Case Report

Colorectal Cancer on the Rise in Children and Young Adults: A Series of Three Cases and Its Implications for Early Detection

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Introduction. Mucinous colorectal adenocarcinoma, a rare type of colorectal cancer (CRC), ranks as the second most common primary malignancy of the gastrointestinal system in children, accounting for 1% of pediatric neoplasms. Its extreme rarity and non-specific symptoms frequently result in delayed diagnosis and poor prognosis. We present three cases of this distinctive condition in adolescents. Case presentations. We present three adolescents with mucinous adenocarcinoma. The first patient complains of hematochezia, fluctuating abdominal pain, fatigue, and weight loss. The second patient complains of melena, left lower abdominal pain, weight loss, and an anal mass. The third patient complains of constipation, urinary retention, and weight loss. A digital rectal examination revealed a mass in the anorectal region, and the abdominal CT scan confirmed a malignant mass in that region. Discussion. The mucinous histopathological type is the most prevalent, demonstrating an increased capacity to invade surrounding stromal tissue. It is primarily found in the proximal colon and is the most common form of pediatric colorectal cancer (CRC). Most cases involve a less frequent type of CRC, which typically presents with non-specific signs and symptoms that often persist for three months before diagnosis. This biological behavior is reported to be associated with its aggressive nature. Furthermore, the delayed diagnosis of colorectal carcinoma in children contributes to the advanced stage of the disease at the time of diagnosis. Some reports estimate that 60% to 80% of children and adolescents present with stage 3 and 4 CRC, leading to a poor prognosis. Conclusion. Mucinous colorectal adenocarcinoma occurs in both children and adolescents despite its rarity. It is the most common histological type of colorectal cancer in the pediatric population and is known to have a poor prognosis. Since symptoms are nonspecific in children, it can lead to a delay in

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diagnosis, and poor prognosis is linked with this delay. This underscores the urgent need for more pediatric prospective studies to guide treatment guidelines, which are currently extrapolated from adults.

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Introduction

Colorectal malignancies are rare malignancies in the pediatric population. Among 1 million people globally, 1-2 children or adolescents are diagnosed with colorectal cancer; however, the incidence has seen a rise.[1] Over 70% of colorectal cancers are sporadic.[2] After primary liver tumors, colorectal cancer is the second most common primary gastrointestinal system malignancy in children, comprising 1% of all pediatric neoplasms.[3] Low awareness of the disease plays a part in delayed diagnosis, causing a poor prognosis compared with adult cases. Non-specific presenting symptoms and symptoms mimicking many benign gastrointestinal conditions in children also cause delayed diagnosis in this population.[4] The youngest age at diagnosis for colorectal cancer is nine months old. However, the most common age range at diagnosis is within the second decade, averaging 15-19 years old.[5]

Mucinous adenocarcinoma is a histological subtype of colorectal cancer (CRC). It is defined as a tumor with >50% of its body showing a mucinous pattern upon histological examination, with a large amount of extracellular mucin produced by secreting acini.[6] It differs in clinical and histopathological features compared with other adenocarcinomas.[6] Mucinous CRC is more commonly located in the proximal colon and is the most frequent form of pediatric CRC. Most patients present with non-specific signs and symptoms.[7][8][9]

Symptoms of colorectal cancer in pediatric patients are not different from those seen in adults. In most cases, chronic abdominal pain, hematochezia or melena, weight loss, persistent iron deficiency, and anemia can be related to colorectal cancer. Typical symptoms of colorectal cancer include vomiting, severe abdominal pain, and bloody stools; however, in children, the symptoms might be restricted to only altered bowel habits. The location of the cancer can be a significant factor in the manifestation of specific symptoms.[3]

Due to its extreme rarity and non-specific symptoms, mucinous colorectal adenocarcinoma in adolescents tends to be diagnosed late and presents with a poor prognosis. This report describes three

pediatric cases diagnosed with mucinous colorectal adenocarcinoma, each with a different disease progression. With this case review, we highlight the significant impact of delayed diagnosis on patient outcomes, underscoring the need for early recognition and detection.

All patients in this series gave informed consent, and this report was written according to the Declaration of Helsinki.

