

Overview on Gastric Cancer

Chapter 1

Gastric neuroendocrine tumors

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1. Introduction

Gastric Neuroendocrine Tumors (NET)s are classified on the basis of criteria that are common to all gastrointestinal and pancreatic neuroendocrine neoplasms. Most neuroendocrine neoplasms of the stomach are NETs –well differentiated, nonfunctioning enterochromaffin-like(ECL) cell carcinoids (ECL cell NETs)-arise predominantly in the corpus-fundus region [1]. Three distinct types are recognized :

1. type I, associated with autoimmune chronic atrophic gastritis (A-CAG) (70-80 percent);
2. type II, associated with multiple endocrine neoplasia type 1 (MEN 1) and Zollinger –Ellison syndrome (ZES) (5 percent)
3. type III , sporadic (i.e not associated with A-CAG or MEN1-ZES) (15-20 percent).

Serotonin producing enterochromaffin (EC) cell , gastrin cell , ghrelin cell or adrenocorticotrophic hormone (ACTH) cell NETs are very rare and may arise in both the corpus-fundus and antrum .

NECs (poorly differentiated endocrine carcinomas), and MANECs (mixed adenoneuroendocrine carcinoma) are also rare and may arise in any part of the stomach [1].

Neuroendocrine Tumor (NET)

NET G1

NET G2

Neuroendocrine Carcinoma (NEC)

Large cell NEC

Small cell NEC

Mixed adenoneuroendocrine carcinoma (MANEC)

EC cell ,serotonin producing NET

Gastrin producing NET(gastrinoma)

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The classification of neuroendocrine tumors (NET) can help guide diagnosis. In 2010, the World Health Organization (WHO) updated its classification of NETs based on tumor site of origin, clinical syndrome, and differentiation [2,3].

1.2. Site of origin

Gastrointestinal and pancreatic neuroendocrine tumors(GNET) (PNET) are commonly divided by site of origin (eg foregut, midgut, hindgut [2]. Of note, PNETs are considered to originate in the foregut [2]. Distal tumors include NETs in other locations such as ear, heart and ovaries [2].

Foregut: Lungs, stomach,first part of duodenum

Midgut: Second part of duodenum, jejunum, ileum, right colon

Hindgut: Transverse, left sigmoid colon, rectum [2,4,5,6]

NETs also exhibit gender distribution: women are more likely to have a primary NET in the lung, stomach, appendix or cecum; men are more likely to have a primary NET in the thymus, duodenum, pancreas, jejunum/ileum, or rectum [3].

Neuroendocrine neoplasms, which are defined as epithelial neoplasms with predominant neuroendocrine differentiation arise throughout the body. The terminology of neuroendocrine neoplasms arising in the digestive tract has evolved over the past two decades to reflect a separation into two major categories:

Neuroendocrine tumors (NETs), which show a solid, trabecular, gyriform, or glandular pattern with fairly uniform nuclei, salt-and-pepper chromatin, and finely granular cytoplasm.

Neuroendocrine carcinomas, which are high grade carcinomas whose morphology and clinical behaviour resembles small cell carcinoma or large cell neuroendocrine carcinoma of the lung.

Poorly differentiated neuroendocrine carcinomas are often associated with a rapid clinical course, while well-differentiated NETs of the digestive system generally have a much better prognosis. However well-differentiated tumors are not a homogeneous group and a

spectrum of aggressiveness. The biologic behaviour of well-differentiated NETs cannot be predicted based on morphology alone.

1.3. Grade and differentiation

The grade of a tumor refers to its biologic aggressiveness [7]. The grading system is based on the rate of proliferation, which is defined by the number of mitoses per 10 high power microscopic fields or per 2mm² (mitotic rate), or as the percentage of tumor cells that immunolabel positively for the Ki-67 antigen (Ki-67 index) [7]. Briefly, low-grade tumors are characterized by low proliferative indices and are considered indolent in nature [8]. High-grade tumors tend to be poorly differentiated, have high proliferative indices, and are thus very aggressive [8].

NETs can also be classified based on differentiation, which refers to the extent to which cancerous, or neoplastic, cells resemble normal cells [7]. Well-differentiated NETs have a typical organoid arrangement of cells with nesting, trabecular, or gyriform patterns [7]. Well-differentiated NET cells produce large amounts of secretory granules with diffuse immun-expression of neuroendocrine markers [7]. In contrast, poorly differentiated NETs have atypical, sheet-like, diffuse and irregular nuclei, less cytoplasmic secretory granules, and limited biomarker immunoeexpression [7]. Well-differentiated NETs are usually of low or intermediate grade, poorly differentiated NETs are usually high grade [2-8].

