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CLINICAL GUIDELINE

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European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for appendiceal neuroendocrine tumours (aNET)

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Abstract

The aim of the present guidance paper is to update the previous ENETS guidelines on well differentiated appendiceal neuroendocrine tumours (NET), providing practical guidance for the diagnosis and management of appendiceal NET (aNET); poorly differentiated neoplasms are dealt with in a separate guidance paper. This paper is structured on a question-answer format in order to also address controversial issues and areas where uncertainty regarding the management and follow-up of aNET exists. All recommendations are offered on the basis of the best available evidence, along with the authors' experiences in managing these neoplasms. Each recommendation for treatment will provide a level of evidence and grade of recommendation as per the GRADE system (adapted in Infectious Disease Society of United States Public Health Service grading system).

KEYWORDS
appendiceal NET, follow-up, histopathological features, right hemicolectomy, vascular and lymphatic spread

1 | INTRODUCTION

Appendiceal neuroendocrine tumours account for 50%–77% of all appendiceal neoplasms and are mostly identified incidentally following appendicectomy for acute appendicitis or after a laparotomy performed for unrelated reasons.[1,2] In the great majority, aNET are low grade (>80% grade 1, G1) and very rarely, if ever, are associated with a secretory syndrome.[2,3] Based on the mode of identification and the

absence of neuroendocrine neoplasm (NEN)-related symptoms, no NEN-related specific diagnostic tools are needed before surgical intervention, and in the great majority of cases no oncological resection is performed. Although appendicectomy alone is usually a sufficient treatment, a number of histopathological parameters are currently considered to be associated with an increased risk of regional lymph node involvement (LN+) raising the issue of further surgery. This has traditionally been performed in the form of right hemicolectomy (RHC), to ensure an adequate oncological resection. ENETS, based on mainly retrospective studies dealing with the management and prognosis of such patients, in 2016 issued practical guidelines to identify patients who are at risk for either concurrent residual disease to the lymph nodes (LN) or development of future recurrence and/or metastases.[3] However, there is still debate as to which are the most robust histopathological parameters justifying RHC or if a less aggressive surgical approach is preferable, and what is the prognostic significance of LN+ and their effect on patients' overall survival (OS). Furthermore, there are no clear-cut recommendations regarding the need and kind of further investigations needed in patients considered candidates for completion surgery following initial appendicectomy. In addition, there is a lack of recommendations for the need and type of any additional treatment in patients at higher risk for developing more extensive disease. There is also no established protocol describing the mode and duration of follow-up of patients undergoing further operation along with the sequalae of the procedure and its impact on the patient's quality of life.

All these issues will be addressed based on the following question-answer format.

1. **What is the current incidence of aNET (G1-3)?**
2. **Which are the pathological parameters that need to be provided for further decision-making?**
3. **How common are LN and distant metastases and carcinoid syndrome (CS) in appendiceal NET? Is LN status an acceptable surrogate of OS?**
4. **Is there any indication for biochemical and/or imaging modalities to be utilised for tumour staging following appendicectomy?**
5. **Which are the robust criteria necessitating treatment decisions; completion RHC vs. appendicectomy alone? Is the benefit of RHC of aNET on OS proven?**
6. **When completion oncological surgery is recommended, is RHC always required or could ileocaecal resection be sufficient, and what is the impact of these procedures on patients' comorbidities/QoL?**
7. **Is there any need for adjuvant therapy in patients with aNET without distant metastases?**
8. **How should advanced disease be managed?**
9. **What is the recommended follow-up protocol after RHC in patients with or without LN+ ? How is follow-up in aNET justified?**

2 | WHAT IS THE CURRENT INCIDENCE OF ANET (G1-3)?

Neuroendocrine tumours of the appendix are rare but are one of the most frequent gastro-entero-pancreatic (GEP) NEN, with an incidence previously reported to be 0.1–0.6/100.000 per year. However, in more recent studies the incidence of aNET has been found to be as high as 0.97/100.000 per year and 1.4/100.000 per year, respectively.[4,5] Improved registration and referral to specialised NET centres may explain this increase, although a real increase in incidence cannot be excluded. Appendiceal NET constitute about 45%–77% of all appendiceal neoplasms.[2,5–11]

Appendiceal NET are more frequently found in women, ranging between 55% and 70% in different studies.[5,7,8,10–12] The median age at diagnosis is 25–40 years, with a range of 4–95 years.[5–8,10–12] The majority of aNET are found in patients operated on for acute appendicitis (80%). The remaining aNET are found in patients undergoing RHC due to colorectal adenocarcinoma or inflammatory bowel disease, and in women having an appendicectomy in relation to surgery for gynaecological disease. More than 90% of the aNET are first diagnosed on pathological examination of the surgical appendix specimen.[5]

Most aNET are located in the tip of the appendix, are less than 2 cm in size, and are G1 (Table 1).[5–8,10–13] Two main histological types of aNET are described; the EC (enterochromaffin)-cell aNET, similar to ileal enterochromaffin cells (EC-cell NET) that are serotonin-positive, and the L-cell aNET, with a trabecular pattern, that are serotonin-negative, glucagon positive and chromogranin B rather than chromogranin A positive (CgA).[5] A rare subtype is tubular aNET, which should be distinguished from adenocarcinomas.[14]

2.1 | Recommendations

1. Appendiceal NET are the most common appendiceal neoplasms. They are increasing in incidence and consist of two distinct cell types (2b-B).
2. The majority are diagnosed following appendicectomy for acute appendicitis or after laparotomies for other pathologies (2b-B).

3 | WHICH ARE THE PATHOLOGICAL PARAMETERS THAT NEED TO BE PROVIDED FOR FURTHER DECISION-MAKING?

Appendiceal NET are mostly of small size, <1 cm, frequently associated with an inflammatory reaction, and may not be visible to the surgeon or even the pathologist on macroscopy. Thus, embedding the entire tip in two longitudinal pieces along with the body and resection margin in transverse sections is advised.[14] Subsequent steps for a complete and adequate report are included in the recent ENETS publication (*Pathology Synoptic Reporting*) that contains templates for well defined, reproducible and standardised pathological features and biomarkers.[15] The systematic use of this template is aimed at increasing the comparability of the parameters between different retrospective series from 1990 to 2019. Problems have occurred due to missing parameters, variability in interpretation of histoprognostic factors, and confusion of interpretation of pathology reports because of modifications of the classification (Table 1).

TABLE 1 Histopathological criteria of aNET at initial surgery derived from the main recent retrospective studies.

