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 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].

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 co-existing 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
The prognosis for appendiceal carcinoids is good because mostly was suspected when a yellowish, firm tumor is found (Figs. 1, 2). Intraoperatively, carcinoid of the appendix should 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. 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 ileocolic resection 2 weeks after the operation. The need for ileocolic 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.

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 ileocolic 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).

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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