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Unmet needs in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3).

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Abstract

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are classified based upon morphology and graded upon proliferation rate as either well-differentiated low-grade (G1-G2) neuroendocrine tumours (NET) or poorly differentiated high-grade (G3) neuroendocrine carcinoma (NEC). Recently, a new subgroup of well-differentiated high-grade pancreatic tumours (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 primary tumour site, differentiation, proliferation rate and molecular alterations. In this review we discuss the existing data on diagnostics, treatment and biomarkers on this patient group, the unmet needs and the future perspectives.

Introduction and perspectives

Gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are classified based upon morphology and graded upon proliferation rate as either well-differentiated low-grade (G1-G2) neuroendocrine tumours (NET) or poorly differentiated high-grade (G3) neuroendocrine carcinoma (NEC) by the WHO 2010 on tumours of the digestive system (1). Recently, a new subgroup of well-differentiated high-grade pancreatic tumours (NET G3) has been defined (2). Concerning the present WHO neuroendocrine nomenclature; tumour and well differentiated are equated regardless of proliferation rate, just as carcinoma and poorly differentiated are equated. NET is therefore only used for well-differentiated tumours (G1-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 primary tumour 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 turning into better epidemiologic, clinical and treatment characterisation. Possible prognostic and predictive factors for patients with GEP NEC or NET G3 are highly needed by clinicians to aid 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 have been 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 two 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 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 was 34 months with localized disease, 14-16 months with regional disease and 5 months with distant disease, but 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). Mean survival in GEP NEC patients with metastatic disease treated with chemotherapy is 11-12 months (5, 7, 11, 12). Poor performance status, high tumour burden, liver metastases, high proliferation rate and elevated lactate dehydrogenase (LDH) 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 constitutes probably 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). Its relevance outside the pancreas remains to be studied. An important step will be a detailed agreement on how to identify and classify NET G3, and a 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 for the digestive system and the 2017 classification for

endocrine tumours (includes pancreatic NEN), NEN G3 are defined as neoplasms with a high proliferation rate (Ki-67 index >20% or >20 mitotic figures/2mm^2) but frequently the Ki-67 is above 70% for NEC (1, 2, 5, 7, 17). Most studies show that a higher Ki-67 proliferation rate is a worse prognostic factor and may be predictive for 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 number 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. Synaptophysin staining is usually positive, whereas CgA may be negative (1, 2, 7). NEC encompasses two 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 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 relevant for treatment and prognosis. ^{18}FDG-PET/CT is usually positive in NEC and could be of prognostic value based on SUVmax values (31). The relevance of somatostatin receptor imaging (SRI) in NEC patients is uncertain, but is negative in a 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 characterizing 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-neuroendocrine neoplasm (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 neuroendocrine neoplasm 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 neuroendocrine neoplasms that appear histologically well differentiated have a Ki-67 >20 %, usually in the 20-50 % range (5, 18, 35, 36). High-grade neoplasm (Ki-67>20%) with a well differentiated morphology are now defined as NET G3 in the 2017 WHO classification for neuroendocrine neoplasms of the pancreas (2, 19). The majority of these tumours are indeed located in the pancreas. Few data are available to assess the true incidence of NET G3 relative to poorly differentiated NECs, but they seem to constitute about 15-20% of high-grade NEN (5, 13, 37). Survival of patients with NET G3 is significantly better than 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 to be ambiguous (38). A pathological standardization of how to define NET G3 is needed. Molecular genetic markers as DAXX, ATRX, MEN1 mutations in NET G3 and Rb1 and TP53 alterations in NEC G3 may be a way to aid diagnosis (23, 36, 38). There are now several ongoing efforts to define better and obtain more data on NET G3. SRI may be clinically relevant to perform in NET G3 or if the Ki-67 is below 55% as peptide receptor radionucleotide therapy (PRRT) could be a possible treatment option for selected patients (39).

THERAPEUTICS

Due to 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 localised primaries. Extensive NEC disease is almost invariably treated by systemic chemotherapy. In contrast, optimal therapy for localized disease, a potentially curable condition, is presently neither consistent nor uniform.

