SIOP Europe
the European Society for Paediatric Oncology

European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

EXPeRT

NEUROENDOCRINE TUMORS OF THE APPENDIX IN CHILDREN AND ADOLESCENTS STANDARD CLINICAL PRACTICE RECOMMENDATIONS

DISCLAIMER

These ESCP guidance documents were produced by the relevant tumour group or specialist committee as recommendations on current best practice. The ESCP guidance documents are not clinical trial protocols.

The interpretation and responsibility of the use of ESCP guidance documents lies fully with the user who retains full responsibility for the use of these guidance documents and his actions and (treatment) decisions based thereon, such as, but without limitation thereto: checking and prescribing certain doses, checking prescriptions, etc. A user should never base its decision solely on the content of these guidance documents and should always check any other relevant medical information that is available and make appropriate use of all relevant medical information.

These guidance documents have been made publicly available by SIOP Europe – the European Society of Paediatric Oncology and the European Reference Network for Paediatric Oncology (ERN PaedCan). It is the responsibility of the user who downloads these documents to make sure that:

- their use within the Paediatric Clinical Unit / Hospital is approved according to the local clinical governance procedures.
- appropriate document control measures are in place to ensure that the most up-to-date locally approved versions are considered.
- any anomalies or discrepancies within the documents are immediately brought to the attention of the relevant special interest group chair and the European Clinical Study Group who has developed the ESCP guidance document.

Every care has been taken whilst preparing these documents to ensure that they are free of errors. Nonetheless, SIOP Europe and ERN PaedCan cannot be held liable for possible errors or mistakes in these guidance documents, nor can SIOP Europe and ERN PaedCan be held liable for any kind of damage resulting out of the use of these guidance documents.

TITLE: NEUROENDOCRINE TUMORS OF THE APPENDIX IN CHILDREN AND ADOLESCENTS

Document version: 5 (January 2025)

This document has been developed by EXPeRT members and collaborators:

Working Group of this recommendation:

- Oncologists: Antje Redlich (Germany), Michaela Kuhlen (Germany), Jelena Roganovic (Croatia), Paraskevi Panagopoulou (Greece), Bajciova Viera (Czech Republic), Brice Fresneau (France), Daniel Orbach (France), Ines B. Brecht (Germany), Tal Ben Ami (Israel), Martine Raphael (The Netherlands).
- Surgeons: Calogero Virgone (WP leader, Italy), Guido Seitz (Germany), Patrizia Dall'Igna (Italy), Sheila Terwisscha van Scheltinga (The Netherlands), Miranda Derselhuis (The Netherlands), Ramon Gorter (The Netherlands), Said Bachiri (The Netherlands)
- Pathologist: Guido Rindi (Italy)
- Radiologist (nuclear medicine physician): Jan Jamsek (Slovenia)

External advisors: Florent Guérin (Pediatric Surgeon, France); Ulrich-Frank Pape (Adult Oncologist, Germany)

EXPeRT members:

President: Daniel Orbach
Vice-president: Ines B. Brecht
Board Members (in alphabetical order):

Tal Ben-Ami
Ewa Bien
Gianni Bisogno
Maja Cesen
Andrea Ferrari
Ricardo Lopez Almaraz
Michaela Kuhlen

Yves Reguerre
Malgorzata Krawczyk
Dominik Schneider
Calogero Virgone

Table of contents

1. Background and rationale

1.1.0 Summary

Pediatric very rare tumors (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical for pediatric age, while others more commonly arise during adulthood and only rarely develop in children. Using the definition *any solid malignancy or borderline tumor characterized by an annual incidence < 2/million children <18 years of age*, the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT) has initially identified a number of pediatric VRT (1). Due to the low number of patients, it is very difficult – or even impossible - to conduct clinical trials on them, and this makes it demanding to develop to evidence-based treatment guidelines. Consequently, the treatment of patients with VRT is often individualized.

Background:

Neuroendocrine tumors (NETs) of the appendix, formerly known as carcinoid tumors, represent a rare entity. They are slow-growing tumors, characterized by an indolent clinical course. Although rare in children and adolescents, NETs are nevertheless the most common gastrointestinal (GI) epithelial tumors in this age group and are usually an incidental finding at histology after an appendectomy (2,3). The precise incidence in relation to the total number of appendectomies is not available. In adults, it has been estimated to be around 0.2%, while the frequency in children has been reported to be 0.169% of all appendectomies (4,5). A recent study estimated an incidence rate of 0.4% of all appendectomies performed in eight tertiary hospitals in the United States (6). Therefore, the general incidence has been reported in a range between 1:100,000 and 1.14:1000000 children per year (3,7,8).
The diagnostic workup and treatment for these tumors, when occurring in children, have not yet been standardized.

Although tumor size is considered the main prognostic variable, as surrogate marker for predicting micrometastases in regional lymph nodes (without impact on prognosis), to define the aggressiveness of the treatment approach, it remains to be established a precise pediatric cut-off that requires treatments more intensive than the simple appendectomy (2,3,9-11). The majority of authors have suggested that the aggressive therapy generally indicated in adults may be not justified in young patients as only one relapse has been described in pediatric patients (2-4,9).

Histopathological risk factors deemed to have a prognostic value are reported in older literature and in adult guidelines. According to these publications, in adult patients, secondary right hemicolectomy (RHC) in order to allow an adequate mesenteric lymph nodes dissection should be performed for tumors with size equal to or more than 2 cm in diameter (12-15), involvement of the mesoappendix (11,13,16-18), vascular or lymphatic invasion, elevated mitotic index or high proliferative index (Ki-67) (11,19), and R1 resection. As an alternative for RHC, also partial coecectomy or ileocecal resection (ICR) may be indicated for R1 tumors (20).

Nevertheless, there is currently no evidence of a prolonged overall survival (OS) and event-free survival (EFS) after RHC compared to the group of patients with above mentioned risk factors, who did not receive any kind of secondary surgical treatment (17,21). In addition, two recent meta-analyses (22,23) highlighted that bowel function problems are common in adults undergone right or left colon resection for cancer, and they seem to remain stable over time. Very few recommendations have been developed in children and adolescents.

Objective:

To establish internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with NETs of the appendix (“Standard of care recommendations for children with VRT”).

1.1.1 Background

Appendiceal NETs are rare with a prevalence of 0.169% reported by Doede et al. (5). Parkes et al. reported an incidence of 1.14 per million children per year (7). Male and female ratio is slightly imbalanced toward female sex (4).

In the pediatric population, a systematic review lead by Njere and colleagues, of a total of 958 published cases up to 2018, found a 100% OS and EFS (4), and the same results were found, more recently, in another systematic review focused on “high risk” cases (incomplete resection, tumor at base of appendix, grade 2 NET, lymphovascular or >3 mm mesoappendiceal invasion of tumor cells) (9). More recently, a Polish case series (24) reported a patient who suffered two local recurrences (both successfully treated with surgery only), and, in a German case series retrieved from insurances databases, a case with distant metastatic spread at diagnosis was included (25), but for these cases available data are very limited. These are, so far, the only cases of relapsed and metastatic appendiceal NETs reported internationally. To date, there are more than 1000 published cases with no reported mortality and an estimated relapse rate of less than 0.1% (4,24,25).

In the pediatric age group, metastases involving only regional lymph nodes are reported (4,9,26,27). These nodal lesions are represented by microscopic foci of NETs, and their prognostic value is still to be determined as well as their role in the natural history of the disease (9,26-28).

