Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms

Louis de Mestier^{a,b} Jérôme Cros^c Cindy Neuzillet^d Olivia Hentic^b Axel Egal^d
Nelly Muller^b Olivier Bouché^a Guillaume Cadiot^a Philippe Ruszniewski^b
Anne Couvelard^e Pascal Hammel^d

^aDepartment of Hepato-Gastroenterology and Digestive Oncology, Robert-Debré University Hospital, Reims, Departments of ^bGastroenterology and Pancreatology, ^cPathology, and ^dDigestive Oncology, ENETS Centre of Excellence, Beaujon Hospital and Paris-Diderot University, APHP, Clichy, and ^eDepartment of Pathology, ENETS Centre of Excellence, Bichat Hospital and Paris-Diderot University, APHP, Paris, France

Keywords

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Abstract

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) are a heterogeneous subgroup of rare neoplasms that represent about a third of all poorly differentiated neuroendocrine carcinomas (PDNEC). MiNEN combine a neuroendocrine component, usually a PDNEC, and a non-neuroendocrine component, generally an adenocarcinoma, both accounting for at least 30% of the neoplasm. MiNEN are classified as high-, intermediate-, or low-grade malignancies depending on the metastatic potential of the tumour components. High-grade malignant component should be considered even if it represents <30% of the tumour. The prognosis of MiNEN is generally intermediate between those of the two “pure” components composing it. The aim of this comprehensive review of the literature is to suggest a standardized management of MiNEN. An increasing body of evidence suggests that PDNEC components share molecular abnormalities with

their adenocarcinoma counterparts, but also display additional alterations. This advocates for a common origin, and that the presence of a PDNEC component in an adenocarcinoma could indicate a turning point in carcinogenesis.

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Introduction

Neuroendocrine neoplasms (NEN) are a heterogeneous group of rare neoplasms that represent 1% of all digestive malignancies [1]. The 2017 World Health Organization classification of NENs relies on the histological grade, based on the proliferation index (Table 1) [2]. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN), which were previously termed “MANEC” for “mixed adeno-neuroendocrine carcinoma,” are defined by the association of at least two morphologically different neoplastic components, including one neuroendocrine [2–6]. Although heterogeneous, MiNEN are usually highly aggressive neoplasms with poor prognosis and thus should be managed as non-neuroendocrine cancers rather than classical NEN.

Fig. 1. Place of MiNEN in the spectrum of neuroendocrine and non-neuroendocrine neoplasms (adapted from Volante et al. [3]). Between the two extremes of pure neuroendocrine and non-neuroendocrine neoplasms, MiNEN can display various percentages of each component (ranging theoretically from 1 to 99% of the whole neoplasm) as well as various morphological organizations from isolated neuroendocrine cells within a non-neuroendocrine neoplasm to a well-organized neuroendocrine component. Currently, both components composing a MiNEN must represent at least 30% of the whole tumour.

Due to their rarity and heterogeneity, the histogenesis, classification, and therapeutic management of MiNEN are complex and ill-defined. The aim of this review is to discuss the relevance of their pathological classifications and to provide an overview of location-specific clinical and prognostic features while focusing on recent insight into histogenesis and therapeutic issues. To provide a comprehensive and up-to-date review on the current state of knowledge on MiNEN, we searched PubMed, Web of Science and Google Scholar electronic databases for relevant articles published between 1990 and 2016, with no language restrictions, using the following keywords: “mixed neuroendocrine-non-neuroendocrine neoplasm,” “mixed adeno-neuroendocrine carcinoma,” „mixed endocrine-exocrine carcinoma,” “collision tumour,” and “amphicrine tumour.” A total of 141/234 articles fit our criteria for review and analysis, excluding a number of case reports or limited case series.

