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Considerations in the Management of Younger Patients With Colorectal Cancer

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Abstract: The incidence of colorectal cancer in patients ages 18 to 49 years has increased by 51% throughout the past 3 decades. In the United States, recent guidelines lowered the initial screening age to 45 years. More than 75% of colorectal tumors in younger patients are diagnosed based on the onset of symptoms, such as rectal bleeding, abdominal pain, weight loss, or anemia. In most cases, these individuals do not have a family history of colorectal cancer. On average, the diagnosis of colorectal cancer in younger patients occurs from 6 months to several years after symptoms first arise. As a result, younger patients diagnosed with colorectal cancer tend to present with advanced disease. If a younger patient does not have any contraindications, it is appropriate to consider treatment with a triplet chemotherapy combined with a biologic. The impact of treatment can be greater for younger patients than for older individuals. Even mild or moderate toxicities can strongly impact their daily lives. Younger patients with colorectal cancer are likely to have a higher risk for long-term treatment-related sequelae, particularly because they tend to present with advanced disease and will receive therapy for a prolonged period.

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Examining the Increase in Colorectal Cancer in Younger Patients

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Screening guidelines from the American Cancer Society and the United States Preventive Services Task Force (USPSTF) now recommend that screening for colorectal cancer in the general population begin at age 45 years.[1,2] This change recognizes the rising prevalence of early-onset colorectal cancer in the United States and worldwide (Figure 1).[3-6] The USPSTF found that lowering the screening age to 45 years will confer an additional 22 to 27 life-years per 1000 people based on the screening modality and frequency (assuming 100% adherence; Figure 2).[2] Previously, most articles described younger patients as below the age of 50 years. It seems likely that the new definition of younger patients will encompass those younger than 45 years.

Up until 2015, approximately 7% of all patients with colorectal cancer were younger than 40 years.[7-9] The American Cancer Society performed a breakdown of age groups for patients with colorectal cancer in 2020 (Table 1).[6] A diagnosis of colorectal cancer is expected in approximately 18,000 patients ages 49 years and younger; this estimate consists of 11,540 cases of colon cancer and 6400 cases of rectal cancer. Approximately 3600 of these patients will die of the disease.

This increase has been reported not only in the United States, but also in Asia and Europe. A recent article evaluated the incidence of colorectal cancer from 2004 to 2016 in Europe.[10] The study found an increase of nearly 8% per year among individuals ages 20 to 29 years. There was a 5% increase per year for those ages 30 to 39 years.

Hypotheses for the Increase

The increase in cases of colorectal cancer among younger patients is multifactorial. Researchers are investigating multiple aspects of early-onset colorectal cancer. It is known that a poor diet and obesity may be associated with the development of colorectal cancer.[11,12] The Nurses' Health Study examined the change in a patient's body mass index (BMI) and the risk of colorectal cancer.[13] The investigators found that the risk of colorectal cancer

Table 1. Estimated Number of Colorectal Cancer Cases and Deaths in the United States in 2020 by Age

	Cases			Deaths[a]
Age	**Colorectal**	**Colon**	**Rectum**	**Colorectal**
0-49 years	17,930	11,540	6390	3640
50-64 years	50,010	32,290	17,720	13,380
65+ years	80,010	60,780	19,230	36,180
All ages	147,950	104,610	43,340	53,200

Estimates are rounded to the nearest 10 and exclude in situ carcinoma.

[a]Deaths for colon and rectal cancers are combined because a large number of rectal cancer deaths are misclassified as colon.

Adapted from American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf. Accessed May 10, 2021.[6]

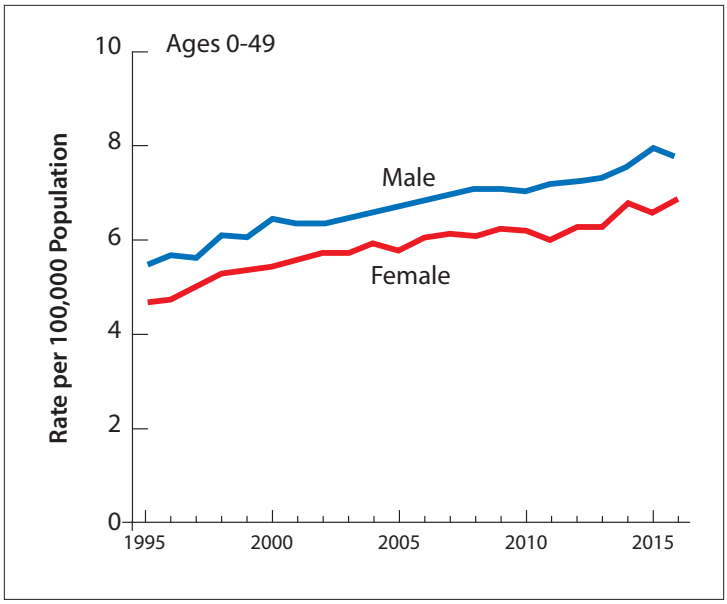

Figure 1. Trends in colorectal cancer incidence in the United States from 1995 to 2016 as assessed by the American Cancer Society, based on data from the North American Association of Central Cancer Registries, 2019. Rates are age-adjusted to the 2000 US standard population. Incidence rates are adjusted for reporting delays and exclude data from the appendix. Adapted from American Cancer Society. Colorectal Cancer Facts & Figures 2020-2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2020-2022.pdf.[6]

was increased in people with a BMI higher than 30. In addition, increased risk corresponded to a greater increase in a person's BMI from age 18 years to the present. A study conducted in northern Europe found that young men with a higher BMI relative to when they were a child had an increased risk of colorectal cancer.[14] It is not just obesity that increases the risk of colorectal cancer. Dietary habits may play a role. Also, it should be noted that the presumption is that these cases are sporadic colorectal carcinoma arising in patients who do not have an inherited risk factor for Lynch syndrome.

There is interest in the microbiome and the impact of dysbiosis.[15] Researchers are evaluating whether high-fat diets relate to the development of colorectal cancer as people mature from an adolescent to an adult.[16] The use of antibiotics may also have an impact.[17]

Demographic Features

In the United States, there are clear demographic features that are associated with colorectal cancer. Increased rates of colorectal cancer are seen in areas of the country with higher rates of obesity, poor dietary habits, and a sedentary lifestyle.[18] A recent study evaluated geographic trends in the diagnosis of colorectal cancer in younger patients.[18] Rates were assessed from 2001 to 2005 and again from 2011 to 2015. There was a higher incidence of colorectal cancer in certain states with populations that were less physically active and that had higher rates of obesity.

People should try to learn as much as possible about their family history. Approximately 75% to 80% of patients have sporadic colorectal cancer.[18] However, people with a first-degree relative are at increased risk, even if they do not have Lynch syndrome.[19]

Screening Recommendations

In 2018, the American Cancer Society changed their guidelines to recommend that screening begin at age 45 years.[1] In May 2021, the USPSTF published a statement with a grade B recommendation for screening of adults ages 45 to 49 years.[2] The American Society for Gastrointestinal Endoscopy has not changed the screening age,[20] but it is likely to do so.

The reduction in the screening age is important. It takes from 5 to 10 years for a polyp to become cancerous. However, I am also seeing patients who are still not old enough to be screened. Patients in their 20s and 30s are being diagnosed with sporadic colorectal cancer. Younger people in the general population should recognize the symptoms of colorectal cancer and report them to their primary care physician (or any other physician). The patient should undergo some type of testing, whether it is a colonoscopy, a stool-based test, or another modality. Any type of test is better than no test.

Patients should inform their physician if their symptoms do not improve with time. Sometimes patients are misdiagnosed because they look so young and healthy that it is hard to believe they could have colorectal cancer. It has been reported that the average duration between the first time that symptoms are noticed and the time of diagnosis is 6 months to several years.[3] Primary care physicians should be aware that a patient with stage 3 or 4 colorectal cancer can still look healthy.

