

# Radical surgical treatment of neuroendocrine tumors of the appendix in children – a Polish multicenter study

Małgorzata Panek<sup>1</sup>, Marek Szymczak<sup>1</sup>, Maria Stepaniuk<sup>2</sup>, Wojciech Górecki<sup>3</sup>, Aleksandra Gawłowska-Marciniak<sup>4</sup>, Przemysław Wolak<sup>5</sup>, Dariusz Zbyrad<sup>6</sup>, Marek Rybkiewicz<sup>7</sup>, Kamila Chrobak<sup>8</sup>, Ryszard Noparlik<sup>9</sup>, Jerzy Niedzielski<sup>10</sup>, Przemysław Janik<sup>11</sup>, Jan Nowak<sup>12</sup>, Witold Miaśkiewicz<sup>13</sup>, Andrzej Kamiński<sup>14</sup>, Wojciech Fischer<sup>15</sup>, Bożena Dembowska-Bagińska<sup>16</sup>, Piotr Kaliciński<sup>17</sup>

<sup>1</sup>Department of Pediatric Surgery and Organ Transplantation, The Children's Memorial Health Institute, Warsaw, Poland

<sup>2</sup>Department of Pathology, The Children's Memorial Health Institute, Warsaw, Poland

<sup>3</sup>Department of Pediatric Surgery, Jagiellonian University Medical College, Krakow, Poland

<sup>4</sup>Department of Pediatric Surgery and Oncology, Central Clinical Hospital Medical University of Lodz, Lodz, Poland

<sup>5</sup>Department of Pediatric Surgery, Urology and Traumatology, Wladyslaw Buszkowski Children's Hospital, Kielce, Poland

<sup>6</sup>Department of Pediatric Surgery and Traumatology, Provincial Hospital, Tarnobrzeg, Poland

<sup>7</sup>Department of Pediatric and Oncological Surgery, Urology and Hand Surgery, Pomeranian Medical University, Szczecin, Poland

<sup>8</sup>Department of Children's Developmental Defects Surgery and Traumatology, Medical University of Silesia in Katowice, Zabrze, Poland

<sup>9</sup>Department of Pediatric Surgery, University Clinical Hospital, Opole, Poland

<sup>10</sup>Department of Pediatric Surgery and Urology, Medical University of Lodz, Lodz, Poland

<sup>11</sup>Department of Urology and Pediatric Surgery, The Ludwik Rydygier Provincial Polyclinic Hospital, Torun, Poland

<sup>12</sup>Department of Pediatric Surgery and Urology, Karol Marcinkowski University Hospital, Zielona Gora, Poland

<sup>13</sup>Department of Pediatric Surgery and Traumatology, ZZOZ, Ostrow Wielkopolski, Poland

<sup>14</sup>Department of Pediatric Surgery and Urology, The Autonomous Public Children's Clinic Hospital of the Medical University of Warsaw, Warsaw, Poland

<sup>15</sup>Department of Pediatric Surgery, Hospital Municipal St. John Paul II, Elblag, Poland

<sup>16</sup>Department of Pediatric Oncology, The Children's Memorial Health Institute, Warsaw, Poland

<sup>17</sup>Department of Pediatric Surgery and Organ Transplantation, The Children's Memorial Health Institute, Warsaw, Poland

## Corresponding author:

Marek Szymczak PhD  
Department of Pediatric Surgery and Organ Transplantation  
The Children's Memorial Health Institute  
Warsaw, Poland  
E-mail: m.szymczak@ipczd.pl

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## Abstract

**Introduction:** The aim of the study was to examine management of pediatric appendiceal neuroendocrine tumors (ANETs) in Poland.

**Methods:** Records of 27 patients with ANET diagnosed incidentally after appendectomy in the last decade.

**Results:** Well-differentiated NET G1/G2 was diagnosed in 25 and well-differentiated neuroendocrine carcinoma G3 in 2 patients. Extended surgery was performed primarily in one instance and secondarily in 10 patients (right hemicolectomy in 9, ileocecal resection in 1) without adjuvant chemotherapy. Follow-up range was 1–121 months. Recurrence after secondary surgery was observed in 1 (3.7%) patient.

**Conclusions:** Applying ENETS guidelines resulted in 100% overall survival of patients with NET.

**Key words:** appendix, neuroendocrine tumor, carcinoid, neuroendocrine neoplasm, appendiceal tumor.

Neuroendocrine neoplasms (NEN) are a rare type of tumors that can arise at any point of the gastrointestinal tract. Appendiceal NENs (ANENs) are a relatively frequent subgroup, with an incidence rate of 0.15–0.6/100 000/year [1]. The 2010 World Health Organization (WHO) classification categorized ANENs into: well-differentiated NENs/G1-G2 (NET-G1/G2), well-differentiated neuroendocrine carcinomas (NEC-G3) and mixed adenoneuroendocrine carcinomas (MANECs), including goblet cell carcinomas (GCC) [2–4]. The majority of those tumors remain asymptomatic and are mostly diagnosed incidentally after appendectomy. ANETs produce a variety of secretory products which are metabolized in the liver and do not cause carcinoid syndrome unless they are metastatic [3, 5, 6]. Indications for extended radical surgery are based on current treatment guidelines published for the adult population, as no treatment algorithm for pediatric patients is available [1]. The objective of this study was to examine management of pediatric appendiceal neuroendocrine tumors (ANET) in Poland.