1.4. 2010 WHO classification

The 2010 WHO classification of tumors of the gastrointestinal tract, liver, and pancreas also endorsed the ENETS (European Neuroendocrine Tumor Society) grading scheme for neuroendocrine neoplasms of the digestive tract. Separating well-differentiated tumors into low-grade (G1) and intermediate grade (G2) categories [8,9]. All poorly differentiated neuroendocrine tumors are high grade (G3) neuroendocrine carcinomas according to this classification scheme.

The best cutoff to separate low-grade (G1) from intermediate grade (G2) tumors is not established. The 2010 WHO classification uses 2 mitoses per 10 HPF, and/or <3 percent Ki-67 staining as the cutoff values [10,11] (Table 1).

Several studies have challenged the assumption that poorly differentiated histology and high tumor grade are equivalent. There is a small subset of patients with neuroendocrine tumors that appear histologically well differentiated with less than 20 mitoses/10 high power fields (HPF, G2 by mitotic count) but are associated with high Ki-67 proliferation indices (>20 percent) that fall into the high-grade (G3) range in the current WHO grading scheme. The clinical behaviour of these grade concordant tumors is somewhat worse than grade-concordant

well-differentiated G2 tumors, but better than that of bona fide poorly differentiated NECs [12].

These data support the view that the current WHO G3 category is in fact heterogeneous, containing two distinct groups of neoplasms, and can be further separated into well-differentiated NET with an elevated proliferation rate (WD-NET,G3) and poorly differentiated NEC. Furthermore, the presence of a cohort of neoplasms with a lower Ki-67 index (20 to 55 percent) within the cohort of high grade neuroendocrine carcinomas, which respond less well to platinum-based chemotherapy but survive longer than those with Ki-67 >55 percent, adds further support to the heterogeneity of the current G3 category [13].

1.5. Assessment of Ki-67 labeling index

The optimal cutoff value for the Ki-67 labeling index to distinguish low, intermediate, and high grade gastroenteropancreatic NETs has not been conclusively established. However, the ENETS, American Joint Committee of Cancer (AJCC) and the 2010 WHO classification include a uniform Ki-67 labeling cutoff <3 percent to define low-grade (G1), 3 to 20 percent for intermediate grade (G2), and >20 percent for high-grade NETs [10,11].

The Ki-67 protein is a large nuclear protein (395 kDa) that is closely associated with the nucleolus and heterochromatin. Ki-67 is expressed in G1, S, G2, and M phase, with a peak level during mitosis. The exact function of Ki-67 is unknown, but it appears to be involved in cell cycle regulation and/or organization of the nucleolus; removal of Ki-67 prevents cell proliferation [14,15]. More recent studies have utilized the monoclonal MIB-1 antibody, which works well on formalin-fixed, paraffin-embedded tissue.

The use of a 3 percent cutoff point to stratify prognosis among well-differentiated pancreatic NETs is supported by subsequent studies [16,17], and most groups, including the ENETS and WHO, use a uniform cutoff of <3 percent to define low-grade (G1) from intermediate grade NETs of the digestive tract [10,11].

Through the mid 2000s, the proliferative rate that was used to define poorly-differentiated (high grade) neuroendocrine carcinomas (NECs) was 10 percent, and this was the rate used in the 2004 WHO classification and in several studies [18]. In 2006, and 2007, the ENETS proposed to raise this rate to 20 percent, which was endorsed by the WHO and AJCC [10,11]. However, at least some data suggest that this cutoff point may require further modification. A clinical study of WHO G3 gastrointestinal NECs found that patients with Ki-67 <55 percent had a lower response rate to platinum-based chemotherapy (15 versus 42 percent, $p < 0.001$), but better survival (14 versus 10 months, $p < 0.001$) than did those patients with Ki-67 ≥ 55 percent [13].

1.6. Other parameters and markers for histologic grading

Lymphovascular and perineural invasion are not part of the grading criteria, although they should be recorded as a prognostic factor. Historically, immunohistochemical staining for PCNA (proliferating cell nuclear antigen) was considered an alternative marker of proliferative activity; however, it fell out of favor due to a lack of reliability [19].

Several other newer markers have been reported to have prognostic value in NETs. CK 19 (cytokeratin -19) is a marker of pancreatic ductal epithelium but also transiently expressed in islet cells. Its expression has been shown to correlate with worse survival in pancreatic NETs [20]. A classification scheme based upon expression of CK 19 and CD 117 (KIT) has been proposed, with CK 19+ CD 117+ pancreatic NETs having the shortest survival [21]. Those markers may be useful in primary NETs, but they appear to have any prognostic significance in metastatic disease, unlike the Ki-67 labeling index [17].