Screening Modality and Frequency	Median Life-Years Gained if Screening Starts at[b]: Age 50 Years	Age 45 Years	Additional Life-Years Gained if Screening Starts at Age 45 Years
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 years[d]	278	303	25
Direct visualization tests			
Colonoscopy every 10 years	310	337	27
CT colonography every 5 years	293	317	24
Flexible SIG every 5 years	264	286	22
Flexible SIG every 10 years plus FIT every year	306	332	26

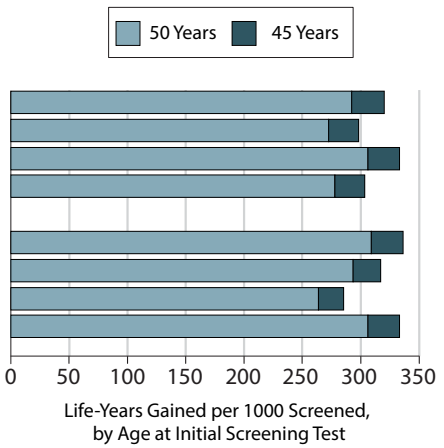

Figure 2. Estimated life-years gained per 1000 people screened by lowering the screening age to 45 years in an analysis from the US Preventive Services Task Force.[a] The estimate is based on 100% adherence.

[a]The outcomes are expressed per 1000 40-year-olds who initiate screening at age 45 vs age 50.

[b]The mean estimate across 3 Cancer Intervention and Surveillance Modeling Network colorectal cancer models is provided.[21,22]

[c]There is considerable uncertainty in model predictions for the HSgFOBT modalities because of imprecision in sensitivity and specificity.[21]

[d]These modalities do not provide an efficient balance of the benefits (life-years gained) vs the harms and burden (ie, lifetime number of colonoscopies) of screening compared with other options for stool-based screening.[21,22]

CT, computed tomography; FIT, fecal immunochemical test (with positivity cutoff of 20 μg of hemoglobin per gram of feces); HSgFOBT, high-sensitivity guaiac fecal occult blood test; sDNA-FIT, stool DNA tests with FIT (multitarget stool DNA test); SIG, sigmoidoscopy. Adapted from Davidson KW et al. *JAMA*. 2021;325(19):1965-1977.[2]

Symptoms

Symptoms of colorectal cancer are similar in younger and older patients. Most patients, in retrospect, notice a change in bowel habits. There may be blood in the stool or a change in the caliber of the stool. In many cases, patients think they have hemorrhoids. More advanced symptoms include night sweats, weight loss, and changing energy levels. More rarely, there are no symptoms at all. Blood work can indicate iron deficiency anemia, which leads to the diagnosis of colorectal cancer.

Recommendations for Physicians

When a patient reports bowel symptoms that do not improve after the first visit, it is important to investigate the cause. In patients with documented bowel irregularities, their insurance plan should cover testing such as flexible sigmoidoscopy or a full colonoscopy, which is the gold standard of care. Virtual colonoscopies are available, but will not allow removal of polyps. A colonoscopy is the preferred modality when there is any potential for polyps. A flexible sigmoidoscopy will miss the entire right side of the colon, which will be affected in a quarter of all patients.

It is important to keep in mind that young patients can develop colorectal cancer. Unfortunately, because most of these patients present several months or even years after symptom onset, they often have stage 4 disease at diagnosis, often with multiple sites of disease involvement that make surgical resection with curative intent less likely.

Conclusion

It is important for young people, caregivers, and health care providers to recognize possible symptoms of colorectal cancer and arrange a colonoscopy or other tests when necessary. If a colonoscopy shows no irregularities, another one is not needed for 5 to 10 years. In my own practice, I recommend a repeat colonoscopy in 5 to 8 years. If a sessile (flat) polyp is found, the patient may need a repeat colonoscopy in another year. When multiple polyps are found, another colonoscopy might be administered after 2 years. Preparation for a colonoscopy is less onerous than it used to be. I tell patients it is one day of discomfort to potentially save their life, and so it is definitely worthwhile.

Disclosure

Dr Eng has no conflicts of interest related to this subject matter to report.

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Disease Characteristics in Younger Patients With Colorectal Cancer

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Traditionally, early-onset colorectal cancer has been defined as disease occurring in patients between the ages of 18 and 50 years.[1] The cutoff of 50 years to define younger patients is arbitrary, and clinicians should instead consider age as a continuum rather than follow a strict numerical definition. However, 50 years is the cutoff most often used in case series that describe the characteristics of tumors originating in younger patients.

The problem of early-onset colorectal cancer is significant. In recent years, there has been an increase in the incidence of colorectal cancer in patients younger than 50 years.[2,3] Among young adult men in the United States, colorectal cancer is both the most frequently diagnosed cancer, as well as the most common cause of cancer-related mortality.[4,5] According to a recent Clinical Practice Update from the American Gastroenterological Association

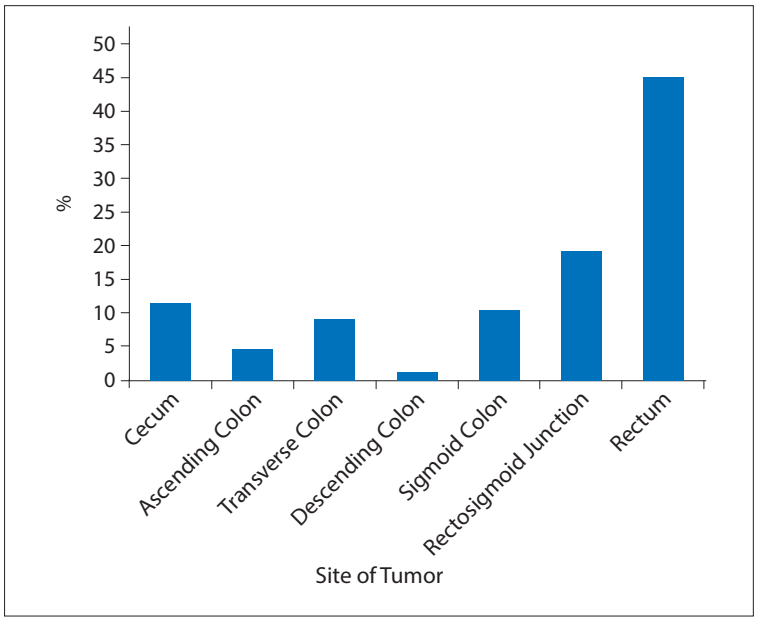

Figure 3. Location of the tumor among patients with early-onset colorectal cancer. Adapted from Riaz R et al. *Intest Res*. 2017;15(2):203-207.[13]

(AGA), the incidence of colorectal cancer in patients ages 18 to 49 years has increased by 51% throughout the past 3 decades.[1,6] During the same period, the incidence of older-onset colorectal cancer decreased by 20%. An incidence rate of 9.2 to 12.2 per 100,000 has been described for early-onset colorectal cancer, with a peak occurrence among those ages 40 to 49 years (accounting for approximately 75% of early-onset cases).[7-9] Tumors associated with early-onset colorectal cancer are often left-sided, and more frequently located in the rectum and distal sigmoid colon as compared with the proximal colon (Figure 3).[10]

In most cases, colorectal tumors in younger patients are not diagnosed as a consequence of a screening procedure. Typically, these individuals do not have a family history of colorectal cancer and therefore do not meet the criteria for high-risk (<50 years) screening. Instead, these cases are typically diagnosed after the onset of symptoms, such as rectal bleeding, abdominal pain, weight loss, or anemia. Overall, it is estimated that more than 75% of colorectal tumors in younger patients are diagnosed based on the onset of symptoms.[11-13] Symptoms associated with right-sided vs left-sided tumors in patients with early-onset colorectal cancer are shown in Figure 4.[13]

Unfortunately, the management of early-onset colorectal cancer in younger patients is further complicated by a delay between the onset of symptoms and the diagnosis. On average, the diagnosis of colorectal cancer is delayed by 6 months in younger patients vs older patients.[1] The reasons for this delay are varied, but include a low level of suspicion by clinicians, a sense of invincibility that leads younger patients to ignore symptoms, and, in some health systems, a lack of medical insurance. As a result, younger patients diagnosed with colorectal cancer tend to present with high-risk stage 3 or 4 disease (reported in 61% of early-onset patients vs approximately 50% in older-onset patients).[14,15] This observation suggests that the increase over time that has been reported is real, and does not represent a shift in the age at diagnosis owing to early detection.

