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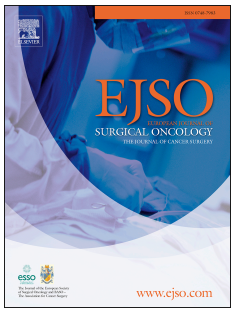

Lymph node metastases are more frequent in paediatric appendiceal NET ≥1.5□cm but without impact on outcome – Data from the German MET studies

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CRediT author statement

Michaela Kuhlen: Conceptualization, Methodology, Formal analysis, Resources, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition. **Marina Kunstreich:** Investigation, Data Curation, Writing - Review & Editing, Project administration. **Ulrich-Frank Pape:** Conceptualization, Writing – Original Draft.. **Guido Seitz:** Investigation, Writing - Review & Editing. **Lienhard Lessel:** Investigation. **Christian Vokuhl:** Investigation, Resources, Writing - Review & Editing. **Michael C. Frühwald:** Investigation. **Peter Vorwerk:** Methodology, Investigation, Resources, Funding acquisition. **Antje Redlich:** Methodology, Formal analysis, Resources, Data Curation, Visualization, Project administration, Funding acquisition.

Original Article

Lymph node metastases are more frequent in paediatric appendiceal NET ≥1.5 cm but without impact on outcome – data from the German MET studies

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Abstract

Background: Paediatric appendiceal neuroendocrine tumours (appNET) are very rare tumours, mostly detected incidentally by histopathological evaluation after appendectomy. Treatment recommendations are based on adult data considering high-risk NET as defined by European Neuroendocrine Tumour Society (ENETS) guidelines for completion right-sided hemicolectomy (RHC). Recent data suggest that less aggressive therapy may be justified.

Procedure: Analysis of children and adolescents with appNET prospectively registered with the German Malignant Endocrine Tumour (MET) studies between 1997 and 2022.

Results: By December 2022, 662 patients (64.7% females, 35.3% male) had been reported. Median age was 13.3 years [4.5-17.9], median duration of follow-up 2.2 years [0-10.9]. No distant metastases were reported. Tumour size was <1cm in 63.5%, 1-2cm in 33.2%, and >2cm in 3.2% of patients. WHO grade 1 and 2 tumours were diagnosed in 76.9% and 23.1% of patients, respectively. Lymphovascular invasion and lymph node metastases were associated with tumour size ≥1.5 cm. 27.0% of patients presented with high-risk NET according to ENETS criteria. Of those, only 55.9% underwent secondary oncological right hemicolectomy. Neither distant metastases, nor recurrences or disease-related deaths occurred in patients with appendectomy only as well as in patients with completion RHC. Overall and event-free survival were both 100%.

Conclusions: Internationally harmonized consensus recommendations on treatment of children and adolescents with appendiceal NET are urgently needed to avoid completion RHC in high-risk patients.

Introduction

Neuroendocrine tumours of the appendix (appNETs) are the second most frequent tumours of the gastrointestinal tract in children and adolescents [1]. They are usually incidental findings following appendectomy for acute appendicitis [2-5]. The frequency of appNETs in all appendectomies in paediatric patients was reported between 0.17% and 0.4% [3, 6-8]. This corresponds to an estimated incidence of 1:0.1 and 1.14:1 million children and adolescents per year.

In children and adolescents, appNETs are usually highly differentiated slow-growing tumours without endocrine functional activity [3]. Their management has remained

controversial [2, 5, 9-17]; most of the algorithms available were adopted from adults [18-20]. Across the recommendations, tumour size was considered the most important surrogate marker for predicting micrometastases in regional lymph nodes. Correspondingly, appendectomy was deemed sufficiently in tumours smaller than 1.5 or 2 cm, whereas completion oncological right-sided hemicolectomy (RHC) was recommended for larger tumours.

However, appNETs in children and adolescents seem to behave differently from their adult counterparts with reported risk of distant metastases being virtually absent [3]. Njere et al. conducted a systematic review on 958 paediatric cases: no distant metastasis or relapse were reported in any patient [3]. Thereafter, a Polish case series reported one patient sustaining two local recurrences [12]. Duess et al. reported one case with distant metastatic spread at diagnosis [8]. Only recently, van Amstel et al. conducted a systematic review on 1,112 children and adolescents with appNETs including 145 patients with high-risk appNETs [21]. They demonstrated no recurrences in high-risk patients treated with secondary completion surgery just as without secondary surgery. Consequently, secondary RHC seems not to be justified any longer.

