A National Long-Term Study of Neuroendocrine Tumors of the Appendix in Children: Are We Too Aggressive?

Christelle Sommer[1] Fabienne Gumy Pause[2] Manuel Diezi[3] Anne-Laure Rougemont[4] Barbara E. Wildhaber[1]

[1] Department of Pediatric Surgery, Hopitaux Universitaires de Geneve Hopital des Enfants, Geneva, Switzerland
[2] Department of Pediatric Hemato-oncology, Hopitaux Universitaires de Geneve Hopital des Enfants, Geneva, Switzerland
[3] Unit of Pediatric Hemato-oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Canton of Vaud, Switzerland
[4] Division of Clinical Pathology, Hopitaux Universitaires de Geneve, Geneva University Hospitals, Geneva, Switzerland

Address for correspondence Christelle Sommer, Dr. Med., Department of Pediatric Surgery, Hopitaux Universitaires de Geneve Hopital des Enfants, Geneve, GE 1205, Switzerland (e-mail: christelle.sommer@hopitalvs.ch).

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Abstract

Background Pediatric neuroendocrine tumors (NETs) of the appendix are mostly detected incidentally after appendectomy for acute appendicitis. NET management is a matter of controversy. In this national, multicenter study, we aimed to establish guidelines based on our results and the literature.

Methods Medical records of children (0–16 years) with NET of the appendix, treated in Switzerland (1991–2012), were reviewed.

Results Forty cases (28 girls) were analyzed. Median age at diagnosis was 12.7 years (interquartile range [IQR]: 4.0). Tumor size was 0.1–24 mm (median: 0.6, IQR: 0.6). Four patients (10%) underwent additional surgery because of either tumor size $>$ 15 mm (1/4), extension to the mesoappendix (1/4), or incomplete resection (2/4). Three patients with a tumor of $\geq$ 20 mm had no additional surgery. No patient had lymph node metastases. All patients were in complete remission at the last follow-up (median: 3.0 years, IQR: 10.9).

Conclusion We conclude from this study and from an extensive review of the literature that two criteria may point to the need for additional surgery, i.e., the possibility of regional lymph node involvement: tumor size $>$ 20 mm and incomplete surgical resection margins. Childhood NET of the appendix has an excellent prognosis.

Keywords
- neuroendocrine tumor
- carcinoid
- appendix
- children

Introduction

According to the 2010 World Health Organization (WHO) classification, neuroendocrine neoplasms (NENs) of the appendix comprise neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and mixed adenoneuroendocrine carcinomas (MANECs).[1] The etiology of NETs is not well understood. To date, it is thought that NETs of the gastrointestinal tract derive from pluripotent progenitor cells that develop a neuroendocrine phenotype.[2] Most NETs of the appendix are composed of serotonin-producing enterochromaffin (EC) cells.[3] Although "carcinoid" is still listed as a synonym for NET G1, it is no longer recommended to use the term "carcinoid" with the exception of the histopathological International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) classification.[1] The terms and definitions of NENs in the

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literature have changed over time. In 2010, the WHO proposed a definition for the different NENs including the NETs of the appendix.[1] Tumor size, node involvement, and metastasis status (TNM) stages are defined according to The American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS) classifications.[4] In eighth edition (2017) of the AJCC Cancer Staging Manual,[5] invasion of the subserosa and mesoappendix—omitted in the previous edition—has been added. Therefore, similar to the ENETS classification,[6] subserosa or mesoappendix infiltration identify pT3 tumors.[5]

In children, NETs of the appendix are the most frequent tumors of the gastrointestinal tract.[7–9] Between 78 and 97% of children having an appendiceal NET are incidentally diagnosed after appendectomy for acute appendicitis.[10] The overall incidence of this tumor in children varies from 1 to 1.14 case(s) per million children annually.[11,12] Prevalence of NETs on the occasion of an appendectomy is reported to vary between 0.09% and 0.47%.[11,13,14]

There is much debate about the appropriate management of NETs of the appendix in children. No consensus exists among the various authors and recommendations.[7,12,14,15]

The aim of this study was to describe the cohort and management of pediatric patients with NETs of the appendix in Switzerland. In the light of our results, different existing guidelines will be reviewed with the goal of finding a consensus and suggesting updated management guidelines.