Historically, a proportion of these patients were elected to a second surgery, mostly represented by RHC with mesenteric lymphadenectomy, in consideration of the presence of known risk factors (size >1.5 or 2 cm; tumors of the appendiceal base with or without suspicious residuals, mesoappendiceal invasion, lymphovascular invasion, serosal breach); this approach is historically derived from adult guidelines. This has represented an overtreatment of the patients with benign clinical course regardless of the presence of risk factors and/or whether a second surgery is performed (2-4,9). Moreover, despite clinical evidence, the appeal to more extensive surgeries is occasionally still present in recent publications (10,26,31-34).

Although the evidence is retrieved almost exclusively from retrospective data and some larger prospective studies, the 5-year OS for children affected by appendiceal NETs is estimated to be 100% and the EFS slightly less than 100% (with only one patient presenting a local relapse reported so far): EFS and OS remain 100% also when considering only “high risk” cases as defined by van Amstel and colleagues (4,9,28). These excellent outcomes strongly suggest that a more conservative approach should be considered as the gold standard.

Most pediatric papers published in the last years have disputed the need of a second surgery (2-4,21,33,34) including RHC and less extensive procedures (limited ileocecal resections and/or cecectomies), but also of prolonged follow-up (2,4) after diagnosis.

National recommendations for diagnosis, treatment and follow-up of NETs of the appendix in pediatric age are available in France, Italy and Germany (2,3,11). The latter recommended a more aggressive approach, suggesting RHC for tumors >1.5 cm in diameter in consideration of the rate of observed lymph node metastasis in order to prevent distant metastasis. The national groups of Italy and France,

on the other hand, did not suggest RHC or other second surgery for any case, also when tumor' size exceeded 2 cm, and, in addition, de-escalated progressively the burden of follow-up investigations considering the absence of relapse risk. The German group recently published an analysis, demonstrating that neither tumor size >1,5 cm nor other associated risk factors correlated with disease recurrence or secondary metastatic spread in the subgroup of patients treated with appendectomy only (35). There was one patient with probable R1 resection due to adhesion to mesoappendix, who underwent second surgery. Residual tumor tissue was detected in the specimen. In 19 children with R1-, R2- or unclear resection status, no residual tissue of the primary tumor was detected (35).

In the adult population, the situation is different, being RHC advocated for all tumors larger than 2 cm in diameter and tumors >1 and <2 cm with associated risk factors.

The European Neuroendocrine Tumor Society (ENETS) guidelines, last published in 2023, recommend appendectomy alone for a well-differentiated appendiceal NET ≤2 cm and RHC in tumors >2 cm, or in tumours >1 and <2 cm with unclear margins, and high G2 and G3 (36). In addition, it is suggested that ileocecal resection may be an alternative to RHC in pediatric patients (36).

The North American Neuroendocrine Tumor Society (NANETS) guidelines, last published in 2010, recommend RHC in adult patients with evidence of a tumor invasion at the base of the appendix, with tumors >2 cm, with indeterminate size, with incompletely resected tumors, with lymphovascular invasion, and with meso-appendiceal invasion. In addition, RHC is recommended in patients with intermediate to high-grade tumors, with mixed histology, and with nodal involvement at appendectomy. However, they do not recommend applying these guidelines to the pediatric population, since different clinical behavior and outcomes have been reported (37).

Other published national guidelines are available, and the recommendations for adults therein are in line with those proposed by these two international societies (38-40).

Despite this suggested aggressive approach, also in the adult world, there is a debate regarding the benefits which RHC may add in the clinical course of well-differentiated appendiceal NET. Data supporting a less aggressive approach have been reported since early 2000' (18,41), nonetheless this debate has so far not led to a change in the clinical management of adults affected by appendiceal NET with recurrence and mortality rates ranging around 91-96% (42-45). The presence of conflicting data is probably due to the rarity of these neoplasms and to the fact that, in the largest case series from national registries, it is not often possible to distinguish well-differentiated forms from undifferentiated or mixed tumors and report correctly whether the mortality may be due to tumor progression or other causes. In the last years, however the aggressive approach suggested by international guidelines has been partially considered leading to the overtreatment of these patients (46-50). Pawa and colleagues in 2017 highlighted how the current adults' guidelines are really effective in identifying patients at risk of nodal metastases. At the same time, they underlined that the impact of nodal disease on patients' EFS and OS is still uncertain (46). Similar results have been shared by mono-institutional analyses performed in national centers of excellence (47-49). A European retrospective multi-institutional cohort study, focused on well-differentiated appendiceal NETs between 1 and 2 cm in size, found that RHC does not confer any advantage after appendectomy in completely resected NETs of 1–2 cm, and that regional lymph

node metastases are clinically irrelevant although present in up to 20% of their cohort (50). The appropriate approach for incompletely resected well-differentiated NETs and for NETs larger than 2 cm remains elusive, given the fact that, also in these subgroups, regional lymph node metastases may be similarly of no clinical significance (47-53).

Therefore, appendiceal NETs, both in pediatric and adult age, are indolent tumors, which may involve locoregional lymph nodes in a discreet rate (up to 20% in adult series, and 10-15% in pediatric age) and exceptionally spread to distant sites, though the clinical course seems to be remarkably better in children and adolescents (since metastatic spread and cancer-specific mortality are virtually absent in this group). The reasons behind this unexpected indolent course, compared to NETs occurring in other GI and non-GI sites, are largely unexplained: a favourable biology or an early diagnosis (appendiceal NETs may be removed/detected earlier assuming they can cause appendicitis) could be plausible explanations, but so far, they are not sufficient.
Conversely current data demonstrate that the vast majority of patients are cured by appendectomy alone rendering further surgical approaches to prevent local or distant recurrences or to benefit higher EFS or OS not necessary.

Here we present the internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with NETof the appendix established by the European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT). These recommendations are primarily focused on well-differentiated NET of the appendix, since high grade tumors, poorly differentiated entities/neuroendocrine carcinomas (NEC) and tumors with mixed histology (Mixed Neuroendocrine Non Neuroendocrine Neoplasms - MiNEN, Goblet Cell Carcinoids - GCC) are only exceptionally observed in the pediatric and adolescent age and should be treated according the existing guidelines for the adult population.

2. Methodology

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from Level I to V and the grades of recommendation A to E (*Table 1) (54)*.

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

EXPeRT members recognized that due to the rarity of this tumor, no evidence of Level I to II exists. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the “strength” of recommendations will be categorized by additional grading (Grade A to E).

To identify tumors that need shared recommendations, EXPeRT members designed the following procedure:

- Identification of the tumor of interest on the basis of its relevance, and previous EXPeRT experience, (i.e., data analysis and publication). Tumors should be classified as VRT (i.e. < 2/100.000/inhabitants/year), not already analyzed in previous Expo-r-Net project

(pleuropneumoblastoma, pancreatoblastoma, thymic tumors, rare sarcomas), not included in specific international protocols and frequent enough to be of interest[1].

- Designation of two main coordinators for each VRT based on their experience (data analysis, publications, personal experience).

Coordinators must:

- Analyze the medical literature and select the relevant papers.

- Propose a series of recommendations in the form of a first draft of recommendations.

- Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, into a selected expert group of EXpERT members and annotated.

- A mature version of recommendations will be produced, taking into account proposals from the group of selected EXPeRT members.

- The annotated draft will be then proposed to external experts identified by the coordinators based on a recognized experience on the tumor (pediatrician, medical oncologist, radiation oncologist, surgeon…).

- The final version will be validated by the whole group. In case of remaining disagreements, a vote will be done, during a physical consensus meeting, to agree on in a final consensus.

- Validated version will be submitted for publication in an open-source peer review journal.

The final document including recommendations will be available on EXPeRT website.

NB: These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of their patients. The EXPeRT members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members of these groups via the EXPeRT website: ***https://vrt.cineca.it***

3. Patient group

3.3.1 Diagnostic Criteria

NETs of the appendix are mostly diagnosed by the pathologist as an incidental finding, after the appendix is removed due to appendicitis or as a side procedure performed during another abdominal surgery. Therefore, clinical manifestations are those of appendicitis, such as abdominal pain and fever, and leukocytosis.

