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Review Article

Management and outcome of high-risk neuroendocrine tumors of the appendix in children; A systematic review

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ABSTRACT

This study systematically reviewed the literature to investigate the value of secondary surgery for children with a high-risk neuroendocrine tumor (NET) of appendix. A systematic search was performed in PubMed, Embase and Web of Science. All randomized controlled trials, cohort studies, and case series reporting on the management and outcomes of patients (<20 years) with a histopathologically proven NET of the appendix were eligible for inclusion. Two authors independently selected eligible articles, assessed risk of bias, and extracted data. The outcomes of patients with a high-risk NET treated with secondary surgery were compared to those treated without secondary surgery. Primary outcomes were recurrence rate and disease-free survival. The literature search yielded 667 articles, of which 29 were included. These studies reported on 1112 patients, of whom 145 (13%) had high-risk NET. Heterogeneity between studies was large and risk of bias was serious in 26 and moderate in three studies. Secondary surgery after primary appendectomy was performed in 64 of 145 patients (44%). Length of follow-up ranged between 0 and 612 months. In both treatment groups no recurrences were reported, and thus disease-free survival was 100%. Based on current literature, the value of secondary surgery for pediatric high-risk NET of the appendix may be questioned. However, evidence is scarce, of low-quality, and heterogeneity between studies is large. Large international studies with adequate follow-up are needed to generate high-quality evidence on this topic.

1. Background

Neuroendocrine neoplasms (NENs) of the appendix are very rare in children, but are still the most frequently found gastrointestinal tract tumors after lymphomas [1]. As described by the recently updated World Health Organization classification, three different subgroups of NENs are distinguished; neuroendocrine tumors (NETs), neuroendocrine carcinomas (NECs), and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs). Treatment strategies of these subgroups of NENs are different, as prognosis of NECs and MiNENs is significantly poorer compared to NETs [2]. International societies have developed guidelines to provide guidance and uniformity in the management of NENs of the appendix [3]. Cornerstone is surgery, reserving somatostatin analogues for sporadic patients with distant metastases and/or

Abbreviations: NEN, Neuroendocrine Neoplasm; NET, Neuroendocrine Tumor; NEC, Neuroendocrine Carcinoma; MiNEN, Mixed Neuroendocrine non-neuroendcrine neoplasm; ENETS, European Neuroendocrine Tumor Society; NANETS, North American Neuroendocrine Tumor Society; hrQoL, health related Quality of Life; IAA, Intra-abdominal abscess; ROBINS-I, Risk Of Bias In Non-randomised Studies of Interventions.

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carcinoid syndrome. The guideline describes that NECs and MiNENs should be treated with oncological right-sided hemicolectomy, irrespective of tumor size. For NETs, however, surgical treatment depends on tumor size and various histopathological risk factors predicting potential aggressive behavior (i.e. incomplete resection, tumor at base of appendix, grade 2 NET, lymphovascular or >3 mm mesoappendiceal invasion of tumor cells). In these guidelines, patients with tumors <1 cm (pT1) or 1–2 cm (pT2) without risk factors for aggressive behavior are considered to be at low risk of lymphatic metastasis and/or recurrent disease (low-risk NET of the appendix) and an appendectomy is recommended. While patients with tumors >2 cm (pT3) or 1–2 cm (pT2) with risk factors for aggressive behavior are considered to be at high-risk of lymphatic metastasis and/or recurrent disease (high-risk NET of the appendix) [4–11]. Complementary right-sided hemicolectomy is recommended in these patients to completely ensure that no residual tumor is left behind and no tumor metastasis to lymph nodes has occurred [3,12].

These recommendations, however, are predominantly based upon studies in the adult population. Questions are now raised whether or not these recommendations are also applicable in children. Especially the value of a complementary right-sided hemicolectomy is questioned for pediatric patients with a high-risk NET of the appendix, as it appears that residual tumor and positive lymph nodes are found in only very few patients and most importantly disease-free survival is reported to be excellent. Therefore this systematic review aimed to investigate the value of secondary surgery for children and adolescents <20 years old treated for a high-risk NET of the appendix in terms of recurrences and disease-free survival.

2. Methods

Before the start of the systematic review, the protocol was registered at PROSPERO: International prospective register of systematic reviews (identification number CRD42021281199). This study was reported according to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [13]. Only previously published data was analysed and therefore ethical approval and written informed consent were not required.

