Grade 2 according to the WHO 2010 classification. Among the 8 cases with WDNEC according to WHO 2000, 5 and 3 were G1 and G2, respectively, according to the WHO 2010 classification. All of the 19 cases with PDNEC according to the WHO 2000 classification were found to be G3 according to WHO 2010 classification. No differences were found between the classifications in the poorly differentiated group with a full correlation between the two classifications. Among the 5 cases with WDNET according to WHO 2000, 3 had a mitosis count of 2-20 mitoses/10 HPF and a Ki-67 proliferation index of 3-20%; the other 2 cases had a mitosis count of <2 mitoses/10 HPF and a Ki-67 proliferation index of 3-20%, with a G2 classification according to WHO 2010. Five cases with WDNEC according to the WHO 2000 classification had a mitosis count of <2 mitoses/10 HPF, a Ki-67 proliferation index of ≤2%

Table 3. Distribution of features of tumors

Tumor size	
≤1 cm	15 (38.5%)
1-2 cm	5 (12.8%)
>2 cm	19 (24.7%)
Mitosis	
<2	50 (64.9%)
2-20	23 (29.9%)
>20	4 (5.2%)
Proliferation index	
≤%2 Ki 67	48 (62.3%)
%3-20 Ki 67	11 (14.3%)
>%20 Ki 67	18 (23.4%)
Angiolymphatic invasion	
Present	25 (32.5%)
None	52 (67.5%)
Metastasis	
Present	20 (26%)
None	57 (74%)
Perineural invasion	
Present	15 (19.5%)
None	62 (80.5%)
Non-ischemic tumor necrosis	
Present	20 (26%)
None	57 (74%)
Cytological atypia	
Present	25 (32.5%)
None	52 (67.5%)

and were classified as G1 according to WHO 2010 classification. Two of 5 pancreas resection patients had metastases; both tumors were classified as G2 according to WHO 2010 and as WDNET according to WHO 2000. Five tumors (tumor size >2 cm) with a Ki67 index of ≤2% were G1 according to WHO 2010 and WDNEC according to WHO 2000. Five of the 50 WDNET cases were identified as G2 according to WHO 2010, which signifies the malignant potential of low-grade neuroendocrine tumors (Table 4).

Statistical analysis: No differences between the WHO 2000 and WHO 2010 classifications were observed accordingly (p=1.000). For the measurement of consistency of the two classifications, the kappa value was determined as 0.696. The consistency of the two classifications was found to be statistically significant (p<0.0001). Kendall's tau-b value for the correlation of the two classifications was found to be 0.807 (p<0.0001).

Although WHO 2000 seems to be a better classification to predict prognosis, since it is based on various parameters, such as depth of invasion, angiolymphatic invasion, and presence of metastasis, it was concluded that there was no difference between the WHO 2000 and WHO 2010 classification, which is based on only the number of mitoses and Ki-67 proliferation index.

DISCUSSION

Neuroendocrine tumors are rare epithelial tumors displaying neuroendocrine differentiation and may develop in any localization in the body. They comprise a heterogeneous group with embryological and biological differences, although they are histologically similar (9). They cause clinical symptoms according to the peptide hormones they release (1). They are most frequently seen in the gastrointestinal system (70%) and the bronchopulmonary system (25%). In the gastrointestinal tract, they are localized in the small bowel (28%), appendix (19%), and rectum (13%) (10).

The scarcity of information about their biological behavior and differences in their epidemiological and clinical features results in an uncertainty in the diagnosis, treatment, and follow-up of these patients. Similarly, confusion exists for the grading, staging, and systematic nomenclature of these tumors (6,7,10).

The first classification of the GEPNET was performed by Williams and Sandler in 1963. They divided these tumors into three groups with different clinicopathological features according to their embryological origins. The first group, foregut tumors, consisted of the tumors of the stomach, duodenum, upper jejunum, and pancreas; the second group, named midgut tumors, consisted of the lower jejunum, ileum, appendix, and cecum, and the third group consisted of colon and rectum tumors. However, highly variable behavioral characteristics of the tumors were observed for tumors in each of these groups; therefore, this system was of limited value in routine practice (11). The first WHO classification was proposed in 1980, which included the first formal usage of the "carcinoid" tumor. The endocrine tumors of the pancreas and thyroid, paragangliomas, small-cell lung carcinomas, and Merkel cell skin tumors were grouped differently from carcinoids (12). A classification of lung, pancreas, and intestine neuroendocrine tumors was recommended by Capella and others in 1995. According to this classification, tumors were evaluated according to their macroscopic features (size, metastasis), histopathological features (such as cellular differentiation, neuroinvasion, angioinvasion, lymphatic invasion, and proliferative activity), and clinical characteristics (hormone secretion). Based on this classification system, tumors were divided into 3 groups: benign, unknown malignant potential, and malignant (11). The classification of WHO published in 2000 was a revised

Table 4. Distribution of characteristics of the ten cases that were categorized differently according to the WHO 2000 and 2010 classifications