The pathologic criteria according to the most recent WHO classification (Appendix 1) classifies those as well-differentiated neuroendocrine tumors (low G1, intermediate G2, and high grade G3 NET), neuroendocrine carcinomas (large cell type – LCNEC, and small cell type - SCNEC), and Mixed Neuroendocrine Non-Neuroendocrine neoplasms (MiNEN, including well-differentiated tumors and poorly differentiated tumors; “goblet cell carcinoid” are adenocarcinomas and not MiNEN) (26).

Appendiceal NETs are staged as per the AJCC/ENETS staging system (Appendix 1) that was recently upgraded to the 9th edition (55).

Carcinoid syndrome (CS) is defined as “chronic diarrhea and/or flushing in the presence of systemic elevated levels of serotonin or its metabolite 5-hydroxyindolacetic acid (5-HIAA)” (56). It is reported to be associated to well-differentiated NETs mostly originating from the GI tract, and less frequently from lung, ovary, pancreas, or unknown origin. Other symptoms may include bronchospasm or abdominal pain. Since serotonin and other hormones produced by the tumor and causing the onset of CS are inactivated by the liver, CS is a sign of a large secreting tumor burden bypassing the portal flow and usually equalizing bulky liver metastasis.

CS has not been described in pediatric age. Njere and colleagues, reported in the systematic review12 children with flushing (2/12 also present diarrhea), but without evidence of large tumor burden demonstrating CS (4). Since a massive metastatic involvement of the liver may be seen only exceptionally in pediatric age, other causes of flushing or diarrhea should be taken into consideration (56).

3.3.2 Imaging (after appendectomy)

3.3.2.1 Primary tumor and its loco-regional tumor extension:

Imaging after appendectomy seems to have a limited role since the resolution of ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) is hardly useful to detect residual disease smaller than 1 cm or nodal micrometastasis defined as a metastatic focus with a size between 0.2 and 2.0 mm, and represent the only reported extra-appendicular possible disease in these patients (57,58); similarly, somatostatin receptor imaging (SRI) techniques might miss or underdetect lymph node micrometastases, and reports of the pitfalls of SRI have been published (59-64).

However, in a recent adult study (60), it has been underlined how SRI may have two major advantages: positron emission tomography-CT (PET/CT) using 68Ga-labeled somatostatin analogs (i.e. [^{68}Ga]Ga-DOTA-TOC and [^{68}Ga]Ga-DOTA-TATE) reveal several additional metastases compared to conventional radiological methods (CT/MRI); and demonstration of tumor receptor expression may select patients eligible for peptide receptor radionuclide therapy (PPRT).
In the past, ^{111}In-Pentetreotide scintigraphy (OctreoScan®) was widely used in the post-appendectomy staging of pediatric patients with appendiceal NETs, but it is universally recognized that OctreoScan® is nowadays replaced by SRI-PET study such as [^{68}Ga]Ga-DOTA-TOC and [^{68}Ga]Ga-DOTA-TATE.
De Lambert and colleagues reported that none of their patients had abnormal octreotide scintigraphy, even those with positive lymph nodes on pathological examination after secondary surgery. Volpe et al. published a case report of a 5-year-old child with a 5 cm-diameter NET of the appendix with one positive lymph node and normal octreotide scintigraphy (2). In the Italian TREP Project series, Virgone reported a patient with a positive octreotide scintigraphy who underwent without positive nodes at second surgery, and another patient, with a positive OctreoScan® and abnormal levels of 5-hidroxyindolacetic acid (5-HIIA), who had a node positive for micrometastasis at second surgery (3). Boxberger et al. concluded, in their prospective study on 237 patients, that octreotide scintigraphy was not sensitive enough to be routinely suggested (11).

In almost all pediatric patients, however, nodal micrometastases are the unique possible target and, since the resolution of both conventional and functional imaging is suboptimal for this aim, there is no evidence to support the routine utilization of both conventional and SRI imaging techniques *[Level IV; Grade E]*.

A cautionary attitude can be accepted in patients with one or a combination of risk factors in pediatric age:

- R1/microscopic residuals (tumors located to the base of the appendix)
- Size >2 cm
- Grade >2
- Positive nodes at the time of appendectomy.

In these patients a postoperative abdominal MRI (suspicious microscopic residuals, size >2 cm, positive nodes found at the time of appendectomy), or SRI (tumor grade >2 or NEC, suspicious microscopic residuals), or PET/MRI-CT (tumor grade >2 or NEC, suspicious microscopic residuals) are not recommended but can be performed at discretion of the treating physician and/or following Multidisciplinary team (MDT) discussion *[Level IV; Grade C]*

3.3.2.2 Distant metastasis

The initial stage assessment should be limited, as only one case of metastatic disease in the pediatric population has been reported so far. In the very rare case when clinical metastatic spread is suspected (25), it should include:

- MRI scan of the abdomen.
- Functional imaging (SRI): SRI-PET studies such as [^{68}Ga]Ga-DOTA-TOC and [^{68}Ga]Ga-DOTA-TATE; PET-MRI with hepatospecific contrast agents when liver metastases are suspected (64); PET-CT when site of metastases is thought to involve mesentery, bone or lungs.
- Laboratory investigations including serum 5-HIIA, Chromogranin A (CgA), Neuron-specific Enolase (NSE). *[Level V; Grade C]*

3.3.3 Histopathology

Careful histopathological evaluation should be undertaken, and doubtful cases should be referred for second opinion to tertiary centers *[Level IV; Grade A]*. The histopathological work-up varies according to the type of specimen submitted and is performed according to standard routine methods. For appendectomy specimen, the entire appendix should be processed *[Level IV; Grade A]*. Conventional hematoxylin and eosin (HE) stain and immunohistochemistry (IHC) forCgA, synaptophysin and Ki-67 (MIB-1 clone) should be performed to allow proper grading, staging and margin assessment (65). Other IHC test may be performed and include hormones (serotonin, Glycentin and Peptide YY [PYY]) for distinguishing serotonin-producing enterochromaffin-cell (EC) versus L-type cell tumors and somatostatin receptor type 2/5 ($SSR_{2/5}$). The report should contain the following informations: type of resection, tumor site, tumor size, tumor type (NET, NEC, MiNEN) and grade (65), stage (AJCC 9th ed) (54), mitotic index and Ki-67% in clear, infiltration level, resection margin(s) status, invasion of vessel (hematic and lymphatic) and nerves, number of lymph-nodes and number of positive lymph nodes (66) *[Level IV; Grade A]*.

3.3.4 Molecular pathology

There are no recommended molecular tests for appendiceal NETs (67).

.

3.3.5 Additional assessments (after appendectomy)

Serum levels:

- CgA: generally in normal range, since levels correlate with tumor load
- NSE: utility not confirmed

Urinary levels:

- 5-HIIA: not recommended unless CS is suspected

Traditionally, laboratory investigations included the measurement of the urinary levels of 5-HIIA, which are elevated in case of bulky residual disease or large liver metastases, but none of these conditions have been encountered in the pediatric population. It is therefore reasonable to avoid any laboratory marker measurements in the follow-up of these patients *[Level IV; Grade D]*.

4. Treatment details

4.3.1 General considerations

- **MDT** consultation is mandatory at diagnosis and during therapy for those patients with tumors presenting with risk factors (size >2 cm, suspicious residuals, grade 3, positive nodes found at appendectomy, suspicious nodal and distant metastases, local relapse, CS) as reported below *[Level IV; Grade A]*.
- Patients/families should be offered to participate in a **prospective clinical trial (or in a registry)** when available, with **data collection** in national or international databases to improve the knowledge of this disease *[Level IV; Grade B]*.
- Post-appendectomy treatment of NET of the appendix should be avoided as much as possible, since the outcome of these entities in the pediatric population is generally favorable irrespectively of the extent of a second surgery and the presence of risk factors *[Level III; Grade B]*.