Case Presentation

Case 1

A 16-year-old male presented with hematochezia for the past two months, accompanied by intermittent intense abdominal pain and a weight loss of 5 kg. The patient also reported weakness and extreme fatigue. During the physical examination, abdominal tenderness was noted, bowel sounds were normal, and no abdominal distension was observed. A digital rectal examination revealed a mass palpated 6 cm from the anterior cutaneous line, with no blood or feces present on the gloves. Vital signs were within normal limits. An abdominal CT scan confirmed the presence of a malignant mass in the high rectosigmoid wall, approximately 7 cm long, located 10 cm from the anocutaneous line. Minimal fat stranding was observed without any obstruction on the proximal side. Multiple lymphadenopathies were found along the perirectal mesocolon, right para-obturator, bilateral internal para-iliac, and right external para-iliac regions. The CT scan also showed a fatty liver and hepatomegaly, with multiple liver nodules suggesting metastasis. Following these findings, we performed a sigmoid colostomy and mass biopsy. Histological results confirmed mucinous adenocarcinoma. The patient was diagnosed with stage four mucinous rectal adenocarcinoma (cT3NxM1). A low anterior resection was performed four weeks after the colostomy and biopsy. The patient remained stable after surgery. Although adjuvant chemotherapy was administered as scheduled, lung metastatic lesions developed, and the patient's condition worsened, leading to respiratory distress.

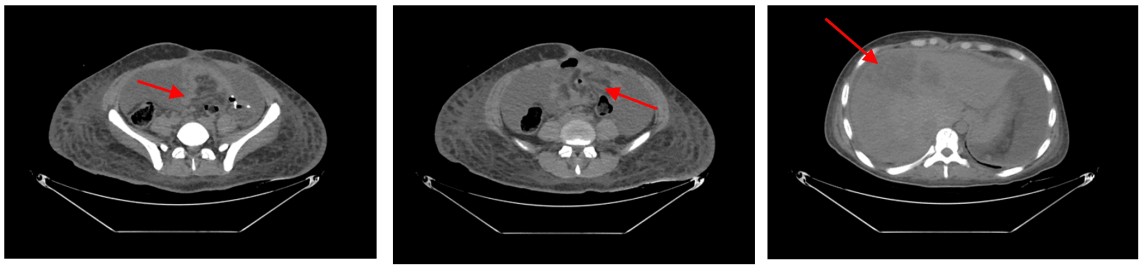

Figure 1. Abdominal non-contrast CT showing mass and hepatic nodule suggesting metastasis

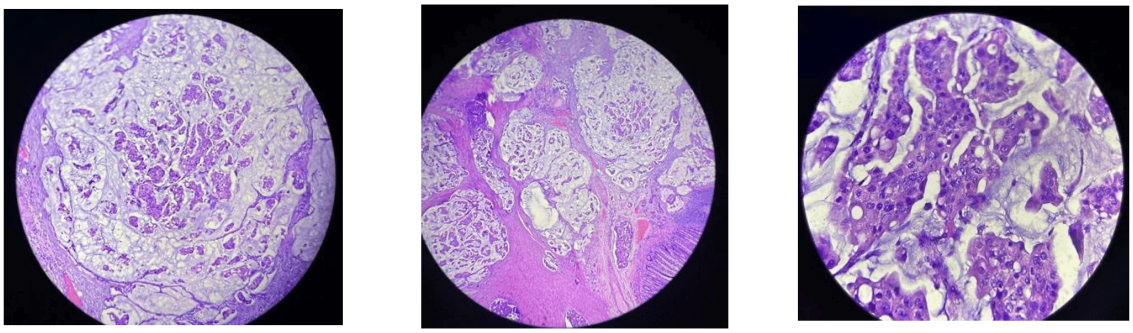

Figure 2. A (HE 40x), B (HE 100x), C (HE 400x): The mucinous adenocarcinoma tumor mass is arranged in glandular, cribriform, and infiltrative patterns interspersed with pools of mucin.

Case 2

A 16-year-old female presented with loose stools and blood lasting for the past 3 months. The patient also reports a mass in the anal region that tends to bleed. Additionally, she has experienced left lower quadrant abdominal pain and has lost approximately 12 kilograms over the last 5 months. Each time she passes gas, there are slimy secretions and fecal matter. Physical examinations showed typical vital signs. Colonoscopic findings revealed multiple nodular masses. Biopsy and sigmoid colostomy were performed to divert fecal matter. Abdominal CT indicated a malignant mass on the rectal wall that narrowed the lumen of the rectum (Fig. 3). Histological results confirmed mucinous carcinoma. The patient was diagnosed with stage three mucinous rectal adenocarcinoma (cT4NxM0). Following the colostomy surgery, she was scheduled for neoadjuvant radiotherapy before definitive treatment. While under

observation during radiotherapy, the tumor progressed to progressive disease, with infiltration into the vagina observed. It was then decided to proceed with R1 resection surgery.

