NEN493318 - Neuroendocrinology - ISSN 0028–3835 (for internal use only)

Code 3	PE	CE	Copy edited	Figures	Tables	Suppl. mat.	Typesetting
NEN	bd	asp	18.09.18	0	0		tb

Language	E	Second Language		Third Language		Template_Art	ZU

Internal info:

Neuro endocrinology

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Article title	Unmet Needs in High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms (WHO G3)
Article title second language	
Article title third language	
Subtitle	
Short title	Gastroenteropancreatic WHO G3 Neuroendocrine Neoplasms
Section title	Conference Report

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Citation line	Journal			
	Neuroendocrinology			
10.1159/000493318	Article-Nr	493318	CCCode	
ISSN	0028–3835			
ISBN				

Received	
Accepted	
Revised	
Published online	Published online: ■■■
Copyright statement	© 2018 ©2018S. Karger AG, Basel
Copyright description	

Keywords	Keywords
	Neuroendocrine neoplasm Neuroendocrine tumor Neuroendocrine carcinoma

Keywords Second Language	

Keywords Third Language	

Abbreviations	

Abstract	Abstract

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are classified based on morphology and graded based on their proliferation rate as either well-differentiated low-grade (G1 to G2) neuroendocrine tumors (NET) or poorly differentiated high-grade (G3) neuroendocrine carcinomas (NEC). Recently, a new subgroup of well-differentiated high-grade

pancreatic tumors (NET G3) has been defined. The GEP NEN G3 group consisting of both NEC and NET G3 has recently been shown to be a quite heterogeneous patient group concerning prognosis and treatment benefit, depending on factors such as the primary tumor site, differentiation, proliferation rate, and molecular alterations. In this review we discuss the existing data on diagnostics, treatment, and biomarkers in this patient group, the unmet needs, and the future perspectives.

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Introduction and Perspectives

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are classified based on morphology and graded based on their proliferation rate as either well-differentiated low-grade (G1 to G2) neuroendocrine tumors (NET) or poorly differentiated high-grade (G3) neuroendocrine carcinomas (NEC) by the WHO 2010 classification of tumors of the digestive system [1]. Recently, a new subgroup of well-differentiated high-grade pancreatic tumors (NET G3) has been defined [2]. Concerning the present WHO neuroendocrine nomenclature, tumor and well differentiated are equated regardless of the proliferation rate, just as carcinoma and

poorly differentiated are equated. NET is therefore only used for well-differentiated tumors (G1 to G3), whereas NEC implies a poorly differentiated G3 carcinoma. The term NEN G3 covers all high-grade neuroendocrine malignancies (both NET G3 and NEC). The NEN G3 group has recently been shown to be a quite heterogeneous patient group concerning prognosis and treatment benefit, depending on factors such as the primary tumor site, differentiation, proliferation rate, and molecular alterations. Based on this new knowledge there is a huge unmet need for high-quality pathological and molecular classification that translates into better epidemiologic, clinical, and treatment characterization. Possible prognostic and predictive factors for patients with GEP NEC or NET G3 are highly needed by clinicians to aid in treatment selection for these patients. GEP NEC are usually highly aggressive, with a propensity for early metastases and a dismal prognosis [3–7]. Data on GEP NEC are sparse and treatment has been extrapolated from small-cell lung cancer data. Specific data on GEP NEC are now emerging and the new understanding has shown that this is a specific disease entity. There has been an increase in the incidence of GEP NEC over the last 2 decades, although more awareness of this entity among pathologists could partly explain this increase [3, 8–10]. NEC can originate anywhere in the GEP tract, but they are mainly located in the esophagus, stomach, pancreas, and large bowel [7, 11–14]. Given their aggressive nature, most patients have metastatic disease at the time of presentation [5, 7, 13–15]. In general, high-quality epidemiological data on NEC are lacking, especially as data on differentiation and proliferation rates to ensure a correct diagnosis are often not available in registries. In the SEER database the median survival is 34 months with localized disease, 14–16 months with regional disease, and 5 months with distant disease, but it varies by primary site [4, 14]. Long-term relapse-free survival is possible among NEC patients with localized disease and seems to depend on the primary site location, but inaccurate TNM classification precludes firm conclusions [14, 16]. The mean survival in GEP NEC patients with metastatic disease treated with chemotherapy is 11–12 months [5, 7, 11, 12]. A poor performance status, a high tumor burden, liver metastases, a high

proliferation rate, and elevated lactate dehydrogenase levels are usually baseline negative prognostic factors for survival in metastatic disease [7, 11–13, 17]. Data on the NET G3 subgroup are extremely scarce. NET G3 constitute about 15–20% of the NEN G3 group, are mainly located in the pancreas, and have a better prognosis than NEC [2, 5, 13, 18, 19]. Their relevance outside of the pancreas remains to be studied. A detailed agreement on how to identify and classify NET G3 will be an important step, and reclassification will probably be needed for many cases after such a standardization of diagnostic criteria.