Methods

We included patients with the diagnosis of a NET of the appendix, aged 0 to 16 years, from January 1991 to December 2012. Patient data were gathered retrospectively from the 10 largest hospital centers in Switzerland surgically treating children, searching their local surgery, oncology, and pathology databases. The hospitals visited were university hospitals of Basel, Bern, Geneva, Lausanne, and Zurich, and the cantonal hospitals of Aarau, Bellinzona, Lucerne, St. Gallen, and Sion. These data findings were completed with the data from the national Swiss Childhood Cancer Registry (SCCR) (www.childhoodcancerregistry.ch). The medical history, protocols of surgery, histopathological findings, modalities of the additional work-up and of treatment, follow-up time, and final outcome of each patient were recorded. Analysis was performed after having anonymized the database.

We excluded patients who were declared "anonymous" in the SCCR and thus could not be further identified, and patients found in the Registry for whom treating hospital information was missing. Reporting NET of the appendix was optional in the SCCR.

Results were reported as median and interquartile range, and mean with standard deviation. Mann–Whitney and Spearman's tests (correlation coefficient: 0.69) were used to calculate p values; $p < 0.05$ was considered to be significant.

The study protocol was approved by the ethical committees of the cantons of Geneva (12–272) and Vaud (232/13), the other hospitals aligned with the original Geneva approval.

Results

Patient Demographics

Forty-three patients with NET of the appendix were identified, of which 40 were included in the study. The reason for excluding the three patients was insufficient data (patients declared "anonymous" in the Swiss Childhood Cancer Registry, or not associated with a hospital), thus preventing adequate conclusions. All tumors were detected incidentally on the occasion of the histopathological analysis after appendectomy for acute appendicitis in otherwise asymptomatic patients.

Patients' descriptions are summarized in ►Table 1. All patients were without recurrence and alive at their last follow-up-consultation.

Neuroendocrine Tumor Characteristics

NET characteristics are described in ►Table 2. Most of the tumors were localized in the apex. According to the TNM classification by the AJCC, a majority of the NETs were pT1a stage tumors ($\leq$ 1 cm) (84%; 31 patients), or pT1b tumors ($>$ 1–2 cm) (14%; 5 patients); a pT2 stage ($>$ 2–4 cm or invasion of cecum) was diagnosed in one patient. A vast majority of the tumors (24/27; 88.9%) were grade 1 (G1) tumors ($<$ 2 mitoses per 10 high power fields, K_i-67 index $\leq$ 2%). Surgical margins were positive in 2 of 31 patients.

We found a significant correlation between tumor localization and tumor size: smaller tumors were significantly located more toward the tip of the appendix than larger ones ($p = 0.009$) (►Fig. 1). Association between tumor size and age was not significant ($p = 0.388$). Significant correlation between tumor size and infiltration depth was observed: larger tumors infiltrated outer layers of the appendix more often ($p < 0.001$; ►Fig. 2).

Work-up after Diagnosis and Follow-up

Work-up and follow-up after diagnosis were very variable, as shown in ►Fig. 3A, B: 24 of 40 (60%) patients had a work-up at diagnosis; 22 of 40 (55%) patients had a follow-up; 19 of 40 (47.5%) patients had a work-up and a follow-up; and 13 of 40 (32.5%) had neither work-up nor follow-up.

Table 1 Patient descriptive

$N = 40$		
Gender	Female	28 (70%)
	Male	12 (30%)
Age (y)	Range	5.8–16.6
	Mean	12.5 (SD 2.8)
	Median	12.7 (IQR 4.0)
Follow-up (y)	Range	0–13.2
	Mean	4.4 (SD 4.0)
	Median	3 (IQR 10.9)

Abbreviations: IQR, interquartile range; SD, standard deviation

Table 2 Histopathological characteristics of analyzed neuroendocrine tumors

Diagnosis ($n = 38$)		*N*	%
	NET without appendicitis	8	21.1
	NET with appendicitis	30	78.9
Perforation of appendix ($n = 37$)			
	Yes	2	5.4
	No	35	94.6
Localization of NET ($n = 37$)			
	Apex of appendix	30	81.1
	Mid region of appendix	4	10.8
	Base of appendix	3	8.1
NET size ($n = 37$)			
	0.1–1 cm	31	83.8
	> 1–2 cm	5	13.5
	> 2 cm	1	2.7
Infiltration ($n = 35$)			
	Submucosa	3	8.6
	Muscularis externa	9	25.7
	Subserosa	16	45.7
	Serosa	7	20.0
Extension into mesoappendix ($n = 37$)			
	Yes	4	10.8
	No	33	89.2
NET grade ($n = 27$)			
	G1	24	88.9
	G2	3	11.1
Surgical resection ($n = 31$)			
	R0	29	93.5
	R1	2	6.5

Abbreviation: NET, neuroendocrine tumor.