A less aggressive treatment approach is corroborated by a recent retrospective, Europe-wide, pooled cohort study by Nesti et al. in 278 adult patients [22]. In this study, the presence of regional lymph node metastases was not associated with other presumed risk factors defined by the ENETS guidelines (which are tumour location, tumour grade, lymphovascular invasion, and mesoappendiceal infiltration) [20]. The study further provided evidence that patients with regional lymph node involvement almost never developed metachronous distant metastases. The authors concluded that regional lymph node metastases are clinically irrelevant and that RHC after complete resection of an appNET of 1-2 cm size by appendectomy is not indicated. The issue of secondary surgery, namely RHC, was taken up by the most recent revision of ENETS guideline of 2023 [19]. Accordingly, in appNETs of 1-2 cm size, oncological resection should now only be considered in factually extremely rare high grade 2 and grade 3 tumours.

In the light of these data, the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) [23] decided to establish internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with appNETs. In preparation for this, we analyse data from 662 children and adolescents with appNETs registered with the German Malignant Endocrine Tumours (MET) studies.

Patients and Methods

Children and adolescents aged <18 years with histopathologically confirmed diagnosis of appNET were prospectively registered in the national multicentre MET studies of the German Society for Paediatric Oncology and Haematology (GPOH) between January 1997 and December 2022. We included patients who met diagnostic criteria as per histopathological diagnosis by the German paediatric reference pathologist (79.3%) or - if not conducted - by the local pathologist (20.7%). TNM staging was performed according to the AJCC staging system (7^{th} and 8^{th} edition as appropriate). Patients with neuroendocrine carcinomas (NECs; grade 3) and mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs) as well as goblet cell carcinomas (previously termed goblet cell carcinoids, GBC) were excluded from this analysis. Some of the patients with appNETs (n=237) were reported on previously [24]. Informed consent was obtained from patients and/or legal guardians as appropriate. Follow-up for this study was completed on 31^{st} of December 2022.

The GPOH-MET 97 protocol and the GPOH-MET 2013 registry were approved by the ethics committees of the University of Luebeck (Approval number 97125) and the Otto-von-Guericke-University Magdeburg (Approval number 174/12), Germany.

Demographic, clinical, pathological, treatment, and outcome data were extracted from original source data. Frequencies were related to cases with recorded data. Data were entered into an electronic case report form by the study centre. Histopathological information (tumour location, tumour size, grading, lymphovascular invasion, mesoappendiceal infiltration, serosal

invasion, pTNM) was extracted from the reference pathology report if available or from the local pathologist´s report. Complete resection and micrometastases in regional lymph nodes were defined as per the pathologist`s report. Type of primary and secondary surgery was defined as reported in the original source data and classified according to appendectomy (only), ileocecectomy, and RHC. We defined `intraoperatively recognized´ in case a tumour was reported by the surgeon. Complications of primary and secondary surgery were entered as text entries excluding complications typically associated with appendicitis such as pus, secretion in the abdominal cavity, and adhesions.

Details on the GPOH-MET 97 protocol and the GPOH-MET 2013 registry were published previously [24]. Briefly, in the GPOH-MET 97 protocol, appendectomy was recommended for tumours < 1 cm, completion oncological RHC in tumours ≥ 1 cm. Since 2009, secondary RHC was recommended only in completely resected appendiceal NET ≥ 1.5 cm. For incompletely removed tumours ≤ 1.5 cm, a local follow-up resection with lymph node sampling was recommended [24].

For this analysis, the TNM classification (Table 1) and definitions of histopathological risk factors (i.e. incomplete resection, tumour at base of appendix, grade 2 NET, lymphovascular invasion, mesoappendiceal invasion >3 mm) were considered and retrospectively employed according to ENETS guidelines of 2016 [19, 20]. Tumour grading was determined according to the WHO 2010 classification (G1 NET Ki-67 index ≤ 2%; G2 NET Ki-67 index 3-20%; G3 NEC Ki-67 index >20%).

Patients with appNETs of 1-2 cm size were split in subgroups on the basis of: (1) histopathological risk factors (low-risk NETs without any histopathological risk factor and high-risk NETs in the presence of ≥ 1 risk factor); (2) surgical approach [appendectomy and appendectomy with secondary oncological RHC or ileocecal resection (hereafter referred to as RHC)].

Study outcomes were the frequency of regional lymph node metastases, the association between regional lymph node metastases and histopathological risk factors, and overall and event-free survival with and without secondary RHC. For outcome analysis of secondary surgery versus primary surgery, only high-risk patients according to ENETS 2016 guidelines criteria were included.

Statistical analyses

Statistical analyses were performed using SPSS version 26. Data visualization and graphs were created using SPSS and R version 4.3.0 using the `tidyverse´, `haven´, and `pROC´ packages. The cumulative relative frequency for each histopathological parameter (tumour size, grade 2 tumours, lymphavascular invasion, regional lymph node involvement for age and grade 2 tumours and serosal invasion for tumour size) was calculated as the sum of the relative frequencies of all the parameters that come before it added to the relative frequency for that parameter. On unverifiable regression analysis, visualization of the cumulative relative frequency of two metric variables was created using geom_smooth() in R, method=`loess´. Differences between categorical variables were determined by the chi-squared test. Yates correction was used as appropriate. A *P* value of < 0.05 was considered significant.