The treatment flowchart proposed by the PARTNER group is detailed in *Appendix 2*.

4.1.2 Chemotherapy

NET of the appendix can usually be cured by resection only. In case of distant metastases in pediatric patients, re-assessment by an experienced pathologist is strongly advised for aiming at excluding appendiceal NEC and MiNEN. In case of NEC, MDT discussion including among others adult oncologists and nuclear radiologists is mandatory to consider individual treatment options based on tumor characteristics, including systemic treatment analogue to the treatment of colonic adenocarcinoma *[Level IV; Grade B]*.

3.1.3 Local treatment (after appendectomy)

As mentioned, appendectomy alone seems to be curative in all pediatric patients with NET of the appendix, irrespectively of presenting risk factors *[Level III; Grade A]*. Therefore, the need for a second surgery in this age group is largely debated and it should be reserved only to a highly selected subgroup of patients after MDT discussion.

The risk factors that could be taken into consideration in the pediatric population are *[Level IV; Grade B]*:

- R1/microscopic residuals (tumors located to the base of the appendix)
- Size >2 cm
- Grade >2
- Positive nodes at the time of appendectomy
- Suspicious secondary lesions found at postoperative imaging

Other risk factors as reported by adult guidelines seem not to apply to the pediatric population *[Level III; Grade E]:*

- Lymphovascular invasion

- Serosal breach (perforated appendix) or tumor rupture
- Invasion of the mesoappendix

A second surgery may be performed but with different aims and results:

- RHC: it is aimed to improve local control, and it allows a complete regional lymphadenectomy
- Ileocecal resection: it is aimed to improve local control and it allows only a partial regional lymphadenectomy
- Partial cecectomy or pull string-suture removal: local (primary tumor) control only

3.1.3.1 Appendiceal NET without risk factors (<2 cm, completely resected)

In this group of patients, a second surgery is discouraged as no benefit in terms of OS and EFS can be retrieved from the literature. In particular, tumors between 1 cm and 2 cm in major diameter are properly cured by appendectomy alone, and the suggestion to treat these patients considering younger age as a risk factor, as argued in the ENETS guidelines, is not supported by clinical evidences *[Level III; Grade A].*

3.1.3.2 Appendiceal NET with risk factors (serosal breach/tumor rupture, mesoappendiceal invasion, lymphovascular invasion)

These findings may be present in up to 20% of cases, alone or in combination (serosal breach/tumor rupture, mesoappendiceal invasion, lymphovascular invasion). As mentioned before, though they are considered risk factors in adult guidelines, there is no evidence that these are associated with higher risk in the pediatric age group. Appendectomy alone should be considered curative in these patients *[Level III; Grade A].*

3.1.3.3 Appendiceal NET with size >2 cm

In this group of patients,a second surgery did not have an impact on OS and EFS. Appendectomy alone should be considered curative in these patients *[Level IV; Grade A].*

3.1.3.4 Appendiceal NET with histologically proven incomplete resection or located to the base of the appendix (suspicious microresiduals)

Around 6-7% of NETs are located at the base of the appendix and/or are treated with a marginal resection. Traditionally, in these patients a re-excision has been performed: in those who underwent RHC or a limited cecal resection, residual tumors or positive nodes were detectable only in a minority of cases (around 6-10%%) (2-4,9,35). In addition, patients with the same indications and observed without second surgery did not experience local or distant relapse, and are in complete remission even at longer follow-up. In addition, the presence of nodal histological involvement does not correlate to the patient outcome and should not be a surrogate marker to decide the need of RHC (2-4,9,35).

These data suggest that appendectomy alone is sufficient, and no second surgeries should be deemed necessary *[Level IV; Grade D].* However, MDT discussion is advised on a local and/or on a national level, if needed to be discussed the role of limited complementary cecectomy/ileocecal resection in case of R1 resection *[Level IV; Grade B].*

3.1.3.5 Appendiceal NET with nodal involvement at appendectomy

One to 2% of cases may have positive nodes found at appendectomy when the mesoappendix is removed together with the appendix. However, once again, in children there is not evidence proving that nodal microfoci of appendiceal NET may lead to lower EFS and OS, and most reported cases were only observed with an uneventful follow-up (4,9,11,35).

These data suggest that appendectomy alone is sufficient, and no second surgeries should be deemed necessary *[Level IV; Grade D]*. However, MDT discussion is advised on a local and/or on a national level *[Level IV; Grade B]*.

3.1.3.6 Appendiceal NET with suspicious nodal or distant lesions

Patients with these characteristics are very rarely observed. In the series published by Virgone and colleagues (3), two patients had a second surgery because of a suspected liver metastasis and of SRI-positive nodes, respectively: the liver lesion was found to be a focal nodular hyperplasia (FNH) and the node was positive for NET micrometastases. Since in pediatric age loco-regional nodal metastases have no impact on EFS and OS and the occurrence of distant metastases has not been reported so far, appendectomy alone may be considered sufficient when nodal metastases are suspected (35). *[Level IV; Grade B]*

Biopsy/second surgery of distant lesions may be indicated when clinical and radiological data do not allow to rule out distant metastases. However, a central review (or second review) of the initial diagnosis, and MDT discussion are always recommended on a local and/or on a national level *[Level IV; Grade B]*.

3.1.3.7 Appendiceal NET grade 3

G3 NET are extremely rarely encountered in children and adolescents: only 2 patients with G3 NET have been reported so far and both did well after appendectomy alone (22).

Appendectomy alone may be considered sufficient in most cases, and no second surgeries should be necessary. However, MDT discussion is always recommended on a local, and/or on a national level, if needed, and when other risk factors are present (R1, size > 2 cm). In addition, follow-up is recommended in these subset of patients. *[Level V; Grade B]*

3.1.3.8 Local Relapse

Only one patient with a local relapse has been reported so far (24): the patient underwent resection of the relapse (located to the recto-vesical pouch, G1 well-differentiated NET) and achieved second complete remission.

Surgery should be considered as the treatment of choice *[Level V; Grade C]*, but MDT discussion is always recommended on a local, and/or on a national level*[Level V; Grade B].*

3.1.3.9 Poorly differentiated NEN (neuroendocrine carcinoma) and other histology

These very rare histologies (NEC, MiNEN) usually show more aggressive course and should be considered malignant tumors. There are no data regarding the onset or the real incidence in pediatric age and even in the adolescent group. Appendiceal goblet cell carcinoid is no longer considered as a neuroendocrine tumor, and in the last WHO classification is identified as goblet cell adenocarcinoma (68,69). The existing guidelines for adults do recommend treating them as colonic adenocarcinoma. Referral to the adult oncology team is recommended to plan properly any diagnostic and therapeutic strategy. *[Level IV; Grade A].*

Discussion by a Multidisciplinary Team (MDT) is highly recommended in case of R1 resection, tumors larger than 2 cm, high grade lesions and NEC, MINEN, and in those with suspicious residual at the post-appendectomy investigations (imaging and laboratory assessment), when performed. *[Level V; Grade B]*.

5. Assessment in case of distant metastasis

Patients with metastatic disease should undergo clinical and radiological evaluation before, during and after the end of treatment. Contrast-enhanced CT scan with , or MRI, or PET/MRI-CT may be adopted depending on the primary tumor location. Other imaging evaluation should include all known metastatic sites and should be considered depending on clinical evaluation *[Level V; Grade B].*

Due to the rarity of metastases, biopsy with histopathology analysis of all distant lesions should be performed to confirm the diagnosis *[Level V; Grade B]*.