2.1. Participants and type of studies

All studies reporting on the management of histopathologcally proven high-risk (pT2 with risk factors and pT3) NET of the appendix in children and adolescents <20 years old were considered for inclusion. All NETs were classified according to the European Neuroendocrine Tumor Society (ENETS) classification, based on the histopathological features that were described in the original studies and divided into low-risk and high-risk NETs of the appendix. pT2 NETs of the appendix were considered as a high-risk NET, if any of the following risk factors were reported: Incomplete resection, tumor at base of appendix, grade 2 NET, lymphovascular or >3 mm mesoappendiceal invasion of tumor cells. Studies that reported results of the treatment of goblet cell carcinoid, mixed adenoneuroendocrine carcinoma or grade 3 neuroendocrine carcinoma of the appendix were excluded. Randomized controlled trials, prospective or historical cohort studies, and case series were included in the review. Case reports, expert opinions and letters to the editor were excluded. Languages were restricted to English, German, French and Dutch. Lastly, only studies that reported on our primary outcomes were eligible for inclusion. Primary outcomes of this review were recurrence rate and disease-free survival.

2.2. Types of interventions

The intervention group was defined as those patients with a high-risk NET of the appendix that were treated with secondary surgery (such as right hemicolectomy, ileocaecal resection or caecectomy) after initial appendectomy. The control group consisted of patients that were not treated with secondary surgery after appendectomy.

2.3. Search methods

In order to identify all relevant publications we performed a comprehensive search in the bibliographic databases PubMed, Embase, and Web of Science from inception up to July 18, 2022, in collaboration with a medical information specialist. The following terms were used (including synonyms and closely related words) as index terms or free-text words: "Neuroendocrine Tumors", "Carcinoid", "Appendix", "Adolescent", "Child", "Infant". The references of the identified articles were searched for relevant publications. Duplicate articles were excluded. The full search strategies for all databases can be found in Appendix 1.

2.4. Study selection and data extraction

Eligible articles were screened by two independent reviewers (PA, AM) based on title and abstract and subsequently full text articles were assessed according to the predefined in- and exclusion criteria. Discrepancies were resolved by consensus and in case of disagreement a third reviewer was consulted (RG). After article selection, two reviewers (PA, AM) independently extracted data from the included studies, according to a predefined data extraction form. Collected variables were general information (author, year, methodology, patient characteristics), histopathological findings (localization of NET, NET size, criteria for secondary surgery, NET invasion, surgical resection margins, classification of NET according to ENETS classification), primary appendectomy findings (preoperative suspicion of NET, intraoperative suspicion of NET, surgical approach, appendiceal perforation), secondary interventions (type of resection, reason for secondary surgery, histopathological findings after secondary surgery (number of positive lymph nodes, residual tumor), and follow-up data (recurrences, survival, complications, imaging studies, outpatient check-ups and health-related Quality of Life (hr-QoL)).

2.5. Outcomes and definitions

The primary outcomes of this systematic review were recurrence rate and disease-free survival. Recurrence rate was defined as imaging and/or histopathologically proven NET of the appendix or metastasis after initial resolution of disease. Disease-free survival was defined as alive and without recurrence of disease at moment of follow-up of the original studies.

Secondary outcomes were overall survival defined as alive at moment of follow-up of the original studies and postoperative complication rate, defined as the proportion of patients experiencing at least one complication after secondary surgery. Complications included, but were not limited to:

- Intra-abdominal abscess (IAA), defined as a radiologically confirmed accumulation of purulent fluid in a walled-off space within the abdominal cavity.
- (Adhesive) bowel obstruction requiring readmission (diagnosis based on clinical signs and symptoms such as a history of constipation, nausea, vomiting and distended abdomen)

- Superficial and Deep Surgical Site Infection, as defined by the CDC criteria [14].
- Anastomotic leakage, as defined by the International Study Group of Rectal Cancer (ISREC) [15,16].

If possible, complications were listed according to the Clavien-Dindo classification [17].

Other secondary outcomes were the number of additional imaging studies during follow-up (including ultrasound, (PET-) Computed Tomography, Magnetic Resonance Imaging, and octreotide scintigraphy), length of follow-up (days), number of outpatient check-ups (both regular outpatient visits and telephone check-ups), health-related Quality of Life as measured by hr-QoL specific questionnaires, and cost-effectiveness of the treatment strategies, including direct and indirect medical costs.

2.6. Risk of bias and quality of evidence assessment

The Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool was independently applied by two reviewers (PA, AM) [18]. Risk of bias domains were assessed according to predefined definitions. Of specific interest were the risk of bias domains regarding confounding and missing data. Risk of bias due to confounding was considered low in randomized controlled trials, moderate in prospective and retrospective cohort studies that described baseline characteristics of the intervention and control groups, and serious in those studies that did not describe baseline characteristics for the intervention and control groups. Bias due to missing data was assessed serious if more than 50% of patients were lost to follow-up, moderate if less than 50% but more than 5% of patients were lost to follow-up, and low if less than 5% of patients were lost to follow-up.

