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REVIEW

Rectal neuroendocrine carcinoma: case report of a rare entity and perspective review of promising agents

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Abstract

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of tumours, which can be classified into neuroendocrine tumours (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs). To date, there is no consensus regarding the optimal therapy, which usually depends on the primary location and classification, according to morphological features of differentiation and proliferation rates. Nevertheless, multidisciplinary strategies combining medical treatments and locoregional strategies have yielded better efficacy results. Here, we report the case of a patient diagnosed with a nonfunctional rectal NECs with metastatic widespread to pelvic lymph nodes and bilateral lung metastases. The patient received three cycles of platinum-etoposide, concomitantly with palliative radiotherapy. Although CT scan after three cycles showed a significant partial response, there was an early fatal progression only 3 months after having stopped systemic therapy. As formerly described in the literature, this case highlights the aggressive behaviour of NECs, rare tumours that often present in advanced stages at diagnosis. Lately, new insights into the molecular biology of NECs have unveiled the possibility of using novel drugs, such as targeted agents or immunotherapy, in molecularly selected subgroups of patients. In this review, we discuss the current management of this rare entity and provide an overview of the most relevant molecular findings, whilst illustrating the potential value that prescreening panels can offer, searching for actionable targets (MSI/dMMR, PD-L1, $BRAF^{v600E}$) to guide therapy with promising agents that could fill a void in this disease.

Keywords: chemotherapy, epigenetic, gastro-entero-pancreatic neuroendocrine neoplasms, immunotherapy, molecular alterations, neuroendocrine carcinomas, radiotherapy, targeted agents.

Citation

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Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous family, including a wide range of malignancies derived from the diffuse endocrine system cells. NENs differ from adenocarcinomas in their cell of origin, as they arise from enterochromaffin cells distributed across a diversity of tissues.[1] NENs are commonly classified according to their embryological and anatomical site of origin, proliferation index (immunohistochemistry for Ki-67) and their ability to secrete bioactive peptides (functional *versus* nonfunctional).[2] International efforts led by the World Health Organization (WHO) and the European Neuroendocrine Tumour Society (ENETS) have lately established a specific standard classification.[3] Based on morphologic, proliferation and biologic features, this prognostic classification aims to better tailor the type of tumour with optimal therapeutic strategies for these patients.[4] Within this classification, NENs are mainly subdivided into well-differentiated (WD) and poorly differentiated (PD) NENs.

WD-NENs comprise neuroendocrine tumours (NET) G1, with mitosis <2/10 high-power field (HPF) and Ki-67 index ≤2%, and NET G2, with mitosis 2-20/10 HPF and Ki-67 index 3–20%.[5] Histologically, they usually present without necrosis, with a cytoplasm enriched with secretory granules, which are

stained for neuroendocrine markers. NET G1 and G2 are usually asymptomatic slow-growing neoplasms, with a more indolent course, which can present characteristic hormone-producing patterns (e.g. insulinoma for insulin-secreting tumours[6]). A third subclass of tumours, NET G3, fit also within the WD-NETs although they present higher mitosis >20 HPF and Ki-67 index >20%. NET G3 can still retain molecular aspects of WD-NENs (e.g. lower level of genomic instability and possibility of functioning products).[7]

Surgery and locoregional therapies are the best treatments whenever feasible for WD-NETs.[8] Unfortunately, more than 50% of NETs are diagnosed with advanced unresectable disease. Systemic chemotherapy has been historically regarded as the first-line option for rapidly progressive symptomatic WD-NETs. Streptozocin with fluoroprimidines, temozolamide or doxorubicin have been the preferred regimens, achieving overall response rates of 6–69%.[9–12] However, the widespread expression of somatostatin receptors amongst WD-NETs has enabled the use of somatostatin-receptor gamma scans for accurate staging,[13] providing the rationale for the development of peptide receptor-targeted radionuclide therapy.[14] Furthermore, somatostatin analogues such as lanreotide[15] and octreotide[16] have shown a significant improvement in progression-free survival (PFS) rates amongst WD-NET patients. Also, a better understanding of WD-NET molecular biology has led to the development of new targeted therapies. WD-NETs are highly vascularized tumours that express vascular endothelial growth factor and its receptor (VEGF/VEGFR).[17] In 2011, 37.5 mg daily of sunitinib, a multitargeted tyrosine kinase inhibitor reported improved efficacy compared to placebo in advanced WD-pancreatic NETs [mPFS 11.4 *versus* 5.5 months, the hazard ratio (HR) 0.42; 95% confidence interval (CI): 0.26–0.66; $p<0.001$].[18] The mammalian target of rapamycin (mTOR) is an intracellular kinase that plays a crucial role as a central regulator of growth, proliferation, cellular metabolism and angiogenesis and has been implicated in the molecular pathogenesis of NETs.[19] The *RADIANT-3* study showed that 10 mg of daily oral mTOR inhibitor everolimus, improved PFS amongst patients with pancreatic NET G1-2 compared with placebo (mPFS 11 *versus* 4.6 months, HR 0.35; 95% CI: 0.27–0.45; $p<0.001$).[20] The *RADIANT-4* study provided additional efficacy data of everolimus in a broaden population of advanced nonfunctional progressive WD-NETs of lung or any gastro-entero-pancreatic (GEP) origin.[21] Treatment for advanced NET G3 is not yet standardized, considering chemotherapy as the gold standard, particularly if the aim is a secondary surgery. Primary tumour removal and surgical debulking of hepatic metastases can reduce the symptoms and improve the pharmacological management and quality of life of these patients.[22] The preferred systemic regimen in NET G3 should be in line with that implemented in NET G1-2 with Ki-67 index under 55%, whilst it might be appropriate to switch in line with that implemented in PD-NENs when Ki-67 is above 55%.[23]

