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Contents

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Contents

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Contents

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MINIREVIEWS

Mixed neuroendocrine non-neuroendocrine neoplasms in gastroenteropancreatic tract

Sebastián Díaz-López, Jerónimo Jiménez-Castro, Carlos Enrique Robles-Barraza, Carlos Ayala-de Miguel, Manuel Chaves-Conde

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Abstract

Mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) are a heterogeneous group of malignant neoplasms that can settle in the gastroenteropancreatic tract. They are composed of a neuroendocrine (NE) and a non-NE component in at least 30% of each tumour. The non-NE component can include different histological combinations of glandular, squamous, mucinous and sarcomatoid phenotypes, and one or both of the components can be low-or high grade malignant. Recent changes in the nomenclature of these neoplasms might lead to great deal of confusion, and the lack of specific clinical trials is the main reason why their management is difficult. The review aims to clarify the definition of MiNEN and analyze available evidence about their diagnosis and treatment options according to their location and extension through careful analysis of the available data. It would be important to reach a general consensus on their diagnosis in order to construct a classification that remains stable over time and facilitates the design of clinical trials that, due to their low incidence, will require long recruitment periods.

Key Words: Mixed neuroendocrine non-neuroendocrine neoplasms; Mixed adeno-neuroendocrine carcinomas; Mixed tumours; Gastroenteropancreatic; Treatment; Etiology; Diagnosis

Core Tip: In this review we try to clarify definition of mixed neuroendocrine (NE) non-NE tumours that have been changed along past years and analyze available evidence about their diagnosis and treatment options according to their location and extension. We have to bear in mind that we do not have validated protocols or clinical guidelines on the management of this group of diseases, although most authors propose treating mixed NE non-NE neoplasm with the high-grade NE component as treatment target. In any case, the lack of high-quality scientific evidence, based on randomised clinical trials, makes it essential to deepen our knowledge of this group of neoplasms.

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INTRODUCTION

The first description of the mixed tumour (neuroendocrine non-neuroendocrine tumour) was given by Cordier who, defined a gastric tumour with an endocrine and an exocrine component in 1924[1]. In 1987, Lewin[2] proposed a group of mixed glandular-endocrine composite tumours inside carcinoid tumours and divided them into three categories: collision, composite and amphicrine[3]. In 2000, a classification of endocrine neoplasms was adopted that included mixed exocrine-endocrine carcinomas, with each component present in at least 30% of the tumour. This cut-off point was established because it is very unusual for a less represented component to influence the biological behaviour of the cancer [4,5]. In 2010, the World Health Organization (WHO) International Histological Classification of Tumours[6] classified the mixed neoplasms composed of a neuroendocrine (NE) and an exocrine component as "mixed adeno-neuroendocrine carcinomas" (MANECs) and, in 2017, the term MANEC was reclassified as "mixed neuroendocrine non-neuroendocrine neoplasm" (MiNEN)[7], with the term "exocrine" being replaced by the more general term "non-neuroendocrine" to include all the possible histological variants, which are glandular, squamous, mucinous and sarcomatoid phenotypes, and the term "carcinoma" being replaced by the term "neoplasm" because sometimes one or both components are low-grade malignant[8,9]. Figure 1 shows the evolution of this concept over the years.

MiNEN classifies the heterogeneous spectrum of possible combinations of NE and non-NE elements, and the combinations of morphologies are largely determined by site of origin. Non-NE neoplasms with focal NE differentiation (NNE-NED) are non-NE neoplasms that show NE differentiation but do not reach the 30% threshold, so do not meet the criteria for consideration as MiNENs. This threshold was established arbitrarily and may change in the future as we learn more about these malignancies[10].

In 2006, a classification system for NE neoplasms was proposed based on the Ki-67 index and was formally adopted by the WHO classification in 2010. Thus, NE tumours with low Ki-67 scores (≤ 20%-grade 1 or 2) were called NE tumours (NETs), while tumours with high Ki-67 scores (> 20%-grade 3) were divided into two types: Poorly differentiated tumours, called NECs, and well-differentiated tumours, as for Grade 1 and 2 tumours, were called NETs. Any NE neoplasm, whether NET or NEC, can constitute the NE component of a MiNEN. In Table 1, we can see the classification of the NE component according to morphology, mitoses and differentiation[6-9,11]: Most MiNENs have a poorly differentiated NE component and are usually diagnosed in advanced stages, while low-grade MiNENs are rare and mainly located in the gastrointestinal tract[5,12].

Morphologically, they can be divided into three types: collision, compound and amphicrine, summarised in Table 2 [13].

LITERATURE REVIEW

The methodology used in this article is a narrative review through careful analysis of the available data. We conducted a PubMed search of articles published in English up to and including July 2023, using the terms "mixed tumours", "mixed neuroendocrine non-neuroendocrine neoplasms", "mixed adeno-neuroendocrine carcinomas", "gastroenteropancreatic tract", "treatment", "etiology", and "diagnosis". No exclusion criteria were used. We selected articles based on their relevance and interest to the review. Some additional articles were retrieved from the reference lists of previously selected articles.

ETIOLOGY AND PHYSIOPATHOLOGY

There are three theories about the origin of MiNENs, the first proposing that both components derive from a common pluripotent stem cell progenitor that achieves the NE and non-NE phenotypic differentiation during carcinogenesis (Figure 2). The second one also defends a monoclonal origin but with a gradual process, NE trans/dedifferentiation developing from a non-NE epithelial phenotype by the progressive accumulation of genetic aberrations that can include

Table 1 Classification of neuroendocrine component according to morphology, mitoses, and differentiation

Neuroendocrine component	Mitotic index	Ki-67
NET G1	Mitotic index < 2 per 10 high-power field	Ki-67 < 3%
NET G2	Mitotic index 2-20 high-power field	Ki-67 3%-20%
NET G3	Mitotic index > 20 high-power field	Ki-67 > 20%
Poorly differentiated neuroendocrine cancers	Mitotic index > 20 high-power field	Ki-67 > 20%

NET: Neuroendocrine tumours; G: Grade.

