



# European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma

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## Abstract

This ENETS guidance paper, developed by a multidisciplinary working group, provides up-to-date and practical advice on the diagnosis and management of digestive neuroendocrine carcinoma, based on recent developments and study results. These recommendations aim to pave the road for more standardized care for our patients resulting in improved outcomes. Prognosis is generally poor for digestive NEC, most are advanced at diagnosis and median survival in metastatic disease is 11–12 months. Surgery can be of benefit for localized disease after extensive preoperative imaging. Carboplatin in combination with etoposide is recommended as first-line treatment for metastatic disease. Irinotecan with fluoropyrimidines has the best evidence as second-line treatment. Immunotherapy plays a minor role in biomarker-unselected patients. Molecular profiling if available is encouraged to identify new targets. More prospective clinical trials are highly needed to fulfil the unmet needs in this field, especially on new predictive and prognostic biomarkers and to improve survival of patients with advanced disease.

## KEYWORDS

diagnosis, digestive, NEC, neuroendocrine carcinoma, neuroendocrine neoplasms

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## 1 | INTRODUCTION

This ENETS guidance paper aims to answer 10 major questions on clinical, pathological as well as molecular diagnostics, prognostic factors and management of digestive neuroendocrine carcinoma (NEC) (Table 1). Data were identified by MEDLINE database searches and expert opinion/recommendations given according to the best available evidence and author's experiences. Each recommendation for treatment and diagnosis will have a level of evidence and grade of recommendation as per the GRADE system<sup>1</sup> (Table S1). In the paper, the term localized disease is used for the combined group of stage I–III cases. High-grade neuroendocrine tumors (NET G3) have a different prognosis, treatment, genetics and outcome compared to NEC, and will not be covered in this guidance paper. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN), which is an entity of controversy, will be covered in Q10.

## 2 | GENERAL BACKGROUND

### 2.1 | Epidemiology

Digestive NEC is a rare entity with an aggressive natural history, frequently characterized by early, extensive metastatic disease.<sup>2</sup>

**TABLE 1** Ten major questions on clinical, pathological as well as molecular diagnostics, prognostic factors and management of digestive neuroendocrine carcinoma (NEC).

Q1	What clinical examinations for diagnosis and staging should be performed in a newly diagnosed digestive NEC?
Q2	What pathological workup is needed for a newly diagnosed digestive NEC?
Q3	What are the prognosis and prognostic factors for digestive NEC?
Q4	How should surgery, chemoradiation and neoadjuvant chemotherapy be used in localized (stage I–III) digestive NEC?
Q5	Should adjuvant chemotherapy be given for localized (stage I–III) digestive NEC?
Q6	What should be given as first-line treatment for metastatic digestive NEC?
Q7	What should be given as second- and third-line treatment for metastatic digestive NEC?
Q8	Should immunotherapy (immune checkpoint inhibitors) be used for treatment of digestive NEC?
Q9	Is molecular/genetic based therapy an option for digestive NEC?
Q10	How should high-grade digestive MiNEN be diagnosed and treated?

Abbreviation: MiNEN, mixed neuroendocrine-non-neuroendocrine neoplasms.

The annual incidence of digestive NEC is 0.5–0.8/100,000.<sup>2–4</sup> Large-cell digestive NEC is twice as common as small-cell digestive NEC (0.36 vs. 0.18/100,000).<sup>4</sup> Among 162,000 NEC cases during 1973–2012, digestive NEC were the most frequent extra-pulmonary site (37%). Colorectal primaries accounted for 41% of digestive NEC, while upper gastrointestinal and pancreatic origins accounted for 23% and 20%, respectively.<sup>2</sup> Small-cell NEC are more commonly encountered in esophageal, gall bladder and anal NEC. Risk factors for digestive NEC are not well elucidated. Presenting symptoms depend on the primary site, and in metastatic disease usually with generalized systemic symptoms. Digestive NEC are almost always non-functioning.

### 2.2 | Digestive NEC vs. small-cell lung cancer

Traditionally, extra-pulmonary NEC have been considered to be similar to small-cell lung cancer (SCLC). However, there are major differences such as their pathological definitions that include expression of neuroendocrine markers and a much higher incidence compared to digestive NEC. Furthermore, unlike digestive NEC, SCLC is strongly associated with smoking, frequent brain metastases and higher response rates to platinum-based chemotherapy.<sup>5,6</sup> Digestive NEC differ genetically from SCLC<sup>7,8</sup> and from head/neck and cervical NEC.<sup>9,10</sup> Due to their differences, one should therefore be careful in extrapolating data from SCLC and extra-pulmonary NEC to digestive NEC. In this paper, data are focused specifically on digestive NEC.

### 2.3 | Prognosis and survival

Patients with localized digestive NEC may be cured with surgery; however, relapse is frequent and associated with a poor prognosis. The digestive NEC entity is completely different from well-differentiated digestive NET. Patients with localized NET G1–2 have a 5-year survival of 70%–80% while 5-year survival for localized NEC is 25%–40%.<sup>11</sup> Furthermore, patients with metastatic small intestinal NET (G1–G2) have a median survival of 8–10 years and metastatic pancreatic NET (G1–G2) 3–5 years while median survival for metastatic digestive NEC treated with chemotherapy is 11–12 months. In contrast to other cancers where immediate disease progression on first-line treatment in metastatic disease is rare (<10%–15%), this is seen after first-line treatment in up to 30% for digestive NEC and progression free survival (PFS) is only 4–5 months.<sup>12–15</sup> This clearly illustrates the aggressiveness of the disease and the need for improvement of treatment.

#### Recommendation

Treatment of patients with digestive NEC beyond general established principles should be considered in a multidisciplinary tumor board setting at a specialized center (grade 5A).

### 3 | DIAGNOSIS

#### 3.1 | Q1: What clinical examinations for diagnosis and staging should be performed in a newly diagnosed digestive NEC?

Digestive NEC are rarely functional and clinically significant hormone-related symptoms are almost never seen. Clinical signs and symptoms are therefore mainly related to the primary tumor location and tumor burden. Chromogranin A (CgA) and neuron specific enolase (NSE) in blood are elevated in approximately 60% of patients.<sup>12,16</sup> Recent retrospective data suggest that elevation of twice the upper normal level of these biomarkers are prognostic for digestive NEC, but the clinical usefulness has to be confirmed in prospective trials.<sup>15,16</sup> There is no evidence for secretion of serotonin from digestive NEC and measurement of 5-hydroxyindole-acetic acid (5-HIAA) is not recommended. Measurement of other hormones should only be done when clinical symptoms indicate secretion of that hormone. The mRNA-based NETest has been evaluated for its prognostic and predictive value in NET,<sup>17</sup> but has not been studied in NEC. Other biomarkers that are elevated in approximately 20%–30% of patients include CEA and CA19.9, but their clinical relevance remains to be established.<sup>16</sup> Several retrospective cohort studies have been performed to identify new predictive and/or prognostic biomarkers. In a pancreatic NET G3/NEC study ( $n = 42$ ), FAS ligand blood level was lower in NEC compared to control samples.<sup>18</sup> To identify regional and metastatic spread, all patients must be examined by thoracic and abdominal computerized tomography (CT). Brain CT/MRI examination is only indicated if clinical signs of brain metastases are present. Digestive NEC are <sup>18</sup>F-FDG PET/CT avid. Due to the high risk of metastatic disease, we recommend <sup>18</sup>F-FDG PET/CT to be performed for localized disease before surgery and considered before start of adjuvant chemotherapy to establish possible metastatic disease as this will have therapeutic consequences. <sup>18</sup>F-FDG PET/CT is generally not necessary when metastatic disease is present, but can be used to establish tumor burden, as well as the response to chemotherapy.<sup>19</sup> Digestive NEC may be positive on somatostatin receptor imaging, especially in the lower Ki-67 range (<55%). <sup>68</sup>Ga-SSA-PET-CT is, however, only relevant in the rare cases when peptide receptor radionuclide therapy (PRRT) is considered (see Q7).<sup>20</sup>