	Pawa et al.[12]	Brighiet al.[8]	Raul-Petit et al.[11]	Galanopoulos et al.[10]	Alexandraki et al.[7]	Alabraba et al.[6]	Holmager et al.[5]	Shibahara et al.[13]	Nesti et al.[19]	
Type of study										
Country	UK	Italian	French	UK	EU	UK	Denmark	Canada	EU	
Number of centres	3	11	12	1	5	1	1	1	40	
Number of patients	215	435	403	263	166	102	335	70	278	2267 total
Study period	14 years	1990–2015	2010–2017	10 years	1992–2019	1990–2016	2000–2019	2005–2019	2000–2010	
Histological characteristics of the aNET on initial surgery										
Number of cases with histology	215	435	403	72/263[e]	166	102	335	70	278[f]	2076 total
Appendectomy/other surgery/NA, %	90/10/0	NA	93/7/0	74/26/0	100/0	80/20/0	89/11/0	90/10/0	100/0/0	NA: 21%
Median tumor size, mm (range)	9.8 (1–50)	7 (NA)	9 (5–65)	NA	NA	12.7 (1–60)	7 (1–45)	5 (0.5–29)	NA	NA: 17%
Size (<1/1–2/>2 cm/NA)%	44/32/24/0	NA	60/29/9/2	40/31/29/0	45/43/8/3	43/42/15/0	72/23/3/2	73/21/6/0	0/100/0/0	NA: 22%
Appendiceal length (yes, NA)	NA	NA	Yes	NA	NA	NA	NA	NA	NA	NA: 80%
Localisation (tip/body/base/NA)%	NA	65/11/4/21	51/18/7/24	18/69/13/0	55/17/11/12	63/26/11/0	76/13/6/5	86/8/3/0	82/NA/10/8	NA: 22%
Grade (G1/G2/G3/NA), %	93/4/0.5/0	83/8/ 0/9	84/8/ 0.2/7	88/12/0/0	87/11/0/2	94/5/1/0	82/14/0.3/4	95/5/0/0	85/9/6	NA: 5%
Median Ki-67 in % (range if available)	NA	1	1	NA	NA	NA	1 (1–35)	NA	NA	NA: 57%
Layers extension (SM/MM/Sub-meso/SER[a]), %	NA/NA/8/15	NA	NA/NA/NA/3	NA	NA	NA	NA	17/34/42/8	NA	NA: 97%
Mesoappendiceal invasion (no/yes (<3/≥3 mm) /NA) %	92/8 (NA/NA)/0	50/39 (26/13)/11	62/28 (23/5)/9	36/64 (56/8)/0	52/46 (NA/NA)/2	NA	64/34 (NA/NA)/2	58/42 (NA/NA)/0	NA/39 (29/10)/61	NA: 18% NA/mm:47%
Vascular[b] invasion (yes/no/NA), %	7/93/0	12/66/22[c]	7/43/50	17/83/0[d]	11/86/3	NA	12/56/32	14/86/0	22/69/9	NA: 21%
Perineural invasion (yes/no/NA), %	NA	NA	7/22/71	18/82/0	15/84/3	NA	NA	10/90/0	NA	NA: 80%
R1 (yes/no/NA), %	4/96/0	NA	8/86/6	0/100/0	NA	NA	5/94/1	3/97/0	6/91/3	NA: 36%
pTNM used	ENETS, UICC7th	ENETS, UICC7th	ENETS, UICC7th	ENETS	UICC8th	ENETS	Not used	UICC8th	Not used	
Extended IHC (yes/%glucagon + / %serotonin+)	No	No	No	No	No	No	Yes/41/74	Yes/36/79	No	

Note: Decimal are removed, number are rounded down (<0.5) or up (≥0.5), except for numbers <1, for a better presentation and understanding.

Abbreviations: aNET, appendiceal NET; IHC, immunohistochemistry; MP, muscularis propria; NA, not available; R1, microscopic positive margin resection; SER, serosa; SM, submucosa; Sub-meso, submucosa or mesoappendix.

[a]Serosal invasion or pT4 (ENETS and UICC classifications).

[b]Vascular invasion refers to blood vascular invasion and lymphatic vascular invasion not separated.

[c]Immunohistochemical markers available to detect vessels (CD31, CD34).

[d]In this study vascular means blood vessels; lymph vessel infiltration is also available (17/55/0).

[e]In Galanopoulos et al.,[10] pathological data are available only in RHC patients ($n = 72$ of 263 patients).

[f]In Nesti et al.,[19] all NETs are 1–2 cm.

3.1 | Morphological analysis and mandatory immunohistochemical (IHC) staining

As for all digestive NET, morphological analysis is completed by mandatory IHC staining for CgA and synaptophysin to confirm the neuroendocrine nature of aNET and evaluate their proliferative activity (Ki-67 index).[14–16] Additional immunohistochemical stains to identify hormones can also be performed (**see Q1**). Recent studies have demonstrated a high expression of serotonin, and to a lesser extent glucagon, serotonin being associated with worse pathological factors.[5,13]

3.2 | Tumour size

Tumour size, corresponding to the largest diameter, is measured on microscopy slices since most tumours are not detected on macroscopy. This is a fundamental criterion for deciding on further surgery, as tumours larger than 2 cm in their greatest diameter are generally treated by oncologic completion RHC (**see Q5**). Tumours >2 cm are relatively rare with great variations in their frequency between studies (3% to 24%, Table 1).

3.3 | Localisation of tumour

Localisation of tumour (tip, base or close to the base) has to be reported. The most common location is the tip (51%–86%), rarely the base (3%–11%) (Table 1). In cases of R0 resection the minimal distance to resection margins should be noted.

3.4 | Local extension

The microscopic tumour extension has to be noted, that is, the maximal infiltration in the various layers of the wall.[15] This is possible on haematoxylin and eosin (HE) stains, substantiated further with CgA IHC that helps to find small infiltrative nests as synaptophysin strongly stains the myenteric plexus. The depth of mesoappendix infiltration (i.e., < or >3 mm) proposed in the ENETS 2006 classification[17] is also incorporated in the ENETS standardised reporting.[15] However, this level of extension in the mesoappendix is reported in only 39% (range 8%–64%) of cases in recent studies (Table 1).

3.5 | Vessel invasion

Vessel invasion includes blood vessel invasion and lymphatic vessel invasion and are both recommended by the ENETS synoptic reports for aNET.[15] However, whereas vessel invasion is reported in the majority of recent retrospective studies, in 94% of 2076 cases at initial surgery, blood and lymphatic vessel invasion were not separated except in one study in RHC specimens only[10] (Table 1, **see Q5**). In that study, 12% and 17% of patients had blood vessel and lymphatic vessel invasion respectively, with the latter having a greater risk of LN+[10] (**see Q5**). However, separating blood from lymphatic vessel invasion can be difficult morphologically with low interobserver reproducibility.[8]

Perineural invasion (Pn) is also a factor included in the ENETS standardised report although it is rarely reported in retrospective studies.[15] It has been analysed in two recent studies and was detected in 28% and 10% of cases, respectively[11,13] (**see Q5**).

3.6 | TNM staging

In addition to WHO differentiation and grading, the TNM staging is mandatory including the criteria described: size, maximal depth of parietal infiltration (submucosa, muscularis propria, subserosa or serosa), blood vessel invasion (V0/V1), lymphatic vessel invasion (L0/L1), perineural invasion (Pn0/Pn1) and resection margins (R0/R1/R2). To classify as pT, the last eighth edition of UICC TNM is recommended although it does not take into account aNET with size between 1 and 2 cm, as all ≤2 cm aNET are considered as pT1[18]; the ENETS TNM, while modified since 2006, is also frequently considered (Table 2). All successive TMN versions may produce confusion, especially when analysing data from retrospective studies that have been performed over prolonged periods of time (Table 2).[18] In all TNM classifications, the definition of pT4 refers to serosal perforation with or without infiltration of adjacent organs.[18] In a recent ENETS sponsored retrospective Europe-wide pooled cohort study of 1–2 cm aNET in size, serosal perforation/pT4 was found in 18.7% (52/273) of cases.[19] However, only two of these 52 cases associated with metastatic peritoneal spreading had a pathologically-confirmed serosal perforation. Moreover, these two patients were successively treated by electrocoagulation of peritoneal metastases or RHC, and none of the 52 patients developed disease recurrence or died during a follow-up period of >10 years.[19]

These findings highlight the importance of obtaining the proper definition of pT4 that is probably difficult to be made in an inflammatory appendix, where the inflammation itself can be responsible for the perforation. Therefore, true tumour infiltration responsible for perforation and peritoneal spreading (pT4) is probably overestimated in this context. The pathological analysis must be specific and perforation secondary to appendicitis should not be reported as pT4, but only when this is directly related to the tumour itself.