2.7. Data analysis

Patients were classified as low risk-NET and high-risk NET according to the ENETS classification [3]. Analyses were performed on patients with a high-risk NET. The group of patients treated with secondary surgery after appendectomy (intervention group) were compared to the group of patients that did not undergo secondary surgery after appendectomy (control group). Review Manager version 5.3.5 was used to perform meta-analyses on the primary outcomes, recurrence rate and disease-free survival, if events were reported. The Mantel-Haenszel method was used to compute risk ratios and their corresponding 95%CI. Heterogeneity was assessed with the Higgins I^2 inconsistency test, with an I^2 of more than 50% considered as substantial. Meta-analyses were performed using a random effects model. For the secondary outcomes only descriptive statistics were performed.

3. Results

3.1. Search

The literature search generated a total of 1097 references: 438 in PubMed, 487 in Embase and 172 in Web of Science. After removing duplicates of references that were selected from more than one database, 667 references remained. Of these, 498 references were excluded after screening for title and abstract. Full text of 169 references were assessed and subsequently 140 references were excluded due to various reasons. Therefore, 29 studies were included in this systematic review. The flowchart of the search and selection process is presented in Fig. 1.

3.2. General characteristics of the included studies

Designs of the included studies were two prospective and 27 retrospective cohort studies [7–10,19–43]. The general characteristics of the studies are presented in Table 1. A total of 1112 patients with a NET of the appendix (both low risk and high-risk NET) were included in these studies, of whom 254 were male and 593 were female. For 265 patients gender data was missing. Age of the patients ranged between 9 months and 19.5 years. Follow-up duration ranged between 0 months and 51 years.

Histopathological characteristics of all (both low-risk and high-risk) NETs are displayed in Table 2. Tumor location was reported in 19 studies [7–9,19–21,23–26,30–32,34,35,37,38,40,41,43]. In 485 of 873 cases (55.6%) the NET was located at the tip of the appendix, 161 NETs (18.4%) were found at the body of the appendix, 55 (6.3%) at the base of the appendix, and location was not reported in 172 cases. The extent of invasion into the deepest layer of the appendix was described by 20 studies [7,9,19–26,28,29,32,36–39,41–43]. NET invasion into the subserosa was found most frequently (175/662 cases; 26.4%), followed by invasion into the muscularis (125/662 cases; 18.9%) and invasion into the serosa (118/662 cases; 17.8%). Invasion of the deepest layer of the appendix was not described for 164 cases. Mesoappendiceal invasion was reported in 26 studies and was found in 264 patients (27.8%) [7–10,19–29,32–34,36–43]. Lymphovascular invasion was reported in 11 studies and was found in 58 of 520 patients (11.2%) [7–9,19,20,22,23,27,28,39,41]. Seven studies described perineural invasion in 40 of 141 patients (28.4%) [19,20,22,27,36,39,41]. Resection margins were positive in 31 of 823 patients (3.8%) [7,8,10,19,20,22,23,27,32–34,37–41,43].

3.3. Quality of the studies

Risk of bias on the primary outcomes (recurrence rate and disease-free survival) was assessed as serious for 26 studies [9,10,19–39,41–43] and moderate for three studies [7,8,40] (Table 3). The interrater reliability for overall judgement of risk of bias according to the ROBINS-I was almost perfect (96% agreement). Bias due to confounding was serious in 26 studies and moderate in only three. These three studies reported that the baseline characteristics of the intervention and control groups were comparable. Bias due to missing data was low in 7 studies (less than 5% of patients lost to follow-up), moderate in 17 studies (less than 50%, but more than 5% of patients lost to follow-up), and serious in 5 studies (more than 50% of patients lost to follow-up).

3.4. High-risk NETs

A high-risk NET was found at histopathological examination in 145 patients, 90 with a pT2 NET with risk factors and 55 with a pT3 NET. Secondary surgery was performed in 64 patients (intervention group), while 81 patients were observed without secondary surgery (control group). Indications for secondary surgery are displayed in Table 1. Most frequent indication for secondary surgery was mesoappendiceal invasion, which was found in 51 patients with a high-risk pT2 NET (57%). In the intervention group right hemicolectomy was performed in 43 patients (68%), ileocecal resection in 9 patients (14%), caecectomy in 2 patients (3%), and data regarding type of resection was missing in 10 patients (16%).