MiNEN: Definition and Classification

MiNEN are neoplasms with two distinct neuroendocrine and non-neuroendocrine cell populations [2]. They can be morphologically classified into three entities: collision, composite, and amphicrine MiNEN (Fig. 1, 2) [4–

Table 1. The 2017 World Health Organization classification of neuroendocrine neoplasms [2]

	Ki67, %	Mitotic index, mitoses per 10 high-power fields
Grade 1	<3	<2
Grade 2	3–20	2–20
Grade 3	>20	>20
	Grade	Differentiation
G1 neuroendocrine tumour	Grade 1	Well differentiated
G2 neuroendocrine tumour	Grade 2	Well differentiated
G3 neuroendocrine tumour	Grade 3	Well differentiated
G3 neuroendocrine carcinoma	Grade 3	Poorly differentiated
MiNEN	All grades	Association of a neuroendocrine and a non-neuroendocrine component

Fig. 2. Multiple histological patterns of MiNEN. **a** Colon composite MiNEN (left, haematoxylin-eosin-saffron staining, $\times 100$) composed of a mucin-producing adenocarcinoma component (upper right, Alcian blue staining, $\times 200$) intermingled with a poorly differentiated neuroendocrine carcinoma component (lower right, chromogranin A immunolabeling, $\times 200$). **b** Pancreatic collision MiNEN (left, haematoxylin-eosin-saffron staining, $\times 50$) composed of a well-differentiated adenocarcinoma (upper right, haematoxylin-eosin-saffron staining, $\times 100$), separated by a fibrous band from a poorly differentiated small-cell carcinoma (lower right, haematoxylin-eosin-saffron staining, $\times 100$). **c** Pancreatic

amphicrine MiNEN (left, haematoxylin-eosin-saffron staining, $\times 100$) with cells expressing both neuroendocrine (upper right, chromogranin A immunolabeling, $\times 100$) and acinar (lower right, Bcl-10 immunolabeling, $\times 100$) differentiation markers. **d** Pancreatic ductal adenocarcinoma entrapping and invading a neuroendocrine islet (haematoxylin-eosin-saffron staining, $\times 200$). The neuroendocrine cells have features of transdifferentiation toward an exocrine phenotype (cytoplasmic mucin in clarified cells). This confirms “ductuloinisular” pancreatic cell plasticity but should not be mistakenly diagnosed as MiNEN.

7]. Collision MiNEN may be morphologically suspected by the juxtaposition without mixing of two coexisting, malignant cell populations that do not usually have a common precursor and that remain topographically separate without transition between the two. Composite MiNEN involve two morphologically distinct components that coexist in an intermingled population, or with one predominant component and a focal area of another minority component. Diagnosis of MiNEN is usually facilitated by the presence of at least one well-differentiated

component (Fig. 2a, b). However, the two components may be difficult to identify with conventional morphological techniques, particularly when they are poorly differentiated, and their identification may require additional immunohistochemical techniques. In addition to morphological features, the diagnosis of adenocarcinoma is helped by the histochemical Alcian blue staining and the immunohistochemical expression of cytokeratins, or Bcl-10 for acinar-cell carcinoma [2].

Amphicrine MiNEN is composed of a single cell population that displays the phenotypes of at least two neoplasms. These neoplasms are exceptional and have been described in the stomach, pancreas, appendix, and colon [8, 9]. They mostly associate neuroendocrine and adenocarcinoma phenotypes, with their cytoplasm containing both neuroendocrine secretory granules and mucin droplets. Amphicrine carcinomas with acinar-cell and neuroendocrine (mostly poorly differentiated neuroendocrine carcinomas – PDNEC) features may also develop in the pancreas (Fig. 2c) [10].