Table 2 Types of mixed neuroendocrine non-neuroendocrine neoplasm according to morphology

Types	Description
Collision	The juxtaposition of two populations of coexisting malignant cells that generally do not have a common precursor and are separated with no transition zone between the two
Composite	Two morphologically distinct components that coexist in an intermixed population or with a predominant component and a focal area of another minority component
Amphicrine	A population of single cells that display the phenotypes of at least two neoplasms

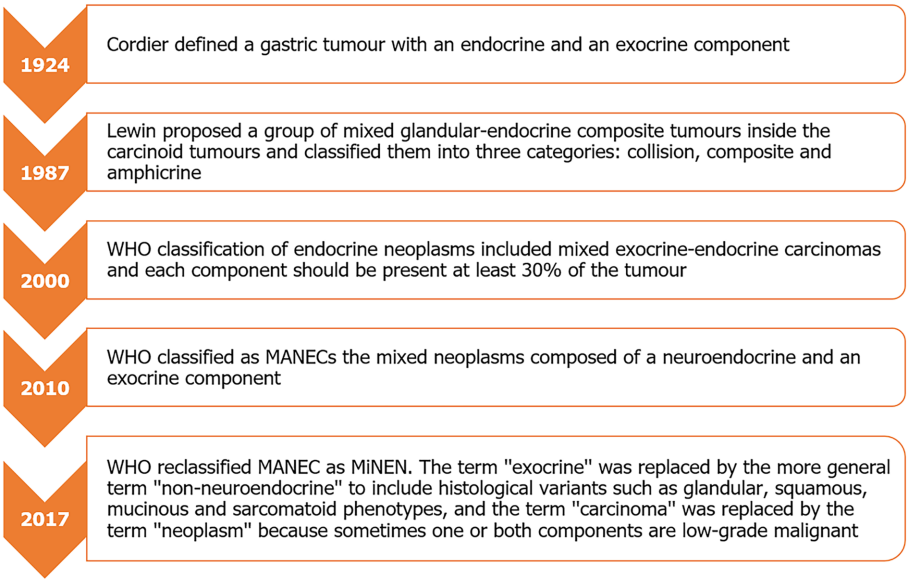

Figure 1 Evolution of the current concept over the years. MANECs: Mixed adeno-neuroendocrine carcinomas; MiNEN: Mixed neuroendocrine non-neuroendocrine neoplasms; WHO: World Health Organization.

stromal microenvironmental changes (Figure 3). The third one establishes that both components emerge differently from precursor cells in a synchronous or metachronous way (Figure 4)[8,14-18].

The first two hypotheses are the most accepted because the majority of chromosomal and genetic abnormalities are found in the NE component rather than the non-NE component, and they suggest that progression from a non-NE to a NE cell phenotype is more frequent. It is assumed that a specific genomic event or catastrophe-a chromoptisis-occurs in an adenocarcinomatous polyp. Among the notable genetic alterations, it has been suggested that the inactivation of SMARC4A and the activation of c-MYC are driver mutations responsible for the transdifferentiation of adenocarcinoma (ADC) to a NE phenotype. TP53 is the most common mutation in MiNEN and the NE component often acquires more mutations than the non-NE component[14,16,19-21].

EPIDEMIOLOGY AND LOCATIONS IN GASTROENTEROPANCREATIC TRACT

The incidence and prevalence of MiNENs are not clear and are probably underestimated. According to the Rare Cancer Surveillance (RARECARE) project of the European Union, in 2008 the incidence was less than 0.1/100000 people per year