3.7 | Recommendations

1. A complete histopathological assessment using updated synoptic report templates (see ENETS synoptic reports) irrespective of the size of the tumour should be used including the following parameters: tumour size and localisation, morphological analysis and immunohistochemical staining for neuroendocrine markers and grading, local extension, invasion of blood vessels

TABLE 2 TNM classification for aNET. Changes in pTNM pathological classifications over time (ENETS, AJCC/UICC 2009 seventh edition, AJCC/UICC 2017 eighth edition).

	pTNM ENETS	AJCC/UICC seventh edition	AJCC/UICC eighth edition
pT1	T ≤ 1 cm and submucosa or muscularis propria invasion	T ≤ 2 cm (T1a ≤ 1 cm; T1b > 1–2 cm)	T ≤ 2 cm
pT2	T ≤ 2 cm and submucosa or muscularis propria or mesoappendix/subserosa invasion ≤3 mm	T > 2–4 cm OR Caecal invasion	T > 2–4 cm
pT3	T > 2 cm and/or mesoappendix/subserosa invasion >3 mm	T > 4 cm OR Ileal invasion	T > 4 cm OR Mesoappendix/ subserosa invasion
pT4	Perforates serosa/peritoneum, or invades other neighbouring organs		

Note: T, size in greatest dimension.
Abbreviation: aNET, appendiceal NET.

(angioinvasion), invasion of lymphatic vessels, perineural extension and TNM staging (2a-B).

2. Special attention should be paid to defining direct serosal involvement by the aNET. Appendicitis-related perforation must be distinguished from a true pT4 tumour perforation, the frequency of which is probably greatly overestimated (2b-B).

4 | HOW COMMON ARE LN AND DISTANT METASTASES AND CARCINOID SYNDROME (CS) IN APPENDICEAL NET? IS LN STATUS AN ACCEPTABLE SURROGATE OF OS?

Similar to many other tumours, aNET can potentially invade adjacent organs and metastasise to regional LN and rarely to distant sites. Previous studies that evaluated LN+ in aNET have also included appendiceal neoplasms that were not diagnosed with the currently accepted histopathological criteria such as "goblet cell carcinoids" that are currently classified as adenocarcinomas.[3,20] In particular, the Surveillance Epidemiology and End Results (SEER) Program Database analysis has reported the presence of LN+ in 49% of patients with aNET.[3,21] A number of retrospective institutional or multicentre studies that have recently been published, having exclusively included patients of various tumour sizes diagnosed with currently acceptable histopathological criteria for aNET, have revealed a significantly lower figure of approximately 5.6%.[5–8,10–13] In a recent study of aNET sized 1–2 cm the estimated figure was 12.8% based on a logistic model[19] (Table 3). All these recent studies are believed to have produced more reliable data regarding LN+ and its potential implications along with the presence of synchronous or metachronous metastases and the presence of CS (Table 3).

Moreover, from a total of 2267 aNET patients included in these studies, 568 (25%) underwent RHC based on the 2016 ENETS guidelines.[3,5–8,10–13,19] Of patients who underwent RHC and for whom complete histopathological data were available, (Tables 1 and 3), 120/495 (24.2%) were found to have LN+, albeit with a wide range of 17%–32% amongst the different studies.

Previous studies have also described patients with distant metastases secondary to aNET as well as the presence of CS.[3,22,23] However, it is not entirely clear whether these distant metastases were directly related to the aNET or other coexisting NET, whereas the presence of the CS was most likely associated with a small intestinal primary NET.[3,10,22] This view is also supported in the Negri study of 1–2 cm aNET, where the presence of distant metastatic disease in five out of nine patients was attributed to a coexisting NEN, most commonly a small bowel NET.[19] Considering also the data derived from all the recently published studies, metastatic disease was described in 12 (8 synchronous) patients (12/2267, 0.5%), whereas aNET-related deaths were described in seven patients although precise information is provided in only three of them; in addition, the duration of follow-up varied significantly[5–8,10–13,19] (Table 3). Only one case of CS has been described in a patient with a G2 aNET (Ki-67 8% in the primary tumour and 12% in liver metastases) who died within 9 months after diagnosis, exhibiting a clinical course that is extremely rare for aNET[12] (Table 3).

Data regarding the potential effect of LN+ in patients with aNET have been inconsistent in previous studies. However, a recent analysis of the SEER database that included 215 patients with apparent well differentiated aNET (period 2004–2012, median follow-up 44 months) who underwent RHC found that 120/215 (55.5%) had LN + versus 95/215 (44.5%) who did not have any LN involvement (LN-). Although this number of LN+ is much higher compared to those obtained from the recent studies (Table 3), probably due to the inclusion of other poorly-defined neoplasms, the OS of apparent well-differentiated aNET with LN+ versus LN- was similar at least for the specific follow-up period.[20] Similarly, all recent studies have shown that OS is not affected by LN+ although in one of the studies there was a trend for better OS in LN- compared to LN+ patients, albeit not statistically significant, and which could be related to the design of that study.[8]

Recently Nesti et al. evaluated LN+, metastatic disease and OS in 278 aNET of 1–2 cm in size.[19] A total of 115 patients underwent RHC in the presence of previously considered "high-risk factors" for harbouring LN+.[3,19] From these 115 patients, 19.6% were LN+.[19] Synchronous metastatic disease was reported in nine patients, but after central review only four metastases were considered as possibly or probably of appendiceal origin, including two cases with peritoneal spread related to the serosal perforation from the primary tumour. In two cases with liver metastases, the diagnosis was suggested but not further confirmed due to the absence of tumour samples.[19]

TABLE 3 Data derived from recently published studies with well-defined aNET histopathological criteria at diagnosis regarding LN involvement, (LN+), risk factors of LN+, and its relationship to OS.