Results

In the MET database, 662 children and adolescents with appNET were registered with a median age at diagnosis of 13.3 years (range, 4.5-17.9). There was a female preponderance [64.7% (428/662) females, 35.3% (234/662) males; $p<0.001$]. The median duration of follow-up was 2.2 years (range, 0-10.9) (Figure 1A). No distant metastasis, recurrence or disease-related death was reported corresponding to an overall and event-free survival of 100%.

Of 596 patients, 66.7% (398/596) presented with acute appendicitis, 16.2% (97/596) with recurrent abdominal pain, and 16.9% (101/596) with other symptoms (including non-

specific flushing in 4 patients). In 87.0% (483/555) of patients, appNETs were diagnosed incidentally on histopathological examination. The tumour was recognised intraoperatively in 13.0% (72/555) of patients.

Histopathological Features

Tumours were located in the tip of the appendix in 76.7% (408/532) of patients, in the middle of the appendix in 15.6% (83/532), in the base of the appendix in 5.1% (27/532), and multifocal/from tip to base of the appendix in 2.6% (14/532). Tumour size was < 1 cm in 63.5% (392/617) of patients, 1-2 cm in 33.2% (205/617), and > 2 cm in 3.2% (20/617). On histopathological examination, submucosal invasion was determined in 8.7% (54/618) of patients, muscularis propria invasion in 29.1% (180/618), subserosal invasion in 56.3% (348/618), and serosal invasion in 5.8% (36/618). Mesoappendiceal invasion was reported in 50.4% (287/569) of patients, blood and lymphatic vessel invasion in 3.7% (22/588) and 7.0% (41/586) of patients, respectively. WHO grade 1 tumours were diagnosed in 76.9% (429/558) of patients and grade 2 tumours in 23.1% (129/558), Ki67 index distribution is displayed in Figure 1B. Extent of resection was microscopically complete in 97.5% (577/592) of patients and microscopically incomplete (i.e. pR1) in 2.5% (15/592) of patients. Regional lymph node metastases were present in 7.6% (10/131) of patients with lymph node sampling/completion RHC. Patient characteristics and histopathological findings of patients who could retrospectively be classified according to ENETS are detailed in Table 2. Results of histopathological findings by age and tumour size are displayed in Figure 3. Tumour size was significantly associated with age (R^2=0.010, p=0.016; Figure 2A).

Surgical procedures

A total of 662 patients underwent appendectomy (Figure 4). Secondary procedures comprised completion oncological RHC (n=64) andileocecectomy (n=26). Tumour residues

were reported in one (of 84; missing data on tumour residues in 6 patients) patient with second surgery, micrometastases in regional lymph nodes (median 0, range 0-4) in 10 (of 131) patients with lymph nodes sampled during first or second surgical procedures.

Secondary surgery in high-risk patients defined by ENETS 2016 criteria

To assess the impact of secondary surgery on outcome, patients (n=612) were classified according to ENETS criteria in low- and high-risk NETs (Table 2). Following ENETS guideline 2016 criteria, 142 patients in the high-risk group presented with pT2 NET with risk factors, 17 patients with pT3 NET and, 20 patients with pT4 NET and, thus, had indications for secondary surgical procedures. Of these patients, 66 (of 166, 39.8%; missing data in 13) patients underwent secondary surgery including RHC in 50 patients, ileocecetomy in 14 patients, and other procedures in 2 patients. One hundred patients with high-risk NET did not undergo any secondary procedure. No distant metastases, recurrences or appNET-related deaths were reported in both groups.

Complications of surgery in patients with appNET

In patients with appendicitis, complications were reported in 2.0% (11/541) of cases including perforation of the intestinal wall with mesenterial bleeding (n=1) and fecal peritonitis (n=2), mechanical ileus (n=1), umbilical fistula (n=1), abscess (n=2), perforation of ovarian cysts (n=3), and troca site hernia with incarcerated omentum (n=1).

Perioperative complications of secondary surgery were reported in 4 (of 88) patients including intestinal ischaemia (n=1), abscess formation (n=2), and adhesive ileus (n=1). Subsequent discomfort/health problems (not further specified) due to treatment of appNET were reported in 41 (of 433) patients [30/342 (8.8%) patients without second procedure versus 11/63 (14.9%) patients with second procedure; p=0.168].

Lymphovascular invasion and micrometastases in regional lymph nodes

The GPOH-MET 97 protocol recommended secondary surgery in appNETs with tumour size ≥ 1 cm until 2008 and tumour size ≥ 1.5 cm thereafter independent of the presence of other histopathological risk factors. Looking into those data in more detail, in patients with tumour size 1-2 cm being the only risk factor, lymphovascular invasion and regional lymph node metastases were present in no and one patient, respectively.