Work-up at diagnosis (►Fig. 3A): *Chromogranin A* (CgA, 13/40 patients): only one patient showed a slightly elevated level (129 ng/mL) (normal range: 27–94 ng/mL) with a spontaneous normalization in subsequent assessments. *5-hydroxyindolacetique acid* (5-HIAA, 18/40 patients): three patients (17%) showed increased 5-HIAA concentrations (53 µmol/24 hour and 54 µmol/24 hour) (normal range: < 34 µmol/24 hour), of which one patient underwent right hemicolectomy (tumor size 18 mm, no lymph node metastases found). *Octreotide scintigraphy* (11/40 patients): abnormal in one patient. This child underwent additional surgery because of positive tumor margins after initial appendectomy yet, despite positive tumor margins on initial pathology and positive scintigraphy, the pathology of repeat resection was negative. *Abdominal ultrasound (US)* (15/40 patients): abnormal in two patients; one patient had some local lymph nodes more than 12 mm with thickening of the cecum wall, one patient had slightly increased size of mesenteric lymph nodes and free liquid. *Abdominal CT (14/40):* five were abnormal with free fluid (2/5) or mild enlargement of lymph nodes (3/5). *Abdominal MRI (1/40):* normal. *Thoracic CT (6/40):* all were normal.

Work-up during follow-up (►Fig. 3B): *CgA* values (12/40 patients): two patients with temporarily elevated levels. *5-HIAA* values (14/40): all normal. *Abdominal US* (21/40): three patients with abnormal imaging findings with enlargement of lymph nodes (> 10 mm). *Abdominal CT* (1/40): normal. *PET-CT* (1/40): normal. *Octreotide scintigraphy* (1/40): pathologic radiotracer activity near the cecum. As for follow-up with abdominal US, 11 of 21 (52%) patients had a scheduled follow-up with a minimum of three US at 1, 3, 6, 9, or 12 months. None of the work-up or follow-up investigations led to the indication for additional surgery.

Additional Surgery

Four of the 40 patients (10%), aged 12 to 15 years, underwent additional surgery. There were various reasons for reoperation. The justification given by the medical team for a patient with a tumor of 5 mm was the existence of controversies in the literature leading to uncertainty about the risk if no reoperation was performed. This patient underwent an ileocecal resection. Two patients had positive resection margins with a tumor size of less than 15 mm (9 and 13 mm, respectively), considered to be an indication for reoperation. The patient with a 9-mm tumor had a right hemicolectomy, whereas the patient with a 13 mm tumor had an ileocecal resection. The fourth patient had right hemicolectomy for an 18-mm tumor. None of these patients (3/4, 1 unknown) showed regional lymph node metastases (0/14, 0/23, 0/38 resected lymph nodes).

Discussion

Generalities

NETs of the appendix in children are rare. In this study, we found an incidence of 1.3 of 1,000 appendectomies performed, which corresponds to the incidences reported in the literature.[13] The diagnosis of NET is usually incidental, as in our study, and described on the histopathological analysis of the appendix, after appendectomy for acute appendicitis.[11]

In most cases, the appendicular NET is localized at the tip of the appendix.[7,12] There is a known correlation between tumor size and NET localization in the appendix: small tumors are more often situated at the tip, whereas larger tumors tend to be at the base.[7] This is also confirmed in the current study: tumor size varied significantly with localization, with smaller tumors sitting more apically. It has also been shown that increasing tumor size is correlated with deeper infiltration up to the serosa.[7] This is confirmed with statistical significance in our study.

Similar to the excellent prognosis we observed in our study, a survival rate of 100% without recurrence is reported in children with NET of the appendix.[9] The reason for the better outcome in the pediatric population is currently not understood.[6] NETs of the appendix in children seem to metastasize extremely rarely in regional lymph nodes and

