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REVIEW

Appendiceal Neuroendocrine Neoplasms: an Update for 2023

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Abstract

Purpose of Review To summarize the literature from the last 5 years on treatment of appendiceal neuroendocrine neoplasms (aNEN). Furthermore, to evaluate the prognostic significance of lymph node metastases, indications for adjuvant treatment, and challenges of the current follow-up regimen.

Recent Findings Simple appendectomy is sufficient in tumors < 1 cm while extended surgery is indicated in tumors > 2 cm. In a multicenter study of aNENs measuring 1–2 cm, extended surgery offered no significant prognostic advantage and is now limited to incomplete tumor resection or high-grade G2 or G3 aNEN. Follow-up remains debatable, as the use of imaging and biomarkers lacks validation.

Summary While surgical procedure is well established in aNEN tumors < 1 cm and > 2 cm, the need for extended surgery in aNEN tumors 1–2 cm is questionable. Future studies should address the prognostic impact of lymph node metastases and the optimal design and duration of follow-up.

Keywords Appendiceal · Neuroendocrine neoplasm · Treatment · Follow-up

Introduction

Appendiceal neuroendocrine neoplasms (aNEN) are the most frequent primary tumors of the appendix [1••]. They are most commonly diagnosed after appendectomy due to appendicitis or surgery for unrelated reasons and are diagnosed in 0.1–0.6% of patients after appendectomy [2, 3•, 4, 5]. Typically, pre-surgical diagnostics are therefore not performed [1••]. In general, aNEN is considered an indolent disease because symptoms and recurrence are exceedingly rare, and the mortality rate is zero [2, 3•, 6, 7, 8•, 9•]. Due to these factors, a randomized controlled trial is difficult to perform. Accordingly, available reports on aNEN are retrospective observational cohort studies ranging from ten to 435 patients [10, 11].

In the majority of patients, simple appendectomy is thus sufficient [1••]. Due to the lack of evidence, selecting patients for extended surgery is challenging [11]. Regarding small aNEN < 1 cm and large aNEN > 2 cm, there is international consensus; tumors with size < 1 cm are sufficiently treated with simple appendectomy, while tumors with size > 2 cm require extended surgery [2, 12]. In patients with aNEN 1–2 cm, mesoappendiceal invasion > 0.3 cm and lympho-vascular invasion should lead to consideration of

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extended surgery according to previous guidelines because they are associated with an increased risk of presence of lymph node metastases [2]. However, due to lack of evidence on hard endpoints such as overall survival, recurrence-free survival, or disease-specific survival, the appropriate treatment of tumors size 1–2 cm is debated [5, 13–17]. Use of the 2016 European Neuroendocrine Tumor Society (ENETS) guidelines resulted in a considerable overtreatment as reported in previous studies [3•, 8•, 18]. The overtreatment has clinical importance, as it is associated with reduced health-related quality of life and short-term morbidity rates of 2–3% [3•, 7, 19]. The aim of this review is to summarize the literature from the last 5 years on treatment of aNEN. Furthermore, to evaluate the prognostic significance of lymph node metastases, indications for adjuvant treatment and the challenges of the current follow-up regimen.

Heterogeneity

There are discrepancies between European and North-American studies as the American Surveillance, Epidemiology and End Results (SEER) Program Database may include adenocarcinomas, but not the indolent forms of aNEN as opposed to the European studies [13, 20]. Therefore, SEER publications report a prevalence of lymph node metastases up to 49%, which contrasts with European studies where the presence of lymph node metastases is only 17–34% [3•, 6, 7, 9•, 16, 19]. Furthermore, the ratio of patients with advanced disease according to TNM status is higher in cohorts from North-American studies compared to cohorts from European studies [13, 21].

Another reason for the heterogeneity between the studies of aNEN is that different endpoints have been reported, and results from both univariable and multivariable regression models have been presented. Both all-cause mortality, disease-specific mortality, recurrence, residual disease, and presence of lymph node metastases have been reported, but due to very low mortality and recurrence rates, the presence of lymph node metastases has been used as a marker of advanced disease [3•, 7, 8•, 9•, 13–15]. However, it is not entirely clear whether the presence of lymph node metastases is associated with a worse prognosis. Furthermore, even though only the large, recent European studies with presence of lymph node metastases are evaluated, there are still differences in which pathological parameters are reported as having prognostic impact [3•, 6, 7, 8•, 9•, 16]. The large, European studies from the last 5 years are presented in Table 1. Information on tumor size, grade, stage, and presence of lymph node metastases is demonstrated, and Table 1 shows that the studies are similar in tumor size, grade, stage, and presence of lymph node metastases. With respect to the association between various pathological biomarkers and the presence of lymph node metastases in the same studies, the results are presented in Table 2. Despite the similarities in registration of aNEN and endpoints, there is no consistency in the importance of pathological biomarkers of presence of lymph node metastases in the different studies as tumor size is a risk factor in three studies while mesoappendiceal invasion is a significant risk factor in one study. However, all studies find that tumor grade, lympho-vascular invasion, and perineural invasion are not significant predictors of lymph node metastases.

