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Retrospective Evaluation of Carcinoid Tumors of the Appendix in Children

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Abstract. Carcinoids of the appendix are rare in children and are usually diagnosed incidentally on histologic investigation following appendectomy for appendicitis. To investigate the significance of the diagnosis of appendiceal carcinoid in children, we conducted a retrospective study of the treatment and follow-up of 36 children with histologically confirmed carcinoid tumors of the appendix. Between 1970 and 2000 a total of 36 patients (25 girls, 11 boys) were diagnosed with appendiceal carcinoid. The median age of the patients at diagnosis was 12.3 years (range 6–16 years). The indication for appendectomy was acute lower right quadrant pain in 27 cases and chronic right lower quadrant pain in 9 patients. In 27 specimens the tumor was localized at the apex, in 7 at the midportion, and in 2 at the base of the appendix. The median tumor diameter was 6 mm (range 3–17 mm). Concomitant severe appendicitis was diagnosed in 14 patients 2 with a perforated appendicitis. In only one tumor were mucin-producing cells detectable. After a median follow-up of 10 years (range 2 months to 30 years) all patients were tumor-free. None of the patients had a synchronous or metachronous noncarcinoid malignant tumor. Appendiceal carcinoids are usually asymptomatic, and the indication for surgical intervention is acute or chronic abdominal pains in the right lower quadrant. For most patients the prognosis is excellent after appendectomy. As in adults, appendectomy is the appropriate treatment.

Although carcinoid tumors of the appendix are rare, they represent the most frequent malignant tumor of the gastrointestinal tract in children. However, few series have dealt with carcinoids of the appendix during childhood [1–9], possibly due to the fact that not every appendiceal specimen was histologically investigated. The prognosis after appendectomy is generally excellent owing to the fact that metastasizing carcinoids of the appendix are seldom observed. Tumor size is accepted to be the most reliable prognostic parameter for metastatic potential. Additionally, localization at the base of the appendix and histologically detected mucin-producing cells are relevant prognostic factors [10]. In contrast, vascular and mesoappendiceal infiltration are not important factors for determining treatment and predicting the outcome. Other prognostic criteria, such as histopathologic and immunohistochemical results, are not yet established. Krishnamurthy and Dayal showed that expression of transforming growth factor-α (TGF-α) was significantly associated with infiltrative growth of gastrointestinal carcinoids but not with a tendency to metastasize [11]. Malignant potential is recognized only by the clinical course. Right hemicolectomy is indicated for tumors with a diameter of more than 2 cm, but much controversy exists about the indication for right hemicolectomy for tumors with a diameter of 1 to 2 cm [6, 12, 13].

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Patients and Methods

Data for this retrospective study were obtained by reviewing the surgical records from the Department of Pediatric and General Surgery, University Hospital, Innsbruck, Austria and various district hospitals in the province of Tyrol, Austria, from 1970 to 2000. All of the patients, who were less than 16 years of age at surgery, had histologically confirmed carcinoid of the appendix. The analysis of the medical records comprised the patients' age, gender, indication for operation, localization of the tumor in the appendix specimen, tumor diameter after fixation with formaldehyde, presence of additional carcinoids, synchronous or metachronous coexisting malignant noncarcinoid neoplasms, presence of mucin-producing cells, and follow-up.

Results

During a 30-year period, 36 children had a histologically confirmed diagnosis of a carcinoid tumor of the appendix (25 girls, 11 boys). The median age at diagnosis was 12.3 years (range 6–16 years). The indication for appendectomy was suspicion of acute appendicitis in 27 patients and chronic abdominal pain in 9. Altogether, 27 tumors were localized at the apex, 7 at the midportion, and 2 at the base of the appendix.

Severe appendicitis was detected histologically in 14 patients, and 2 of these patients had perforated appendicitis (Table 1). One of these patients has the longest uneventful follow-up (30 years) (tumor diameter 5 mm, positioned in the apex, no goblet cells

Table 1. Analysis of patients for whom second-look surgery (ileocecal resection or right hemicolectomy) was discussed.

