Challenges in the Management of Older Patients With Colon Cancer

Efrat Dotan, MD^a; Ilene Browner, MD^b; Arti Hurria, MD^c; and Crystal Denlinger, MD,^a Philadelphia, Pennsylvania; Baltimore, Maryland; and Duarte, California

Key Words

Colon cancer, elderly, older adults

Abstract

Most patients with colon cancer are older than 65 years. Their treatment poses multiple challenges, because they may have age-related comorbidities, polypharmacy, and physical or physiologic changes associated with older age. These challenges include limited data on the ability to predict tolerance to anticancer therapy and the appropriate use of treatment modalities in the setting of comorbidity and concurrent frailty. The low number of older patients enrolled in large clinical trials results in a paucity of evidence to guide oncologists in the appropriate management of this population. In early-stage disease, clinical dilemmas arise regarding the ability of older patients to undergo successful curative surgical procedures and the risk/benefit ratio of adjuvant chemotherapy. The management of metastatic disease raises questions regarding the clinical benefit of various anticancer therapies and the role of combination therapy with possible increased toxicity in the noncurative setting. Overall, the available evidence shows that fit older patients are able to tolerate treatment and derive similar clinical benefits to younger patients. Limited data are available to guide treatment for less-fit, more-vulnerable older patients. This lack

of data leads to variations in treatment patterns in older adults, making them less likely to receive standard therapies. This review provides an overview of the available data regarding the management of older adults with colon cancer in the adjuvant and metastatic settings. (*JNCCN* 2012;10:213–225)

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From ^aDepartment of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania; ^bThe Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland; and ^cDepartment of Medical Oncology, Cancer and Aging Research Program, City of Hope Comprehensive Cancer Center, Duarte, California.

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Correspondence: Efrat Dotan, MD, 333 Cottman Avenue, Philadelphia, PA 19111. E-mail: Efrat.Dotan@fccc.edu

EDITOR

Kerrin M. Green, MA, Assistant Managing Editor, *Journal of the National Comprehensive Cancer Network*

Disclosure: Kerrin M. Green, MA, has disclosed no relevant financial relationships.

AUTHORS AND CREDENTIALS

Efrat Dotan, MD, Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Disclosure: Efrat Dotan, MD, has disclosed no relevant financial relationships.

Ilene Browner, MD, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

Disclosure: Ilene Browner, MD, has disclosed no relevant financial relationships.

Arti Hurria, MD, Department of Medical Oncology, Cancer and Aging Research Program, City of Hope Comprehensive Cancer Center, Duarte, California

Disclosure: Arti Hurria, MD, has disclosed the following relevant financial relationships: Participated in research for: GlaxoSmithKline; Celgene Corporation; Abraxis Oncology. Participated on the advisory board for: GTX.

Crystal Denlinger, MD, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Disclosure: Crystal Denlinger, MD, has disclosed no relevant financial relationships.

CME AUTHOR

Charles P. Vega, MD, Health Sciences Clinical Professor; Residency Director, Department of Family Medicine, University of California, Irvine

Disclosure: Charles P. Vega, MD, has disclosed no relevant financial relationships.

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Analyze colon cancer outcomes among older adults
- Evaluate the use of adjuvant 5-fluorouracil among older adults with colon cancer
- Assess other chemotherapy agents for the treatment of colon cancer among older adults
- Analyze surveillance for colon cancer recurrence among older adults

The field of geriatric oncology is rapidly growing as the average age of the U.S. population steadily rises and the number of older patients diagnosed with cancer continues to increase. Estimates show that 20% of the U.S. population will be older than 65 years by 2030 and that 70% of cancers will occur in this population.^{1,2} Cancer is the leading cause of death among older men and women aged 60 to 79 years.³ Colon cancer, in particular, is commonly seen in older patients, with a median age at diagnosis of 71 years and 40% of cases diagnosed in patients older than 75 years.⁴ The probability of developing colon cancer is 1 in 22 for men and 1 in 24 for women older than 70 years, compared with 1 in 67 for men and 1 in 94 for women aged 60 to 69 years.³ Thus, oncologists should anticipate treating increasing numbers of older patients with colon cancer in the future.

