Approach to the Older Patient with Stage II/III Colorectal Cancer: Who Should Get Curative-Intent Therapy?

Erika Ramsdale, MD, Hanna Sanoff, MD, MPH, and Hyman Muss, MD

OVERVIEW

The majority of new colorectal cancer diagnoses occur in adults 65 and older a rapidly growing segment of the U.S. population. Older adults are a markedly heterogeneous group, and although recent clinical trials in locally advanced colorectal cancer have incorporated limited numbers of older patients, the data cannot be generalized to most older patients. In particular, patients who are not “fit”—those with poor functional reserve, major comorbidities, or who otherwise meet criteria for frailty or “prefrailty”—are poorly represented in published trials. Population-based data demonstrate that older adults are much less likely to be treated in the adjuvant or neoadjuvant settings for stage II/III colorectal cancer, but it is unclear what the basis should be for withholding potentially curative therapy. Age and Eastern Cooperative Oncology Group (ECOG) performance status (PS) are frequently used to determine eligibility for treatment, but data increasingly suggest these are inadequate; the emerging definition of a spectrum of “fit” to “frail” older patients may provide additional guidance. Available data suggest that fit older patients may benefit as much from curative-intent therapy as younger patients. For frail or vulnerable (prefrail) patients, on the other hand, the benefit must be carefully weighed against the risk of toxicity and competing risks from their comorbidities. Life expectancy and patient preferences should always be elucidated. Geriatrician comanagement may be helpful in determining priorities, providing a comprehensive assessment, and modifying competing risk factors. Even many vulnerable or frail patients can successfully complete (and derive benefit from) carefully considered treatment regimens.

Colorectal cancer is the second leading cause of cancer deaths in the United States. In 2012, there were approximately 143,000 new cases of colorectal cancer and nearly 52,000 deaths.1 The majority of these cases occurred in older adults: the average age at diagnosis is 69, with 61% of cases diagnosed in those 65 and older, 37% in people 75 and older, and 12% in people 85 and older.1 Furthermore, 70% of colorectal cancer deaths occur in this older age group. These numbers are projected to increase, with an even greater skew toward older age at diagnosis. By 2030, 20% of the U.S. population will be 65 and older, and more than 71% of incident colorectal cases are projected to occur in this age group.2 It is critical that we determine a method for assessing and treating these older patients, particularly those for whom data are very limited (i.e., the very old, the frail, and those with comorbidities).

CLINICAL TRIALS IN THE ELDERLY

Clinical trials data for older adults with cancer are lacking, compared with that available for younger cohorts. It is well-recognized that older adults are underrepresented in investigational trials, as only about 30% of cancer clinical trial participants are 65 and older.3 In colorectal cancer, approximately 40% of phase II and phase III trial participants are older than 65; using an age cutoff of 70 years, the percentage falls to 15%.3-5 One important barrier to recruitment of older adults is the strict exclusion criteria adopted by most clinical trials, which disqualify patients with significant comorbidities (including prior treatment of malignancies), organ dysfunction, or poor PS, criteria that disproportionately exclude older adults. In fact, in one predictive model, relaxation of the exclusion criteria significantly increased the predicted proportion of older trial participants, almost fully eliminating the observed underrepresentation.3 However, other barriers have been documented and should be considered, including physician hesitancy to recommend clinical trials to older adults, lower health literacy in older populations (and therefore more time required to educate and enroll them), and other social and logistical factors, such as decreased social support and concerns about finances and transportation.6-7

Because of these and other barriers, those older adults who do qualify and get enrolled in clinical trials generally represent only the healthiest and most fit subset of their age cohort. Published clinical trials not only fail to note the heterogeneity of the older population, but they also fail to

From the University of Chicago Medical Center, Department of Medicine, Section of Hematology/Oncology, Chicago, IL; Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, Chapel Hill, NC.

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Corresponding author: Hyman Muss, MD, 170 Manning Dr., Campus Box 7305, Chapel Hill, NC 27599; email: muss@med.unc.edu.