Pathological Parameters

ENETS outlines the parameters that a comprehensive pathology report on aNEN should encompass all standardized pathological biomarkers facilitating comparability across studies [22]. The complete histological assessment should include morphology, tumor size, grade, neuroendocrine markers, localization of tumor (apex, middle, or base), extent of mesoappendiceal infiltration, lympho-vascular invasion, perineural invasion, and TNM staging [1••].

Table 1 The pathological criteria and treatment modalities in the large European studies from the last 5 years on appendiceal neuroendocrine neoplasms

Reference	Year of publication	*n*	Lymph node metastases (%)	Tumor size (< 1, 1–2, > 2 cm/NA) (%)	Tumor grade G1/G2/G3,NA (%)	Distant metastases
Alabraba (9)	2021	102	27	43/42/15/0	94/5/1/0	3 (ileac fossa, bone, liver)
Alexandraki (19)	2020	166	34	45/43/8/3	87/11/0/2	3
Brighi (8)	2020	436	30	NA	83/8/0/9	0
Galanopolous (16)	2019	263	32	40/31/29/0	88/12/0/0	0
Holmager (3)	2021	335	17	72/23/3/2	82/14/0.3/4	0
Pawa (7)	2018	215	24	44/32/24/0	93/4/0.5/2	2 (liver)
Rault-Petit (6)	2019	403	23	60/29/9/2	84/8/0.2/7	0

NA, not available

Table 2 Factors associated with presence of lymph node metastases in multivariable analyses in large European studies from the last 5 years

Reference	Lymph node metastases (%)	Tumor size	Lympho-vascular invasion	Tumor grade	Mesoappendiceal Invasion	Perineural invasion
Alabraba (9)	27	No	No	No	No	No
Alexandraki (19)	34	Yes	No	No	No	No
Brighi (8)	30	Yes	No	No	No	No
Galanopolous (16)	32	No	No	No	No	No
Holmager (3)	17	No	No	No	Yes	No
Pawa (7)	24	No	No	No	No	No
Rault-Petit (6)	23	Yes	No	No	No	No

Tumor Size

Two initial retrospective studies revealed an association between tumor size > 2 cm and the presence of lymph node metastases [12, 23]. Subsequent investigations have consistently supported this, firmly establishing tumor size as a significant prognostic factor [6, 8•, 9•, 24]. The optimal cut-off has been discussed, and 1.5 cm has been suggested in a meta-analyses, which included six studies with a total of 261 patients, but it has not gained wide-spread acceptance, and a 2-cm cut-off is still internationally accepted [1••, 11, 14, 25]. The importance of tumor size is reported in two early studies with residual disease as an endpoint supporting the importance of tumor size [14, 25]. However, no studies have reported that increasing tumor size is associated with a reduction in overall survival or higher risk of recurrence.

Localization

Localization of aNEN is recommended to be reported in the 2023 guidelines The most common location is the tip [3•, 6, 7, 9•, 16]. However, localization is not a prognostic important factor as none of the large, European studies has demonstrated an association with presence of lymph node metastases, survival, or recurrence [3•, 6, 8•, 9•, 16].

Lympho-vascular Invasion

The prognostic importance of lympho-vascular invasion is debatable. All the large European studies find that it is not a prognostic factor of presence of lymph node metastases in a multivariable regression model [3•, 6, 8•, 9•, 16]. With respect to other relevant endpoints such as residual disease, recurrence, or mortality, no association with lympho-vascular invasion has been demonstrated.

Perineural Involvement

The predictive value of perineural involvement is scarcely studied and is only mentioned as pathological risk factor in the 2012 guidelines from the UK and Ireland Neuroendocrine Tumor Society [26]. A univariable association with the presence of lymph node metastases was only found in the French study from 2019 including 403 aNEN patients [6]; thus, there is a need for more studies to evaluate the clinical importance.

Tumor Grade

Another risk factor with an uncertain impact on prognosis is tumor grade, as there have been no reports of reduced overall survival or disease-specific survival related to grade. In general, most tumors are NET G1 with low risk of mortality [3•], and this can contribute to the lack of association between grade and lymph node metastases [3•, 6, 9•, 25]. Only three large studies demonstrated an association between increasing grade and presence of lymph node metastases [7, 16, 27]. More extensive disease or recurrence is most often observed in patients with G2 or G3 aNEN, respectively, as reflected in the 2023 ENETS guidelines stating that oncological RHC should now only be considered in patients with high grade G2 or G3 aNEN [1••, 6, 7, 27]. These recommendations are based on one case from 2017 where a patient with Ki-67 index of 8% in primary tumor and 12% in metastases developed carcinoid syndrome [7]. In contrast, other large, European studies did not find an association with presence of lymph node metastases, but because high-grade aNEN is very rare, it is difficult to find associations with high Ki-67 [3•, 6, 9•].