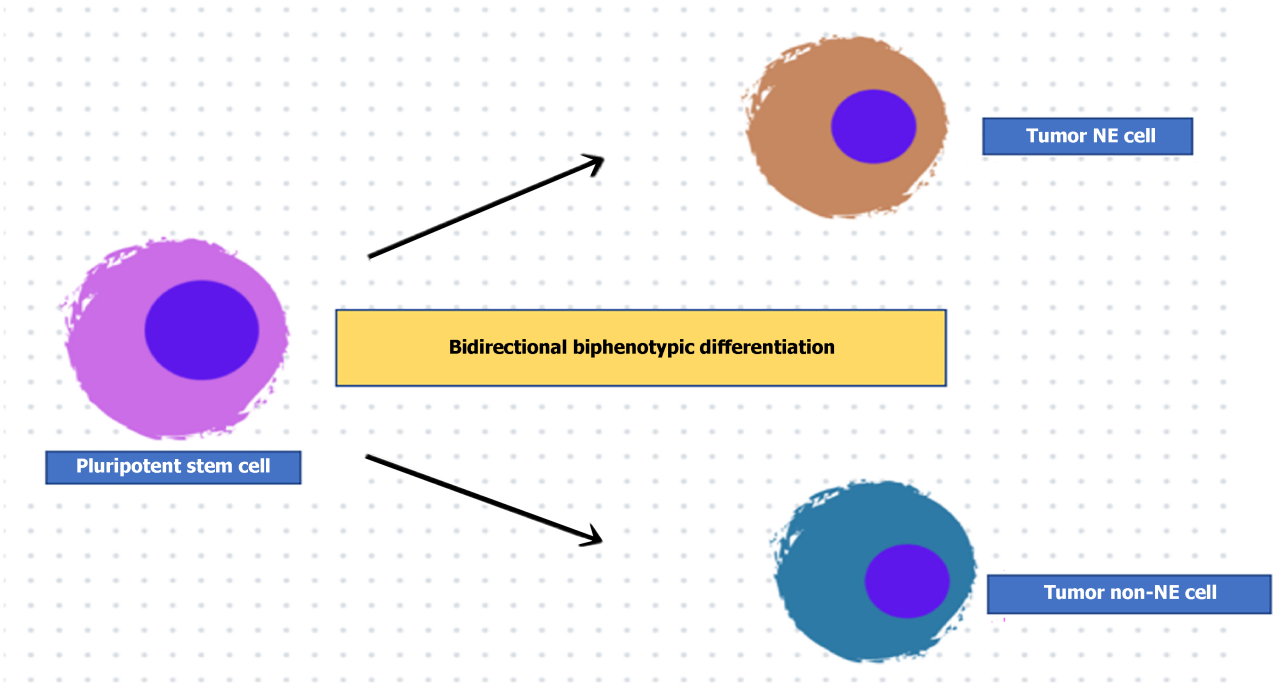

Figure 2 Origin according to the theory of a common pluripotent stem cell progenitor. Non-NE: Non-neuroendocrine; NE: Neuroendocrine.

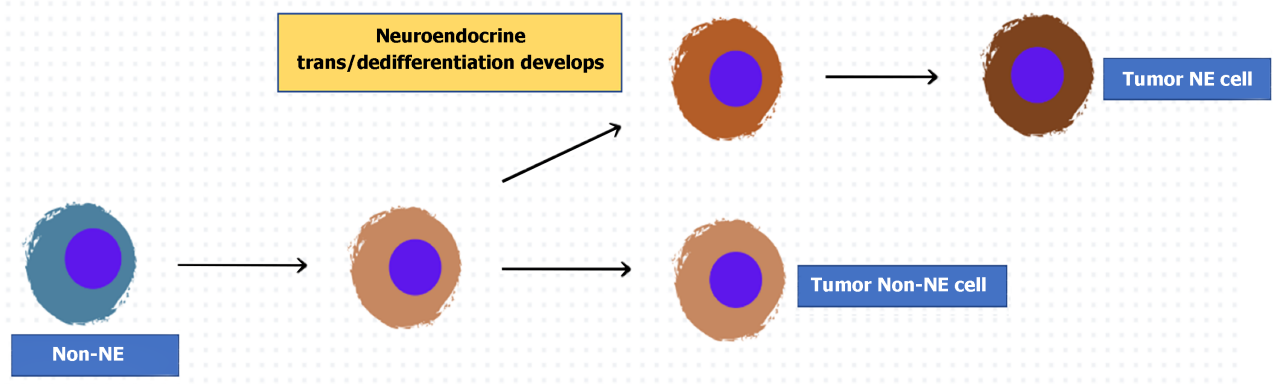

Figure 3 Origin according to the theory of a common monoclonal origin with a gradual process, neuroendocrine trans/dedifferentiation. Non-NE: Non-neuroendocrine; NE: Neuroendocrine.

and there were only 96 cases of MANEC in the entire continent (http://www.rarecare.eu/)[22]. MiNENs account for less than 5% of all digestive NE neoplasms[5,13], although the incidence is probably increasing due to the improvement in diagnostic methods.

This type of tumour usually originates in organs that have NE cells and in which NE tumours frequently develop, such as the pancreas, the appendix, the colon and, less commonly, the small intestine[5,23]. In gastroenteropancreatic (GEP) tract, approximately the 82% of MiNENs are diagnosed as localised tumours and the 18% as metastatic disease[14].

No risk factors have been established but it is suspected that inflammatory bowel disease could be one in colorectal location (CCR)[24-26], autoimmune chronic atrophic gastritis in gastric tumours[27,28] and esophageal neoplasms are associated with Barrett esophagus[29], although none of these has been confirmed as such with certainty.

Next, we discuss the most important aspects of the GEP tract by location.

Esophagus

Esophageal NE neoplasms are rarer than other GEP NE tumours and represent 0.04%-1.00% of all esophageal tumours [30]. In a case series of 69 MiNENs[31], the esophagus and the gastroesophageal junction were identified as the second most common sites of origin (15.9% of cases in the series) after colorectal location.

In the esophagus, the predominant non-NE component is ADC, with the squamous cell component being very rare, to the point that less than 10 cases of MiNEN compound squamous cell carcinoma have thus far been reported in the international literature[32].