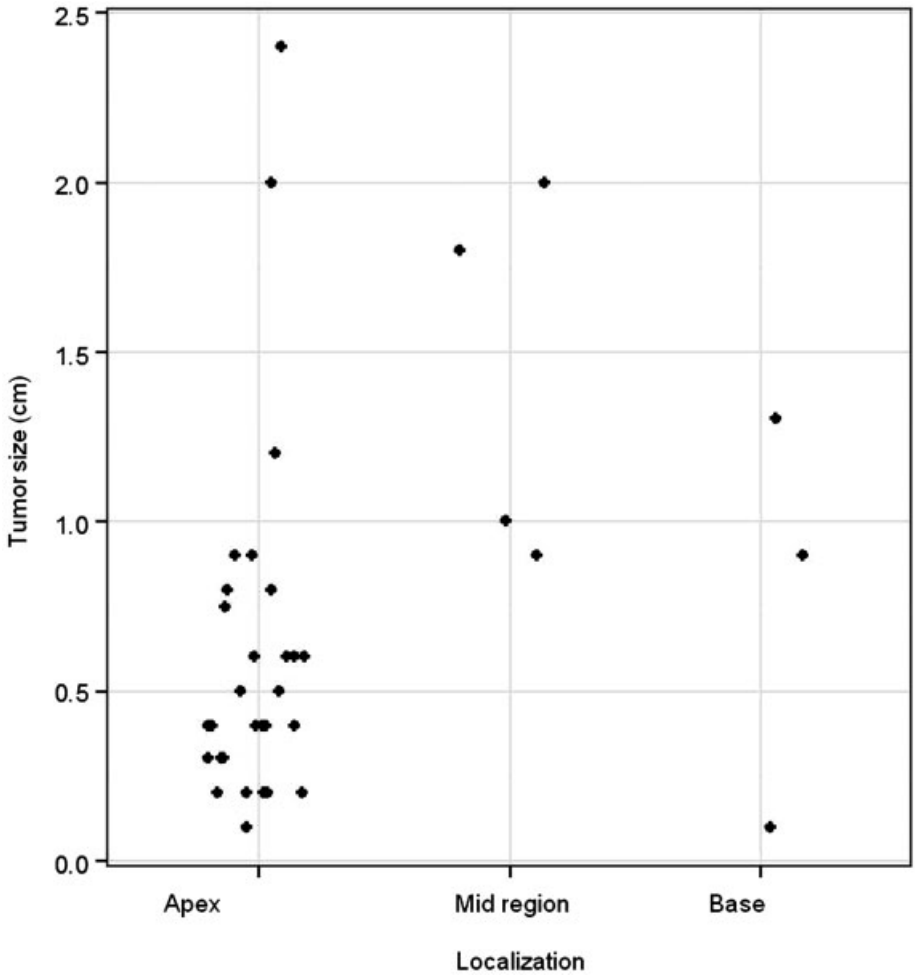

Fig. 1 Difference between neuroendocrine tumor localization and tumor size in the appendix. There is a significant size difference between tumor localization at the tip versus the mid region of the appendix ($p = 0.009$).

have never been reported to cause distant metastases.[9] In France, there are no published reports of adults who underwent appendectomy during childhood and had NET metastasis of indeterminate origin.[14] To our knowledge, there are only 20 pediatric cases reported in the literature showing regional lymph node metastases, in a total of approximately 928 children.[9,14,16–18]

Given the good prognosis, some controversial aspects are currently under discussion, such as criteria for additional surgery, need for laboratory tests and imaging, and optimal intensity and duration of follow-up. ►Table 3 summarizes the current literature of pediatric NET with recommendations for additional surgery, and work-up and follow-up modalities, which will be discussed in the following.

Additional Surgery

To date, the need for additional surgery is not well established. The only two criteria that have clearly been reported for being associated with regional lymph node metastasis and thus potential need for surgery are (1) tumor size and (2) incomplete resection of the tumor.[7,12] However, for point (1) a cut-off size has not been established. In the literature, 10 studies describe a total of 20 children with lymph nodes metastasis. These patients showed a tumor size between 7 and 50 mm with 15 of 19 having a tumor size of $>$ 15 mm, 3 patients with a tumor size of $<$ 15 mm, and 1 patient with an unknown tumor size.[7,12,14,16,17,19–23]

According to Boxberger et al (prospective analysis of 237 patients), a right hemicolectomy is recommended in all patients with a primary tumor size of $>$ 15 mm because of significant risk for developing a local lymph node metastasis. In the situation of a tumor size of $\leq$ 15 mm but with incomplete tumor resection, an ileocecal resection and strict lymph node sampling is advised.[7] Contrariwise, Virgone et al (review of 113 patients) suggest additional surgery only for patients with a NET of $>$ 20 mm and at least one positive result in the recommended work-up (5-HIAA, US, CT, MRI, octreotide scintigraphy); in cases of a NET of $<$ 20 mm but associated with pathological 5-HIAA levels and a positive octreotide scintigraphy, the authors recommend that further surgery should also be performed, as for cases with positive resection margins.[12] Finally, according to the multicenter study by De Lambert et al (114 analyzed cases),