	Pawa et al.[12]	Brighi et al.[8]	Raul-Petit et al.[11]	Galan et al.[10]	Alexandraki et al.[7]	Alabraba et al.[6]	Holmager et al.[5]	Shibahara et al.[13]	Nesti et al.[19]
Type of study									
Country	UK	Italian	French	UK	EU	UK	Denmark	Canada	EU
Number of involved tertiary centres	Multicentric ($n = 3$)	Multicentric ($n = 11$)	Multicentric ($n = 12$)	Single ($n = 1$)	Multicentric ($n = 5$)	Single ($n = 1$)	Single ($n = 1$)	Single ($n = 1$)	Multicenter ($n = 40$)
Number of patients	215	435	403	263	166	102	335	70	278
Study period of inclusion	July 2001–December 2015	January 1990–December 2015	January 2010–January 2017	January 2006–December 2016	August 1992–July 2019	1990–2016	2000–2019	2005–2019	2000–2010
Study population									
Median age in years	33.2	29	27.3	42	31	39.4	34	36.5	36
Female (%)	60.5%	79%	64%	NA	71.2%	52%	63%	60%	60.4%
Carcinoid syndrome	1 case	0?	0	NA	0?	0?	0?	0	0
Distant metastatic disease	2 (liver) synchronous		0	0	1 synchronous, 2 metachronous	3 (ileac fossa, bone, liver)[a]		0	4 synchronous (perit. liver)[c]
Surgery and LN resection									
N patients' surgery with LN resection	49/215	69/435	100/403	72/263	58/166	30/102	63/335	12/70	112/278
% of surgery with LN resection	23%	16%	25%	27%	34.9%	30%	18.8%	NA	12.8%
LN+, n/N (%)	12/49 (24.5%)	21/69 (30.4%)	23/100 (23%)	23/72 (32%)	NA/58	8/30 (27%)	11/63 (17.4%)	NA	22/112 (19.6%)
Factors associated with LN+ (univariate analysis)	NA	Tumour size, LVI, Ki67	Tumour size, LVI, Pn, pT	Grade, LVI	NA	Tumour size	Tumour size, deep mesoap. invasion, R1	NA	NA
Factors associated with LN+ (multivariate analysis)	NA	Tumour size	Tumour size	NA	Tumour size >2 cm	-	Deep mesoap. invasion, R1	NA	NA
Best cutoff for size (ROC analysis) to predict LN+	NA	15.5 mm	19.5 mm	NA	NA	NA	13 mm	NA	NA
Follow-up									
Median time of follow-up	38.5 months	NA but 20% of patients with at least 10 years	3 months	NA	NA	6.2 years	66 months	4 years and 8 months	13 years

TABLE 3 (Continued)

	Pawa et al.[12]	Brighi et al.[8]	Raul-Petit et al.[11]	Galan et al.[10]	Alexandraki et al.[7]	Alabraba et al.[6]	Holmager et al.[5]	Shibahara et al.[13]	Nesti et al.[19]
Number of recurrences	0	0	1 (G3, 14 mo later)	0	3 (liver, bone, or LN)	1 (16.5 years later)	0	0	0
Effect on survival	>99% at 5 and 10 years	Mean OS 275 months[b]	NA	No death	No death	5-year 98% OS 10-year 92% OS	No death	1 unrelated death	No death

Note: Included data regarding metastatic disease and the carcinoid syndrome. 0?, probable but not clearly stated; mesoap: meso-appendiceal invasion; perit, peritoneal; R1, resection with microscopic invasion; LVI, lymphovascular invasion.

Abbreviations: aNET, appendiceal NET; EU, European Union; LN, lymph node; LN+, LN involvement, mesoap, meso-appendiceal invasion; LVI, lymphovascular invasion; NA, not available; OS, overall survival; perit, peritoneal; Pn, perineural invasion; R1, residual tumor; UK, United Kingdom.

[a]No relapse in 2 after 8 years of follow-up.

[b]Nonsignificant trend of 78 months in LN+ 141 months in LN−.

[c]No recurrence after 13 years of follow-up.

4.1 | Recommendations

1. LN+ is relatively uncommon in aNET, and even in the presence of apparent "high-risk factors" only a fourth at most of patients will be found to have LN+ following RHC (2b-B).
2. LN+ is not associated with increased risk of recurrence or metastatic disease and is not related to OS (2b-B).
3. Metastatic disease is extremely rare, and when present necessitates the exclusion of a concomitant NEN, most commonly an ileal NET (2b-B).

5 | IS THERE ANY INDICATION FOR BIOCHEMICAL AND/OR IMAGING MODALITIES TO BE UTILISED FOR TUMOUR STAGING FOLLOWING APPENDECTOMY?

Following confirmation of an aNET after appendicectomy, the aim of these modalities is to identify patients in whom appendicectomy is curative and patients who may have residual disease and could be candidates for further treatment.[2,3] However, there is currently paucity of data as to whether any form of commonly employed NEN biomarkers [such as CgA and/or 5-HIAA (5-hydroxy-indole-acetic-acid)] or imaging studies are needed, and when these should be utilised.[2,3] Although some studies have found increased CgA levels in patients with metastatic disease, this has not been extensively studied in aNET whereas the sensitivity of CgA in identifying low-burden residual disease, particularly in the LN, is limited.[3,23,24] Similarly, although the CS has been described in some patients with aNET, epidemiological studies have shown that this is extremely rare and thus 5-HIAA estimation in 24 h urine samples or plasma measurements are not routinely performed (Table 3). However, these biomarkers could be utilised if, after an appendicectomy, patients are found to have distant metastases or exhibit symptoms of the CS, although with low probability that these may be directly related to aNET.[2,3,19] Very few data are currently available regarding the role of new more sensitive biomarkers such as the *NETest* in identifying residual disease,[25] while the role of circulating tissue DNA has not been explored as yet in these patients.[26]

In aNET with tumour size >2 cm, imaging of the abdomen with computerised tomography (CT) or magnetic resonance imaging (MRI) and CgA measurement are performed, as the possibility of metastatic disease increases in such lesions.[2,3] Although many would also recommend imaging in aNET with a high Ki-67 proliferation index, there is no consensus or evidence as to whether this approach should be undertaken irrespective of tumour size and which Ki-67 value should be considered as the appropriate cutoff level.[2] Similarly, following the findings of the Nesti et al. study, tumour serosal infiltration (pT4) could also constitute a potential risk factor for peritoneal spreading but this event was very rare (2/273 cases in 1–2 cm aNET); these two cases were cured by peritoneal local ablation with no deleterious effect on survival.[19] Previous guidelines have suggested that somatostatin receptor imaging (SRI), preferably with ^{68}Gallium-labelled somatostatin receptor (SSTR) positron emission tomography

(68Ga-DOTA-SSTRT-PET/CT), should be employed in the presence of suspected distant metastases or when curative resection was not completely assured.[3] A recent retrospective study that evaluated the routine early role of 68Ga–DOTA-TATE-PET/CT in order to evaluate residual disease in aNET, including patients with "high-risk" histopathological features, such as size >2 cm and Ki-67 values >2%, concluded that there was no added value if performed within 18 months following appendicectomy.[27] However, cases where 68Ga-DOTA-SSTRT-PET/CT has identified residual disease in the LN and elsewhere have also been described, but these results should be considered with caution following the findings of several studies where the majority of the metastases found were related to a coexisting NEN, mainly ileal.[19,22,23]

5.1 | Recommendations

1. Conventional existing non-specific markers, such as CgA and 5-HIAA levels, are of limited value in identifying residual or localised disease following appendectomy (4-C). They can be used though in the presence of distant metastases and in the rare cases of CS after excluding a concomitant small intestinal NET (Figure 1) (4-B).
2. Morphological (CT/MRI) imaging could be considered in patients with robust "high risk factors" for residual or more advanced disease such as aNET >2 cm in size and high G2 and G3 tumours (4-C).
3. Functional imaging (preferable with 68Ga-DOTA-SSTRT-PET/CT) could be performed in the presence of positive findings on morphological imaging (4-B).