Lymphovascular invasion was significantly associated with tumour size (R^2= 0.531, p<0.001). Receiver operating characteristics (ROC) analysis and calculation of the optimal cut-off point for tumour size by estimation of the Youden´s index revealed a cut-off point of 14.5 mm as optimal for predicting lymph node metastases (determined by histopathological evaluation of lymph nodes sampled during secondary procedures; sensitivity 80.0%, specificity 59.2%; Figure 3). Lymph node metastases were more frequently present in tumours ≥ 1.5 cm size than in tumours < 1.5 cm size [14.0% (8/57) versus 2.7% (2/73); p=0.039].

No association was observed between lymph node metastases and lymphovascular invasion (p=1.00), grading (p=0.604), mesoappendiceal infiltration (p=0.850), serosal invasion (p=1.00), tumour location (p=0.618), and ENETS stage (p=0.522).

Discussion

We here have reported on 662 children and adolescents with NET of the appendix including 179 patients with high-risk appNET prospectively registered with the MET studies, a national multicentre registry. In line with previous reports and recent systematic reviews, our data confirm the excellent outcome with an overall and event-free survival of 100% [2, 3, 11, 21, 25-28]. Lymphovascular invasion and lymph node involvement were associated with tumour size ≥ 1.5 cm but not with outcome.

In our study, 33.2% of patients presented with appNET of 1-2 cm tumour size. Therapeutic decision making, specifically indicating completion RHC, in these patients is

considered challenging as on the one hand metastases have been reported in few adult appNET patients, particularly in patients with tumours > 1.5 cm while on the other hand these seem to be rather rare occurrences and surgical overtreatment may cause surgery-related morbidity [20, 29-31]. This is in fact partially corroborated by our data with an optimal cut-off of 1.5 cm tumour size to predict the presence of lymph node metastases. However, no event (i.e. metastases, relapse, death) occurred in any of the patients in our study questioning the clinical relevance of lymph node metastases in appNET in children and adolescents. In fact, only one child with local recurrence of appNET (no details on tumour size etc. given) [12] and no secondary distant metastases in children and adolescents with appNET were reported so far [3, 21, 32].

According to the criteria of the ENETS guideline of 2016 [20], a total of 179 patients in our study presented with high-risk NETs including 142 patients with pT2 tumours with histopathological risk factors. Of those, 39.8% underwent secondary surgical procedures in addition to initial appendectomy. No disease-related events occurred in patients with appendectomy only as well as in patients with secondary surgical procedures. By systematic review of the published literature on paediatric appNET, van Amstel et al. identified 145 out of 1,112 patients with high-risk NET [21]. Of those, 64 (44.1%) patients underwent secondary surgery whereas 81 (55.9%) patients were only monitored. No distant metastases, recurrences or disease-related deaths were reported in these patients. Njere et al. also did not report any recurrence or NET-related death in those 189 (of 958; 19.7%) paediatric patients fulfilling criteria for secondary surgery, who were observed after appendectomy only (120 of 189; 63.5%) [3]. Of note, this included 12 patients with a tumour size >2 cm, one patient with a grade 2 tumour, 5 patients with vessel invasion, and 4 patients with positive resection margins. In line with our data, Njere et al. also reported an association between tumour size and risk of positive lymph nodes which was likewise without clinical relevance.

In the retrospective analyses by Nesti et al. [22] and Pawa et al. [33] on a total of 493 adult patients with appNET, the clinical relevance of lymph node metastases and, thus, indicating RHC in tumours with 1-2 cm size, was also questioned. In the most recent ENETS guideline of 2023 risk stratification is based on tumour size (<1 cm, 1-2 cm, and >2 cm) and grade (grade 1, low grade 2, and high grade 2) [19]. Oncological resection is recommended in patients with tumour size >2 cm, in patients with tumour size 1-2 cm and high grade 2 (no cut-off value defined) as well as in patients with incomplete resection. As no distant metastases, recurrences or disease-related deaths were observed in any paediatric patient reported so far, cut-off values for grade 2 tumours in children and adolescents with appNET cannot be calculated. Of note, Ki-67 index >10% was only determined in one patient with grade 2 tumour in our study.

It should not go unmentioned that our study is limited by data availability, missing information on depth of mesoappendiceal infiltration, on indications for secondary surgical procedures (particularly in patients with < 1 cm tumour size), on reasons for not carrying out secondary surgery, systematic assessment of the severity of complications occurring after complementary surgery [34], as well as short follow-up among others. However, there are no validated data to prove the relevance of the underreported extent and measured depth of subserosal and/or mesoappendiceal infiltration [19, 20]. Nevertheless, our data underline the urgent need to establish internationally harmonized consensus recommendations for children and adolescents with appendiceal NET allowing for less aggressive treatment [9, 26, 35-38].