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capture the details that are most relevant to older patients, such as low grades of toxicity that may have dramatic effects on the function of older patients. Age, performance status (generally the ECOG PS), and a limited comorbidity assessment are generally included in the demographic data, but physicians interpreting the data may be unsure how it maps onto their complex older patients. There is increasing agreement that age alone is a poor index of overall health and functioning, but other factors that are likely to be more prognostic and predictive are only rarely assessed and reported in trials. ECOG PS is a subjective and insufficient measure of functional status in the elderly, and more descriptive data are needed.8

PHYSIOLOGIC RESERVE: FIT VERSUS FRAIL

One concept that seems apt to better stratify older patients than age is the concept of physiologic reserve, or the ability to compensate in response to stressors. Older patients are dispersed on a wide spectrum, with those who are independent and at low risk for functional decline (i.e., “fit”) on one end, those at high risk for functional decline and death (i.e., “frail”) on the other, and those with varying levels of vulnerability along the spectrum. Assessing fitness in older patients with cancer, in addition to providing a more thorough description of this heterogeneous cohort, may help target potential interventions (e.g., development of treatments specifically for frail individuals) and aid in the development of clinical decision-making tools.9

Given the complex interaction of multiple factors that constitute reserve, the definition and measurement of frailty are still evolving. One tool commonly applied to older patients with cancer (the Balducci frailty criteria) identifies a frail patient as meeting one or more of the following criteria: (1) older than 85, (2) dependence in one or more activities of daily living (ADL), (3) presence of three or more comorbidities, or (4) the presence of one or more geriatric syndromes (e.g., dementia, depression, osteoporosis, falls, incontinence, failure to thrive).10 Another tool validated in older patients with cancer is the Vulnerable Elders Survey-13, a 13-item self-administered questionnaire incorporating overall health status and assessment of the level of difficulty achieving common tasks (e.g., writing, walking a quarter mile, bathing, managing money).11 In community-dwelling older adults, a proposed “frailty phenotype” presents with at least three of the following criteria: unintentional weight loss (≥ 10 pounds in the past year), self-reported exhaustion, weakness (measured by grip strength), slow walking speed, and low physical activity (Fig. 1).12

All three of these assessment tools derive from a more general tool known as the Comprehensive Geriatric Assessment (CGA), a systematic multidisciplinary evaluation of an older adult across multiple domains, including physical functioning, comorbid conditions, cognition, psychological state, social support, and nutritional status.10 This is a powerful tool for describing and stratifying older adults beyond age and ECOG PS, and can be harnessed to help answer several critical questions in older patients with cancer. In addition to classifying patients as fit or frail, it has specifically been used to predict survival outcomes, guide dosing of chemotherapy agents, and predict the risk of chemotherapy toxicity.13-16 The use of a full CGA in routine clinical practice is currently limited by several factors: the time-intensive nature of the assessment, the multiplicity of tools available for each domain of the CGA, and the need for multidisciplinary resources and expertise in interpreting the results. Work is ongoing to produce brief but standardized versions of the CGA for use as clinical decision tools.

KEY POINTS

- The majority of colorectal cancer occurs in older adults (65 or older).
- Clinical trials have generally only included the most “fit” older adults, yielding data that can not be generalized to a heterogeneous older cohort.
- Physiologic reserve, or the ability of the body to compensate in response to stressors, is a useful concept in older adults; criteria have emerged to characterize whether an older patient is “fit,” “frail,” or somewhere in between.
- Fit older patients may benefit as much as younger patients from curative-intent therapy for locally advanced colorectal cancer.
- For frail or vulnerable (“prefrail”) patients, treatment decisions are complex and individualized, but some general recommendations can be derived from the available data and expert consensus.

![Fig 1. Criteria for assessing frailty](image)

Abbreviation: BMI, body mass index.
DETERMINING APPROPRIATE THERAPY IN OLDER PATIENTS WITH COLORECTAL CANCER

Combining the available knowledge from clinical trials with measures that detect vulnerability (“pre frailty”) or overt frailty in older patients with colorectal cancer may provide better guidance for treatment decisions than using age alone. We review possible implications in the treatment of stage II/III colon cancer in the adjuvant setting, and stage II/III rectal cancer in the neoadjuvant and adjuvant settings.

ADJUVANT THERAPY FOR COLON CANCER

Multiple large clinical trials demonstrate that adjuvant fluorouracil monotherapy (i.e., 5-FU/LV or capecitabine) improves survival in stage II and III, although the absolute benefit in stage II is quite small.23,24 A pooled analysis of seven of these adjuvant 5-FU trials (3,351 patients) demonstrated that adults 70 and older (506 patients) derived as much benefit as younger patients for the endpoints of overall survival and time to recurrence, with no excess toxicity.25 A similar survival benefit from adjuvant 5-FU was confirmed in large population-based cohorts of older patients in the SEER-Medicare program.26,27