Each component of a MiNEN must theoretically account for at least 30% of the whole neoplasm (Fig. 1) [11]. This threshold was arbitrarily proposed in 1987 [3, 5]. It was hypothesized that the prognosis was influenced by the predominant histological component rather than one accounting for <30% of the entire neoplasm. Besides, it aims at preventing clinicians from managing too often these rare neoplasms without treatment guidelines. Nevertheless, a minor (i.e., <30%) PDNEC component can impair prognosis [12–14]. In addition, this cut-off value only applies to resected samples after examination of the entire neoplasm specimen and particular caution should be taken when evaluating biopsy specimens due to a potential sampling bias (Table 2). The definition of MiNEN also excludes non-neuroendocrine neoplasms with a scattered expression of neuroendocrine markers with no identifiable neuroendocrine cell morphology. This is frequent (40–80% depending on the location) when systematically studying neuroendocrine marker immunostaining in resected adenocarcinoma specimens [6, 7, 12]. It has no or uncertain prognostic influence, although a positive impact has been suggested in oesophageal adenocarcinoma [13], whereas a negative one was evoked in gastric adenocarcinoma [15, 16], cholangiocarcinoma [17], and colorectal adenocarcinoma [18, 19]. Nevertheless, it does not yield therapeutic changes. Hence, systematic search for neuroendocrine marker expression in adenocarcinomas may lead to a risk of over-diagnosed pseudo-MiNEN and should not be performed unless a distinct cell component with neuroendocrine morphology is suspected.

In the previous World Health Organization NEN classifications, MiNEN was referred as MANEC for “mixed adeno-neuroendocrine carcinoma,” which was not representative of all MiNEN and did not take into account their heterogeneity, since (1) all non-neuroendocrine components are not only adenocarcinoma, but can also be squamous-cell carcinoma, and (2) all MiNEN are not carcinoma, especially those that combine two low-grade

Table 2. Proposal for exploration of neuroendocrine differentiation in case of MiNEN suspicion

<i>Circumstances</i>		
– Observation of a well-differentiated neuroendocrine morphology with an organoid/nodular/solid/trabecular growth pattern		
– Observation of a poorly differentiated component (small- or large-cell type)		
<i>Methods</i>		
– Paraffin-embedded blocks of each cm of tumour to take into account intra-lesion heterogeneity in the quantification of each component		
– Identification of neuroendocrine cell morphology		
– Identification of neuroendocrine markers		
1st choice: chromogranin A and synaptophysin		
2nd choice: CD56 (especially for poorly differentiated carcinoma)		
– Identification of the main prognostic factors: grading (differentiation, Ki67) and lymphovascular invasion (and which component)		
<i>Current conclusions</i>		
– MiNEN (each component accounts for ≥30% of the neoplasm)		
– Non-neuroendocrine neoplasm with focal neuroendocrine component (the neuroendocrine component accounts for <30% of the neoplasm)		
– Non-neuroendocrine neoplasm with focal neuroendocrine marker expression (no neuroendocrine component is identifiable morphologically)		

Table 3. Classification of MiNEN according to their grade of malignancy

	Non-neuroendocrine component	Neuroendocrine component
High-grade MiNEN	Carcinoma ^a or adenoma	Poorly differentiated neuroendocrine carcinoma (G3) of small- or large-cell type
Intermediate-grade MiNEN	Carcinoma ^a	Well-differentiated neuroendocrine tumour (G1–G2)
	Amphicrine carcinomas	
Low-grade MiNEN	Adenoma	Well-differentiated neuroendocrine tumour (G1–G2)

Adapted from La Rosa et al. [6]. ^a Carcinoma generally consists of adenocarcinoma but can be squamous-cell or acinar-cell carcinoma as well.

components, explaining that the abbreviation “MANET” for “mixed adeno-neuroendocrine tumour” had been proposed [6].

La Rosa et al. [6, 12] proposed a classification of MiNEN based on malignancy grade that takes into account the heterogeneity of these malignancies (Table 3). High-grade MiNEN generally combine a non-neuroendocrine carcinoma (usually adenocarcinoma, but possibly squamous-cell carcinoma or acinar-cell carcinoma in the pancreas as mentioned above) or an adenoma (villous or tubulo-villous) with a PDNEC component, which is generally more aggressive [20–24]. The prognosis of intermediate-grade MiNEN is generally determined by the non-neuroendocrine component rather than the G1 or G2 NET component. However, both components can metastasize in a poorly predictable fashion. Finally, low-grade MiNEN associate a G1 or G2 NET and a less aggressive non-neuroendocrine component, i.e. adenoma [6]. The latter has mainly been described in the stomach [25, 26], ileum [27], and colon/rectum [28, 29].

