Neuro endocrinology

Neuroendocrinology (DOI:10.1159/000443165)
(Accepted, unedited article not yet assigned to an issue)

Advanced Release: January 5, 2016

www.karger.com/nen

Received:
Accepted after revision:

Consensus guidelines for neuroendocrine neoplasms of the Appendix (excluding goblet cell carcinomas)

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Epidemiology and Prognosis

Neuroendocrine neoplasms (NEN) of the appendix are a relatively frequent subgroup of NEN with an approximate incidence 0.15-0.6/100,000/year and with a slight female preponderance in Western series [1-12]. Although frequently reported NEN [13] most cases are of an early stage [12-14]. The reported incidence has increased in more recent years [1,6] and the overall incidence rate is probably roughly within the same order among different races although some differences have been reported [1,12,15-18]. Furthermore common practice in performing appendicectomies may also influence the reported incidence of appendiceal NEN [19,20].

Appendiceal NEN comprise the largest subgroup of appendiceal neoplasms with approximately 30 to 80% of all appendiceal neoplasms [1,13,14,21-24]. Mean age at diagnosis has been reported between 38 and 51 years [6,24-26]. However, appendiceal NEN have also been reported in pediatric patients between 4.5 and 19.5 years of age [2,4,17,27-29] but population-based data are not available for this special subgroup.

The prognosis of the majority of appendiceal NEN is excellent in the series that report outcome on limited tumour stages with 5-year survival rates (YSR) of 100% or close to this [7,14,11,25,30-32]. However, the whole cohort including all tumour stages does not show such a favourable prognosis, with 5-YSR ranging between 70 and 85% [11,25,30,31,33]. Advanced stages with distant metastases have been reported with a much poorer prognosis and a 5-YSR of as low as 12–28% [1,11,14] . However, it is not clear to what extent more 'malignant' histologies such as goblet cell carcinoids (GCC) or mixed adenoneuroendocrine carcinomas (MANEC) with a poorer prognosis per se were included in such series.

Minimal Consensus Statement on Epidemiology and Prognosis

Appendiceal NEN present with an incidence of 0.15-0.6/100,000/year. They are diagnosed slightly more often in female than in male patients at an average age of 40–50 years. Appendiceal NEN are, however, much more frequently diagnosed incidentally during appendicectomy with a rate of approximately 3–5/1,000 appendicectomies. Racial differences may occur but data are inconclusive. In contrast, malignant tumours seem to occur more often in Caucasians compared to other races. Appenidceal NEN may also rarely occur in children but apparently with an excellent long-term outcome. While at a limited stage, survival is extremely good (local disease: 5-YSR 95–100%, regional disease: 85–100%), the few cases with distant metastasis present with relatively poor survival figures (5-YSR: < 25%).

From the available data it is concluded that an appendiceal NEN with a size <1 cm, with invasion up to the subserosa or mesoappendiceal invasion up to 3 mm, and clear surgical margins, poses no further risk of recurrence after appendicectomy.

Most tumours (70%) are located at the tip of the appendix. However, tumours at the base of the appendix, tumours of 1-2 cm in diameter, tumors with deep mesoappendiceal invasion or margin invasion, confer a relevant risk of recurrence and further surgical procedures are warranted although no data have literally proven a survival benefit by more aggressive surgery.

Clinical Presentation

Most appendiceal NEN in adults as well as in childeren are incidental findings in post-appendicectomy specimen and therefore no characteristic tumour-specific symptomatology is established [5,17]. However, symptoms that lead to appendicectomy such as right lower abdominal pain are indirectly associated with appendiceal NEN, although due to their most frequent localisation at the tip of the appendix (approx. 70%) these tumours are very likely not causative of acute appendicitis [34-41]. In the rare cases of distant metastases these may cause symptoms related to the localisation of the metastasis.

A carcinoid syndrome is an extreme exception in metastatic patients [35,36,38] and more likely associated with an intestinal primary tumour.

Minimal Consensus Statement on Clinical Presentation

Appendiceal NEN are rarely symptomatic in the large majority of cases due to the incidental nature of their diagnosis. However, tumours with extensive local disease or distant metastases may appear symptomatic with abdominal pain, a tumour mass effect or signs of bowel obstruction. An association with the carcinoid syndrome is extremely rare and indicates metastatic disease.

Diagnostic Procedures

Since most appendiceal NEN are incidentally diagnosed at postoperative histology, diagnostic procedures relate mostly to postoperative staging, follow-up and to the rare cases with suspected or evidenced distant metastasis.

Imaging

There are no specific diagnostic studies focusing on appendiceal NEN only, and therefore the considerations which apply to small intestinal NEN are considered also valid for appendiceal NEN and have not been changed since the previous version of the guideline.

Cross-sectional imaging using CT or MRI with modern protocols should be used to rule out locoregional or distant metastasis [42-45]. NEN limited to the appendix may be detected by transabdominal ultrasonography which in spite of its investigator-dependent limitations is the least invasive procedure but has not been validated. Endoscopy is rarely helpful unless the

tumour is locally advanced and infiltrates the caecum which is a very rare situation, and thus colonoscopy for tumour detection is not recommended [46]. In the context of the potentially increased incidence of secondary neoplasms, general recommendations regarding colorectal cancer screening should be followed. Somatostatin receptor imaging (SRI) using either indium-111-somatostatin receptor scintigrapphy (SRS; including SPECT) or positron emission tomography (PET) scanning using gallium-68-labelled somatostatin analogues (SSA) in combination with CT may be considered in cases when curative resection is not completely assured or when distant metastasis is suspected [45].

Laboratory Tests

Chromogranin A (CgA) can be used as a tumour marker in appendiceal NEN like in small intestinal NEN and is particularly useful to differentiate NEN from GCC since it has been described to be increased in appendiceal NEN [47,48]. However, its role for regular follow-up (particularly for detection of recurrent disease) has not been thoroughly studied. It is indicated in metastatic disease as a follow-up parameter like in other NEN. In the extremely rare patient with carcinoid syndrome, urinary 5-HIAA may be useful [49].

Minimal Consensus Statement on Diagnostic Procedures

For the majority of well-differentiated appendiceal NEN diagnosed incidentally, with a maximum diameter <1 cm and R0 resection, no postoperative diagnostic procedure is required. For well-differentiated tumours of 1 to < 2 cm and R0 resection there are no clear data, but a single CT or MRI of the abdomen to rule out lymph node or distant involvement may be justified. In cases with deep mesoappendiceal infiltration or angioinvasion and tumours >2 cm, CT or MRI of the abdomen and SRI (SRS or SR-PET/CT) should be performed.

CgA may be used as a surrogate parameter in advanced metastatic appendiceal NEN but has not been particularly validated for diagnosis and follow-up of appendiceal NEN.

Pathology and Genetics

Histopathological characterisation of appendiceal NEN includes immunohistochemical proof of the neuroendocrine tumour entity by immunohistochemical staining for synaptophysin and CgA, as well as for Ki-67 to determine the proliferative capacity of the tumour [50-52].

The Ki-67 index also determines the tumour grading according to the current WHO classification (see table 1) [50,52] . NEN of the appendix are usually grade 1 or 2 (Ki-67-index < 20%) and thus should be considered NET [53]. Appendiceal G2-NET are considered to comprise at higher risk for recurrence and/or metastasis, however, direct proof of this is

still pending and has in fact been challenged [54]. Besides WHO-grading TNM-staging according to either UICC/AJCC or ENETS (best both) is recommended [52,53,55,56].

In cases of higher tumour grades one shoudl indeed suspect either a GCC or MANEC but rare caeses of a "true“ neuroendcrine carcinoma (G3-NEC) may occur. Neither is considered a neuroendocrine tumour (NET) and thus beyond the scope of this guideline. The management of these neoplasms should be tailored to the respective adenocarcinomas [46,56].

Stratification According to Size, Localisation and Extent of Invasion

There is no substantial change of criteria used for stratifying therapeutic decision in appendiceal NEN since the previous guideline. Thus, for extensive discussion this chapter refers the reader to the previously published guideline and just summarizes the key criteria a caregiver should have available for the therapeutic decision [46].

Summary of main prognostic features of appendiceal NEN

A. SIZE

- Tumours <1 cm (T1a according to UICC/AJCC and T1 according to ENETS; table 1) can be cured by simple appendicectomy with an excellent almost 100% long-term survival in both children and adults [5,27,28,3757| although some publications have described lypmh node metastasis [14,19] while others have not [38,58];

-T umors >1 cm but < 2cm (T1b according to UICC/AJCC and T2 according to ENETS; table 1) are most challenging for decision finding, because metastases seem to occur only rarely in this subgroup but the subgroup *per se* comprises 5–25% of all appendiceal NEN. However, a risk of metastasis seems to exist, particularly in cases >1.5 cm [5,7,14,19,41,54,57,58-60]:

- Tumors >2 cm are rare (less than 10%) but may carry a risk of metastases of up to 40% [7,37,60] therefore justifying a radical oncological resection and long-term follow-up (T2 according to UICC/AJCC and T3 according to ENETS; table 1). Metastasis has been observed in some cases of these appendiceal NET [60] while not by others [61];

- Tumors extending beyond the appendix by invading peritoneum or adjacent organs (T4 according to UICC/AJCC and ENETS, table 1), infiltrating lymph nodes (N1 according to UICC/AJCC and ENETS, table 1) or metastasizing to distant organs (M1 according to UICC/AJCC and ENETS, table 1) are no longer considered limited disease and require are systemic oncological because of poorer long-term outcome [46,53,56].

B. **Localisation within the appendix**

Most appendiceal NEN are located at the tip of the organ (60–75%) while some are located at the middle portion (5–20%) and the smallest fraction (less than 10%) at the base of the appendix. Although there is no clear correlation with outcome, incomplete resection resulting in recurrence and metastases may likely occur more frequently with an appendiceal NET located next to or at the base of the appendix [37,46,56].

C. Extent of invasion into the mesoappendix and vascular invasion:

The extent of tumor cell invasion into the mesoappendix (T2 vs. T3 stage according to ENETS, not considered by UICC/AJCC, see table 1) can relatively frequently be observed in up to 20% of adults and up to 40% in children [27,62,63]. While infiltration of the appendiceal serosa does not seem to be associated with poorer outcome, invasion into the mesoappendix shows a higher rate of vascular (V1) or lymph vessel invasion (L1) than in cases without. Furthermore, a depth of invasion >3 mm has been suggested to reflect the aggressiveness of the disease. Therefore the TNM classification by ENETS uses this criterion to distinguish T2 from T3 tumours (even in case of tumours <2 cm) [52].

The pathology report should therefore report:

- pTNM-stage,
- WHO-grading,
- Vascular (V0/1) or lymph (L0/1) vessel invasion and
- A statement on mesoappendix infiltration (and the extent oft he latter).

These criteria or risk factors can then be used as a logical and likely but hitherto formally unproven rationale for decision making of whether a right hemicolectomy should be recommended or whether it seems likely safe to not do so (see figure 1).

Minimal Consensus Statement on Pathology and Genetics

Histology is always necessary to establish the diagnosis. Cytology may be helpful, particularly in the rare metastatic setting. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for CgA and synaptophysin. Both the mitotic count per 10 HPF (2 mm^2, at least 40 fields at 40 x magnification), evaluated in areas of highest mitotic density, and Ki-67 index (MIB1 antibody; % of 2,000 cells in areas of highest nuclear labelling), should be reported (table 2). The histopathology report should allow for a correct classification according to the current WHO criteria.

ENETS-TNM staging differs for T stages from AJCC/UICC/WHO-TNM staging for appendiceal tumours. It is strongly recommended to use the ENETS-TNM classification in addition to the AJCC/UICC/WHO system and to indicate this in the pathology report (table 1).

Furthermore, vascular and lymphvacular invasion should be stated as aides to clinical decision making (figure 1). No genetic association has been reported thus far and therefore there is currently no need for any genetic testing.

Surgical Therapy

Two surgical procedures can be applied to treat local or loco-regional appendiceal NEN: simple appendicectomy and oncological right-sided hemicolectomy.

As outlined above, appendiceal NEN are frequently diagnosed incidentally at appendicectomy for suspected or manifest acute appendicitis. The NEN may either be already detected during this procedure or afterwards on histological evaluation. Similarly to the staging criteria including the risk factors mentioned above, the surgical strategy should be tailored to the individual situation (figure 1) and according to the data disscussed in the section above. In general following statements apply tot he specific situations:

1. Appendiceal NET (G1/2) smaller than 2 cm can be cured by simple appendicectomy unless incompletely resected (R1-resection status) or any of the below discussed additional siituations occur in which right sided hemicolectomy should be considered (see below) or performed (R1-resction status after initial appendicectomy).

- Appendiceal NET (G1/2) >2cm should be treated with oncological right-sided hemicolectomy. However, small G1/2-NET appear the most frequently observed clinical situation and therefore the arguments for decision-making are specified as follows:
    - o T1 (ENETS) or T1a (UICC/AJCC) NET (i.e. <1 cm): Generally simple appendicectomy is curative and sufficient (if resection status is R0). The only exception could be the extremely rare situation when the NEN is located at the base of the appendix or when a mesoappendiceal invasion >3 mm is discovered histopathologically. Under these circumstances, completion of the resection seems advisable, although a worse prognosis has not been proven and a higher complication rate than with simple appendicectomy has to be considered [5,7,14,19,41,54,57,59].
    - o T2 (ENETS) or T1b (UICC/AJCC) NET; >1 cm but <2 cm: Lymph node or distant metastases seems unlikely but possible since it has been reported several times. Thus, long-term definitive curation can be achieved with a right-sided hemicolectomy, however, increased peri- and postoperative morbidity need to be weighed against the small but existing risk of incomplete resection by appendicectomy or late recurrence (particularly in many relatively young patients). This risk may be higher if the size is >1.5 cm, particularly in children,

but evidence is too weak to exclude patients with appendiceal NET <1.5 cm from these considerations.

- Additional risk factors have been defined for assiting in decision making under these circumstances:
  - WHO-grading: G2
  - Angio- (V1) or lymphangio- (L1) invasion
  - Mesoappendiceal infiltration >3 mm

  If one or more of these risk factors coexist it is recommended to discuss right-sided hemicolectomy with patients particularly
- T3 (ENETS) or T2 (UICC/AJCC) or higher stage NET (i.e. > 2 cm): Right-sided hemicolectomy with oncological lymph node dissection is advised due to the clearly increased risk of lymph node metastasis and long-term tumour recurrence and/or distant metastasis. The operation can be performed as the initial surgical intervention as a second intervention after initial (diagnostic) appendicectomy [61].
- Appendiceal NEC (grade 3, Ki67 >20 %) should, irrespective of the tumour size, be treated using an oncological right-sided hemicolectomy and be managed as in cases of adenocarcinomas.

In pediatric patients outcome after appendiceal NET-resection has been extremely favourable in the NET group between 1 and 2 cm and even in NET >2 cm subgroup and thus these guidelines explicitly do not apply to this specific population. The cause of the even better outcome in the pediatric population is currently not understood [5,64].

Minimal Consensus Statement on Surgical Therapy

It is generally felt that a well-differentiated appendiceal NEN <2 cm is cured by appendicectomy independent of the location of the tumour. Thus, right hemicolectomy is justified only in those rare tumours 1–2 cm but with positive or unclear margins or with deep mesoappendiceal invasion (ENETS T2), higher proliferation rate (G2) and/or angioinvasion. Tumours with a diameter >2 cm should be treated by right hemicolectomy.

Follow-Up

In cases of curative resection of appendiceal NEN <1 cm by simple appendicectomy, no specific follow-up strategy has been recommended [46,65]. For cases with right-sided hemicolectomy due to a size >1 cm but without proof of lymph node involvement or any other residual disease in the resected specimen, again a specific follow-up strategy does not seem to be necessary [66]. For cases with involvement of the lymph nodes or any cases with resected distant metastases, however, longterm follow-up because of the proven invasiveness of the tumour is advised. Finally, the patient with an appendiceal NEN with a

size between 1 and 2 cm who has not received right-sided hemicolectomy for whatever reason (comorbidity, no consent, hesitancy, etc.) but with risk factors (i.e. localisation at the base of the appendix, mesoappendiceal invasion >3 mm, NET-G2 or angioinvasion), regular follow-up due to the presumed risk of lymph node metastases seems advisable but benefit for prevention of tumour recurrence or an influence on longterm outcome is unproven [66]. It should be considered that neither determination of surrogate parameters (i.e., CgA or 5-HIAA) nor indirect non-invasive imaging have been studied for their sensitivity for detection of metastasis or local tumour recurrence in this specific setting. Cumulative exposure to irradiation with repetitive scanning may be an argument to use MRI rather than CT scanning in the younger and particularly the fertile patient (female or male) [45]. The role of colonoscopy or transabdominal ultrasound imaging has not been established in this setting and is not recommended. However, it seems rational to apply transabdominal ultrasound to extend intervals between MRI or CT examinations. Although unproven, lifelong awareness of the potential of these slowly growing tumours to recur should be kept in mind in appendiceal NEN >2 cm or >1 cm with risk factors [46, 65].

Minimal Consensus Statement on Follow-Up

For guidelines regarding follow-up strategies, we recommend to follow the ENETS standards of care [120].

For well-differentiated tumours, diagnosed incidentally, with a maximum diameter <1 cm and R0 resection, no follow-up is required.

For well-differentiated tumours of 1–2 cm and R0 resection, there are no sufficient data for a clear-cut decision. Most participants of the consensus conference suggest no regular follow-up. However, in cases with risk factors follow-up may be considered, although a specific schedule is not recommended.

All other patients with either tumours >2cm, metastases or additional risk factors (R1-resection), should be followed initially after 6 and 12 months postoperatively and then annually, although this approach has also not been validated.

Please also refer to consensus guideline updates for other gastro-entero-pancreatic (GEP) neuroendocrine tumours [67-72, this issue].

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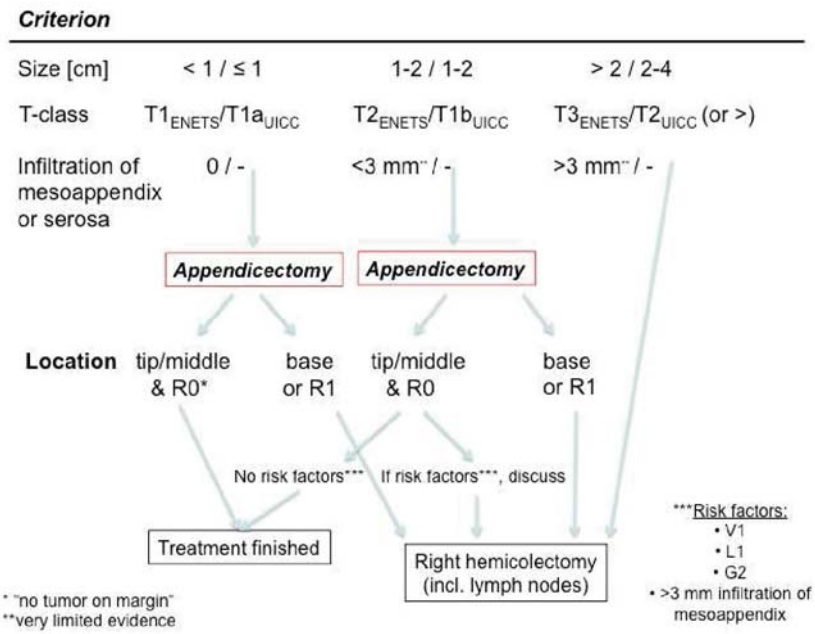

Figure 1 Therapeutic algorithm for small appendiceal NET.

V1: vascular invasion; L1: lymphatic invasion; G2: grade 2 tumour (Ki-67: 3-20)

Table 1 Grading classification of neuroendocrine neoplasms according to WHO 2010

Grading	Ki67-index	Mitotic rate
NET-G1	≤ 2%	<2/10HPF
NET-G2	3–20%	2–20/10HPF
NEC-G3	>20%	>20/10HPF

Table 2 TNM-staging for appendiceal NEN according to either ENETS or UICC/AJCC classification

	ENETS	UICC/AJCC
T – primary tumour		
x	primary tumour not assessed/assessible	
0	no evidence of any primary tumour	
1	tumour ≤ 1cm with infiltration of submucosa and muscularis propria	
1a		tumour ≤ 1cm
1b		tumour > 1cm but ≤ 2cm
2	tumour ≤ 2cm with infiltration of submucosa, muscularis propria and/or minimal (≤ 3mm) infiltration of subserosa and/or mesoappendix	tumour > 2cm but ≤ 4cm or with extension into the ceum
3	tumour >2 cm and/or extensive (> 3mm) infiltration of subserosa and/or mesoappendix	tumour > 4cm or with extension into the Ileum
4	tumour with infiltration of peritoneum and/or other neighbouring organs	tumour with perforation of peritoneum or invasion of other adjacent structures
N – regional lymph node metastasis		
Nx	regional lymph nodes not assessed/assessible	
N0	no regional lymph node metastasis	
N1	locoregional lymph node metastasis/-es	
M – distant metastasis		
MX	distant metastasis not assessed/assessible	
M0	no distant metastasis	
M1	distant metastasis/-es	

Neuroendocrinology (*International Journal for Basic and Clinical Studies on Neuroendocrine Relationships*)
Journal Editor: Millar R.P. (Edinburgh)
ISSN: 0028-3835 (Print), eISSN: 1423-0194 (Online)
www.karger.com/NEN