Mesoappendiceal Invasion

The importance of mesoappendiceal invasion > 0.3 cm is debated. We have demonstrated its relevance in relation to the presence of lymph node metastases [3•], but this finding has not been supported by other studies [3•, 6, 8•, 9•, 16].

Lymph Node Metastasis

Several European studies have shown that regional lymph node metastases are a common finding [3•, 6, 7]. However, the same studies also found that the clinical relevance of lymph node metastases is debatable as they were not associated with a worse prognosis [3•, 6, 8•, 9•, 28]. With respect to recurrence, only one study reported relapse after 16.5 years in a patient with a 4-cm tumor [9•].

The relevance of lymph node metastases was recently questioned in a retrospective European multicenter cohort study [29••] including 278 patients with aNEN 1–2 cm who had undergone either simple appendectomy or oncological RHC. Patients were recruited from 40 hospitals with a median follow-up duration of 13 years. There was no difference in prognosis in patients irrespective of the type of surgery, the presence of lymph node metastases was clinically irrelevant, and finally the risk factors used in the 2016 ENETS guidelines had no influence on the prognosis [29••]. Therefore, the authors suggested that oncological RHC is not indicated after the complete resection of aNEN measuring 1–2 cm via appendectomy, thereby eliminating a potential source of overtreatment. As this is a recent study, the number of extended surgeries may be reduced in the years to come.

Treatment

The treatment for local and loco-regional aNEN involves surgery, which can be either primary surgery (comprising simple appendectomy or ileocaecal resection) or extended surgery (including oncological right-sided hemicolectomy (RHC) or ileocaecal resection) [1••]. Ileocaecal resection has been used in patients with primary NET in the terminal ileum or caecum and is less invasive surgery compared to RHC [30]. One observational study reports that patients undergoing RHC are considered to have more advanced disease as there were more patients with lymph node metastases compared to patients undergoing ileocaecal resection, but the prognosis was similar [30]. Because there is a considerable overtreatment in aNEN, ileocaecal resection can be used in aNEN patients with a low risk of lymph node metastases [1••]. Therefore, the ENETS guidelines from 2023 suggest that ileocaecal resection is sufficient in children or young adults [1••]. In addition, they recommend extended surgery for patients with tumor size > 2 cm, positive resection margins, or 1–2 cm aNEN with high-grade G2 or G3 [1••]. This reduces the need of extended surgery compared to previous guidelines [1••, 2].

Adjuvant Therapy

As previously described, aNEN G3 are very rare, and although only oncological RHC has been performed, the administration of adjuvant therapy has not been reported [1••]. Instead, these patients have been followed life-long with diagnostic imaging or biochemically with Chromogranin A. Recurrence has been described in one patient after 14 months, but standard use of adjuvant therapy is not recommended due to lack of data. Rather, cases should be discussed at the local multidisciplinary tumor board. We recommend that patients with high-grade aNEN or advanced disease are followed as patients with small intestinal NEN with somatostatin receptor imaging, CT, or magnetic resonance imaging (MRI).

Follow-up

The current follow-up strategy depends on type of surgery and histopathological features, but how follow-up should take place is unknown. If an aNEN < 1 cm is completely resected, there is no need for follow-up [1••]. For tumors > 1 cm, follow-up should be discussed at the multidisciplinary tumor boards if tumor has a high Ki-67 index defined as "high G2 or G3"; otherwise, no follow-up is indicated [1••]. The Ki-67 cut-off value cannot be defined due to the small numbers of high-grade aNEN [1••]. Traditionally, the presence of lymph node metastases after RHC has led to life-long follow-up [2], but the indication for follow-up is controversial as it has not been shown to improve prognosis in patients with aNEN. The current guidelines recommend follow-up of patients with lymph node metastases if the tumor is a high-risk tumor (size > 2 cm, high G2 or G3) [1••]. Moreover, biochemistry (Chromogranin A, 5-hydroxyindoleacetic acid) has not been validated in long-term follow-up of aNEN, and a previous study has also questioned the routine use of Chromogranin A as a biomarker in the follow-up of patients with aNEN [31]. Therefore, the use of biomarkers should be limited to cases with distant metastases and carcinoid syndrome.

