

## Colon Adenoma and Carcinoma Among Adult Survivors of Childhood and Young Adult Cancer

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### ABSTRACT

**AIMS:** Early initiation of colorectal cancer (CRC) screening is recommended for survivors of childhood and young adult cancer who were treated with radiotherapy to a field including the colon or rectum. Yet, little is known about colonoscopy findings in this population.

**MATERIALS AND METHODS:** We conducted a retrospective investigation of colonoscopies performed between 2005 and 2015 in our institution among adult survivors of childhood and young adult cancer. Data were collected on cancer-related exposures, procedure indication, and findings. Advanced adenomatous lesions were defined as: large adenoma ( $\geq 1$  cm),  $\geq 3$  adenomas, tubulovillous pathology, high grade dysplasia, or CRC. Screening yield was defined as having an adenoma or advanced adenomatous lesion among those who were asymptomatic at colonoscopy.

**RESULTS:** A total of 1,189 survivors were identified. Of these, 183(15%) had at least one colonoscopy for any indication. Median age at cancer diagnosis was 16.6 years (range, 0-39.9) and at colonoscopy was 34.9 years (range 6.6-65.9). Colonoscopy was performed in 118(65%) survivors for diagnostic reasons, in 53(29%) for asymptomatic screening and in 12(7%) for surveillance. Overall, 43(24%) had at least one adenomatous finding; 29 (16%) had an advanced adenomatous lesion and 7(4%) had CRC. Of the 53 survivors who underwent screening colonoscopy, 18 had an adenomatous finding, resulting in a screening yield of 33%.

**CONCLUSIONS:** Adult survivors of childhood and young adult cancer have significant findings on colonoscopy. Use of screening colonoscopy may need to be expanded, although further study is needed.

**Key words:** Colon adenoma; Adenocarcinoma; Survivorship

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### INTRODUCTION

Survivors of childhood and young adult cancer are at risk of delayed complications of treatment including subsequent malignant neoplasm (SMNs). SMNs are the second leading cause of premature mortality in this patient population after disease recurrence, and early initiation

of screening for some cancers has been advocated<sup>[1-4]</sup>. Subsequent gastrointestinal neoplasms, including colorectal cancer (CRC), occur more frequently and at a younger age in survivors of childhood and young adult cancers when compared to the general population<sup>[2,5-10]</sup>. Radiation exposure and alkylating agents have been implicated as risk factors for secondary CRC in childhood cancer survivors<sup>[2,9,11-13]</sup>. Notably, survivors who received abdominal or pelvic radiation have a similar cumulative incidence of CRC as individuals with at least two first-degree relatives with CRC<sup>[7]</sup>.

The Children's Oncology Group Long-Term Follow-Up Guidelines recommends that survivors exposed to  $\geq 30$  Gy of radiation to an area that includes that abdomen or pelvis undergo colonoscopy beginning 10 years after radiation or at age 35 years, whichever occurs last<sup>[14,15]</sup>. Yet, little is known about the incidence of pre-cancerous adenomas and evidence supporting CRC screening is limited. It is also unclear whether colon cancer in survivors follows the same adenoma to carcinoma pathway as the general population. This pathway is the foundation for using screening colonoscopy for prevention of CRC by detecting the precancerous adenoma and removing it. Our study aimed to determine the screening yield of colonoscopy among survivors of childhood and young adult cancer, with the overall goal of supporting or refuting a role for colonoscopy for CRC detection or prevention in this population.

## METHODS

We conducted a retrospective study of all colonoscopies performed in survivors of childhood and young adult cancers followed in the Adult Long-Term Follow-Up (ALTFU) Program at Memorial Sloan Kettering between July 1, 2005 and December 31, 2015. This study was approved by the institutional review board.

All ALTFU patients who had undergone colonoscopy or flexible sigmoidoscopy were identified; charts underwent a detailed review. Indication for procedure (screening, surveillance, or diagnosis) was determined. Recognizing differences in terminology, for the purposes of this work, screening colonoscopy was defined as colonoscopy performed for the intent of detecting adenoma or CRC and in the absence of symptoms. Surveillance colonoscopies were defined as colonoscopies performed for follow up after a history of prior abnormal colonoscopy. Diagnostic procedure was defined as colonoscopy performed for symptom evaluation including anemia, diarrhea, constipation, hematochezia, melena, change in bowel habits, abdominal pain or abnormal abdominal imaging. Findings at colonoscopy were recorded; associated histopathology was documented focusing on the presence of any adenomatous lesion or cancer. Advanced adenomatous lesions were defined as tubular adenoma  $\geq 1$  cm,  $\geq 3$  tubular adenomas, tubulovillous pathology, high grade dysplasia or carcinoma.

Initial cancer and treatment related factors such as cancer diagnosis, date of primary diagnosis, chemotherapy and radiation exposure, diagnosis of Lynch syndrome, and date of last visit to ALTFU or date of death were recorded. Existing chemotherapy records, with special attention to alkylating agents, were reviewed. Radiotherapy records were reviewed for field and prescribed radiation dose.

Individuals missing an endoscopy report or those who had a procedure for placement of a colon stent were excluded from the analysis. Screening yield was defined as percentage of patients with adenoma or advanced adenomatous lesions divided by all patients who underwent colonoscopy for screening purposes. All statistical analysis was performed using STATA (STATACorp; College Station, Texas).

## RESULTS

A total of 1,189 survivors were identified. Of these, 183 had at least one colonoscopy for any indication (15.4%). Table 1 describes the characteristics of these survivors. Median age at diagnosis of cancer was 16.6 years (range, 0-39.9) and colonoscopy was performed at a median age of 34.9 years (range, 6.6-65.9). Table 2 describes cancer and treatment-related characteristics. The most common cancer diagnosis was lymphoma 86 patients (47%); 102 patients received prior abdominal radiation (56%) with a median dose of 1990 Gy. A total of 112 (61%) patients received an alkylating agent as part of their initial treatment. Colonoscopy was performed in 118 patients (65%) for diagnostic purposes, in 53 patients (29%) for screening purposes and in 12 patients (7%) for surveillance.

Of the 53 patients who underwent screening colonoscopy, the median age of colonoscopy was 34.9 years (range 2.0-65.9) and the median interval from radiation at the time of colonoscopy was 17.4 years (range 0-54.0). Within the screening group, 48 (91%) of patients had a history of radiation therapy in a field that included the abdomen or pelvis and 38 (71%) received an alkylating agent as part of their cancer treatment.

Table 3 describes the colonoscopy findings. Of the 183 patients who underwent colonoscopy for any cause, 43 (24%) patients had at least one adenomatous finding; 29 (16%) were advanced adenomatous lesions and 7 (4%) were colorectal adenocarcinoma. Locations of adenocarcinomas included one in the sigmoid colon, one in the rectosigmoid colon, three in the ascending colon, two in the rectum. Notably, of the 7 patients with colorectal adenocarcinoma, one was subsequently diagnosed with Lynch syndrome. Two other patients were suspected of having Lynch syndrome but did not have confirmatory testing.

Of the 53 survivors who had a screening colonoscopy, 54 adenomatous findings among 18 survivors were discovered, 30 in the right colon (cecum, ascending colon, transverse colon) and 24 in the left colon (rectum, rectosigmoid, sigmoid); this resulted in a screening yield of 33%. Of those undergoing screening colonoscopy, 10 (19%) had an advanced adenomatous lesion including 3 (6%) with an adenocarcinoma. The adenocarcinomas were located in the sigmoid colon, rectosigmoid colon and ascending colon. Two of the three adenocarcinomas arose in a tubulovillous adenoma.

**Table 1** Characteristics of 183 childhood and young adult cancer survivors who underwent colonoscopy.

Characteristic	N (%)
Colonoscopy / flexible sigmoidoscopy performed	183
Body mass index (kg/m <sup>2</sup> ), median (range)	24.5 (15.4-44.8)
History of diabetes mellitus	12 (6.6%)
History of inflammatory bowel disease	3 (1.6%)
Current or former smoker	52 (28.4%)
Family history of colon cancer	40 (21.9%)
Indication for procedure	
Diagnostic	118 (64.5%)
Screening	53 (29.0%)
Surveillance	12 (6.6%)
Age at diagnosis (years), median (range)	16.6 (0-39.9)
Age at colonoscopy (years), median (range)	34.9 (6.6-65.9)
Years from diagnosis of cancer, median (range)	16.5 (0-39.9)
White	162 (88.5%)
Hispanic (any race)	21 (11.5%)
Male	90 (49.2%)

Among survivors who underwent screening colonoscopy ( $N = 53$ ) the median age at the time of colonoscopy for those patients with adenomatous findings ( $N = 18$ ) was 44.5 years (range, 8.9-58.4) while the median age among those without adenomatous findings ( $N = 35$ ) was 42.6 years (range, 28.2-65.9). The median age of cancer diagnosis among patients with adenomatous findings was 20.3 years (range 14.2-39.8) and in those without adenomatous findings was 22.6 years (range 1.0-38.0 years).

## DISCUSSION

In this population of survivors of childhood and young adult cancer who underwent colonoscopy in the absence of symptoms, screening yield for pre-cancerous or cancerous lesions was 33% at a median age at colonoscopy of just under 35 years old. To date, there is a paucity of information regarding adenomatous lesions in survivors of childhood and young adult cancers. Furthermore, screening guidelines are limited by lack of supporting evidence of benefit with early initiation of screening. Our study shows that survivors of childhood and young adult cancer have significant findings on colonoscopy with a screening yield higher than what would be expected in an average risk population of the same age. As a comparison, prior studies have reported a  $\leq 10\%$  prevalence of adenomatous polyps among average-risk patients aged 40-50 and a 20% prevalence in average risk patients  $\geq 50$ <sup>[16-18]</sup>. At the same time, the significant number of adenomatous findings supports a pre-cancerous, screening-amenable stage for colorectal cancers in this population.