**Methods.** We performed a retrospective chart analysis of the surgical registry of patients with diagnosis of ANEN in our center during the last 10 years (2009–2018) and we sent a questionnaire to all Polish pediatric surgery departments. We analyzed age, sex, clinical symptoms, diagnostics, surgical procedures, histopathology results, qualification criteria for secondary surgery and post-operative results. Histopathological evaluation included size and the location of the tumor, grading, resection margin, serosal or mesoappendix infiltration, angioinvasion and presence of lymph node metastases. The histopathological evaluation of ANENs was based on the 2010 WHO classification in force in the studied period of time. Indications for extended radical surgery

were based on the 2016 ENETS (European Neuroendocrine Tumor Society) guidelines for the adult population [1].

Approval for the study was obtained from the Bioethics Committee of the Children's Memorial Health Institute of Warsaw (No. 11/KBE/2019 of 20.03.2019).

**Results.** Data from 14 out of 67 (21%) departments of pediatric surgery in Poland were obtained. During the analyzed decade NET was diagnosed in 27 children, including 4 patients from our institution. The frequency of ANET occurrence in patients after appendectomy in our series was 0.1–0.3%. The patients and tumor characteristics, treatment and outcome are shown in Table I. All tumors were diagnosed incidentally after appendectomy. In 25 cases surgery was performed due to acute appendicitis. In 1 case the appendix was removed additionally during another procedure. One patient underwent laparotomy for intestinal intussusception on Meckel's diverticulum and after finding an appendiceal tumor extended radical treatment (ileo-cecal pole resection – ICR) was performed as a first line surgery. Laparotomy was performed in 19 (70.4%) cases, laparoscopy in 8 (29.6%) with one conversion. The diagnosis was established post-operatively. Histopathological examination revealed a well-differentiated endocrine tumor G1/G2 in 25 and well-differentiated neuroendocrine carcinoma G3 in 2 patients.

Simple appendectomy (SA) was the only surgical procedure in 16 (59.3%) patients. In 2 patients of this group in spite of fulfilling criteria for radicalization no additional procedure was performed.

One patient with NET < 1 cm underwent ICR as primary surgery (in our study classified as the radical group). The secondary surgery was performed in 10 out of 27 cases (37%): right hemicolectomy (RHC) in 9, and ICR in one instance. Three patients

**Table I.** Patients' characteristics, treatment and outcome

Parameter	All	SA	ICR + RHC
Number of patients	27	16	11
Mean age (range) [years]	15 (6–17.7)	15 (6–17.5)	15 (11–17.7)
Sex ratio (F/M)	13/14	9/7	4/7
Open appendectomy	19	10	9
Laparoscopic appendectomy (conversion)	8 (1)	6	2 (1)
Tumor size < 1 cm	13	11	2
Tumor size 1–2 cm	10	4	6
Tumor size > 2 cm	4	1	3
Median follow-up (range) [months]	24 (1–121)	36 (1–121)	24 (3–48)
Recurrence (%)	1 (3.7%)	0	1 (9.1%)

SA – simple appendectomy, ICR – ileo-cecal resection, RHC – right hemicolectomy.

with a tumor bigger than 2 cm and 6 patients with tumor size between 1 and 2 cm were qualified for a radical operation. In the group with tumor size 1–2 cm only one additional criterium for secondary surgery was fulfilled in 3 patients, 2 criteria in one instance and 3 criteria in 2 children. In 1 case none of the qualification criteria were obtained – a patient with tumor size less than 1 cm, localized at the base of the appendix. He was referred to another hospital and underwent ICR. Neither of two histopathologically confirmed carcinoma cases was qualified for radical surgery, as the benchmarks were not met.

In the specimen obtained from radical surgery well-differentiated G1 neuroendocrine tumor near the ileo-cecal valve with negative lymph nodes was found in 1 case. Histopathological examination revealed lymphatic metastases in only one instance.

The median long-term follow-up for the SA group was 36 months, range from 1 to 121 months. The median long-term follow-up for the ICR + RHC group was 24 months, range from 3 to 48 months. One patient developed recurrence in the recto-vesical pouch 18 months after radical surgery (a patient with tumor remnants in second histopathology). He underwent re-laparotomy and the mass was removed. Histopathological examination revealed well-differentiated G1 NET. The child is doing well without any signs of recurrence since during 84 months of observation after re-operation. None of the patients from both groups underwent adjuvant chemotherapy. The overall survival rate was 100%.