Conclusion

No recurrence or disease-related death occurred in 662 children and adolescents with appendiceal NET irrespective of tumour size, the presence of histopathological risk factors, and treatment. An internationally harmonized less aggressive treatment approach for app NET of 1-2 cm in size with adequate follow-up instead of secondary RHC may be justified.

Declaration of interest

None.

Author contribution

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Figure legends

Figure 1. Histogram (A) on the duration of follow-up in children and adolescents with NET of the appendix (n=662) and (B) Ki67-index (n=564).

Figure 2. Histopathological findings by age (A-D) and by tumour size (E-F). (A) Tumour size, (B) grade 2 tumours, (C) lymphovascular invasion, (D) regional lymph node involvement, (E) grade 2 tumours, and (F) serosal invasion.

Figure 3. Receiver operating characteristics (ROC) analysis and calculation of the optimal cut-off point for tumour size by estimation of the Youden´s index. Optimal cut-off point of 14.5 mm for predicting lymph node metastases.

Figure 4. Flow-chart on surgical procedures in 662 children and adolescents with NET of the appendix. Primary appendectomy was performed in 662 patients. Depending on tumour size, type of secondary surgeries and number of patients are depicted in intended boxes.

Table legends

Table 1. TNM classifications (ENETS, AJCC/UICC) for appendiceal NET (appNET)

Table 2. Patient characteristics and histopathological findings in 612 children and adolescents with NET of the appendix classified according to the ENETS 2016 criteria

Figure legends

Figure 1. Histogram (A) on the duration of follow-up in children and adolescents with NET of the appendix (n=662) and (B) Ki67-index (n=564).

Figure 2. Histopathological findings by age (A-D) and by tumour size (E-F). (A) Tumour size, (B) grade 2 tumours, (C) lymphovascular invasion, (D) regional lymph node involvement, (E) grade 2 tumours, and (F) serosal invasion.

Figure 3. Receiver operating characteristics (ROC) analysis and calculation of the optimal cut-off point for tumour size by estimation of the Youden´s index. Optimal cut-off point of 14.5 mm for predicting lymph node metastases.

Figure 4. Flow-chart on surgical procedures in 662 children and adolescents with NET of the appendix. Primary appendectomy was performed in 662 patients. Depending on tumour size, type of secondary surgeries and number of patients are depicted in intended boxes.

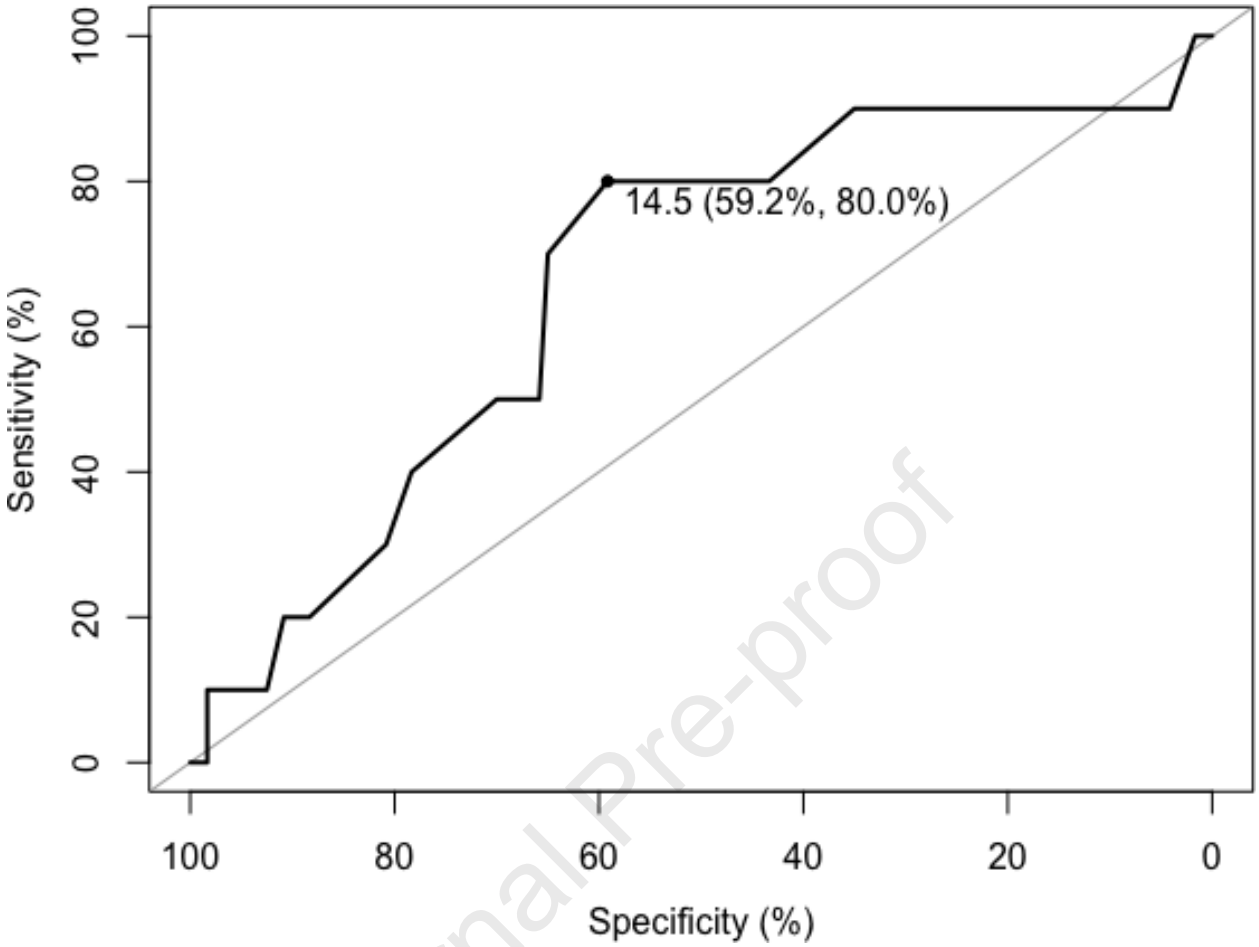
Table 1. TNM classifications (ENETS, AJCC/UICC) for appendiceal NET (appNET)