3.5. Primary outcomes: recurrence rate and disease-free survival

No recurrence was reported and thus disease-free survival was 100% for both intervention and control group. Because no events were reported in both the intervention and control group, it was

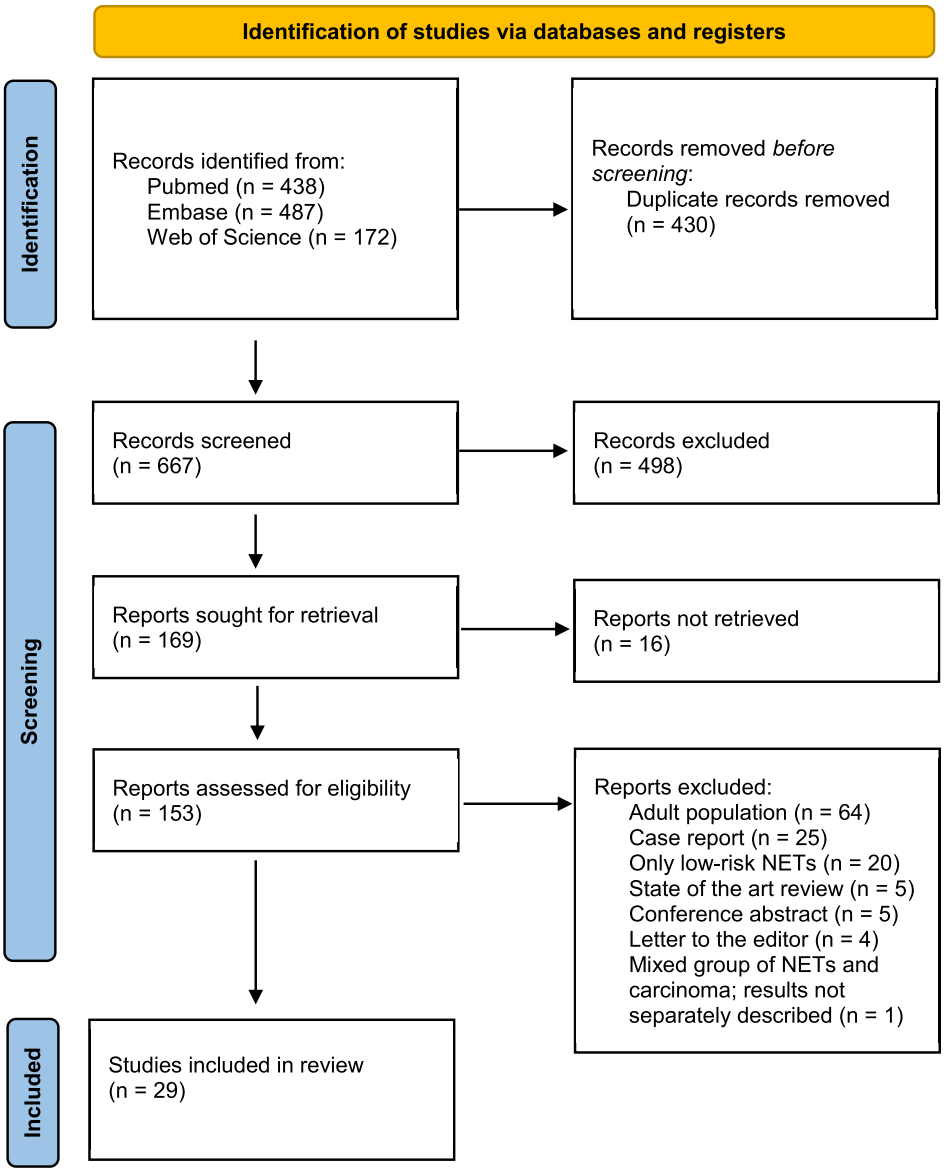

Fig. 1. PRISMA flowchart.

not possible to perform a meta-analysis for comparison of secondary surgery and observation for patients with a high-risk NET. The number of positive lymph nodes at histopathological examination after secondary surgery was described in 13 studies [7–9,19,21,22,27–29,37,38,40,41]. In ten out of 30 patients (33%) one to three positive lymph nodes were found. Residual tumor at histopathological examination was described in ten studies and was found in two out of 33 patients (6%) [7–10,19,22,29,37,40,41].

3.6. Secondary outcomes

3.6.1. Overall survival

Overall survival was reported in 23 studies, but was not described for patients with a high-risk NET specifically [7–10,19–26,28,29,31,32,34,36,38,40–43]. Therefore the intervention and control group could not be compared with regard to overall survival. Three studies described four deaths, all unrelated to the NET of the appendix, resulting in an overall survival of 99.6% in the total population of all children with a NET (including low-risk and high-risk NETs) [9,10,21].

3.7. Complications after secondary surgery

Three studies reported on postoperative complications after secondary surgery for a high-risk NET [8,27,41]. All 20 patients in these studies underwent right hemicolectomy and only one (5%) developed an intra-abdominal abscess. Treatment for this complication was not described and therefore the Clavien-Dindo classification could not be applied.

3.8. Additional imaging studies after appendectomy

Data regarding additional imaging studies for diagnostic work-up after appendectomy for the intervention and control group could be extracted from 11 studies [8,20,22,24,25,28,32–34,39,40]. In these studies, 45 patients with a high-risk NET were observed after primary appendectomy. Imaging studies were performed in 26 of 45 patients (58%) and consisted of MRI, CT, chest X-ray, and

Table 1
General characteristics.

