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ORIGINAL ARTICLE

Long-term outcomes in pediatric appendiceal carcinoids: Turkey experience

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Abstract

The tendency of non-operative management of appendicitis let us explore the natural history of appendiceal carcinoids, compare them with appendicitis patients, and determine the possibility of deciding the extent of the surgery and post-operative follow-up on behalf of the intraoperative findings. A retrospective review was performed of patients with appendicitis between 2009 and 2017. Of 2781 patients, 10 (0.36%) were diagnosed with appendiceal carcinoids. Sixty percent were female with an average age of 13.10 ± 1.73. The mean tumor size was 0.97 ± 0.34 cm with 70% located at the tip. Majority had an insular pattern ($n = 9$), six had subserosal fat tissue invasion, one had extension to mesoappendix, one had vascular invasion, and two had lymphatic invasion. The average mitotic index was 3.20 ± 1.40/50HPF, and Ki 67 activity was 3 ± 1.7%. The mean follow-up period was 66.40 ± 25.92 months. Patients were further evaluated with ultrasonography ($n = 10$), CT ($n = 3$), and MRI ($n = 10$). Serum markers including chromogranin ($n = 9$), NSE ($n = 6$), and 5-HIAA ($n = 6$) were normal. None required further treatment and had any symptoms of carcinoid syndromes or recurrences post-operatively.

Conclusion: Other than appendectomy, no additional surgery or follow-up is required in appendiceal carcinoids less than 1.5 cm in size, regardless of the lymphoid or vascular invasion.

What is Known:
- *The treatment of patients with a 1–2-cm tumor is not clear in both the pediatric and adult populations, and additional resection is needed.*
- *Patients are monitored post-operatively with radiological and/or biochemical testing.*

What is New:
- *Appendectomy is curative for tumors less than 2 cm.*
- *No additional surgery or follow-up is required in appendiceal carcinoids less than 1.5 cm in size regardless of the lymphoid or vascular invasion.*

Keywords Appendicitis · Carcinoid tumor · Children · Neuroendocrine tumors

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Abbreviations

5-HIAA	5-Hydroxyindoleacetic acid
ANOVA	Analysis of variance
CT	Computerized tomography
ENETS	European Neuroendocrine Tumor Society
HPF	High-power field
IBM	International Business Machines
MRI	Magnetic resonance imaging
NSE	Neuron-specific enolase
RHC	Right hemicolectomy
SPSS	Statistical package for the social sciences
UK	United Kingdom
USG	Ultrasonography
WHO	World Health Organization

Introduction

Carcinoid tumors are rare tumors of childhood which arise from neuroendocrine cells of the gastrointestinal tract and tracheobronchial tree [1]. Although appendiceal carcinoid is the most common gastrointestinal epithelial tumor in the pediatric population, its incidence is 0.08% of all masses found in children undergoing an appendectomy [5, 6]. The diagnosis is most commonly made through histopathologic examination after an appendectomy due to appendicitis. In the adult population, radical surgical excision is the treatment of choice in the tumors larger than 2 cm. Due to the low probability of preoperative diagnosis and the dubious nature of the disease in the childhood, it is difficult to establish guidelines for the pediatric population. There is an anecdotal report of a patient with a tumor larger than 2 cm in the pediatric population and disease free for 10 years after an appendectomy in opposition to current guidelines [3, 5, 9]. As there is a tendency toward non-operative management of appendicitis, the probability of experiencing more advanced stage appendiceal carcinoids is higher than ever. We intend to present the natural history and long-term outcomes of appendiceal carcinoids in the pediatric population, compare them with appendicitis patients, and determine if it is feasible to determine the extent of surgery and post-operative follow-up based on the intraoperative findings.

Methods

After Institutional Review Board approval was obtained (2017/2615), data of all appendicitis cases were assembled through an institutional database between 2009 and 2017 and augmented with the hospital electronic medical record. Data was collected by demographics, and pre- and post-operative course. Diagnosis of appendicitis and extent of the surgery was determined through clinical, laboratory, radiological, and operative findings of the patients by separate surgeons while staging of the appendiceal carcinoid was based on the WHO and ENETS guidelines [5, 6]. Parental consent was obtained both for surgical approach and publication of the case. Statistical analysis was performed with IBM SPSS Statistics 20.0.0 (Il, Chicago) software by using ANOVA with p values of less than 0.05 considered significant.