The addition of oxaliplatin to adjuvant 5-FU (FOLFOX) offers improved disease-free and overall survival for patients with stage III, and possibly high-risk stage II, colon cancer.28 In contrast to the multiple studies supporting similar benefit of adjuvant 5-FU in older patients, mounting evidence suggests that if there is a benefit to the addition of oxaliplatin in older patients with colon cancer, it is small. Subset analyses of the landmark MOSAIC and NSABP C-07 trials found no suggestion of a survival benefit in patients 70 and older for the addition of oxaliplatin (mortality hazard ratio [HR] for MOSAIC 1.10, 95% CI 0.73–1.65; for C-07 1.32, 95% CI 1.03–1.70).29 Disease-free survival was also no better in older patients treated with oxaliplatin/5-FU than in older patients treated with 5-FU. In contrast, a subgroup analysis of the XELOXA trial found no interaction between age and disease-free survival in a regimen adding oxaliplatin to a fluoropyrimidine, though the point estimate in the older subgroup was closer to the null.23,24 A large population-based analysis showed a small improvement in survival from adjuvant oxaliplatin in patients older than 75, but that benefit was marginal.25

Therefore, although the exact role of oxaliplatin in older patients is evolving, there are unequivocal data showing that adjuvant 5-FU improves survival in older patients and is quite well-tolerated. However, despite these data, increasing age is significantly associated with a lower likelihood of receiving any adjuvant chemotherapy. Although 78% of patients younger than age 55 receive adjuvant therapy, only 65% of those 65 to 74, 47% of those 75 to 79, and 24% of those older than 80 are treated.26 Although these may simply represent the most fit among their cohorts, it is unclear how treatment decisions are being made in these patients. Given the lack of interaction between age and benefit of 5-FU in the trials described above, it is clear that factors other than age should determine who should be treated with adjuvant therapy.

A general approach to therapy decisions in older patients with colon cancer for whom adjuvant therapy is indicated, should begin with an assessment of the patient’s life expectancy; tools are available to assist with this.27,28 A healthy, fit 75-year-old man, for example, has a life expectancy of more than 14 years, but a frail 75-year-old man has a life expectancy of only 4.9 years. Most colon cancers will recur within three years, and nearly all patients with recurrences will die within 5 years; in patients with significant competing mortality risks, however, even a 15% improvement in survival may not warrant a six-month course of adjuvant therapy.29

In particular, although mortality risk from the chemotherapy itself is generally quite low, it is associated with adverse effects that may potentiate or be potentiated by comorbidities or other vulnerabilities of the older patient, leading to morbidity or worsened quality of life. For example, peripheral neuropathy is the most common adverse effect from oxaliplatin, which may significantly worsen pre-existing sensory symptoms from diabetes or lumbar stenosis and lead to increased falls and disability.30 In these patients, the small incremental efficacy of oxaliplatin is not worth the risk of debilitating neuropathy.

Attenuated regimens may also be reasonable for older patients who are prefrail or frail. Eliminating the bolus of 5-FU from infusioned regimens may significantly mitigate hematologic toxicity.31 Moreover, some data indicate that three months of adjuvant therapy may be noninferior to six months.31 This is currently being further tested in several large phase III trials, but in the meantime it may be reasonable to truncate therapy in older patients who develop significant adverse events during treatment. Oxaliplatin should not be given to frail patients, nor should it be given to patients with preexisting neuropathy. It should be considered on a case-by-case basis for fit patients, as data for efficacy in older patients are not compelling, and oxaliplatin adds significant potential adverse effects even for the healthiest patients. If oxaliplatin is added to a fluoropyrimidine for fit patients, it should be discontinued if significant toxicity emerges. Figure 2 summarizes a general algorithm for older patients, incorporating these recommendations.

NEOADJUVANT AND ADJUVANT THERAPY FOR RECTAL CANCER

Compared with cancers arising in the colon, cancers arising in the rectum have a higher rate of local recurrence. In addition to adjuvant chemotherapy, therefore, perioperative radiation therapy with 5-FU or capecitabine chemosensitization has been employed to reduce this risk.32,33 Neoadjuvant chemoradiotherapy is the standard of care for locally advanced (T3N0 or TanyN1 and higher) rectal cancer based on the German randomized trial demonstrating that preoperative chemoradiotherapy, incorporating infusional 5-FU and 50.4 Gy radiation therapy in 28 fractions, was superior to...
postoperative chemoradiotherapy with greater compliance, less toxicity, and lower local recurrence; however, a survival benefit was not confirmed. Neoadjuvant chemoradiotherapy is followed by total mesorectal excision and subsequent adjuvant chemotherapy.

