Adolescent and Young Adult Colorectal Cancer

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Abstract

Although the overall incidence of colorectal cancer (CRC) in adolescents and young adults (AYAs) is low, it has seen an increase over the past 2 to 3 decades, which contrasts with the trend of decreased incidence in the older population. This phenomenon is conceivably caused by a lack of routine CRC screening in the young population and lifestyle issues, including the obesity epidemic and dietary factors. Hereditary genetic syndromes (eg, familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer syndrome) and known predisposing medical conditions (eg, inflammatory bowel disease) account for only a minority of CRC cases in AYA. Younger patients with CRC commonly present with more advanced disease at diagnosis and exhibit specific molecular and clinical characteristics associated with a distinct biologic phenotype of CRC compared with older individuals. Matched for stage, however, the prognosis of patients with young-onset CRC is similar to or better than that for older patients. A surprising paucity of data exists on outcomes associated with modern systemic cytotoxic and biologic therapy specifically in young patients with CRC. The toxicity pattern of these treatments, however, differs between young and older patients, partly because of the lower rate of pertinent comorbidities in younger adults. Issues regarding surgical management in the setting of hereditary syndromes and fertility preservation while on therapy are of particular importance to the younger patient population. Future studies should seek to increase understanding of the distinct tumor biology of AYA patients with CRC and the consequences of treatment interventions to optimize outcomes for this population. (*JNCCN* 2013;11:1219–1225)

Incidence of Colorectal Cancer in Adolescents and Young Adults

The incidence of colorectal cancer (CRC) in young adults is relatively low. CRC is typically a disease of older adults, with the average age of colon cancer diagnosis approaching 70 years. The likelihood of patients younger than 40 years developing CRC is approximately 1:1200, compared with 1:25 for persons older than 70 years.¹ CRC is the third leading cause of cancer-related death among 20 to 39 year olds, behind leukemia and brain/nervous system cancers. The incidence of CRC in patients younger than 20 years is extremely low, approximately 0.03%, based on SEER data.²

Although the incidence of CRC is decreasing in the older adult population, several epidemiology studies over the past decade have reported an increase among young adults.^{3–5} A SEER database analysis found a rate of 2.1 per 100,000 persons of colon cancer and 1.4 per 100,000 persons of rectal cancer among 20 to 40 years olds.⁴ The study also noted a 17% increase in the incidence of colon cancer and a 75% increase in rectal cancer among 20 to 40 year olds from 1973 through 1999.

A more recent SEER database study evaluating the incidence of CRC among 20 to 49 year olds from 1992 through 2005 found an increase of 1.5% in men and 1.6% in women per 100,000 young persons.⁵ Rates increased for every age decade examined (20–29, 30–39, and 40–49 years), particularly in the youngest individuals (20–29 years), in whom incidence increased 5.2% in men and 5.6% in women per year over the 13-year period. The increase was primarily driven by left-sided tumors, especially rectal cancers. This is in stark contrast to the overall trend in CRC incidence, which declined by 2.6% for men and 2.1% for women from 1998 to 2009, largely attributed to be an effect of CRC screening.³

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Etiology

The exact cause for this alarming trend in young adults is unclear, but has largely been attributed to dietary factors and the rising rate of obesity among young Americans.⁵ Most CRC cases in young adults seem to be sporadic. A systemic review of the literature on young adults with CRC revealed that only 16% had a documented predisposing factor, such as inflammatory bowel disease (ulcerative colitis, Crohn disease, and regional enteritis), familial adenomatous polyposis (FAP), or hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, and 22% had family history of CRC.⁶

The 2 major known familial syndromes associated with CRC in young adults are HNPCC (or Lynch syndrome) and FAP. Both of these genetic disorders demonstrate autosomal dominant inheritance and constitute 2.0% and 0.1% to 1.0% of all adult cases of CRC, respectively.⁷ It is unusual for patients with FAP to develop carcinoma before the third decade: 7% are diagnosed by age 20 years, and 15% by age 25 years. HNPCC is believed to be the cause of up to 10% of cases occurring before 50 years of age, with CRC diagnoses usually in the 40s.⁸ Genetic predispositions for CRC are summarized in Table 1.

HNPCC is caused by germline mutations in 1 of 4 mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Ninety percent of mutations affect *MLH1* or *MSH2*, whereas mutations in *PMS2* are the most infrequent. The biologic consequences of the mutation differ between the affected genes. The age-dependent risk for developing CRC varies and is higher for mutations in *MLH1* and *MSH2* than *MSH6* (Figure 1).⁹ By age 40 years, 6% and 8% of patients with mutations in *MLH1* and *MSH2*, respectively, will have been diagnosed with CRC, compared with only 1% of patients with mutated *MSH6*. In addition, patients with mutations in *MSH6* are unlikely to develop other HNPCC-associated cancers, such as ovarian, stomach, urothelial, small bowel, and biliary cancers.