Table 1: Histopathology of Neuroendocrine Tumors [8]

Histological Classification	Well differentiated (Low grade ,G1)	Moderately Differentiated (Intermediate Grade,G2)	Poorly Differentiated (High Grade, G3)
Appearance	Monomorphic population of small, round cells	*	Cellular pleomorphism
Prognosis	Prolonged survival	Intermediate	Poor
Mitotic rate	<2	2-20	>20
Ki-67 index *	<3%	%3-20	>20%
Necrosis	Absent		Present

*Not well defined in medical literature.

Ki-67 index applies only to WHO and European Neuroendocrine Tumor Society (ENETS) classification of gastroenteropancreatic NET.

2. Clinical syndrome

NET can also be classified as functional or nonfunctional [4]. NETs are considered functional when a specific clinical syndrome is induced due to the excessive production of hormones by the tumor cells; approximately two-thirds of NETs are functional [2]. Examples of functional NETs include carcinoid tumors, which can result in carcinoid syndrome, and functional pancreatic NET (insulinomas, gastrinomas, vasoactive intestinal peptide (VIP)omas, glucagonomas and somatostatinomas [4].

Nonfunctional NETs are not associated with a clinical syndrome, but can still produce symptoms related to the presence of the tumor or its metastases (eg abdominal pain and bloating) [7,22]. Functional and nonfunctional PNET may be benign or malignant [4].

2.1. Staging system

The WHO also endorsed staging neuroendocrine neoplasms using the specified TNM-based system. The most recent 7th edition of the AJCC staging manual, which reflects a modification of proposal by ENETS [10], includes separate TNM staging systems for NETs of the appendix, pancreas, stomach (table 2), small bowel/ampulla of Vater, and colorectal primary sites .

2.2. TNM staging of gastric net

Table 2: American Joint Committee on Cancer Staging for NET of the Stomach (AJCC Cancer Staging Manual, seventh edition /2010, published by Springer, New York ,Inc.) [23].

Stage 0	Tis	Stomach	Carcinoma in situ/ dysplasia(tumor size less than 0.5 mm),confined to mucosa	N0 No regional lymph node metastases	M0 No distant metastases
Stage I	T1	Stomach	Tumor invades lamina propria or submucosa and size 1 cm or less	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIA	T2	Stomach	Tumor invades muscularis propria or size greater than 1 cm	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIB	T3	Stomach	Tumor penetrates subserosa	N0 No regional lymph node metastases	M0 No distant metastases
Stage III A	T4	Stomach	Tumor invades visceral peritoneum(serosal) or other organs or adjacent organs or adjacent structures	N0 No regional lymph node metastases	M0 No distant metastases
Stage IIIB	Any T			N1 Regional lymph node metastases	
Stage IV	Any T	Stomach		Any N	M1

3. Clinical guidelines for the treatment of gastric neuroendocrine tumors

The following organizations have issued clinical guidelines for the treatment of carcinoid tumors:

National Comprehensive Cancer Network (NCCN)

North American Neuroendocrine Tumor Society (NANETS)

European Neuroendocrine Tumor Society (ENETS)

European Society for medical Oncology (ESMO)
UK and Ireland Neuroendocrine Tumor Society (UKI NETS) [24].

3.1. Treatment for locoregional disease

NCCN guidelines recommend resection as the primary treatment for most carcinoid tumors of the gastrointestinal (GI) tract, lung and thymus. Specific recommendations vary by tumor subtype. However, for neuroendocrine tumors at any site, cholecystectomy is recommended during surgical resection if treatment with a somatostatin analog (i.e, octreotide, lanreotide) is planned, due to the increased rate of biliary problems associated with long-term use of these agents [24].

For gastric tumors, the NCCN recommendations are as follows [24]:

*With hypergastrinemia and tumors ≤ 2 cm: Endoscopic resection with biopsy or observation; or octreotide or lanreotide for patients with Zollinger –Ellison syndrome .

*With hypergastrinemia and tumors >2 cm: Endoscopic resection and regional lymphadenectomy; endoscopic resection, if possible, or surgical resection

*With normal gastrin levels: Radical gastric resection and regional lymphadenectomy: endoscopic or wedge resection can be considered for tumors ≤ 2 cm .

In 2013, NANETS released updated guidelines with the following recommendations for treatment of gastric carcinoid tumors [25]:

- Type I or II, <1 cm: Surveillance or endoscopic removal
- Type I, 1cm to <2 cm: Surveillance with repeat endoscopy every 3 years or endoscopic resection
- Type II, 1cm to <2 cm: Endoscopic resection
- Type I, ≥ 2 cm (≤ 6 polyps), or type II ≥ 2 cm: Endoscopic resection, if possible , or open surgical resection
- Type I, ≥ 2 cm (>6 polyps): Individualized treatment required; surveillance, endoscopic resection, or surgical resection.
- Type III: Partial gastrectomy and lymph node dissection

The 2016 revised ENETS guidelines prefer conservative management strategies over surgery for type I tumors. The guidelines recommend resection of tumors ≥ 10 mm performed by endoscopists experienced in gastric tumor, using either endoscopic mucosal resec-

tion (EMR) or endoscopic submucosal dissection(ESD) [26].