Patient no.	Size (mm)	Age (years)	Localization	Goblet cells	Extended surgery	Perforation
1	5	15	Base	No	Ileocecal resection	No
2	17	14	Base-midportion	No	No	No
3	3	14	Apex	Yes	No	No
4	14	10	Apex	No	No	No
5	13	12	Apex	No	No	No
6	13	16	Apex	No	No	No
7	5	12	Apex	No	No	Yes
8	7	13	Midportion	No	No	Yes

Of the 36 patients with carcinoid of the appendix, 6 had tumor features that were possible indications for extended surgery. Only one patient underwent ileocecal resection because the tumor was located at the base with no clear resection margin. Two patients with associated perforated appendicitis had an uneventful follow-up (4 and 30 years, respectively).

detected). The second patient with perforated appendicitis and tumor growth beyond the serosa of the appendix was operated on 8 months after appendectomy for an intraabdominal abscess and has no evidence of disease after 4 years of follow-up (tumor diameter 7 mm, no goblet cells, localization in the midportion of the appendix). One of our 36 patients had a carcinoid tumor with mucus-producing cells and a tumor diameter of 3 mm located at the apex; therefore hemicolectomy was not performed (Table 1).

A second operation was necessary in four patients. One had persistent pain 6 months after appendectomy, and cecopexy was performed because of his cecal mobility, thought to be causing intermittent obstruction. A second patient was operated on for small bowel obstruction on the seventh postoperative day. The third patient underwent reoperation because of incomplete resection of a carcinoid at the base of the appendix; he had an ileocecal resection 2 weeks after the first operation. The fourth patient in this group had a perforated appendicitis and was operated on 8 months after appendectomy for an intraabdominal abscess.

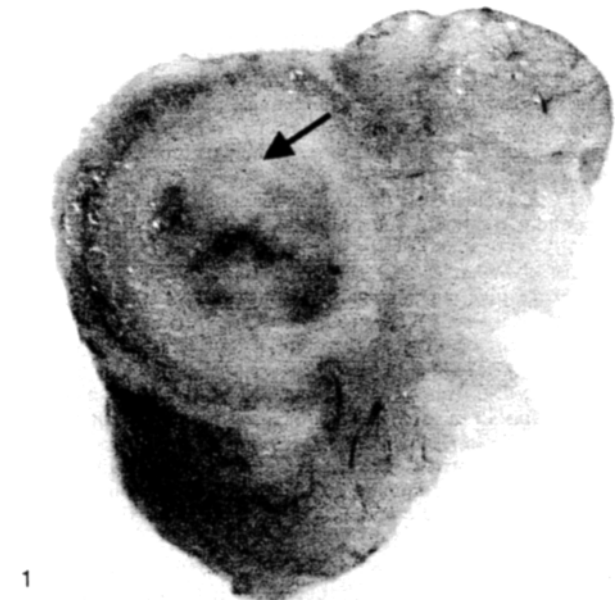
All 36 patients were tumor-free after a median follow-up period of 10 years (range 2 months to 30 years). None of the patients had elevated serotonin metabolites in the urine, nor were metastases detectable by abdominal ultrasonography.

Discussion

Carcinoids of the appendix, although rare, are the most abundant malignant tumors of the gastrointestinal tract in children and adolescents [7]. The frequency of appendiceal carcinoids in appendiceal specimens from children range from 0.085% to 0.169% of all histologically investigated appendiceal specimens, which is lower than that in adults [8]. Appendiceal carcinoid is typically undiagnosed preoperatively and usually not associated with neuroendocrine symptoms [12, 13]. Carcinoid syndrome is observed only when retroperitoneal or liver metastases coexist, which is rare and is never seen in children [12]. It is striking that neither in the literature nor in our series were any of the appendiceal carcinoids detected preoperatively when ultrasonography of the abdomen was performed. Intraoperatively, carcinoid of the appendix should be suspected when a yellowish, firm tumor is found (Figs. 1, 2). The prognosis for appendiceal carcinoids is good because mostly they behave like a benign tumor. Compared to carcinoids in other locations, the good prognosis seems to be a consequence of a different neuroendocrine origin of the tumor cells [14]. Other reasons for the good prognosis are the slow growth of carcinoid tumors and symptoms such as acute or chronic abdominal pain, which result in appendectomy and early removal of the whole organ. Moreover, carcinoids of the appendix usually do not metastasize when the tumor size is smaller than 1 cm.