Results

There were 2781 patients admitted to our institution due to appendicitis between 2009 and 2017. Of those patients, 10 (0.36%) were diagnosed as appendiceal carcinoids. Patients' characteristics are summarized in Table 1. The mean age of the patients at presentation was 13.10 ± 1.73 years with a slight female dominance (F/M: 3/2). All patients had signs and symptoms of acute abdomen with a mean duration of symptoms being 2.40 ± 2.17 days; none had signs or symptoms of carcinoid syndrome or other tumor. While 60% of the patients had leukocytosis with average white blood cell count 11,978 ± 5139, only two patients had thrombocytosis with overall mean platelet value 353,100 ± 127,748. All patients had preoperative abdominal graph and ultrasonography with no additional finding other than appendicitis, one with an ovarian cyst. The mean reported appendix diameter was 5.80 ± 0.98 mm on ultrasound. All patients underwent open surgery through a transverse right lower quadrant skin crease incision across McBurney's point. In 40% of the cases, appendicitis was complicated by perforation. The average length of post-operative hospital stay was two ± 1.08 days.

During the same time interval, the mean age of the patients for the whole group was 11.01 ± 3.28 years with a 61.1% female dominance ($p = 0.425$, $p = 0.876$). Sign and symptoms of the patients were also comparable between two groups. The average white blood cell count was 15,458 ± 5548 in patients without appendiceal carcinoids, while the mean platelet count was 289,260 ± 88,025 ($p = 0.064$, $p = 0.126$). The majority of the cases were diagnosed with complicated appendicitis without abscess (47.6%).

In the majority of the cases (70%), the tumor was located in the distal part of the appendix with the average tumor size of 0.97 ± 0.34 cm. Three patients (30%) had a tumor less than 1 cm while the rest had a tumor size between 1 and 2 cm. In one case (10%), the tumor had a tubular pattern. Six (60%) patients had subserosal fat tissue invasion, with one patient displaying invasion to the serosa. Only patient number 5 had an extension to mesoappendix. The surgical margin was free of tumor cells in all cases. A single patient (10%) had vascular invasion, with two (20%) patients demonstrating lymphatic invasion. None of the patients showed perineural invasion. Synaptophysin was strongly expressed in all patients' pathology specimens (Fig. 1). The average mitotic index was 3.20 ±

Table 1 Patients demographics and tumor characteristics

Patient number	1	2	3	4	5	6	7	8	9	10
Age (years)	12	10	12	13	14	16	12	15	13	14
Gender	Male	Female	Female	Male	Male	Female	Male	Female	Female	Female
Abdominal pain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vomiting	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No
Diarrhea	No	No	Yes	No	No	No	No	No	No	No
X-ray	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Usg	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Appendix size (cm)	6.50	6.00	4.00	7.00	6.00	4.50	5.50	6.00	7.00	5.50
Diagnosis	Non-complicated appendicitis	Complicated appendicitis with abscess	Complicated appendicitis without abscess	Complicated appendicitis without abscess	Non-complicated appendicitis	Incidental	Non-complicated appendicitis	Complicated appendicitis without abscess	Non-complicated appendicitis	Non-complicated appendicitis
Additional pathology	None	None	None	Meckel diverticulitis	None	Ovarian cyst	None	None	None	None
Tumor										
Localization	Distal	Distal	Distal	Distal	Distal	Middle	Middle	Middle	Distal	Distal
Size (cm)	1.50	1.20	1.30	0.70	1.10	0.40	0.70	1.00	0.65	1.10
Growth pattern	Tubular	Insular	Insular	Insular	Insular	Insular	Insular	Insular	Insular	Insular
Grade	2	2	2	2	2	1	1	1	1	1
Mitotic index (50 HPF)	3	5	4	4	4	1	2	2	2	5
Invasion	Subserosal fat	Subserosal fat	Serosa	Subserosal fat	Subserosal fat	Submucosa	Muscularis mucosa	Muscularis mucosa	Subserosal fat	Subserosal fat
Surgical margin	–	–	–	–	–	–	–	–	–	–
Vascular invasion	No	No	No	No	No	No	Yes	No	No	No
Lymphatic invasion	No	No	Yes	No	No	No	Yes	No	No	No
Perineural invasion	No	No	No	No	No	No	No	No	No	No
Chromogranin		Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Synoptopsin	+	+	+	+	+	+	+	+	+	+
NSE	Normal	Normal	Normal	Normal	Normal			Normal		
Ki 67%	4	4	3	5	6	1	2	2	2	1
Follow-up (months)	68	70	74	75	87	88	89	63	48	2
CT					Normal	Normal		Normal		
MRI	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
HIAA		Normal	Normal		Normal	Normal		Normal	Normal	