Presentation

Because patients younger than 50 years without a clear family history of CRC, polyps, or known genetic predisposition do not fall under the current guidelines for screening, most (>80%) are diagnosed with symptomatic disease.^{6,10,11} Presenting

symptoms are typically related to the site of the bowel lesion, and younger patients more frequently show left-sided tumors. In a systematic review, 22% of patients younger than 50 years presented with lesions in the ascending colon, 11% in the transverse colon, 13% in the descending colon, and 54% in the sigmoid and rectum.⁶ Therefore, in addition to general symptoms from colon cancer such as abdominal pain, fatigue, and weight loss, younger patients are more likely to present with symptoms associated with a left-sided lesion, including rectal bleeding and altered bowel pattern.¹²

A large retrospective analysis identified 1025 patients aged 50 years and younger diagnosed with CRC seen at the Mayo Clinic between 1976 and 2002, without established risk factors for CRC, including inflammatory bowel disease, polyposis syndromes, or a known genetic predisposition.¹⁰ The mean age at presentation was 42.4 years, and 86% of patients were symptomatic at diagnosis. The most common initial symptoms were rectal bleeding (51%), change in bowel habits (18%), abdominal pain (32%), weight loss (13%), nausea/vomiting (7%), and melena (2%).

Younger patients commonly experience a delay in diagnosis, sometimes exceeding 6 months,^{6,12} possibly leading to more findings of advanced disease at presentation compared with older patients. In one population-based study comparing CRC in 20 to 40 year olds versus 60 to 80 year olds, the stage distribution was 10.6% versus 18.6% for stage I; 23.0% versus 29.0% for stage II; 31.5% versus 22.8% for stage III; and 24.5% versus 17.3% for stage IV, respectively.⁶ These findings are concordant with those of other studies of younger patients showing more advanced disease at presentation.^{12,13}

A host of issues likely contributing to the delay in diagnosis of younger adults with colon cancer was summarized by Bleyer et al¹⁴ in 2006. Both physicians and young adult patients are less likely to attribute symptoms to an underlying malignancy. In addition, the health care system is underused by adolescents and young adults (AYAs) because of several factors, including lack of health care insurance. However, the differences in stage presentation between younger and older adults may also be related to differences in the biology of colon cancer in these populations.

Table 1 Genetic Syndromes Predisposing for Young-Onset Colorectal Cancer

Genetic Syndrome	Mutation	Frequency	Risk of CRC	Median Age of CRC Presentation (y)	Clinical Presentation
FAP	APC gene on chromosome 5q21, autosomal dominant	1%–2% of all CRC, mutation in 1:7,000–22,000	90% by age 45 y	39	Multiple (>100) adenomatous polyps in the colon and rectum developing after the first decade of life Multiple clinical variations with extracolonic tumors and attenuated forms
Hereditary nonpolyposis CRC (Lynch syndrome)	Mismatch repair enzyme genes (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , and <i>PMS2</i>), autosomal dominant	2%–5% of all CRC	40%–80% by age 75 y	44	MSI-H phenotype Various extracolonic cancers common Amsterdam and Bethesda guidelines for clinical diagnosis
MYH-associated polyposis	<i>MYH</i> gene, autosomal recessive	1% of all CRC, 1%–2% of population carry <i>MYH</i> mutation	35%–53% in lifespan	35–45	Broad clinical spectrum sometimes resembling attenuated FAP
Peutz-Jeghers syndrome	<i>STK11</i> gene at chromosome 19p13.3, autosomal dominant	<1% of all CRC, mutation in 1:25,000–300,000	39% by age 70 y	60	Extracolonic cancers common Melanocytic macules on lips, and perioral and buccal regions Multiple GI hamartomatous and adenomatous polyps
Juvenile polyposis syndrome	<i>MADH4 (SMAD4/DPC4)</i> gene at chromosome 18q21 (15%–20%); or bone morphogenic protein receptor 1A (<i>BMPR1A</i>) gene at chromosome 10q22 (25%–40%); autosomal dominant	<1% of all CRC	17%–68% by age 60 y	35–45	Hamartomatous polyposis throughout the GI tract, can present with diarrhea, GI tract hemorrhage, and protein-losing enteropathy

Abbreviations: CRC, colorectal cancer; FAP, familial adenomatous polyposis; GI, gastrointestinal; MSI-H, higher rate of microsatellite instability.

Tumor Biology

Multiple studies have shown that the biologic phenotype of CRC in young adults differs from that in older adults.¹⁵ As expected, a higher rate of microsatellite instability (MSI-H) is found among younger patients. The largest series (n=607) by Gryfe et al¹⁶ found a 17% rate of MSI-H tumors in patients younger than 50 years. Multiple case series involving small numbers of the youngest patients with colon cancer (including children

and adolescents) report MSI-H rates ranging from 46% to 73%, with rates trending higher as the age of the study population decreases.^{17–21}

Most MSI-H tumors in young adults are caused by a sporadic mutation, or are from hypermethylation of one of the MMR genes promoter regions, rather than related to a germline mutation.²² MSI-H tumors are associated with a better overall prognosis in the overall population, and in young adults.^{16,23} In contrast to microsatellite stable or low tumors

Figure 1 Age-dependent risk for developing colorectal cancer (CRC) according to mutation for patients with hereditary nonpolyposis colorectal cancer.

Data from Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011;305:2304–2310.

(MSS/MSI-L) in which *BRAF* mutation carries a poor prognosis, *BRAF* mutant status does not carry a poor prognosis in MSI-H cancers.²⁴ The higher rates of MSI-H tumors may explain why younger patients have similar or improved survival rates compared with older patients, when matched stage by stage.^{6,25}

A subset of AYAs has more aggressive tumor biology, contributing to poorer outcomes.^{10,26–29} These tumors are more commonly mucin-producing, poorly differentiated, and have signet ring histology. The incidence of mucin-producing tumors is greater in patients younger than 30 years, and the rates increase as the age at diagnosis decreases.^{17,27} A SEER database review of 1736 patients younger than 40 years found that mucinous and poorly differentiated tumors occurred in 21% and 27% in young adults, respectively, compared with 12% and 15% in older adults.²⁹ The underlying mechanisms responsible for the more aggressive tumor biology among young patients remain unknown, but clearly not all of these patients have a readily identifiable genetic predisposition.^{15,17,30}

Treatment

AYA patients have the same standard treatment recommendations for all stages of CRC as older adults.³¹ Standard staging after diagnosis includes a CT scan of the chest, abdomen, and pelvis, and laboratory studies, including a CBC, liver and renal function

tests, and carcinoembryonic antigen levels. AYA patients should be assessed for genetic risk factors and referred for genetic testing accordingly. MSI testing should be performed on pathologic specimens to assess for evidence of Lynch syndrome.

Surgical Management

For AYA patients without a known genetic disposition, segmental colectomy is the standard of care. AYA patients with FAP generally undergo colectomy by the end of their second decade of life.³² Surveillance requirements and quality of life issues should be considered when deciding on surgical management of AYA with HNPCC. HNPCC patients who undergo segmental colectomies require frequent colonoscopies; however, those who undergo subtotal or total colectomies with ileorectal anastomosis require less-invasive surveillance methods, such as flexible sigmoidoscopies.³³ Change in bowel patterns after total colectomies may affect daily activities: 25% of patients undergoing total colectomy will have 5 or more bowel movements per day, and 30% will have issues with fecal incontinence.^{34,35}

Adjuvant Therapy for Stage II and III Colon Cancer

Patients with high-risk stage II and III disease should undergo 6 months of oxaliplatin-based therapy with either modified FOLFOX6 (5-FU, leucovorin, oxali-

platin) or XELOX (capecitabine, oxaliplatin), which have been shown to improve outcomes in randomized phase III clinical trials.^{36,37} Patients with low-risk stage II disease should be tested for MSI, and no adjuvant therapy is recommended in those found to have MSI-H tumors.

Younger patients are more likely to receive adjuvant therapy, especially for stage II disease, compared with their older counterparts. Quah et al¹¹ found that 39% of patients aged 40 years or younger received adjuvant chemotherapy for stage II disease, compared with only 14% of older patients, even though the clinical and pathologic tumor characteristics were similar. Because younger patients have a higher rate of MSI-H tumors, a larger proportion of younger patients with stage II disease may exist who may not benefit from adjuvant chemotherapy.^{38,39} Given that the overall prognosis for younger patients with colon cancer is similar or improved compared with older patients, this same principle likely applies to younger patients, and adjuvant chemotherapy is unnecessary for younger patients with stage II disease and MSI-H tumors, although this has not been studied in detail.

The benefits of adjuvant therapy in young adults have been studied using the Adjuvant Colon Cancer Endpoints (ACCENT) database.²⁵ Of the 33,574 patients from 24 randomized phase III clinical trials, 5817 (17.3%) were younger than 50 years, 1758 (5.2%) were younger than 40 years, and 299 (0.9%) were younger than 30 years. Approximately 68% of patients had stage III disease. In this analysis, younger patients had similar recurrence-free survival (RFS) as older patients. When patients younger than 40 years were compared with those aged 40 years and older, the 5-year RFS rate was 68.4% and 66.8%, respectively, with a hazard ratio of 1.02 (95% CI, 0.94–1.11; $P=.62$). Similar findings were seen when the patients were grouped by younger than 50 years and 50 years and older. Disease-free and overall survivals were higher among the younger patients, likely because of the fewer competing causes of death among younger patients.

Metastatic Disease

Treatment for metastatic CRC includes combination chemotherapy (oxaliplatin and/or irinotecan with a fluoropyrimidine) plus a biologic agent (bevacizumab, cetuximab, and panitumumab). A surprising lack of data exists on survival outcomes in AYAs compared with older adults with current standards of palliative therapy. Most population studies indicate

that the AYA population with stage IV disease fares similarly as the older adult population with stage IV disease in terms of survival. Given the adjuvant therapy data, the benefit derived from modern chemotherapy regimens involving irinotecan and oxaliplatin is likely age-independent. More studies are needed regarding the outcomes and tolerance of biologic therapies, including bevacizumab, aflibercept, cetuximab, panitumumab, and regorafenib, in AYA patients. In addition, no detailed data on outcomes after potentially curative metastasectomy are available for young versus old patients with CRC. This highlights the importance of enrolling this patient population in clinical trials.

Treatment Side Effects

Tolerance of Therapy

In the aforementioned ACCENT analysis, younger patients tolerated adjuvant treatment as well as, if not slightly better than, older patients.²⁵ However, younger patients likely have a different side effect profile than older patients. Although younger patients had a significantly lower incidence of grade 3+ leukopenia and stomatitis, they tended to have more grade 3+ nausea and vomiting. In younger patients, the aggressive use of antiemetics may improve treatment tolerability and compliance, and thereby completion of the recommended therapy.

Impact of CRC Therapy on Fertility

The effects of oxaliplatin, irinotecan, and biologic agents on fertility in men and women are largely unknown. 5-FU is believed to cause a temporary reduction in sperm count for men and to have a low risk for causing amenorrhea in women.⁴⁰ Among 50 women with gastrointestinal cancers who responded to a reproductive health survey (no details on specific treatment regimen provided), infertility increased from 15% to 30% as age increased from 18 to 40 years.⁴¹ Preclinical studies suggest oxaliplatin may have moderate gonadal toxicity, but the long-term effects are unknown.⁴² Depending on the patient's desire to have children and the clinical situation, potential risk for toxicity and fertility preservation options, including sperm banking for men and oocyte/embryo cryopreservation for women, should be discussed with all AYA patients.⁴⁰

Survival and Prognosis

Previously, younger patients were believed to always have more aggressive disease and worse prognosis than older adults.⁶ However, when matched for stage, survival rates seem to be similar or better for young adults than for older adults.^{6,11,43} A large population-based study using the SEER database evaluated 5-year CRC-specific survival outcomes in 1334 patients aged 20 to 40 years compared with 46,457 patients aged 60 to 80 years.⁴³ Despite the higher rates of stage III or IV disease and poor tumor differentiation, younger patients had an equivalent, and in some stages better, prognosis than older patients. For younger versus older patients, the 5-year stage-specific survival was 93.3% versus 94.9% ($P =$ not significant) for stage I disease, 88.6% versus 82.7% ($P=.01$) for stage II disease, 58.9% versus 57.2% ($P =$ not significant) for stage III disease, and 18.1% versus 6.2% ($P<.001$) for stage IV disease, respectively.

Most patients studied in the young adult literature were ages 20 to 50 years, and little is known regarding the survival of adolescents treated with the current multidisciplinary approach to CRC. Children and adolescents diagnosed with CRC have been reported to have a very poor prognosis.^{2,26,30,44} However, much of the literature on survival in adolescents consists of small case series, which is not surprising given the rarity of CRC in this population. In addition, most of the reports on the youngest patients with CRC are from before the introduction of new standards of care, including oxaliplatin-based regimens, adequate nodal dissection, and biologic agents.

The largest series of pediatric/adolescent cases was a SEER database study in which the features and survival outcomes of 159 patients from 1973 to 2005 were compared with those of adults.² This study confirms the poorer survival of children and adolescents compared with adults: the 5-year survival rates were 40% and 60%, respectively, and the 10-year survival rates were 31% and 54%, respectively ($P<.001$). Interestingly, although survival outcomes improved over that period for adults, no survival improvements were seen in children and adolescents.

Conclusions

Although the rising incidence of CRC in AYAs in the past decades is well documented, understanding of epidemiologic, genetic, and biologic factors

leading to this increase is incomplete. In addition, CRC in AYA patients exhibits a clinical, histologic, and molecular phenotype, which sets it apart from cancers diagnosed in older individuals for yet unknown reasons. The lack of detailed information on outcomes associated with modern cytotoxic and biologic therapies in young patients with CRC warrants refined retrospective and prospective analyses of treatment effects in this specific population in clinical trials to elucidate whether the characteristic biologic phenotype and molecular alterations found in AYA CRC should lead to specific treatment interventions.

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