#### Recommendation

No blood biomarkers are established for routine use in digestive NEC. Thoracic/abdominal CT is mandatory to perform. <sup>18</sup>F-FDG PET/CT should be performed in localized disease (grade 2aB) and may be performed for advanced disease if the result may alter selection of treatment.

#### 3.2 | Q2: What pathological workup is needed for a newly diagnosed digestive NEC?

##### 3.2.1 | How to make the diagnosis of NEC

Neuroendocrine carcinoma (NEC) are poorly differentiated neuroendocrine neoplasms (NEN) and have a high-grade proliferative capacity defined by a Ki-67 >20% (WHO G3), with a Ki-67 usually >50%. They are classified into small-cell (SC-NEC) and large-cell type (LC-NEC).<sup>21</sup> SC-NEC are characterized by diffuse, non-organoid architecture with highly atypical small sized cells with scant cytoplasm, hyperchromatic nuclei and inconspicuous nucleoli. LC-NEC are composed of larger cells which display a well-developed cytoplasm and a polymorphous nucleus with prominent nucleoli in a subset of cases. Both may commonly exhibit geographic necrosis. Immunohistochemistry (IHC) is mandatory for the diagnosis of digestive NEC with two recommended neuroendocrine markers, synaptophysin and CgA. NEC may lack or express low level of CgA, especially in SC-NEC. INSM1, a transcription factor may help in this setting with an 85% sensitivity in NEC.<sup>22</sup> The utility of IHC for other neuroendocrine markers, such as neuron-specific enolase (NSE) and CD56 is hampered by the lack of specificity for NEN, are generally not used and are discouraged in digestive NEC. Organ-specific markers, such as TTF1 are of poor value in NEC. Evaluation of proliferative activity by IHC for Ki-67 indicates rapid tumor growth.

##### 3.2.2 | Molecular characteristics of digestive NEC by next generation sequencing (NGS)

Molecular characteristics of digestive NEC have recently been described.<sup>7,8</sup> Digestive NEC seem to have a lower rate of mutations in *TP53* and fewer *RB1* alterations compared to SCLC, and other genes are more frequently altered.<sup>7,8</sup> The most frequently mutated genes in digestive NEC are *TP53* (64%), *APC* (28%), *KRAS* (22%), *BRAF* (20%) and *RB1* (14%).<sup>7</sup> However, Rb deficiency, assessed by all genomic alterations (mutations and copy number alterations) and by protein expression is much more common and is present in up to 50% of digestive NEC.<sup>7,8</sup> Most reports group different digestive locations with relatively few cases, but alterations seem to vary according to the primary tumor.<sup>7,23</sup> Esophageal NEC seem genetically similar to SCLC.<sup>24</sup> In the colon primaries, *BRAF*, *APC* and *KRAS* mutations are most frequent (49%, 40% and 31% respectively). Microsatellite instability (MSI) is seen in 5% of digestive NEC, associated with *BRAF* V600E mutation in the (frequently right) colon.<sup>7</sup> The presence of MSI or *BRAF* V600E mutation may have consequences for treatment of metastatic disease. Liquid biopsy with circulating tumor DNA may in the future be an alternative for molecular tumor analyses in digestive NEC patients.<sup>25</sup>

### 3.2.3 | How to distinguish NEC from NET G3

NET G3 have a high proliferation rate with Ki-67 >20%, but are well differentiated with morphological and molecular similarities to NET G1-2. The differential diagnosis between NET G3 and NEC (especially LC-NEC) can be difficult on morphology, even with the help of new additional histological criteria analyzing the stroma of the tumor.<sup>26</sup> Ki-67 alone cannot be used, although a recent report shows that the 55% cutoff is best to discriminate NEC from NET G3.<sup>27</sup> When morphology is ambiguous, immunohistochemistry (IHC) can be performed with a panel of antibodies: ATRX/DAXX (loss of expression favors pancreatic NET), Menin (loss of expression favors pancreatic/lung NET), Somatostatin receptor-2 (high expression favors NET), TTF1 (high expression in digestive primary favors NEC), Rb (loss of expression favors NEC) and p53 (either strong and diffuse expression or complete loss of expression favors NEC).<sup>28</sup> Some of these markers could be analyzed by NGS testing, especially in case of unclear IHC result, but IHC-NGS correlation data on large series are so far lacking. A deficient mismatch repair (dMMR) phenotype is highly suggestive of NEC, but detected in only 5%–10% of cases.<sup>7</sup>

### 3.2.4 | How to distinguish NEC from adenocarcinoma expressing NE markers

Conventional digestive adenocarcinoma may express neuroendocrine markers, preferentially synaptophysin and CD56, and to a lesser extent CgA. This is reported in colon adenocarcinoma, especially in dMMR BRAF mutated adenocarcinoma, and possibly associated with worse prognosis.<sup>29</sup> A recent study on 1002 colorectal adenocarcinoma reports that the percentage of synaptophysin staining tumor cells has no impact on prognosis in otherwise morphologically conventional adenocarcinoma, whereas MiNEN (adenocarcinoma + NEC) (see Q10) have a worse prognosis.<sup>30</sup> This indicates that synaptophysin IHC should not be performed on typical adenocarcinoma, and should be restricted to carcinoma whose morphology on HE indicates a neuroendocrine differentiation, or shows a neuroendocrine component that could indicate a mixed tumor. Distinguishing LC-NEC from adenocarcinoma with neuroendocrine features can be difficult, especially when they are poorly differentiated and synaptophysin or chromogranin not diffuse and strongly positive. In these cases, the tumor is best classified as an adenocarcinoma with neuroendocrine features.

#### *Recommendation*

The histopathological diagnosis of NEC relies on poorly differentiated morphology, Ki-67 > 20% and positive immunohistochemical staining for synaptophysin ± CgA (grade 1A). INSM1 can help in cases with focal/negative CgA expression. When morphology is ambiguous concerning a possible NET G3, a panel of antibodies can be of use including p53, Rb1 and if pancreatic primary ATRX, DAXX and Menin. Testing for MSI and BRAF should be considered if it can influence treatment choice (grade 2bB).