Overall, with the exclusion of the low-grade neoplasms, MiNEN are generally highly aggressive neoplasms with poor prognosis and thus should be managed as non-neuroendocrine cancers rather than classical NEN. Finally, the degree of differentiation of a “pure” non-neuroendocrine neoplasm component may have a prognostic implication (for example, in gastric, pancreatic, or colonic adenocarcinoma, or oesophageal squamous-cell carcinoma) but with no or limited therapeutic consequences. Similarly, it appears to be irrelevant in MiNEN and is not part of the proposed grade classification [6, 12].

Organ-Specific Features and Prognosis

MiNEN usually originate from organs that contain neuroendocrine cells and in which “classical” NENs are known to develop, such as pancreas, appendix, colon, and to a lesser degree small intestine [3, 7, 12].

Oesophagus

MiNEN usually develop in the lower third portion of the oesophagus and are highly malignant [6, 12]. Rare cases of amphicrine MiNEN with multiple differentiation phenotypes (adenocarcinoma, neuroendocrine and squamous-cell carcinoma) have been reported [7]. In a series of 40 patients with oesophageal PDNEC, an adenocarcinoma or squamous-cell carcinoma component was found in 38 and 3% of cases, respectively [30]. MiNEN were less

frequently metastatic than “pure” PDNEC (25 vs. 54%, $p = 0.036$), and patient survival was better (28 vs. 15 months, $p = 0.031$).

Conversely, a focal neuroendocrine component can be found in 8% of oesophageal adenocarcinomas, and could be associated with a more favourable tumour stage, but similar survival [13].

Stomach

Gastric MiNEN account for approximately 7% of all gastric NEN and 25% of all gastric PDNEC, although their prevalence has not been specifically explored [14, 20, 31]. They are usually highly malignant and combine a well-differentiated adenocarcinoma and a PDNEC component, the latter commonly developing from deeper layer of the gastric wall [6, 12, 32, 33]. In fact, some studies from Asian countries reported that nearly 70% of gastric PDNEC contained at least a minor adenocarcinoma component [31, 34]. Should this be confirmed and replicated in Western countries, it would question the existence of true “pure” PDNEC of the stomach, which might all be associated with adenocarcinoma. Intermediate-grade MiNEN combining type 1 gastric NEN and adenocarcinoma have also been described, mainly in the setting of chronic atrophic gastritis [6].

Survival of patients with gastric MiNEN is similar or slightly better than that of patients with “pure” gastric PDNEC [14, 20, 31–33]. The threshold of 30% for the PDNEC component in gastric MiNEN has been questioned [14, 33]. In one series including 88 patients with non-metastatic MiNEN, the estimated cut-off above which the PDNEC component negatively influenced prognosis was 10% [14]. Indeed, the 5-year survival rates of patients treated for a gastric adenocarcinoma were 86 and 53% if they contained less or more than 10% of a PDNEC component, respectively ($p < 0.0001$). Conversely, there was no difference in survival among all neoplasms with a PDNEC component accounting for >10%, including in patients with “pure” PDNEC, regardless of the extent [14]. Hence, although this warrants confirmation studies and validation in Western population, it underlines that the current 30% arbitrary threshold may have insufficient prognostic value, and irrelevant therapeutic consequences.

Pancreas

Pancreatic MiNEN represent 0.5% of all pancreatic adenocarcinomas [10] and 5% of all pancreatic NEN [35]. Their diagnosis is limited by a sampling bias due to the small samples obtained using endoscopic ultrasound-

guided fine-needle aspiration [36–38]. The neuroendocrine component is usually a large-cell type PDNEC, but can occasionally be a well-differentiated G1 or G2 NET [12, 39]. When the neuroendocrine component is well differentiated, a hormone secretory syndrome may occur similarly to “pure” pancreatic NET [40, 41]. The non-neuroendocrine component may have a ductal or acinar phenotype. Although association of intraductal papillary mucinous neoplasms and NET might not always be random [42, 43], true MiNEN with both of these components are very rare but do exist [44, 45]. Of note, 40–80% of pancreatic adenocarcinomas entrap neuroendocrine islets, which may lead to over-diagnosing MiNEN (Fig. 2d) [10, 46, 47]. Similarly, 5–10% of pancreatic NEN may entrap non-neoplastic ductules, and these “ductuloinsular” NEN should not be mistakenly diagnosed as MiNEN [10, 48, 49]. The prognosis of pancreatic MiNEN is intermediate between pure adenocarcinoma and pure G1–G2 NET [38, 39], and similar to that of “pure” PDNEC [35, 39, 50].