Very little data are available to guide therapy in older adults; although the German trial included older patients, subset analyses are not yet available. A population-based study of 1,807 adults 65 and older with stage II or III rectal cancer from the SEER database reported that only 37% received chemoradiotherapy and that increasing age was associated with decreasing odds of treatment. In a small (36 patients) prospective cohort of older adults (70 and older, characterized as either “fit” or “vulnerable” based on comorbidities) with locally advanced rectal cancer who were receiving neoadjuvant chemoradiotherapy, all patients were able to complete full-dose radiation therapy but only 64% were able to complete all chemotherapy. Grade 3 to 4 gastrointestinal was less than 10% in both groups but chemotherapy regimens were not consistent.

Another option for neoadjuvant treatment is short-course radiotherapy, given as 5 Gy over five days without fluoropyrimidine immediately before surgery, as investigated in the Dutch Total Mesorectal Excision (TME) and Swedish Rectal Cancer trials. In a subset analysis of the Dutch TME trial, patients 75 and older had improved response to preoperative radiotherapy compared with younger patients, as well as improved cancer-specific survival which was not evident in the younger cohort. However, complications were increased in older patients (51% vs. 42%, p = 0.008) and were more likely to be fatal; 6-month mortality was increased because of both general (odds ratio [OR] 3.74, p = 0.002) and surgical complications (OR 4.93, p < 0.001) compared with younger patients. Increased mortality from this regimen has been linked to large treatment volumes and is likely mitigated by irradiating limited fields without loss of efficacy.

Although there is expert consensus that older fit patients should be considered for similar neoadjuvant therapy as younger patients, treatment for patients with vulnerability or frailty should be carefully considered based on life expectancy, patient preferences, and logistical issues (for example, willingness/ability to receive daily radiation and to travel to a high-volume cancer center). In addition, the local recurrence risk following modern TME is only 11%. Modern staging techniques can further stratify this risk, identifying a subgroup of patients with an exceptionally low risk of local recurrence.

**FIG 2. Suggested algorithm for the adjuvant treatment of older patients with colorectal cancer.**
recurrence. In those with a lower risk of local recurrence, such as high T3N0 cancers without threatened circumferential margin based on the distance of the tumor from the mesorectal fascia on MRI, careful consideration should be given to whether radiotherapy is necessary.41,42 However, given the catastrophic effect of local recurrence, neoadjuvant radiotherapy should be considered for all older patients with intermediate risk cancers. Adjuvant 5-FU decreases the risk of both local and systemic rectal cancer recurrence.33 The role of adjuvant oxaliplatin is currently being tested in large randomized trials, but given the marginal benefit in older adults with stage III colon cancer, adjuvant 5-FU or capcitabine may be the preferred choice given the substantial added toxicity of a trimodality rectal cancer regimen.

CONCLUSION
The majority of stage II and III colorectal cancers are diagnosed in older adults, but data to guide treatment decisions in this group are still limited. Choosing not to give neoadjuvant or adjuvant therapy to these patients may preclude a chance for cure. Population-based analyses indicate that older adults are far less likely to be given adjuvant therapy compared to younger cohorts. On the other hand, older adults are a heterogeneous population with widely variable levels of physiologic reserve and functional capacity. Treatment may lead to unacceptable levels of toxicity that subvert quality of life or even cause death, and these risks are particularly compelling in frail or vulnerable (prefrail) patients with competing risks for morbidity/mortality. Clearly, the risks of both undertreatment and overtreatment must be carefully weighed.

Before making any treatment decisions in older patients with stage II/III colorectal cancer, life expectancy should be estimated using available tools, and the patient’s goals and preferences should be elicited and discussed. An attempt should be made, in conjunction with life expectancy estimations, to determine the level of frailty, either by applying the criteria listed in Fig. 1, applying the Balducci frailty criteria, or using a screening instrument such as the VES-13. Patients that meet criteria for frailty should be referred to a geriatrician for comprehensive assessment and management of competing risks if the decision is made to pursue therapy.

Figure 2 outlines our recommendations for the adjuvant treatment of colon cancer in older adults, based on the evidence available. Data for the perioperative management of older rectal cancer are much more limited, but evidence suggests that age alone should not be the basis for treatment decisions. To better answer the questions facing oncologists, it is crucial that clinical trials are designed with older adults in mind. More descriptive data (for example, elements of the CGA) should be collected, and trials should be designed to include a more representative range of older adults.

Disclosures of Potential Conflicts of Interest


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