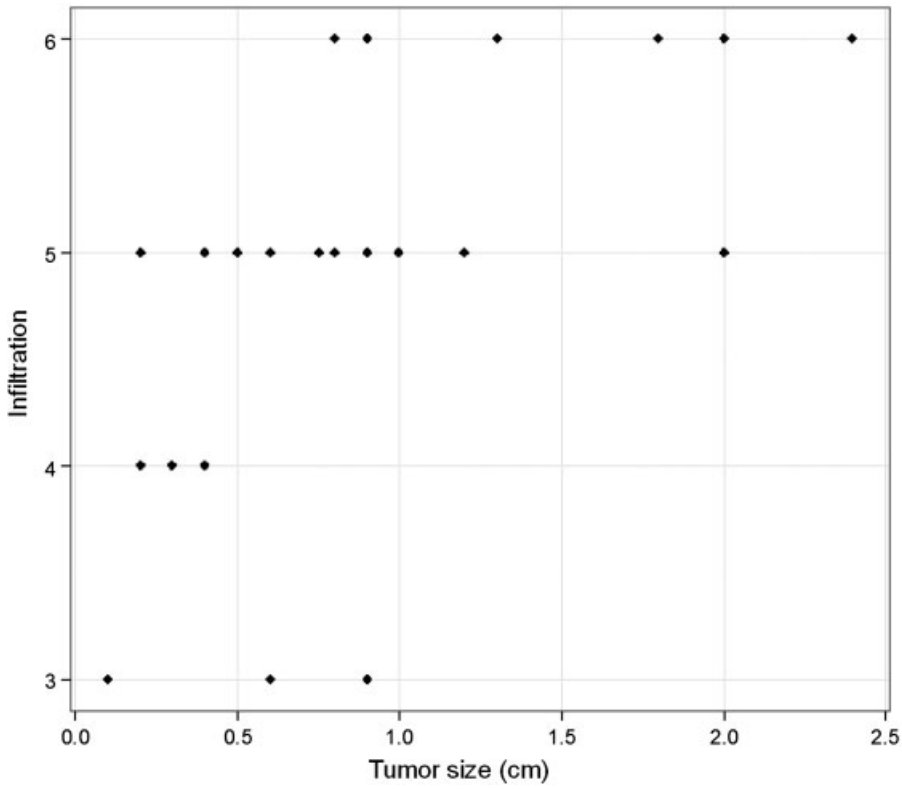

Fig. 2 Correlation between tumor size and depth of infiltration within the appendiceal wall. Increasing tumor size is correlated with deeper infiltration into the appendix up to its serosa ($p < 0.001$), Spearman's correlation coefficient 0.69. 3: submucosa, 4: muscularis externa, 5: subserosa, 6: serosa.

appendectomy alone, in all cases even if incomplete resection, seems to be curative for appendiceal NETs in children, with no influence on life expectancy.[14]

In our study, 4 of 37 patients had extension into the mesoappendix. Although two patients had an additional surgery showing no positive lymph nodes (0/14, 0/38) or residual tumor, all of them were without recurrence to date with a mean follow-up of 4.4 years (range: 2.1–9.3 years). Based on the discussions in the literature and our own experience, we conclude that invasion of the mesoappendix does not seem to influence outcome in children,[24,25] and we believe that it should not be an indication for additional surgery, as long as the resection is R0.[13] These tumors might be treated with simple appendectomy alone.[26]

Work-up after Diagnosis

The role of serum markers (CgA, 5-HIAA) and octreotide scintigraphy to identify local or distant metastasis are also still controversial. Laboratory analyses of 5-HIAA and CgA levels do not seem to be sensitive enough to detect local metastatic disease after diagnosis of an incidental NET after appendectomy.[7] Indeed, also in our study of the three children with elevated 5-HIAA concentrations, one underwent additional surgery but did not show residual or metastatic tumor tissue, and one patient had an elevated CgA concentration at the initial work-up, which normalized thereafter, without influencing decision-making and one patient had a normalized value at next follow-up.

Similar to serum markers, octreotide scintigraphy has not been proven to help tremendously. Octreotide scintigraphy might not be reliable in determining the presence of little tumor tissue and shows a greatly reduced sensitivity for detecting NET masses of < 10 mm;[27] furthermore, false positive results were found in up to 10% of patients.[12] Eleven patients of our cohort had an octreotide scintigraphy in the initial work-up and the only patient who had a positive scintigraphy and underwent additional surgery (indicated because of an incomplete primary tumor resection) did not reveal any residual or metastatic tumor tissue.

Follow-up

There is no consensus in the literature regarding modalities of follow-up of children with appendicular NET after initial management. As for laboratory investigations, in our series, 2 of 12 patients showed slightly elevated levels of serum CgA during follow-up; these findings resolved spontaneously in subsequent control analysis, not influencing medical attitude. During follow-up, abdominal US is most often performed.[7,13,19,28] In our study, 6 of 21 patients having undergone abdominal US showed nonspecific pathologic findings such as free intraperitoneal fluid and temporarily enlarged mesenteric lymph nodes, yet again with no impact on patient management and outcome. This is underlined in the literature where no single abdominal US examination revealed a pathologic finding associated with the NET.[26] Abdominal US has a high performance for detecting liver

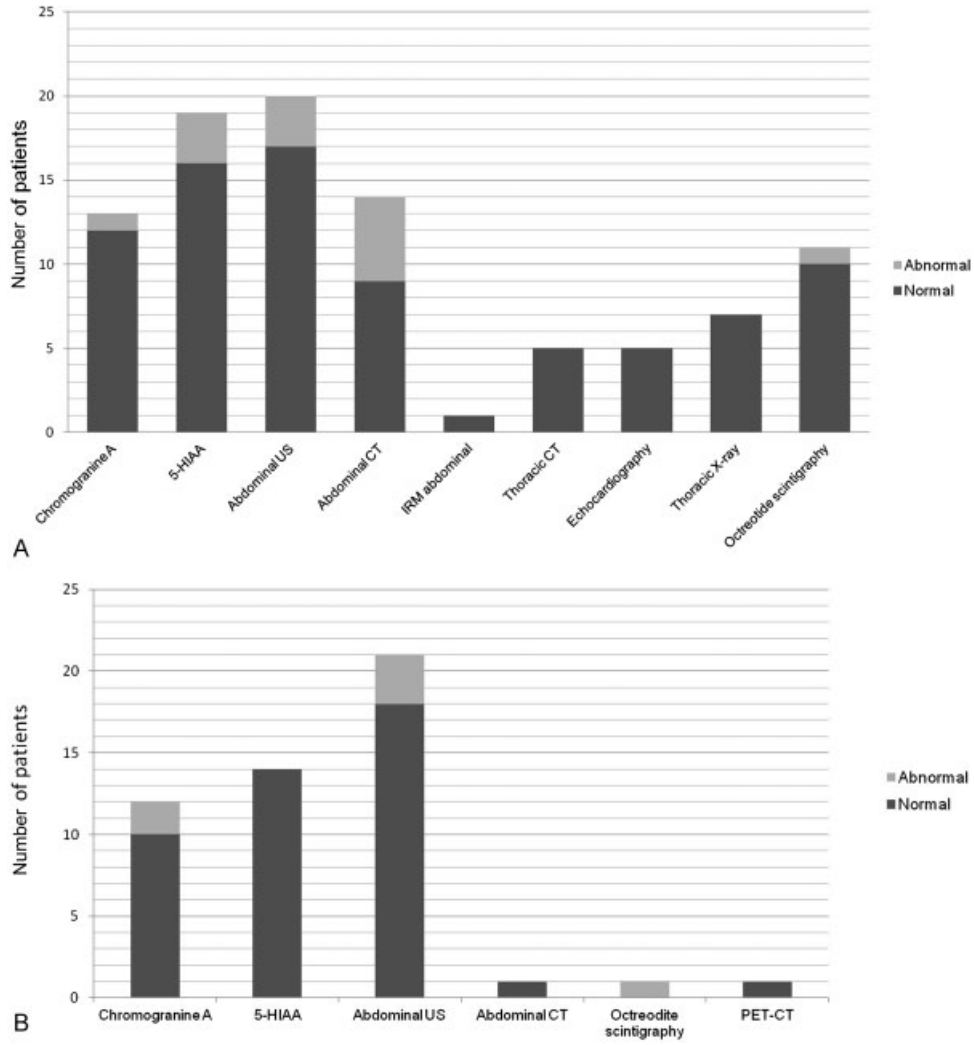

Fig. 3 (A) Work-up at diagnosis. (B) Follow-up investigations. 5-HIAA, 5-hydroxyindolacetique acid; CT, computed tomography; US, ultrasound.

metastasis, but these have never been reported in children.[14] Thus, no recommendations can be issued to include abdominal US in pediatric patient management.[26]

As for the length of follow-up, it ranges from 2 months to 51 years in the literature.[26] Even if most authors believe that appendiceal NET shows a benign behavior, they paradoxically suggest a long-term follow-up of 10 years.[7,24] A regular follow-up might have been recommended for the presumed risk of lymph node metastasis, but prevention of tumor recurrence or influence on long-term outcome is not proven.[6] A long-term follow-up would permit a registry to validate guidelines to be established.