In most cases, appendectomy is the treatment of choice. So far, the tumor diameter of the carcinoid is the most important parameter for predicting metastatic potential; and as a consequence, right hemicolectomy is suggested only for tumors larger than 2 cm. The need for ileocecal resection or even right hemicolectomy is controversial for tumors with a diameter of 1 to 2 cm because the frequency of metastases in these cases is unknown. Thirlby et al. reported 46 metastasizing carcinoids of the appendix [15]. Only five of these tumors had a diameter of 1 to 2 cm. All other tumors exceeded 2 cm. There is one case report of a metastasizing appendiceal carcinoid with a tumor diameter of 6 mm [16]. Ileocecal resection or right hemicolectomy is also suggested when the tumor is located at the base of the appendix or in intermediate-type tumors with the presence of mucus-producing cells. Questionable factors favoring extended surgery are vascular, lymphatic, or mesoappendiceal infiltration [10, 12]. Vascular infiltration was suspected in 40% of another published series by light microscopy but was zero after performing immunocytochemistry with CD31 [17]. In one case of our series, the carcinoid was located at the base of the appendix, and we therefore performed ileocecal resection 2 weeks after appendectomy. In the other case, in which the carcinoid tumor was located near the base and had a diameter of 17 mm, we did not perform ileocecal resection because the tumor was located 5 mm away from the resection margin (Table 1).

When young patients and their parents are confronted with the diagnosis of a possibly malignant tumor that has been resected, it is not yet clear whether these patients should be followed up. We suggest risk-adapted follow-up, but which patients are at risk? Six of our patients had microscopic tumors of 3 mm. It is difficult to imagine that such a tumor would have an impact on a patient's life expectancy. Recently, however, information has come to light associating carcinoids with synchronous and metachronous noncarcinoid malignant neoplasms [18]. In the Surveillance Epidemiology and End Results (SEER) registry [18], appendiceal carcinoids were associated with noncarcinoid malignant tumors in 14.6% of patients. These associated tumors commonly were carcinomas of the gastrointestinal tract. In a recent study presenting eight carcinoid tumors in children, two patients had associated adenocarcinomas of the colon [9]. Whether this justifies long-term follow-up with stressful and expensive investigations is not yet clear. In our study, none of the patients had a synchronous or



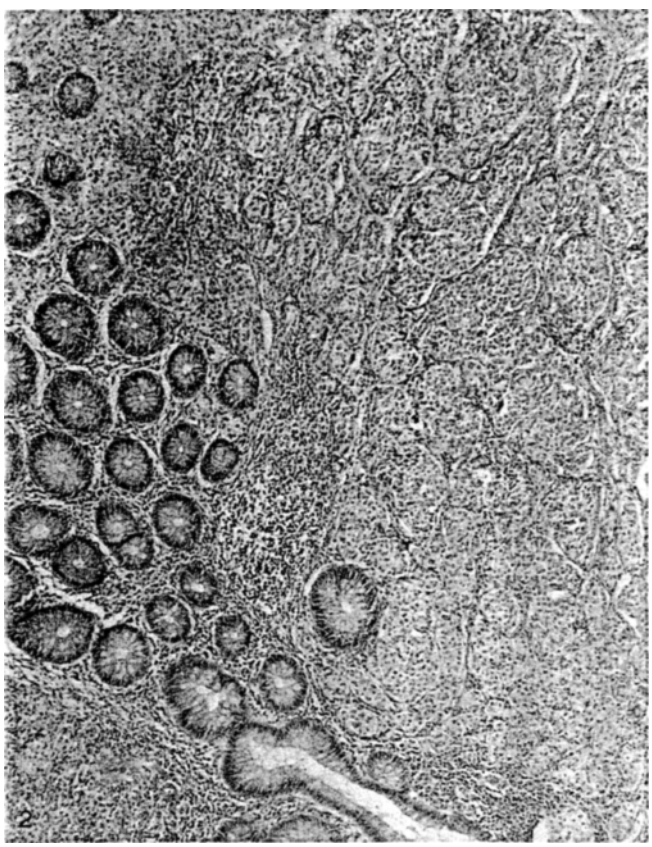


Fig. 1. Cross section through the appendiceal wall. There is a typical slightly yellowish surface at the place marked by the arrow.