## 4 | PROGNOSIS AND PROGNOSTIC FACTORS

### 4.1 | Q3: What are the prognoses and prognostic factors for digestive NEC?

#### 4.1.1 | Prognosis

The prognosis for patients with digestive NEC is generally poor despite recent advances in both diagnostics and treatment. Long-term relapse-free survival is however possible among patients with localized disease (stage I–III) after multimodality therapy.<sup>11</sup> Digestive NEC data from SEER show a median survival of 33.9 m in patients with local disease (stage I–II), 16.3 m with locoregional disease (stage III), and 5.2 m with distant disease.<sup>2</sup> Corresponding overall five-year survival rates were 42%, 25.6%, and 4.7%, but varied depending on primary tumor site and morphology. Median survival in metastatic patients not given palliative chemotherapy is one month, and in patients receiving chemotherapy is 11–12 months.<sup>12,13,15,31,32</sup> Palliative chemotherapy should be considered within 1–2 weeks if possible since performance status may deteriorate quickly, preventing any treatment. Two-year survival was 14% and three-year survival was 9.5% in the Nordic NEC cohort receiving palliative chemotherapy.<sup>12</sup>

#### 4.1.2 | Prognostic factors

Most data indicate that surgery for localized disease improves survival, but stage and the primary tumor site is relevant with colon NEC having the best outcome after surgery (see Q4). Large-cell morphology seems to result in a slightly better survival compared to small-cell morphology in both localized and metastatic disease.<sup>2,11,33,34</sup> The presence of metastatic disease and the number of metastatic sites are of adverse prognostic significance.<sup>15</sup> Performance status (PS) is one of the most significant prognostic signs and patients with metastatic disease and PS >1 have a significantly shorter survival: PS 0: 18 m, PS 1: 12 m and PS 2: 5 m.<sup>12</sup> Elevated CgA and NSE may be indicative of a worse prognosis in metastatic disease as well as elevated common blood tests such as lactate dehydrogenase (LDH), platelet count, aspartate aminotransferase (AST) and alkaline phosphatase (ALP).<sup>12,15,35</sup> Patients with metastatic disease from esophagus or large bowel have a worse prognosis compared to other primary sites.<sup>12,13</sup> Cases with a higher proliferation rate (Ki-67 >55%) have a shorter survival in most studies.<sup>12,36</sup> A GI-NEC score to prognosticate overall survival included five variables: presence of liver metastases, ALP, LDH, PS and Ki-67, and identified two distinct patient cohorts.<sup>37</sup> <sup>18</sup>F-FDG-PET avid disease correlates with worse prognosis in NEC patients.<sup>38</sup> Emerging data show a possible benefit of analyzing gene mutations, which may possibly guide treatment.<sup>7,8</sup> In contrast to colorectal adenocarcinoma, BRAF V600E mutations do not seem to be prognostic for colorectal NEC and few prognostic molecular markers have been found for digestive NEC.<sup>39</sup> Rb1 status does not seem to provide any prognostic information.<sup>39–42</sup>

### Recommendation

Prognostic factors should be taken into consideration when planning treatment of NEC. The most important prognostic factors to consider for localized disease is the presence of regional lymph node disease (stage III) and primary tumor site. The most important prognostic factor to consider for metastatic disease is performance status >1 (grade 3aB).

## 5 | TREATMENT

### 5.1 | Q4: How should surgery, chemoradiation and neoadjuvant chemotherapy be used in localized (stage I–III) digestive NEC?

#### 5.1.1 | Surgery

Surgery is the main potential curative option for digestive NEC, but 5-year survival after surgery only reaches 25%–40% in patients with initial localized disease (stage I–III). Therefore, even in the setting of clinically localized disease at diagnosis, many patients have a poor prognosis with rapid disease progression with a high proclivity for metastatic dissemination. Optimal staging with <sup>18</sup>F-FDG PET/CT should be performed before consideration of surgery. The data supporting benefit from resection come from retrospective studies noting that surgery can be curative for patients with digestive NEC who have apparently localized disease. Data from 1640 localized digestive NEC showed a 5-year survival of 42% for stage II disease and 25.6% for stage III disease, with some differences according to the primary tumor site.<sup>2</sup> Among 112 stage I–III digestive NEC patients with an R0 surgical resection, 5-year disease-free survival was 33.8% and 5-year survival 42%.<sup>43</sup> In a recent multicenter study, 60 patients with stage I–III digestive G3 NEN (72% NEC) had radical surgery with overall survival (OS) after 2 years 58.5% in the NEC subgroup.<sup>44</sup> Among 2245 patients with non-metastatic GEP NEN G3, resection (in 1549 patients) was associated with better long-term outcomes compared to no surgery at all (5-year OS 39% vs. 10%).<sup>45</sup> An obvious bias is that patients with poor performance status, serious comorbidities or deteriorating health status are generally not operated on. In a study of 2314 cases with stage I–III digestive NEC, 5-year survival rate after surgery was 29.2%, with significant differences according to primary tumor site and morphology.<sup>11</sup> Colon NEC had the best 5-year survival (39.7%), while gallbladder/biliary NEC the lowest (20.9%). Small-cell morphology was associated with worse survival compared to non-small cell histology (17.7 vs. 22.3 m). A multivariable model showed that even in patients undergoing chemoradiation, surgery was the only prognostic variable that significantly affected survival in stages I–II patients (HR 0.63) and showed a strong trend in stage III patients (HR 0.77). A propensity score matching between 233 digestive non-metastatic NEC patients without surgery and 233 digestive non-metastatic NEC surgical patients, reported that radical surgery was significantly associated ( $p < .001$ ) with improved survival.<sup>34</sup>

Primary tumor site is a factor when considering surgery in localized digestive NEC, as survival varies according to the primary site.<sup>2,11</sup> For localized esophageal NEC, initial surgery seems inferior to initial chemoradiation, especially for stage III.<sup>46,47</sup> In a cohort of 630 pancreatic NEC cases, surgery was, after propensity score matching, significantly and independently associated with improved survival (36 vs. 8 months).<sup>48</sup> In a large colorectal NEC cohort, surgery was a beneficial prognostic factor for OS in a multivariable analysis.<sup>49</sup> In another study of 502 NEC stage I–III 3-year survival after surgery was 40% versus 18% in cases without surgery.<sup>33</sup> Patients with localized non-small cell colorectal NEC had better survival benefit after surgery (21 vs. 6 m), compared to small-cell (18 vs. 14 m), questioning the benefit of surgery for localized small-cell anorectal NEC.