Material	Age	Gender	Tumor size*	Mitosis	Proliferation index	Angiolymphatic invasion	Metastasis	Perineural invasion	Cytological atypia	Non-ischemic tumor necrosis	WHO 2000	WHO 2010
Stomach endoscopy	54	F		2-20	%3-20	-	-	-	-	-	WDNET	G2
Pancreas resection	58	F	>2 cm	<2	≤%2	-	-	-	+	-	WDNEC	G1
Pancreas resection	23	F	>2 cm	<2	≤%2	+	-	+	-	+	WDNEC	G1
Appendectomy	14	M	≤1 cm	2-20	%3-20	+	-	-	-	-	WDNET	G2
Pancreas resection	46	F	>2 cm	2-20	%3-20	-	+	-	+	-	WDNET	G2
Stomach endoscopy	45	M		<2	%3-20	+	-	-	+	-	WDNET	G2
Pancreas resection	55	F	>2 cm	<2	≤%2	-	-	-	-	-	WDNEC	G1
Gastrectomy	64	M	>2 cm	<2	≤%2	-	-	-	-	-	WDNEC	G1
Colon resection	58	M	>2 cm	<2	≤%2	-	-	-	-	+	WDNEC	G1
Pancreas resection	75	M	>2 cm	2-20	%3-20	+	+	-	-	-	WDNET	G2

M: male; F: female; (-): absent; (+): present; WDNET: well-differentiated endocrine tumor; WDNEC: well-differentiated neuroendocrine carcinoma; G 1, 2: Grade 1, 2
* The size of the tumors was evaluated in the resection materials.

type of the Capella classification. In this classification, terms, such as well-differentiated endocrine tumor, well-differentiated endocrine carcinoma, and poorly differentiated endocrine carcinoma, were introduced. Pure endocrine tumors and mixed endocrine-exocrine tumors were grouped separately. For the assessment of more detailed prognostic parameters according to localization and biological features, tumors were subdivided into subgroups depending on the tumor site: the stomach, duodenum (and proximal jejunum), ileum (including distal jejunum), appendix, colon, rectum, and pancreas neuroendocrine tumors. Nevertheless, this classification resulted in confusion in the grading, staging, and systematic nomenclature of these tumors, as well as uncertainties in patient management.

The morphological/biological criteria used in the classification of GEP-NETs are in addition to histological criteria, tumor diameter, presence of angioinvasion, proliferative activity, presence of metastasis, and depth of invasion. The functional activity of the tumor and the association with hereditary diseases were evaluated. In the WHO classifications of the gastrointestinal tract (2000) and pancreas (2004) NETs, a hybrid classification using both the staging information (dimension and extent of the tumor- primary location versus metastasis) and grading (proliferative rate) is used (6,7,12).

Two different classifications systems for grading and staging were proposed by the European Neuroendocrine Tumor Society (ENETS) to facilitate diagnosis and treatment, and guidelines were developed accordingly (13,14). Localization-specific tumor differences, tumor differentiation, and placement of the neuroendocrine tumors in the malignant category in the long-term follow-up are among other causes of the development of a new classification. The WHO 2010 grading classification is based on the ENETS schema. A variety of changes were performed in the new classification, including the terminology. For example, the word "neuroendocrine" describes neoplastic cells expressing neural markers, such as synaptophysin, and "neuroendocrine neoplasm" covers well- or poorly differentiated neuroendocrine tumors. Neuroendocrine neoplasms of the gastrointestinal system and pancreas are divided into well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas. Well-differentiated neuroendocrine tumors are grouped as G1 (equal to carcinoid) and G2 according to their proliferation indexes. G3, on the other hand, is a small-cell and large-cell neoplasm subtype (6-8). In a study of Jernman et al. (15) in 73 cases with rectal neuroendocrine tumors, 9 out of 11 tumors with G2 classification, according to WHO 2010, metastasized during the follow-up. None of the 61 tumors with G1 classification metastasized, and the WHO 2010

classification was found to be more beneficial in predicting the potential of metastasis of the neuroendocrine tumors compared to the WHO 2000 classification. In a study of Endo et al. (16) in 22 gastric neuroendocrine tumors, 81 cases were G1, 5 were G2, and 16 were NEC. All NET G2 and NEC cases had metastases, and 3-year survival rates were 20% and 7%, respectively, whereas NET G1 showed a 3-year 100% survival. Two studies concluded that Ki-67 index and the mitotic index are helpful for the clinician in demonstrating the potential of malignancy and metastasis of the neuroendocrine tumors of the gastrointestinal system and thus in planning the treatment (17-19).

In our series of 77 cases, 10 of them were categorized differently according to the WHO 2000 and 2010 classifications. Lymph node metastases were defined in 2 cases whilst diagnosed and therefore classified as WDNET according to the WHO 2000 classification, though they were classified as G2 according to the WHO 2010 classification. Angiolymphatic invasion was observed in one of these cases. Five cases who underwent resection were classified as WDNEC, because their tumor diameter were greater than 2 cm but were classified as G1 according to the WHO 2010 classification. In our series, the WHO 2010 classification was regarded as indicative in pointing out the potential of metastases. Although the WHO 2000 classification, which is based upon criteria, like depth of invasion, angiolymphatic invasion, and metastases, is regarded as superior in determining prognosis, no statistical differences were observed when compared with the WHO 2010 classification, which is based merely upon mitosis and Ki-67 proliferation index. Our report should be regarded as a preliminary study. The classification systems were compared in relation to the prognostic factors of WHO 2000 and the mitosis and Ki-67 criteria of WHO 2010 classifications. In our study, the WHO 2000 classification, which is based upon factors well known for their importance in all malignant tumors, like angiolymphatic invasion, perineural invasion, and tumor diameter, was not found to be superior in grading in regard to the WHO 2010 classification.

For these reasons stated above, genetic and immunohistochemical studies, including survival and prognostic parameters comprising new classification systems based on large series of GEPNETs, are needed.

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