Despite this large and growing patient population, older patients have traditionally been underrepresented in prospective randomized clinical trials, possibly because of eligibility criteria that specify performance status and comorbidity requirements. Hutchins et al.⁵ compared the proportion of patients older than 65 years with each type of cancer enrolled in SWOG trials versus the proportion of older patients in the general U.S. population with the same disease. Only 40% of patients with colon cancer enrolled in clinical trials were older than 65 years, whereas more than 70% of patients with colon cancer in the general U.S. population surpassed this age limit. More recently, similar results were shown in evaluations of enrollment of older oncology patients in NCI-sponsored phase II and III studies and in FDA

cancer drug registration studies.⁶⁻⁸ These low rates make it difficult to practice evidence-based medicine while treating geriatric patients with cancer.

Challenges in the Management of Older Oncology Patients

Predicting Life Expectancy and Benefit of Treatment

The management of older patients with colon cancer must be tailored to the patient's overall functional status, life expectancy, risk of cancer- and treatment-related morbidity, competing comorbidities, and desire to receive therapy. In 2006, the CDC estimated the average life expectancy for 65-year-old men and women to be 17.0 and 19.7 years, respectively; and for 75-year-old men or women to be 10.4 and 12.3 years, respectively.⁹ Walter and Covinsky¹⁰ developed a life expectancy estimate according to which 25% of 70-year-old men have a life expectancy of an additional 18 years, 50% have an additional 12 years, and 25% have an additional 7 years.¹⁰

In older patients with early-stage colorectal cancer, life expectancy was strongly associated with age and burden of chronic illness in a large retrospective cohort study.¹¹ In this study, the presence of 3 or more chronic conditions resulted in a decrease in life expectancy of approximately 12 years in a 67-year-old man. A similar trend was noted in women and in patients 81 years of age. In another study by the same group, data from more than 29,000 older patients with early-stage colorectal cancer were examined for effect of comorbid conditions on survival.¹² The study confirmed the effect of comorbid conditions on 5-year survival in patients with early-stage colorectal, wherein patients with stage I cancer and no chronic comorbidities had a 5-year survival rate of approximately 78% compared with 50% among patients with 2 or more chronic comorbidities.

The aging process results in physiologic decline in vital organ function, which can directly affect chemotherapy tolerance. However, it is becoming evident that advanced age alone should not preclude patients from receiving standard anticancer therapy and that the patient's biologic age rather than their chronologic age should guide treatment decisions. Studies have shown that medically fit older patients can tolerate commonly used chemotherapy regimens as well as younger patients when provided along with adequate supportive care.¹³ Data from 460 patients in the prospective Pre-

operative Assessment of Cancer in the Elderly (PACE) study found that those with a limited performance status (defined by an ECOG performance status of 2 to 4, abnormal activities of daily living, and dependence in instrumental activities of daily living [IADL]) at baseline had a lower tolerance to surgery and chemotherapy and inferior clinical outcomes compared with younger patients.¹⁴ A multivariate analysis showed increased surgical morbidity among patients with an ECOG performance status of 2 to 4, dependency IADL, or a high score in the Brief Fatigue Inventory.

The Geriatric Assessment

Multiple tools have been developed to evaluate frailty in older patients. The comprehensive geriatric assessment (CGA) is a multidisciplinary evaluation of a patient's functional status, comorbidities, psychological state, social support, cognitive function, and nutritional status.¹⁵ However, incorporation of the CGA into a busy oncology practice is hindered by the amount of time required to complete this assessment. Given the need to simplify the geriatric assessment, research is ongoing to develop a simple screening tool to identify older patients who would benefit from a more thorough geriatric assessment such as the CGA.^{15–19} Available tools include the Vulnerable Elders Survey (VES-13), which has been adopted as the official screening tool for older patients by the EORTC, and has a sensitivity and specificity for detecting disabilities of 87% and 62%, respectively.^{17,20} Compared with the VES-13 scale, ECOG performance status evaluation was found to have similar ability to predict for abnormalities on a CGA.²¹ The development of simplified scales will allow oncologists to place patients on a fitness scale between “fit” (good performance status, limited comorbidities or geriatric syndromes) and “frail” (poor performance status, multiple comorbidities or geriatric syndromes). Fit patients have increased risk of morbidity or mortality from their cancer. Frail patients, who have limited life expectancy because of other medical conditions, are more likely to experience morbidity and mortality from other comorbidities than from their cancer. The treatment approach of patients in these 2 categories differs, with more aggressive treatment for fit patients and more conservative therapies for frail patients. Taking the differing outcomes of these groups into account, the patient and oncologist can develop a treatment plan in a shared decision-making process

that incorporates physical and physiological considerations, cancer- and comorbidity-related outcomes, and the patient's health and treatment goals.