Surgery

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 multi-modality 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). Five-year survival for localized disease depends on primary site; for colorectal, stomach, and pancreas primaries 5-year survival is 40-50%, but less for anal (15%) and oesophageal (25%) primaries (14). For regional disease 5-year survival varies from 29-27% in colon and pancreas to only 9% in oesophageal primaries (14). Surgery as part of the treatment should therefore be considered for all localized and regional GEP NEC patients with exceptions for oesophageal primaries. Several small series confirm poor results after surgical treatment of oesophageal NEC, especially for stage III disease where chemoradiation seems better (45, 46). 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 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 high 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 should 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 rapid initiation of systemic treatment before the performance status (PS) deteriorates to the extent that the patient is no longer fit enough to receive chemotherapy. After diagnosis of advanced disease, 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 from 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 1st - and 2nd 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%, 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 comparing patients treated with 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, response rate and survival were numerically better for irinotecan/etoposide treatment compared to cisplatin/etoposide but the 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 vs CAPTEM chemotherapy as first-line treatment in GEP NEC with 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 vs 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 a 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 1st-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 more than three 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 most benefit seems to be for patients with a Ki-67< 60% (25). Irinotecan- and oxaliplatin-based chemotherapy may benefit as second-line treatments with response rates of 16-31% and 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 2nd-line studies. The French PRODIGE 41-BEVANEC phase II study will assess the efficacy of bevacizumab in combination with FOLFIRI as 2nd-line palliative treatment of GEP NEC after failure of platinum-based 1st-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 extra-pulmonary NEC.

Other treatment options

Everolimus

The mTOR pathway is up-regulated in 70-80% of NEC and the mTOR inhibitor everolimus has been shown to be effective in a preclinical GEP NEC model (55-57). An ongoing German multi-center study (EVINEC) is using everolimus as 2-line treatment in 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 median PFS 6 months and OS 28 months after start of everolimus treatment (58).

Peptide receptor radionuclide therapy (PRRT)

Peptide receptor radionuclide 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 ^{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 have shown very promising response and survival data with acceptable toxicity profile especially for the Ki-67 ≤55% subgroup, the majority of whom had failed prior chemotherapy (39). The outcome appears superior to other previously

reported treatment modalities, with an overall median PFS of 9 months and median OS of 21 months. Importantly, the median OS for patients with Ki-67≤55% was 41 months and only 7 months if 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 lead multi-center 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 – Merkel-Cell carcinoma (61). A benefit in metastatic Merkel-cell carcinoma was also seen for another anti-PD-L1 antibody, 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 is 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 extra-pulmonary NEC has started in US (NTC03136055).

BIOMARKERS

Potential biomarkers embrace a spectrum of genes, mRNAs, microRNAs, single nucleotide polymorphisms (SNPs), proteins and metabolites being associated with cancer and having a role in detection (screening, diagnosis) and management (prognosis, treatment response, monitoring). It is obvious that the reliable identification of new biomarkers constitutes a critical step in personalizing treatment of patients with NEN G3. The role of serum markers such as chromogranin A (CgA) and NSE in GEP NEC is not well established, although CgA is elevated in many patients and may be a good prognostic marker (5, 7, 11). Few data exist on genetic molecular tissue markers regarding prognosis and predictive treatment benefit in NEC (24, 66), but next generation sequencing data are expected to emerge rapidly. Initial molecular NEC studies report 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 to be 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 response to platinum-based chemotherapy in pancreatic NEC patients (36). One large NEC molecular gene profile study including 274 GEP NEC has 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 tumour cells is currently the best predictive biomarker for benefit of immunotherapy and expression of PD-L1 in neuroendocrine tumour tissue seem 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 have frequently MSI-H (20, 64, 65). Growing evidence supports a tumour-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 antitumour activity in small-cell lung cancer or large-cell neuroendocrine neoplasms (76). MicroRNAs are small non-coding RNAs with important functions in modulating gene expression and 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 miRNAs in these settings is far to be consolidated and very little is known about the role of microRNAs 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 as e.g. differentiation, proliferation rate, 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 for 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 need to better explored. Biomarkers for prognosis and treatment have to be developed and analyzing 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 in regard to 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 tumour tissue specimens including liquid biopsy to look for new therapeutic targets in GEP NEC and NET G3.

References.

1. Bosman FT CF, Hruban RH, Theise ND. . WHO classification of tumours of the digestive system. . 4th ed. Lyon: IARC Press; 2010.
2. Klöppel G CA, Hruban RH, Klimstra DS, Komminoth P, Osamura RY, Perren A, Rindi G. Neoplasms of the neuroendocrine pancreas. ed 4. Lyon ed: 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. European journal of cancer. 2013;49(8):1975-83.
4. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer. 2014;120(18):2814-23.
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. Endocrine-related cancer. 2015;22(4):657-64.
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(2):186-94.
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. European journal of cancer. 2017;79:158-65.
8. Shafqat H, Ali S, Salhab M, Olszewski AJ. Survival of patients with neuroendocrine carcinoma of the colon and rectum: a population-based analysis. Diseases of the colon and rectum. 2015;58(3):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. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2016;42(10):1471-7.
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.
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. Annals of oncology : official journal of the European Society for Medical Oncology. 2013;24(1):152-60.
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 science. 2014;105(9):1176-81.
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(1):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. 2017:In Press.
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. The American journal of surgical pathology. 2014;38(4):437-47.
16. Fitzgerald TL, Mosquera C, Lea CS, McMullen M. Primary Site Predicts Grade for Gastroenteropancreatic Neuroendocrine Tumors. The American surgeon. 2017;83(7):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;109(5).