6 | WHICH ARE THE ROBUST CRITERIA NECESSITATING TREATMENT DECISIONS; COMPLETION RHC VS. APPENDICECTOMY ALONE? IS THE BENEFIT OF RHC OF ANET ON OS PROVEN?

Current ENETS guidelines recommend completion RHC in the presence of aNET size >2 cm, cases of R1/2 resection, or aNET of 1–2 cm in size in the presence of additional "risk factors" such as mesoappendiceal invasion (MAI) >3 mm, Ki-67 values >2% and vessel invasion.[3] However, there are currently no prospective data available to evaluate the validity of these "risk factors" as to whether:

1. They can accurately predict the presence of LN+ and/or distant disease.
2. LN+ is a surrogate marker of local/distant recurrence and/or OS.
3. Performing RHC avoids distant recurrence and improves OS.

Over the last years a number of studies that included aNET patients diagnosed with the currently defined histopathological criteria have tried to address these issues[5–8,10–12,19] (Tables 1 and 3). Of the patients operated, based on the previously mentioned "high risk factors" for LN+, 17% to 30% were found to have LN+ with the most consistent risk factor being tumour size >2 cm. Other risk factors that were also identified, albeit not in all studies, were: tumour grade, MAI, microscopic invasion of the resection margin (R1 status), vessel invasion, and Pn invasion.[5–8,10–12]

6.1 | Tumour size

Tumour size >2 cm is considered the most important criterion for the decision for RHC in the ENETS, NANETS, NCCN, UKINETS, and TNCD guidelines.[3,28–31] None of these guidelines recommend RHC in case of aNET <10 mm; these recommendations differ for aNET measuring between 10 and 20 mm. For this latter group, several different tumour size cutoffs have recently been proposed capable to predict LN+ that range from 13 mm (area under ROC curve-AUROC of 0.89 [0.85–0.94]),[5] 15.5 mm (AUROC of 0.75 [0.64–0.87]),[8] and 19.5 mm.[11] However, it appears as the 2 cm is probably the best cutoff level as it is associated with the highest percentage of LN+ compared to smaller sized tumours. The percentage of LN+ in aNET according to their size (<1, 1–2, >2 cm) after RHC is highly variable ranging between 15%–24%,[10,11] 32%–38%,[10,11] and 43%–57%.[6,10,11] However, it should be noted that these patients were selected for RHC due to the presence of various "high-risk" factors and an element of bias is likely to be present.[6,10,11]

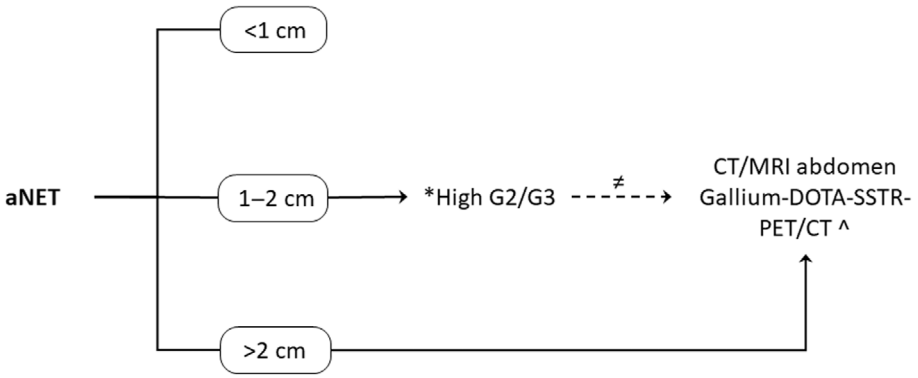

FIGURE 1 Proposed staging imaging studies of appendiceal NET (aNET) before right hemicolectomy (RHC) according to risk for distant disease. *Based on findings on Refs. 6,7,12. ^ MRI preferred for young patients. ≠ Following MDT discussion of individual patients (also considered in rare cases of < 1cm with high G2 aNET). CT, computerised tomography; G, grade; Gallium-DOTA-SSTRs-PET/CT, 68-gallium-labeled somatostatin receptor positron emission tomography; MDT, multidisciplinary team; MRI, magnetic resonance imaging.

6.2 | Mesoappendiceal invasion (MAI)

MAI >3 mm in case of an aNET of 1–2 cm in size is found in 4%–34% of cases and is considered a risk factor favouring RHC in several guidelines (ENETS, NANETS, UKINETS, TNCD),[3,28–30] but not in the NCCN.[31] However, there are no clear data in the literature to prove that 3 mm is the most valid size limit for performing RHC. MAI was associated with LN+ after multivariate analysis in one, identifying a MAI of 1 mm as the optimal cutoff value (AUROC of 0.72 (0.58–0.86),[5] but not in other studies.[8,11]

6.3 | R1 (microscopic invasion of resection margin)

This is encountered in 5% (range 3%–8%) of cases and more often in aNET localised at the appendiceal base. R1 status was associated with LN+ after multivariate analysis in one but not all studies.[5,8] However, irrespective of its association with LN+, R1 resection is considered as an indication for further surgery to eradicate any residual disease.[2,3] An independent robust relationship between the location of aNET at the appendiceal base and the risk of LN+ has not been established and does not appear sufficient to justify RHC when the resection is R0 without any other worse prognostic factors.

6.4 | Vessel invasion

The presence of vessel invasion of aNET 1–2 cm in size is found in 7%–12% of cases and is one risk factor favoring RHC in several guidelines including ENETS, NANETS, UKINETS, TNCD[3,28–30] but not in the NCCN.[31] Vessel invasion was associated with LN+ after univariate analysis but not after multivariate analysis in two studies.[8,11]

6.5 | Perineural invasion (Pn)

This risk factor is not included in the TNCD, ENETS, NCCN, NANETS[3,28,29,31] guidelines, but is included in UKINETS[30] for 1–2 cm tumour size aNET. This was not often evaluated in most of the recent studies,[5,6,8,12] but was found to be associated with LN+ in 2/6 (33%)[23] and 6/15 patients (40%)[11] respectively when examined. Further studies are warranted to evaluate the significance of this factor.

6.6 | Tumour grade

The majority of aNET, 82%–94%, are G1 and only 0.02%–1% were G3 in the main recent studies with available data (Table 1). Although no direct association between LN+ and grade was found in several studies, this is most probably related to the small number of aNET harbouring higher-than-G1 tumours. Only one study demonstrated a statistically significant correlation between grade and LN+, as 8/9 patients with G2 aNET had LN+ that was not affected by tumour size.[10,12] Furthermore, patients who developed extensive disease or experienced recurrence had mostly G2 or G3 aNET respectively.[11,12] However, there are currently insufficient data to suggest a specific Ki-67 cutoff value amongst patients with G2 aNET that confers a higher risk for LN+, although it could be speculated that there could be a continuum in the risk based on increasing Ki-67 values similar to other GEP-NET.