Considerations in the Treatment of Early-Stage Colon Cancer in Older Patients

Curative Surgery

Available evidence suggests that fit older patients can benefit from curative surgical management.^{22,23} Despite surgery being the primary intervention for treatment of early-stage colon cancer, a large retrospective review of 28 studies, including more than 34,000 patients, found that older patients are less likely to be offered curative surgery for colon cancer than their younger counterparts.²⁴ This disparity in treatment occurs despite multiple retrospective studies showing the safety and tolerability of surgery in older adults, even those older than 80 years.^{22,23,25} The risk of increased postsurgical morbidity in older patients has been debated in the literature and is related to surgical expertise and patient selection. This risk increases with the presence of comorbidities and with urgent surgical procedures.^{22,24} Laparoscopic procedures offer minimally invasive treatment approaches for older patients and are associated with significantly less morbidity.²⁶ A thorough preoperative assessment using tools such as the PACE scale¹⁴ and performing surgery on an elective (rather than emergent) basis can optimize treatment outcomes.

Adjuvant 5-Fluorouracil Chemotherapy

The percentage of older patients receiving chemotherapy in the adjuvant setting for stage II/III colon cancer is lower than among younger patients. One report found that 78% of patients younger than 55 years, 47% of patients aged 75 to 79 years, and 24% of patients older than 80 years with stage III colon cancer received adjuvant chemotherapy.²⁷ Similar percentages were seen in a SEER Medicare population-based analysis of patients with stage III colon cancer.²⁸ In this analysis, the documented survival of patients aged 75 to 84 years with early-stage disease was sufficient to warrant consideration of adjuvant chemotherapy. Because cancer was found to be the primary cause of death in this population, adjuvant therapy is likely to improve disease outcomes.

The lower rates of adjuvant therapy use among older patients with colon cancer might be the result of a diminished desire of both patients and physicians

to pursue adjuvant therapy secondary to a perceived increase in adverse events in this population. In an analysis by Schrag et al.,²⁸ a slight increase in rates of hospitalization for adjuvant 5-fluorouracil (5-FU)–related adverse events was seen with advanced age (7% for patients aged 65–74 years; 9% for those aged 75–79 years; 13% for those aged 85–89 years). Sargent et al.²⁹ performed a pooled analysis of more than 3000 patients from 3 large randomized trials assessing the benefit of 5-FU–based adjuvant chemotherapy over observation. In a subanalysis of 500 patients older than 70 years, an improvement in overall survival (hazard ratio [HR], 0.76; 95% CI, 0.68–0.85) and time to tumor recurrence (HR, 0.68; 95% CI, 0.6–0.76) was seen with adjuvant chemotherapy. In contrast to the data by Schrag et al.,²⁸ no significant increase in adverse events was noted among older patients compared with their younger counterparts, except for increased leukopenia.

Other groups have also shown benefit from 5-FU–based adjuvant chemotherapy in older patients.^{30–32} Jesup et al.³³ studied the use of adjuvant chemotherapy in octogenarians with stage III colon cancer through data from the National Cancer Database between 1990 and 2002. Despite a lower rate of chemotherapy use, the group that received adjuvant therapy derived similar benefit to younger patients in the cohort. Neugut et al.³⁴ studied the optimal duration of adjuvant chemotherapy among more than 1700 older patients with stage III colon cancer, and found a benefit associated with 5 to 7 months of adjuvant therapy with 5-FU (> 1–4 months). Colon cancer–specific mortality nearly doubled for patients treated for 1 to 4 months compared with those treated for 5 to 7 months.

The appropriate modality for administering 5-FU in the adjuvant setting is not clear. In metastatic disease, infusional 5-FU results in higher response rates, longer survival, and less toxicity compared with bolus dosing.^{35,36} Capecitabine was shown to be as effective as bolus-dose 5-FU in the adjuvant setting in a phase III trial.³⁷ However, the trend toward improved disease-free survival that was seen in the intent-to-treat population treated with capecitabine was not maintained in the subgroup analysis of patients older than 70 years.

Older patients with stage II colon cancer pose an even greater treatment dilemma because of the limited data available to guide the management of these patients and the general questionable benefit of adjuvant therapy in this setting. The QUASAR (Quick and Simple and Reliable) group's prospective study

of adjuvant bolus-dose 5-FU in stage II colon cancer evaluated the benefit of single-agent 5-FU. Adjuvant 5-FU in addition to surgery had a 3.6% absolute benefit on overall survival (95% CI, 1.0–6.0). A subgroup analysis suggested a trend toward reduced benefit of therapy in patients older than 70 years (HR, 1.13; 95% CI, 0.74–1.75).³⁸ With this limited overall benefit, adjuvant 5-FU for stage II colon cancer should be evaluated carefully in the older population and reviewed against competing comorbidities and causes of death.