Pancreatic acinar-cell type carcinoma is rare (1–2%). It contains a neuroendocrine component accounting for >30 or <30% of the neoplasm in 30 and 15–30% of cases, respectively [50]. Both components can coexist separately, or form composite MiNEN with intermingled cell populations, whose morphological identification may be difficult but facilitated by immunohistochemical evidence of neuroendocrine (chromogranin-synaptophysin) and acinar (Bcl-10) components (Fig. 2c) [10, 38, 45, 50]. The presence of a neuroendocrine component in an acinar-cell carcinoma could improve its prognosis [51].

Biliary Tract and Gallbladder

MiNEN arising from extrahepatic bile ducts and the gallbladder account for 5 and 35%, respectively, of all cholangiocarcinomas and NEN of these primary sites [52, 53]. Conversely, intra-hepatic biliary MiNEN are extremely rare [12]. These neoplasms are generally composed of PDNEC and pleomorphic adenocarcinoma [12]. The median overall survival of patients affected (12.2 months) appears to be slightly better than those with “pure” biliary PDNEC (9.6 months) [52, 53].

Duodenum and Ampulla of Vater

MiNEN can develop in the duodenum and often combine an intestinal-phenotype adenocarcinoma with a well-differentiated somatostatin-secreting NET. They are mostly superficial, not highly aggressive, and distant spreading is rare [7].

Some 30 cases of ampullary MiNEN have been reported in the literature [52, 54, 55]. The neuroendocrine com-

ponent is usually located in the deepest layers; thus, most lesions are misdiagnosed as adenocarcinoma before surgical resection [55]. Half of ampullary MiNEN have an intermediate grade of malignancy, combining well-differentiated G1–G2 NET and adenocarcinoma components that generally have an intestinal phenotype with a better prognosis than bilio-pancreatic phenotype.

Small Intestine

MiNEN originating from the jejunum and ileum are rare. They usually include a well-differentiated NET associated with an adenoma or adenocarcinoma component, with an intermediate grade of malignancy [4, 6]. MiNEN with a PDNEC component are exceptional, like “pure” PDNEC from these primary sites.

Appendix

Appendicular MiNEN, previously called “adenocarcinoid tumours,” account for about 10% of all appendicular malignancies [56]. They usually involve both adenoma and well-differentiated neuroendocrine components, explaining the usually intermediate or low grade of malignancy. Most appendicular MiNEN are discovered at the systematic pathological examination of resected surgical specimens in patients operated on for an acute appendicitis, although 20–30% are identified incidentally [57–59]. Their prognosis is much worse than that of “pure” appendicular well-differentiated NEN and rather close to that of adenocarcinoma, depending on the rate of adenocarcinoma component and the presence of signet-ring adenocarcinoma [56–61]. Indeed, in a recent analysis of the SEER database, median overall survival for patients with appendix MiNEN was 6.5 years, while it was 2.1, 13.8, and 39.4 years for those with signet-ring cell carcinoma, goblet-cell carcinoid and typical NET [56].

Besides, “goblet-cell carcinoids” are calciform-type neoplasms that include mucus-secreting cells developing from the submucosa, with signet-ring cell morphology. Although they can have scattered neuroendocrine differentiation, they may rather be considered peculiar adenocarcinoma arising from the “appendicular glands” and should not be classified as NEN [6, 60]; thus, detailed description will not be provided herein. Finally, tubular-type appendicular carcinoids are not MiNEN but low-grade NET with glandular architecture.