Author	Study design	Age range (years)	No. of patients	pT1	pT2	pT3	High-risk NETs	Indications for secondary surgery	Intervention group	Control group	Follow-up period (months)
Akova (2018)	Retrospective cohort	10–16	10	4	6	0	4	G2: 3; G2 + MI: 1	0	4	2–89
Barno (2018)	Retrospective cohort	13–18	8	3	5	0	4	Base: 2; MI: 2	2	2	2–326
Boxberger (2013)	Prospective cohort	4–20	237	165	52	10	21	TS: 10	9	1	0–153
Corpron (1995)	Retrospective cohort	6–19	22	8	5	0	4	MI: 4	1	3	18–360
Dall'Igna (2005)	Retrospective cohort	5–17	14	6	4	0	3	MI + R1: 3	3	0	24–214
De Lambert (2016)	Retrospective cohort	5–17	114	?	?	10	29	MI: 16; TS: 10 LVI: 2; G2: 1	10	19	1–120
Fernandez (2015)	Retrospective cohort	8–17	28	17	10	1	5	MI: 3; LVI: 1; TS: 1	5	0	12–156
Hatzipantelis (2010)	Retrospective cohort	4–13	19	18	1	0	1	MI: 1	0	1	6–118
Henderson (2014)	Retrospective cohort	8–15	27	13	10	0	7	MI: 7	0	7	1–193
Jonsson (1989)	Retrospective cohort	4–15	18	17	1	0	1	MI: 1	0	1	26–351
Kartal (2022)	Retrospective cohort	6–17	15	4	10	1	2	TS: 1, MI: 1	0	2	3–159
Kim (2014)	Retrospective cohort	7–17	13	10	2	1	1	TS: 1	1	0	8–154
Kulkarni (2013)	Retrospective cohort	10–18	7	5	2	0	1	LVI: 1	1[a]	0	1–84
Moertel (1990)	Retrospective cohort	6–20	23	15	3	3	6	LVI: 3; TS: 3	2	4	9–612
Neves (2006)	Retrospective cohort	4–17	8	5	3	0	1	MI: 1	1	0	42
Njere (2018)	Retrospective cohort	8–16	11	6	5	0	2	missing	1	1	1–72
Parikh (2018)	Retrospective cohort	0–19	109	?	?	11	11	TS: 11	8	3	120–312
Pelizzo (2001)	Retrospective cohort	8–18	10	8	0	2	2	TS: 2	2	0	36
Pérez-Albert (2017)	Retrospective cohort	8–16	17	14	2	0	1	MI + base + R1: 1	0	1	4–92
Prommegger (2002)	Retrospective cohort	6–16	36	4	4	0	4	Base or MI: 4	0	4	2–360
Ranaweera (2019)	Retrospective cohort	0–18	32	20	7	5	12	TS: 5; missing:7	12	0	1–60
Ryden (1975)	Retrospective cohort	7–14	30	17	1	1	1	TS: 1	0	1	24–288
Scott (2011)	Retrospective cohort	7–15	47	21	14	2	2	TS: 2	1	1	?
Sommer (2019)	Retrospective cohort	5–16	40	31	5	1	2	R1: 1; TS: 1	1	1	0–158
Spunt (2000)	Retrospective cohort	8–15	5	1	3	0	2	R1 + MI: 2	2	0	6–244
Vandevelde (2015)	Retrospective cohort	9–15	21	15	5	0	4	LVI: 2; MI + LVI: 1; MI: 1	0	4	0–6
Virgone (2014)	Prospective cohort	0.75–17	113	?	?	5	5	TS: 5	1	4	1–151
Wu (2017)	Retrospective cohort	6–17	45	30	5	0	5	MI: 2; missing: 3	1	4	1–150
Yalcin (2022)	Retrospective cohort	7–16	33	19	5	2	2	TS: 2	0	2	5–227

MI: Mesoappendiceal invasion; LVI: lymphovascular invasion; TS: Tumor size; R1: Positive resection margin.
[a] Primary surgery was a total colectomy for familial adenomatous polyposis (FAP).

octreotide scintigraphy. In the group of patients that underwent secondary surgery, 15 of 16 patients (94%) underwent imaging studies consisting of ultrasound, CT, and octreotide scintigraphy. Only two studies compared the intervention and control group with regard to the number of additional imaging studies during follow-up after diagnostic work-up and secondary surgery or appendectomy only [8,32]. In these studies, five of 11 patients (45%) that underwent secondary surgery were assessed clinically during follow-up, of whom three with both clinical examination and imaging, and four had urinary levels of 5-HIAA tested. In the group of patients that were observed after appendectomy, ten of 20 patients were (50%) were assessed clinically during follow-up, of whom nine with both clinical examination and imaging [8,32].