Pathologic Characteristics

Some other important differences between tumors originating in younger vs older patients are related to clinical pathologic characteristics. In terms of histology, early-onset colorectal cancers are more frequently mucinous as compared with later-onset disease.[16] Additionally, signet ring cell histology, which tends to be relatively rare in the overall colorectal cancer population (<1%), is more common among younger patients (3%-13%).[15,17,18] The tumors in younger patients are often poorly differentiated or not differentiated at all, so they are characterized as high grade.[19]

An important question is whether colorectal cancer in younger patients is more likely to be hereditary. It is not known how many of these tumors are related to hereditary, genetically determined syndromes or instead are detected in families with a high incidence of colorectal cancer, in whom the specific alterations responsible for the disease are not established or recognized. In the overall population, the majority of colorectal cancers are sporadic. Among patients with early-onset colorectal cancer, the number of tumors that are traced to a family history is much higher (approximately 50%). In 30% of these cases,

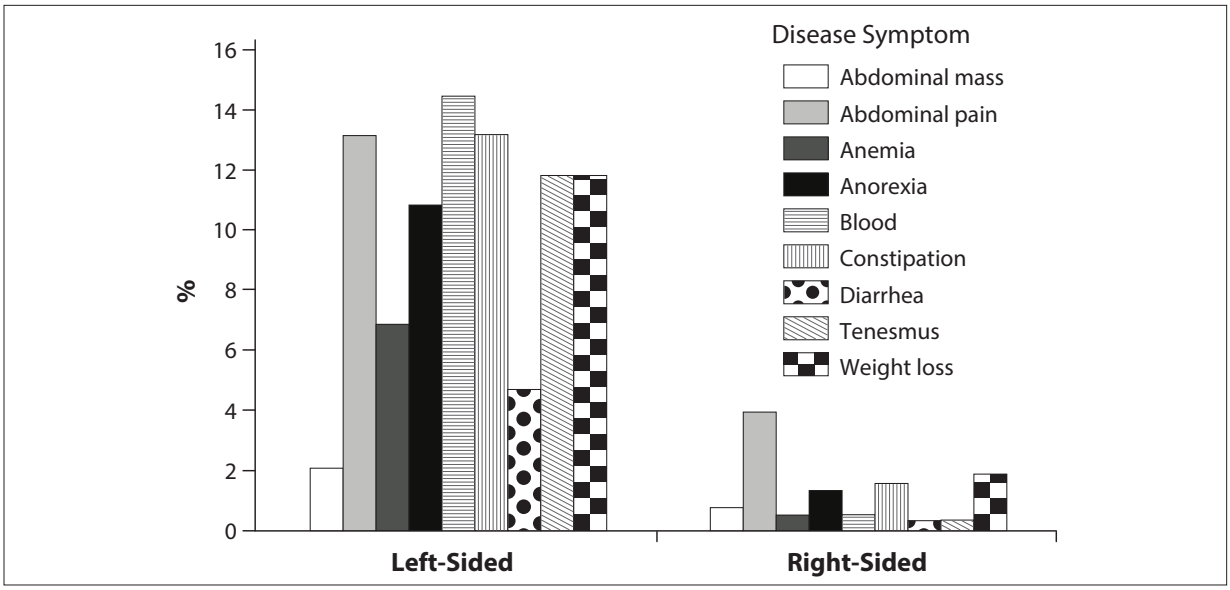

Figure 4. Symptoms associated with right-sided vs left-sided tumors in patients with early-onset colorectal cancer. Adapted from Riaz R et al. *Intest Res*. 2017;15(2):203-207.[13]

a specific hereditary syndrome is not identified.

Among hereditary forms of colorectal cancer, Lynch syndrome deserves consideration. Microsatellite instability is found independently of the diagnosis of a germline syndrome in approximately 10% to 15% of colorectal cancers in the overall population; this percentage increases to 25% to 30% among patients younger than 50 years.[20] Microsatellite instability is especially common among those younger than 30 years. It is likely that this increase is caused mainly by the higher percentage of younger patients affected by Lynch syndrome, which appears to be responsible for approximately 30% of hereditary forms.

Overall, among younger patients with colorectal cancer, approximately 25% have tumors caused by a germline mutation, and approximately half of these patients have Lynch syndrome.[21,22] Other hereditary syndromes include familiar adenomatous polyposis and *MUTYH*- and *NTLH1*-associated polyposis. A small number of younger patients have germline mutations in polymerase epsilon (POLE) proofreading domains and Li-Fraumeni syndrome, which is caused by the *TP53* germline mutation.

Molecular Characteristics

There is a higher prevalence of microsatellite instability among early-onset colorectal cancer. The frequency of *RAS* mutations differs in various reports. Overall, the prevalence of *RAS* mutations in younger patients appears similar to that in the overall population (in whom the mutation is reported in approximately 50%). There is no significant difference with regard to the prevalence of *BRAF* mutations among younger vs older patients. Early-onset colorectal cancers may have a higher incidence of *BRCA* mutations and other alterations affecting genes involved in the homologous recombination system. Like MSI-high tumors, these homologous recombination–deficient tumors deserve particular consideration for genetic reasons and hopefully to help inform treatment selection in the near future.

Unique features of early-onset colorectal cancers include a high prevalence of long interspersed nucleotide element-1 (LINE-1) hypomethylation and the co-occurrence of microsatellite and chromosomal instability, which is rare among older patients.[23]

Disease Aggression

There are limited data regarding the aggressiveness of disease in younger patients, and whether prognosis corresponds to age at diagnosis. There are no solid data showing that these tumors are more aggressive. It has been shown that these patients may be overtreated,[24] particularly in the adjuvant setting for localized disease in early stages. This more aggressive treatment does not translate into gains in survival or long-term prognosis. This observation should be taken into account when selecting management options for younger patients with colorectal cancer.

Disclosure

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Addressing the Needs of Younger Patients With Colorectal Cancer

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Clinicians sometimes fail to recognize the impact a cancer diagnosis can have on a younger person. In fact, the impact can be far greater for younger patients than for older, retired individuals. Younger patients are not accustomed to consuming health care on a daily basis like older people are. They also tend to have busy lives, often raising children and maintaining a career. In many cases, patients must continue to work because they obtain health insurance through their employer. Younger patients therefore may not have a great deal of freedom in their schedules. What does that mean for clinicians? That we have to be ever more effective, efficient, and understanding.

Many of our patients believe that because they are younger, they will tolerate treatment better. In fact, levels of toxicity appear similar, but adverse events are more disruptive for younger patients. Even the mild and moderate toxicities of grade 1 or 2 that are common with treatments can strongly impact their daily lives.

Adherence to treatment among younger patients is high, for the most part. Younger patients are typically eager to carefully follow instructions regarding treatment, in order to ensure the maximum benefit of therapy. Adequate support is the key to treatment adherence for any patient, regardless of age.