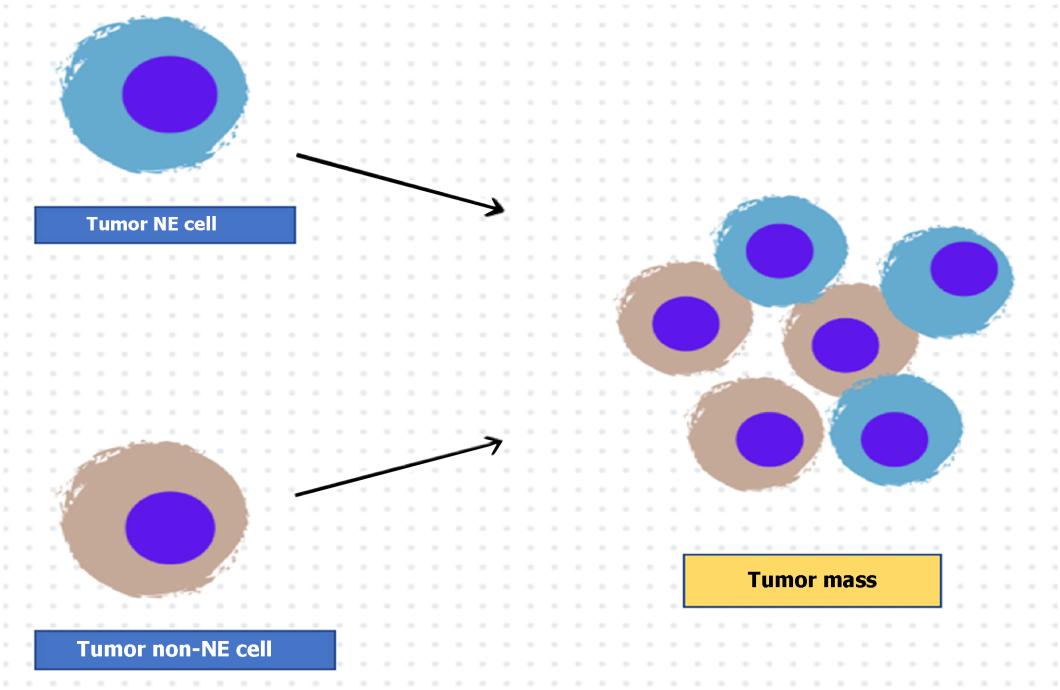

Figure 4 Origin according to the theory of an epithelial and endocrine components that arise differently from precursor cells in a synchronous or metachronous manner. Non-NE: Non-neuroendocrine; NE: Neuroendocrine.

The average age at diagnosis is 66 years and there is a greater prevalence in males (ratio 6:1). Over 50% of cases originate in the lower third of the esophagus. Most patients present with symptoms such as dysphagia and weight loss; pain or bleeding is less common, and only a small proportion of patients are asymptomatic, with tumours being discovered incidentally during endoscopy[30].

In a series of 40 cases of esophageal NE tumours, MiNENs were less frequently metastatic than poorly differentiated NE carcinomas (25% *vs* 54%, $P = 0.036$) and patient survival was higher (28 months *vs* 15 months, $P = 0.031$)[33].

Gastric

Gastric MiNENs represent approximately 7% of all gastric NENs and 25% of all poorly differentiated gastric NE carcinomas, although their prevalence is not entirely known. They can be large, polypoid, ulcerative and/or stenotic lesions. The NE component is usually a NEC, less commonly a NET, and the non-NE component is usually an ADC or, rarely, a squamous cell carcinoma, especially when located in the cardiac region[30,34].

Some Asian studies show that almost 70% of poorly differentiated gastric NE carcinomas contain at least a minor ADC component[35,36].

According to the literature[37], men are the most frequently affected (ratio 2:1) at 65 years of age (range: 41-76 years). The diagnosis of MiNENs is usually late, with non-specific gastric cancer symptoms, and the diagnosis is often made in advanced stages of the disease, with distant metastasis at the time of diagnosis. Because of this, it is assumed that the prognosis is worse than for isolated ADC or pure NEC[37], although some studies suggest that the prognosis is the same or even slightly better[30].

Pancreatic

Pancreatic MiNENs represent 0.5% of all pancreatic ADCs and 5% of all pancreatic NENs[13].

The NE component is usually a NEC but may occasionally be a G1 or G2 NET. The epithelial component can be an acinar-an acinar-MiNEN, which is the most common neoplasm-or a ductal-an adeno-MiNEN[38,39].

The preoperative diagnosis of MiNEN is rare and its treatment is mainly based on postoperative pathological examination. Between 40% and 80% of pancreatic ADCs contain NE islets, which may lead to overdiagnosis of MiNEN. Similarly, 5% to 10% of pancreatic NENs may contain non-neoplastic ducts that should not be misdiagnosed as MiNENs. The prognosis of pancreatic MiNEN is intermediate between that of pure ADC and that of pure G1-G2 NET, and similar to that of "pure" NEC[13,38].

According to a study by Angelico *et al*[38], the cases of pancreatic adeno-MiNEN tested in the literature occur mainly in men (ratio 4:1) with a mean age of 61.7 years (range: 24-82). The presenting symptoms are abdominal pain, obstructive jaundice, weight loss, anaemia, and nausea and/or vomiting, and in 25% of cases diagnosis is incidental. The location is mainly in the head of the pancreas and almost a fifth of the cases are located in the body or tail of the pancreas. Most are diagnosed in the advanced stages (III or IV).

Gallbladder and biliary tract

MiNENs originating in the extrahepatic bile ducts and the gallbladder account for 5% to 35% of all cholangiocarcinomas and NENs from these primary sites, with intrahepatic biliary MiNENs being extremely rare. They are generally composed of an NEC and pleomorphic ADC. According to the available evidence, over the 33% of gallbladder NECs contain an ADC component (MiNEN)[40].

Most are found after cholecystectomy for cholecystitis, surgery for suspected biliary malignancy or autopsy[13,40].

The prognosis depends on the stage at diagnosis and the exact histological components. In a study by Wang *et al*[40], most tumours were diagnosed as advanced disease although the 100% of patients underwent resection surgery with a median survival of 11.5 months. In another study by Kim *et al*[41], the median survival of 20 patients with curatively resected biliary NE tumours was 13.7 months.

Duodenum, jejunum, and ileum

MiNENs can develop in the duodenum and often combine an intestinal phenotype ADC with a well-differentiated somatostatin-secreting NET. They are mostly superficial, not very aggressive and rarely metastasise.

Half of all ampullary MiNENs have an intermediate grade of malignancy, combining well-differentiated G1-G2 NETs and ADC components.

Poorly differentiated NECs and MiNENs of the jejunum and ileum are rare, and usually include a well-differentiated NET associated with an adenoma or ADC component, with an intermediate degree of malignancy[13,42].