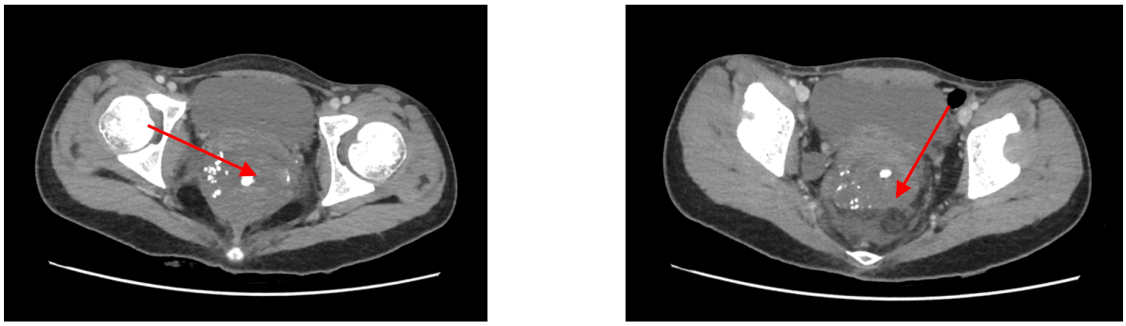

Figure 3. Abdominal contrast CT shows the mass. (A) Mass in the rectum with contrast enhancement. (B) Arrow pointing at the narrowed rectal lumen

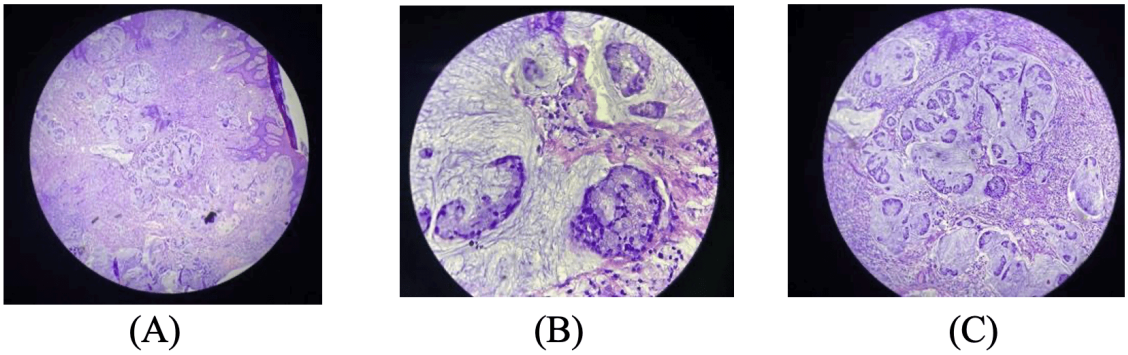

Figure 4. Histological finding: A (HE 40x), B (HE 100x), C (HE 400x): Mucinous adenocarcinoma is arranged in glandular, cribriform, and infiltrative patterns, interspersed with mucin pools

Case 3

A 17-year-old female presented with one month of urinary retention and chronic constipation lasting four months. The patient reports significant weight loss during this four-month period. Additionally, there was a loss of appetite accompanied by nausea and vomiting. The patient also complains of hematuria and pain during urination. There is a family history of thyroid cancer on the patient's father's side. An MRI examination revealed a contrast-enhancing mass in the sigmoid colon with papillary wall

thickening (the image has since been lost). A sigmoidectomy showed a 13x12x7.5 cm mass (Figure 5) with adhesions to the level of the pelvis. No metastases were found in the lungs, liver, lymph nodes, or intra-abdominal area. Histological results indicated mucinous adenocarcinoma with epithelial proliferation and mitosis (Figure 2). Following the surgery, a 12-cycle chemotherapy regimen was initiated. The patient is currently on the 11th cycle with 3,170 mg of 5-FU as adjuvant therapy, 170 mg of oxaliplatin, and 520 mg of leucovorin. The patient gained 19 kg, increasing from 29 to 48 kilograms after chemotherapy, and is clinically stable without significant complaints.

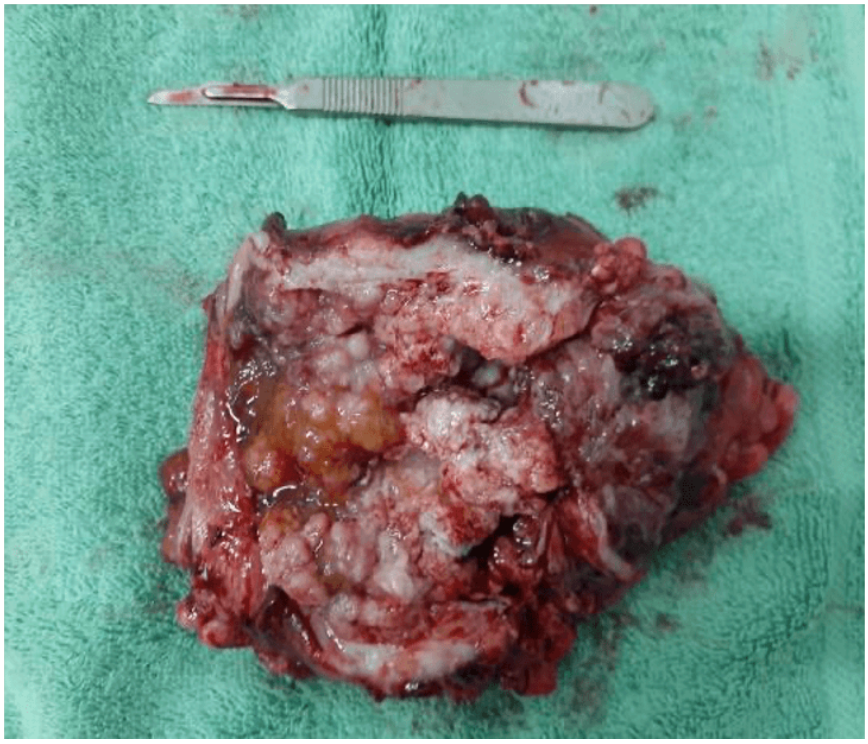

Figure 5. Gross pathology of the tumor

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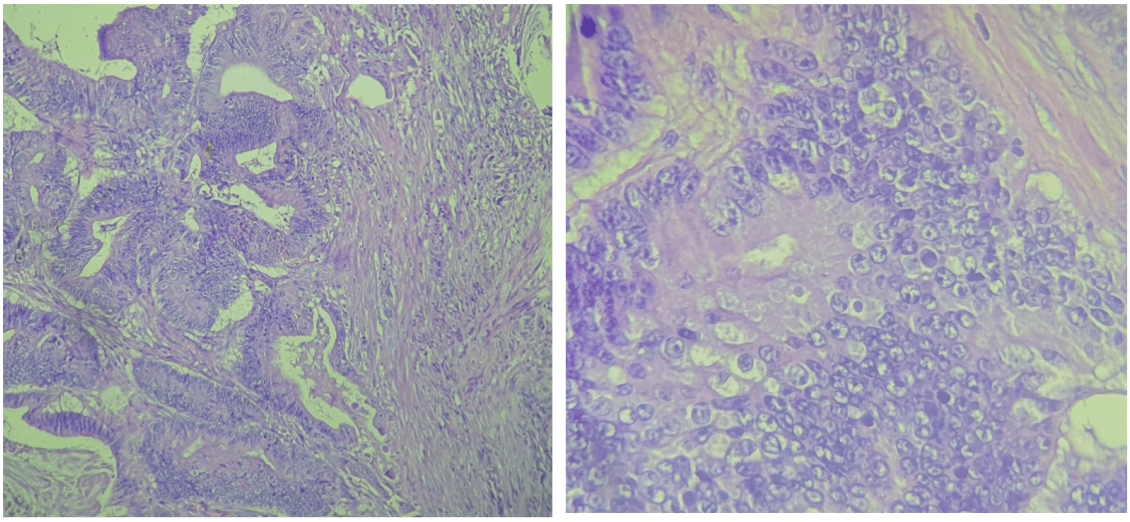

Figure 6. Histologic slide showing features of mucinous adenocarcinoma. Glands were arranged in a dense back-to-back pattern, and epithelial proliferation and mitosis were shown.

Discussion

Despite its rarity, it is evident that adenocarcinoma occurs in children and adolescents. A study on adenocarcinoma in the South Korean pediatric population showed that almost half of all patients had a 2-month or more delay from initial symptom onset to diagnosis. Regardless of family history, the diagnosis of pediatric adenocarcinoma was relatively delayed, with a tendency for diagnosis at an advanced stage.[7] The majority of patients were also diagnosed with distant metastasis. This is also demonstrated in the case that we present here. For all of the patients, colorectal carcinoma was not an initial diagnosis.

Colorectal carcinoma is a tumor of older adults; its frequency peaks at age 65 years. In the general population, it has a 5-6% incidence.[5] Because it is rare in children and adolescents, it is frequently overlooked in the differential diagnosis of abdominal pain, weight loss, and anemia.[10] Data from Surveillance, Epidemiology, and End Results (SEER) suggest that colorectal cancer has a similar natural history in 15 to 29-year-old patients to that in older patients.[11] Moreover, the majority of reported cases are older adolescents, while prepubertal cases are very unusual.[12] Despite being mostly sporadic, genetic diseases are predisposing pathologies that increase the risk of colorectal carcinoma[1], as shown in Case 3.

Decreased appetite, weight loss, changes in bowel habits, and rectal bleeding with changes in stool consistency may be observed in children with colorectal cancer.[13] In our cases, all patients exhibited these symptoms. Children and adolescents also often present with acute abdominal conditions, such as obstruction, perforation, or severe pain mimicking appendicitis.[14] Sometimes, the symptoms might be restricted to only altered bowel habits.[15] The presentation of colorectal cancer is related to its primary site within the large bowel. Tumors of the cecum and descending colon may become cumbersome before symptoms appear.[13] Tumors of the rectum and sigmoid colon may be associated with stool caliber changes, dyschezia, hematochezia, and anemia.[16] Additionally, right-sided cancer can manifest as a mass, anemia, diarrhea, or intussusception. Meanwhile, left-sided cancer can manifest as obstruction, bleeding, or altered bowel habits.[8] Regarding the anatomical distribution of colorectal cancer, studies have shown that in adults, colorectal cancer occurs more commonly on the left side. In contrast, in children, the site of involvement varies and is equally distributed in all parts of the colon.[17] The nonspecific signs and symptoms often contribute to delayed diagnosis. Some reports estimate that 60-80% of children and adolescents are diagnosed in stages 3 and 4.[18] In the pediatric population, colorectal cancer occurs relatively more in males than in female children, with a ratio of 2:1.[19]

Once the diagnosis is suspected, further investigation usually includes abdominal X-rays, barium enema, colonoscopy, and eventually an abdominal CT scan, which will either show obstruction, narrowing of the colonic lumen, or an abdominal mass.[13] Depending on the situation, a colonoscopy with a polyp excision or an initial biopsy with delayed excision of the mass would be the next step.[16] A biopsy is required for the diagnosis of colorectal cancer; a biopsy may be obtained during colonoscopy or laparotomy.[20] In our center, we perform a biopsy followed by resection.

Most colorectal cancers in adults are moderately differentiated or well differentiated.[7] In contrast, more than half of reported childhood colorectal cancer cases are poorly differentiated adenocarcinoma, many of which are of the signet ring cell type.[13] Mucinous histology was considerably more frequent in the pediatric population than in adults. This likely reflects a difference in biology between pediatric and adult colorectal cancer.[10]

Mucinous colorectal cancer in the pediatric age group is a rare and unexpected diagnosis. This subtype of adenocarcinoma is characterized by copious mucinous components that amount to at least 50% of the tumor volume and a large amount of extracellular mucin produced by secreting acini.[21] This is distinct from signet-ring adenocarcinoma, an unusual variant in which mucin remains inside the cell. It is well

known for its aggressiveness,[22] differing in clinical and histopathological features from other adenocarcinomas.[6] Signet-ring adenocarcinoma is more commonly located in the proximal colon and is the most frequent form of pediatric colorectal cancer. The majority have a sporadic form of the disease.[15][23] These tumors also behave more aggressively. They have a poorer response to chemotherapy but are also associated with extensive intramural spread and peritoneal carcinomatosis.[10] The significance of the histological pattern of mucinous carcinoma of the colon and rectum has been controversial since it was first described by Parham.[24] Using mucinous histology as a separate prognostic indicator has been controversial.[6]

There are cases of colorectal cancer linked to hereditary causes, specifically Lynch Syndrome, also known as hereditary nonpolyposis colorectal cancer. It is an autosomal dominant condition caused by mutations in DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6, PMS2, or EPCAM.[25] Studies have reported cases of children with Lynch Syndrome associated with early-onset colorectal cancer. A definitive diagnosis can be made through genetic testing for both the patient and the parent.[26]

Knowledge of pediatric adenocarcinoma treatment still needs to be improved. Hence, treatment principles follow those in adult adenocarcinoma, according to other studies.[7][10] Following adult principles of treatment, the mainstay of therapy is complete surgical resection.[27] The principle for the surgical approach involves complete resection of the primary tumor (with a minimum 5cm free margin), its lymphatic bed, and any other involved organs. This may include the dissection of retroperitoneal lymph nodes, which is done in patients with resectable tumors, and it has been found to have a meaningful impact on the overall survival of the patients. Without complete surgical resection, a cure is not possible.[14][28] Left-sided tumors require subtotal colectomy, and right-sided tumors require extended hemicolectomy. However, the extent of the colectomy will depend on the tumor location, nature of the primary pathology, and intent of the resection.[29] Statistics show a higher incidence of unresectable, residual disease, and metastasis rate in pediatric colorectal cancer.[3]

According to TNM staging, adjuvant chemotherapy and radiotherapy are required, but the treatment regimens are controversial.[15] For cases with advanced tumor stages at presentation (stage III and IV), surgery becomes challenging and sometimes not possible. A study by Hill et al. reported chemotherapy and radiotherapy as initial treatment.[10] Other studies reported the use of platinum-based agents and 5-fluorouracil, which were used as the first-line chemotherapy in colorectal cancer. Some cases also add bevacizumab.[7] These adjuvant multiagent chemotherapy regimens based on a fluorouracil backbone

with folinic acid, oxaliplatin, or irinotecan, and possibly cetuximab or bevacizumab as mentioned earlier, are typically used in advanced-stage disease, as well as in high-risk localized disease. There is little role other than palliation, except in rectal carcinoma. Since pediatric prospective clinical trials are still lacking, treatment guidelines must be extrapolated from adult trials.[14]

The Tumor Node Metastases (TNM) staging system of the American Joint Committee on Cancer (AJCC) for International Cancer Control is the choice for a colorectal cancer staging system.[30] Dukes-MAC staging systems are used together to predict the prognosis. In both these staging systems, stages A and B are curable. However, as in both cases presented in this report, most pediatric patients are diagnosed with advanced-stage carcinoma with a poor prognosis. Another reason for poor prognosis in pediatric patients is histological grading. In adults, mucinous adenocarcinoma accounts for less than 5% of the cases. However, in children, more than 50% of patients are diagnosed with mucinous adenocarcinoma, and so are our cases, which carry a poor prognosis.[12]

The prognosis of the disease is influenced by factors such as aggressive histological subtypes (i.e., signet ring and mucinous adenocarcinoma), advanced tumor grade, and advanced stage of the disease.[28] [29] Long-term survival rates in pediatric colorectal cancer were 20-50% in several studies.[12][18] Another study by Sultan et al.,[31], reported pediatric colorectal patients through the Surveillance, Epidemiology, and End Results database from 1973 to 2005. The database confirmed the poor prognosis of pediatric colorectal cancer (i.e., mucinous adenocarcinoma and signet ring cell carcinoma). The 5-year survival estimate in that study was approximately 40%. This low survival rate is associated with the pathologic feature of poor differentiation.[7][31] The only predictors of inferior outcome besides stage were incomplete resection, mucinous histology, the proportion of signet ring cells more than 10%, and the absence of an in situ component.[10]

Conclusion

Mucinous colorectal adenocarcinoma occurs in both children and adolescents despite its rarity. It is the most common histological type of colorectal cancer in the pediatric population and is known to have a poor prognosis. Poor prognosis is linked with diagnosis delay, as symptoms may be nonspecific for children. Lynch syndrome is also known to be associated with colorectal cancer in adolescents; however, a definitive diagnosis requires genetic testing. Treatment guidelines are still extrapolated from adults, as pediatric prospective studies are still lacking.

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Declarations

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