3.9. Number of outpatient visits and surveillance strategies

In none of the studies, the number of outpatient visits and telephone check-ups were compared between the patients with a high-

Table 2
Histopathological characteristics.

Author	Cases	Tumor location			Extent of invasion (deepest layer appendix)					Mesoappendiceal invasion	Lymphovascular invasion	Perineural invasion	R1 resection	NET grade
		Base	Mid	Tip	Mucosa	Submucosa	Muscularis	Subserosa	Serosa					
Akova (2018)	10	0	3	7	0	1	2	6	1	1	3	0	0	5 G1, 5 G2
Barno (2018)	8	3	–	4	0	1	3	0	4	4	0	1	0	8 G1
Boxberger (2013)	237	15	47	151	0	9	57	109	17	122	11	–	11	40 G1, 21 G2
Corpron (1995)	22	0	1	13	0	3	0	0	11	5	–	–	–	–
Dall'Igna (2005)	14	–	–	–	4	–	–	2	5	5	0	0	3	14 G1
De Lambert (2016)	114	12	25	61	–	–	–	–	–	20	7	–	3	48 G1, 1 G2
Fernandez (2015)	28	1	18	1	–	–	1	–	1	3	3	–	1	–
Hatzipantelis (2010)	19	0	0	19	4	2	3	0	8	2	–	–	–	–
Henderson (2014)	27	0	0	20	1	1	5	3	1	14	–	–	–	27 G1
Jonsson (1989	18	1	3	11	0	7	1	7	3	3	–	–	–	–
Kartal (2022)	15	–	–	–	–	1	–	11	2	1	–	–	–	14 G1, 1 G2
Kim (2014)	13	–	–	–	–	–	–	–	–	7	1	1	1	–
Kulkarni (2013)	7	–	–	–	1	1	2	1	1	1	3	–	–	7 G1
Moertel (1990)	23	5	3	12	7	–	–	–	10	6	18	–	–	–
Neves (2006)	8	–	–	–	1	1	–	–	3	1	–	–	–	–
Njere (2018)	11	0	3	–	–	–	–	–	–	–	–	–	–	–
Parikh (2018)	109	–	–	–	–	–	–	–	–	–	–	–	–	–
Pelizzo (2001)	10	2	0	8	5	–	1	2	–	2	–	–	1	–
Pérez-Albert (2017)	17	–	–	–	–	–	–	–	–	2	–	–	2	3 G1, 1 G2
Prommegger (2002)	36	2	7	27	–	–	–	–	–	1	–	–	1	–
Ranaweera (2019)	32	–	–	16	–	–	–	–	–	–	–	–	1	–
Ryden (1975)	30	–	–	–	0	3	7	0	16	4	–	14	–	–
Scott (2011)	47	8	11	16	0	4	11	0	15	8	–	–	1	–
Sommer (2019)	40	3	4	30	–	3	9	16	7	4	–	–	2	24 G1, 3 G2
Spunt (2000)	5	–	–	–	–	–	–	–	–	2	–	–	2	–
Vandevelde (2015)	21	–	–	–	–	2	7	4	2	4	8	1	0	–
Virgone (2014)	113	2	11	62	–	–	–	–	5	28	–	–	2	84 G1, 4 G2
Wu (2017)	45	0	19	16	–	8	9	8	–	10	4	23	0	8 G1
Yalcin (2022)	33	1	6	11	–	5	7	6	6	4	–	–	0	–

G1: Grade 1; G2: Grade 2.

Table 3
Risk of bias on the primary outcomes.

Author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall Risk of Bias
Akova (2018)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
Barno (2018)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Boxberger (2013)	Moderate	Low	Low	Low	Moderate	Moderate	No information	Moderate
Corpron (1995)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
Dall'Igna (2005)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
De Lambert (2016)	Moderate	Low	Low	Low	Moderate	Moderate	No information	Moderate
Fernandez (2015)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Hatzipantelis (2010)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Henderson (2014)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Jonsson (1989)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Kartal (2022)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
Kim (2014)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
Kulkarni (2013)	Serious	Low	Low	Low	Low	Moderate	No information	Serious
Moertel (1990)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Neves (2006)	Serious	Low	Low	Low	Serious	Moderate	No information	Serious
Njere (2018)	Serious	Low	Low	Low	Serious	Moderate	No information	Serious
Parikh (2018)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Pelizzo (2001)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Pérez-Albert (2017)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Prommegger (2002)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Ranaweera (2019)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Ryden (1975)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Scott (2011)	Serious	Low	Low	Low	Serious	Moderate	No information	Serious
Sommer (2019)	Serious	Low	Low	Low	Serious	Moderate	No information	Serious
Spunt (2000)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Vandevelde (2015)	Serious	Low	Low	Low	Serious	Moderate	No information	Serious
Virgone (2014)	Moderate	Low	Low	Low	Low	Moderate	No information	Moderate
Wu (2017)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious
Yalcin (2022)	Serious	Low	Low	Low	Moderate	Moderate	No information	Serious