Diagnostics

The optimal pathologic classification of GEP NEN G3 remains controversial and recent retrospective studies suggest that they include different morphological, molecular, clinical, and prognostic entities [13, 20–24]. In the WHO 2010 classification of the digestive system and the 2017 classification of endocrine tumors (including pancreatic NEN), NEN G3 are defined as neoplasms with a high proliferation rate (Ki-67 index >20% or >20 mitotic figures/2 mm^2) but frequently the Ki-67 index is above 70% for NEC [1, 2, 5, 7, 17]. Most studies have shown that a higher Ki-67 proliferation rate is a worse prognostic factor and may be predictive of treatment benefit, although further validation of this is necessary [5, 7, 11, 13, 17, 25–27]. The specific Ki-67 value should therefore always be provided in pathology reports as an absolute measure of the hot spot, i.e., the area with the highest score and possibly complemented by recording heterogeneity [28]. The ENETS classification system has been formally validated in prognostic studies; however, the validation is only for its prognostic relevance, not to optimally stratify therapy. The diagnosis requires histologic examination with immunohistochemical staining for markers of neuroendocrine differentiation. Synaptophys in staining is usually positive, whereas chromogranin A may be negative [1, 2, 7]. NEC encompasses 2 pathological entities: small-cell and large-cell carcinoma. There is a small-cell histological preponderance in the squamous cell

parts (esophagus and anus) and a large-cell carcinoma in the glandular parts [14]. Small-cell carcinoma was the first category described in both the lungs and the GEP tract, and for this reason most of the published literature is focused on small-cell carcinoma. The classic description of small- and large-cell NEC does not perfectly translate to the GEP tract [29, 30]. At this time the clinical relevance of a distinction between small-cell and large-cell NEC is uncertain, and future clinical and molecular studies are awaited as results may reveal differences that are relevant for treatment and prognosis. ^{18}FDG-PET/CT is usually positive in NEC and could be of prognostic value based on SUV_{max} values [31]. The relevance of somatostatin receptor imaging (SRI) in NEC patients is uncertain, but it is negative in ther majority of patients, and ^{18}FDG PET/CT has a much higher sensitivity than ^{68}Ga- PET in NEC [32]. Functional imaging may have a future role in characterization of G3 neoplasms, especially when the sample biopsy is limited. NEC may contain different neoplastic components. If the neoplasm consists of a neuroendocrine component and a gland-forming component, both exceeding 30%, the new 2017 WHO classification defines it as a mixed neuroendocrine-non-NEN (MiNEN), replacing the previously term MANEC (mixed adeno-neuroendocrine carcinoma) at least in the pancreas [2, 33]. At present, high-grade MiNEN are treated similarly to pure NEC as studies are lacking to compare outcomes and the natural history of the disease appears to be determined by the NEC component [34]. Studies are awaited for optimal definition, characterization, and management of MiNEN. This encompasses the significance of the relative proportions of the mixed components as well as of molecular commonalities or differences of these components.

The terms high-grade NEN and poorly differentiated neuroendocrine carcinoma have been used synonymously. While all poorly differentiated neuroendocrine cancers have a high proliferation rate, not all NEN with a proliferation rate above 20% are poorly differentiated. A subset of patients with large-cell NEN that appear histologically well differentiated have a Ki-67 >20%, usually in the range of 20–50% [5, 18, 35, 36]. High-grade neoplasms (Ki-67 >20%) with

a well differentiated morphology are now defined as NET G3 in the 2017 WHO classification for NEN of the pancreas [2, 19]. The majority of these tumors are indeed located in the pancreas. Few data are available to assess the true incidence of NET G3 relative to poorly differentiated NEC, but they seem to constitute about 15–20% of high-grade NEN [5, 13, 37]. The survival of patients with NET G3 is significantly better than that of of patients with NEC [5, 13, 18, 35]. Morphological classification based on differentiation is, however, at present challenging. In a highly specialized NET center, NET pathologists only achieved diagnostic consensus in one third (11/33) of pancreatic G3 cases during a morphological review assessment and 61% of the cases were regarded as ambiguous [38]. A pathological standardization of how to define NET G3 is needed. Molecular genetic markers such as DAXX, ATRX, and MEN1 mutations in NET G3 and Rb1 and TP53 alterations in NEC G3 may aid diagnosis [23, 36, 38]. There are several ongoing efforts to define better and obtain more data on NET G3. It may be clinically relevant to perform SRI in NET G3 or if Ki-67 is below 55% as peptide receptor radionucleotide therapy (PRRT) could be a possible treatment option for selected patients [39].

Therapeutics

Due to a lack of data, much of the treatment algorithm for NEC has been based on small-cell lung cancer data. For the new subgroup NET G3 even less data are available. Treatment of NEC is a challenge for clinicians as NEC are characterized by a high proclivity for metastatic dissemination even in patients with clinically localized primaries. Extensive NEC disease is almost invariably treated with systemic chemotherapy. In contrast, the optimal therapy for localized disease, a potentially curable condition, is presently neither consistent nor uniform.