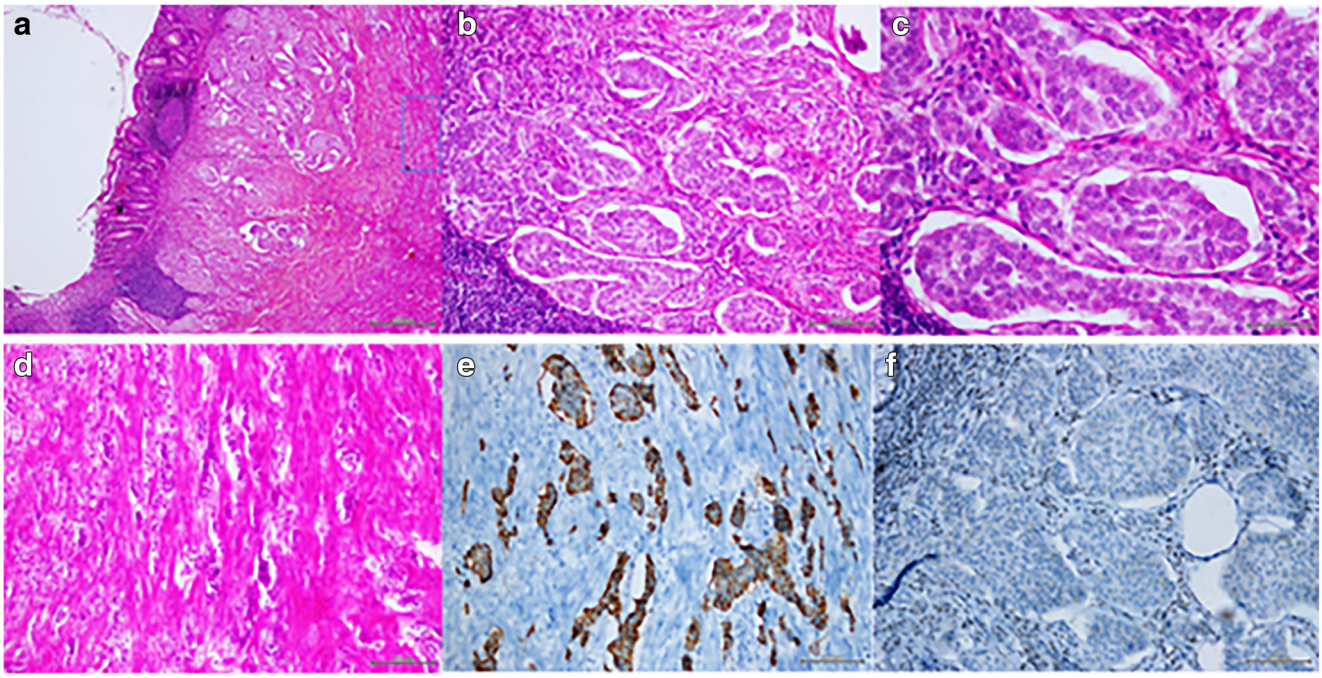

Fig. 1 Histologic and immunochemistry features of the tumor tissue. **a** A neoplastic proliferation that forms solid islands within the appendix mucosa (H&E × 40). **b**, **c** Magnified carcinoid cells (H&E × 200, × 400, respectively). **d** Infiltration of the muscularis mucosa by the tumor cells (H&E × 200). **e** Strongly expressed synaptophysin activity within the tumor cells (× 200). **f** Expressed Ki 67activity which is approximately 1% (× 200)

1.40/50HPF, and the average Ki 67 activity was 3 ± 1.7%. Half of the patients were grade 1; the rest were grade 2.

All patients were referred to pediatric oncology post-operatively. Seven patients did not meet criteria for secondary surgery. The remainder of the patients were closely followed non-operatively. All patients were followed at 3-month intervals for the first year, 6-month intervals for the second year, and yearly thereafter. The mean follow-up period was 66.40 ± 25.92 months. All patients had serial USG examinations while three patients (30%) had computerized tomography, with all patients undergoing magnetic resonance imaging. Serum markers were normal, 60% of whom NSE was measured while chromogranin was measured in 90% of the patients and 5-HIAA was measured in 60% of the patients. None of the patients had signs or symptoms of carcinoid syndromes or recurrences post-operatively.

Discussion

Although appendiceal carcinoids are rare tumors in childhood, they are still the most common epithelial tumors in the gastrointestinal system. Due to the tendency of pediatric surgeons toward non-operative treatment of appendicitis, the incidence and prevalence of the disease may increase in the future with more advanced stage tumors. Due to its rarity, guidelines were adopted mostly from adult studies [4]. However, there is not enough data to prove that the pattern of the disease in childhood mimics the pattern in adults. Due to the rare nature of the disease with limited single institution experience, the lack of a defined natural history of these tumors is another barrier to establish efficient guidelines. The pre-operative and intraoperative diagnosis of the disease is also difficult per the sign and symptoms of the carcinoid syndrome are as rare as the disease itself.