6. Side effects associated with treatment

Type of treatment	Main side effects
Surgery (right hemicolectomy, ileocecal resection)	General complications: bleeding, surgical site infection Short term complications: - ileus - anastomotic leak - stricture - ureteral injuries Long term complications - augmented intestinal motility (loss of the ileocecal valve)

6. Supportive treatment

After surgery, general supportive postoperative treatment (i.e., analgesia, GI motility, nutrition, wound surveillance and scar nursing) are recommended *[Level V; Grade A]*.

7. Genetic considerations

Diets and colleagues (70) recently reported a subset of patients with appendiceal NET and characteristics suspicious for a cancer predisposition syndrome, but only one patient was found to have familial adenomatous polyposis (FAP). Interestingly, they reported up to four patients with a multifocal tumor, which is a very rare occurrence in pediatric appendiceal NETs. In addition, they demonstrated a higher incidence of Crohn´s disease. The authors hypothesized that the finding of an appendiceal NET in patients affected by FAP or Crohn´s disease may be explained by three different theories:

- Higher number of colectomies in these patients which may lead to more incidental findings of appendiceal NETs
- Chronic inflammation which may lead to hyperstimulation of endocrine cells resulting in cell hyperplasia and tumor development
- Common genetic factors which may predispose to both conditions.

Moreover, a possible genetic driver in the onset of some appendiceal NETs is supported by the finding of one familial case (71).

As mentioned, no specific genetic predisposition has been reported to date. In this context, there is no specific need for genetic counselling in pediatric appendiceal NETs *[Level IV; Grade E]*. This option may

be discussed and should thus be proposed on an individual basis depending on family history and preferences *[Level IV; Grade B]*.

8. Patient follow-up

The traditional follow-up investigations adopted for pediatric appendiceal NET have been variably used in published case series. Current evidence demonstrates that conventional imaging (MRI, CT) and functional imaging (scintigraphy with 111In-Pentetreotide, later replaced by other SRI) can be useful only in a very limited number of cases, even though they have been performed sparsely in the past without or with few per protocol criteria. The same point can be made for blood (NSE, CgA) and/or urine markers (5-HIIA).

It has been widely demonstrated that both imaging and markers may detect a residual disease when the tumor burden is high (57-63). However, this is almost never seen in pediatric patients.

In detail, 5-HIIA is not recommended unless CS is present, CgA is generally in normal range, since its levels correlate with tumor load, and NSE has not been proven to be useful in appendiceal NETs (59).

The resolution limits of the various radiological methods should be emphasized: MRI and CT scan may detect tumors or residuals > 1 cm, while [^{68}Ga]Ga-DOTA-TOC, [^{68}Ga]Ga-DOTA-TATE PET-CT and other SRI are usually not useful in low stage NETs as most follow-up SRI-PET studies in low risk patients are negative and the risk of false positive findings should not be minimised. (57-63).

The length of follow-up has traditionally been recommended for 5 to 10 years except for those cases with R0 tumors <1 cm, and tumors between 1 and 2 cm with no lymph-node metastases at second surgery.

This suggests that very few patients should be followed-up for 5 (or 10) years after diagnosis, and that both imaging and marker assay should be used in a very limited subset of patients.

Although it is not clear how to define a risk stratification for eligibility to follow-up, it is evident that a routine surveillance should not rely on markers and functional imaging, since the vast majority of pediatric appendiceal NETs are low stage tumors.

Our follow-up recommendations *[Level IV; Grade C]* are as follows:

- Appendiceal NETs < 2 cm which have been completely resected (R0), and without other risk factors (G3, N1): no follow-up is recommended
- Appendiceal NETs ≥2 without risk factors: 5 years of follow-up including yearly clinical evaluation and abdominal ultrasound scan
- Appendiceal NETs <2 cm with risk factors (R1, G3, N1): 5 years of follow-up including yearly clinical evaluation and abdominal ultrasound scan
- Appendiceal NETs ≥2 cm with risk factors (R1, G3, N1): postoperative abdominal MRI scan (or CT scan) at diagnosis (SRI-PET only in case of equivocal MRI/CT findings), and 5 years of follow-up including yearly clinical evaluation and abdominal ultrasound

The follow-up flowchart proposed by the PARTNER group is detailed in *Appendix 3*.

9. Reference list

1. Ferrari A, Brecht IB, Gatta G, Schneider DT, Orbach D, Cecchetto G, Godzinski J, Reguerre Y, Bien E, Stachowicz-Stencel T, Ost M, Magni C, Kearns P, Vassal G, Massimino M, Biondi A, Bisogno G, Trama A. Defining and listing very rare cancers of paediatric age: consensus of the Joint Action on Rare Cancers in cooperation with the European Cooperative Study Group for Pediatric Rare Tumors. Eur J Cancer. 2019;110:120-6.
2. de Lambert G, Lardy H, Martelli H, Orbach D, Gauthier F, Guérin F. Surgical Management of Neuroendocrine Tumors of the Appendix in Children and Adolescents: A Retrospective French Multicenter Study of 114 Cases. Pediatr Blood Cancer. 2016;63(4):598-603.
3. Virgone C, Cecchetto G, Alaggio R, Ferrari A, Bisogno G, Conte M, Inserra A, Fagnani AM, Indolfi P, Salfi N, Dall'Igna P. Appendiceal neuroendocrine tumours in childhood: Italian TREP project. J Pediatr Gastroenterol Nutr. 2014;58(3):333-8.
4. Njere I, Smith LL, Thurairasa D, Malik R, Jeffrey I, Okoye B, Sinha C.. Systematic review and meta-analysis of appendiceal carcinoid tumors in children. Pediatr Blood Cancer. 2018;65(8):e27069.
5. Doede T, Foss HD,Waldschmidt J. Carcinoid tumors of the appendix in children-epidemiology, clinical aspects and procedure. Eur J Pediatr Surg. 2000;10:372–7.
6. Zeineddin S, Aldrink JH, Bering J, Hoyt DW, Kastenberg ZJ, Brungardt J, Dasgupta R, Rinehardt HN, Malek MM, Ziogas IA, Roach JP, Craig BT, Rothstein DH, Lautz TB. Multi-institutional assessment of the prevalence of neuroendocrine tumors in children undergoing laparoscopic appendectomy for acute appendicitis in the United States. Pediatr Blood Cancer. 2023;70(11):e30620.
7. Parkes SE, Muir KR, Al Sheyyab M, Cameron AH, Pincott JR, Raafat F, Mann JR. Carcinoid tumours of the appendix in children 1957–1986: incidence, treatment and outcome. Br J Surg. 1993;80:502–4.
8. Duess JW, Lange A, Zeidler J, Blaser J, Dingemann C, Ure BM, Lacher M, Gosemann JH, Hofmann AD. Appendiceal Carcinoids in Children-Prevalence, Treatment and Outcome in a Large Nationwide Pediatric Cohort. Medicina (Kaunas). 2022;59(1):80.
9. van Amstel P, Mahieu A, Bakx R, de Vries R, Raphael MF, Derikx JPM, van Heurn LWE, Gorter RR. Management and outcome of high-risk neuroendocrine tumors of the appendix in children; A systematic review. Eur J Surg Oncol. 2023;49(2):329-38.
10. Simon CT, Ehrlich P, Hryhorczuk A, Rabah R, Sedig L, Stoll T, Heider A. Well- Differentiated Neuroendocrine Tumors of the Appendix in Children and Adolescents: A Clinicopathologic Study. Pediatr Dev Pathol. 2023;26(3):250-8.
11. Boxberger N, Redlich A, Böger C, Leuschner I, von Schweinitz D, Dralle H, Vorwerk P. Neuroendocrine tumors of the appendix in children and adolescents. Pediatr Blood Cancer. 2013;60(1):65-70.
12. Moertel CG, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. Cancer. 1968;21:270–8.

13. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: Treatment and prognosis. N Engl J Med. 1987;317:1699–701.
14. Bowman GA, Rosenthal D. Carcinoid tumors of the appendix. Am J Surg. 1983;146:700–703.
15. Anderson JR, Wilson BG. Carcinoid tumours of the appendix. Br J Surg. 1985;72:545–6.
16. Syracuse DC, Perzin KH, Price JB,Wiedel PD, Mesa-Tejada R. Carcinoid tumors of the appendix. Mesoappendiceal extension and nodal metastases. Ann Surg. 1979;190:58–63.
17. Spunt SL, Pratt CB, Rao BN, Pritchard M, Jenkins JJ, Hill DA, Cain AM, Pappo AS. Childhood carcinoid tumors: The St Jude Children's Research Hospital experience. J Pediatr Surg. 2000;35:1282–6.
18. Bamboat ZM, Berger DL. Is right hemicolectomy for 2.0-cm appendiceal carcinoids justified? Arch Surg. 2006;141:349–52.
19. Tchana-Sato V, Detry O, PolusM, Thiry A, Detroz B, Maweja S, Hamoir E, Defechereux T, Coimbra C, De Roover A, Meurisse M, Honoré P. Carcinoid tumor of the appendix: A consecutive series from 1237 appendectomies. World J Gastroenterol. 2006;12:6699–701.
20. Dall'Igna P, Ferrari A, Luzzatto C, Bisogno G, CasanovaM, Alaggio R, Terenziani M, Cecchetto G. Carcinoid tumor of the appendix in childhood: The experience of two Italian institutions. J Pediatr Gastroenterol Nutr. 2005;40:216–9.
21. Corpron CA, Black CT, Herzog CE, SellinRV, Lally KP, Andrassy RJ. A half century of experience with carcinoid tumors in children. Am J Surg. 1995;170:606–8.
22. Verkuijl SJ, Furnée EJB, Kelder W, Hoff C, Hess DA, Wit F, Zijlstra RJ, Trzpis M, Broens PMA. Long-term Bowel Dysfunction and Decline in Quality of Life Following Surgery for Colon Cancer: Call for Personalized Screening and Treatment. Dis Colon Rectum. 2022;65(12):1531-1541.
23. Verkuijl SJ, Jonker JE, Trzpis M, Burgerhof JGM, Broens PMA, Furnée EJB. Functional outcomes of surgery for colon cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2021;47(5):960-969.
24. Panek M, Szymczak M, Stepaniuk M, Górecki W, Gawłowska-Marciniak A, Wolak P, Zbyrad D, Rybkiewicz M, Chrobak K, Noparlik R, Niedzielski J, Janik P, Nowak J, Miaśkiewicz W, Kamiński A, Fischer W, Dembowska-Bagińska B, Kaliciński P. Radical surgical treatment of neuroendocrine tumors of the appendix in children - a Polish multicenter study. Arch Med Sci. 2021;17(4):1128-31.
25. Duess, JW Lange A, Zeidler J Blaser J, Dingemann C Ure BM Lacher M, Gosemann JH, Hofmann AD. Appendiceal Carcinoids in Children–Prevalence, Treatment and Outcome in a Large Nationwide Pediatric Cohort. Medicina (Kaunas). 2022;59(1):80.
26. Couvelard A, Perren A, Sipos B. Appendiceal neuroendocrine neoplasms. In: WHO classification of tumors. Tumors of the digestive tract, 5th edition Lyon: International Agency for Research on Cancer. 2019; pp 152-5.
27. Parikh PP, Perez EA, Neville HL, Hogan AR, Sola JE. Nationwide overview of survival and management of appendiceal tumors in children. J Pediatr Surg. 2018;53(6):1175–80.
28. Mishra PR, Stringer MD. Appendiceal carcinoid tumors: a plea for critical reporting. Pediatr Surg Int. 2020;36(4):539-40.

29. Ranaweera C, Brar A, Somers GR, Sheikh F, Pierro A, Zani A. Management of pediatric appendiceal carcinoid: a single institution experience from 5000 appendectomies. Pediatr Surg Int. 2019;35(12):1427-30.
30. Johnson PR. Gastroenteropancreatic neuroendocrine (carcinoid) tumors in children. Semin Pediatr Surg. 2014;23(2):91-5.
31. Sommer C, Gumy Pause F, Diezi M, Rougemont AL, Wildhaber BE. A National Long-Term Study of Neuroendocrine Tumors of the Appendix in Children: Are We Too Aggressive? Eur J Pediatr Surg. 2019;29(5):449-57.
32. Wu H, Chintagumpala M, Hicks J, Nuchtern JG, Okcu MF, Venkatramani R. Neuroendocrine Tumor of the Appendix in Children. J Pediatr Hematol Oncol. 2017;39(2):97-102.
33. Henderson L, Fehily C, Folaranmi S, Kelsey A, McPartland J, Jawaid WB, Craigie R, Losty PD. Management and outcome of neuroendocrine tumours of theappendix—a two centre UK experience. J Pediatr Surg. 2014;49:1513–7.
34. Kim SS, Kays DW, Larson SD, Islam S. Appendiceal carcinoids in childrenmanagement and outcomes. J Surg Res. 2014;192:250-3.
35. Kuhlen M, Kunstreich M, Pape UF, Seitz G, Lessel L, Vokuhl C, Frühwald MC, Vorwerk P, Redlich A. Lymph node metastases are more frequent in paediatric appendiceal NET ≥1.5 cm but without impact on outcome - Data from the German MET studies. Eur J Surg Oncol. 2024;50(4):108051.
36. Kaltsas G, Walter T, Knigge U, Toumpanakis C, Santos AP, Begum N, Pape UF, Volante M, Frilling A, Couvelard A. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for appendiceal neuroendocrine tumours (aNET). J Neuroendocrinol. 2023;35(10):e13332..
37. Boudreaux JP, Klimstra DS, Hassan MM, Woltering EA, Jensen RT, Goldsmith SJ, Nutting C, Bushnell DL, Caplin ME, Yao J; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas. 2010;39(6):753-66.
38. Bednarczuk T, Zemczak A, Bolanowski M, Borowska M, Chmielik E, Ćwikła JB, Foltyn W, Gisterek I, Handkiewicz-Junak D, Hubalewska-Dydejczyk A, Jarząb M, Junik R, Kajdaniuk D, Kamiński G, Kolasińska-Ćwikła A, Kopacz-Wróbel K, Kowalska A, Królicki L, Kunikowska J, Kuśnierz K, Lewiński A, Liszka Ł, Londzin-Olesik M, Marek B, Malczewska A, Nasierowska-Guttmejer A, Nowakowska-Duława E, Pavel ME, Pilch-Kowalczyk J, Reguła J, Rosiek V, Ruchała M, Rydzewska G, Siemińska L, Sowa-Staszczak A, Starzyńska T, Stojčev Z, Strzelczyk J, Studniarek M, Syrenicz A, Szczepkowski M, Wachuła E, Zajęcki W, Zgliczyński W, Zieniewicz K, Kos-Kudła B. Neuroendocrine neoplasms of the small intestine and the appendix - update of the diagnostic and therapeutic guidelines (recommended by the Polish Network of Neuroendocrine Tumours) Endokrynol Pol. 2022;73(3):549-83.
39. Ito T, Masui T, Komoto I, Doi R, Osamura RY, Sakurai A, Ikeda M, Takano K, Igarashi H, Shimatsu A, Nakamura K, Nakamoto Y, Hijioka S, Morita K, Ishikawa Y, Ohike N, Kasajima A,

Kushima R, Kojima M, Sasano H, Hirano S, Mizuno N, Aoki T, Aoki T, Ohtsuka T, Okumura T, Kimura Y, Kudo A, Konishi T, Matsumoto I, Kobayashi N, Fujimori N, Honma Y, Morizane C, Uchino S, Horiuchi K, Yamasaki M, Matsubayashi J, Sato Y, Sekiguchi M, Abe S, Okusaka T, Kida M, Kimura W, Tanaka M, Majima Y, Jensen RT, Hirata K, Imamura M, Uemoto S.. JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis. J Gastroenterol. 2021;56(11):1033-44.