Colon and Rectum

Colorectal MiNEN are among the most frequent types of MiNEN. “Pure” NET and MiNEN accounted for 1.1 and 2.4% of 988 surgically resected colorectal neoplasms,

Fig. 3. Hypothesis of colorectal MiNEN development during the adenoma-adenocarcinoma multi-step sequence. The PDNEC component of colorectal MiNEN harbours additional molecular alterations in addition to those shared with their associated adenocarcinoma/adenoma component, such as mutations in the *CDKN2A*, *PAX6*, *SMARCA4*, or *INT2* genes, those encoding for

proteins of the *APC*/β-catenin pathway, or those involved in the *AKT*/mTOR pathway. Inspired by the colorectal carcinogenesis sequence proposed by Vilar and Gruber [98]. MMRp, mismatch repair proficient; MMRd, mismatch repair deficient; PDNEC, poorly differentiated neuroendocrine tumour.

respectively [62]. Rectal MiNEN only accounted for 1–3% of rectal NEN, while colonic MiNEN represent 14–20% of colonic NEN [63, 64].

Most colonic NEN (85%) are PDNEC, which contain a non-neuroendocrine component in 25–40% of cases [21, 65–68]. The latter is usually an adenocarcinoma, but adenoma or squamous-cell carcinoma is found in about 45–65, 30–35%, and 5% of cases, respectively, mostly arising from the mucosa, while the neuroendocrine component frequently develops from deeper layer of the colon wall and may be missed when no further resection of the primary tumour is performed following biopsies.

The prognosis of colorectal MiNEN is worse than that of “pure” adenocarcinoma, and closer to that of PDNEC, especially at metastatic stage [21, 63]. The metastatic risk seems correlated to the grade of the neuroendocrine component [66]. Accordingly, when the latter is a PDNEC, it is almost always present in metastases, while the adenocarcinoma is only present in about 30% of cases [66]. When the neuroendocrine component is well-differentiated, the type of cell population in the metastases is difficult to predict and does not always correspond to the most aggressive or most prevalent component in the primary tumour [66].

Finally, approximately 5% of colorectal MiNEN have a low grade of malignancy, combining tubulovillous

adenoma with G1–G2 NET. They usually present as polyps <3 cm in diameter and can occasionally cause a carcinoid syndrome [6, 66, 69].

Pathogenesis and Molecular Findings

The carcinogenesis of MiNEN has still not been elucidated, due in part to the lack of preclinical models. Although common origin and precursor may be suggested by amphicrine MiNEN [8], this is less evident for collision or composite MiNEN [6]. Molecular studies uniformly reported that when the neuroendocrine component is poorly differentiated, it shares similar genomic abnormalities than the adenocarcinoma component which supports a common origin, whatever the site of primary. Regardless the methodology used (including SNP chips and next generation sequencing), the two components display loss of heterozygosity (LOH) at multiple loci and mutations in key oncogenes, such as the *APC*, *TP53*, or *RB* genes [34, 66, 67, 70–74]. These studies also showed that the PDNEC component contains additional mutations compared to the adenocarcinoma counterpart (Fig. 3) [66, 70–75].

Besides, radiotherapy and chemotherapy might favour genomic instability and transdifferentiation towards the

PDNEC component, based on observations that the number of neuroendocrine markers-positive cells increased following neo-adjuvant treatments [18, 65]. This strongly suggests that the PDNEC component develops during a classic adenoma-adenocarcinoma sequence. Such event can occur at various stages, including early stages such as adenoma, since cases of MiNEN combining PDNEC and adenoma, without adenocarcinoma, have been reported (Fig. 3) [66, 71].

PDNEC mutational signature seems more specific of their primary locations and similar to that of adenocarcinomas of same site, rather than a common neuroendocrine signature [66, 67, 70–73, 75–77]. For instance, the molecular study of 867 PDNEC of various origins showed that *CDKN2A/B* and *APC* mutations were present in 27 and 3% of pancreatic PDNEC (28.3 and 2.5% in pancreatic adenocarcinomas [78]), respectively, compared to 6 and 47% of colon PDNEC (9.8 and 49.3% in colon adenocarcinomas [78]), respectively [79]. In addition, 10–15% of PDNEC and MiNEN originating from colon, rectum, or stomach have a mismatch repair-deficient phenotype [21, 24, 75, 80]. These neoplasms have an increased methylation profile and prolonged survival, similar to what is observed in elderly patients with sporadic colorectal adenocarcinoma and mismatch repair deficiency due to the methylation of promoter of specific genes, which supports a common carcinogenic pathway between PDNEC/MiNEN and adenocarcinoma. It could be possible that these patients with such mismatch repair-deficient metastatic MiNEN might benefit from immunotherapy; accumulating evidence shows that this is possible in those with colorectal adenocarcinoma [81].

Conversely, well-differentiated NET components of MiNEN do not harbour similar genetic alterations described in the adenoma/adenocarcinoma counterpart, such as LOH of *APC*, *KRAS*, and *TP53*, but display specific alterations that are usually found in NET (but not PDNEC), such as LOH of *VHL* [66, 72, 80]. Although these low-grade MiNEN may indicate an earlier stage of carcinogenesis, they may also represent true collision MiNEN with an independent carcinogenic pathway.

Management of MiNEN

The treatment of MiNEN has not been codified yet due to their rarity and heterogeneity. Figures 4 and 5 show our suggestions for the management of both non-metastatic and metastatic MiNEN, respectively. Generally, aggressiveness and prognosis are driven by the most aggressive

neoplastic component [3, 4, 6, 7]. In localized MiNEN of the digestive tract, endoscopy-guided tumour biopsies may not reach the neuroendocrine component for the reasons exposed before, thus potentially leading to its under-diagnosis.

The treatment of metastatic MiNEN should logically target the neoplastic component responsible for the metastatic spreading rather than rely on the characteristics of the primary, since the neuroendocrine and non-neuroendocrine components can metastasize together but also separately, even in collision MiNEN [82]. Nevertheless, metachronous metastases are rarely biopsied, and nuclear medicine tools cannot help distinguishing between adenocarcinoma and PDNEC because, for example, both components display ¹⁸FDG positron-emitting tomography positivity, and negative somatostatin receptor scintigraphy due to lack of somatostatin receptors expression [83]. The cell type present in tumour emboli on resected primary tumours may be similar to that found in lymph node and distant metastases; thus, its analysis could be an alternative to metastasis biopsy [22].

High-Grade MiNEN

The prognosis of localized high-grade MiNEN is better than that of “pure” PDNEC. Similarly, they should be treated by curative-intent surgery whenever feasible [84]. Surgical resection of localized pancreatic MiNEN containing acinar-cell carcinoma might improve survival [50, 63, 66]. The potential benefit of adjuvant treatments following resection of localized MiNEN is still undefined, although some retrospective data have suggested a favourable effect [24, 30, 38, 39, 68, 85].

Like in “pure” PDNEC and adenocarcinoma, the benefit/risk ratio does not seem to support performing extensive surgical resection in locally advanced MiNEN [63, 84]. The first-intent treatment of an advanced disease should include systemic chemotherapy combining etoposide and a platinum salt by analogy with PDNEC, and notably because the expression of ERCC1 (protein repairing the DNA damages caused by platinum salts) may be stronger in MiNEN than in adenocarcinoma of same location [24]. Upon progression, the first-line etoposide-platinum regimen could be reintroduced if this disease is controlled without chemotherapy for >3 months [84]. Otherwise, the use of combinations of 5-fluorouracil and irinotecan or temozolomide [63, 84] or amrubicin has been suggested [86–88]. Limited data reported that somatostatin receptor (SSTR2) expression was very uncommon in gastric (0/8) [20], colon (0/8) [68], or biliary (2/9) [53] high-grade MiNEN. Hence, long-acting somatosta-

Fig. 4. Proposal for standardization of the management of non-metastatic MiNEN. The mainstay of treatment of non-metastatic MiNEN and the only chance of cure remains surgical resection. If an adjuvant treatment is indicated, or if the neoplasm is not resectable, the type of chemotherapy depends on the grade of malignan-

cy of each component. 5FU, 5-fluorouracil; Doxo, doxorubicin; DTIC, dacarbazine; GEM, gemcitabine; IRI, irinotecan; OX, oxaliplatin; STZ, streptozotocin; TEM, temozolomide; VP16, etoposide.

tin analogues or peptide-radionuclide radiation therapy must not be used in high-grade MiNEN, similarly to “pure” NEC.