Our findings support recent results from a smaller study performed by Daly and colleagues of 54 young cancer survivors undergoing early colonoscopic screening<sup>[19]</sup>. This study included patients who had received prior abdominal radiation  $\geq 10$  years prior to colonoscopy. Of 54 survivors with a median age of 45 years, 24 patients were found to have polyps, of which 15 (27.8%) were pre-cancerous polyps (tubular adenoma, tubulovillous adenoma or serrated adenoma). Four of these patients had high-risk features including  $\geq 3$  adenomatous polyps and/or high grade dysplasia. There were no colon cancers detected in the study. As was seen in our study, Daly et al demonstrated a screening yield higher than what would be expected for an average risk population. However, this study was restricted to patients aged 35-49 years who received radiation to the abdominopelvic region, and no colon cancers were identified. In contrast, we report 3 out of 53 patients with screening colonoscopy had colorectal cancer; two arising in areas of tubulovillous adenoma.

In order to target survivors at highest risk for subsequent colorectal malignancies, it is critical to identify risk factors associated with development of these lesions. In cohort studies of childhood and young adult cancer survivors, abdominal radiation is the primary risk factor that has been shown to be associated with gastrointestinal SMN. In a 2012 report from the Childhood Cancer Survivor Study, investigators examined over 14,000 survivors of childhood cancer diagnosed between 1970 and 1986 in 26 centers across the US and Canada<sup>[2]</sup>. Those who received abdominal or pelvic radiation had an increased 30-year cumulative incidence of gastrointestinal (GI) SMN, including CRC, when compared with those who had not received radiation. On multivariate analysis abdominal radiation was associated with  $> 5$  fold increased risk of GI SMN. High-dose procarbazine and platinum exposure were independently associated with an increased GI SMN risk among those who had been treated with radiation ( $> 3$  and  $> 7$  fold respectively). Due to the small number of cancers in that study, radiation dose could not be examined

**Table 2** Cancer diagnosis and treatment characteristics among 183 childhood and young adult cancer survivors who underwent colonoscopy.

Characteristic	N (%)
<b>Diagnosis</b>	
Lymphoma	86 (47.0%)
Leukemia	37 (20.2%)
Sarcoma	30 (16.4%)
Central nervous system tumor	7 (3.8%)
Other	23 (12.6%)
Hematopoietic cell transplant	59 (32.2%)
Radiotherapy to abdomen, spine, or pelvis	102 (55.7%)
Median radiation dose (range)	1990 cGy (180-5580)
Cyclophosphamide, yes	112 (61.2%)

**Table 3** Colonoscopy findings among 183 childhood and young adult cancer survivors who underwent colonoscopy.

Finding	Colonoscopy for any reason (N = 183)	Screening colonoscopy (N = 53)*
Colorectal cancer	7	3
High grade dysplasia	2	2
Tubulovillous adenoma	5	0
$> 3$ tubular adenomas	10	3
Tubular adenoma $> 1$ cm	5	2
Tubular adenoma, other	14	8
Advanced adenomatous lesions §	29 (15.8%)	10 (18.9%)
Any adenomatous lesion	43 (23.5%)	18 (34.0%)

\* Defined as colonoscopy to detect colon cancer in the absence of symptoms. § Defined as large adenoma ( $\geq 1$  cm), 3 or more adenomas, tubulovillous pathology, high grade dysplasia, or carcinoma.

in detail. Furthermore, investigators from the British Childhood Cancer Survivor Study, a cohort of 17,981 5-year survivors of childhood cancer, reported a cumulative incidence of CRC for patients treated with abdominopelvic radiation of 1.4%; very similar to the 1.2% cumulative incidence among patients with at least two first-degree relatives affected by CRC<sup>[7]</sup>.

Because of the retrospective nature and sample size in this study, we did not test for associations between colonoscopy findings and history of radiation therapy or alkylating agent chemotherapy. However, it is important to note that we observed adenomas and advanced adenomatous lesions among young patients who had received lower doses of radiation and in the absence of alkylating agent chemotherapy.

Although there are limitations to our study, this study is one of the largest to date evaluating colonic adenomas in survivors of childhood and young adult cancers. Additionally, our study revealed a significant number of high-risk adenomatous lesions, which lends support to the idea that treatment-related CRC follows the pathway of adenoma to cancer and suggests benefit in colonoscopy and polypectomy at an early stage. Further studies evaluating long-term outcomes and natural history of patients with adenomatous lesions on initial colonoscopy will aid in understanding this pathway in this unique set of patients.

The Children's Oncology Group Long-Term Follow-Up Guidelines currently recommends initiation of screening among survivors treated with  $\geq 30$  Gy abdominal radiation starting 10 years after exposure or at age 35, whichever is later<sup>[15]</sup>. Despite these guidelines, a prior study has shown that more than 70% of survivors at increased risk for CRC are not being screened as recommended<sup>[20]</sup>.

Our study supports the Children's Oncology Group

recommendation and suggests it could go further to reach more at-risk survivors. As has been demonstrated before, adenoma detection and removal in the general population drastically reduce the risk of colon cancer and CRC-related mortality<sup>[21,22]</sup>. Future prospective studies may provide additional clarification on the role of screening and early removal of adenomatous polyps for prevention of CRC development among survivors of childhood and young adult cancer.

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