**Discussion.** Neuroendocrine tumors (NET) comprise the largest subgroup of all appendiceal neoplasms with approximately 30-80% of all tumors [1]. The occurrence rate of ANETs in all patients undergoing appendectomies, mostly for suspected acute appendicitis, is about 0.3–0.9% [5, 7–9]. In children and adolescents ANETs are found in 0.08% of appendectomy specimens [6, 10] and account for 0.1% of all pediatric malignancies [5].

The metastatic potential of NETs is low and correlates well with tumor size [1, 7, 10, 11]. Some reports suggest that appendiceal perforation worsens the outcome, due to the potential for metastatic seeding [12]. Kim *et al.* reported in a 20-year retrospective analysis that in their experience perforation of the appendix with NET did not affect patients' long-term follow-up [11]. Metastases are mostly limited to regional lymph nodes [6, 10, 11]. Tumors bigger than 2 cm have been correlated with high risk of nodal metastasis up to 40% [1, 4]. The overall prognosis is excellent, with the 5-year survival rate close to 95–100%. Advanced disease with distant metastases and “more malignant” histology such as GCC or MANEC are associated with poorer outcome [1].

The 2016 ENETS guidelines are intended for the adult population, as data for the pediatric population are scarce. Currently binding qualification criteria for extended radical surgery are: tumor bigger than 2 cm or tumor size 1–2 cm with at least one risk factor: non-radical resection, G3 grading, serosal or mesoappendix infiltration, angioinvasion, lymph node metastasis or tumor localization on the base of the appendix [1]. The main controversy considering decision-making comes with ANENs sized 1–2 cm. Therefore some studies question the need for RHC in children.

Vandavelde found no tumor recurrence among 22 children with ANEN smaller than 2 cm after simple appendectomy, even in 5 cases with mesoappendix involvement. His results suggest that mesoappendix involvement may not necessarily influence the outcome [5].

In a French retrospective multicenter study of 114 pediatric patients with appendiceal NET the authors identified 19 patients who fulfilled one or more eligible criteria for RHC, but the procedure was not performed. In the follow-up all patients remained alive and disease-free [13]. In turn, Volpe *et al.* reported a case of a 5-year-old girl with metastatic appendiceal tumor, which measured 5 cm [6]. Cernaianu identified a rare case of NET smaller than 1 cm with mesoappendix infiltration and loco-regional lymph node metastasis [10]. Shapiro in a long-term follow-up evaluation identified 2 patients with ANEN smaller than 2 cm, who underwent RHC as they fulfilled one additional risk factor. In both cases nodal involvement in the colectomy specimen was found [9]. Likewise, we also identified a patient with NET < 2 cm with lymph node involvement in histopathological examination after right hemicolectomy.

In a joint German, Austrian and Swiss 14-year-long prospective study 237 cases of pediatric appendiceal NET were presented. The authors found that the most significant factors predicting the lymph node metastases were mass size (> 15 mm), localization in appendix (in the middle and at the base of the appendix) and the completeness of resection. The authors recommended ileo-cecal pole resection (ICR) as a secondary surgery for incompletely resected tumors < 15 mm and RHC for tumors > 15 mm in the pediatric population [14].

Considering the long life expectancy and risk of late recurrence RHC is recommended in patients with appendiceal NET > 2 cm. There is a discrepancy among various studies concerning the necessity of performing RHC in children with ANEN sized 1–2 cm. The survival rates for children with lymph node metastasis after appendectomy alone argue against the radicalization of treatment [5, 11, 13]. Nevertheless, nodal involvement can lead to long-term tumor recurrence or distant metastases [1, 15]. Varisco in his meta-analysis reported sev-

eral cases of metastatic disease, after simple appendectomy as well as right hemicolectomy. The median time of treatment failure was 24 months, with the majority of metastatic tumors occurring 36 months after initial diagnosis [15]. In our study we identified a case of ANET metastasis to the recto-vesical pouch 18 months after RHC. Pathology examination after appendectomy revealed incompletely resected ANEN > 2 cm with mesoappendix infiltration and lymph node involvement. In the RHC specimen loco-regional recurrence was detected. Given the morbidity and mortality rate associated with RHC in pediatric patients, but also the risk of tumor recurrence, the authors support applying ENETS guidelines in children.

In conclusion, NETs of the appendix are mostly diagnosed incidentally after appendectomy. The need for secondary treatment remains a matter of discussion, as opposing reports can be found in the literature. Applying ENETS guidelines in our pediatric patients with ANEN resulted in 100% overall survival. We want to point out the need to develop guidelines for the treatment of ANETs in children, despite their rarity.

### Conflict of interest

The authors declare no conflict of interest.

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