For type II tumors, limited excision can be recommended, but this should be patient tailored at multidisciplinary NET centers of excellence. Type III tumors should be treated similarly to gastric adenocarcinoma with surgery (partial or total gastrectomy with lymph node dissection). Systemic therapy is required for inoperable or stage 4 disease [26].

4. References

1. Solcia E, Klöppel G, and Sobin LH (eds.) (2000). *Histological Typing of Endocrine Tumours*. Springer–Verlag: Berlin-New York.
2. Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. *Cancer Metastasis Rev.* 2011; 30(suppl 1):3-7.
3. Yao JC, Hassan M, Phan A et al, One hundred years after ‘carcinoid’: epidemiology and prognostic factors for neuroendocrine tumors in 35825 cases in the United States .*J Clin Oncol* 2008;26:3063-3072.
4. National Comprehensive Cancer Network.NCCN clinical practice guidelines in oncology: neuroendocrine tumors. [https://www.nccn.org7professionals/physician_gls/pdf/neuroendocrine .pdf](https://www.nccn.org7professionals/physician_gls/pdf/neuroendocrine.pdf). Accessed june 27,2016.
5. Vinik AI, Renar IP. Neuroendocrine tumors of carcinoid variety.In: DeGroot L, ed. *Endocrinology*. 3rd ed. Philadelphia, PA: WB Saunders ;1995:2803-2814.
6. National Cancer Institute. General Information about pancreatic neuroendocrine tumors (islet cell tumors). [http://www.cancer .gov/types/pancreatic/hp/pnet-treatment-pdg](http://www.cancer.gov/types/pancreatic/hp/pnet-treatment-pdg). Accessed June 27,2016.
7. Kulke MH, Anthony LB, Bushnell DL, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* .2010;39:735-752.
8. 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;39:707-712.
9. Hruban RH, Pitman MB, Klimstra DS. *Tumors of the pancreas, ARP/AFIP*, Washington, DC 2007.P.422.
10. Rindi G; Klöppel G, Alhman H, et al. TNM staging of foregut (neuro) endocrine tumors: a consensus proposal including a grading system.*Virchows Arch* 2006;449-:395.
11. Rindi G, Arnold R, Bosman FT, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system.In : *WHO Classification of Tumors of the Digestive System*, 4th ed , Bosman TF, Carneiro F, Hruban RH, Theise ND(Eds), International Agency for research on cancer (IARC), Lyon 2010.p.13.
12. Basturk O, Yang Z, Tang LH, et al. The high grade (WHO G3)pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol* 2015;39:683.
13. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3):the NORDIC NEC study. *Ann Oncol* 2013; 24:152.
14. Brown Dc, Gatter KC.Ki-67 protein: the immaculate deception? *Histopathology* 2002;40:2.
15. Yerushalmi R, Woods R Ravdin PM,et al. Ki-67 in breast cancer: prognostic and predictive potential. *Lancet Oncol* 2010;11:174.
16. Jann H, Roll S, Couvelard A, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis

classification determines clinical outcome .Cancer 2011;117:3332.

17. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assesment of Ki-67 labeling index in well –differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg pathol 2011;35;853.
18. Pape Uf, Berndt U, Müller–Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2008;15:1083.
19. La Rosa S, Sessa F, Capella C, et al. Prognostic criteria in nonfunctioning pancreatic endocrine tumours. Virchows Arch 1996;429:423.
20. Deshpande V, Fernandez-del Castillo C, Muzikansky A, et al. Cytokeratin 19 is a powerful predictor of survival in pancreatic endocrine tumors Am J Surg Pathol 2004;28:1145.
21. Zhang L, Smryk TC, Oliveira AM , et al. KIT is an independent prognostic marker for pancreatic endocrine tumors: a finding derived from analysis of islet cell differentiation markers. Am J Surg Pathol 2009;33:1562.
22. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008;9:61-72.
23. Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Handbook. 7th ed. New York, NY: Springer, 2010.
24. [Guideline] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine Tumors, Version 2.2016. NCCN. Available at http://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. May 25, 2016; Accessed: October 2, 2016.25-[Guideline] Kunz PL, Reidy-Lagunes D, Anthony LB, et al; North American Neuroendocrine Tumor Society. Consensus guidelines for the management and treatment of neuroendocrine tumors. Pancreas. 2013 May. 42 (4):557-77. [Medline]. [Full Text].
26. [Guideline] Delle Fave G, O’Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, et al. ENETS Consensus Guidelines Update for Gastroduodenal Neuroendocrine Neoplasms. Neuroendocrinology. 2016. 103 (2):119-24. [Medline]. [Full Text].