#### 5.1.2 | Chemoradiation

There is remarkably little data on the use of chemoradiation for localized digestive NEC. Many patients have probably been given chemoradiation as a part of the initial treatment for a suspected adenocarcinoma. The two major questions are: does preoperative chemoradiation before surgery add benefit compared to surgery alone and can definite chemoradiation replace surgery? The relatively high proportion (27%) of margin-positive resections found after surgery ( $n = 519$ ) of digestive NEC raises the possibility that down-staging with neoadjuvant therapy may enhance complete resection rate and lower the risk of local and systemic recurrence.<sup>31</sup>

In the US National Cancer Database, radiotherapy for digestive NEC was frequently used in esophageal (74%), rectal (61%) and anal (83%) NEC,<sup>11</sup> principally in younger patients and in higher stage disease. Among 127 patients with localized small-cell esophageal carcinoma, three-year survival was superior after chemoradiation compared to surgery and chemotherapy (50% vs. 24%).<sup>46</sup> Results were especially better after chemoradiation of stage III disease. All patients with definitive chemoradiation had a complete response, 43% recurred at other sites, but those without distant recurrence had a remarkable long survival. Chemoradiation ( $n = 22$ ) for patients with locally advanced esophageal NEC resulted in a 77% clinical complete response rate with a 5-year OS of 45%.<sup>50</sup> Postoperative radiotherapy and/or chemotherapy after esophageal NEC resection (63/67 localized) was associated with significantly better prognosis in one study, but not for stage I–IIA in another study.<sup>51,52</sup> The benefit of chemoradiation for localized rectal NEC is unknown, with distant recurrence as the major problem for these patients rather than an isolated local recurrence. In a recent US study as many as 60% of rectal NEC received chemoradiation and surgery.<sup>11</sup> In patients undergoing chemoradiation, surgery was still the only prognostic variable that significantly improved survival. Chemoradiation may, however, provide long-term local control in anorectal NEC.<sup>53,54</sup> A Surveillance, Epidemiology and End Results (SEER) based analyses of 71 small-cell rectal cancers found that radiation therapy was associated with improved survival; however, only 14/28 cases without radiation therapy received surgery.<sup>55</sup> Locally advanced rectal NEC should be discussed



in a multidisciplinary setting, especially in cases of planned major surgery. It seems reasonable to pursue initial chemoradiation for anal NEC.<sup>54</sup>

### 5.1.3 | Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (chemotherapy before surgery) has several advantages. It gives an opportunity to treat early possible metastatic disease while it is microscopic, which might increase survival. It can downsize the primary tumor, thus improving resectability. Furthermore, it enables better selection of patients that can benefit from delayed primary tumor surgery, thus avoiding surgery and surgical morbidity in patients that develop metastatic disease during neoadjuvant chemotherapy. These advantages are especially relevant for digestive NEC, which has a high distant recurrence rate after surgery. In addition, the relatively high proportion (27%) of margin-positive resections found after surgery of digestive NEC ( $n = 519$ ) raises the question if downstaging with neoadjuvant therapy may lower the risk of systemic recurrence.<sup>31</sup> Most localized cases of NEC are however, initially misdiagnosed as adenocarcinoma in biopsy-based assessments and initially treated as adenocarcinomas. Many digestive NEC studies do not separate if chemotherapy was given in adjuvant, neoadjuvant or perioperative setting, and pure neoadjuvant studies are rare. In a study ( $n = 69$ ) of locally advanced gastric NEC/MiNEN, neoadjuvant chemotherapy (various regimens) was associated with improved survival.<sup>56</sup> Among 152 small-cell esophageal cancer patients, survival and PFS was better in stage III patients who underwent neoadjuvant chemotherapy.<sup>52</sup> Preoperative ( $n = 54$ ), postoperative ( $n = 224$ ) and perioperative chemotherapy ( $n = 9$ ), were all associated with improved survival rates in digestive NEC.<sup>31</sup> Neoadjuvant chemotherapy seems to be a reasonable option if the risk of systemic recurrence is higher than average, or if an observation period is warranted before possible surgery of the primary tumor to avoid surgery in patients progressing on chemotherapy.

#### Recommendation

For fit patients with localized resectable digestive NEC, surgical resection should be considered, especially if a simple R0 resection can be performed.<sup>18</sup> F-FDG PET/CT should be performed before consideration of surgery. In cases where major surgery is required, individualized treatment decisions can be considered. For localized esophageal and anal NEC, we suggest initial chemoradiation. The benefit of chemoradiation for resectable rectal NEC is uncertain. Neoadjuvant chemotherapy before consideration of delayed primary tumor surgery is a treatment option (grade 4B).

## 5.2 | Q5: Should adjuvant chemotherapy be given for localized (stage I–III) digestive NEC?

The majority of digestive NEC patients with stage II–III undergoing resection will develop recurrence, mostly distant, suggesting that there

is a place for adjuvant chemotherapy. Retrospective studies on the use of adjuvant treatment have at least two major areas of bias: patients with worse prognostic factors may more often receive adjuvant chemotherapy, but patients in poor general condition and with comorbidities may receive adjuvant chemotherapy less frequently. In a large cohort study with 1861 digestive NEC patients, 519 patients underwent curative resection, and postoperative chemotherapy ( $n = 224$ ) was associated with improved survival (HR 0.58).<sup>31</sup> A retrospective study in 73 localized digestive NEC showed also that chemotherapy had a positive prognostic impact on survival.<sup>57</sup> Among 2245 patients with localized digestive NEC, 1549 underwent curative resection.<sup>45</sup> Use of chemotherapy in resected patients was associated with shorter survival in the unadjusted analysis, but the study did not separate if chemotherapy was given in the adjuvant setting or as later palliative chemotherapy at recurrence. After propensity score matching, no survival benefit was seen for patients receiving adjuvant chemotherapy (138/276 patients) after surgery for stage I–III gastric NEC.<sup>58</sup> Postoperative chemotherapy given to 213/759 cases with gastric, pancreatic or small-intestinal NEC (unusual high number of small-intestinal NEC) was not associated with improved survival.<sup>59</sup> Postoperative chemotherapy and/or radiotherapy after esophageal NEC resection (63/67 localized) was associated with significantly better prognosis.<sup>51</sup> Postoperative adjuvant chemotherapy did not increase survival in stage I–IIA small-cell esophageal carcinoma.<sup>52</sup> Among 806 resectable colorectal NEC patients, 49% received adjuvant chemotherapy with significantly better median and 5-year survival.<sup>60</sup> The results were consistent across subgroups stratified by surgical margin and pathologic T and N stage. Two other reports also found patients receiving adjuvant chemotherapy after surgery for colorectal and rectal NEC had a survival benefit.<sup>49,61</sup> Patients with right-sided colorectal NEC may benefit less from adjuvant treatment compared to those with left-sided disease.<sup>60</sup> None of the studies separated out stage II and III, but the high recurrence rate also seen in patients with stage II disease suggest that there is a place for adjuvant treatment also for stage II. Adjuvant chemotherapy may be considered for stage III cases and discussed individually for patients with stage II disease. The benefit of adjuvant chemotherapy may depend on the primary tumor site.

The recommended adjuvant chemotherapy regimen has been 4–6 cycles with cisplatin or carboplatin and etoposide, based on its use in the metastatic setting and the 4–6 cycles of cisplatin/etoposide used together with radiation for limited-stage SCLC.<sup>62</sup> The adjuvant chemotherapy regimen is however not specified in most digestive NEC studies, although platinum/etoposide was probably used for the majority of patients. In a Chinese study, adjuvant chemotherapy was given according to ENETS guidelines, which was platinum/etoposide<sup>58</sup> and in a French study, 86% patients received platinum/etoposide.<sup>57</sup> The high rate of immediate disease progression seen for this regimen in the metastatic setting (Q6), may question if platinum/etoposide is the optimal adjuvant regimen, at least concerning colorectal NEC. Some centers have therefore preferred an adenocarcinoma regimen (5-FU backbone) based on the primary tumor site – without any other available data to support such an approach. The ongoing phase II study comparing

FOLFIRINOX versus platinum/etoposide for metastatic digestive NEC could provide response rate data to guide future selection of adjuvant chemotherapy.