When metastases contain a prominent adenocarcinoma component, which is rare because the PDNEC is almost always – at least in part – present in metastases, treatment should be similar to that given for “pure” adenocarcinomas [63].

Intermediate-Grade MiNEN

Like in high-grade MiNEN, curative-intent resection of localized disease should be proposed whenever possible, followed by adjuvant chemotherapy depending on the pathological factors of relapse [61, 63, 68, 84]. In case of metastases, primary tumour resection can be discussed, when symptomatic, following organ-specific cancer guidelines (mainly for colorectal neoplasms). Systemic chemotherapy regimens should be tailored based on a panel of agents that have shown to be effective in both digestive adenocarcinomas and NET (Fig. 4, 5).

Fig. 5. Proposal for standardization of management of metastatic MiNEN. The treatment should target the components present within the metastases, depending on their respective grades of malignancy.

Low-Grade MiNEN

Since these neoplasms combine adenoma and well-differentiated G1–G2 NET components, the prognosis is driven by the latter component as it can metastasize, and thus should be the targeted. Localized tumours should be surgically resected, or endoscopically for those located within an accessible site of the gastrointestinal tract [6, 66, 89]. For locally advanced tumours, a curative-intent surgical resection with lymphadenectomy should be performed. Treatment in the rare cases of metastatic forms, which usually originate from the NET component, should be similar to that of “pure NET” of the same origin based on current guidelines [90, 91]. Especially, metastatic low-grade MiNEN (and metastatic intermediate-grade MiNEN with predominant NET component) frequently express type 2 somatostatin receptors (SSTR2) and could be

treated with long-acting somatostatin analogues [92, 93] and/or peptide-radionuclide radiation therapy [94], since survival benefit was demonstrated in “pure” NET with these treatments. For the same reasons, everolimus could be useful in these patients [95, 96], although the frequent mutations of the Akt/mTOR pathway seen in “pure” NET have not been specifically explored in MiNEN [97].

Conclusion

The grade of MiNEN depends on the metastatic and life-threatening potential of each component. The most common forms combine adenocarcinoma and PDNEC components, with prognosis being intermediate between that of “pure” adenocarcinoma and that of “pure”

PDNEC of same origin. Therapeutic management should be based on the most aggressive neoplastic component, which can only be reliably determined by the analysis of a resected specimen, even if it accounts for less than 30% of the neoplasm.

The unresolved question about the existence of “pure” PDNEC should be further explored. Future research should confirm whether the PDNEC component of MiN-EN is a result of additional genomic alterations in an adenocarcinoma; otherwise, to identify the pathogenic pathways involved in this carcinogenic “turning point” is strongly needed, in particular using whole-genome sequencing. More accessible genomic material should be studied, such as circulating tumour cells or DNA; these liquid biopsies could be an innovative approach to more broadly characterize the genetic landscape of MiNEN. Finally, the minimum percentage from which each neoplastic component has a prognostic impact must be specified (and especially in biopsy samples, which do not take neoplasm heterogeneity into account, in contrast to surgical specimens), in order to determine which patients may benefit from the most targeted treatment.

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Author Contributions

Study concept and design: L.M., J.C., P.H. Acquisition of data: L.M., J.C., C.N., P.H. Analysis and interpretation of data: L.M., J.C., C.N., O.H., N.M., G.C., P.R., A.C., O.B., P.H. Drafting of the manuscript: L.M., J.C., C.N., A.C., O.B., P.H. Critical revision of the manuscript for important intellectual content: L.M., J.C., C.N., O.H., N.M., G.C., P.R., A.C., O.B., P.H. Study supervision: L.M., G.C., P.R., A.C., O.B., P.H.

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