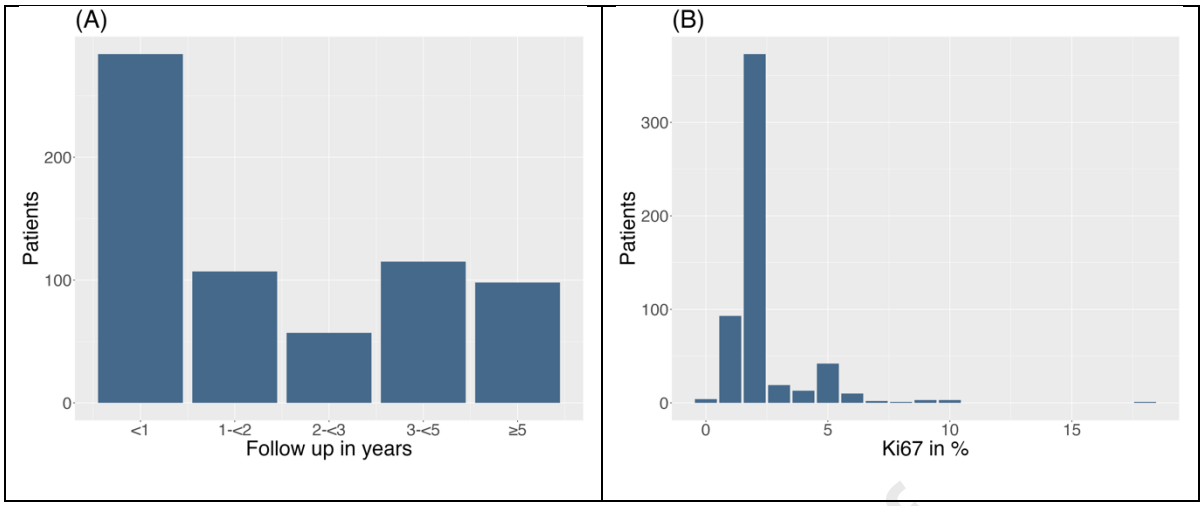
	pTNM ENETS	**AJCC/UICC 7th edition**	**AJCC/UICC 8th edition**
pT1	< 1 cm and submucosa or muscularis propria invasion	≤ 2 cm (T1a ≤1 cm; T1b >1–2 cm)	≤ 2 cm
pT2	1-2 cm and submucosa or muscularis propria or mesoappendix/subserosa invasion ≤3 mm	> 2–4 cm OR caecal invasion	> 2–4 cm
pT3	> 2 cm and/or mesoappendix/subserosa invasion > 3 mm	> 4 cm OR ileal invasion	> 4 cm OR mesoappendix/subserosa invasion
pT4	Perforates serosa/peritoneum, or invades other neighbouring organs		

Table 2. Patient characteristics and histopathological findings in 612 children and adolescents with NET of the appendix classified according to the ENETS 2016 criteria