### Recommendation

Adjuvant chemotherapy with 4–6 cycles of platinum/etoposide may be considered after radical surgery of localized digestive NEC (grade 4B).

## 5.3 | Q6: What should be given as first-line treatment for metastatic digestive NEC?

Rapid referral for consideration of first-line palliative chemotherapy is important given the frequent rapid decline in PS. Based on small-cell lung cancer treatment, cisplatin or carboplatin in combination with etoposide has been a cornerstone in the treatment of metastatic digestive NEC. Retrospective series have shown a response rate (RR) of 30%–50%, PFS 4–6 m and OS 11–12 m<sup>12–15</sup> (Table 2). Immediate disease progression without any benefit of this regimen has been reported in up to 30% in digestive NEC and 60% in colorectal NEC<sup>12,13</sup> (Table 2), which is higher than 5%–15% usually seen in oncology. Colorectal primaries seem to have the shortest OS with only 7.6–8 m.<sup>12,13</sup> The NORDIC NEC study found similar RR, PFS and OS for carboplatin/etoposide and cisplatin/etoposide in digestive NEC.<sup>12</sup> Cisplatin should therefore be replaced with the better tolerated carboplatin. Toxicity rates were comparable between oral and intravenous etoposide in extra-pulmonary NEC (61/113 digestive), with similar PFS although there was a trend towards a shorter OS for oral etoposide.<sup>63</sup> In Nordic NEC ( $n = 236$ ), no statistical differences was observed in PFS or OS comparing 24 h etoposide infusion (PFS 3.8 m, OS 14.5 m), 2 h etoposide infusion (PFS 5.6 m, OS 11.0 m) or oral etoposide (PFS 5.4 m, OS 11.3 m).<sup>64</sup> More data are needed for a final advice on oral etoposide. Most

studies gave 4–6 cycles of platinum/etoposide; the number of cycles will also depend on the general patient condition and tolerability.

Given the limited benefit of platinum/etoposide, there have been attempts to improve first-line treatment. Two recent Asian randomized trials comparing cisplatin/etoposide versus irinotecan/cisplatin in metastatic digestive NEC (mainly upper GI) found no differences in RR (40%–50%), PFS or OS (10–12 m).<sup>32,65</sup> A subgroup analyses observed that cisplatin/etoposide produced a more favorable OS in cases with pancreatic NEC; however, this finding should be interpreted with caution due to the small sample size.<sup>32</sup> Both studies showed similar rates of severe adverse events for both regimens, but different toxicity profiles with lower rates of myelotoxicity and greater rates of diarrhea with irinotecan/cisplatin. Data for FOLFOX or FOLFIRINOX in digestive NEC are scarce and restricted to few case series, awaiting results from a phase II trial comparing FOLFIRINOX versus platinum/etoposide (NTC04325425). A first-line study of temozolomide/capecitabine (CAPTEM) versus platinum/etoposide in non-small cell digestive NEC and NET G3 was closed early due to poor accrual.<sup>66</sup> Among 62 evaluable patients, RR, PFS and OS with CAPTEM were 9%, 2.4 m and 12.6 m versus 10%, 5.4 m and 13.6 m with platinum/etoposide. The study interpretation is limited by including both NET G3 and NEC patients. Data are insufficient to recommend CAPTEM as general alternative regimen to the current standard of care. Possible selection of alternative first-line regimens can be individualized based on patient features, primary tumor site as well as Ki-67. Patients with Ki-67 in the lower range (<55%), might be candidates for less toxic treatments, as they have a lower RR to platinum/etoposide.<sup>12</sup> Everolimus/temozolomide combination treatment in a first-line phase II trial had little benefit in digestive NEC.<sup>67</sup> The current data are insufficient to support the first-line use of targeted agents in NEC. There are no data to support the use of somatostatin analogs in NEC, and they should not be used in NEC. For possible use of immunotherapy in first-line treatment- see Q8.

**TABLE 2** Prospective and retrospective studies on first-line chemotherapy in advanced digestive neuroendocrine carcinoma.

Reference	Design	Treatment	No	Diff	RR %	PD %	PFS	OS
Sorbye et al. (2013) <sup>12</sup>	Retrospective	Etoposide + cisplatin or carboplatin	252	G3	31	36	4 m	11 m
Yamaguchi et al. (2014) <sup>13</sup>	Retrospective	Cisplatin + etoposide or irinotecan	258	Poor	28 vs. 50		4 vs. 5.2 m	7.3 vs. 13 m
Heetfeld et al. (2015) <sup>14</sup>	Retrospective	Platinum + etoposide	113	Poor	35	27	5 m	16.4 m <sup>a</sup>
Walter et al. (2017) <sup>15</sup>	Retrospective	Platinum + etoposide	152	Poor	50	27	6.2 m	11.6 m
Morizane et al. (2022) <sup>32</sup>	Phase III	Cisplatin + etoposide or irinotecan	170 <sup>c</sup>	Poor <sup>b</sup>	55 vs. 53	13 vs. 15	5.6 vs. 5.1 m	12.5 vs. 10.9 m
Zhang et al. (2020) <sup>65</sup>	Phase II	Cisplatin + etoposide or irinotecan	66	Poor	42 vs. 42	36 vs. 13	6.4 vs. 5.8 m	11.3 vs. 10.2 m

Note: Only retrospective studies with  $n > 100$  and prospective studies with  $n > 60$  were included.

Abbreviations: Diff, differentiation; OS, overall survival; PD, progressive disease at first evaluation; PFS, progression-free survival; RR, response rate.

<sup>a</sup>Stage mixture.

<sup>b</sup>Five cases NET G3.

<sup>c</sup>Mainly upper GI.

There are scarce data on predictive factors for response to platinum/etoposide treatment. Patients with PS 2 had a higher percentage of immediate disease progression compared with PS 0 (61% vs. 26%).<sup>12</sup> Non-small-cell NEC (73% digestive), had a worse RR (32% vs. 55%) and disease control rate compared to small-cell, and worse PFS if Ki-67 >55%.<sup>68</sup> There has been a controversy if Rb1 inactivation can be used as a marker for treatment benefit of platinum/etoposide. Increased RR was found for pancreatic NEC with Rb loss and/or KRAS mutations in fine needle aspiration cytology samples, with no PFS data and better OS for wild-type.<sup>69</sup> Other data have been conflicting, frequently showing some effect on RR, but not for PFS. In a multicenter trial, Rb status had no significant impact on RR, PFS or OS in platinum/etoposide treated metastatic extra-pulmonary NEC patients (38% digestive).<sup>40</sup>

#### Recommendation

Carboplatin/ etoposide is recommended as first-line treatment for metastatic digestive NEC. Irinotecan/cisplatin may be considered an alternative option. Other regimens can be considered based on patient features, primary tumor site as well as Ki-67 (grade 2bB). Somatostatin analogs should not be used for antiproliferative therapy in NEC (grade 4B).