All current data indicate that tumour size >2 cm is the most consistent risk factor associated with LN+ (Tables 1 and 3). All other remaining "high risk" factors are not consistently verified in all studies, whereas in some studies the presence of more than one "high risk" factor was not associated with LN+ following RHC.[5,32] Although this could be related to the retrospective nature of the studies and the lack of central histology review, it raises concerns as to whether the presence of these apparent "high risk" factors should be an indication for RHC. This is clinically significant as the great majority of the recent, albeit retrospective studies, have not established that LN+ is a surrogate marker of local/distant recurrence and/or OS particularly in 1–2 cm tumours.[19] It needs to be explored, though, whether a specific Ki-67 cutoff value could be as robust an indicator as tumour size, favouring RHC, considering that many patients harbouring G2 aNET are found to have LN+,[10,12] whereas the role of Pn invasion needs to be more extensively studied.[11,23] Considering existing limitations, a meta-analysis of most of the recent publications found that size >2 cm, vessel invasion and Pn invasion were predictive of LN+.[9] Another meta-analysis also found size and vessel invasion being associated with LN+.[33]

Although no prospective studies are available to provide high quality data regarding the validity of "high-risk" factors in predicting residual disease, synchronous or metachronous metastatic disease and/or their association with OS, indirect data can be extrapolated from studies where patients fulfilling the criteria for RHC did not undergo the procedure. A total of 19 of 29 paediatric patients who fulfilled one or more of the previously mentioned "high-risk" factors did not undergo RHC and were only followed up, without any recurrences been detected.[34] A subsequent meta-analysis in children evaluated 37 studies including 958 patients, 120 of whom fulfilled the criteria for RHC but had only an appendicectomy.[35] After a median follow-up of 4.8 years no recurrences were detected.[35] Similarly, in an adult series, 15/64[12] and 4/34[6] of patients who fulfilled at least one "high-risk" factor were also followed-up with a median of 31 months (range 14–138 months) and 4.7 years (range 4.3–12.9) without undergoing RHC, respectively. None of these patients had evidence of recurrence, metastatic disease or died as a result of the aNET.[6,12,34] Considering that these patients had a 17%–30% probability of having LN+ it appears that this was not associated with an adverse outcome. However, the number of adult patients included and duration of follow-up do not allow for any strong conclusions to be drawn from these studies.

A recently published study evaluated 178 aNET patients with tumour size 1–2 cm who fulfilled at least one of "high-risk factor" for

RHC as defined in the 2016 ENETS guidelines.[3,19] The authors found that long-term OS was similar in patients who underwent appendicectomy ($n = 163$) compared to those who had RHC ($n = 115$). It was estimated that patients who underwent appendicectomy had an overall rate of 12.8% of LN+ but this did not appear to be clinically relevant. As already mentioned, only two patients with tumour-related serosal infiltration (pT4) had synchronous distant peritoneal metastases detected during initial surgery, treated by local peritoneal excision, and a further two patients had synchronous liver metastases not histopathologically confirmed. No patients developed clinically obvious metastases during a >10 year follow-up period, and there were no tumour-related deaths. Based on these findings it appears that RHC following complete resection in aNET measuring 1–2 cm in size is not generally indicated as there appears to be no benefit to the patients, whereas RHC could have consequences, particularly in young patients. As there are currently no similar data for aNET <1 cm in size addressing their proliferation index, such rare cases should be discussed in a dedicated NEN multidisciplinary team (MDT).

6.7 | Recommendations

1. Completion RHC is indicated in tumours >2 cm in size and in incomplete appendicectomies (R1/R2) (Figure 2) (2b-B).
2. Completion RHC is not generally recommended in completely resected tumours ≤2 cm in size (2b-B).
3. In resected 1–2 cm in size aNET certain risk factors, including high grade aNET and an individual patient's expectations may justify completion RHC. There is a lack of evidence as to whether RHC is of any benefit in the presence of serosal perforation (5-C).

7 | WHEN COMPLETION ONCOLOGICAL SURGERY IS RECOMMENDED, IS RHC ALWAYS REQUIRED OR COULD ILEOCAECAL RESECTION BE SUFFICIENT, AND WHAT IS THE IMPACT OF THESE PROCEDURES ON PATIENTS' COMORBIDITIES/QOL?

The guidelines of several societies advocate oncologic RHC as the procedure of choice in patients with aNET fulfilling histological criteria for completion intestinal resection, a procedure that can be associated with short- and long-term postoperative morbidity, along with long-term health-related quality of life (HRQoL) impairment.[3,28,36]

Ileocaecal resection either as first line surgery or as completion surgery has also been applied in some patients,[11,36] mainly in paediatric populations.[37,38] Although the indication for ileocaecal resection instead of RHC in aNET remains unclear, resection of the ileocaecal artery at its origin from the superior mesenteric artery is recommended.[36]

Factors to consider when deciding on one of the two types of intestinal resection, are the LN yield, short-term surgical morbidity, and long-term outcome regarding HRQoL. Although none of these factors has been analysed in aNET patients, the outcome of ileocaecal resection versus RHC has been studied in patients with NET of the terminal ileum or caecum.[39] Patients who underwent RHC had more LN evaluated versus those who had ileocaecal resection (median, 18 vs. 14, $p = .004$), but the oncological long-term outcome was similar. While RHC was associated with increased operation time and intraoperative blood loss compared to ileocaecal resection (both $p < .05$), there was no difference in the incidence and severity of postoperative morbidity (both $p > .05$). Based on the retrospective data available in the literature, and as no direct comparison exists between the two procedures, a randomised controlled trial would be desirable.

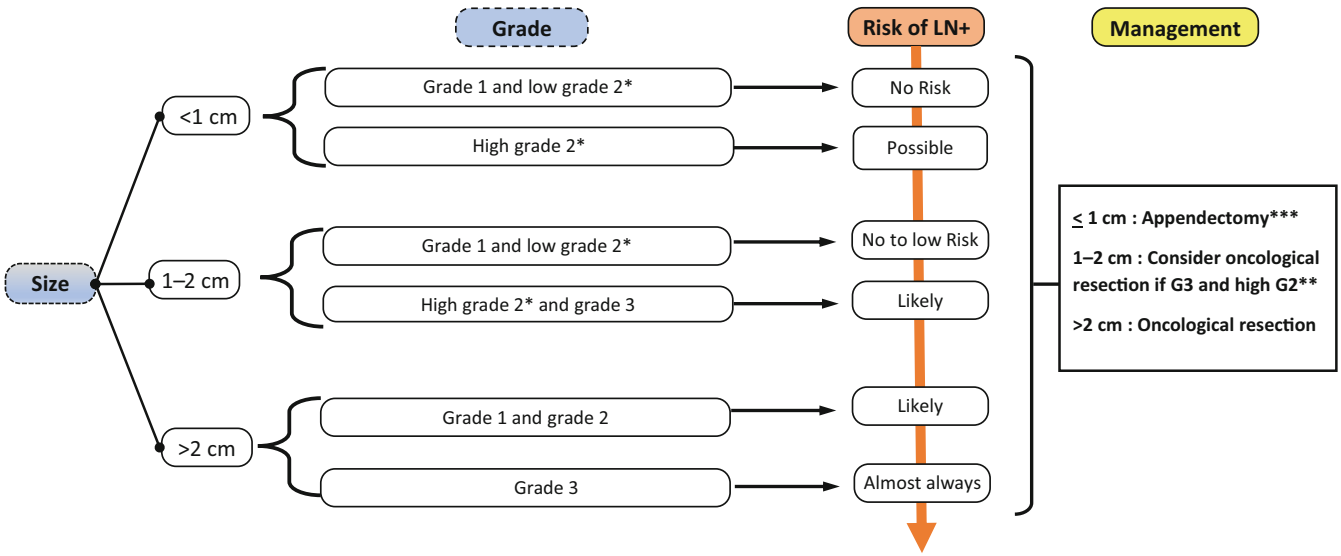

FIGURE 2 Risk stratification of lymph node involvement and management of appendiceal NET (aNET) according to the most robust risk factor "size". All patients with incomplete resection (R1) are considered for completion surgery. *There is insufficient data to suggest a Ki-67 cut off value among patients with grade 2 aNET that confers a higher risk for LN+. **No cut-off KI-67 value has been defined ***Discuss cases in MDT if high G2. LN+, lymph node involvement; MDT, multidisciplinary team.