	Low-risk NET		**High-risk NET**		
	pT1 (< 1 cm)	**pT2 (1-2 cm) w/o risk factors**	**pT2 (1-2 cm) with risk factors**	**pT3 (> 2 cm)**	**pT4**
	N=391	**N=42**	**N=142**	**N=17**	**N=20**
Age at diagnosis, years					
Mean	13.1	13.1	13.6	14.0	13.8
Median	13.2	13.0	13.9	14.4	13.6
Range	5.7-17.9	4.5-17.5	7.6-17.7	9.4-17.5	10.7-15.6
Sex					
Female	60.1%	64.3%	73.9%	82.4%	80.0%
Male	39.9%	35.7%	26.1%	17.6%	20.0%
Tumour location					
Tip	82.8%	63.6%	68.3%	33.3%	66.7%
Middle	11.8%	30.3%	20.3%	25.0%	20.0%
Base	3.6%	6.1%	8.1%	16.7%	6.7%
Multifocal	1.8%	0%	3.2%	25.0%	6.7%
Not available	N=53	N=9	N=9	N=5	N=5
Extent of invasion					
Submucosa	12.0%	12.2%	0%	5.9%	0%
Muscularis propria	39.6%	26.8%	7.0%	11.8%	0%
Subserosa	46.9%	56.1%	85.9%	76.5%	15.0%
Serosa	1.6%	4.9%	7.0%	5.9%	85.0%
Not available	N=7	N=1	N=0	N=0	N=0
Mesoappendix infiltration					
No	62.9%	100%	8.8%	26.7%	10.5%
Yes	37.1%	0%	91.2%	73.3%	89.5%
Not available	N=35	N=6	N=5	N=2	N=1
Blood vessel invasion					
No	96.8%	100%	95.7%	88.2%	89.5%
Yes	3.2%	0%	4.3%	11.8%	10.5%
Not available	N=21	N=5	N=4	N=0	N=1
Lymphatic vessel invasion					
No	93.8%	100%	90.4%	82.4%	88.9%
Yes	6.2%	0%	9.6%	17.6%	11.1%
Not available	N=21	N=5	N=6	N=0	N=2
Resection margin					
R_0	98.9%	100%	94.7%	86.7%	86.7%
R_1	1.1%	0%	5.3%	13.3%	13.3%
Not available	N=16	N=2	N=10	N=2	N=5
Tumour grade					
Grade 1	84.8%	100%	56.2%	47.1%	64.7%
Grade 2	15.2%	0%	43.8%	52.9%	35.3%
Not available	N=28	N=7	N=5	N=0	N=3
Tumour size, cm					
1 - < 1.5 cm	n.a.	69.0%	57.0%	n.a.	30.0%
≥ 1.5 - < 2 cm	n.a.	31.0%	43.0%	n.a.	50.0%
Regional lymph nodes metastases*	N=42	N=11	N=53	N=14	N=9
No	100%	90.9%	88.7%	85.7%	88.9%
Yes	0%	9.1%	11.3%	14.3%	11.1%