risk NET that underwent secondary surgery and those that were observed after appendectomy. Standardized surveillance strategies for all patients (without differentiation between low-risk and high-risk NET) have been reported in six studies [20,22,27,28,40,42]. Surveillance strategies consisted of serial ultrasounds, CT-scans or MRI at different intervals of every 3–6 months, gradually reduced to once a year after disease-free survival of one or two years. Additionally, in some studies urine 5-hydroxyindoleaceticacid (5-HIAA) and chromogranin A levels were determined as well. Octreotide scintigraphy was performed in cases of abnormal 5-HIAA or abnormal findings at imaging studies [40].

3.10. Quality of Life

None of the studies reported on Quality of Life of patients.

3.11. Cost-effectiveness

None of the studies reported direct or indirect costs of the treatment strategies.

4. Discussion

This systematic review included 29 studies reporting on 145 patients (<20 years old) with a high-risk NET of the appendix, of whom 81 were solely monitored after appendectomy and 64 underwent secondary surgery consisting of right hemicolectomy, ileocecal resection or caecectomy. Disease-free survival was 100% in both the group of patients that were observed after appendectomy (control group) and the group of patients that underwent secondary surgery (intervention group). During the follow-up period, ranging from no follow-up to 51 years, no recurrences were reported. The number of additional imaging studies for diagnostic work-up and during follow-up were comparable between the intervention and control group. Only one complication was reported, but this outcome might have been underreported in the included studies, as complication rates up to 50% after right hemicolectomy have been reported in the adult population [44]. Thus far, no studies have reported hr-QoL or cost-effectiveness of both treatment strategies. As disease-free survival seems to be 100% after appendectomy only and other secondary outcomes are

reported to be comparable between groups, the value of secondary surgery for children with a high-risk NET of the appendix might be questioned. Although risk of bias of the included studies was moderate to severe and high quality data with adequate follow-up is lacking, appendectomy without secondary surgery seems to be sufficient for children with a high-risk NET of the appendix.

Guidelines have been developed by the European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) in order to aid in the management of patients with a NET of the appendix. The ENETS guideline was published in 2016 and recommends right hemicolectomy for patients with a pT2 NET with risk factors for aggressive behavior (i.e. tumor at the base of the appendix, lymphovascular invasion, grade 2 tumor, and >3 mm infiltration of the mesoappendix) or a pT3 NET. For these high-risk NETs an increased risk of lymphatic and distant metastasis has been reported and therefore right hemicolectomy is advised as a definitive long-term cure. The NANETS guideline recommends right hemicolectomy in patients with a NET at the base of the appendix, in patients with tumors greater than 2 cm, in those with tumor where size cannot be determined, those with incompletely resected tumors, those with lymphovascular invasion, those with invasion of the mesoappendix, and in patients with intermediate to high grade tumors. These recommendations are based on studies in adult populations, that found a 5-year survival rate of 70–85% for the whole cohort including all tumor stages. In case of advanced disease with distant metastases an even poorer prognosis with a 5-year survival rate of 12–28% has been reported [12,45–47].

In contrast to the adult population, distant metastases and advanced disease at presentation have not been described in children. It might be possible that some goblet cell carcinomas or neuroendocrine carcinomas have been included in these studies on adult populations, leading to worse outcomes. Nonetheless, in current literature no recurrences have been reported and disease-free survival seems to be 100% in the pediatric population. Therefore the clinical course of NETs of the appendix seems to be more benign in children compared to the adult population, although large studies with adequate follow-up are needed to confirm this hypothesis. This raises the question whether or not secondary surgery is necessary in patients younger than 20 years diagnosed with a high-risk NET of the appendix. Since right hemicolectomy might be of no benefit for (disease-free) survival, the harm of potential complications should be taken into consideration. Data regarding complications after right hemicolectomy for any indication are scarce for the pediatric population, but in adults complication rates of 31–53% have been described [44,48]. Although right hemicolectomy in case of treatment of NET of the appendix is an elective procedure and thus a lower complication rate is expected, the study of Bamboat et al. found a complication rate of 50% after right hemicolectomy for NET of the appendix [5]. In our systematic review, only three studies reported complications after secondary surgery and a complication rate of 5% was found. It can be questioned whether or not this is an underestimation of the complication rate, as the majority of the studies did not mention complication rates after secondary surgery and large heterogeneity existed in the follow-up of patients.