Surgery

The treatment recommendations for patients with apparently localized disease are not based on prospective data, and supporting evidence from heterogeneous retrospective studies

is limited. There is expert consensus that surgery alone is rarely curative and that patients with limited disease should probably receive multimodality based treatment. Surgery as part of the treatment can be curative in patients with localized disease even with regional lymph node disease; however, the data often does not distinguish between NET G3 and NEC [8, 9, 40–44]. The 5-year survival for localized disease depends on the primary site; for colorectal, stomach, and pancreas primaries the 5-year survival is 40–50%, but it is less for anal (15%) and esophageal (25%) primaries [14]. For regional disease the 5-year survival varies from 27–29% in the pancreas and colon to only 9% in esophageal primaries [14]. Surgery as part of the treatment should therefore be considered for all localized and regional GEP NEC patients with exceptions for esophageal primaries. Several small series confirm poor results after surgical treatment of esophageal NEC, especially for stage III disease where chemoradiation seems better [45, 46]. The optimal therapy for localized disease, particularly in older patients with important comorbidities, remains an unanswered question. Metastatic surgery for GEP NEC is not recommended, but published data are scarce [47–50]. A recent retrospective study indicates that some highly selected patients may benefit from liver surgery [51].

Data on surgery specifically for NET G3 are scarce. NET G3 patients should probably receive the same approach to surgery of the primary and metastatic disease as patients with NET G2 [19, 41]. Prospective data on surgery from good-quality registries based on an updated pathology classification and with modern radiologic staging are necessary to decide the benefit of primary resection according to stage and primary site and to further investigate the possible benefit of metastatic surgery.

Adjuvant Chemotherapy

The aggressive behavior of GEP NEC warrants consideration of adjuvant therapy after radical resection, although there are no studies examining postoperative chemotherapy. For resected patients adjuvant therapy with 4–6 cycles of cisplatin/carboplatin and etoposide is generally recommended [6, 49, 52]. A neoadjuvant approach before surgery can be considered

although data are lacking. A prospective phase III study concerning the benefit of adjuvant chemotherapy would be of great interest; however, such a study will be difficult to perform due to the number of patients generally needed in adjuvant studies.

A new question is whether NET G3 patients should receive adjuvant chemotherapy or be treated as NET G2 patients without any adjuvant therapy [19].

Palliative Chemotherapy

Metastatic GEP NEC is an aggressive disease where rapid referral to an oncologist is necessary to consider a rapid initiation of systemic treatment before the performance status deteriorates to the extent that the patient is no longer fit enough to receive chemotherapy. After the diagnosis of advanced disease, the median survival in the Nordic series was only 1 month in patients not receiving chemotherapy compared to 11–14 months in patients given palliative chemotherapy, suggesting that the benefit of palliative chemotherapy is probably substantial [11]. Metastatic GEP NEC is responsive to systemic chemotherapy, but virtually all patients eventually progress and die of their disease. The available data on outcomes from palliative chemotherapy are from retrospective data. Most guidelines advocate the use of platinum-based chemotherapy combined with etoposide as first-line palliative chemotherapy [6, 49, 52, 53]. The optimal duration of such treatment has not been established. NEC have an intermediate to high response rate and often an acceptable efficacy-toxicity ratio to platinum-based therapy.

Recent results have questioned the benefit of this platinum-based therapy in low-range Ki-67 patients. NET G3 have a low response rate to cisplatin/etoposide and an unfavorable efficacy-toxicity ratio. It should probably not be given to NET G3 patients as first-line treatment [19]. Prospective larger first- and second-line chemotherapy studies are highly needed for both GEP NEC and NET G3.

First-Line Chemotherapy

Results from 3 recent large retrospective studies show that first-line treatment with cisplatin/carboplatin and etoposide results in a response rate of 30–50%, a PFS of 4–6 months, and a median survival of 11–16 months [5, 7, 11]. In the Nordic study, no differences in outcomes were seen when comparing patients given cisplatin-based treatment versus carboplatin-based treatment [11]. This study included both NEC and NET G3 neoplasms, and neoplasms with Ki-67 <55% were much less responsive to platinum-based chemotherapy but had a significantly longer survival. In a Japanese study on 258 patients with poorly differentiated GEP NEC, the response rate and survival were numerically better for irinotecan/etoposide treatment compared to cisplatin/etoposide but treatment regimen was not an independent predictive factor for survival [12]. A Japanese phase III study comparing irinotecan/etoposide to cisplatin/etoposide in patients with NEN G3 is currently recruiting. A US intergroup is running a randomized phase II trial of cisplatin/etoposide versus CAPTEM chemotherapy as first-line treatment for GEP NEC with a non-small cell histology (NCT02595424), but inclusion has been slow. Another US phase II study is giving FOLFIRINOX to GEP NEC patients in all lines (NTC03042780). A Nordic phase II study using temozolomide and everolimus as first-line treatment in patients with metastatic NEN G3 with Ki-67 21–55% has almost completed recruitment (NCT02248012). An Australian randomized trial is planned to compare platinum-etoposide versus nab-paclitaxel-carboplatin in high-grade NEN (AGITG).

The optimal first-line palliative treatment for patients with metastatic NET G3 is unclear [19]. Several recent retrospective studies suggest relatively low response rates to platinum/etoposide regimens in patients with NET G3 [5, 18, 36]. It has been suggested that these patients may benefit from medical treatments used in NET G2, but prospective data are lacking.