Fig. 2. Histology of typical classic carcinoid of the appendix with monomorphous cell clusters infiltrating the appendiceal wall.

metachronous noncarcinoid malignant tumor diagnosed. In the series of Moertel et al., who presented 23 appendiceal carcinoids of the appendix during the first two decades of life, one patient died 33 years after appendectomy for a metastasizing adenocarcinoma of the colon [5].

One should encourage the pathologist to look carefully for the presence of mucin-producing cells. However, though intermediate-type tumors have a worse prognosis, we recommend ileocecal resection for these tumors only when the diameter exceeds 1 cm. For microscopic tumors not exceeding 5 mm, comparison with incidentalomas or early cancer is reasonable while stressing to the patients and their parents that diagnosis of a potential malignant disease seems questionable. Yearly follow-up with determination of serotonin metabolites and abdominal ultrasonography should be done in patients whose tumor diameter was more than 5 mm.

Résumé. Les tumeurs carcinoïdes de l'appendice sont rares chez l'enfant et sont diagnostiqués habituellement de façon fortuite sur la pièce d'appendicectomie réalisée pour syndrome appendiculaire. Afin d'évaluer la signification du diagnostic de tumeur carcinoïde chez l'enfant, nous avons réalisé une étude rétrospective du traitement et du suivi chez 36 enfants porteurs d'une tumeur carcinoïde de l'appendice. Entre 1970 et 2000, on a fait le diagnostic de tumeur carcinoïde de l'appendice chez 36 patients, 25 filles et 11 garçons, dont l'âge médian au moment du diagnostic a été de 12.3 ans (extrêmes: 6–16 ans). L'indication de l'appendicectomie a été une douleur aiguë de la fosse iliaque droite dans 27 cas et une douleur chronique de la fosse iliaque droite chez 9 patients. En ce qui concerne la localisation de la tumeur, sur 27 pièces, la tumeur a été localisée à la pointe dans 18 cas, dans la portion moyenne pour sept cas, et chez deux, à la base. La médiane du diamètre a été de 6 mm (extrêmes: 3–17 mm). Chez 14 patients on a diagnostiqué une appendicite sévère concomitante, deux fois avec perforation. On a détecté des cellules riches en mucine dans une seule tumeur. Après un suivi d'une médiane de 10 ans (extrêmes: 2 mois–30 ans,) tous les patients étaient sans tumeur. Aucun des patients n'a eu de tumeur maligne non carcinoïde synchrone ou métachrone. Les tumeurs carcinoïdes de l'appendice sont habituellement asymptomatiques et l'indication d'intervention chirurgicale est la douleur aiguë ou chronique de la fosse iliaque droite. Pour la plupart des patients, le pronostic est excellent après appendicectomie. Comme chez l'adulte, l'appendicectomie est le traitement approprié.

Resumen. En el niño los tumores carcinoides de apéndice son muy raros y se diagnostican al efectuar el estudio histopatológico del apéndice extirpada por apendicitis. Para averiguar la transcendencia clínica del carcinoide apendicular infantil, se realiza un estudio retrospectivo del tratamiento y evolución clínica de 36 niños con diagnóstico de carcinoide apendicular confirmado histopatológicamente. Entre 1970 y 2000, 36: 25 niñas y 11 niños, fueron diagnosticados de carcinoma apendicular. La edad media de los pacientes fue 12.3 años (rango 6–16 años). La indicación de apendicectomia vino dada, en 27 casos por dolor agudo en el cuadrante inferior derecho y en 9 por molestias crónicas. En 27 especímenes el tumor estaba situado en el apex, en 7 en la porción media y en 2 en la base apendicular. El diámetro medio del tumor fue de 6 mm (rango 3–17 mm). En 14 casos el carcinoide coincidía con una apendicitis aguda y en 2 con apendicitis perforada. En sólo un tumor se detectaron células productoras de mucina. Tras un seguimiento medio de 10 años (rango 2 meses–30 años) todos los pacientes estaban sanos. Ninguno desarrolló tumores malignos no carcinoides ni sincrónicos ni metacrónicos. Los carcinoides apendiculares son, por lo general, asintomáticos y la indicación quirúrgica se establece por dolor agudo o crónico en el cuadrante inferior derecho. Para la mayoría de los pacientes el pronóstico, tras apendicectomía, es excelente. Al igual que en los adultos, la apendicectomía constituye el tratamiento de elección.

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