The heterogeneity in follow-up of patients is a major limitation to the current evidence and the results of our systematic review. Follow-up duration ranged between no follow-up and 51 years in the studies that were included in this review [7,9]. Furthermore, large heterogeneity in the method of follow-up existed between studies. Some authors contacted general practitioners for follow-up data or contacted all national pediatric surgeons and oncologists, whereas others only used medical records from the hospital in which the patient was initially treated [8,9,37]. It can be questioned if these methods of follow-up are completely accurate to determine disease-free survival of patients. It might therefore be possible that the 100% disease-free survival that was found in our systematic review is an overestimation of the actual disease-free survival rate. High quality data with adequate and extensive follow-up is needed in order to draw evidence-based conclusions on disease-free survival and recurrence rates.

For patients with a low-risk NET of the appendix, no specific follow-up strategy seems to be necessary according to the current guidelines [3,49]. Similarly, for patients that underwent right hemicolectomy for a high-risk NET of the appendix but without proof of lymph node involvement or residual disease, no follow-up strategy is advised. It could be a significant benefit of right hemicolectomy compared to observation after appendectomy only, if no (or only limited) follow-up is necessary after secondary surgery. However, in the studies included in our systematic review, differences between those patients that underwent secondary surgery and those that were observed after appendectomy with regard to surveillance strategies and follow-up were not clearly described. In the two studies that described the number of additional imaging studies during follow-up, no difference was found for patients that underwent secondary surgery compared to those that were observed after primary appendectomy [8,32].

For patients with lymph node involvement or residual disease after right hemicolectomy and for patients with a high-risk NET that were observed after primary appendectomy, long-term follow-up is advised due to the presumed risk of lymph node metastasis but any benefit for the prevention of recurrence or influence on long-term outcomes is unproven [3,49]. No consensus has been reached on the type of imaging studies or laboratory markers that are needed during follow-up of patients with a high-risk NET of the appendix. This systematic review revealed several surveillance and follow-up strategies, consisting of serial abdominal ultrasounds or CT-scans at different intervals for the detection of potential recurrence of disease. It can be questioned if imaging studies are an adequate follow-up method for these slowly growing tumors, especially in the early postoperative period. Sensitivity of imaging modalities for detecting metastasis or local recurrence have not been investigated and meanwhile patients are repetitively exposed to irradiation in case of CT-scan. Although laboratory markers such as urine 5-HIAA and serum CgA have been used for follow-up of patients with NET of the appendix as well, several studies concluded that these markers were not sensitive to detect metastasis [7,8].

High quality data is also needed in order to determine the optimal follow-up strategy for patients with a high-risk NET of the appendix, as extensive follow-up might not be necessary. This may be of major influence on the quality of life of both patients and parents. It is well known that the diagnosis of cancer itself (and not only its treatment and complications) has a significant negative impact on quality of life of both the child and parents [50–53]. Furthermore, it has been reported that worse parents' quality of life is due to worse child quality of life, low parent resilience and especially higher fear of recurrence [52]. Reducing this fear of recurrence and limiting follow-up duration, if feasible, can therefore significantly improve quality of life.

This systematic review is limited by the heterogeneity between the included studies, which is one of the reasons that no meta-analysis could be performed. As discussed, method and duration of follow-up differed significantly between studies. Furthermore, due to the retrospective design, the included studies were prone to bias by indication. The reason to choose for secondary surgery in some patients with a high-risk NET and for appendectomy with subsequent observation in others, was not described in the majority of studies. Besides, we chose to classify and analyze all NETs

according to the ENETS guidelines, which limits extrapolation of results to the UICC/AJCC classification. Lastly, all studies in this review were assessed as moderate to severe risk of bias, indicating that high-quality data is lacking.

In conclusion, this systematic review found a 100% disease-free survival of children and young adults (<20 years old) with a high-risk NET of the appendix, both in the group of patients that underwent secondary surgery and in those patients that were treated with appendectomy without secondary surgery. Therefore, secondary surgery does not seem to improve the risk of recurrence, indicating that appendectomy might be sufficient treatment. However, risk of bias was moderate to serious for the included studies and adequate follow-up was lacking. Large (international) prospective studies with adequate follow-up are needed to generate high-quality evidence regarding the necessity of secondary surgery in children with high-risk NET of the appendix.

CRediT authorship contribution statement

Paul van Amstel: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Amber Mahieu:** Formal analysis, Investigation, Data curation. **Roel Bakx:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Ralph de Vries:** Methodology, Investigation, Writing – review & editing. **Martine F. Raphael:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Joep P.M. Derikx:** Conceptualization, Methodology, Writing – review & editing, Supervision. **LW Ernest van Heurn:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Ramon R. Gorter:** Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing, Supervision.

Declaration of competing interest

The authors have no conflicts of interest to disclose for the submitted work. Outside the submitted work Dr. Ramon R. Gorter and Dr. R. Bakx received a (governmental) ZonMw grant for research in the field of complex appendicitis in the pediatric population. Grant Number: 80-85009-98-2007.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.10.021.

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