18. Velayoudom-Cephise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocrine-related cancer. 2013;20(5):649-57.
19. Coriat R, Walter T, Terris B, Couvelard A, Ruszniewski P. Gastroenteropancreatic Well-Differentiated Grade 3 Neuroendocrine Tumors: Review and Position Statement. The oncologist. 2016;21(10):1191-9.
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. The American journal of surgical pathology. 2012;36(4):601-11.
21. Fazio N, Milione M. Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: New insights and treatment implications. Cancer Treat Rev. 2016;50:61-7.
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. Clinical cancer research : an official journal of the American Association for Cancer Research. 2016;22(4):1011-7.
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(4):587-98.
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 Treatment Reviews. 2017;56(Supplement 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(20):4617-22.
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. Journal of Cancer. 2014;5(8):628-32.
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. Endocrine-related cancer. 2015;22(3):289-98.
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(3):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? The American journal of surgical pathology. 2008;32(5):719-31.
30. Hirabayashi K, Zamboni G, Nishi T, Tanaka A, Kajiwara H, Nakamura N. Histopathology of gastrointestinal neuroendocrine neoplasms. Frontiers in oncology. 2013;3:2.
31. Binderup T, Knigge U, Loft A, Federspiel B, Kjaer A. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clinical cancer research : an official journal of the American Association for Cancer Research. 2010;16(3):978-85.
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. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2010;51(5):704-12.
33. La Rosa S, Sessa F, Uccella S. Mixed Neuroendocrine-Nonneuroendocrine Neoplasms (MiNENs): Unifying the Concept of a Heterogeneous Group of Neoplasms. Endocrine pathology. 2016;27(4):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.

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. The American journal of surgical pathology. 2015;39(5):683-90.
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. Clinical Cancer Research. 2017;23(16):4625-32.
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(1):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. The American journal of surgical pathology. 2016;40(9):1192-202.
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. European Journal of Nuclear Medicine and Molecular Imaging. 2017.
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. Annals of surgical oncology. 2016;23(5):1721-8.
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(3):862-71.
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 gastroenterology. 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. The American journal of surgical pathology. 2013;37(7):949-59.
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. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2016;42(10):1464-70.
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. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2013;106(3):317-22.
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. Journal of thoracic disease. 2016;8(6):1250-6.
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. Annals of oncology : official journal of the European Society for Medical Oncology. 2012;23 Suppl 7:vii124-30.
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(2):172-85.

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(6):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. The Lancet Oncology. 2014;15(1):e8-21.
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. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(9):1682-9.
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 oncologica. 2014;53(10):1284-97.
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(3):281-94.
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. Endocrine-related cancer. 2012;19(6):751-7.
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 chemotherapy and pharmacology. 2010;65(5):889-93.
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(4):331-40.
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. Targeted oncology. 2011;6(2):65-8.
58. Panzuto F, Rinzivillo M, Spada F, Antonuzzo L, Ibrahim T, Campana D, et al. Everolimus in Pancreatic Neuroendocrine Carcinomas G3. Pancreas. 2017;46(3):302-5.
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(2):176-85.
60. Armaghany T VG TS, 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 2017;35(33):(suppl abstr e15694).
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. The New England journal of medicine. 2016;374(26):2542-52.
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. The Lancet Oncology. 2016;17(10):1374-85.
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(2):151-60.
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 Archiv : an international journal of pathology. 2013;462(1):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. Endocrine-related cancer. 2015;22(1):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. The Lancet Oncology. 2015;16(9):e435-e46.
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. European journal of gastroenterology & hepatology. 2012;24(12):1430-7.
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(1):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. Human pathology. 2015;46(12):1890-900.
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 research : an official journal of the American Association for Cancer Research. 2005;11(2 Pt 1):450-8.
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. Human pathology. 2013;44(7):1391-9.
72. Bergsland EK RR, Stephens P, Ross JS, Bailey M Olshen A, editor Genomic profiling to distinguish poorly differentiated neuroendocrine carcinomas: a new clinicopathologic entity. . ASCO Meeting Abstr; 2016.
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. Journal of Cancer. 2016;7(9):1044-8.
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 & disease. 2017;8(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. International journal of cancer. 2016;138(4):927-38.
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. The Lancet Oncology. 2017;18(1):42-51.
77. Siravegna G, Marsoni S, Siena S, Bardelli A. Integrating liquid biopsies into the management of cancer. Nature reviews Clinical oncology. 2017;14(9):531-48.
78. Zatelli MC, Grossrubatscher EM, Guadagno E, Sciammarella C, Faggiano A, Colao A. Circulating tumor cells and miRNAs as prognostic markers in neuroendocrine neoplasms. Endocrine-related cancer. 2017;24(6):R223-R37.

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