Swiss Algorithm

Based on the above discussion, it is difficult to draw conclusions for the correct initial management (additional surgery), work-up, and modalities of follow-up of children with appendicular NET. This study and the review of the pediatric literature emphasize that in Switzerland, as elsewhere, the management of pediatric appendicular NET is very heterogeneous and that there is an obvious lack of a consensus regarding guidelines for its management. In general, and summarizing the above discussion, we find in the literature two general attitudes: (1) the "cautious attitude," which takes the view that since NETs of the appendix can be considered as potentially malignant tumors, with rare but extremely occasional and sporadic regional lymph node metastases, additional surgery under certain conditions and regular follow-up is recommended;[7,12] and (2) the "trivializing attitude," a more recent approach which defines childhood appendiceal NETs as nonaggressive tumors that do not need further surgical therapy or follow-up at all.[14] It might be reasonable to establish a "Swiss compromise" between these two attitudes, taking into account medical evidence-based, psychological, and economic considerations. Taken together, (1) the literature suggests that neither laboratory nor imaging studies help to reliably define residual or recurrent disease; (2) the excellent long-term outcome in children without any reported case of recurrence or fatality; and (3) the fact that follow-up is stressful with risks of psychosomatic disease and even suicide,[7] we propose the management guidelines described in ►**Fig. 4**. For unclear cases, when the criteria are ambiguous, a multidisciplinary

Table 3 Review of the current literature of pediatric NET with recommendations for additional surgery as well as work-up and follow-up modalities

Studies	Year	No. of patients	Positive lymph node after additional surgery	Recommendations for additional surgery	Recommendations for work-up	Recommendations for follow-up
Andersson and Bergdahl[20]	1976	25	1	–	–	–
Volpe et al[21]	2000	1	1	–	–	Lifelong follow-up necessary
Prommegger et al[28]	2002	35	0	> 10 mm: ileocecal resection	–	> 5 mm: yearly follow-up with serotonin metabolites and abdominal US
Dall'Igna et al[24]	2005	14	0	–	Investigations must be limited to 5-HIAA and US Scintiscans may be performed in case of increase of 5-HIAA or doubtful image	"Longer follow-up" for tumors > 2 cm
Cernaianu et al[19]	2010	1	1	–	–	–
Scott and Upadhyay[26]	2011	47	0	< 20 mm: appendectomy alone	–	–
Boxberger et al[7]	2013	237	9	RHC for tumor > 15 mm < 15 mm + incomplete resection: ileocecal pole resection and strict lymph node sampling	–	Every 3 month for the first year Twice a year for the second year Once a year from 3rd to 10th year (abdominal US, CgA, 5-HIAA)
Kulkarni and Sergi[22]	2013	7	1	> 20 mm with mesoappendix involved or residual tumor: RHC < 20 mm appendectomy alone	–	< 20 mm, no metastasis: clinical and imaging follow-up may be adequate, no need of neuroendocrine markers
Kim et al[17]	2014	13	1		< 20 mm, no invasion of mesoappendix, complete resection: no work-up	< 20 mm, no invasion of mesoappendix, complete resection: no follow-up > 20 mm, invasion of mesoappendix, incomplete resection: 6 monthly 5-HIAA, CgA for 2 years and then yearly for 2 years MR/CT imaging at 6 months, followed by yearly for 5 years
Virgone et al[12]	2014	113	1	Positive work-up Incomplete resection	Complete resection + > 20 mm: 5-HIAA, US, CT/IRM, Octreotide scintigraphy	–
Henderson et al[9]	2014	27	0	Incomplete NET excision: RHC	–	–
Lyons et al[23]	2015	1	1	ENETS guidelines	ENETS guidelines	ENETS guidelines
de Lambert et al[14]	2016	114	3	No surgery	No work-up	No follow-up
Wu et al[16]	2017	45	1	RHC is not indicated in resected tumors "recommend less aggressive approach"	Serum biomarkers + octreoscans unhelpful in absence of carcinoid syndrome	–
Pérez-Albert et al[18]	2017	17	0	–	–	–

Abbreviations: 5-HIAA, 5-hydroxyindolacetique acid; CgA, chromogranin A; CT, computed tomography ; ENETS, European Neuroendocrine Tumor Society; MRI, magnetic resonance imaging; RHC, right hemicolectomy; US, ultrasound.