CCR

The colon is the most frequent site for MiNENs. Watanabe *et al*[43] found that around 3.2% of all colorectal cancers (CRCs) in Japanese hospital records were MiNENs. In another study[44] of 988 resected CRCs, MiNENs represented 2.4% of the total number. In a Bayesian analysis of CRC by Grossi *et al*[45], the average age of diagnosis was 64.2 years with a standard deviation of 13.6 years and there was no predominance of gender. The most frequent location was the appendix followed by the ascending colon, and 31.8% of cases at diagnosis had metastatic disease. The onset symptoms are similar to those of other colorectal neoplasms, that is, changes in bowel habits, abdominal pain and weight loss, among others, with systemic symptoms of NE tumours of the gastrointestinal tract, such as carcinoid syndrome, being very infrequent [23,43,46,47].

DIAGNOSIS AND PATHOLOGICAL ANATOMY

There is usually only a small biopsy sample for diagnosis. The two components may be difficult to identify using conventional morphological techniques, particularly when poorly differentiated. Biopsies may not accurately distinguish MiNENs from their pure counterparts, especially since this distinction depends on a quantitative threshold. In Frizziero *et al*[14], only one third of the cases were able to identify the presence of mixed histology.

To establish the NE diagnosis, immunohistochemical positivity of at least two of the following markers is necessary: Synaptophysin, chromogranin (CgA), CD56, and insulinoma-associated protein 1, and the calculation of Ki67 for tumour grading[8,23,43,46-48].

It is important that pathologists determine the percentage of each component, emphasising the 30% threshold. As mentioned above, NNE-NED are neoplasms in which this threshold is not reached. A scattered minor NE component in a NNE malignancy does not significantly affect prognosis, although recent studies have shown that the presence of NEC > 10% could be clinically relevant, so it is possible that, in the future, the definition changes again[2,49]. Regardless of the cut-off point, it is important to note that tumours can present a discordant NED spectrum and that only a subset of these tumours should be classified as MiNENs.

In ADC samples, there may be cell groups with aberrant expression of NE markers, especially synaptophysin and CgA, but without recognisable NE morphology, which can lead to confusion. Neoplasms that grow too large and invade physiological NE structures, such as acinar ADC in the pancreas that can include normal physiological islets of Langerhans, should also not be confused with MiNENs, despite the danger of positive staining for NE markers[50].

The non-NE component of MiNEN is ADC in 92% of cases. Squamous cell carcinoma, hepatocellular carcinoma and mixed adenosquamous carcinoma are the most common of the remaining non-NE components in the cases reported thus far[14]. It is recommended that the same molecular studies be performed on the ADC component of the MiNEN as would be performed on an ADC tumour from the same anatomical organ. Mutations affecting mismatch repair (*MMR*), *BRAF V600E*, and *Her-2* have been shown to occur in both components of MiNEN, suggesting the interesting option of using the same targeted therapies during treatment as those used in ADC tumours[19,51,52]. In addition to these genes, others have been sequenced in a significant proportion within MiNEN, such as PTEN, PI3KCA and RB1[16,18,51,53].

Furthermore, endocrine tumour cells can be divided according to histomorphological criteria into small and large. The small cell morphology here is similar to that of small cell carcinoma elsewhere, that is, small, uniform and with round or oval nuclei. In contrast, large cell NECs (LCNECs) have a larger cell size than small cell carcinoma. Distinguishing LCNEC from small cell carcinoma may sometimes be difficult. The Ki-67 index may be useful as the rate of LCNEC ranges from 40% to 80%, while small cell carcinoma averages 80%. In MiNEN, the NEC component is more commonly an LCNEC than a small cell carcinoma[10,43,54].

Currently, there is no classification within the broad spectrum of MiNEN, even though it groups together heterogeneous components with a multitude of possible combinations that could have prognostic and therapeutic implications. Simply designating a tumour as MiNEN is insufficient and sometimes conveys little useful information. La Rosa *et al*[55]

used a division that can help us in the management of this disease: (1) High grade: NEC component is the most present; (2) Intermediate grade: Tumours in which the non-NE component is the most aggressive, such as ADC with a NET component; and (3) Low grade: Indolent tumours in which a NET is the most aggressive component.

METASTATIC DISEASE

In a study of 129 patients[56], 76.3% with MiNEN and 23.7% with NNE-NED, 80 underwent surgical removal of the primary tumour and lymph nodes (LN), and 34 with distant metastases underwent biopsy of both the primary tumour and the metastatic lesions. Of the patients with LN metastasis, 68.8% exhibited a pure NE or ADC/squamous carcinoma (AS) component in metastatic LNs, while 20% showed different components in different LNs, and only 11.2% exhibited both NE and AS components in the same LN. In the patients with distant metastases, 26.5% of the distant metastases had coexisting NE and AS components, 70.6% had a pure NE component and 2.9% had a pure AS component.

In the case of metastatic disease, both components can metastasise, but it is more common for the poorly differentiated component to do so (in most cases it is the NE component), and the histological subtype of the primary tumour is not a good predictor of the pattern of metastasis. It has been suggested that a second look at the biopsy be taken in the following situations[14,57]: (1) In the presence of synchronous distant metastases when the original sample is from the primary tumour; (2) In metastatic recurrence of a previously resected MiNEN; and (3) In development of new or rapidly growing metastatic lesions during treatment, in the setting of otherwise stable disease.

The most frequent metastatic locations are the liver followed by lung and LNs[31].

PROGNOSTIC

The NE component usually dictates the prognosis[58-60]. In retrospective analyses, the grade and the differentiation of the components have been shown to have a direct impact on survival[61]. According to initial classification proposed by La Rosa *et al*[5] the prognosis depends on the TNM and the type of tumour, and no differences were found in prognosis when comparing NEC and MANEC (P = 0.82), so it is assumed that the prognosis is determined by the endocrine component.