40. de Mestier L, Lepage C, Baudin E, Coriat R, Courbon F, Couvelard A, Do Cao C, Frampas E, Gaujoux S, Gincul R, Goudet P, Lombard-Bohas C, Poncet G, Smith D, Ruszniewski P, Lecomte T, Bouché O, Walter T, Cadiot G; Thésaurus National de Cancérologie Digestive (TNCD).. Digestive Neuroendocrine Neoplasms (NEN): French Intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, GTE, RENATEN, TENPATH, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Dig Liver Dis. 2020 May;52(5):473-92.
41. Assadi M, Kubiak R, Kaiser G. Appendiceal carcinoid tumors in children: does size matter? Med Pediatr Oncol. 2002;38(1):65-6.
42. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008 20;26(18):3063-72.
43. Onyemkpa C, Davis A, McLeod M, Oyasiji T. Typical carcinoids, goblet cell carcinoids, mixed adenoneuroendocrine carcinomas, neuroendocrine carcinomas and adenocarcinomas of the appendix: a comparative analysis of survival profile and predictors. J Gastrointest Oncol. 2019;10(2):300-6.
44. Mullen JT, Savarese DM. Carcinoid tumors of the appendix: a population-based study. J Surg Oncol. 2011;104(1):41-4.
45. Guzman C, Boddhula S, Panneerselvam N, Dodhia C, Hellenthal NJ, Monie D, Monzon JR, Kaufman T. Appendiceal Carcinoid Tumors: Is There a Survival Advantage to Colectomy over Appendectomy? J Gastrointest Surg. 2020;24(5):1149-57.
46. Pawa N, Clift AK, Osmani H, Drymousis P, Cichocki A, Flora R, Goldin R, Patsouras D, Baird A, Malczewska A, Kinross J, Faiz O, Antoniou A, Wasan H, Kaltsas GA, Darzi A, Cwikla JB, Frilling A.. Surgical Management of Patients with Neuroendocrine Neoplasms of the Appendix: Appendectomy or More. Neuroendocrinology. 2018;106(3):242-51.
47. Alabraba E, Pritchard DM, Griffin R, Diaz-Nieto R, Banks M, Cuthbertson DJ, Fenwick S. The impact of lymph node metastases and right hemicolectomy on outcomes in appendiceal neuroendocrine tumours (aNETs). Eur J Surg Oncol. 2021;47(6):1332-8.
48. Holmager P, Willemoe GL, Nielsen K, Grøndahl V, Klose M, Andreassen M, Langer SW, Hansen CP, Kjær A, Federspiel BH, Knigge U. Neuroendocrine neoplasms of the appendix: Characterization of 335 patients referred to the Copenhagen NET Center of Excellence. Eur J Surg Oncol. 2021;47(6):1357-63.

49. Storan D, Swan N, Swan K, Thuillier R, Skehan S, Gallagher T, O'Shea D, O'Toole D. Clinical features and outcomes of appendiceal neuroendocrine tumours: 10 year audit from the Irish NET Centre of Excellence. J Neuroendocrinol. 2023:e13329.
50. Nesti C, Bräutigam K, Benavent M, Benavent M, Bernal L, Boharoon H, Botling J, et al. Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: a retrospective, Europe-wide, pooled cohort study. Lancet Oncol. 2023;24(2):187-94.
51. Daskalakis K, Alexandraki K, Kassi E, Tsoli M, Angelousi A, Ragkousi A, Kaltsas G. The risk of lymph node metastases and their impact on survival in patients with appendiceal neuroendocrine neoplasms: a systematic review and meta-analysis of adult and paediatric patients. Endocrine. 2020;67(1):20-34.
52. Mehrvarz Sarshekeh A, Advani S, Halperin DM, Conrad C, Shen C, Yao JC, Dasari A. Regional lymph node involvement and outcomes in appendiceal neuroendocrine tumors: a SEER database analysis. Oncotarget. 2017;8(59):99541-51.
53. Toumpanakis C, Fazio N, Tiensuu Janson E, Hörsch D, Pascher A, Reed N, O Apos Toole D, Nieveen van Dijkum E, Partelli S, Rinke A, Kos-Kudla B, Costa F, Pape UF, Grozinsky-Glasberg S, Scoazec JY; The ENETS 2016 Munich Advisory Board Participants; ENETS 2016 Munich Advisory Board Participants. Unmet Needs in Appendiceal Neuroendocrine Neoplasms. Neuroendocrinology. 2019;108(1):37-44.
54. Dykewicz CA, Centers for Disease Control and Prevention (U.S.), Infectious Diseases Society of America, American Society of Blood and Marrow Transplantation. Summary of the Guidelines for Preventing Opportunistic Infections among Hematopoietic Stem Cell Transplant Recipients. Clin Infect Dis. 2001;33(2):139-144.
55. Chauhan A, Jain D, Shi C, Gress DM, Williams AJ, Madera M. AJCC Cancer Staging System: Neuroendocrine Tumors of the Appendix (Version 9 of the AJCC Cancer Staging System). Samantha Thomas, Elliot Asare & Mary Kay Washington (eds). October 16, 2023.
56. Grozinsky-Glasberg S, Davar J, Hofland J, Dobson R, Prasad V, Pascher A, Denecke T, Tesselaar MET, Panzuto F, Albåge A, Connolly HM, Obadia JF, Riechelmann R, Toumpanakis C. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease. J Neuroendocrinol. 2022;34(7):e13146.
57. Ronot M, Dioguardi Burgio M, Gregory J, Hentic O, Vullierme MP, Ruszniewski P, Zappa M, de Mestier L. Appropriate use of morphological imaging for assessing treatment response and disease progression of neuroendocrine tumors. Best Pract Res Clin Endocrinol Metab. 2023:101827.
58. Sundin A, Arnold R, Baudin E, Cwikla JB, Eriksson B, Fanti S, Fazio N, Giammarile F, Hicks RJ, Kjaer A, Krenning E, Kwekkeboom D, Lombard-Bohas C, O'Connor JM, O'Toole D, Rockall A, Wiedenmann B, Valle JW, Vullierme MP; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging. Neuroendocrinology. 2017;105(3):212-44.