Treatments for colorectal cancer increasingly include

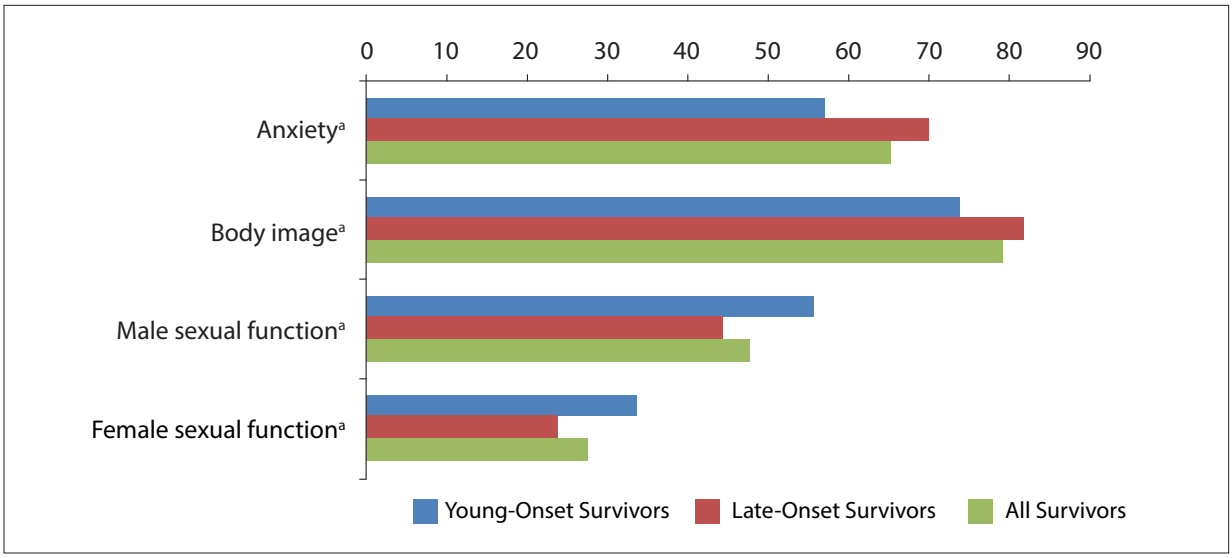

Figure 5. Functional domain scores among patients with early-onset colorectal cancer as assessed by the EORTC CR29. A higher score indicates better functioning. EORTC CR29, European Organization for Research and Treatment of Cancer Colorectal Cancer module. [a]*P*<.05. Adapted from Bailey CE et al. *J Gastrointest Surg*. 2015;19(1):180-188.[4]

aggressive local therapies, such as surgeries, liver-directed therapies, radiation techniques, and interventional radiology techniques. These aggressive interventions are used more often in the younger population than in older patients. Of course, the goal of eradicating disease must be balanced against the risks associated with these aggressive procedures.

For example, it is more common to recommend leucovorin, fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) plus biologic agents in frontline therapy in younger patients, given the newer data suggesting that this treatment improves response, progression-free survival, and overall survival.[1,2] If patients have unresectable tumors, then we quickly shift to maintenance therapy using capecitabine and bevacizumab as the standard. This approach enables younger patients in particular to get back to work and raising their families.

Considerations Regarding Fertility and Long-Term Impact of Treatment

Some younger patients may have questions regarding the impact of their treatment on fertility. As summarized in the AGA Clinical Practice Update on young adult–onset colorectal cancer, it appears that surgery for colorectal cancer does not negatively impact fertility.[3] Chemotherapy has a moderate risk for impaired fertility, but this risk varies according to the type, dose, and duration. It is important that these factors are discussed with patients, who might choose to pursue fertility preservation before beginning treatment for colorectal cancer.

Another point raised in the AGA Clinical Practice Update was that younger patients with colorectal cancer are likely to have a higher risk for long-term treatment-related sequelae, particularly because they tend to present with advanced disease.[3] In a cross-sectional study of 830 long-term survivors of colorectal cancer (approximately 10.8 ± 3 years from diagnosis), younger patients reported higher rates of anxiety, negative body image, and embarrassment with bowel movements as compared with older patients (Figures 5 and 6).[4] Therefore, the needs for young adult survivorship may differ, as these patients will likely require long-term attention. As the authors of this study concluded, the initial age at cancer diagnosis should be strongly considered as a basis for designing tailored and individualized survivorship care programs.

Impact on Future Research

The incidence of colorectal cancer in younger patients may be a catalyst to drive more research in this disease. We have struggled with increasing funding for colorectal cancer research. Families and friends of younger patients who are diagnosed with colon cancer are mobilizing unlike ever before. Young people with colon cancer will likely generate a social wave that will lead to more research, which should help improve management of all patients with this disease.

Disclosure

Dr Marshall has received funds from Bayer, Taiho, Ipsen, Caris, Indivumed, Merck, Pfizer, and Daiichi.

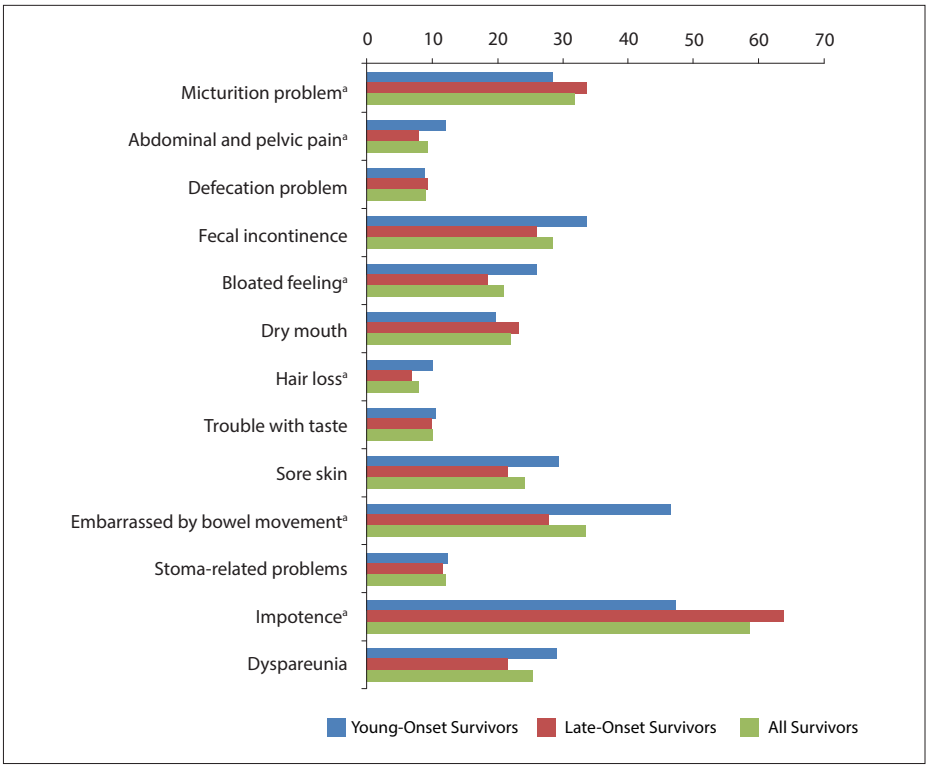

Figure 6. Symptom domain scores among patients with early-onset colorectal cancer as assessed by the EORTC CR29. A higher score indicates a higher level of symptomatology. EORTC CR29, European Organization for Research and Treatment of Cancer Colorectal Cancer module. [a]*P*<.05. Adapted from Bailey CE et al. *J Gastrointest Surg*. 2015;19(1):180-188.[4]

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Treatment Selection for Younger Patients With Metastatic Colorectal Cancer

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Most younger patients with colorectal cancer are otherwise fairly healthy and can tolerate aggressive chemotherapy. When selecting the most appropriate treatment options in younger patients with early-onset metastatic colorectal cancer, the first aspects to consider are the goals of treatment. The overall goal of treatment is to prolong the patient's survival to the greatest extent possible, while ensuring that he or she lives as well as possible.

If a younger patient does not have any contraindications to more aggressive therapy, it is appropriate to initiate treatment with triplet chemotherapy combined with a biologic. This aggressive regimen includes 5-FU, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) plus bevacizumab. When administered correctly—including omitting the 5-FU bolus and allowing flexibility in the dosing according to the patient's side effects—this regimen can usually be tolerated well. In my experience, most