### 5.4 | Q7: What should be given as second- and third-line treatment for metastatic digestive NEC?

It remains unclear what is the best second-line therapy in digestive NEC. Fluoropyrimidines given in combination with either irinotecan (FOLFIRI), oxaliplatin (FOLFOX/CAPOX) or temozolomide (CAPTEM) are the most common clinical-practical options in absence of data from prospective and randomized trials. Evidence supporting the use of these regimens is quite poor coming mostly from retrospective series summarized in Table S2 and in a meta-analysis.<sup>70</sup> Response rates are seen in 10%–30%, PFS 2–4 months (range: 1.2–6.0) and OS 5–7 months (range: 3.2–22). Data suggested that temozolomide-based chemotherapy may be most effective in cases with Ki-67 values in the 21%–55% range, however, these studies did not include pathological review and might have included NET G3 cases. There is limited experience with the triple combination regimen FOLFIRINOX (oxaliplatin/irinotecan/fluorouracil). Recently, prospective studies have reported results on second-line irinotecan-based therapy. A phase II study comparing FOLFIRI alone versus FOLFIRI + bevacizumab ( $n = 133$ ) showed no difference in RR (18%–26%), PFS (3.5–3.7 m) or OS (7–8.9 m).<sup>71</sup> A randomized trial used docetaxel ( $n = 29$ ) or liposomal-irinotecan +5-fluorouracil (5FU)/folinic acid ( $n = 29$ ) in extra-pulmonary NEC (69% digestive) refractory to platinum-based chemotherapy.<sup>72</sup> Liposomal-irinotecan/5FU achieved RR 10.3%, PFS 3 m, 6 m PFS rate 31% and OS 9 m, but it remains unclear if liposomal-irinotecan is superior to conventional irinotecan. Studies do not support the use of docetaxel or topotecan in digestive NEC (Table S2). Retreatment with platinum/etoposide might be an option after a treatment break, as patients who progress after

discontinuation of first-line treatment may still be platinum sensitive. In the Nordic NEC study retreatment with the same platinum-based regimen yielded a response rate of 15%, with another 27% achieving stable disease.<sup>12</sup> Rb1 status did not affect neither PFS nor survival in second-line treatment ( $n = 121$ , 36% digestive).<sup>41</sup> BRAF V600E mutations are frequent in colorectal NEC, and a BRAF inhibitor combination may be a second-line treatment option in BRAF V600E mutated digestive NEC cases (see Q9). A small metastatic digestive NEC subgroup of 5% show MSI, which is a tumor-agnostic marker for the benefit of immune checkpoint inhibitors (see Q8).

Surgery for metastatic disease is generally not recommended due to poor prognosis, rapid disease progression and a short survival, but may be considered in rare cases for highly selected patients with limited disease without rapid disease progression where an R0 resection is possible. In a Nordic GEP-NEN G3 database of 840 patients, 32 patients (24 NEC) had resection or radiofrequency ablation of liver metastases.<sup>73</sup> Five-year survival rate was 43%, with Ki-67 <55% and adjuvant chemotherapy as independent significant prognostic factors. There are no data on the use of liver embolization/ SIRT for NEC.

Patients with digestive NEC rarely express somatostatin receptors and in general the expression is weak, therefore very few cases might be considered for peptide receptor radionuclide therapy (PRRT). A retrospective study on the use of PRRT in digestive high-grade NEN ( $n = 149$ ) mostly as second or further line treatment, found a RR of 40%. Pathological local reclassification was done in cases when differentiation status was lacking in the original pathology report. Among the NEC subgroup (41%), significantly better PFS (11 vs. 4 m) and OS (22 vs. 9 m) was seen in cases with Ki-67 <55% (30% of cases) compared to Ki-67 >55% (11% of cases).<sup>20</sup> If there are spatially discordant (<sup>18</sup>F-FDG positive/ SRI negative) lesions, PRRT is contraindicated.<sup>74,75</sup>

#### Recommendation

There is no clear standard of care to treat patients with metastatic digestive NEC who have failed first-line platinum-based chemotherapy. Most used and recommended agents in this setting are fluoropyrimidines in combination with either irinotecan, oxaliplatin or temozolomide, with the best evidence for irinotecan-based regimens (grade 2bB). Surgery of metastatic disease or PRRT is generally not recommended (grade 5D).

### 5.5 | Q8: Should immunotherapy (immune checkpoint inhibitors) be used for treatment of digestive NEC?

Despite the success in the treatment of traditionally similar malignancies such as SCLC and Merkel cell carcinoma, the activity shown by immune checkpoint inhibitors (ICI) in metastatic digestive NEC have generally been disappointing. In a previous study, the rationale for the use ICI in NEC was based on a PD-L1 expression between 14% and 50%, a suspected high tumor mutational burden (TMB) and a broad



range of multiple immune cells like T cells, macrophages as well as dendritic cells infiltrating NEN.<sup>76</sup>

### 5.5.1 | Microsatellite instability (MSI) and tumor mutational burden (TMB)

MSI is seen in 5% of metastatic digestive NEC.<sup>7</sup> MSI is an agnostic tumor marker for the benefit of ICI. The US Food and Drug Administration (FDA) has approved pembrolizumab in pretreated tumors with MSI regardless of tumor type and site, whereas the European Medicines Agency (EMA) has approved pembrolizumab for only five MSI tumor types that include endometrial, gastric, small bowel, biliary and colorectal cancers (histology not specified) in the refractory setting. Pembrolizumab has also approval for first-line treatment and nivolumab + ipilimumab for second-line treatment of MSI metastatic CRC (adenocarcinoma not specified). Although NEC were not included in the registration studies, we propose that digestive NEC should be tested for MSI/dMMR with the potential to use ICI if available.

A high TMB (usually >10 mutations/million base pairs), has a better response to ICI, although recent data have shown that this may vary according to primary tumor site. Pembrolizumab has FDA approval for unresectable/metastatic solid tumors with high TMB (>10). The TMB in digestive NEC is generally (and surprisingly) low, with a median TMB of around 5 in studies.<sup>23</sup> Relatively few cases have TMB >10, and in a recent study 9/10 cases with TMB >10 had MSI.<sup>39</sup> A metastatic NEN ICI study found increased RR in patients with high TMB or PD-L1 expression  $\geq 10\%$ .<sup>77</sup> Identification of targets predictive of immunotherapy may support the use of ICI as a second-line treatment. Lack of identification of these markers does not preclude patients from the possible benefit of ICI since reported RR and 6 m PFS rates for dual PD1/CTLA4 blockade are slightly higher in the largest ICI study in GEP NEC (12% and 15%)<sup>78</sup> as compared to reported mutation rates.