59. Oberg K, Couvelard A, Delle Fave G, Gross D, Grossman A, Jensen RT, Pape UF, Perren A, Rindi G, Ruszniewski P, Scoazec JY, Welin S, Wiedenmann B, Ferone D; Antibes Consensus Conference participants. ENETS Consensus Guidelines for Standard of Care in Neuroendocrine Tumours: Biochemical Markers. Neuroendocrinology. 2017;105(3):201-11.
60. Saponjski J, Macut D, Sobic-Saranovic D, Ognjanovic S, Bozic Antic I, Pavlovic D, Artiko V. Somatostatin receptor scintigraphy in the follow up of neuroendocrine neoplasms of appendix. World J Clin Cases. 2020;8(17):3697-707.
61. Carrasquillo JA, Chen CC. Molecular imaging of neuroendocrine tumors. Semin Oncol. 2010;37(6):662-79.
62. Hope TA, Allen-Auerbach M, Bodei L, Calais J, Dahlbom M, Dunnwald LK, Graham MM, Jacene HA, Heath CL, Mittra ES, Wright CL, Fendler WP, Herrmann K, Taïeb D, Kjaer A. SNMMI Procedure Standard/EANM Practice Guideline for SSTR PET: Imaging Neuroendocrine Tumors. J Nucl Med. 2023;64(2):204-210.
63. Moses WW. Fundamental Limits of Spatial Resolution in PET. Nucl Instrum Methods Phys Res A. 2011;648(S1):S236-S240.
64. Hope TA, Pampaloni MH, Nakakura E, VanBrocklin H, Slater J, Jivan S, Aparici CM, Yee J, Bergsland E. Simultaneous (68)Ga-DOTA-TOC PET/MRI with gadoxetate disodium in patients with neuroendocrine tumor. Abdom Imaging. 2015;40(6):1432-40.
65. Couvelard A. Appendiceal neuroendocrine neoplasms. Digestive System, Tumours WHO Classification of Tumours. 5th ed. WHO; 2019:152-5.
66. van Velthuysen MF, Couvelard A, Rindi G, Fazio N, Hörsch D, Nieveen van Dijkum EJ, Klöppel G, Perren A. ENETS standardized (synoptic) reporting for neuroendocrine tumour pathology. J Neuroendocrinol. 2022;34(3):e13100.
67. Rindi G, de Herder WW, McCluggage WG, Moch H, Osamura RY, Papotti M, Travis WD. Neuroendocrine tumours. In: WHO Classification of Tumours Editorial Board. Endocrine and neuroendocrine tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022. (WHO classification of tumours series, 5th ed.; vol. 10
68. Assarzadegan N, Montgomery E. What is New in the 2019 World Health Organization (WHO) Classification of Tumors of the Digestive System: Review of Selected Updates on Neuroendocrine Neoplasms, Appendiceal Tumors, and Molecular Testing. Arch Pathol Lab Med. 2021;145(6):664-77.
69. Misdraji et al. Appendiceal goblet cell adenocarcinoma. Digestive System, Tumours WHO Classification of Tumours. 5th ed. WHO; 2019:149-51.
70. Diets IJ, Nagtegaal ID, Loeffen J, de Blaauw I, Waanders E, Hoogerbrugge N, Jongmans MC. Childhood neuroendocrine tumours: a descriptive study revealing clues for genetic predisposition. Br J Cancer. 2017;116(2):163-8.
71. Ghattas S, Hadeer RA, Maalouf H, Al Bitar J, Younes A, Rahban H, El Rassi Z. A Case of Familial Appendiceal Neuroendocrine Tumor. ACG Case Rep J. 2023;10(8):e01121.

APPENDIX 1 – Classification and Staging

AJCC/ENETS staging (9th edition)

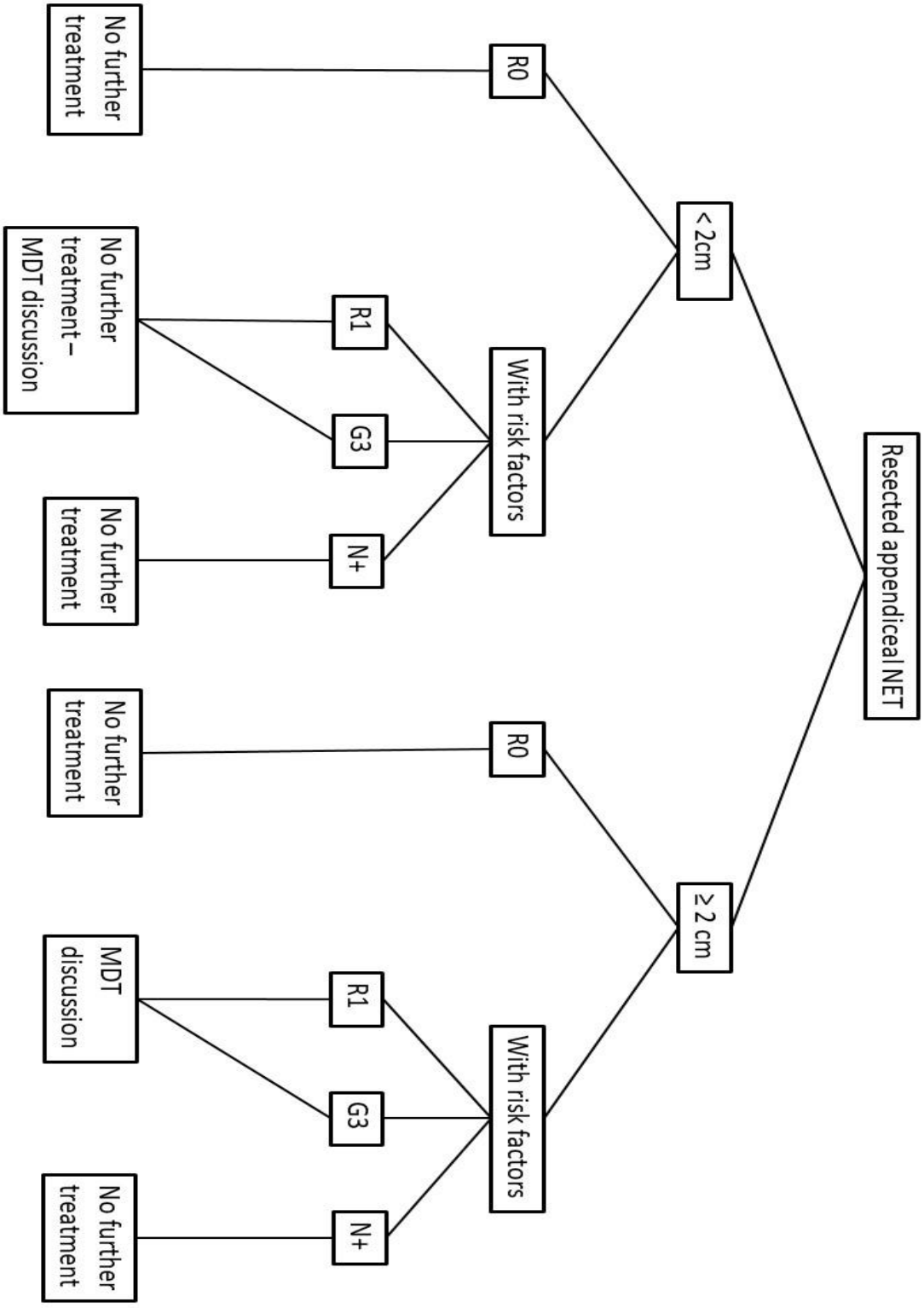
	pTNM ENETS	AJCC/UICC 8th edition
pT1	T ≤ 1 cm and submucosa or muscularis propria invasion	T ≤ 2 cm
pT2	T ≤ 2 cm and submucosa or muscularis propria or mesoappendix/subserosa invasion ≤3 mm	T > 2 and < 4 cm
pT3	T > 2 cm and/or mesoappendix/subserosa invasion >3 mm	T > 4 cm OR mesoappendix/ subserosa invasion
pT4	Perforates serosa/peritoneum, or invades other neighboring organs	

WHO Classification (5th edition)

Terminology	Differentiation	Grade	Mitoses	Ki67%
NET G1	Well-Differentiated	Low	<2/2mm^2	< 3%
NET G2		Intermediate	2-20/2mm^2	3-20%
NET G3		High	>20/2mm^2	> 20%
NEC Small Cell	Poorly Differentiated	High	>20/2mm^2	> 20%
NEC Large Cell				

Legenda: NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.

APPENDIX 2 – Post-appendectomy treatment flowchart – EXPeRT group proposal



APPENDIX 3 – Follow-up flowchart – EXPeRT group proposal