Second-Line Chemotherapy

After first-line treatment, no further standard therapy has been established for GEP NEC and no studies have compared chemotherapy versus best supportive care. Patients who

progress for more than 3 months after discontinuation of first-line platinum-based treatment may still be platinum sensitive [11]. Several small retrospective studies suggest that GEP NEC patients can benefit from further lines of chemotherapy after failure of platinum/etoposide treatment [25–27, 54]. Temozolomide-based chemotherapy resulted in a 33% response rate and a PFS of 6 months, and the most benefit seems to be for patients with a Ki-67 <60% [25]. Irinotecan- and oxaliplatin-based chemotherapy may be beneficial as second-line treatments with response rates of 16–31% and a PFS of 2.3–6.2 months [27, 54]. A recent retrospective study with FOLFIRI or FOLFOX resulted in a very short median PFS (<3 months) and OS (<6 months) [7]. Patients with a Ki-67 in the lower range (<50–60%) seem to do better in many of these retrospective small second-line studies. The French PRODIGE 41-BEVANEC phase II study will assess the efficacy of bevacizumab in combination with FOLFIRI as second-line palliative treatment of GEP NEC after failure of platinum-based first-line therapy (NCT02820857). The randomized phase II NET-02 UK study will start in 2018, randomizing between nanoliposomal irinotecan and 5-FU/folinic acid or docetaxel as second-line therapy in patients with poorly differentiated extrapulmonary NEC.

Other Treatment Options

Everolimus

The mTOR pathway is upregulated in 70–80% of NEC and the mTOR inhibitor everolimus was shown to be effective in a preclinical GEP NEC model [55–57]. An ongoing German multicenter study (EVINEC) is using everolimus as a second-line treatment for NEN G3 (NCT02113800).Everolimus was given to 15 patients with pancreatic NET G3 with Ki-67 ≤55%, mainly after first-line treatment; the results were promising, with a median PFS of 6 months and an OS of 28 months after the start of everolimus treatment [58].

Peptide Receptor Radionucleotide Therapy

PRRT is regularly used for G1-G2 NET with a high uptake on SRI. The benefit of PRRT in patients with a higher proliferation rate is unknown. Preliminary studies have shown effectiveness in patients with aggressive-grade neoplasms with an ^{18}FDG-avid and concordant SSTR expressing phenotype [59]. A single-center retrospective study reported the use of PRRT in 17 high-grade neuroendocrine cases with a median PFS of 12 months [60]. A recent retrospective study of 29 patients treated with PRRT showed very promising response and survival data with an acceptable toxicity profile especially for the patients in the Ki-67 ≤55% subgroup, the majority of whom had failed prior chemotherapy [39]. The outcome appears to be superior to those of other previously reported treatment modalities, with an overall median PFS of 9 months and a median OS of 21 months. Importantly, the median OS for patients with a Ki-67 ≤55% was 41 months and only 7 months if the Ki-67 was >55%. Hence, PRRT is potentially a therapeutic option for patients with Ki-67 ≤55% or NET G3 with a high uptake on SRI. An Australian led multicenter randomized phase II study is under development under the auspices of ENETS to examine the benefit of PRRT in patients with GEP NEC or NET G3.

Immunotherapy

Immunotherapy with programmed cell death-1 protein (PD-1) checkpoint inhibitors has shown great promise in widely different cancers. Recently, phase II data with the PD-1 inhibitor pembrolizumab showed a 56% objective response rate in neuroendocrine cancinoma of the skin, i.e., Merkel cell carcinoma [61]. A benefit in metastatic Merkel cell carcinoma was also seen for another anti-PD-L1 antibody, i.e., avelumab [62]. As GEP NEC has a high mutational burden, immunotherapy could be of value for many NEC patients [20, 63–65]. Several immunotherapy trials are ongoing in G3 patients. A trial with PDR001 (an anti-PD1 monoclonal antibody) has finished accrual with GEP NEC as one of 4 cohorts in the study (NCT02955069). The DUNE trial from GETNE exploring the combination of durvalumab (PDL1 monoclonal antibody) and tremelimumab (CTL4 monoclonal antibody) is currently ongoing with a G3 cohort (EudraCT 2016-002858-20). A phase II trial exploring pembrolizumab monotherapy and

pembrolizumab combined with either irinotecan or paclitaxel in previously treated high-grade extrapulmonary NEC has started in the USA (NTC03136055).

Biomarkers

Potential biomarkers embrace a spectrum of genes, mRNA, microRNA, single-nucleotide polymorphisms, proteins, and metabolites being associated with cancer and having a role in detection (screening and diagnosis) and management (prognosis, treatment response, and monitoring). It is obvious that the reliable identification of new biomarkers constitutes a critical step in personalizing the treatment of patients with NEN G3. The role of serum markers such as chromogranin A and NSE in GEP NEC is not well established, although chromogranin A is elevated in many patients and may be a good prognostic marker [5, 7, 11]. Few data exist on genetic molecular tissue markers regarding the prognosis and predictive treatment benefit in NEC [24, 66], but next-generation sequencing data are expected to emerge rapidly. Initial molecular NEC studies reported similar genomic abnormalities with an adenocarcinoma, but that it also contains additional mutations [24, 64, 67]. The mutational signature in NEC seems to be specific to their primary location and similar to the adenocarcinoma of the same site, rather than having a common neuroendocrine signature [64, 67–69]. Achaete-scute homolog 1, KRAS, TP53, and RB1 alterations seem to be markers of poor differentiation and may help to differentiate NEC from NET G3 [23, 36, 38, 70, 71]. Rb loss may predict the response to platinum-based chemotherapy in pancreatic NEC patients [36]. One large NEC molecular gene profile study including 274 GEP NEC presented initial results showing that the GEP NEC group had a lower rate of TP53 and alteration RB1 than small-cell lung cancer and other genes were more frequently altered [72]. PD-L1 protein expression on tumor cells is currently the best predictive biomarker for the benefit of immunotherapy, and expression of PD-L1 in NET tissue seems to be significantly associated with NEN G3 [73, 74]. Microsatellite instability (MSI) is a

hypermutable phenotype caused by the loss of DNA mismatch repair activity where immunotherapy seems to work especially well and colorectal NEC frequently have MSI-H [20, 64, 65]. Growing evidence supports a tumor suppressor role for Notch-1 signaling in NEC [24, 75, 76]. Delta-like protein 3 (DLL3) inhibits Notch receptor activation and has been identified as a novel putative therapeutic target in NEC including small-cell lung cancer, where it is expressed in more than 80% of patients. Rovalpituzumab tesirine is an antibody drug against DLL3 and has recently shown encouraging single-agent antitumor activity in small-cell lung cancer or large-cell NEN [76]. MicroRNA are small noncoding RNA with important functions in modulating gene expression and they have significant roles in cancer development, growth and metastasis, inflammation, fibrosis, and angiogenesis. Recently, a high focus on liquid biomarkers to select patients who will benefit from different types of treatments has emerged [77]. The available literature data clearly show that tissue miRNA profiling may potentially represent a prognostic biomarker in NEN [78]. However, the role of circulating miRNA in these settings is far from being consolidated and very little is known about the role of microRNA in tissue and blood in patients with GEP NEC. Studies prospectively evaluating circulating miRNA in different NEN types (and stages) and their levels after the different available therapeutic approaches are still lacking.

Future Developments

Emerging data has further shown that the NEN G3 group is quite heterogeneous where prognosis and probably treatment will in the future depend on subgroup characteristics such as differentiation, proliferation rate, and molecular profile including SRI uptake and primary location. We recommend using NEC, NET G3, and MINEN or uncertain G3 as a classification for all high-grade NEN as well as specifications of TNM, Ki-67, and primary location. Prospective clinical trials as well as cancer registries will allow the development of more

sophisticated grading classifications and provide clinicians with better prognostic and predictive tools for selection of treatment. A systematic expert pathological review will be critical to avoid misinterpretation of new study results and to better understand the place of new therapeutic options within the new subgroups of NEN G3. Introduction of the concept of molecular classification as an adjunct to pathology will evolve.

The major unmet needs as we see them are: adequate diagnosis by a systematic expert pathologist review and a shared definition of NEC based on differentiation and grade, and prospective data from good-quality registries providing information on incidence and treatment based on updated pathology and modern radiology. The heterogeneity of the NEN G3 group illustrated by the new NET G3 category needs to be better explored. Biomarkers for prognosis and treatment have to be developed and analysis of genetic molecular markers will be important. Newer treatment options must be explored in the heterogeneous NEN G3 group, and we need to define possible subgroups with regard to the optimal therapy. Prospective treatment studies using drugs other than platinum/etoposide chemotherapy or newer personalized options are ongoing or under development. Active translational research as a part of all clinical studies should be established with collection of tumor tissue specimens including liquid biopsy to look for new therapeutic targets in GEP NEC and NET G3.

Appendix

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References

1 Bosman FT, Carneiro F, Hruban RH, Theise ND: WHO Classification of Tumours of the Digestive System, ed 4. Lyon, IARC Press, 2010.

2 Klöppel G, Couvelard A, Hruban RH, Klimstra DS, Komminoth P, Osamura RY, Perren A, Rindi G. Neoplasms of the Neuroendocrine Pancreas, ed 4. Lyon, IARC Press, 2017.

3 Korse CM, Taal BG, van Velthuysen ML, Visser O: Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. Eur J Cancer 2013;49:1975–1983.

4 Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC: Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer 2014;120:2814–2823.

5 Heetfeld M, Chougnet CN, Olsen IH, Rinke A, Borbath I, Crespo G, et al: Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2015;22:657–664.

6 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, et al: ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology 2016;103:186–194.

7 Walter T, Tougeron D, Baudin E, Le Malicot K, Lecomte T, Malka D, et al: Poorly differentiated gastro-entero-pancreatic neuroendocrine carcinomas: are they really heterogeneous? Insights from the FFCD-GTE national cohort. Eur J Cancer 2017;79:158–165.

8 Shafqat H, Ali S, Salhab M, Olszewski AJ: Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. Dis Colon Rectum 2015;58:294–303.

9 Mosquera C, Koutlas NJ, Fitzgerald TL: Localized high-grade gastroenteropancreatic neuroendocrine tumors: defining prognostic and therapeutic factors for a disease of increasing clinical significance. Eur J Surg Oncol 2016;42:1471–1477.

10 Leoncini E, Boffetta P, Shafir M, Aleksovska K, Boccia S, Rindi G: Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. Endocrine 2017;58:368–379.

11 Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, 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;24:152–160.

12 Yamaguchi T, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, et al: Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. Cancer Sci 2014;105:1176–1181.

13 Milione M, Maisonneuve P, Spada F, Pellegrinelli A, Spaggiari P, Albarello L, et al: The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. Neuroendocrinology 2017;104:85–93.

14 Dasari AMK, Byers L, Sorbye H, Yao J: Comparative Study of Lung and Extrapulmonary Poorly Differentiated Neuroendocrine Carcinomas: A SEER Database Analysis of 162983 Cases. Cancer 2018;124:807–815.

15 Basturk O, Tang L, Hruban RH, Adsay V, Yang Z, Krasinskas AM, et al: Poorly differentiated neuroendocrine carcinomas of the pancreas: a clinicopathologic analysis of 44 cases. Am J Surg Pathol 2014;38:437–447.

16 Fitzgerald TL, Mosquera C, Lea CS, McMullen M: Primary site predicts grade for gastroenteropancreatic neuroendocrine tumors. Am Surg 2017;83:799–803.

17 Lamarca A, Walter T, Pavel M, Borbath I, Freis P, Nunez B, et al: Design and Validation of the GI-NEC Score to Prognosticate Overall Survival in Patients With High-Grade Gastrointestinal Neuroendocrine Carcinomas. Journal of the National Cancer Institute 2017, DOI: 10.1093/jnci/djw277.

18 Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al: Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 2013;20:649–657.

19 Coriat R, Walter T, Terris B, Couvelard A, Ruszniewski P: Gastroenteropancreatic well-differentiated grade 3 neuroendocrine tumors: review and position statement. Oncologist 2016;21:1191–1199.

20 La Rosa S, Marando A, Furlan D, Sahnane N, Capella C: Colorectal poorly differentiated neuroendocrine carcinomas and mixed adenoneuroendocrine carcinomas: insights into the diagnostic immunophenotype, assessment of methylation profile, and search for prognostic markers. Am J Surg Pathol 2012;36:601–611.

21 Fazio N, Milione M: Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: new insights and treatment implications. Cancer Treat Rev 2016;50:61–67.

22 Tang LH, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, et al: Well-differentiated neuroendocrine tumors with a morphologically apparent high-grade component: a pathway

distinct from poorly differentiated neuroendocrine carcinomas. Clin Cancer Res 2016;22:1011–1017.

23 Konukiewitz B, Schlitter AM, Jesinghaus M, Pfister D, Steiger K, Segler A, et al: Somatostatin receptor expression related to TP53 and RB1 alterations in pancreatic and extrapancreatic neuroendocrine neoplasms with a Ki67-index above 20%. Mod Pathol 2017;30:587–598.

24 Girardi DM, Silva ACB, Rêgo JFM, Coudry RA, Riechelmann RP: Unraveling molecular pathways of poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: a systematic review. Cancer Treat Rev 2017;56(suppl C):28–35.

25 Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C, Oberg K: Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. Cancer 2011;117:4617–4622.

26 Olsen IH, Knigge U, Federspiel B, Hansen CP, Skov A, Kjaer A, et al: Topotecan monotherapy in heavily pretreated patients with progressive advanced stage neuroendocrine carcinomas. J Cancer 2014;5:628–632.

27 Hadoux J, Malka D, Planchard D, Scoazec JY, Caramella C, Guigay J, et al: Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. Endocr Relat Cancer 2015;22:289–298.

28 Perren A, Couvelard A, Scoazec JY, Costa F, Borbath I, Delle Fave G, et al: ENETS consensus guidelines for the standards of care in neuroendocrine tumors: pathology – diagnosis and prognostic stratification. Neuroendocrinology 2017;105:196–200.

29 Shia J, Tang LH, Weiser MR, Brenner B, Adsay NV, Stelow EB, et al: Is nonsmall cell type high-grade neuroendocrine carcinoma of the tubular gastrointestinal tract a distinct disease entity? Am J Surg Pathol 2008;32:719–731.

30 Hirabayashi K, Zamboni G, Nishi T, Tanaka A, Kajiwara H, Nakamura N: Histopathology of gastrointestinal neuroendocrine neoplasms. Front Oncol 2013;3:2.

31 Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A: ^{18}F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res 2010;16:978–985.

32 Binderup T, Knigge U, Loft A, Mortensen J, Pfeifer A, Federspiel B, et al: Functional imaging of neuroendocrine tumors: a head-to-head comparison of somatostatin receptor scintigraphy, 123I-MIBG scintigraphy, and 18F-FDG PET. J Nucl Med 2010;51:704–712.

33 La Rosa S, Sessa F, Uccella S: Mixed neuroendocrine-nonneuroendocrine neoplasms (MiNENs): unifying the concept of a heterogeneous group of neoplasms. Endocr Pathol 2016;27:284–311.

34 de Mestier L, Cros J, Neuzillet C, Hentic O, Egal A, Muller N, et al: Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. Neuroendocrinology 2017;105:412–425.

35 Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, 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;39:683–690.