*defined by histopathologic evaluation





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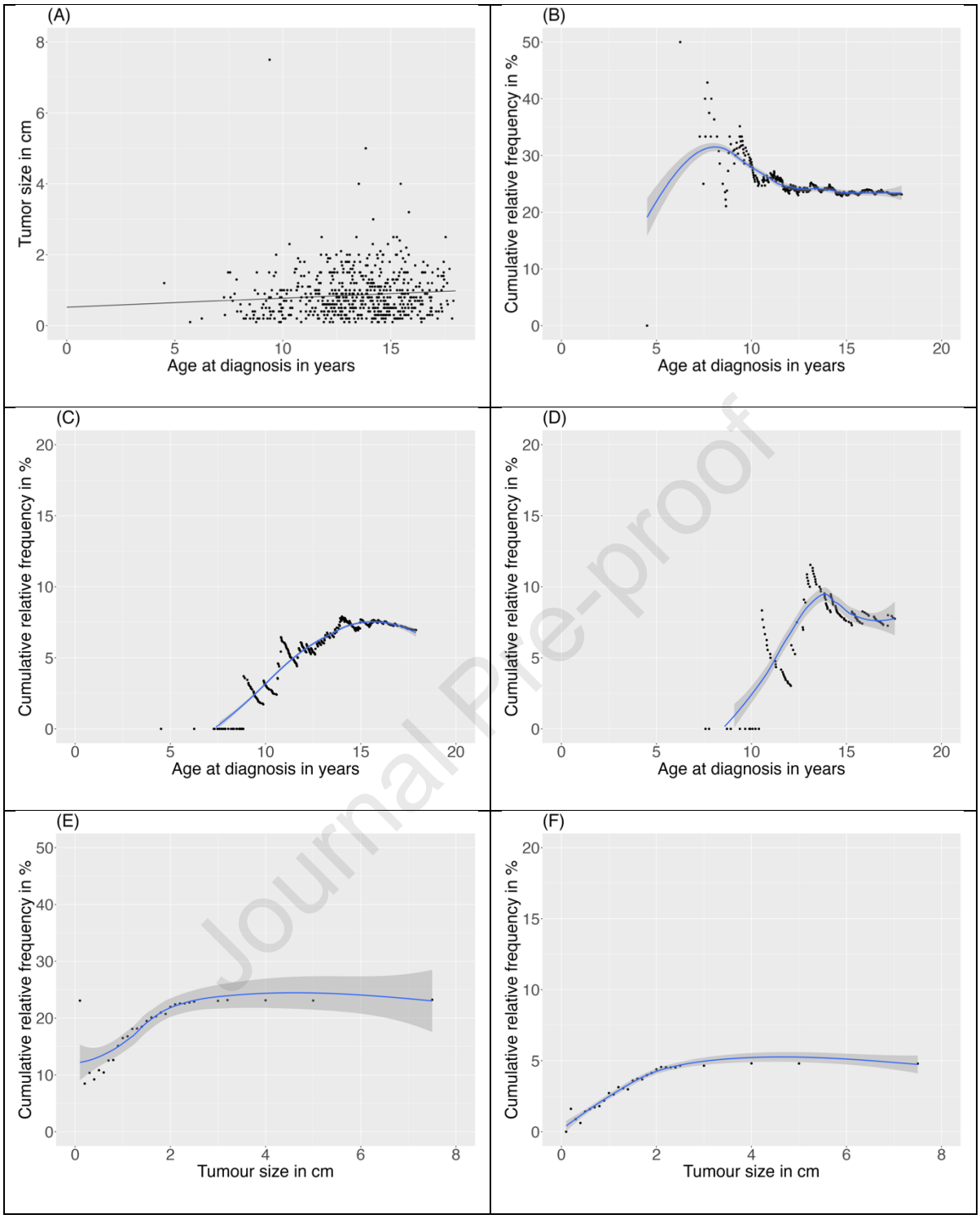

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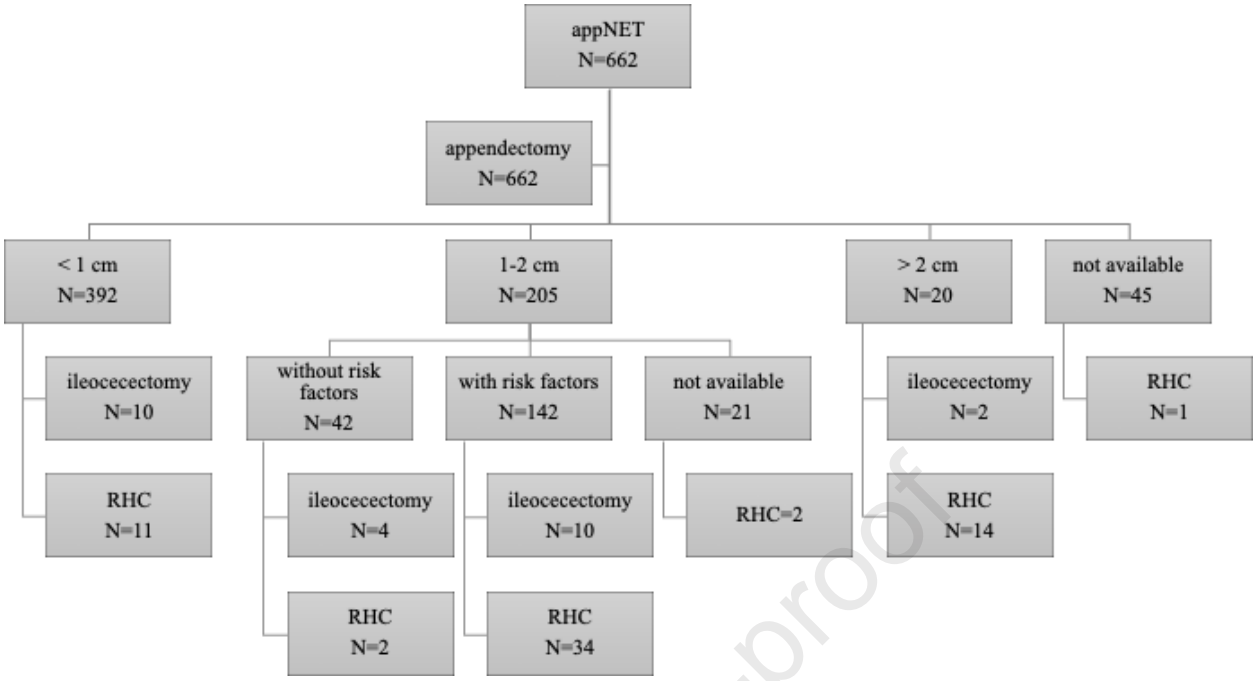

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: