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Case report

# Does radiotherapy prior to surgery improve long term prognosis in pediatric colorectal cancer in lower- and upper-middle income countries with limited resources? Our experience and literature review

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ABSTRACT

Colorectal carcinoma in children and adolescents is extremely rare, with an annual incidence <0.3 cases per million, most frequently reported in the second decade of life. It accounts for severe morbidity and poor prognosis owing to the low index of suspicion, delayed diagnosis, advanced stage at presentation and the aggressive tumor nature. Patients present with abdominal pain, vomiting, constipation, abdominal distension, rectal tenesmus, iron-deficiency anemia, change in bowel habit and weight loss. Rectal bleeding is an uncommon presentation in children. Bowel obstruction presents frequently in children compared to adults. In 90% of pediatric cases, colorectal carcinoma occurs sporadically. In 10%, predisposing conditions and syndromes are identified. We present a case study of a 12-year-old female with advanced colorectal cancer without a predisposing disease or syndrome, who received radio-chemotherapy ten weeks prior to radical abdominopelvic surgery, followed by radio-chemotherapy post-operatively, with a positive outcome.



## Case presentation

A twelve-year-old female presented with a two-year history of intermittent rectal bleeding and a four-month history of vague abdominal pain, vomiting, abdominal distension, rectal tenesmus and fourteen-kilogram weight loss. She experienced increased frequency of non-mucoid and non-bloody stools two weeks prior to admission. No predisposing medical or family history was recorded.

On examination, there were signs of iron-deficiency anemia, abdominal tenderness and a palpable pelvic mass. On digital rectal examination, the mass was palpable at 9 cm from the anal verge. Carcinoma-embryonic androgen (CEA) was 11.3 ug/L (0.0–2.6 ug/L) and Cancer Antigen 19-9 (CA19-9) was 318 kU/mL (0–35 kU/mL).

A pelvic magnetic resonance (MR) scan performed at a referring facility demonstrated a locally invasive rectosigmoid mass with mesorectal lymphadenopathy. Computer tomography scan revealed a lesion located in the rectosigmoid colon at 10 cm above the anal verge, that had concentric irregular colonic mural thickening. There was infiltration of the uterus anteriorly, infiltration of the ovaries and adnexa laterally, mesenteric fat infiltration posteriorly and local pelvic lymphatic spread. No distal hepatic or lung metastasis were present. [Fig. 1a and b]

Colonoscopy confirmed the absence of polyps, synchronous or metachronous lesions within the colon. The tumor was graded as stage C (T4bN2M0) irresectable colorectal carcinoma with invasion of uterus and ovaries.

A diverting palliative colostomy was performed. The patient received neo-adjuvant palliative chemotherapy/radiotherapy 5-fluorouracil (5-FU): 400 mg/m$^2$/d for 4 days with Leucovorin 20 mg/m$^2$/d repeated after 21 days commenced with concurrent radiation therapy of 45 Gy in 25 fractions to the primary.

Ten weeks after completion of chemo-radiotherapy, the patient complicated with acute bowel obstruction, seen on conventional abdominal radiography, and mild bilateral hydronephrosis seen

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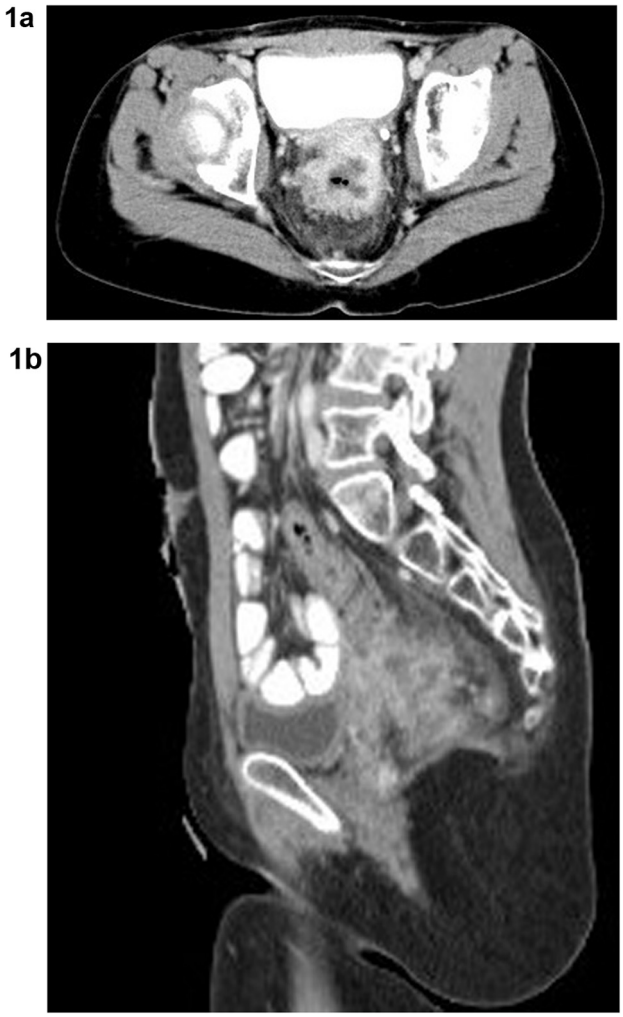


**Fig. 1.** Axial (1a) and sagittal (1b) Contrast Enhanced CT (CECT) in a 12-year-old female shows a circumferential irregular enhancing mass within the distal colon that represents non-syndromic pediatric colorectal carcinoma. Note the irregular margins of the tumor infiltrating the uterus anteriorly. The tumor has complicated with subsequent colonic obstruction necessitating radical resection post neoadjuvant radio-chemotherapy.

on abdominal ultrasound. No hepatic metastasis were detected. Emergency radical abdominoperineal resection of the tumor, total abdominal hysterectomy of the infiltrated uterus, bilateral ovaries and proximal vagina with clear surgical resection margin was achieved.

Histopathologically the tumor consisted of irregularly shaped glands infiltrating the submucosa, muscularis propria and serosal fat. The neoplastic glands contained abundant mucin in more than 50% of the tumor. The glands were lined by cells exhibiting nuclear pleomorphism and prominent nucleoli. Mitoses were focally observed. There was minimal tumor inflammatory stromal response present. The mesorectal lymph nodes were involved. The tumor was classified as a stage T4N1M1b according to the TNM anatomical pathology classification system. [Fig. 2a and b]. The tumor was microsatellite stable with preserved MLH1, MSH2, MSH6, APC and PSM2 genes [Fig. 2c electrogram]. The immunohistochemical analysis excluded non-polyposis colorectal cancer (HNPCC).

Post-operative fluoroscopy showed that the operation was complicated by a posterior rectal fistula. (Fig. 3).

The patient is presently 15 years old, doing well, with no recurrence and requests closure of the diverting colostomy for social reasons.

## Discussion

We present a case of sporadic colorectal cancer in a 12-year-old female, free of recurrence three years after presentation. Immunohistochemistry did not detect instability of MLH1, MSH2, and PMS2 genes. We emphasize that even in the absence of predisposing factors; a high index of suspicion for a malignant colorectal tumor should be borne for any child with signs and symptoms of intestinal obstruction, intractable abdominal pain, alteration in bowel habits and gastrointestinal bleeding.

Colorectal adenocarcinoma represents about 98% of colonic cancers. The World Health Organization (WHO) recognizes six subtypes of colorectal adenocarcinoma which includes, cribriform-comedo, medullary, micropapillary, mucinous, serrated and signet ring cell carcinoma. Poorly differentiated mucinous adenocarcinoma, in adolescents, although very rare, is the most common histological subtype of colorectal carcinoma with its aggressive tumor characteristics [1,2,4,6,9]. Patients with mucinous carcinoma have a poorer 5-year survival rate than non-mucinous tumors [9].

Our clinical examination included digital rectal examination with early cross-sectional pelvic imaging [5]. Carcinoembryonic antigen (CEA) assay was elevated, despite this not being an effective marker for monitoring mucinous colorectal carcinoma in children and adolescents [12]. In pediatric patients, tumors can be located anywhere in the colon and rectum [4,6,7,9,10]. This patient's tumor was located in the distal rectosigmoid colon as seen in adults [9]. Colorectal carcinomas in children often extend beyond the bowel wall and are metastatic when diagnosed [9].

Current practice recommends that staging guidelines for adults be applied to children with colorectal carcinoma [2]. The most frequent pathological presentation is modified Duke Stage C (disease limited to lymph nodes) and D (disseminated disease) [3,5–8,10,13]. Our patient was stage C, and would be deemed irresectable if the adult staging system is applied.

Imaging plays a significant role in the detection, diagnosis, staging and follow-up of colorectal carcinoma. Single contrast enema under fluoroscopic guidance shows the level of mechanical obstruction and area of luminal narrowing [2]. Air-contrast barium enema or CT colonoscopy shows mucosal destruction, the presence of asymmetrical irregular short segment luminal narrowing and overhanging borders and characteristics of any sessile or pedunculated polyps [14]. Fluoroscopy and CT virtual colonoscopy yield comparable results to colonoscopy for colorectal carcinoma detection by experienced observers [14].

Radiological staging relies on Multidetector Computer Tomography (MDCT) with or without Magnetic Resonance Imaging (MRI). Features of colorectal carcinoma include presence of polyps; asymmetrical mural thickening and irregularity of the mural surface; peri-colonic fat infiltration; loss of tissue fat planes between the colon and surrounding muscles; spread to adjacent organs; metastasis to the mesenteric nodes, peritoneum, hepatic metastasis via the portal venous system; and lungs metastasis [2,11,14–16]. MRI is more sensitive than MDCT for liver metastasis [14]. Lower gastrointestinal bleed can be identified during the arterial phase of MDCT, but is less sensitive and specific in children than in adults [16]. Multidetector Computer Tomography is unable to differentiate and distinguish different layers of the rectal wall and is therefore unable to differentiate T1 and T2 tumors using the international TNM staging, [15] and is less accurate than endoscopic ultrasound and MRI. Our patient did not have polyps in the colon, nor synchronous or metachronous lesions.

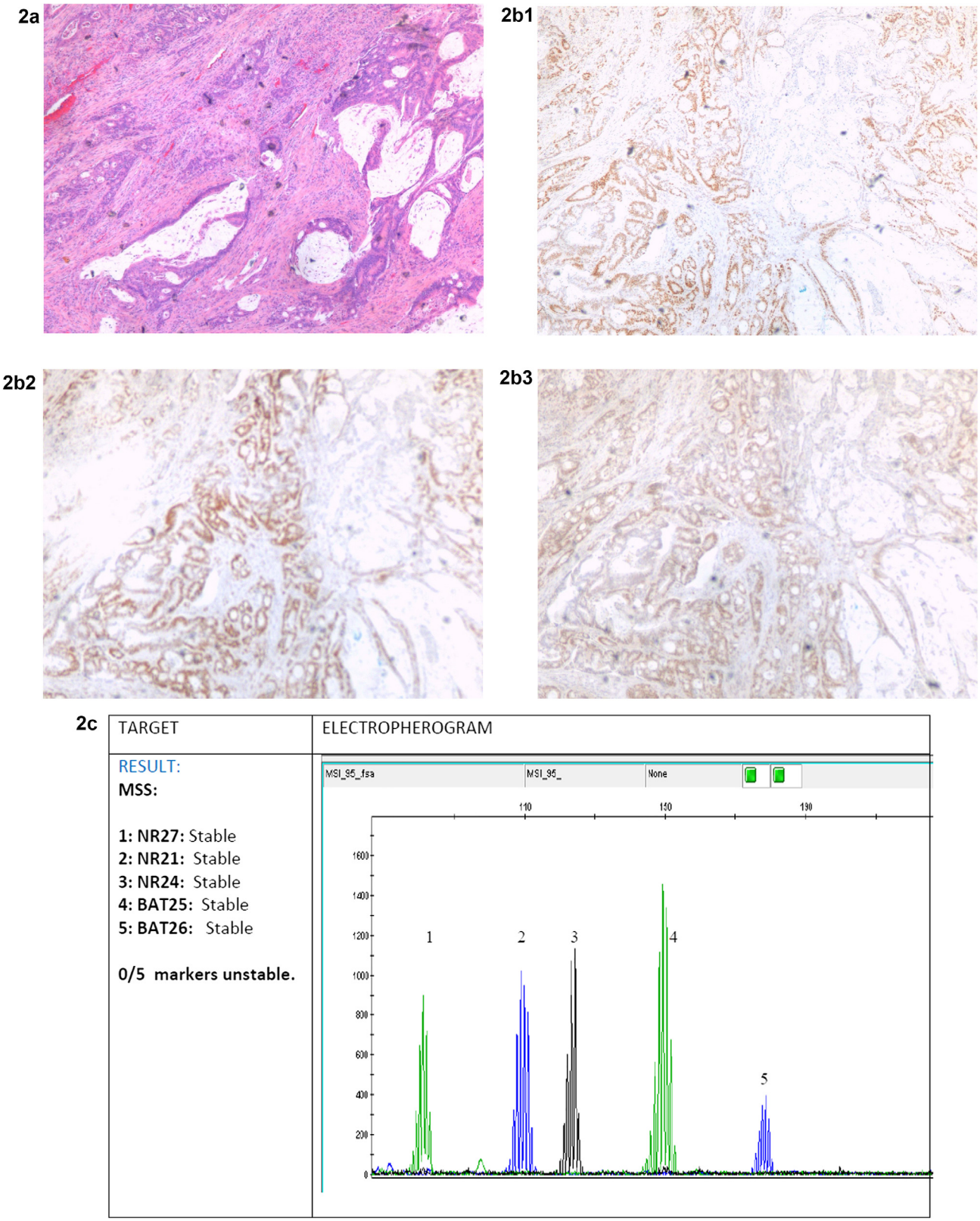


**Fig. 2.** Sporadic mucinous pediatric adenocarcinoma of the resected mucinous adenocarcinoma is demonstrated [2a]. Immunohistochemical preserved MLH1 [2b1]; MLH2 [2b]; and PMS2 genes [2c], read together with the electropherogram polymerase chain reaction (PCR) show stable microsatellite MLH1, MLH2, PMS2 genes, and is important to help exclude an underlying syndromic etiology.

The role of fluorodeoxyglucose positron emission tomography (FDG-PET) scans in the surveillance of colorectal carcinoma in the pediatric population is unclear, as opposed to its role in adults where it is well established. Mucinous colorectal carcinomas, that are predominant in children are non-FDG avid. Non-mucinous carcinomas are seen in adults are FDG-PET avid [2,13,14].

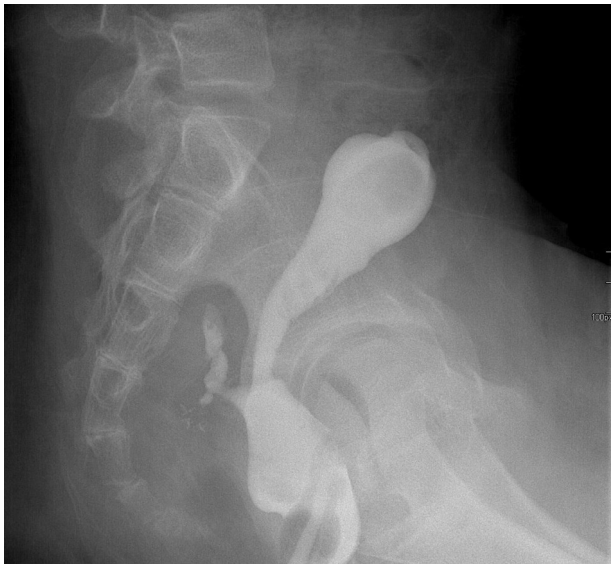

**Fig. 3.** Sagittal fluoroscopic image shows posterior rectal fistula as a complication of radical surgical resection. The fistula is treated conservatively. The patient is recurrence free as confirmed on barium enema and with magnetic resonance imaging [not shown].

Abdominal radiography demonstrates large bowel dilatation, multiple air fluid levels proximal to the lesion, and a paucity of gas in the rectum in children and adolescence indicating bowel obstruction or intussusception [2,8]**.** Chest radiography is used to screen for hilar and lung metastasis; and to exclude free intraperitoneal air [2]. Transabdominal or endoscopic ultrasound is used to detect bowel wall thickening, the level of bowel cut-off, the size and nature of the tumor mass, the presence of local infiltration into the pelvic organs, presence of uncontained fluid in the pelvis and peritoneum, metastasis to the lymph nodes, mesentery, peritoneum and liver. Color Doppler ultrasound shows an increase in doppler signal consistent with increased vascularity of the tumor [14].

## Radiochemotherapy

As pediatric colorectal carcinoma is rare, consultation with a medical oncologist experienced with adult colorectal carcinoma is advised. Latest adult treatment guidelines can be adapted for the individual pediatric patient [7]. The paucity of treatment guidelines and rarity of this condition makes large scale clinical trials less likely [2]. The literature suggests that 5-fluorouracil and leucovorin is the standard treatment [7]. Our patient received 5-fluorouracil (5-FU): 400 mg/m$^2$/d for 4 days with Leucovorin 20 mg/m$^2$/d repeated after 21 days commenced with concurrent radiation therapy of 45 Gy in 25 fractions to the primary prior to radical surgery.

## Surgical management

Radical surgical resection of the affected bowel, its lymphatics, infiltrated organs and areas of distal metastasis is the basis for standard management in the literature. Surgical exploration should include the peritoneum and omentum for intraperitoneal deposits and should be conducted in a center experienced with this type of surgery [2,7]. This cancer may infiltrate the omentum and ovaries [7]. In our patient, radical surgical resection was undertaken ten weeks after neo-adjuvant radiochemotherapy, and removed the colorectal tumor, the infiltrated uterus and ovaries; and the draining lymphatics. This was followed by radiochemotherapy after the surgery. The patient is recurrence free three years after the operation.

An overview of the published literature of sporadic colorectal carcinoma in children is presented in Table 1, showing that there are only two reports from the African continent.

**Table 1**
Literature review of sporadic colorectal cancer in children and adolescents.

| Literature | Reports | Year of publication | Country | No. of cases | Age (years) | Sex | Site of tumor | Pathology |
|---|---|---|---|---|---|---|---|---|
| Medicine | Li et al. [17] | 2017 | China | 1 | 13 | M | 1TC | SR - Immature enteric ganglion cells |
| Adv Anat Pathol | Galliani et al. [18] | 2015 | United States of America | 1 | 14 | F | 1TC | Adenocarcinoma |
| Oncol Lett | Yang et al. [19] | 2015 | China | 1 | 9 | M | 1TC | SR |
| Case Rep Oncol Med | Pamukcu et al. [20] | 2013 | Turkey | 1 | 19 | M | 1SC | SR |
| Hematol. Oncol. Stem. Cell Ther | Al-Tonbary et al. [21] | 2013 | Egypt | 3 | 12–13 | 2 M: 1F | 1DC: 1RS: 1RC | 2MA: 1 Moderately differentiated adenocarcinoma |
| Diagn Cytopathol | Agrawal et al. (cited by [21]) | 2011 | India | 1 | 11 | M | 1RS | MA |
| Eur J Pediatr | Malik et al. (cited by [21]) | 2011 | India | 1 | 11 | M | 1RC | Invasive poorly differentiated signet ring carcinoma grade 3 |
| West Afr J Med | Ibrahim et al. [5] | 2011 | Nigeria | 2 | 16–18 | 2 M | Unavailable | Unavailable |
| Case Report Med | Muccillo et al. (cited by [21]) | 2010 | Brazil | 1 | 12 | M | 1AC | MA |
| J Cancer Res Ther | Chattopadhyay et al. (cited by [21]) | 2010 | India | 1 | 10 | F | 1DC | Poorly differentiated MA |
| Afr J Paediatr Surg | Sharma et al. (cited by [21]) | 2009 | India | 2 | 14 | 1 M: 1F | 1RS | MA |
| Pediatr Surg Int | Salas-Valverde et al. [6] | 2009 | Costa Rica | 11 | 7–17 | 7 M: 4F | 3TC: 2AC: 1 Hepatic flexure: 1 Splenic flexure: 1DC: 1SC: 2 Multiple segments | 7MA: 2 Adult form of non-MA: 1 Moderately differentiated adenocarcinoma: 1 Poorly differentiated adenocarcinoma |
| Pathol Int | Jeong et al. (cited by [21]) | 2008 | Korea | 1 | 13 | F | 1RS | Well-differentiated adenocarcinoma |

**Table 1** (*continued*)

| Literature | Reports | Year of publication | Country | No. of cases | Age (years) | Sex | Site of tumor | Pathology |
|---|---|---|---|---|---|---|---|---|
| Pediatr Blood Cancer | Ferrari et al. [3] | 2008 | Italy | 7 | 9–18 | 4 M: 5F | 2AC: 1Splenic flexure: 1DC: 3SC | 4MA: 2 Moderately differentiated adenocarcinoma: 1 Poorly differentiated adenocarcinoma with neuroendocrine differentiation |
| Pediatr Surg Int | Angelini et al. [22] | 2005 | Italy | 1 | 12 | F | 1SC | Adenocarcinoma |
| Eur J Pediatr Surg | Radhakrishnan et al. [23] | 2003 | United Kingdom | 8 | 10–16 | 3 M: 5F | 4AC: 1DC: 3SC | 2MA: 6 Adenocarcinoma |
| J Indian Assoc Pediatr Surg | Chana et al. (cited by [21]) | 2001 | India | 1 | 12 | M | 1RC | Well-differentiated MA |
| J Pediatr Surg | Karnak et al. [10] | 1999 | Turkey | 20 | 7–16 | 12 M: 8F | 1 CC: 2AC: 3TC: 1DC: 5SC: 8RC | 16MA: 4 Adenocarcinoma |
| Pediatr Surg Int | Sebbag et al. [24] | 1997 | Israel | 3 | 16–19 | 1 M: 2F | 2 SC: 1CC | 1MA: 2 Adenocarcinoma |
| J Postgrad Med | Redkar et al. [25] | 1993 | India | 1 | 11 | F | 1RC | CA |
| Yonsei Med J | Hwang et al. [26] | 1993 | Korea | 1 | 12 | M | 1TC | Adenocarcinoma |
| J Pediatr Surg | Brown et al. [27] | 1992 | South Africa | 7 | 10–15 | 4 M: 3F | 3AC: 1DC: 1SC: 2RC | 3 MA: 2 MA/SR: 2 Adenocarcinoma |
| Cancer | Rao et al. [28] | 1985 | United States of America | 30 | 8–25 | 17 M: 13F | 6CC: 4AC: 5TC: 5DC: 6SC: 4RC | 25MA: 5Adenocarcinoma |
| Surgery | Goldthorn et al. [29] | 1983 | United States of America | 7 | 11–20 | 1 M: 6F | 3 MT: 1DC: 1 SC: 2RC | 1MA: 6Adenocarcinoma |
| Am J Surg | Enker et al. [30] | 1977 | United States of America | 1 | 14 | F | 1TC | Adenocarcinoma |

AC = ascending colon, CA = colloid adenocarcinoma, CC = cecum, DC = descending colon, F = female, M = male, MA = mucinous adenocarcinoma, MA/SR = mucus-secreting adenocarcinoma with "signet ring" pattern, MT = multiple, RC = rectum, SC = sigmoid colon, SR = signet ring cell carcinoma, TC = transverse colon.

## Conclusion

Locally advanced stage C sporadic pediatric mucinous colorectal adenocarcinoma without distal metastasis, is in remission three years after being treated with chemoradiotherapy prior to abdominopelvic resection.

Initial treatment with radiotherapy prior to radical surgical resection may improve long term prognosis in pediatric colorectal cancer.

## Author contribution

Yacoob Omar Carrim, primary author, conceived and designed the study. Acquisition of data, Analysis and interpretation of data. Drafting the article. Critical revision for important intellectual content. Final approval of the version to be published

Luvo Gaxa, substantial contributions to conception and design. Analysis and interpretation of data. Revising it critically for important intellectual content. Final approval of the version to be published.

Francisca van der Schyff, analysis and interpretation of data. Final approval of the version to be published.

Nndweleni Meshack Bida, analysis and interpretation of data. Final approval of the version to be published.

Fareed Omar, critical revision for important intellectual content. Final approval of the version to be published.

Zarina Lockhat, Critical revision for important intellectual content. Final approval of the version to be published.

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