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EDITORIAL

The classification of neuroendocrine neoplasms: "Neuroendocrine carcinomas" revisited – a 2017 update and future perspectives

Ivan Kruljac[1], **Ulrich-Frank Pape**[2]

[1]Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb Medical School, Vinogradska Cesta 29, 10000, Zagreb, Croatia
[2]Department of Hepatology and Gastroenterology, ENETS Center of Excellence for Neuroendocrine Tumors, Charité Campus Mitte and Virchow Clinic, Charité University Medicine, Charitéplatz 1, 10117 Berlin, Germany

Corresponding author:
Ivan Kruljac, Department of Endocrinology, Diabetes and Metabolic Diseases "Mladen Sekso", University Hospital Center "Sestre Milosrdnice", University of Zagreb Medical School, Vinogradska Cesta 29, 10000 Zagreb, Croatia, Telephone: 00385992179089, e-mail: ivkruljac@gmail.com

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Neuroendocrine neoplasms (NEN) encompass a wide range of epithelial neoplasias with substantial variations in both tumor biology and clinical presentation. The biology of each NEN depends on its primary tumor localization, cellular morphology, mitotic activity, and clinically manifest expression of autonomous hormone secretion of either a peptide hormone or biogenic amine. NEN can arise in virtually every epithelial organ, but approximately three-quarters of all NEN originate from the gastrointestinal tract [1]. According to the current World Health Organization (WHO) 2010 classification, gastroenteropancreatic (GEP) NEN are classified into three grading subgroups based on the mitotic activity and Ki67 immunostaining: G1 (mitotic count <2/10 HPF and/or Ki-67 index <3%), G2 (mitotic count 2-20/10 HPF and/or Ki-67 index 3-20%), and G3 (mitotic count >20/10 HPF and/or Ki-67 index >20%). G1 and G2 NENs have well-differentiated morphology and are referred to as G1 or G2 neuroendocrine tumors (NET), while G3 NEN are considered poorly differentiated and referred to as neuroendocrine carcinomas (NEC). G3 NEC is subdivided into large cell and small cell carcinomas, based on presumed but yet unproven differences in clinical outcomes. This classification was demonstrated many times to be very effective in predicting prognosis, and to some degree, response to treatment. However, regardless of this classification, treatment approaches substantially differ between pancreatic NEN (PanNEN) and gastrointestinal NEN (GINEN) as well as between NET and NEC [2-4].

While substantial progress has been made during the last decade in the palliative treatment of G1 and G2 NET, G3 NEC were largely uniformly treated as one highly malignant subgroup which is amenable to a

curative surgical approach in only a small early tumor stage subgroup and mostly requires systemic cytotoxic chemotherapy treatment including platinum compounds as has been establish in the 1980s and 1990s.

However, Sorbye et al. first published their analysis demonstrating that the G3 group is more heterogeneous in terms of both prognosis and response to treatment [5]. The results of this NORDIC NEC study established the following hypothesis: Patients with Ki-67<55% have a poorer response rate to platinum-based chemotherapy (15% vs. 42%, P < 0.001), however a better overall survival than patients with Ki-67≥55% (14 vs. 10 months, P < 0.001) suggesting this subgroup demands a different treatment approach due to different tumor biology. Therefore, the authors proposed a more differentiating classification of G3 NEC into G3a (Ki67 20-55%) and G3b (Ki67>55%). The NORDIC NEC study did not provide information on the cellular morphology or differentiation of NEC.

The latter issue was first addressed in a publication by Velayoudom-Cephise et al. in 2013 as well, who studied a group of GEP and thoracic G3 NEC (Ki67>20%) without small cell morphology [6]. In their thorough analysis, it turned out that almost 50% of their cases presented a well-differentiated tumor cell morphology (G3-WDNET) which coincided with other tumor biological features more characteristic of G2 NET such as higher levels of serum chromogranin A, urinary 5-hydroxyindoleacetic acid, and positivity on clinical somatostatin receptor imaging. Reversely, the group with large cell morphology and poor differentiation (G3-LCNEC) demonstrated characteristics of poor differentiation as shown by higher levels of neuron specific enolase and higher glucose uptake on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning. Consecutive survival analysis revealed a substantially longer median survival for the G3-WDNET group as compared to the G3-LCNEC group although statistical significance could not be obtained (probably due to small sample size and relatively large ranges likely due to some heterogeneity in treatment courses). However, this publication added histomorphological characteristics as important criteria to better understanding and both prognostic stratification and tailoring of treatment strategies to the results from the NORDIC NEC study.

In another study published in 2015, Basturk et al. observed that some PanNET show discordance between the mitotic rate and Ki67 index, usually having a Ki67 index in the G3 range but a mitotic rate suggesting G2 [7]. These PanNET were categorized as grade-discordant (n = 19) and compared with 53 grade-concordant G2 PanNET and 43 pancreatic grade-concordant G3 NEC. The mean Ki67 index significantly differed between the groups: 8.1% in G2 PanNET (range, 3-20%), 40% (range, G3 PanNET 24-80%), and 70% G3 NEC (range, 40-98%), respectively. One should note that the median Ki67 index was significantly lower in discordant cases, but some patients had Ki67 index as high as 80%. A difference was observed in terms of overall survival; patients with grade-discordant G3 had significantly longer survival compared with grade-concordant G3 (median survival of 54.1 vs. 11 months and 5 years survival of 29.1% vs. 16.1%; P = 0.002) and their survival was similar to that of concordant G2 PanNET (median survival of 67.8 months and 5 years survival of 62.4%, thus no statistically significant difference). This study added further evidence to the recognition of a new subset of G3 patients: Well-differentiated G3 PanNET.

At the same time, a larger multicentric study was published by a European group, which analyzed 204 patients with G3 GEP NEN gathered from 8 European centers by Heetfeld et al. [8]. Overall, 37 patients were classified as NET G3 and 167 as NEC G3. The pancreas was the primary site in 65% of patients with NET G3 and only 25% of patients with NEC G3. The median overall survival (OS) was substantially higher in NET G3 patients (99 vs. 17 months in NEC; HR = 8.3; P < 0.001). An additional value of this study is the authors' analysis of the efficacy of platinum-etoposide as first-line chemotherapy. Disease control rate and progression-free survival (PFS) were significantly higher in NEC compared to NET G3 (P < 0.05), but the overall survival was significantly longer in NET G3 resembling the results from the NORDIC NEC study [8]. Because the morphology of G3 NET has an obvious impact on both poorer treatment response to cisplatinum-based standard chemotherapy and nevertheless better outcome, refinement of the current classification seems appropriate and necessary.

However, the appropriate modality and/or criteria to determine morphology still needs to be defined. A study

on interobserver variability was conducted on 33 G3 NEN patients (from pancreatic and non-pancreatic primary tumor origin) by Tang et al. [9] three pathologists individually analyzed the slides after hematoxylin and eosin staining, without knowing Ki67 values. All three agreed on the classification in 33% of patients, while the remaining was classified as ambiguous. Immunohistochemistry was useful in differentiating these cases; DAXX or ATRX protein expression suggested well-differentiated NETs, while abnormal p53, Rb, and SMAD4 expression characterized G3 NEC [9]. Although a consensus has not been made concerning which immunohistochemistry marker to use for the diagnosis of NET G3, p53 seems to be a good and technically already established candidate. A previous study showed that p53 is positive in >95% of G3 NEC (both small- and large-cell), while it is negative in all patients with G1 and G2 NETs [10]. One should bear in mind that these results were (once again) obtained from a small cohort that included a total of 20 NEC and 10 NET patients; furthermore, this study did not analyze patients with G3 NET separately. Just recently, Scarpa et al. performed whole genome sequencing of 102 primary PanNETs and defined the genomic events that characterize their pathogenesis. This study is a cornerstone for future detection of biomarkers and for individualized treatment [11].

Nevertheless, as evidence has accumulated (and further can be expected to be published in the upcoming years), the WHO has refined the G3-classification of NEN will publish new guidelines by the end of 2017, which will divide the current G3 group based on tumor morphology into NET G3 and NEC G3.

This new classification will certainly help to improve patient care but put us at the beginning of a new scientific development of appropriate treatment of NET G3 according to evidence-based criteria. Although it seems logical that treatment options used in G2 NET should be effective in G3 NET patients, this assumption requires validation through prospective clinical trials.

Despite improvements in the stratification of patients with GEP-NEN, several issues remain. The current classification is a good tool in terms of prognosis; however, it is not very useful in predicting treatment response (but has also not been studied for this aspect in detail). The majority of patients with metastatic G1 intestinal and pancreatic NET respond well to treatment with somatostatin analogs (SSA) [12]. However, there is a considerable number of patients in this group who do not respond well to SSA, especially patients with PanNET. There are currently no reliable biomarkers that could help identify these patients. Even more variability in terms of treatment response exists in the G2 NET group. The majority of patients with newly diagnosed metastatic NEN are classified as G2, which is also a very heterogeneous group. A detailed exploration of recently published clinical trials can contribute to better understanding of the current state of knowledge and needs for future refinement.

First, the CLARINET study investigated the efficacy of the SSA lanreotide in the treatment of metastatic GEP-NET with a Ki67 index <10%. Approximately, half of the patients had PanNET. Lanreotide, as compared with placebo, was associated with significantly prolonged progression-free survival (median 32.8 vs. 18.0 months, $P < 0.001$; hazard ratio for progression or death, 0.47; 95% confidence interval [CI], 0.30-0.73). Subgroup analysis showed that lanreotide had similar efficacy in midgut NET and PanNET and similar efficacy in G1 and G2 NET [13,14]. The results of the CLARINET study demonstrate that the SSA lanreotide can be used in all patients with GEP NET with a Ki67 index <10%, regardless of the primary tumor site and grading group and has, therefore, been approved by authorities in Europe and the US for these indications.

The second important trial is the RADIANT-3 trial, which investigated the efficacy of everolimus in patients with metastatic G1 and G2 PanNET. The median progression-free survival was 11.0 months with everolimus as compared to 4.6 months with placebo (hazard ratio for disease progression or death from any cause with everolimus, 0.35; 95% confidence interval [CI], 0.27 to 0.45; $P < 0.001$). Similar efficacy of sunitinib has also been demonstrated in patients with PanNET [15]. Contrary to the CLARINET study, the efficacy of everolimus in subgroup analysis was higher in patients with G2 PanNET than in G1 PanNET [16]. Interestingly, the recently published overall outcome analysis was suggestive of a small but potentially meaningful survival benefit for the

everolimus-treated patients [17]. In addition to these results, the RADIANT-4 trial enrolled patients with all (non-pancreatic) GI-NET and lung NET, and confirmed that the everolimus is effective for both lung and GI-NET (except for ileal NET), and particularly patients with G2 NET and patients with high liver tumor burden benefited the most from everolimus [18].

The results from these recent hallmark clinical trials in NET indicate that patients with metastatic G1 GI and PanNET can be effectively treated with SSA. Moreover, patients with low G2 intestinal NET (Ki67<10%) can effectively be treated with SSA, while the best medical evidence-based treatment option for high G2 PanNET (Ki67>10%) seems to be everolimus. However, in some countries, everolimus is approved only as a second-line treatment, after failure of SSA. In those cases, patients with high G2 PanNET receive SSA, whose efficacy is not well known and probably small, if abundant at all.

However, published guidelines also consider other systemic treatment options such as streptozotocin- and/or temozolomide-based chemotherapy as well as somatostatin receptor mediated radionuclide therapy (peptide receptor-mediated radionuclide therapy [PRRT]), all of which are not available everywhere throughout Europe (and the world) [19-21]. Furthermore, evidence levels are at best moderate when compared to SSA, everolimus, sunitinib, and PRRT. With regard to the latter modality just recently another hallmark clinical trial has been published, the NETTER-1-study, which demonstrated excellent PFS advantage of PRRT versus double-dose octreotide in small intestinal NET progressive on standard-dose octreotide [22].

This raises further concerns regarding the current classification scheme, with the possibility of dividing the G2 group into low G2 (Ki67<10%) and high G2 (Ki67>10%). This way, patients with high G2 PanNET might be classified to receive either everolimus or chemotherapy as first-line treatment. Capecitabine and temozolomide (CAPTEM) or streptozotocin and 5-fluorouracil chemotherapy are also frequently used in G2 PanNET, particularly progressive high G2 PanNET [23-25]. However, CAPTEM might also be considered in progressive G2 GINET as later line treatment, although evidence is very limited. Interestingly, an increased sensitivity to CAPTEM-regimen has been suggested as a primary treatment strategy for low G3 NEN (particularly G3 NET) from the aforementioned retrospective analyses. Furthermore, hepatic tumor load has been analyzed in PROMID, CLARINET and non-trial patients and may also be considered for decision-making [14,26,27]. However, prospective clinical trials with these regimens and the different clinical situations are needed to confirm efficacy and establish the precise clinical indication.

A final aspect is the extent to which one can make use of functional NEN imaging by different PET-tracers for treatment decision. Obviously, the choice of treatment depends on the tumor burden as well as the treatment goal (long-term stable disease - "tumoristasis" - or reduction of tumor burden - "tumoricidality" - as with severe clinical symptoms or in the case of potential neoadjuvant treatment). Although FDG-PET proved to be useful in prognostic evaluation (PFS and overall survival), it is unclear whether it can help us choose specific treatment [28]. For instance, patients with both G3 NET and G3 NEC show high uptake of FDG, but we know that patients with G3 NETs will not respond well to platinum-based chemotherapy [8]. However, FDG could theoretically be used as a tool for treatment decision-making in patients with G2 intestinal and pancreatic NETs, and future prospective trials are needed. 3'-deoxy-3'-^{18}F-fluorothymidine (^{18}F-FLT) PET showed even better prognostic accuracy than FDG, which was completely independent from Ki67 index, but future validation trials are needed [29].

In conclusion, tumor morphology or cellular differentiation possibly accompanied by p53 immunostaining is key factors in differentiating patients with G3 NEN and can be used for selecting candidates for specific treatment (Figure 1). Patients with G2 NET are also a rather heterogeneous group, and we urgently need biomarkers that will effectively stratify patients for prediction of response to specific treatments as the options are fortunately increasing (Figure 1). The discovery of such biomarkers would probably lead to future changes in classification, and consequently to improved care for patients with NENs. Until then, we are left to use beyond the application of currently published guideline recommendations, a more or

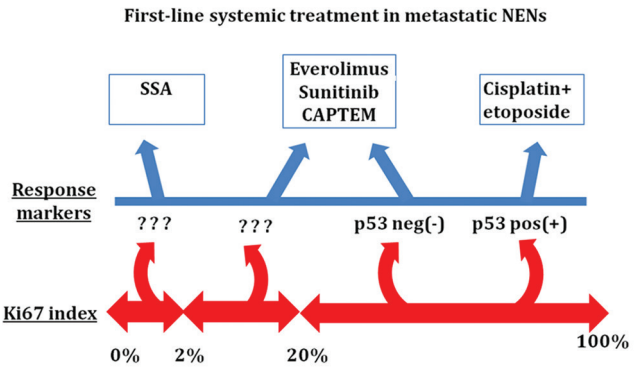

Figure 1. The impact of morphology and p53 immunostaining of G3 neuroendocrine neoplasms on the choice of first-line systemic treatment. It also highlights the impact of missing markers of treatment response in G1 and G2 neuroendocrine tumors

less individualized approach for each patient with G2 NET and select specific treatments based on the primary tumor site, tumor burden, somatostatin receptor scintigraphy, FDG-PET findings, and Ki67 grading. It appears that the "odyssee in the land of small tumors" as described by one of the oncological godfathers of NEN, Charles Moertel, in his 1987 Karnofsky lecture still continues.

Author contributions

Both authors have equally contributed to this paper in terms of concept and design, drafting and gave their final approval.

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