Although patients with aNET who undergo RHC are young with fewer comorbidities, present with negligible tumour load, and have surgery in an elective setting, related complications still range from 5% to 15%.[40] In the largest series on 403 aNET patients, 90-days morbidity after completion RHC or ileocaecal resection was 15%.[11] The 90-day mortality was nil. Most complications after RHC are minor and do not require any operative intervention (Clavien Dindo grade I and II).[39,41] Those with limitations in bowel function still seem to cope well, as their HRQoL is not severely impaired.[41]

A single study has particularly addressed global HRQoL using the EORTC-QLC-C30 questionnaires in aNET patients treated either with simple appendicectomy or RHC, also including a matched healthy control group.[7] Overall, HRQoL was not significantly impaired in patients undergoing RHC (49 patients) compared with appendicectomy alone (30 patients). However, analyses in functional and symptom scales revealed that impaired social functioning, diarrhoea, and financial difficulties were more frequently reported in the RHC group. In addition, diarrhoea was mainly attributed to RHC as further comparison between the appendicectomy group and the group of healthy controls did not yield any statistical significance on this particular outcome.[7]

7.1 | Recommendations

1. Oncologic RHC is considered as a standard resection for completion surgery (3b-B).
2. As an alternative to RHC, Ileocaecal resection could be applied particularly in paediatric and young patients (4-B).
3. Both procedures are associated with low morbidity and marginal impact on QoL (3b-B).

8 | IS THERE ANY NEED FOR ADJUVANT THERAPY IN PATIENTS WITH ANET WITHOUT DISTANT METASTASIS?

As noted above, G3 aNET are extremely rare, with a reported incidence less than 1% in some of the largest published series[5–8,10–12] (Table 3). Although these patients had undergone completion RHC, there are no reports regarding administration of adjuvant systemic treatment post-RHC, even in the one patient in whom recurrence was noted 14 months later. Also, despite the presence of LN+ in 17%–30% of patients undergoing RHC, only radiological follow-up (with cross-sectional and/or molecular imaging) with no adjuvant systemic treatment had been offered in those patients.[5,6,8,10–12,42] Finally, there are no data regarding the administration and outcomes of adjuvant systemic treatment post-appendicectomy in patients who fulfilled the criteria, but eventually declined, completion RHC. Therefore, adjuvant systemic chemotherapy in aNET post-RHC cannot be recommended. However, it could be considered on an individual basis, in some extremely rare clinical scenarios, such as the presence of LN+ in G3 aNET in the RHC specimen, following discussion at a dedicated NEN MDT.

8.1 | Recommendation

1. There is currently no need for adjuvant therapy in patients with aNET as the vast majority are low grade tumours (5-B).

9 | HOW SHOULD ADVANCED DISEASE BE MANAGED?

Distant metastatic disease (DMD) in NEN originating from the small bowel is relatively common, ranging between 40% and 50%.[3] Metastases are commonly found in the liver followed by the bone in approximately 15% of cases.[3] This seems to be the case for the majority of NEN originating from the small bowel but there is a paucity of data regarding DMD that originate from the appendix[2] (Table 3). Although older series have presented cases of aNET with DMD, these studies were hampered by the great majority also including other NEN pathologies.[3]

In most of these cases treatment directed against DMD follows the guidelines for the management of DMD issued by ENETS for intestinal NEN.[3] This view is further supported by the findings of the Nesti et al. study where the majority of distant metastases were attributed to a coexisting NEN, most commonly an ileal NET.[19] Surgical treatment options include liver surgery and/or locoregional and ablative therapies.[3,23] A number of antiproliferative therapies have been used in the literature in aNET patients that include long-acting somatostatin analogues, molecular targeted therapies, peptide receptor radionuclide therapy and chemotherapy.[3,7,12,23] Choosing the most appropriate therapy depends on tumour characteristics (grade and tumour growth) and overall disease burden, along with the functional status of the tumour and the patient's performance status.[3]

9.1 | Recommendation

1. Management of the rare cases of metastatic aNET should be similar to that of other gastrointestinal NET considering that in a significant proportion these could be related to a coexisting ileal NET (4-B).

10 | WHAT IS THE RECOMMENDED FOLLOW-UP PROTOCOL AFTER RHC IN PATIENTS WITH OR WITHOUT LN+ ? HOW IS FOLLOW-UP IN ANET JUSTIFIED?

There is a relatively paucity of data regarding specific follow-up protocols in patients with aNET after RHC according to the presence of LN + or not. Patients with aNET without LN+ after RHC are generally considered "cured" and do not require further follow-up.[2,3] However, even in these cases follow-up could be considered in the presence of tumour size >2 cm, and high G2 and G3 tumours due to the potential risk of late recurrences following discussion in a dedicated NEN MDT.[6,11] Such an approach has not been substantiated in all recent

studies although most have a relatively short follow-up period,[5–8,10–13] except in one study that had a follow-up period >10 years.[19] In the latter study no recurrences were noted, but further studies are needed to demonstrate whether such patients need regular follow-up, and also the precise means and intensity of follow-up.

Patients with aNET who have LN+ following RHC, without evidence of DMD, have traditionally been kept under surveillance with several of the recent studies having implemented a follow-up protocol similar to that used for small bowel NET.[5–7,12] Both morphological and functional imaging modalities, preferably with ^{68}Ga-DOTA-SSRT-PET/CT, have been utilised, albeit with different intervals and variable length of follow-up, compared to small bowel NET protocols.[5–7,12] It should be stressed though that recent retrospective studies have not found an impact of LN+ on local recurrences, subsequent DMD and/or OS.[5–7,11,12,19]

Two recent studies that have followed up patients with LN+ post-RHC similar to small bowel NET with CT/MRI imaging and SRI, including ^{68}Ga-DOTA-SSTRT-PET-CT, every 6–12 months, did not find any evidence of recurrence and/or distant metastases during a follow-up period of 38.5 and 66 months, respectively.[5,12] However, no specific duration and intensity of follow-up have been proposed.[5,6,12] It could thus be speculated that patients exhibiting "high risk" factors such as tumour size >2 cm and high grade G2 and G3 aNET could constitute a group requiring consideration of follow-up. Older studies in patients with aNET >2 cm who had not undergone a RHC and were followed up for a significant period of time (although without using the currently available follow-up means), showed no recurrence or evolution to metastatic disease.[43] Similarly, although no specific follow-up modalities were mentioned in the Nesti et al. study, no recurrences, distant metastases or deaths were described in aNET 1–2 cm in size with LN + after >10-year follow-up period.[19] The duration and intensity of any follow-up should also take into consideration the natural history of the disease and the potential sequelae of radiation exposure as the majority of patients with aNET are of young age.