### 5.5.2 | Two strategies in using ICI for NEC: Adding ICI to first-line treatment or monotherapy ICI (single/double) in later lines

The NICE-NEC single-arm phase II trial used first-line treatment nivolumab combined with carboplatin/etoposide followed by maintenance nivolumab in 38 patients with NEN G3 of GEP (82%) or unknown origin.<sup>79</sup> The response rate was 54%, disease control rate 84%, PFS 5.7 months and 39% of patients were free of progression after 6 months. Benefit was less in colorectal primaries. The inclusion of NET G3 patients (29%) represents a limitation of this study since PFS/OS are more favorable in NET G3 than NEC. It currently remains unclear if addition of immunotherapy to standard first-line chemotherapy results in a better outcome in digestive NEC patients. Data from a randomized phase II/III study (NCT05058651) will answer this question.

Interpretation of available studies on ICI for platinum refractory digestive NEC (2/3-line treatment) is often challenging, due to inclusion of multiple primary sites (including lung), frequent lack of information about MSI status and TMB, and lack of details about the type of GEP NEN G3 enrolled (well differentiated NET G3 or poorly differentiated NEC). Most of the data are in combined populations of NEC/NET G3.

Studies with single-agent therapy ICI have shown very low response rates, whereas trials of combined targeting of both PD-(L)1 plus CTLA-4 inhibitors have been more promising, with some patients achieving long-term disease control. A preliminary report of a retrospective evaluation of 34 patients with G3 NEN (79% NEC, 21 GEP) treated with nivolumab and ipilimumab reported an objective response rate of 15% with PFS 1 m.<sup>80</sup> A summary of the most relevant prospective studies with ICI in platinum refractory digestive NEC is shown in Table S3. A prospective study of nivolumab + ipilimumab in 19 patients (9 GEP) with G3 NEN (median Ki-67 80%) reported RR 26%, PFS only 2 months but with some long-term responders as one-third of patients were still progression-free at 6 months.<sup>81</sup> A preliminary report of the prospective DUNE study with durvalumab plus tremelimumab in NEN G3 reported an objected response rate of 9% and 9 months survival rate of 36% among GEP NEN G3 patients.<sup>82</sup> In the NIPINEC phase II trial, 185 pts (93 GEP NEC /92 lung NEC) with platinum-refractory disease were randomized between nivolumab alone versus nivolumab + ipilimumab.<sup>78</sup> The primary endpoint was RR at 8 weeks. RR was 7.2% for nivolumab versus 14.9% for nivolumab/ipilimumab, PFS 1.8 versus 1.9 m and OS 7.2 m versus 5.8 m. Six month PFS rate was 15%. The vast majority of NEC patients do not benefit from ICI. For the few cases who respond to ICI, median duration of response has been reported to be 5–21 months, although follow-up is still limited in these trials (Table S3).

#### Recommendation

ICI should, if available be considered for metastatic digestive NEC with MSI and/or high TMB progressing after first-line chemotherapy. As there are limited treatment options and a potential for durable sustained remission with immunotherapy in some cases, dual ICI may be an option for later line treatment if available. However, the vast majority of digestive NEC patients do not benefit from ICI and available clinical data are not sufficient for the use of ICI in general routine practice (grade 2bC).

### 5.6 | Q9: Is molecular/genetic based therapy an option for digestive NEC?

Molecular characteristics of digestive NEC have recently been described (see Q2). Regarding potential treatment selection, the data are still limited particularly with respect to outcome based on a molecularly selected therapy. Nevertheless, a high fraction of potentially targetable mutations has been identified in metastatic digestive NEC.<sup>7</sup> MSI or high TMB appear at present to be the only possible biomarkers

to predict the benefit of ICI (see Q8). *BRAF V600E* mutations are found in 28%–47% of colorectal NEC/MiNEN.<sup>83,84</sup> This means that colorectal NEC is among the most frequent *BRAF* associated solid malignancies, second only to melanoma and papillary thyroid cancer. In a recent study, right-sided colon NEC was the only primary tumor site with a high number of *BRAF V600E* mutations (in 57%).<sup>7</sup> Case reports have shown benefit of *BRAF*-inhibitor combination treatment for *BRAF* mutated colorectal NEC.<sup>85</sup> The combination of a *BRAF*- and *EGFR*-inhibitor (encorafenib + cetuximab) has EMA/FDA approval for second-line treatment of metastatic colorectal cancer. Although the registration studies only included adenocarcinoma cases, the approval is not limited to these. FDA granted in 2022 accelerated approval for the *BRAF*/MEK inhibitor combination dabrafenib + trametinib for patients with advanced solid tumors with a *BRAF V600E* mutation as a tumor agnostic indication. Other mutations with a targeted therapy available are not frequent in digestive NEC (*KRAS G12C* 3%, *RET* mutations 3%, *HRAS* mutation 0.5%, *NTRK* fusions 0.3%).

#### Recommendation

In *BRAF V600E* mutated digestive NEC cases, a *BRAF* inhibitor combination is an option to consider. Since druggable key mutations are present in NEC, we recommend early molecular profiling by panel sequencing (grade 4A).

## 5.7 | Q10: How should high-grade digestive MiNEN be diagnosed and treated?

### 5.7.1 | How to make the diagnosis of MiNEN and to distinguish it from NEC

Epithelial tumors composed of a neuroendocrine and a non-neuroendocrine component are called in all digestive locations “mixed neuroendocrine-non-neuroendocrine neoplasms” (MiNEN).<sup>86</sup> On HE stained sections the two components are clearly separated, with the arbitrary threshold of 30% each. Therefore, it is impossible to formally diagnose a MiNEN on a biopsy sample, where just a description of the two components is feasible. Moreover, the diagnosis can frequently be missed in biopsies of metastases, as recently shown in 80 digestive MiNEN patients where 71% of patients had only the NEN component present in the metastases.<sup>87</sup> MiNEN are especially frequent in the colon or stomach, in which the adenocarcinoma component is usually combined with LC-NEC.<sup>88,89</sup> They are infrequent in the appendix, since the former “goblet cell carcinoid” is now classified among exocrine tumors as goblet cell adenocarcinoma. The prognosis of colon MiNEN (adenocarcinoma + NEC) is worse than for the adenocarcinoma subtypes<sup>90</sup> and is related to the Ki-67 index of the NEC component.<sup>91</sup> Molecular studies have reported similar profiles in digestive NEC and MiNEN. Colorectal MiNEN and LC-NEC share genetic alterations with adenocarcinomas, such as mutations in *APC*, *KRAS*, *TP53* genes as well as MSI, suggesting a possible common clonal origin.<sup>92</sup>

### 5.7.2 | Treatment of MiNEN

The MiNEN entity is complex and treatment controversial. Surgery is the only potential curative option for initial localized digestive MiNEN. 5-year survival after surgery has been reported to be 20%–50%.<sup>58,89</sup> In seven retrospective studies on digestive NEC/MiNEN, a positive prognostic effect of surgery was indicated with PFS 8–32 months and OS 21–92 months.<sup>93</sup> A recent study found no differences in OS or DFS between high-grade NEN and MiNEN after surgery.<sup>43</sup> This indicates that patients with MiNEN like NEC can benefit from surgery if an R0 resection can be obtained. In a large retrospective study, gastric MiNEN or gastric NEC had a worse prognosis after surgery compared to gastric adenocarcinoma.<sup>58</sup> Possible use of radiotherapy and neoadjuvant chemotherapy in localized MiNEN could be discussed in a multidisciplinary setting, as scarce data are available. The benefit of adjuvant chemotherapy after radical surgery has not been proven for MiNEN, but the high recurrence rate and adjuvant data from digestive NEC and adenocarcinoma support consideration of adjuvant chemotherapy at least in cases with affected lymph nodes. Which adjuvant chemotherapy regimen to use after radical surgery, that is a NEC or adenocarcinoma regimen, might depend on the predominant component, considering always not only the more prevalent, but the more aggressive histology. One option is to base the adjuvant regimen on the tumor component present in the regional lymph nodes. In a study of 80 patients with digestive MiNEN, 69% had only one component metastasized to lymph nodes, usually the more aggressive NEC component (42/55).<sup>87</sup> Lymph node metastatic pattern seemed to be associated with the proportion of the two components within the primary. The high immediate progression rate that platinum/etoposide has for metastatic NEC may question if this regimen is the optimal adjuvant regimen for at least colorectal MiNEN. In a European study, use of adjuvant/neo-adjuvant chemotherapy and chemoradiation were more commonly in adenocarcinoma-like than NEC-like cases.<sup>89</sup> After propensity score matching, no survival benefit was seen for patients receiving adjuvant chemotherapy (134/268 patients) after surgery for stage I–III gastric MiNEN.<sup>58</sup>

Clinical management of metastatic disease is controversial as there are only retrospective series with limited sample sizes. It remains unclear whether MiNEN should be treated as a NEC or an adenocarcinoma. At present, there appears to be two main opinions in the field: Treatment should be based on the predominant histological component or treatment should target the more aggressive component within the tumor, regardless of proportion as even a minor NEC component can impact prognosis. As OS in MiNEN is extremely poor in the majority of patients, with median OS very similar to NEC and the neuroendocrine component is judged by many to be the most relevant one,<sup>89</sup> it has been argued for the use of platinum-etoposide as the backbone treatment of MiNEN. Moreover, this is in line with the finding that most distant metastases are composed of NEC or mixed components, regardless of the proportion of the two components in the primary. Among 34 digestive MiNEN patients, 71% had only the NEN component (68% NEC, 3% NET G2) in the metastases, 26% had both components and one patient (3%) adenocarcinoma only.<sup>87</sup>

The choice of systemic treatment for metastatic digestive MiNEN seems at present to vary considerably whether a NEC regimen (platinum/etoposide) or an adenocarcinoma regimen (5FU-backbone based on primary tumor site) is chosen as the first-line treatment strategy<sup>89</sup> and might depend on clinician (e.g., NEN vs. digestive oncologist) and center experience. Regimens used for digestive adenocarcinoma have proven to be active for digestive NEC in later lines (see Q7). Performing tumor tissue NGS could potentially help to select the systemic treatment for these patients especially if MSI or a BRAF V600E mutation is found.

#### Recommendation

Patients with localized digestive MiNEN should be considered for surgery and adjuvant chemotherapy (grade 3bB). First-line treatment of metastatic MiNEN is controversial, both platinum/etoposide and fluoropyrimidines in combination with oxaliplatin or irinotecan may be considered (grade 5D).

## 6 | SUMMARY

This ENETS guidance study, developed by a multidisciplinary working group, provides up-to-date and practical advice on the diagnosis and management of digestive neuroendocrine carcinoma, based on recent developments and study results. These recommendations aim to pave the road for more standardized care for our patients resulting in improved outcomes. Prognosis is generally poor for digestive NEC, most are advanced at diagnosis and median survival in metastatic disease is 11–12 months. Surgery can be of benefit for localized disease after extensive preoperative imaging. Carboplatin in combination with etoposide is recommended as first-line treatment for metastatic disease. Irinotecan with fluoropyrimidines has the best evidence as second-line treatment. Immunotherapy plays a minor role in biomarker-unselected patients. Molecular profiling if available is encouraged to identify new targets. More prospective clinical trials are highly needed to fulfil the unmet needs in this field, especially on new predictive and prognostic biomarkers and to improve survival of patients with advanced disease.

#### AUTHOR CONTRIBUTIONS

**Halfdan Sorbye:** Conceptualization; data curation; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Enrique Grande:** Data curation; investigation; writing – original draft; writing – review and editing. **Marianne Pavel:** Data curation; investigation; writing – original draft; writing – review and editing. **Margot E.T. Tesselaar:** Data curation; investigation; writing – original draft; writing – review and editing. **Nicola Fazio:** Writing – original draft; writing – review and editing. **Nicholas REED:** Data curation; investigation; writing – original draft; writing – review and editing. **Ulrich Peter Knigge:** Data curation; investigation; writing – original draft; writing – review and editing. **Emanuel Christ:** Writing – original draft; writing – review and editing.

**Valentina Ambrosini:** Writing – original draft; writing – review and editing. **Anne Couvelard:** Data curation; investigation; writing – original draft; writing – review and editing. **Eva Tiensuu Janson:** Conceptualization; data curation; investigation; methodology; writing – original draft; writing – review and editing.

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Halfdan Sorbye has received honoraria for speaker engagements from Novartis, Ipsen, Bayer, SAM Nordic, Pierre Fabre and for single advisory board engagement from Hutchinson, ITM, AAA, Bayer. Enrique Grande has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, Astra Zeneca, Bayer, Blueprint, Bristol Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, IPSEN, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, Astra Zeneca, Astellas, and Lexicon Pharmaceuticals. Marianne Pavel has received honoraria for speaker engagements from AAA, IPSEN, Boehringer-Ingelheim, MSD, Novartis, Amgen, Recordati and Lilly and for advisory boards from AAA, IPSEN, Novartis, Riemser and from Hutchmed for other services. Nicola Fazio has received honoraria for speaker engagements, advisory roles from AAA, Ipsen, Hutchinson, Merck, MSD, Novartis, Pfizer. NF has received research grants from AAA, Ipsen, MSD and Merck. Emanuel Christ has received honoraria for speaker engagements from Novartis, Ipsen, Pfizer, HRA Pharma, Novo Nordisk and AAA and for advisory boards from AAA, Pfizer, HRA Pharma, Recordati Pharma GmbH and Novo Nordisk. Nicholas Simon Reed has received honoraria for speaker engagements, advisory roles or funding of continuous medical education from Novartis/AAA, Ipsen, Bayer, Roche, Eisai, Merck. Ulrich Knigge has received research grants from Novartis, Ipsen, MSD and Debiopharm. Ulrich Knigge has received honoraria for speaker engagements, from Novartis, Ipsen and Pharmanovia. Margot Tesselaar has received honoraria for advisory boards from Novartis, Ipsen and Merck. Valentina Ambrosini has received speakers fees for EANM/ESMIT/ESMO. Eva Tiensuu Janson: has received honoraria for speaker engagements from Ipsen. Anne Couvelard declare no conflict of interests.

#### PEER REVIEW

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/jne.13249>.

## DATA AVAILABILITY STATEMENT

Data Availability are not relevant for a guidance paper

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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## APPENDIX A: Participants of the ENETS Guidance Paper Consensus Meeting – 13 October 2022

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