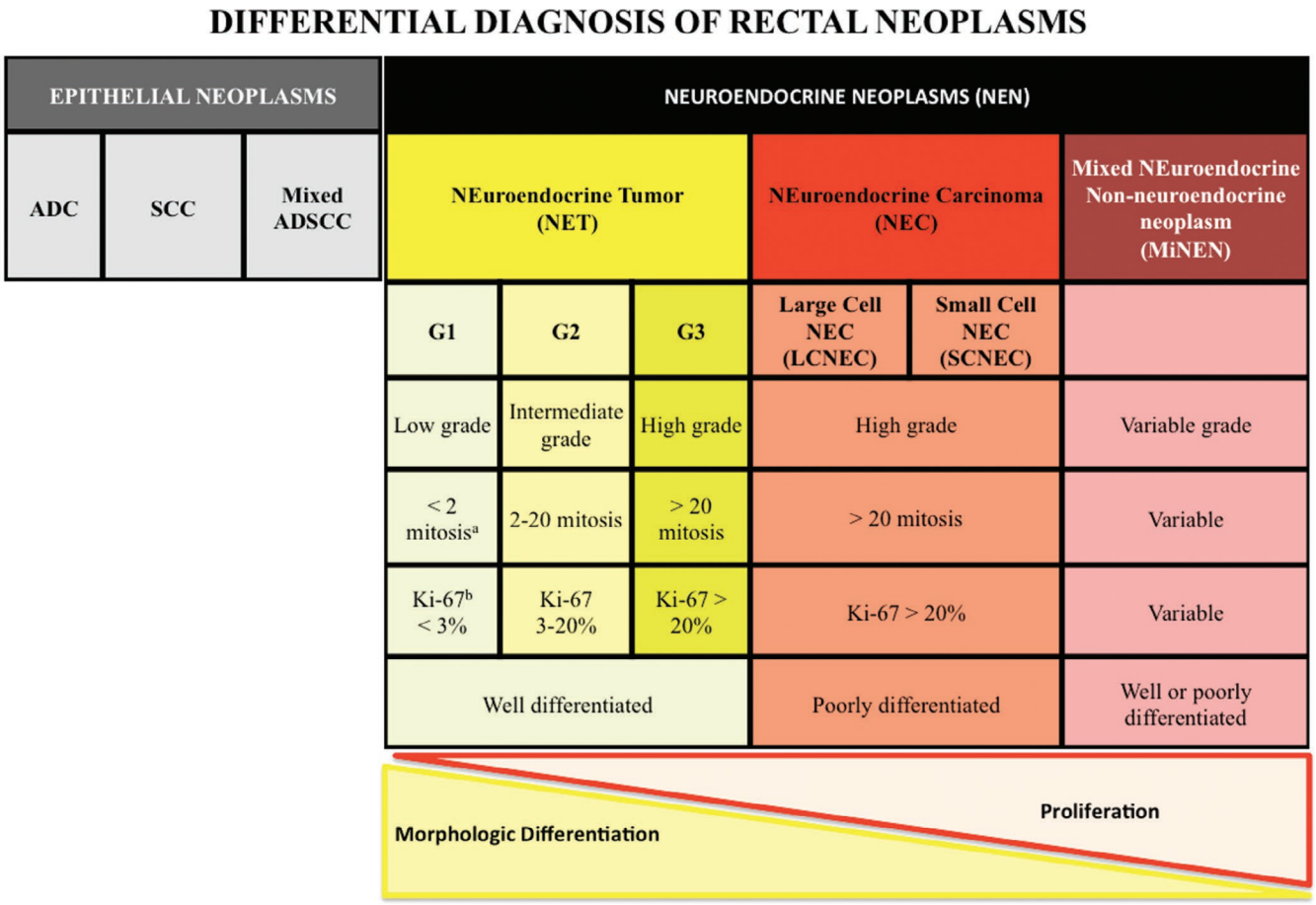
PD-NENs encompass a subgroup of tumours whose molecular aspects resemble the carcinoma counterpart. PD-NENs or neuroendocrine carcinomas (NECs) enclose a heterogeneous group of high-grade neoplasms defined by mitosis >20 HPF and Ki-67 index >20%. In fact, the data published by Milione M. and colleagues suggested that GEP-NECs could be better classified using different prognostic categories: median overall survival (mOS) of 43.6 months in NEC type A with good differentiation and Ki-67 20–55%, 24.5 months in NEC type B with poor differentiation and Ki-67 20–55%, and 5.3 months in NEC type C with poor differentiation and Ki-67 ≥55% ($p<0.0001$).[24] Overall, NECs are often subclassified into large-cell NECs (LCNECs) or small-cell NECs (SCNECs) according to morphological cell criteria, both characterized by an aggressive clinical behaviour. Histologically, NEC tumours present nest-like formations, and usually confluent areas of necrosis, with perineural and vascular infiltration.[25] As undifferentiated tumours, they hardly become functioning tumours.[26] NEC primary tumours are usually found in the lungs.[27] Noteworthy, NECs represent less than 1% of all NENs, with GEP origin accounting for less than 1% of the cases.[28] Traditionally, metastatic PD-NENs have been treated with systemic chemotherapy, mostly platinum-containing regimens.[29]

Finally, mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are considered a third entity within the NEN family, tumours that display neuroendocrine traits coexisting with a variable proportion of non-neuroendocrine histology.[30] MiNENs include a broad spectrum of possible combinations between both elements, conferring a huge variability of morphologies largely determined by the site of origin.[31] Evidence from the literature is limited and inconsistent but results from a large retrospective study highlighted that patients with advanced MiNENs usually receive systemic chemotherapy according to protocols established for adenocarcinomas or NECs from that same site of origin.[32] MiNENs have been described as aggressive neoplasms due to their high-grade neuroendocrine component, usually progressing soon after the initiation of palliative therapy, and translating into poor survival outcomes that mimic those of pure NECs.[33]

NENs are considered rare malignancies, though over the past decades the incidence of GEP-NENs is steadily rising particularly in older adults.[34] This increased incidence has been related to early detection of small WD-NENs, frequently depicted by chance during radiographic imaging and surveillance endoscopies. Data from the Spanish National Cancer Registry (RGETNE) showed that the small intestine was the most common primary site of GEP-NENs, with rectal tumours accounting only for 6% of the cases.[1] Rectal NENs exhibit the greatest relative increase in the incidence of all GEP-NENs, with an estimated annual incidence of 1.04 per 100,000 people.[35] In this context, the accurate pathological diagnosis and classification is crucial when facing a newly diagnosed rectal NENs, thus its clinical expression, prognosis and optimized therapeutic approach will significantly differ depending on the subtypes.[36] Figure 1 proposes a diagnostic algorithm for rectal tumours.[37]

Here, we present a case report of a rectal NECs, a very rare entity, focusing on a multidisciplinary treatment approach. We emphasize on a combined treatment with palliative chemotherapy and radiotherapy, depicting further molecular considerations that could help in delineating new therapeutic strategies beyond progression to standard treatment.

Figure 1. Diagnostic algorithm for rectal neoplasms.



Abbreviations: ADC (ADenoCarcinoma); SCC (Squamous Cell Carcinoma); ADSCC (ADenoSquamous Cell Carcinoma).
[a]Mitotic count is expressed by 10 HPF: high power field=2 mm², at least 40 fields evaluated in areas of highest mitotic density.
[b]Ki-67 index: % of 2000 tumor cells in areas of highest nuclear labeling.

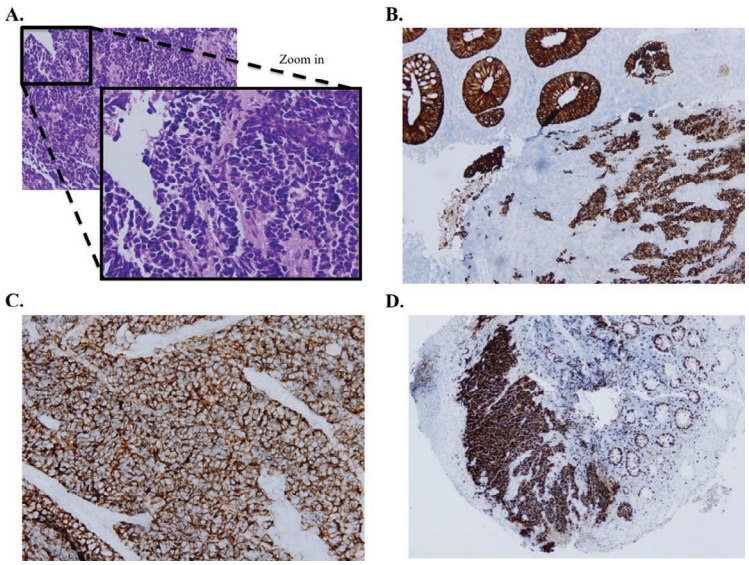
The differential diagnosis of a rectal tumour includes considering epithelial and neuroendocrine neoplasms. Epithelial tumours comprise adenocarcinomas (ADCs), squamous carcinomas (SCCs) or mixed adeno-squamous carcinomas (ADSCCs). Neuroendocrine neoplasms (NENs) are currently subdivided in three different categories, comprising neuroendocrine tumours (NETs), neuroendocrine carcinomas (NECs) and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs). NETs include G1, G2 and G3 tumours, depending on their proliferation rates (mitosis rate and Ki-67 index), grade (low, intermediate and high) and morphology differentiation (well or poorly) characteristics. NEC tumours can morphologically include large cell (LCNEC) and small cell carcinomas (SCNEC). MiNEN tumours display variable grades of all the possible histopathological characteristics.