According to the WHO and ENETS guidelines and majority of the publications in the literature, secondary RHC is indicated for tumors larger than 2 cm, involvement of mesoappendix, lymphovascular invasion, high mitotic index, or raised proliferative index (Ki 67), and partial cecectomy or ileocecal resection is indicated in patients with tumor-positive specimen margin. However, no prospective study or trial has proved prolonged survival or better outcome in patients with RHC, compared to patients with appendectomy alone. A report by Assadi et al. proposed the use of 2 cm size criteria for secondary surgery per the reports of simple appendectomy in tumors over 2 cm, had only minimal rate of recurrent disease, or not at all [2, 5].

In the literature, there are approximately 935 cases of patients under 18 years of age who presented with the diagnosis of appendiceal carcinoid since its first classification by WHO in 1980. Unfortunately, since the number of appendicitis

patients was not reported in all cases, the exact incidence could not be confirmed. When we review the data for the last 5 years, the incidence of the disease is approximately 0.33% with 0.36% prevalence. While the rate of a second surgery in the literature was 15.32% since 1980, it falls to 5.22% in the last 5 years.

Data in this study corresponds the literature in which the mean age of the patients with appendiceal carcinoids was slightly higher than the mean age of the appendicitis patients and slight female dominance. There was not any patient with a pre-operative diagnosis of the disease. Since the appendiceal carcinoids are non-functional, the importance of surveillance with chromogranin and 5-HIAA levels is controversial. Patients whose serum levels of chromogranin were checked found to have normal levels as stated by Henderson et al. [8].

In our study, one patient was without histopathological diagnosis of appendicitis. Majority of the studies in the literature had a considerable number of patients with histopathological diagnosis, while almost none indicate the exact number of incidental appendectomy patients. The only study by Fallon et al. presented in a large series showed 12 patients out of 28 post-operatively had a diagnosis of appendicitis, all of which had confirmed the diagnosis of appendiceal carcinoid [2]. This high number of incidental appendectomy with appendiceal carcinoid draw attention since there is a tendency in many institutions to follow acute abdomen patients non-operatively.

The approach for the post-operative surveillance of the patients was not clearly defined in any of the studies in the literature. Neither pre-operative or post-operative CT or MRI contribute any beneficial data regarding diagnosis. On the other hand, abdominal USG would be sufficient for the surveillance of liver metastasis of the disease, but this is extremely rare. The impact of the invasion and metastasis of the tumor to the prognosis of the patient is also controversial. Henderson et al. in a large study from the UK stated that all tumors excised were classified as low-grade lesions in (opposition or contradiction) to our current results in which 50% of patients had grade 2 lesions [8]. The surveillance of these patients, other than being inefficient, is also a burden to patients, families, hospitals, and health system [7].

Our study differs from others as it has one of the longest follow-up periods post-operatively without any drop out patients. Additionally, three patients who met the criteria for secondary surgery were followed non-operatively for an average of 83.3 ± 8.14 months without any adverse event. Even patients with mesoappendix and serosa invasion are free of any signs or symptoms. Finally, the approximate tumor size was larger when it was located at the tip of the appendix compared to tumors located in the middle contradicting the literature.

This study has some limitations, first of which is a retrospective cohort. Although no patients were lost to follow-up, the volume of patients is small, mostly due to the rarity of the disease. The absence of tumors over 1.5 cm is another limitation of this study which does not allow us to generalize our findings.

Conclusion

This study confirms the known fact that appendiceal carcinoids are rare tumors of childhood. Although almost always diagnosed post-operatively appendectomy is curative for tumors less than 2 cm. Based on the data in the literature and our study, secondary surgery or post-operative follow-up might not be needed in appendiceal carcinoids less than 1.5 cm in size regardless of the lymphoid or vascular invasion. For the patients with tumor size over 2 cm, a CT or MRI of thorax, abdomen, and pelvis for metastasis work-up would be followed by yearly clinical and abdominal USG follow-up without any serum markers. A biomarker should be established to diagnose this disease pre-operatively.

Authors' contributions FA and EA contributed to all aspects of the manuscript. YNE, NT, SY, SA and UST contributed to collection and analysis of the data and gave critical revisions those were important for the intellectual content and approving the final version of the manuscript.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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