36 Hijioka S, Hosoda W, Matsuo K, Ueno M, Furukawa M, Yoshitomi H, et al: Rb loss and *KRAS* mutation are predictors of the response to platinum-based chemotherapy in pancreatic neuroendocrine neoplasm with grade 3: a japanese multicenter pancreatic NEN-G3 study. Clin Cancer Res 2017;23:4625–4632.

37 Scoazec JY, Couvelard A, Monges G, Guyetant S, Bisot-Locard S, Parot X, et al: Professional practices and diagnostic issues in neuroendocrine tumour pathology: results of a prospective one-year survey among French pathologists (the PRONET study). Neuroendocrinology 2017;105:67–76.

38 Tang LH, Basturk O, Sue JJ, Klimstra DS: A practical approach to the classification of WHO grade 3 (G3) well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma (PD-NEC) of the pancreas. Am J Surg Pathol 2016;40:1192–1202.

39 Thang SP, Lung MS, Kong G, Hofman MS, Callahan J, Michael M, et al: Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN): a single-institution retrospective analysis. Eur J Nucl Med Mol Imaging 2018;45:262–277.

40 Haugvik SP, Janson ET, Osterlund P, Langer SW, Falk RS, Labori KJ, et al: Surgical treatment as a principle for patients with high-grade pancreatic neuroendocrine carcinoma: a Nordic multicenter comparative study. Ann Surg Oncol 2016;23:1721–1728.

41 Crippa S, Partelli S, Bassi C, Berardi R, Capelli P, Scarpa A, et al: Long-term outcomes and prognostic factors in neuroendocrine carcinomas of the pancreas: morphology matters. Surgery 2016;159:862–871.

42 Shen C, Chen H, Chen H, Yin Y, Han L, Chen J, et al: Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. BMC gGastroenterol 2016;16:111.

43 Ishida M, Sekine S, Fukagawa T, Ohashi M, Morita S, Taniguchi H, et al: Neuroendocrine carcinoma of the stomach: morphologic and immunohistochemical characteristics and prognosis. Am J Surg Pathol 2013;37:949–959.

44 Xie JW, Sun YQ, Feng CY, Zheng CH, Li P, Wang JB, et al: Evaluation of clinicopathological factors related to the prognosis of gastric neuroendocrine carcinoma. Eur J Surg Oncol 2016;42:1464–1470.

45 Meng MB, Zaorsky NG, Jiang C, Tian LJ, Wang HH, Liu CL, et al: Radiotherapy and chemotherapy are associated with improved outcomes over surgery and chemotherapy in

the management of limited-stage small cell esophageal carcinoma. Radiother Oncol 2013;106:317–322.

46 Deng HY, Ni PZ, Wang YC, Wang WP, Chen LQ: Neuroendocrine carcinoma of the esophagus: clinical characteristics and prognostic evaluation of 49 cases with surgical resection. J Thorac Dis 2016;8:1250–1256.

47 Oberg K, Knigge U, Kwekkeboom D, Perren A, Group EGW: Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(suppl 7):vii124–vii130.

48 Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al: ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. Neuroendocrinology 2016;103:172–185.

49 Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, et al: The NANETS consensus guidelines for the diagnosis and management of poorly differentiated (high-grade) extrapulmonary neuroendocrine carcinomas. Pancreas 2010;39:799–800.

50 Frilling A, Modlin IM, Kidd M, Russell C, Breitenstein S, Salem R, et al: Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol 2014;15:e8–e21.

51 Galleberg RB, Knigge U, Tiensuu Janson E, Vestermark LW, Haugvik SP, Ladekarl M, et al: Results after surgical treatment of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. Eur J Surg Oncol 2017;43:1682–1689.

52 Janson ET, Sorbye H, Welin S, Federspiel B, Gronbaek H, Hellman P, et al: Nordic guidelines 2014 for diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. Acta Oncol 2014;53:1284–1297.

53 Garcia-Carbonero R, Rinke A, Valle JW, Fazio N, Caplin M, Gorbounova V, et al: ENETS consensus guidelines for the standards of care in neuroendocrine neoplasms: systemic therapy 2 – chemotherapy. Neuroendocrinology 2017;105:281–294.

54 Hentic O, Hammel P, Couvelard A, Rebours V, Zappa M, Palazzo M, et al: FOLFIRI regimen: an effective second-line chemotherapy after failure of etoposide-platinum combination in patients with neuroendocrine carcinomas grade 3. Endocr Relat Cancer 2012;19:751–757.

55 Shida T, Kishimoto T, Furuya M, Nikaido T, Koda K, Takano S, et al: Expression of an activated mammalian target of rapamycin (mTOR) in gastroenteropancreatic neuroendocrine tumors. Cancer Chemother Pharmacol 2010;65:889–893.

56 Bollard J, Couderc C, Blanc M, Poncet G, Lepinasse F, Hervieu V, et al: Antitumor effect of everolimus in preclinical models of high-grade gastroenteropancreatic neuroendocrine carcinomas. Neuroendocrinology 2013;97:331–340.

57 Catena L, Bajetta E, Milione M, Ducceschi M, Valente M, Dominoni F, et al: Mammalian target of rapamycin expression in poorly differentiated endocrine carcinoma: clinical and therapeutic future challenges. Target Oncol 2011;6:65–68.

58 Panzuto F, Rinzivillo M, Spada F, Antonuzzo L, Ibrahim T, Campana D, et al: Everolimus in pancreatic neuroendocrine carcinomas G3. Pancreas 2017;46:302–305.

59 Kashyap R, Hofman MS, Michael M, Kong G, Akhurst T, Eu P, et al: Favourable outcomes of (177)Lu-octreotate peptide receptor chemoradionuclide therapy in patients with FDG-avid neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2015;42:176–185.

60 Armaghany T, Vahdati G, Thamake S, Hamidi M, Amerinia R, Delpassand E: Treatment of high grade metastatic neuroendocrine tumor (mNET) with peptide receptor radionuclide therapy (PRRT): retrospective analysis in a single referral center. J Clin Oncol 2015;33:e15175.

61 Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al: PD-1 blockade with pembrolizumab in advanced Merkel cell carcinoma. N Engl J Med 2016;374:2542–2552.

62 Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al: Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17:1374–1385.

63 Volante M, Monica V, Birocco N, Brizzi MP, Busso S, Daniele L, et al: Expression analysis of genes involved in DNA repair or synthesis in mixed neuroendocrine/nonneuroendocrine carcinomas. Neuroendocrinology 2015;101:151–160.

64 Furlan D, Sahnane N, Mazzoni M, Pastorino R, Carnevali I, Stefanoli M, et al: Diagnostic utility of MS-MLPA in DNA methylation profiling of adenocarcinomas and neuroendocrine carcinomas of the colon-rectum. Virchows Arch 2013;462:47–56.

65 Sahnane N, Furlan D, Monti M, Romualdi C, Vanoli A, Vicari E, et al: Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity. Endocr Relat Cancer 2015;22:35–45.

66 Oberg K, Modlin IM, De Herder W, Pavel M, Klimstra D, Frilling A, et al: Consensus on biomarkers for neuroendocrine tumour disease. Lancet Oncol 2015;16:e435–e446.

67 Karkouche R, Bachet JB, Sandrini J, Mitry E, Penna C, Cote JF, et al: Colorectal neuroendocrine carcinomas and adenocarcinomas share oncogenic pathways: a clinico-pathologic study of 12 cases. Eur J Gastroenterol Hepatol 2012;24:1430–1437.

68 Woischke C, Schaaf CW, Yang HM, Vieth M, Veits L, Geddert H, et al: In-depth mutational analyses of colorectal neuroendocrine carcinomas with adenoma or adenocarcinoma components. Mod Pathol 2017;30:95–103.

69 Takizawa N, Ohishi Y, Hirahashi M, Takahashi S, Nakamura K, Tanaka M, et al: Molecular characteristics of colorectal neuroendocrine carcinoma; similarities with adenocarcinoma rather than neuroendocrine tumor. Hum Pathol 2015;46:1890–1900.

70 Shida T, Furuya M, Nikaido T, Kishimoto T, Koda K, Oda K, et al: Aberrant expression of human achaete-scute homologue gene 1 in the gastrointestinal neuroendocrine carcinomas. Clinical Cancer Res 2005;11:450–458.

71 La Rosa S, Marando A, Gatti G, Rapa I, Volante M, Papotti M, et al: Achaete-scute homolog 1 as a marker of poorly differentiated neuroendocrine carcinomas of different sites: a validation study using immunohistochemistry and quantitative real-time polymerase chain reaction on 335 cases. Hum Pathol 2013;44:1391–1399.

72 Bergsland EK, Roy R, Stephens P, Ross JS, Bailey M, Olshen A: Genomic profiling to distinguish poorly differentiated neuroendocrine carcinomas: a new clinicopathologic entity. J Clin Oncol 2016;34:4020.

73 Kim ST, Lee SJ, Park SH, Park JO, Lim HY, Kang WK, et al: Genomic profiling of metastatic gastroenteropancreatic neuroendocrine tumor (GEP-NET) patients in the personalized-medicine era. J Cancer 2016;7:1044–1048.

74 Cavalcanti E, Armentano R, Valentini AM, Chieppa M, Caruso ML: Role of PD-L1 expression as a biomarker for GEP neuroendocrine neoplasm grading. Cell Death Dis 2017;8:e3004.

75 Meder L, Konig K, Ozretic L, Schultheis AM, Ueckeroth F, Ade CP, et al: NOTCH, ASCL1, p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas. Int J Cancer 2016;138:927–938.

76 Rudin CM, Pietanza MC, Bauer TM, Ready N, Morgensztern D, Glisson BS, et al: Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. Lancet Oncol 2017;18:42–51.

77 Siravegna G, Marsoni S, Siena S, Bardelli A: Integrating liquid biopsies into the management of cancer. Nat Rev Clin Oncol 2017;14:531–548.

78 Zatelli MC, Grossrubatscher EM, Guadagno E, Sciammarella C, Faggiano A, Colao A: Circulating tumor cells and miRNAs as prognostic markers in neuroendocrine neoplasms. Endocr Relat Cancer 2017;24:R223–R237.

Appendix after References (Editorial Comments)

Legend(s)

Table(s)

Footnote(s)