Case report

Written informed consent was obtained from the patient for publication of this report. A 76-year-old female presented with a 1-year history of rectal pain with intermittent bleeding and progressive constipation. A colonoscopy revealed an ulcerative lesion with irregular edges and infiltrative macroscopic aspect, located within the rectal ampulla, partially obstructing the descending colon; proximal to this lesion, there was bowel protrusion suggesting an extrinsic compression. During a colonoscopy, superficial biopsies were taken which showed undifferentiated small cells on the haematoxylin and eosin morphological staining. Further immunohistochemistry evaluation was positive for the neuroendocrine marker synaptophysin, together with the epithelial marker cytokeratin CAM 5.2, with a high Ki-67 index >80%. The negative CDX2 staining indicated that the tumoral cells had barely intestinal differentiation, therefore supporting the final diagnosis of an infiltrating highly undifferentiated SCNEC of the rectum[38] (Figure 2).

The complete staging was performed with pelvic magnetic resonance imaging (MRI), which revealed the extension of the primary rectal tumour through the colon wall, infiltrating the posterior wall of the vagina together with radiological metastases to pelvic lymph nodes. A computed tomography (CT) scan of the chest, abdomen and pelvis confirmed distant bilateral lung metastases. Tumour markers, cancer antigen 125 (CA125), 19.9 (CA19.9) and serum chromogranin A were negative, whilst carcinoembryonic antigen (CEA) was slightly elevated at

Figure 2. Pathology findings of a rectal NEC.



Rectal NEC pathological findings showed undifferentiated small cells with haematoxylin and eosin staining (A). Immunohistochemistry staining was positive for epithelial markers, such as cytokeratin CAM 5.2 (B), and neuroendocrine markers as synaptophysin (C). In this case, Ki-67 index >80% confirmed a high-grade poorly differentiated SCNEC subtype (D).

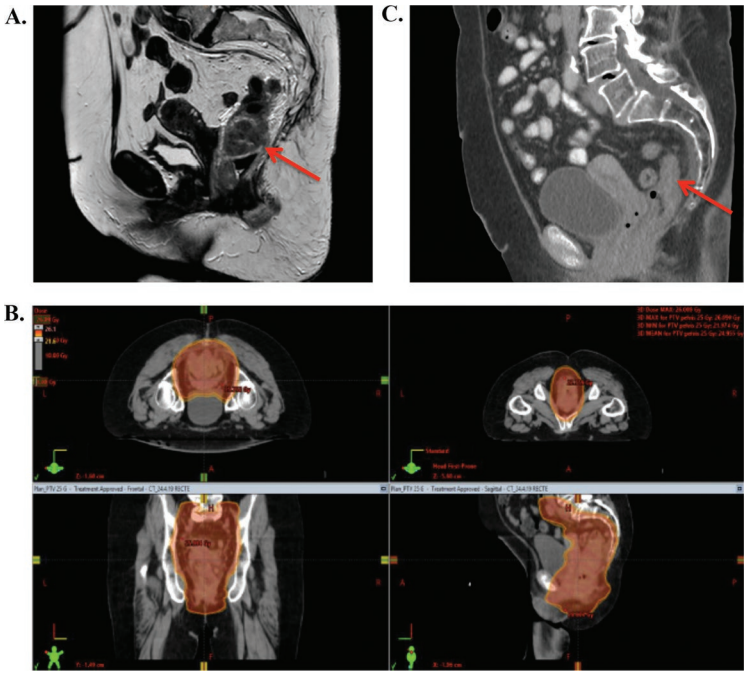
7.57 ng/ml (range 0–5 ng/ml). Twenty-four-hour urinary excretion of 5-hydroxyindoleacetic (5-HIAA) was normal. At her baseline assessment, the patient presented an Eastern Cooperative Oncology Group (ECOG) performance status of 1, due to worsened general condition related to her primary bulky tumour symptoms.

The case was discussed at our Colorectal Tumours Multidisciplinary Team Meeting, and it was deemed a cT4N2aM1 stage IV nonfunctioning rectal SCNEC, being considered for systemic chemotherapy without delay. The patient agreed to start palliative therapy, and upfront treatment with platinum-based chemotherapy was proposed (cisplatin 100 mg/m^2 iv. and etoposide 100 mg/m^2 iv. on day 1 of each cycle, with subsequent etoposide 200 mg/m^2 po. on days 2–3, every 21 days). Given the fact that lower gastrointestinal symptoms were difficult to control with optimized analgesia, external beam radiotherapy was prescribed and administered concomitantly with the first cycle of chemotherapy. Radiotherapy was performed with a volumetric modulated arch therapy technique (VMAT), with two full rotation dynamic arches (counter clockwise and clockwise), administrating a total dose of 25 Gy in 5 Gy daily fractions over her pelvic areas. Gross tumour volume (GTV) included primary tumour and MRI-affected lymph nodes, and clinical target volume (CTV) was conformed including GTV and mesorectal, iliac, obturator and presacral lymph node areas, adding a subclinical margin due to high risk of microscopic disease. CTV plus 1 cm for organ daily motion and uncertainty margin conformed the final planning target volume (PTV). Figure 3A and B illustrates the baseline pelvic MRI and the radiotherapy dosimetric plan.

Radiotherapy was well tolerated, achieving local clinical response only 3 weeks after completing the scheduled dose, with resolution of rectal pain and bleeding. However, the patient was able to receive only three cycles of the preplanned cisplatin and etoposide chemotherapy, due to the significant gastrointestinal and haematological toxicity that she presented, even despite frequent dose reductions and treatment delays. Her first evaluation CT scan showed an overall partial response, with the disappearance of bilateral lung nodules and significant shrinkage of primary rectal tumour and pelvic lymph nodes (Figure 3C). Given the impossibility of maintaining an optimal dose of chemotherapy in an elderly patient, and considering the maximum response achieved, it was agreed with the patient withholding the systemic therapy and start a close surveillance.

Unfortunately, a follow-up CT scan only 3 months after showed new progression of the lung and primary rectal tumours, and new multiple liver metastases. The formalin-fixed paraffin-embedded (FFPE) tissue specimen of the primary tumour underwent molecular profiling using next-generation sequencing techniques (customized panels for mutations with AmpliconSeq -Illumina®-, and potential gene fusions with Nanostring -nCounter®-) (Table 1). However, no relevant targetable alterations were found, and the patient rapidly presented clinical deterioration that urged hospitalization, which precluded the initiation of second-line palliative chemotherapy. The patient died 9 months after the initial diagnosis.

Figure 3. Pelvic MRI and dosimetry volumes for planned radiotherapy treatment.



(A). Pelvic MRI sagittal view shows the primary tumour, a 9-cm rectal mass (red arrow) infiltrating the posterior vaginal wall. **(B).** In the radiotherapy dosimetric view, 95% of the doses covering the involved locoregional lymph nodes are highlighted in red. **(C).** Pelvic CT image 2 months after radiotherapy treatment, showing a local partial response within the primary rectal tumour (red arrow).

Multidisciplinary therapeutic approach of NECs

Considering their aggressive behaviour, newly diagnosed NECs must follow a multidisciplinary approach. If a patient is diagnosed with early-stage disease, upfront surgery should be offered.[39] However, if it is not clear whether surgery is of benefit, especially taking into consideration the anatomical site of the primary and the high risk of systemic recurrences, there is also evidence of long-term survival from selected cases that received definitive chemoradiotherapy (e.g. oesophageal NEC).[40] Nevertheless, there is a general consensus that surgery has to be considered only in cases of the locoregional disease, with a benefit seen of 64.5% 2-year OS.[41] If resection is performed, it seems that patients who receive neoadjuvant or adjuvant therapy benefit the most, suggesting that micrometastases might contribute to poor surgical outcomes amongst limited-stage NECs.[42]

A retrospective review led by Modrek and colleagues in 2015 established that radiotherapy significantly improved the prognosis in the setting of locoregional rectal NECs.[43] The addition of concomitant radiotherapy reported local clinical response and improvement of survival, with 1-year OS of 71.1 *versus* 37.8% for the nonradiotherapy group. The currently available data suggest that there is no standard treatment regarding the optimal dose/fraction of radiotherapy for rectal NECs. The most frequent schedules are those in between 25 and 50 Gy, probably based on historical studies performed with cT3 or N positive rectal adenocarcinomas, or instead following the Swedish scheme – termed short-course radiotherapy or SCRT – for fragile patients, administrating 25 Gy in 5 Gy daily fractions.[44–48] Both options have shown a good safety profile and high rates of local disease control. VMAT, a form of intensity-modulated radiotherapy (IMRT), greatly improved the conformation of the dose to a three-dimensional shape compared to conventional radiotherapy, thus achieving higher doses over tumour areas. The use of this technique drastically reduced acute and chronic toxicities, whilst improved local control.[49,50] Guererro Urbano and colleagues compared several IMRT plans with conventional radiotherapy and reported grade 3-4 bowel toxicities in only 5% of the patients treated up to 50 Gy with pelvic doses.[51] The radiotherapy scheme used in our patient was the short-course radiotherapy, which after its first publication in 2001 by the Swedish group, was compared to a normofractionated scheme, reporting no differences neither in overall survival nor in local control or toxicities.[44,52] In contrast to small-

Table 1. Prescreening analysis by customized next-generation sequencing panels.

AmpliconSeq mutation panel -Illumina®-		
ABL1	FLT3	NOTCH1
AKT1	GATA1	NOTCH4
AKT2	GNA11	NRAS
AKT3	GNAQ	PDGFRA
ALK	GNAS	PIK3CA
APC	HRAS	PIK3R1
BRAF	IDH1	PIK3R5
CDH1	IDH2	PTEN
CDKN2A	JAK1	RB1
CSF1R	JAK3	RET
CTNNB1	KIT	RUNX1
EGFR	KRAS	SMAD4
ERBB2	MAG	SMARCB1
ERBB3	MAP2K1	SRC
ESR1	MET	STK11
FBXW7	MLH1	TP53
FGFR1	MPL	VHL
FGFR2	MSH6	RNF43
FGFR3	MYC	ZNRF3
FGFR4	NF2	
NanoString gene fusion panel -nCounter®-		
EML4 E13-ALK E20	CD44 E1-FGFR2 E3	EIF3E E5-RSPO2_E1
EML4 E20-ALK E20	SLC45A3 E1-FGFR2 E2	EIF3E E5-RSPO2 E2
EML4 E6-ALK E20	FGFR3 E17-AES E2	PTPRK E13-RSPO3 E2
AKAP9 E8-BRAF E9	FGFR3 E17-ELAVL3 E2	PTPRK E1-RSPO3 E2
KIAA1549 E15-BRAF E9	FGFR3 E17-LETM1 intron10	PTPRK E2-RSPO3 E2
KIAA1549 E14-BRAF E9	FGFR3 E17 intron-TACC3 E4	PTPRK E6-RSPO3 E2
KIAA1549 E15-BRAF E11	FGFR3 E17-BAIAP2L1 E2	PTPRK E7-RSPO3 E2
BAG4 E2-FGFR1 E6	FGFR3 E17-TACC3 E4	NAV2 E1-TCF7L1 E4
ERLIN2 E10-FGFR1 E4	FGFR3 E17-TACC3 E8	NAV2 E3-TCF7L1 E4
FGFR1 E17-TACC1 E7	FGFR3 E17-TACC3 E10	VTI1A E2-TCF7L2 E4
FGFR2 E17-AFF3 E8	FGFR3 E17-TACC3 E11	VTI1A E2-TCF7L2 E5
FGFR2 E17-AHCYL1 E2	RANBP17 E28-FGFR3 E1	VTI1A E2-TCF7L2 E6
FGFR2 E17-ATE1 E12	EGFR vIII (E1-E8	VTI1A E3-TCF7L2 E4
FGFR2 E17-BICC1 E3	MET E13-E15	VTI1A E3-TCF7L2 E5
FGFR2 E17-CASP7 E4	LMNA E2- NTRK1 E10	VTI1A E3-TCF7L2 E6
FGFR2 E17-CCDC147 E2	LMNA E2- NTRK1 E11	VTI1A E4-TCF7L2 E4
FGFR2 E17-CIT E23	LMNA E10- NTRK1 E12	VTI1A E4-TCF7L2 E5
FGFR2 E17-FAM76A E2	LMNA E10- NTRK1 E13	VTI1A E4-TCF7L2 E6
FGFR2 E17-GAB2 E2	TPM3 E7-NTRK1 E10	CCDC6 E1-RET E12
FGFR2 E17-KIAA1967 E5	TPR E21-NTRK1 E10	KIF5B E15-RET E12
FGFR2 E17-MCU E2	ETV6 E5-NTRK3 E15	KIF5B E16-RET E12

(Continued)

Table 1. (*Continued*)

NanoString gene fusion panel -nCounter®-		
FGFR2 E17-OFD1 E3	ETV6 E4-NTRK3 E15	KIF5B E22-RET E12
FGFR2 E17-VCL E15	PAX8 E8-PPARG E2	NCOA4 E8-RET E12
FGFR2 E2-WDR11 E20	PAX8 E9-PPARG E2	PRKAR1A E7-RET E12
FGFR2 E16-KIAA1598 E7	PAX8 E10-PPARG E2	CD74 E6-ROS1 E34
FGFR2 E16-TACC3 E11	EIF3E E1-RSPO2_E1	EZR E10-ROS1 E34
FGFR2 E17-NOL4 E7	EIF3E E1-RSPO2_E2	SLC34A2 E4-ROS1 E32

cell lung cancer (SCLC), there is a low incidence of central nervous system metastases amongst limited-stage GEP-NECs; therefore, prophylactic cranial irradiation is not recommended.[26] Palliative radiotherapy may be beneficial for either metastatic locations or primary tumour local symptoms.

Unfortunately, most NEC patients have disseminated disease at diagnosis. It is mandatory that patients with advanced NEC start chemotherapy as soon as possible before their general condition declines rapidly and they are no longer fit for receiving cytotoxics. To date, it is challenging to assess and compare the results of the different chemotherapy treatments amongst NECs, given the fact that the available evidence is based on small retrospective studies from single institutions. Also, most of the studies present mixed cohorts (e.g. NET G3 and NEC), with a combination of GEP locations, and quite often differ in relation to biological characteristics (e.g. wide range of heterogeneity above Ki-67 index >20%). In 1985, Evans and colleagues established cisplatin and etoposide as the former standard treatment for SCLC, instead of historical and more toxic schemes such as cyclophosphamide, adriamicin and vincristine (CAV) triplet.[53] In light of their biological similarities to SCLC and the lack of well-designed randomized trials, platinum-based doublets were then extrapolated for treating extrapulmonary NECs.[54]

Since the early 1990s, small retrospective series supported the implementation of first-line regimens based on cisplatin and etoposide.[55] The cisplatin and etoposide combination was established as the gold standard for metastatic NECs, based on overall objective responses of 42–67%, and the median duration of responses around 8–9.2 months.[29,56] Another platinum salt, carboplatin, was tested as an alternative to cisplatin due to less gastrointestinal, haematological, renal and neurological toxicity.[57] To date, several studies suggested that carboplatin can replace cisplatin, as both drugs are comparable in efficacy.[58] Furthermore, irinotecan combined with cisplatin emerged as an alternative to etoposide although both schemes have not been directly compared.[59,60] Irinotecan is generally the companion choice in Asian patients with SCLC and NEC, as Western populations tend to experience increased gastrointestinal toxicity after irinotecan administration.[61] Retrospective data of NEC patients treated with cisplatin and irinotecan showed response rates of 64% and mPFS of 7.3 months at first line, similar to those yielded with etoposide combinations.[62]

Even though NECs are chemosensitive tumours, they inevitably progress, and second-line strategies have shown scarce efficacy. Rescue chemotherapy for GEP-NECs is not well established. The Nordic NEC study suggested that retreatment with platinum and etoposide could be an option, as up to 42% of patients can achieve restabilization of the disease.[63] Small series showed also the effect of temozolamide-based chemotherapy after progression on first line, as metronomic single agent[64] or associated with capecitabine.[65] Of note, Welin and colleagues reported significant stabilization rates of 71% with temozolamide alone or in combination with capecitabine amongst 25 refractory NEC patients.[66] Most of these studies seem to indicate that temozolamide regimens may be more efficient in NEC patients with Ki-67 index <50%.[67] In a retrospective study, Hentic and colleagues demonstrated that second line with FOLFIRI regimen was a safe and potentially efficient chemotherapy in NEC patients after failure to platinum etoposide (disease control rate of 62% with mPFS of 4 months).[68] However, administration of irinotecan in patients with deranged liver function tests may be a contraindication, and major organ involvement with increased bilirubin levels has shown to predict severe neutropenia. Finally, topotecan has also shown modest antitumour activity in heavily pretreated NEC patients.[69] With only 23% of stabilizations, overall prognosis remained very poor with mOS of only 3.2 months.

The close multidisciplinary cooperation of different specialists involved in several therapeutic areas is warranted in order to seek for the optimal therapeutic strategy in each case.

Molecular insights and novel agents

The molecular features of high-grade NECs have been scarcely understood for many years, thereby limiting the therapeutic options for this rare malignancy. However, the recent development and implementation of next-generation sequencing platforms have unravelled some of the biological insights hidden behind NECs. NECs harbour more proliferative and aggressive clinic-pathologic features,

which largely resemble poorly differentiated gastrointestinal adenocarcinomas. However, translational analysis of a cohort of 25 cases suggested that NECs preserve genomic and epigenetic characteristics inherited from a different cell of origin than the epithelial progenitors of adenocarcinomas.[70] Somatic mutations have been described in 83% NECs, amongst which TP53 is the most prevalent alteration (57%) regardless of the primary site, and KRAS (30%), PIK3CA/PTEN (22%) and BRAF (13%) mutations are also found.[7] Microsatellite instability (MSI) has been found in approximately 10% of gastric and colorectal NECs, and other consistently molecular aberrations, such as Hedgehog, Notch and p16/Rb/cyclin D1 altered signalling pathways, have also been detected.[71] The discovery of potentially actionable targets has widened the therapeutic options for these patients.

BRAF V600E mutations ($BRAF^{V600E}$) have been described across several malignancies.[72] Hence, efforts have focused on developing targeted agents against this promising driver. Initial encouraging results were reported with BRAF inhibitors in monotherapy[72] although the combination of BRAF and MEK inhibitors showed clear superiority for the treatment of metastatic $BRAF^{V600E}$ melanoma.[73] Klempner and colleagues reported dramatic responses to combined BRAF and MEK inhibition in two cases of colonic NEC harbouring $BRAF^{V600E}$, after experiencing progressive disease through platinum-based regimens.[74] These initial results provided strong evidence that $BRAF^{V600E}$ is an oncogenic driver in this molecular subset, supporting the rationale for a personalized medicine strategy. However, it is well described that different mechanisms of resistance to BRAF/MEK inhibition may ultimately lead to reactivation of the MAP kinase pathway in these patients,[75] which could explain the transient benefit seen in some $BRAF^{V600E}$ NEC patients treated with dual blockade.[76] Results of the *BEACON* phase 3 trial, assessing the combination of encorafenib – BRAF inhibitor – plus binimetinib – MEK inhibitor – and cetuximab – EGFR inhibitor – in $BRAF^{V600E}$ metastatic colon cancer, shed some light into the clinical value of this strategy.[77] Thus, the triplet significantly improved median overall survival (mOS 15.3 months) and overall response rate (ORR 48%). In this same direction, Capdevila and colleagues generated a $BRAF^{V600E}$ patient-derived xenograft (PDX) of colonic NEC that was treated with cisplatin-etoposide, encorafenib, cetuximab and the combination of encorafenib plus cetuximab. They identified the mechanism of resistance to BRAF inhibition in NECs through EGFR upregulation, suggesting the potential benefit of dual therapy with BRAF/EGFR inhibition.[78] This fact highlights the complicated role that $BRAF^{V600E}$ might also play in NECs and the need of further deepening into the underlying mechanisms of bypass, to understand which of these patients could benefit most from targeted therapy.

Immune-checkpoint inhibitors (ICI) are arising as a promising strategy within the armamentarium for treating solid tumours. PD-L1 expression has been retrospectively reported amongst 21.9% of patients within a heterogeneous collection of 32 GEP-NEN samples. This PD-L1 expression has been significantly associated with high-grade tumours (41.2% G3 NETs and NECs; p=0.008).[79] Considering that there are limited therapeutic options for NECs, this high proportion of PD-L1 expressors suggests that anti-PD-L1/PD1 blockade might be a useful therapy for this subgroup of tumours. Spartalizumab, an anti-PD-1 antibody, was tested amongst 21 patients with GEP-NEC after progressing one prior chemotherapy line. PD-L1 expression in immune cells >1% was higher amongst NEC patients (43%), which achieved ORR 5% with a disease control rate of 19%.[80] A refractory pancreatic NEC expressing 30% PD-L1 positivity was also treated with off-label ICI pembrolizumab, another anti-PD-1 antibody, demonstrating a significant partial remission of 66%, that translated into a gain of quality of life and pain relief of the patient.[81] GEP-NECs rarely show MSI although the presence of MSI NECs has been associated with distinct biology and a better outcome.[82] In 2017, pembrolizumab was approved by the US Food and Drug Administration (FDA) for MSI-high/deficient mismatch repair tumours (dMMR) independently of origin, following an agnostic-histology approach.[83] Taking into consideration all these premises, immunotherapy stands as a promising treatment option in a difficult-to-find subgroup of metastatic NECs.

Conclusion

Published data from metastatic colorectal NEC treated with cisplatin and etoposide demonstrated a mOS of 9.5 months, with mPFS of only 4.5 months, similar results to those achieved in our case.[84] Patients with high-grade NECs benefit from multidisciplinary approaches, combining systemic chemotherapy regimens and radiotherapy techniques, and carefully considering rescue surgery in selected cases. Nevertheless, NECs commonly present metastatic dissemination at the time of diagnosis, with no available curative treatment. Despite remarkable advances in the management of NENs, only well and moderately differentiated NET patients can benefit from currently approved tyrosine kinase inhibitors, whilst cytotoxic platinum-containing doublets are the backbone therapy for NET G3, NECs, and MiNENs. Unfortunately, the limited activity provides only short-lasting clinical benefit to many patients. During the last decade, we have progressively acquired a more comprehensive description of the targetable genetic features that characterize high-grade NECs. First, BRAF/MEK-directed therapy has emerged as an exciting option for $BRAF^{V600E}$ NEC patients, and recently, ICI responses suggest that a subset of patient may achieve meaningful benefit from immunotherapy.

Treatment for rectal NECs should be highly individualized, based on the tumour burden and symptoms, and the best therapeutic approach for every patient will depend on whether the aim is to slow tumour growth or improve symptoms. There are no currently available defined measures to predict which tumours will or will not respond to treatments, and a major goal in the future will be to identify molecular markers that will facilitate the prediction of the biological behaviour of these tumours. In addition,

given the emergence of functional genomics and expression profiling, both animal and cellular models are needed to investigate further the underlying molecular and genetic biology of NECs. Responses from molecularly targeted agents lack durability, mostly due to adaptive feedback mechanisms that can bypass the blockade or to activate other proliferative pathways. Gaining a deeper knowledge of NEC biology may help a better characterization of NECs, which will ultimately be crucial for optimizing the therapeutic strategy. Physicians should strongly consider performing molecular prescreening panels to all NEC patients, in order to assess potentially actionable targets amongst these patients (MSI/dMMR, PD-L1, $BRAF^{v600E}$). Collaborative groups, aiming to join efforts in the battle of this unmet medical need, should preferably conduct the future rationalized design of clinical trials with novel drugs.

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References

1. Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). *Ann Oncol.* 2010;21(9):1794–1803. https://doi.org/10.1093/annonc/mdq022
2. Modlin IM, Latich I, Kidd M, Zikusoka M, Eick G. Therapeutic options for gastrointestinal carcinoids. *Clin Gastroenterol Hepatol.* 2006;4(5):526–547. https://doi.org/10.1016/j.cgh.2005.12.008
3. Cavalcanti MS, Gonen M, Klimstra DS. The ENETS/WHO grading system for neuroendocrine neoplasms of the gastroenteropancreatic system: a review of the current state, limitations and proposals for modifications. *Int J Endocr Oncol.* 2016;3(3):203–219. https://doi.org/10.2217/ije-2016-0006
4. Pavel M, de Herder WW. ENETS consensus guidelines for the standard of care in neuroendocrine tumors. *Neuroendocrinology.* 2017;105(3):193–195. https://doi.org/10.1159/000457957

5. Bertani E, Ravizza D, Milione M, et al. Neuroendocrine neoplasms of rectum: a management update. *Cancer Treat Rev.* 2018;66: 45–55. https://doi.org/10.1016/j.ctrv.2018.04.003
6. Okabayashi T, Shima Y, Sumiyoshi T, et al. Diagnosis and management of insulinoma. *World J Gastroenterol.* 2013;19(6):829–837. https://doi.org/10.3748/wjg.v19.i6.829
7. Vijayvergia N, Boland PM, Handorf E, et al. Molecular profiling of neuroendocrine malignancies to identify prognostic and therapeutic markers: a Fox Chase Cancer Center Pilot Study. *Br J Cancer.* 2016;115(5):564–570. https://doi.org/10.1038/bjc.2016.229
8. Kunz PL, Reidy-Lagunes D, Anthony LB, et al. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas.* 2013;42(4):557–577. https://doi.org/10.1097/MPA.0b013e31828e34a4
9. Turner NC, Strauss SJ, Sarker D, et al. Chemotherapy with 5-fluorouracil, cisplatin and streptozocin for neuroendocrine tumours. *Br J Cancer.* 2010;102(7):1106–1112. https://doi.org/10.1038/sj.bjc.6605618
10. Meyer T, Qian W, Caplin ME, et al. Capecitabine and streptozocin +/- cisplatin in advanced gastroenteropancreatic neuroendocrine tumours. *Eur J Cancer.* 2014;50(5):902–911. https://doi.org/10.1016/j.ejca.2013.12.011
11. Ramirez RA, Beyer DT, Chauhan A, Boudreaux JP, Wang YZ, Woltering EA. The role of capecitabine/temozolomide in metastatic neuroendocrine tumors. *Oncologist.* 2016;21(6):671–675. https://doi.org/10.1634/theoncologist.2015-0470
12. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. *J Clin Oncol.* 2005;23(22):4897–4904. https://doi.org/10.1200/jco.2005.03.616
13. Corleto VD, Falconi M, Panzuto F, et al. Somatostatin receptor subtypes 2 and 5 are associated with better survival in well-differentiated endocrine carcinomas. *Neuroendocrinology.* 2009;89(2):223–230. https://doi.org/10.1159/000167796
14. Theodoropoulou M, Stalla GK. Somatostatin receptors: from signaling to clinical practice. *Front Neuroendocrinol.* 2013;34(3): 228–252. https://doi.org/10.1016/j.yfrne.2013.07.005
15. Caplin ME, Pavel M, Cwikla JB, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer.* 2016;23(3):191–199. https://doi.org/10.1530/erc-15-0490
16. Rinke A, Wittenberg M, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. *Neuroendocrinology.* 2017;104(1):26–32. https://doi.org/10.1159/000443612
17. Yao JC, Guthrie KA, Moran C, et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. *J Clin Oncol.* 2017;35(15):1695–1703. https://doi.org/10.1200/jco.2016.70.4072
18. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501–513. https://doi.org/10.1056/NEJMoa1003825
19. Jiao Y, Shi C, Edil BH, et al. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science.* 2011;331(6021):1199–1203. https://doi.org/10.1126/science.1200609
20. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514–523. https://doi.org/10.1056/NEJMoa1009290
21. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet.* 2016;387(10022):968–977. https://doi.org/10.1016/s0140-6736(15)00817-x
22. Chawla A, Williams RT, Sich N, et al. Pancreaticoduodenectomy and metastasectomy for metastatic pancreatic neuroendocrine tumors. *J Surg Oncol.* 2018;118(6):983–990. https://doi.org/10.1002/jso.25219
23. Coriat R, Walter T, Terris B, Couvelard A, Ruszniewski P. Gastroenteropancreatic well-differentiated grade 3 neuroendocrine tumors: review and position statement. *Oncologist.* 2016;21(10):1191–1199. https://doi.org/10.1634/theoncologist.2015-0476
24. Milione M, Maisonneuve P, Spada F, 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. https://doi.org/10.1159/000445165
25. La Rosa S, Sessa F. High-grade poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: from morphology to proliferation and back. *Endocr Pathol.* 2014;25(2):193–198. https://doi.org/10.1007/s12022-014-9316-9
26. Garcia-Carbonero R, Sorbye H, Baudin E, et al. ENETS consensus guidelines for high-grade gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. *Neuroendocrinology.* 2016;103(2):186–194. https://doi.org/10.1159/000443172
27. Walter T, Tougeron D, Baudin E, et al. Characteristics, prognosis and treatments of 294 patients with poorly differentiated neuroendocrine carcinoma: the FFCD-GTE national cohort. *J Clin Oncol.* 2015;33:4095–4095. https://doi.org/10.1200/jco.2015.33.15_suppl.4095

28. Voong KR, Rashid A, Crane CH, et al. Chemoradiation for high-grade neuroendocrine carcinoma of the rectum and anal canal. *Am J Clin Oncol.* 2017;40(6):555–560. https://doi.org/10.1097/coc.0000000000000211
29. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer.* 1999;81(8):1351–1355. https://doi.org/10.1038/sj.bjc.6690325
30. Frizziero M, Chakrabarty B, Nagy B, et al. Mixed neuroendocrine non-neuroendocrine neoplasms: a systematic review of a controversial and underestimated diagnosis. *J Clin Med.* 2020;9(1). https://doi.org/10.3390/jcm9010273
31. Elkbuli A, Dowd B, McKenney M, Boneva D. Mixed neuroendocrine and squamous cell carcinoma of the colon: a case report and literature review. *Int J Surg Case Rep.* 2019;60:309–313. https://doi.org/10.1016/j.ijscr.2019.06.060
32. Frizziero M, Wang X, Chakrabarty B, et al. Retrospective study on mixed neuroendocrine non-neuroendocrine neoplasms from five European centres. *World J Gastroenterol.* 2019;25(39):5991–6005. https://doi.org/10.3748/wjg.v25.i39.5991
33. La Rosa S, Marando A, Sessa F, Capella C. Mixed adenoneuroendocrine carcinomas (MANECs) of the gastrointestinal tract: an update. *Cancers.* 2012;4(1):11–30. https://doi.org/10.3390/cancers4010011
34. Lee MR, Harris C, Baeg KJ, Aronson A, Wisnivesky JP, Kim MK. Incidence trends of gastroenteropancreatic neuroendocrine tumors in the United States. *Clin Gastroenterol Hepatol.* 2019;17(11):2212–2217.e2211. https://doi.org/10.1016/j.cgh.2018.12.017
35. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017;3(10):1335–1342. https://doi.org/10.1001/jamaoncol.2017.0589
36. Ramage JK, Valle JW, Nieveen van Dijkum EJM, et al. Colorectal neuroendocrine neoplasms: areas of unmet need. *Neuroendocrinology.* 2019;108(1):45–53. https://doi.org/10.1159/000493767
37. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology.* 2020;76(2):182–188. https://doi.org/10.1111/his.13975
38. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can Brown do for you? *Hum Pathol.* 2019. https://doi.org/10.1016/j.humpath.2019.12.002
39. Ilett EE, Langer SW, Olsen IH, Federspiel B, Kjaer A, Knigge U. Neuroendocrine carcinomas of the gastroenteropancreatic system: a comprehensive review. *Diagnostics (Basel).* 2015;5(2):119–176. https://doi.org/10.3390/diagnostics5020119
40. Honma Y, Nagashima K, Hirano H, et al. Clinical outcomes of locally advanced esophageal neuroendocrine carcinoma treated with chemoradiotherapy. *Cancer Med.* 2020;9(2):595–604. https://doi.org/10.1002/cam4.2708
41. Merola E, Rinke A, Partelli S, et al. Surgery with radical intent: is there an indication for g3 neuroendocrine neoplasms? *Ann Surg Oncol.* 2019. https://doi.org/10.1245/s10434-019-08049-5
42. Alese OB, Jiang R, Shaib W, et al. High-grade gastrointestinal neuroendocrine carcinoma management and outcomes: a national cancer database study. *Oncologist.* 2019;24(7):911–920. https://doi.org/10.1634/theoncologist.2018-0382
43. Modrek AS, Hsu HC, Leichman CG, Du KL. Radiation therapy improves survival in rectal small cell cancer—analysis of surveillance epidemiology and end results (SEER) data. *Radiat Oncol.* 2015;10:101. https://doi.org/10.1186/s13014-015-0411-y
44. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol.* 2005;23(24):5644–5650. https://doi.org/10.1200/jco.2005.08.144
45. Valentini V, Beets-Tan R, Borras JM, et al. Evidence and research in rectal cancer. *Radiother Oncol.* 2008;87(3):449–474. https://doi.org/10.1016/j.radonc.2008.05.022
46. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345(9):638–646. https://doi.org/10.1056/NEJMoa010580
47. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17):1731–1740. https://doi.org/10.1056/NEJMoa040694
48. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006;355(11):1114–1123. https://doi.org/10.1056/NEJMoa060829
49. Teoh S, Muirhead R. Rectal radiotherapy--intensity-modulated radiotherapy delivery, delineation and doses. *Clin Oncol (R Coll Radiol).* 2016;28(2):93–102. https://doi.org/10.1016/j.clon.2015.10.012
50. Droge LH, Weber HE, Guhlich M, et al. Reduced toxicity in the treatment of locally advanced rectal cancer: a comparison of volumetric modulated arc therapy and 3D conformal radiotherapy. *BMC Cancer.* 2015;15:750. https://doi.org/10.1186/s12885-015-1812-x
51. Guerrero Urbano MT, Henrys AJ, Adams EJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys.* 2006;65(3):907–916. https://doi.org/10.1016/j.ijrobp.2005.12.056
52. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol.* 2012;30(31):3827–3833. https://doi.org/10.1200/jco.2012.42.9597

53. Munker S, Vogelhuber M, Bornschein J, et al. EpiCO (epirubicin, cyclophosphamide and vincristine) as treatment for extrapulmonary high-grade neuroendocrine neoplasms. *Zeitschrift fur Gastroenterologie.* 2020;58(2):133–136. https://doi.org/10.1055/a-1042-6504
54. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer.* 1999;81(8):1351–1355. https://doi.org/10.1038/sj.bjc.6690325
55. Fjallskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer.* 2001;92(5):1101–1107. https://doi.org/10.1002/1097-0142(20010901)92:5%3C1101::aid-cncr1426%3E3.0.co;2-v
56. Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. *Cancer.* 1991;68(2):227–232. https://doi.org/10.1002/1097-0142(19910715)68:2%3C227::aid-cncr2820680202%3E3.0.co;2-i
57. Olsen IH, Langer SW, Jepsen I, et al. First-line treatment of patients with disseminated poorly differentiated neuroendocrine carcinomas with carboplatin, etoposide, and vincristine: a single institution experience. *Acta Oncologica (Stockholm, Sweden).* 2012;51(1):97–100. https://doi.org/10.3109/0284186x.2011.582881
58. Heigener DF, Manegold C, Jager E, Saal JG, Zuna I, Gatzemeier U. Multicenter randomized open-label phase III study comparing efficacy, safety, and tolerability of conventional carboplatin plus etoposide versus dose-intensified carboplatin plus etoposide plus lenograstim in small-cell lung cancer in "extensive disease" stage. *Am J Clin Oncol.* 2009;32(1):61–64. https://doi.org/10.1097/COC.0b013e31817be954
59. Yamaguchi T, Machida N, Morizane C, et al. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci.* 2014;105(9):1176–1181. https://doi.org/10.1111/cas.12473
60. Okita NT, Kato K, Takahari D, et al. Neuroendocrine tumors of the stomach: chemotherapy with cisplatin plus irinotecan is effective for gastric poorly-differentiated neuroendocrine carcinoma. *Gastric Cancer.* 2011;14(2):161–165. https://doi.org/10.1007/s10120-011-0025-5
61. Liu X, Cheng D, Kuang Q, Liu G, Xu W. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J.* 2014;14(2):120–129. https://doi.org/10.1038/tpj.2013.10
62. Nakano K, Takahashi S, Yuasa T, et al. Feasibility and efficacy of combined cisplatin and irinotecan chemotherapy for poorly differentiated neuroendocrine carcinomas. *Jpn J Clin Oncol.* 2012;42(8):697–703. https://doi.org/10.1093/jjco/hys085
63. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24(1):152–160. https://doi.org/10.1093/annonc/mds276
64. De Divitiis C, von Arx C, Grimaldi AM, et al. Metronomic temozolomide as second line treatment for metastatic poorly differentiated pancreatic neuroendocrine carcinoma. *J Transl Med.* 2016;14(1):113. https://doi.org/10.1186/s12967-016-0857-1
65. Chatzellis E, Angelousi A, Daskalakis K, et al. Activity and safety of standard and prolonged capecitabine/temozolomide administration in patients with advanced neuroendocrine neoplasms. *Neuroendocrinology.* 2019;109(4):333–345. https://doi.org/10.1159/000500135
66. 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):4617–4622. https://doi.org/10.1002/cncr.26124
67. Olsen IH, Sorensen JB, Federspiel B, et al. Temozolomide as second or third line treatment of patients with neuroendocrine carcinomas. *ScientificWorldJournal.* 2012;2012:170496. https://doi.org/10.1100/2012/170496
68. Hentic O, Hammel P, Couvelard A, 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(6):751–757. https://doi.org/10.1530/erc-12-0002
69. Olsen IH, Knigge U, Federspiel B, et al. Topotecan monotherapy in heavily pretreated patients with progressive advanced stage neuroendocrine carcinomas. *J Cancer.* 2014;5(8):628–632. https://doi.org/10.7150/jca.9409
70. Capdevila J, Mancuso F, Landolfi S, et al. BRAF V600E driven mutations in grade 3 neuroendocrine carcinomas of colon origin: results from genomic and epigenomic profilings and patient-derived mouse model. *15th Annual ENETS Conference; 8-9 March 2018: Barcelona, Spain Abstract B03.* 2018.
71. Girardi DM, Silva ACB, Rego JFM, Coudry RA, Riechelmann RP. Unraveling molecular pathways of poorly differentiated neuroendocrine carcinomas of the gastroenteropancreatic system: a systematic review. *Cancer Treat Rev.* 2017;56:28–35. https://doi.org/10.1016/j.ctrv.2017.04.002
72. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature.* 2002;417(6892):949–954. https://doi.org/10.1038/nature00766
73. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med.* 2014;371(20):1877–1888. https://doi.org/10.1056/NEJMoa1406037

74. Klempner SJ, Gershenhorn B, Tran P, et al. BRAFV600E mutations in high-grade colorectal neuroendocrine tumors may predict responsiveness to BRAF-MEK combination therapy. *Cancer Discov.* 2016;6(6):594–600. https://doi.org/10.1158/2159-8290.cd-15-1192
75. Corcoran RB, Andre T, Atreya CE, et al. Combined BRAF, EGFR, and MEK inhibition in patients with BRAF(V600E)-mutant colorectal cancer. *Cancer Discov.* 2018;8(4):428–443. https://doi.org/10.1158/2159-8290.cd-17-1226
76. Burkart J, Owen D, Shah MH, et al. Targeting BRAF mutations in high-grade neuroendocrine carcinoma of the colon. *J Natl Compr Canc Netw.* 2018;16(9):1035–1040. https://doi.org/10.6004/jnccn.2018.7043
77. Van Cutsem E, Huijberts S, Grothey A, et al. Binimetinib, encorafenib, and cetuximab triplet therapy for patients with BRAF V600E-mutant metastatic colorectal cancer: safety lead-in results from the phase III BEACON colorectal cancer study. *J Clin Oncol.* 2019;37(17):1460–1469. https://doi.org/10.1200/jco.18.02459
78. Capdevila J, Arques O, Hernandez Mora JR, et al. Epigenetic EGFR gene repression confers sensitivity to therapeutic BRAFV600E blockade in colon neuroendocrine carcinomas. *Clin Cancer Res.* 2020;26(4):902–909. https://doi.org/10.1158/1078-0432.ccr-19-1266
79. Kim ST, Ha SY, Lee S, et al. The impact of PD-L1 expression in patients with metastatic GEP-NETs. *J Cancer.* 2016;7(5):484–489. https://doi.org/10.7150/jca.13711
80. Yao JC, Strosberg J, Fazio N, et al. Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin. *Ann Oncol.* 2018;29(Suppl_8):viii467–viii478. https://www.annalsofoncology.org/article/S0923-7534(19)49923-7/pdf
81. Stuven AK, Wiedenmann B. Sustained partial remission of a metastatic NEN using off-label immunotherapy with pembrolizumab. *Oncotarget.* 2019;10(35):3302–3311. https://doi.org/10.18632/oncotarget.26906
82. Sahnane N, Furlan D, Monti M, et al. Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity. *Endocr Relat Cancer.* 2015;22(1):35–45. https://doi.org/10.1530/erc-14-0410
83. Hierro C, Matos I, Martin-Liberal J, Ochoa de Olza M, Garralda E. Agnostic-histology approval of new drugs in oncology: are we already there? *Clin Cancer Res.* 2019. https://doi.org/10.1158/1078-0432.ccr-18-3694
84. Patta A, Fakih M. First-line cisplatin plus etoposide in high-grade metastatic neuroendocrine tumors of colon and rectum (MCRC NET): review of 8 cases. *Anticancer Res.* 2011;31(3):975–978.