In the study by Laenkholm *et al*[62], in 50 patients with GEP-MiNEN, significant prognostic factors were disease stage, surgical resection and performance status at diagnosis. Further analysis of this study reveals that MiNEN had a median overall survival (OS) of 30 months compared with NET (50 months, P < 0.001), GEP-NEC (14 months, P = 0.001) and poorly differentiated ADC (18 months, P = 0.45)[21].

Another study[63] of resectable gastric cancer that included 503 NECs, 401 MiNENs and 2785 ADCs concluded that the 5-year disease-free survival (DFS) was 47.5%, 51.1% and 57.8%, respectively. The shorter DFS of NEC and MiNEN compared with ADC was statistically significant, while the difference between NEC and MiNEN was not.

Chen *et al*[64] established as an independent prognostic factor, the presence of the NE component in over 50% of the tumour mass. In a multivariable analysis of a database by Milione *et al*[65], a Ki67 index of ≥ 55% in the NE component was established as an independent prognostic factor, reaching statistical significance with P < 0.0001. Other factors that reached statistical significance were tumour location (colorectal tumours had worse survival than pancreaticobiliary and gastroesophageal tumours), a mitotic count of 50/10 HPF, and mutations in the *KRAS*, *BRAF*, or *TP53* genes, as previously discussed, and that they were more frequent than in pure ADC.

STAGING

TNM staging does not have a specific protocol for this type of neoplasm and is applied according to AJCC guidelines, using the same protocol as for the anatomical location in which the neoplasm appears. In cases where a NET is the most aggressive component, the protocol for NET from the same anatomical location is used[10].

TREATMENT

The therapeutic management of patients with MiNEN is confusing. Despite being recognised as a clinical entity by the WHO and the European NE Tumor Society, there are no specific validated treatment guidelines available.

The first step in deciding on the management is to present the case to a multidisciplinary committee at the time of diagnosis and jointly decide which attitude to adopt.

Localised disease

The objective is surgery with curative intent, with special importance placed on achieving adequate margins free of neoplasia (R0). The median OS for localized MiNEN, including local and advanced (stages I-III), is 39 months[66] and the median OS for stage IV is 11 months. In a study of 201 patients with surgically resected GEP NE tumours (68% NEC, 23% MiNEN, and 9% G3 NET), the median progression-free survival (PFS) after R0 resection was 10 months and the median

OS was 35 months; for cases with microscopically affected margins (R1), the median PFS was 8 months and the median OS was 22 months; and for patients with macroscopically affected margins (R2 resections), the median PFS was only 2 months and the median OS was 8 months. These differences were statistically significant (R0 *vs* R1 *vs* R2, $P < 0.001$; R0 + R1 *vs* R2, $P < 0.001$). It is notable that among R0 resections, the tumour site did not affect the prognosis.

Neoadjuvant chemoradiation may be considered depending on the location of the tumour (for example, in the rectum) and whether the risk of local recurrence is high. Induction with chemotherapy alone followed by surgery is an option for locally advanced tumours with the goal of facilitating surgery, decreasing postoperative morbidity and delaying adjuvant therapy if indicated. In a study of 69 patients with locally advanced NEC ($n = 50$) or MANEC ($n = 19$) of the stomach who underwent gastrectomy with D2 lymphadenectomy, neoadjuvant chemotherapy (HR: 0.37, $P = 0.025$) was an independent factor affecting prognosis[67]. Although we only have case reports on MiNENs, in the pancreas and the rectum, neoadjuvant therapy would be justified following the guidelines for pure ADC in those sites. Regarding the type of chemotherapy, it would be more appropriate to use guidelines for the non-NE component, since induction is not recommended in NE neoplasms. This is one of the points that should be clarified as soon as possible.

The benefit of adjuvant therapy after resection of localised tumours has not yet been confirmed, although there are some retrospective studies that suggest favourable results, as summarised in Table 3[40,43,67-70].

However, we still do not know which chemotherapy regimen offers the most benefits in the adjuvant setting: Regimens targeting the non-NE component or those targeting the NE component. According to the studies we have reviewed, we must choose the regimen that targets the most aggressive component. In the case of NEC, we should prescribe four to six cycles of adjuvant chemotherapy with a platinum salt (cisplatin/carboplatin) plus etoposide, similarly to the small cell lung cancer (SCLC) protocol[71], and when the non-NE component is the more aggressive, we should choose the treatment regimen according to the location. Adjuvant therapy is not indicated when both components are low grade[72].

Following the above arguments, we summarise the adjuvant treatment recommendations in the algorithm presented in Figure 5.

Advanced and metastatic disease

The treatment of metastatic MiNEN should target the predominant neoplastic component of the metastatic disease rather than the predominant component of the primary tumour. In metastatic stages, the studies currently available recommend treating the most predominant and/or aggressive component, which in most cases is NEC[8].

Surgery should not be performed in locally advanced stages where R0 surgery is not guaranteed, and the disease should be treated as metastatic[59,73]. In such patients, neoadjuvant chemotherapy with or without radiation can be attempted, as mentioned above, for conversion to a resectable tumour, hence the importance of discussing the case in a multidisciplinary committee. In certain cases, such as CRC, induction chemotherapy can be performed for conversion surgery of liver metastases and/or surgical cytoreduction of the primary tumour[74].

As has already been stated, in disseminated disease, a biopsy is necessary in order to know which component has metastasised, since in most cases only one histological component metastasises. Depending on what the subtype is, a decision will be made on the most appropriate scheme. It is important to perform a rebiopsy in metastasic patients who have progressed beyond the first line of treatment to check which component has developed and/or mutated.