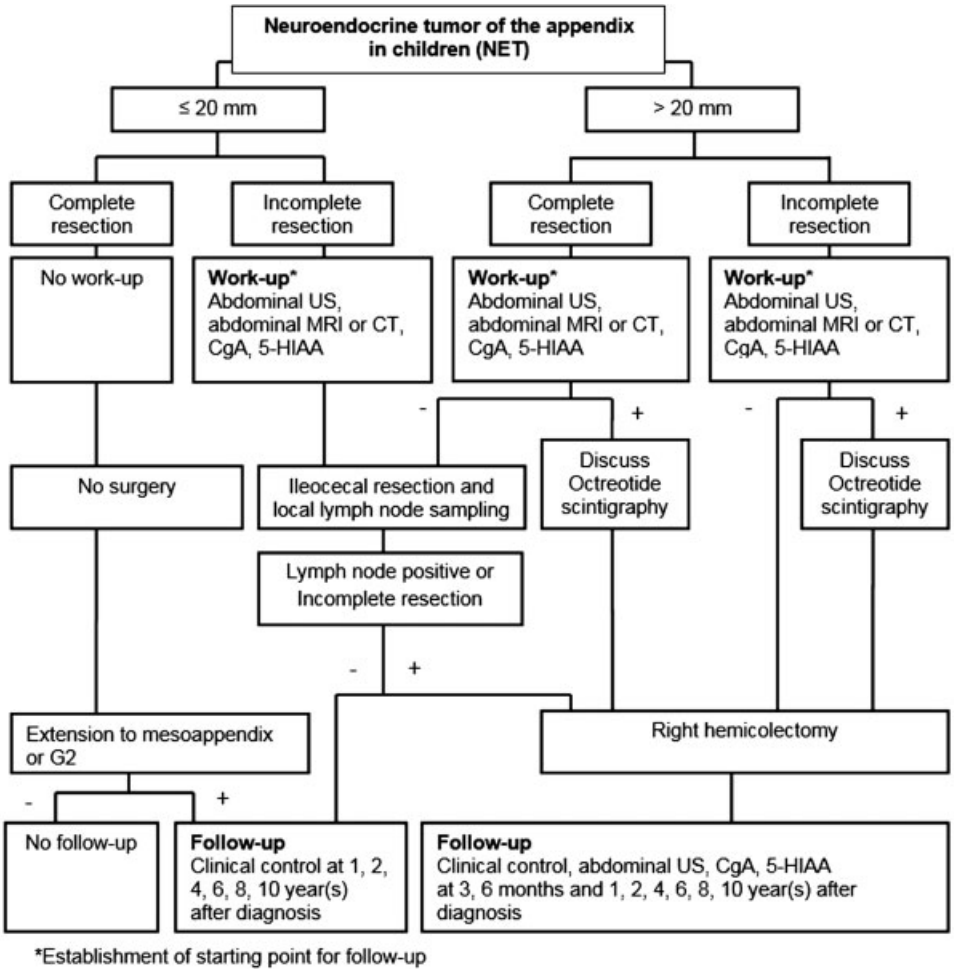

Fig. 4 Proposed guidelines for work-up and follow-up. 5-HIAA, 5-hydroxyindolacetique acid; CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.

discussion with the pathologist, pediatric oncologist, and pediatric surgeon should be considered to take the best decision for the patient's management.

Considering the limited number of studies and the absence of any prospective study, we believe that, despite the reassuring results to date, it is important to maintain a long-term follow-up for selected patients, such as (1) patients with a large tumor size of $>$ 20 mm and/or with positive surgical margins; (2) patients with lymph node involvement after positive work-up (which needs to be done in cases of tumor size $>$ 20 mm or positive resection margins in tumors of $<$ 20 mm), then needing additional surgery; and (3) patients with a small tumor size of $<$ 20 mm with extension to the mesoappendix. We recommend a 10-year follow-up for these cases. If work-up remains negative, patients with childhood appendiceal NET can be considered as disease-free. This rather long follow-up time provides an opportunity to gather sufficient data that may justify a subsequent shortening of the follow-up time. The reason for this approach must be explained to the patient.

According to our algorithm, in our cohort of 29 patients with a complete dataset for judging the necessity of follow-up visits, only five of them would now need to be included in a follow-up program.

Conclusion

Most of the children with NET of the appendix show a benign clinical course with an excellent prognosis, regardless of their pathological risk factors and surgical management. Postoperative serum biomarkers do not seem to be useful. With our proposed algorithm, we expect to reduce the frequency of control visits for these patients. This implies a reduction in the costs and the risks of investigations, while maintaining control over possible relapses and still allowing for reliable and accurate follow-up data collection and secure patient management.

Conflict of Interest

None.

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