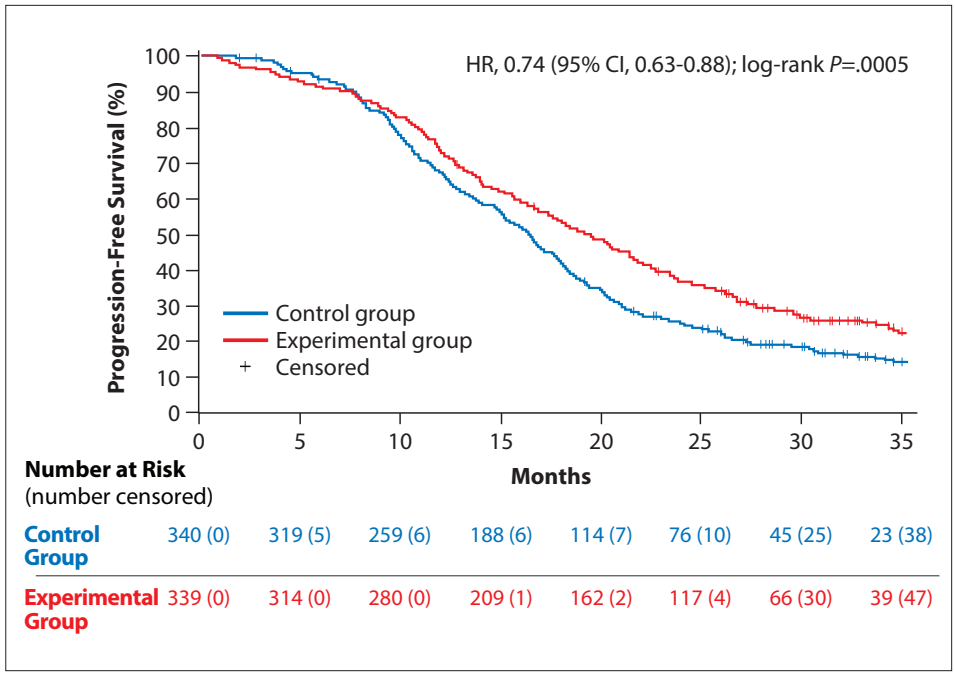

Figure 7. The median progression-free survival 2 in the TRIBE2 trial, which compared first-line FOLFOXIRI plus bevacizumab followed by reintroduction of this regimen upon progression (n=339) vs a sequential strategy of first-line FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab at disease progression. FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, 5-fluorouracil, leucovorin, oxaliplatin, and irinotecan; HR, hazard ratio. Adapted from Cremolini C et al. *Lancet Oncol.* 2020;21(4):497-507.[3]

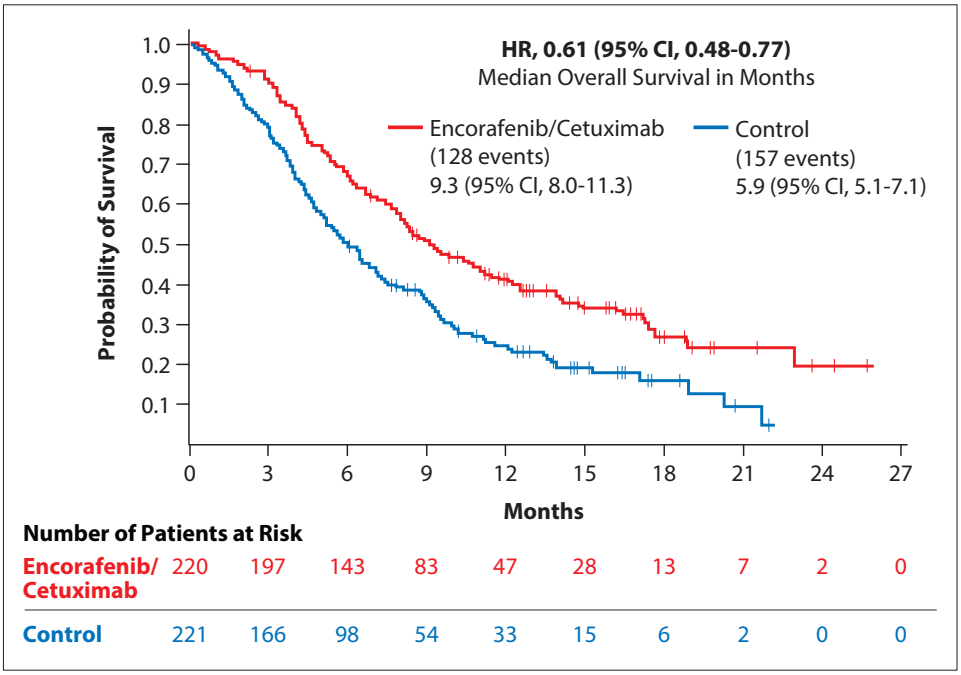

Figure 8. Overall survival among patients treated with encorafenib plus cetuximab vs control regimens in the BEACON trial. HR, hazard ratio. Adapted from Tabernero J et al. *J Clin Oncol.* 2021;39(4):273-284.[5]

younger patients do not require growth factor support (such as pegfilgrastim, filgrastim, or another granulocyte colony–stimulating factor) to maintain their blood counts. In younger patients, the bone marrow tends to be very responsive, and is able to adapt and rebound quickly after this aggressive treatment.

In my practice, I rely on FOLFOXIRI plus bevacizumab as first-line therapy in the majority of younger patients for several reasons. This aggressive regimen was shown to confer a 4-month improvement in overall survival in 2 randomized phase 3 clinical trials.[1-3] The open-label, multicenter phase 3 TRIBE trial enrolled patients with a first occurrence of metastatic disease and an Eastern Cooperative Oncology Group performance status of 0 to 2.[1] The trial randomly assigned patients to treatment with FOLFOXIRI plus bevacizumab (n=252)

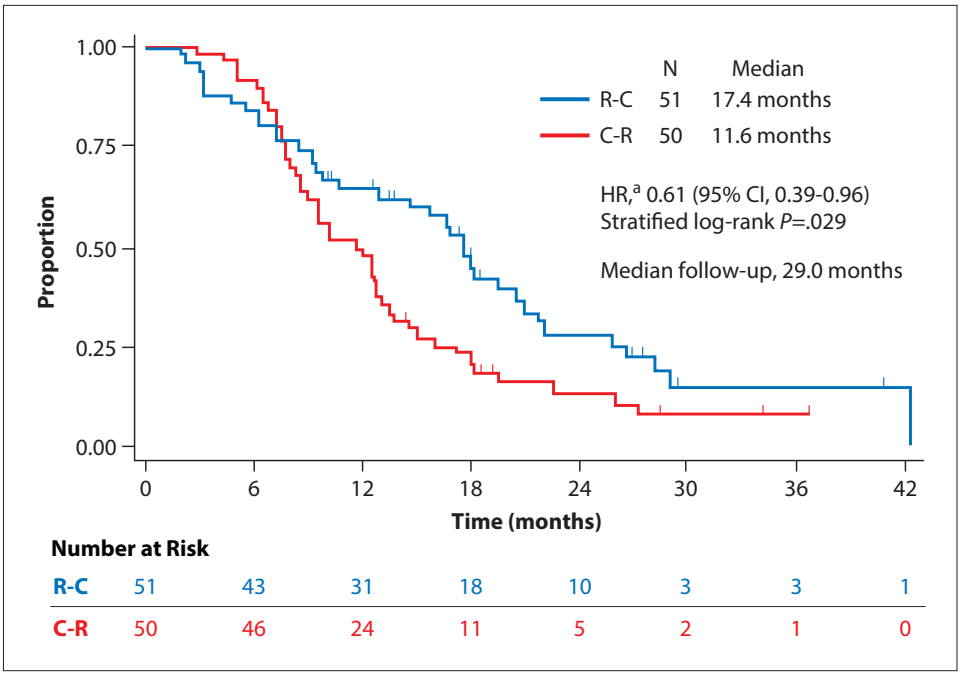

Figure 9. Overall survival in the phase 2 REVERCE trial, which compared the sequence of regorafenib followed by cetuximab (R-C) vs the sequence of cetuximab followed by regorafenib (C-R). [a]Adjusted by intention to use irinotecan. HR, hazard ratio. Adapted from Shitara K et al. *Ann Oncol.* 2019;30(2):259-265.[6]

or leucovorin, 5-FU, and irinotecan (FOLFIRI) plus bevacizumab (n=256). The patients' median age was 60.5 years (range, 52.0-67.5) in the FOLFOXIRI arm and 60.0 years (range, 53.0-67.0) in the FOLFIRI arm. In the primary analysis, FOLFOXIRI plus bevacizumab was associated with a significant improvement in median progression-free survival (12.1 months vs 9.7 months; hazard ratio [HR], 0.75; 95% CI, 0.62-0.90; *P*=.003) and response rate (65% vs 53%; *P*=.006).[1] An updated analysis (median follow-up, 48.1 months; interquartile range [IQR], 41.7-55.6) reported a significant median overall survival benefit with FOLFOXIRI plus bevacizumab vs FOLFIRI plus bevacizumab (29.8 months vs 25.8 months; HR, 0.80; 95% CI, 0.65-0.98; *P*=.03).[2] Patients treated with FOLFOXIRI plus bevacizumab experienced higher rates of toxicity, including grade 3/4 neutropenia, diarrhea, stomatitis, and neurotoxicity.[1]

The open-label, multicenter phase 3 TRIBE2 study compared first-line FOLFOXIRI plus bevacizumab followed by reintroduction of this regimen upon progression (n=339) vs a sequential strategy of first-line FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab at disease progression (n=340).[3] Because this trial was designed to assess the efficacy of the treatment strategy in both the first and second lines of therapy, the primary endpoint was progression-free survival 2 (which was defined as the time from randomization to death or disease progression during any treatment given after the first progression, up to 18 months after the last patient's final visit). At a median follow-up of 35.9 months (IQR, 30.1-41.4), the median progression-free survival 2 was 19.2 months with FOLFOXIRI plus bevacizumab vs 16.4 months with FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab (HR, 0.74; 95% CI, 0.63-0.88; log-rank *P*=.0005; Figure 7). The median overall survival was also significantly prolonged with FOLFOXIRI plus bevacizumab (27.4 months vs 22.5 months; HR, 0.82; 95% CI, 0.68-0.98; *P*=.032).[3]

In my practice, use of this more aggressive regimen upfront has led to some impressive responses; some tumors initially deemed unresectable became resectable. This improvement provides patients with an opportunity for cure when it is possible to resect oligometastatic disease. This important point must be mentioned when discussing first-line therapy with younger patients who have metastatic disease.

Some oncologists have been hesitant to use this triplet regimen, even though it confers a clear survival benefit that surpasses that of other regimens approved for metastatic disease. This hesitancy may arise from a concern that the early use of these active drugs will exhaust later-line options in the event of disease progression. However, the TRIBE2 study demonstrated that it is feasible to reintroduce chemotherapy after a period of maintenance therapy. In most instances, we use FOLFOXIRI plus bevacizumab as induction chemotherapy, administered for approximately 4 months. Usually by this point, the maximal response is observed. Among patients without disease progression, treatment then transitions to maintenance therapy. The maintenance therapy usually consists of 5-FU plus bevacizumab, which allows a much better quality of life. It is not known how long a particular

patient will be able to continue maintenance therapy. On average, most patients receive maintenance treatment for 6 to 8 months, but some can continue maintenance therapy for longer than a year. Maintenance therapy allows the patient to have a break from their aggressive chemotherapy. When the cancer begins to progress, options include reintroduction of FOLFOXIRI plus bevacizumab or a switch to FOLFIRI plus bevacizumab. These treatments lead to good control of the disease and an overall survival benefit.

This aggressive approach is an appropriate strategy for most younger patients with metastatic colorectal cancer. It is necessary to consider the trade-off of more toxicity upfront vs an improvement in survival. It is important to raise these considerations in discussions with the patient. Most younger patients prefer an aggressive approach to treatment.

If the patient opts for a doublet cytotoxic regimen, such as FOLFOX or FOLFIRI with a biologic as first-line therapy, then second-line therapy would consist of the alternate cytotoxic regimen plus a biologic agent. For instance, a patient who started FOLFOX plus bevacizumab in the first-line setting would change to FOLFIRI plus bevacizumab in the second-line setting, and vice versa. It does not matter which doublet cytotoxic regimen is initiated first, as long as the patient receives both regimens during the course of the disease.

Subsequent Lines of Treatment

Selection of subsequent lines of therapy is based on the molecular status of the patient. In patients with *BRAF*-mutated disease, the next line of therapy consists of an epidermal growth factor receptor (EGFR) inhibitor (cetuximab or panitumumab) plus a BRAF inhibitor (eg, encorafenib). This doublet strategy was established in the BEACON trial, in which patients were randomly assigned to receive encorafenib plus cetuximab (doublet-therapy arm), encorafenib plus the MEK inhibitor binimetinib and cetuximab (triplet-therapy arm), or the investigator's choice of either cetuximab and irinotecan or cetuximab and FOLFIRI (control).[4] At the most recent updated analysis, the median overall survival was 9.3 months with encorafenib plus cetuximab vs 5.9 months with the control regimens (HR, 0.61; 95% CI, 0.48-0.77; Figure 8).[5] Grade 3 or higher adverse events were reported in 57% of patients in the doublet-therapy arm compared with 64% of patients in the control arm. Patients randomly assigned to the triplet-therapy arm experienced a similar median overall survival (9.3 months; HR vs control, 0.60; 95% CI, 0.47-0.75) and a higher rate of grade 3 or greater adverse events (66%).

For patients with *KRAS* mutations, the best options in the third-line setting would be a clinical trial for this population or treatment with either regorafenib or trifluridine/tipiracil.

For patients with *BRAF* and *KRAS* wild-type disease, there are data from the REVERCE study suggesting that regorafenib would be the next best treatment after progression on 5-FU, oxaliplatin, irinotecan, and bevacizumab.[6] REVERCE was a phase 2 study that randomly assigned patients with previously treated metastatic colorectal cancer (who were naive to anti-EGFR therapy) to the sequence of regorafenib first followed by cetuximab or cetuximab first followed by regorafenib. The vast majority of patients enrolled in this study had *BRAF* and *RAS* wild-type disease. Patients randomly assigned to receive regorafenib first in the sequence achieved the best outcomes in both progression-free survival and overall survival. The median overall survival was 17.4 months among patients treated with regorafenib first vs 11.6 months in those treated with cetuximab first (HR, 0.61; 95% CI, 0.39-0.96; stratified log-rank P=.0293; Figure 9). The median progression-free survival of the entire sequential treatment was 9.0 months with regorafenib followed by cetuximab vs 7.1 months with cetuximab followed by regorafenib (HR, 0.55; 95% CI, 0.34-0.90; P=.015). In the regorafenib-first arm, grade 3 or higher nonhematologic toxicities were reported in 71% of patients during treatment with regorafenib and in 57% of patients during treatment with cetuximab. In the cetuximab-first arm, grade 3 or higher nonhematologic toxicities were reported in 50% during treatment with cetuximab and in 63% during treatment with regorafenib. Throughout the entire treatment period, quality-of-life scores did not differ significantly between the arms.

This strategy is now under further evaluation in the REVERCE II study, which is collecting more data to confirm the original findings.[7] Until REVERCE II is completed, the REVERCE data provide the best evidence thus far that using regorafenib before cetuximab can improve overall survival for the subset of patients with *BRAF* and *KRAS* wild-type disease.[6]

In patients with *BRAF* and *KRAS* wild-type disease with amplified HER2 expression, a clinical trial with dual HER2-directed therapy is most appropriate. One example is the currently open MOUNTAINEER study, which is evaluating the combination of the conventional anti-HER2 antibody trastuzumab with the novel HER2-directed therapy tucatinib.[8] In an initial report of this study, the combination was well tolerated and met the primary efficacy endpoint of objective response, resulting in a per-protocol expansion of the study.[9]

In my practice, I am always supportive of patients enrolling in clinical trials. Sometimes it can be more difficult for younger patients to participate in clinical trials,

particularly when they have children or are still employed full-time. However, we try to do everything possible to find a clinical trial that can potentially improve their treatment options. We also turn to resources such as the American Cancer Society to help with travel expenses.

Disclosure

Dr Hubbard has performed contracted research with the following companies, with all payments going directly to Mayo Clinic: Boston Biomedical, Effector, Senhwa Biosciences, Merck, Treos Bio, Bayer, Hutchison MediPharma, TRIO, Trovagene, Incyte, and Taiho.

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Considerations in the Management of Younger Patients With Colorectal Cancer: Q&A

Joleen M. Hubbard, MD, Cathy Eng, MD, FACP, FASCO, Chiara Cremolini, MD, PhD, and John L. Marshall, MD

Joleen M. Hubbard, MD The topic of young-adult onset of colorectal cancer is extremely timely. I am seeing a number of younger patients in my clinic with colorectal cancer. Dr Eng, in your discussion, you mentioned a report showing that, on average, patients with colorectal cancer have symptoms 6 months to several years before diagnosis.[1] Patients therefore often present with more advanced disease. What are the most important symptoms that the young adult community should be aware of?

Cathy Eng, MD, FACP, FASCO Education regarding symptoms is important for the general population, as well as for primary care providers and gynecologists. As we all know, guidelines now recommend that screening for colorectal cancer should begin at age 45 years.[2,3] However, most of my patients with early-onset disease are much younger, even in their 20s. These new patients often report symptoms that began years before the diagnosis.

I have several recommendations. First, people should learn about their family history when it is available. Second, people should note any alterations in their bowel habits, whether it is associated pain or any changes in the color, consistency, or regularity of bowel movements, especially if they do not resolve. Symptoms that suggest later-stage disease include discomfort, urgency, and night sweats. Constitutional symptoms may include loss of energy and increased fatigue. Some patients have no symptoms at all, and their diagnosis of colorectal cancer is made after routine blood work taken by their primary care physician shows iron deficiency anemia.

Before a diagnosis of colorectal cancer, patients often attribute their symptoms to other conditions, such as irritable bowel disease or hemorrhoids. People should be aware that when any symptom does not resolve, they should inform their physician, whether a primary care physician, a gynecologist, or another kind.

Joleen M. Hubbard, MD Dr Cremolini, in your section, you discussed the varying degrees of disease aggressiveness in younger adults with colorectal cancer. Do younger patients have worse outcomes than older patients?

Chiara Cremolini, MD, PhD I do not know of any data regarding whether tumors in younger patients are more or less aggressive than in older patients. A recent study showed that younger patients are treated more aggressively,

at least in the early stages of the disease.[4] It is common for younger patients to receive chemotherapy in the adjuvant setting. However, there appears to be no related improvement in the clinical outcome related to this more aggressive treatment.

Joleen M. Hubbard, MD Dr Marshall, how do younger patients appear to tolerate treatment?

John L. Marshall, MD Before treatment begins, most young people are confident that they can handle any adverse events. Then, after a cycle or 2 of treatment, they come in with a long list of complaints about the side effects of treatment. Among the older population—those ages 65 and older—this list is shorter. I do not know whether side effects are in fact less frequent among older patients, or whether these patients are just used to feeling a little off. My interpretation is that younger patients are at a point in life where even minor side effects are disruptive to their daily living. Younger patients must maintain jobs and take care of children. Even the minor side effects of treatments can impact their quality of life. These younger patients report their side effects with the hopes that we can restore normalcy. In contrast, the older population expects that there will be some pain along the way. I doubt that any physiologic differences between younger and older patients impact adverse events.

Joleen M. Hubbard, MD Dr Cremolini, you were the principal investigator of the TRIBE studies, which showed benefit for more aggressive therapy consisting of a triplet cytotoxic agent and a biologic agent upfront.[5,6] Do you think that we should try to reach this level of aggressive treatment in the majority of younger patients?

Chiara Cremolini, MD, PhD This type of analysis of the TRIBE and TRIBE2 trials has not yet been performed.[5,6] An evaluation of patients older than 70 years found that the triplet therapy should be used in only a few selected cases. Investigators will likely evaluate the data specifically in younger patients (<50 years).

My perception is that in the vast majority of cases, younger patients may be able to receive more intensive treatment. We now have robust data supporting the benefit of adding a third cytotoxic agent to the upfront regimen. In most of these patients, or at least those with right-sided disease and/or a *RAS*-mutant tumor, a triplet plus bevacizumab may be the preferred choice.

Joleen M. Hubbard, MD Dr Eng, a common question from younger adults with curable disease concerns lifestyle modifications. What type of diet or physical activities do you recommend?

Cathy Eng, MD, FACP, FASCO The Nurses' Health Study demonstrated the benefits of a healthy diet and exercise for patients with colorectal cancer in general, especially taking into account obesity and the development of early-onset disease.[7] Patients who have been diagnosed with colorectal cancer are at an increased risk for a second primary malignancy.[8] I recommend that patients watch what they eat, follow a nutritious diet, and maintain a healthy weight. A recent analysis of the Nurses' Health Study evaluated obesity, including the change in obesity over time, and the risk of early-onset colorectal cancer among female nurses.[9] Obesity was associated with an increased risk of early-onset colorectal cancer. As compared with women who had gained less than 5.0 kg or had lost weight since the age of 18, the relative risk of early-onset colorectal cancer was 1.65 (95% CI, 0.96-2.81) for those who had gained 20.0 to 39.9 kg and 2.15 (95% CI, 1.01-4.55) for those who had gained 40.0 kg or more (P=.007 for the trend). Some early data have suggested that a high-fat diet is associated with dysbiosis.[10] Dysbiosis may potentially impact the microbiome, contributing to the development of colorectal cancer. It is reasonable to take a baby aspirin every day. Research is evaluating the benefits of vitamin D.[11]

The most important thing is for patients to undergo colonoscopy during the surveillance period. Patients sometimes forget that follow-up colonoscopies are needed every 3 to 5 years until the age of 75.

Joleen M. Hubbard, MD Dr Marshall, what is the role of genetic testing?

John L. Marshall, MD We are clearly underutilizing referrals to our genetic counselors. Most clinicians test for microsatellite instability on nearly every patient, regardless of age. Results from these tests provide insight into whether a patient has an inherited cancer syndrome. However, we are expanding our understanding of the different germlines and inheritable traits beyond just Lynch syndrome. Increasingly, when available, the standard of care is germline testing, preferably performed by genetic counselors. Not all treatment centers have access to genetic counseling. It will fall to oncologists to gain the skills to perform proper testing. Our younger patients deserve broader germline testing, regardless of Lynch syndrome status.

Joleen M. Hubbard, MD What would you recommend for the family members of patients who do not test positive for an inherited syndrome?

John L. Marshall, MD I believe that the current recommendations are naive and reflect the best guess at this

time. The current routine recommendation is that a family member should be screened about 10 years before the patient's age at diagnosis, when there appears to be some increased risk.[12] The issue, however, is that we need simpler screening tests than a colonoscopy. Colonoscopies and fecal occult testing are useful, but they have limitations. I am hoping that in the next decade there will be novel screening tests, perhaps blood-based, that would enable much simpler and broader testing for all patients. These types of tests will transform screening. The current screening modalities are relatively crude, and they do not reflect the variability in the kinds of colon cancers that can develop. I believe that the younger population with colon cancer will drive much of the future research and funding.

Joleen M. Hubbard, MD There is currently an impetus to gain more funding for research to develop better screening methods. Dr Cremolini, are you also seeing an increase in young adults with colorectal cancer in Europe?

Chiara Cremolini, MD, PhD In Europe, we are also seeing an increase in the percentage of cases in young adults. As always happens with this kind of phenomenon in Europe, there is a few years' delay. However, data from European registries clearly show the same trend.[13] In Europe, we are seeing a particular increase in cases of rectal cancer among younger patients. The United States and Europe share similar epidemiologic scenarios.

Cathy Eng, MD, FACP, FASCO Another important consideration for these younger patients is fertility. Fertility should be discussed with the patient before any type of treatment is considered. For example, oxaliplatin has a higher risk of impacting fertility than 5-FU.[14] The patient may benefit from referral to a fertility preservation specialist.

John L. Marshall, MD Adjuvant studies of FOLFOX with or without bevacizumab showed higher rates of infertility and early menopause in the bevacizumab arm.[15]

Joleen M. Hubbard, MD This is another area that should be studied. There are minimal data regarding the risks of oxaliplatin or irinotecan on fertility.

John L. Marshall, MD Many younger patients have rectosigmoid tumors. The ability to avoid pelvic radiation in young women and men would have a huge impact. We hope that studies like PROSPECT will show positive results for a chemotherapy-only neoadjuvant approach.[16]

Cathy Eng, MD, FACP, FASCO Results from this trial are expected in 2022 or 2023. Hopefully, we will have some new information soon. In addition, many younger patients with rectal cancer are considering the watch-and-wait approach, which must be validated in a large trial.