A study of 41 patients undergoing examination somatostatin receptor imaging with ^{68} Ga-DOTATATE PET revealed no significant impact in detecting residual or distant disease [32]. Moreover, eight scans showed indeterminate findings while five scans recommended follow-up with other modalities than ^{68} Ga-DOTATATE PET [32]. The risk of radiation-induced malignancy in these often-young patients needs to be considered, but an age cut-off with respect to follow-up with MRI or CT is not established. Therefore, we propose that MRI is preferred in patients < 40 years whereas CT and PET scan can be used in patients > 50 years with high risk of recurrence or distant metastases. For patients between 40 and 50 years the choice of scanning modality needs to be evaluated on individual basis. In conclusion, the lack of evidence for the potential beneficial effect of follow-up combined with the low risk of recurrence may

potentially result in a change of the indication and duration of follow-up.

Summary and Conclusion

Available studies on aNEN are all retrospective observational studies, but heterogeneous in terms of sample size, differences in registration of aNEN, and endpoints. Several large, European observational studies have used the presence of lymph node metastases as an endpoint for disease morbidity, but they have not demonstrated a reduced overall survival or disease-specific survival in patients with lymph node metastases. In patients with aNEN < 1 cm, appendectomy is sufficient while aNEN > 2 cm requires extended surgery. The indication for extended surgery in patients with aNEN size 1–2 cm is being questioned after a large European study demonstrated that the prognosis was similar irrespective of the form of treatment [29••]. Therefore, the new ENETS guidelines from 2023 have adjusted the indication for extended surgery and now only recommend consideration for tumor size 1–2 cm, if there are positive resection margins or it is a high-grade G2 or G3 aNEN [1••]. Advanced disease is rare; therefore, it is not possible to make guidelines, and we suggest that patients are evaluated at local multidisciplinary tumor boards. We suggest a treatment approach as illustrated in Figure 1.

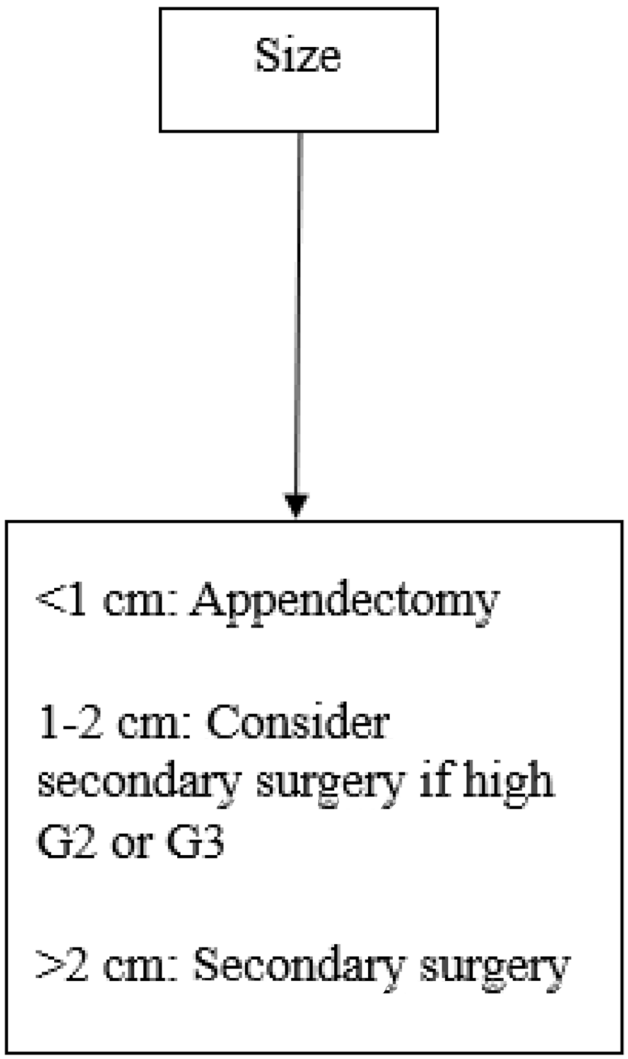

Fig. 1 Proposal for treatment of appendiceal neuroendocrine neoplasms

The optimal design and duration of follow-up remain uncertain. Given the favorable prognosis observed even in patients with lymph node metastases and the absence of any documented improvement in prognosis associated with follow-up, routine long-term or lifelong follow-up involving ionizing-based imaging can in our opinion not be recommended. We suggest that lifelong follow-up is only used in rare cases with a high Ki-67 index, distant metastases, or carcinoid syndrome or in patients with lymph node metastases and a high-risk tumor defined as size > 2 cm or high G2 or G3 aNEN. In our opinion, no follow-up is necessary in other cases.

In conclusion, the use of extended surgery in aNEN is reduced in the 2023 ENETS guidelines which may lead to a reduction of the previous overtreatment. There is a continued need to expand our understanding of the optimal follow-up protocol.

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Declarations

Competing interests The authors declare no competing interests.

Conflict of Interests The authors declare no competing interests.

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- •• Of major importance

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