There are no data regarding the role of CgA in the post RHC follow-up, due to its limited applicability as a follow-up marker after apparently curative surgery.[24] Measurement of urinary or plasma 5-HIAA levels is also of little value in detecting local recurrences, with the exception of the rare cases of metastatic serotonin-secreting tumours (recognising these may be related to a coexisting small bowel NET).[3,19] Evolving biomarkers such as circulating tumour cells (CTCs) or the *NETest* have not extensively been studied to show whether can be predictive of relapse during follow-up, or are not yet readily available or fully validated respectively.[44] Data regarding the safe time for discharge are absent.

10.1 | Recommendations

1. Patients without LN+ post-RHC could be considered "cured" necessitating no further follow-up (3b-B). In the presence of "high risk" factors such as tumour size >2 cm and high G2 and G3 aNET the necessity of follow-up studies could be discussed in a dedicated NEN MDT (Figure 3) (4-C).
2. Patients with LN+ post-RHC if associated with "high-risk" factors could be considered as candidates for follow-up (4-C). The specific protocol, frequency and duration of follow-up need to be precisely defined and include morphological imaging (CT/MRI) and functional imaging preferably with ^{68}Ga-DOTA-SSTR-PET/CT in the presence of positive findings on CT/MRI (5-B).
3. There are no established biochemical and/or molecular biomarkers that could be used for the follow-up of patients with LN+ (4-C). Conventional markers such as CgA and 5-HIAA can be utilised in the rare cases of distant metastases and/or the presence of the carcinoid syndrome (4-B).

11 | SUMMARY

Previous ENETS and other societies' guidelines have recommended RHC in aNET patients exhibiting apparent "high risk"

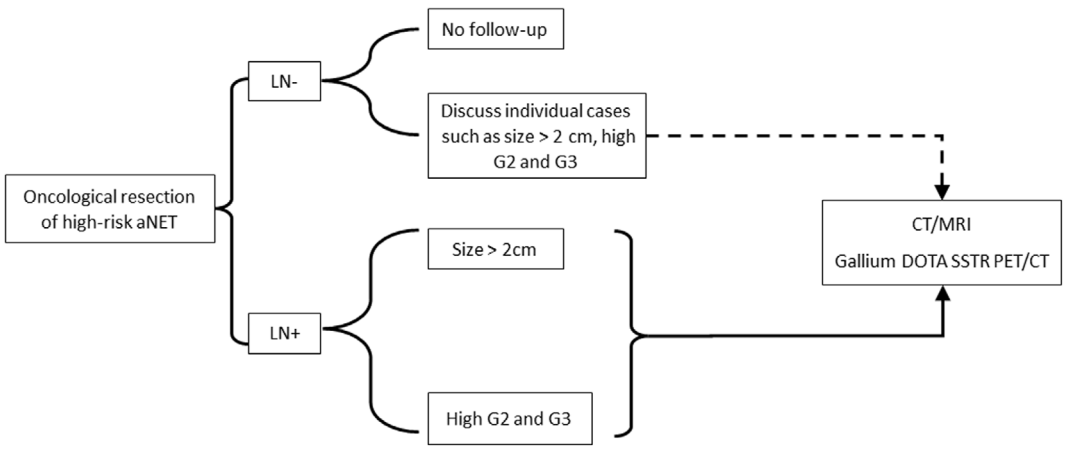

FIGURE 3 Proposed follow-up studies following completion of oncological resection. CT, computerised tomography; G: grade; Gallium-DOTA-SSTR-PET/CT, 68-gallium-labeled somatostatin receptor positron emission tomography; LN+, lymph node involvement; LN−, no lymph node involvement; MRI, magnetic resonance imaging.

histopathological factors to eliminate any residual disease and avoid the risk of late recurrence. Current evidence suggests that additional surgery should probably be offered to fewer patients than previously advocated, based on the presence of such potential "high risk" factors that were merely addressing the presence of LN+. Several large-scale retrospective studies including the retrospective Europe-wide pooled cohort study on aNET 1–2 cm in size have provided evidence that, in contrast to other NET, LN+ in patients with aNET is not associated with increased risk of recurrence, the development of distant metastases and/or increased death rate. The most robust criterion favoring RHC to avoid any metastatic potential appears to be tumour size >2 cm. Additional criteria include incomplete tumour resection and high grade aNET, albeit without a specific Ki-67 cut-off value been defined probably due to the small number of high-grade aNET. These recommendations aim to reduce the number of RHC performed, particularly in young patients with potential sequalae along with their implications on follow-up. However, there are still some areas of uncertainty regarding the need and follow-up means and its duration in patients undergoing RHC along with the specific genetic signature of aNET that is related to their more indolent course. We hope that these recommendations will facilitate a more standardised care for aNET patients by better identifying patients who will benefit from additional surgery, avoiding unnecessary RHC.

AUTHOR CONTRIBUTIONS

Gregory Kaltsas: Conceptualization; data curation; investigation; methodology; project administration; supervision; writing – original draft; writing – review and editing. **Thomas Walter:** Data curation; investigation; writing – original draft; writing – review and editing. **Ulriche Knigge:** Data curation; investigation; writing – original draft; writing – review and editing. **C. Toumpanakis:** Data curation; investigation; writing – original draft; writing – review and editing. **Ana Paula Santos:** Data curation; investigation; writing – original draft; writing – review and editing. **Nehara Begum:** Investigation; writing – review and editing. **Ulrich-Frank Pape:** Writing – review and editing. **Marco Volante:** Writing – review and editing. **A Frilling:** Data curation; investigation; writing – original draft; writing – review and editing. **Anne Couvelard:** Conceptualization; data curation; investigation; methodology; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Thomas Walter: honoraria for speaker engagements from Novartis-AAA, Ipsen, MSD, Keocyt and for advisory board engagement from ITM, Novartis-AAA, Terumo, Sirtex, Anne Couvelard: Nothing to declare, Ulrich Knigge: honoraria for speaker engagement from Novartis, Ipsen and Pharmanovia. Ana Santos: Nothing to declare, Marco Volante: Lilly, Roche and AAA, Gregory Kaltsas: honoraria and research funds from Ipsen, Novartis, Pfizer, Faran, Nehara Begum: Nothing to declare, Christos Toumpanakis: AAA, Ipsen, Novartis: honoraria for lectures, educational grants for NET Unit, AAA, Ipsen: Advisory Boards, Andrea Frilling: Ipsen Speaker, travel, education grant, research grants, honoraria Novartis Speaker, travel, honoraria, research grants. AAA Advisory Board member, travel, honoraria, Clifton Advisory Board member, travel, honoraria, SIRTEX Speaker, travel, honoraria, Uli Pape: honoraria from Advanve Phrama AAA, Ipsen, Novartis and Research funding from Ipsen.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Not applicable.

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SUPPORTING INFORMATION

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

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