NEC as the more aggressive component

By analogy with SCLC, the first line in metastatic or unresectable disease should include systemic chemotherapy combining etoposide or irinotecan and a platinum salt[75]. At the molecular level, there is a greater expression of excision repair 1, a non-catalytic subunit of endonuclease, which participates in DNA repair in the NE component and suggests a better response to the combined treatment of platinum and etoposide[76], although there are studies showing results that are discordant with this molecular explanation. A multicenter retrospective study[77] of gastrointestinal NEC showed the benefit of irinotecan plus cisplatin (IP) over etoposide plus (EP) cisplatin. Of the 258 patients, 62% received IP, 18% EP and 14% FOLFOX. The response rates were 50% for IP and 28% for EP, and the median OS was 13.0 and 7.3 months for IP and EP, respectively. Therefore, an alternative first-line regimen is the irinotecan/cisplatin combination.

In a retrospective study of 101 patients with metastatic MiNEN, there was no significant difference in progression-free survival or OS between non-NE and NE chemotherapy regimens[78].

The optimal number of cycles is not known, although the SCLC guidelines state that 4 to 6 cycles of treatment should be administered, but it is advisable to continue as long as possible in order to achieve the maximum response, always taking tolerance into account[79].

If there few studies of the first line, after progression there are even fewer and the majority are case reports based on recommendations for other types of tumour. First-line treatment can be reintroduced if progression occurs more than 3 months after discontinuation[73]. Otherwise, combinations of 5-fluorouracil and irinotecan, temozolomide[59], amrubicin [80], or streptozocin (STZ)[81] in monotherapy are suggested. Temozolomide with or without capecitabine (CAPTEM), and bevacizumab was administered in the second line after cisplatin-based chemotherapy in a cohort of 25 patients with GEP-NEC with a response rate of 33% and a median OS of 22 months[82]. In another study of temozolomide in monotherapy in 28 patients with NEC, there was no response and the median survival was only 3.5 months, although the patients with Ki-67 lower than 50% did have better outcomes[83].

As noted previously, the amplification of KRAS, *BRAF V600E*, *APC*, *MMR* and *Her-2* can occur in both components of MiNEN, raising the possibility of targeted therapies[10].

Some authors have reported other approaches, such as Lee *et al*[84], who present the case of a 61-year-old man diagnosed with stage IV MANEC of the colon with peritoneal dissemination who was treated, after progression to chemotherapy, with surgery plus hyperthermic intraperitoneal chemotherapy but died 9 months after surgery. Vanacker *et al*[19] prescribed high-dose induction chemotherapy with carboplatin, mitoxantrone and cyclophosphamide followed

Table 3 Adjuvant treatment in mixed neuroendocrine non-neuroendocrine neoplasms

Ref.	Number	Location	Chemotherapy scheme	Result
Wen *et al*[68], 2020	*n* = 67	Biliary tract	Adjuvant CT-RT after R0 (*n* = 22) vs only surgery (*n* = 29); platinum and fluoropyrimidine regimens	OS, *P* = 0.076
Nießen *et al* [69], 2021	*n* = 13	Pancreatic	Adjuvant after surgery (*n* = 11); gemcitabine = 9; platinum-etoposide = 2	At 17-month follow-up, 2 patients were alive with no evidence of disease, 2 were alive with disease and 9 had died from the disease. 2 patients who had received NE regimens were alive
Zheng *et al* [70], 2021	*n* = 777	Gastric	Adjuvant after surgery (*n* = 198); unspecified regimen	DFS, *P* = 0.051
Watanabe *et al* [43], 2016	-	CCR	Adjuvant after surgery (MANEC *n* = 15 *vs* ADC *n* = 23); platinum and fluoropyrimidine regimens	DFS, *P* = 0.268; there were no differences between them
Wang *et al* [40], 2021	-	Gallbladder	Adjuvant after surgery (*n* = 15) *vs* only surgery (*n* = 15); capecitabine	DFS, *P* = 0.916

CT-RT: Chemotherapy and radiotherapy; R0: Adequate margins free of neoplasia; OS: Overall survival; NE: Neuroendocrine; DFS: Disease free survival; CCR: Colorectal cancer; MANEC: Mixed adeno-neuroendocrine carcinomas; ADC: Adenocarcinoma.

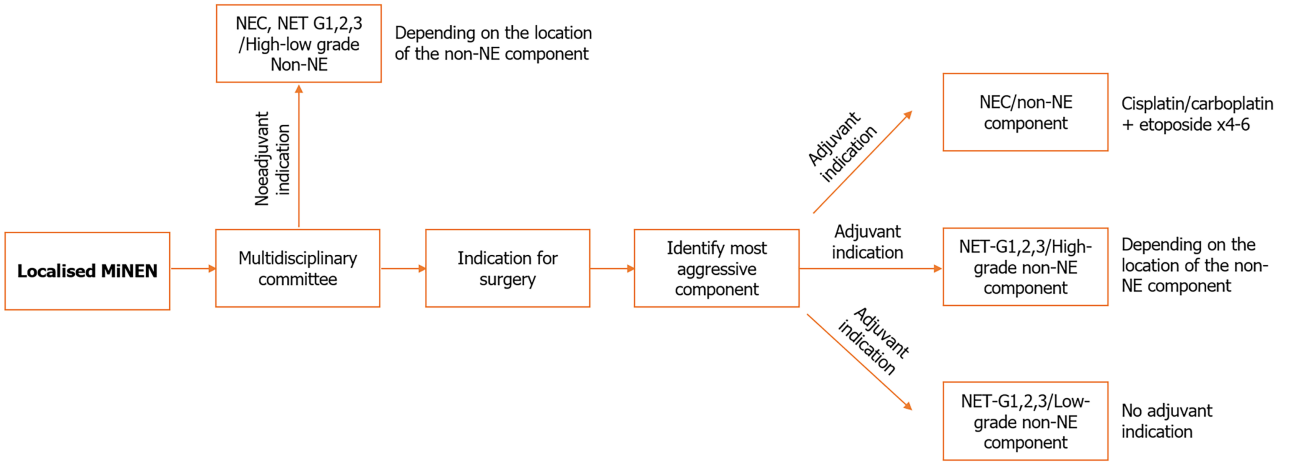

Figure 5 Adjuvant treatment recommendations. NET: Neuroendocrine tumours; NEC: Poorly differentiated neuroendocrine cancers; Non-NE: Non-neuroendocrine; MiNEN: Mixed neuroendocrine non-neuroendocrine neoplasms.

by autologous stem cell transplantation, with DFS of 30 months at the time of publication. In the fourth line of treatment, Stueger *et al*[85] prescribed immunotherapy based on pembrolizumab in a patient with PDL-1 expression of 1%-5%. They reported 14 months of PFS at the time of publication. Semrau *et al*[86] present a stage IV rectal MiNEN with liver involvement treated with chemotherapy based on cisplatin plus irinotecan and fractionated radiotherapy, with complete remission at the beginning but hepatic progression after 3 months of follow-up. They reintroduced cisplatin plus irinotecan followed by stereotactic body radiotherapy in liver metastasis, resulting in complete remission with 5 years of DFS.

High grade non-NE as the more aggressive component

In this case, as in localised disease, management should follow the indications of the clinical guidelines according to the location of the primary tumour.

NET G1, G2 and G3/low non-NE component

The treatment should be similar to that of "pure NETs". Firstly, somatostatin analogues have been proposed for MiNENs with NET G1 and G2 components, since the expression of somatostatin receptor type 5 is 81.8% and 60% in G1 and G2, respectively[47]. Radiotherapy with radionuclides (PRRT) is considered at progression, which has demonstrated a survival benefit, and sunitinib or everolimus in successive lines[75].

In NET G3, the treatment is similar to that of pure NETs and is based on chemotherapy. First-line STZ with 5-fuorouracil, or temozolomide and CAPTEM are the preferred treatment options. In subsequent lines, it is possible to use FOLFOX or everolimus or, if possible, PRRT[75].

Following the above arguments, we summarise the metastatic treatment recommendations in the algorithm presented in Figure 6.

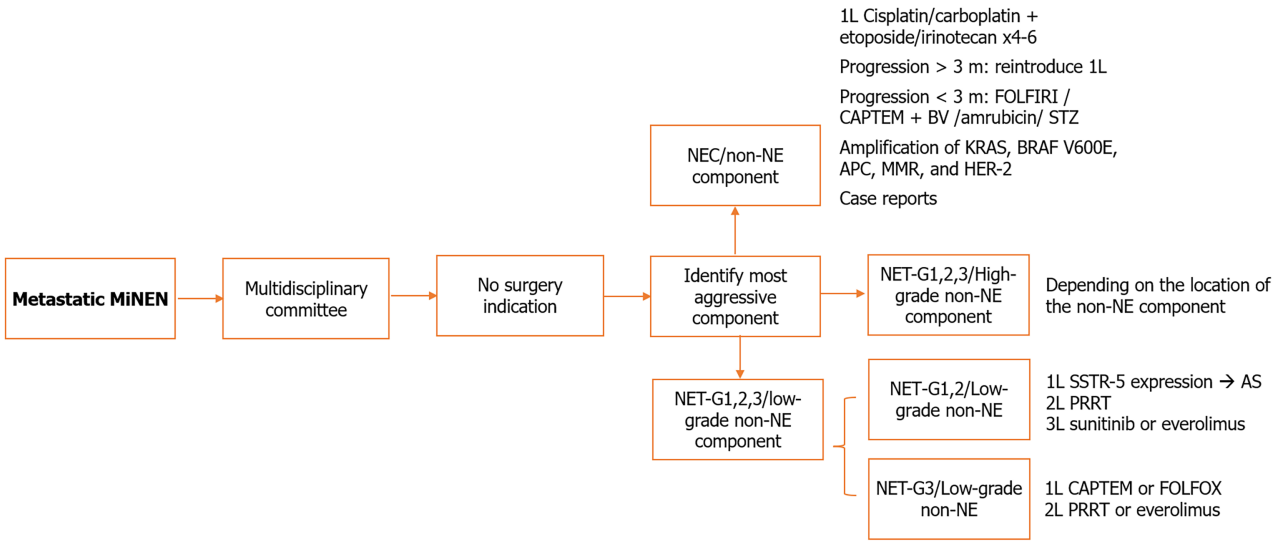

Figure 6 Metastatic treatments recommendations. NET: Neuroendocrine tumours; NEC: Poorly differentiated neuroendocrine cancers; Non-NE: Non-neuroendocrine; M: Month; 1L: First line treatment; 2L: Second line treatment; FOLFIRI: Irinotecan plus 5-fluorouracil; CAPTEM: Capecitabine plus temozolamide; BV: Bevacizumab; STZ: Streptozocin; MMR: Mismatch repair; SSTR-5: Expression of somatostatin receptor type 5; PRRT: Radiotherapy with radionuclides; AS: Somatostatin anologues; FOLFOX: Oxaliplatin plus 5-fluorouracil.

CONCLUSION

There are different treatment strategies but there are, currently, no validated protocols or clinical guidelines on the management of this disease, although most authors propose treating MiNEN with the high-grade NE component as the treatment target. In any case, the lack of high-quality scientific evidence, based on randomised clinical trials, makes it essential to deepen our knowledge of this group of neoplasms so that we can develop a more effective approach to identifying the best treatment strategy and thus improve the current poor results. We also have to bear in mind that over the last two decades there have been many changes in the definition of this type of neoplasm, which has hindered the design, development and execution of large-scale clinical trials. It would be important to reach a general consensus on their diagnosis in order to construct a classification that remains stable over time and facilitates the design of clinical trials that, due to their low incidence, will require long recruitment periods.

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