Disclosures

Dr Hubbard has performed contracted research with the following companies, with all payments going directly to Mayo Clinic: Boston Biomedical, Effector, Senhwa Biosciences, Merck, Treos Bio, Bayer, Hutchison MediPharma, TRIO, Trovagene, Incyte, and Taiho. Dr Eng has no conflicts of interest related to this subject matter to report. Dr Cremolini has received honoraria/consultancy fees from Amgen, Bayer, Merck, MSD, Roche, and Servier. She has received research grants from Bayer, Merck, Roche, and Servier. Dr Marshall has received funds from Bayer, Taiho, Ipsen, Caris, Indivumed, Merck, Pfizer, and Daiichi.

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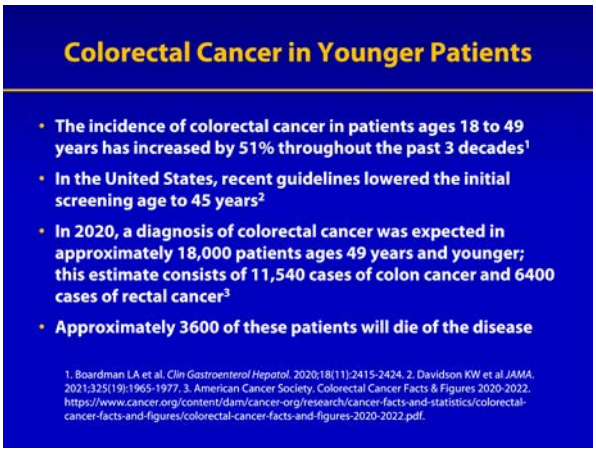

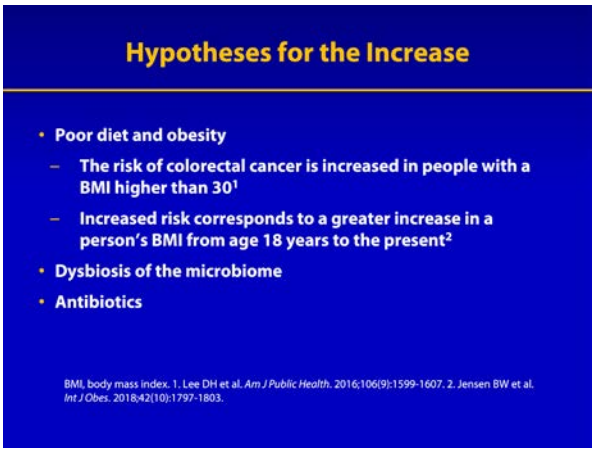

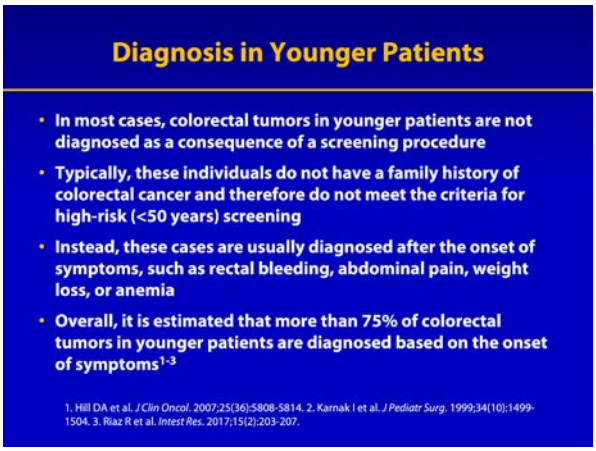

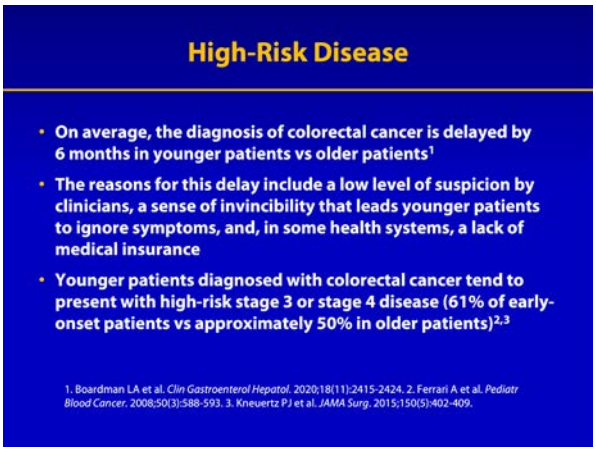

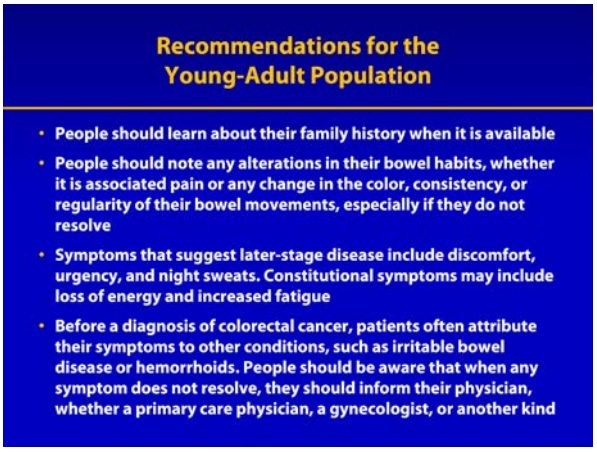

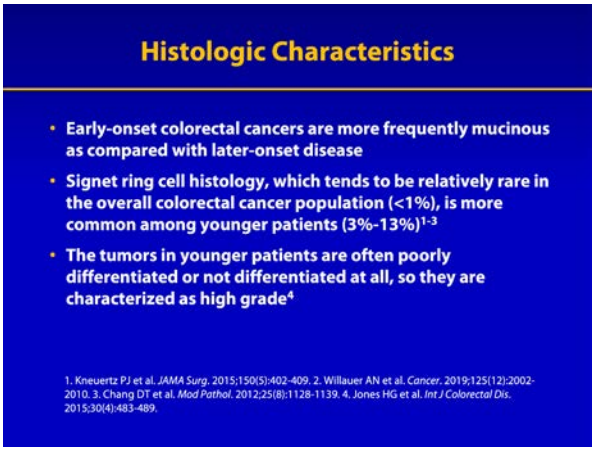

Hereditary Syndromes

- Among younger patients with colorectal cancer, approximately 25% have tumors caused by a germline mutation, and approximately half of these patients have Lynch syndrome[1,2]
- Other hereditary syndromes include familiar adenomatous polyposis and *MUTYH*- and *NTLH1*-associated polyposis
- A small number of younger patients have germline mutations in POLE proofreading domains and Li Fraumeni syndrome, which is caused by the *TP53* germline mutation

POLE, polymerase epsilon. 1. Nguyen LH et al. *JNCI Cancer Spectr*. 2018;2(4):pky073. 2. Hidayat K et al. *Int J Cancer*. 2018;142(4):729-740.

Molecular Characteristics

- There is a higher prevalence of microsatellite instability among early-onset colorectal cancer
- Early-onset colorectal cancers may have a higher incidence of *BRCA* mutations and other alterations affecting genes involved in the homologous recombination system
- Unique features of early-onset colorectal cancers include a high prevalence of LINE-1 hypomethylation and the co-occurrence of microsatellite and chromosomal instability, which is rare among older patients[1]

LINE-1, long interspersed nucleotide element-1. 1. Strum WB, Boland CR. *Dig Dis Sci*. 2019;64(11):3059-3065.

Impact on Younger Patients

- Younger patients tend to have busy lives, often raising children and maintaining a career. In many cases, patients must continue to work because they obtain health insurance through their employer
- Treatment-related adverse events may be more disruptive for younger patients. Even the mild and moderate toxicities of grade 1 or grade 2 that are common with treatments can strongly impact their daily lives
- Younger patients with colorectal cancer are likely to have a higher risk for long-term treatment-related sequelae, particularly because they tend to present with advanced disease[1]

1. Boardman LA et al. *Clin Gastroenterol Hepatol*. 2020;18(11):2415-2424.

Treatment Strategies

- Most younger patients with colorectal cancer are otherwise fairly healthy and can tolerate aggressive chemotherapy
- If a younger patient does not have any contraindications to more aggressive therapy, it is appropriate to consider treatment with triplet chemotherapy combined with a biologic
- It is necessary to consider the trade-off of more toxicity upfront vs an improvement in survival

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