The Role of Oxaliplatin in Adjuvant Therapy

The MOSAIC (Multi-Center International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer) evaluated the combination of oxaliplatin and infusional 5-FU (FOLFOX) versus single-agent infusional 5-FU in the adjuvant setting, establishing FOLFOX as the standard of care for the adjuvant treatment of stage III colon cancer.³⁹ A prespecified subgroup analysis of patients older than 65 years (30% of enrolled patients) did not show a reduction in recurrence risk. The ACCENT (Adjuvant Colon Cancer Endpoints) database, which combines data from 6 large randomized clinical trials in the adjuvant setting, evaluated the benefit of adjuvant oxaliplatin-based therapy in older patients (age > 70 years). No benefit in disease-free or overall survival was seen among older patients with the addition of oxaliplatin to 5-FU for the whole cohort or among patients with stage III disease.⁴⁰ The NO16968 study compared the combination of capecitabine and oxaliplatin with 5-FU and leucovorin in the adjuvant setting, and showed a nonstatistically significant trend toward benefit with the addition of oxaliplatin in patients older than 70 years (HR, 0.87; 95% CI, 0.63–1.18).^{41,42} Based on these reports and the higher rate of toxicity with the addition of oxaliplatin, these regimens are used less frequently in the treatment of older patients with early-stage colon cancer.⁴³ In summary, single-agent 5-FU seems to provide benefit for older patients in the adjuvant setting, mainly those with stage III disease, whereas the benefit from combination chemotherapy with 5-FU and oxaliplatin in the adjuvant setting remains controversial.

Surveillance

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer define a surveillance schedule for patients with early-stage colon

cancer who have completed their curative surgery and chemotherapy treatments (for the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).⁴⁴ This schedule includes periodic physical examination, serial carcinoembryonic antigen monitoring, use of radiographic evaluation in high-risk patients, and surveillance colonoscopy after treatment completion. Four meta-analyses were performed, all showing an improvement in overall survival among patients undergoing intense surveillance.^{45–48} In addition, these analyses showed improvements in the rate of detection of asymptomatic recurrences and an increase in the rate of metastasectomy with curative intent.

The data regarding the use of these guidelines among older colorectal patients are limited. A study by Cooper et al.⁴⁹ found that only 17.2% of patients older than 66 years received follow-up testing at the recommended intervals compared with 60.2% who received testing less frequently. Lack of adherence to guidelines was associated with advancing age and increasing number of comorbidities. Given the improvement in outcomes associated with early detection of recurrence in colon cancer, fit older patients should follow the same surveillance schedule as younger patients with early-stage colon cancer.

Summary

Available data show that surgery, adjuvant chemotherapy, and aggressive surveillance have similar benefit in fit older and younger patients with early-stage colon cancer, although adverse events tend to be more common in older patients. The decision is more complex for frail older patients, for whom a treatment strategy should be determined through a shared decision-making process between the patient and the oncologist. Table 1 summarizes the available evidence regarding management of older patients with early-stage colon cancer. Table 2 summarizes important information on the management of older patients with early-stage colon cancer.

Issues in the Treatment of Metastatic Colon Cancer in Older Patients

Surgical Considerations

Early studies evaluating the surgical resection of liver metastases in colorectal cancer reported an increase in procedure-related complications among older patients. However, overall and disease-free survivals

in older patients compared favorably with those of their younger counterparts.^{50,51} Recently, a large, international, multicenter cohort reported outcomes of more than 7000 liver resections for colorectal metastasis in patients older than 70 years.⁵² Older patients were less likely to receive perioperative chemotherapy and more likely to have limited surgical procedures. The 60-day postoperative mortality rate was higher (3.8% vs. 1.6%; $P < .001$) and the 3-year overall survival rate was lower (57.1% vs. 60.2%; $P < .001$) among older patients compared with younger patients. No difference in overall survival was seen among the subcategories of ages (70–75 years; 75–80 years; > 80 years). Predictors for decreased survival were more than 3 hepatic metastases, presence of extrahepatic disease, and lack of postoperative chemotherapy.

Robertson et al.⁵³ performed a similar analysis on 3957 Medicare enrollees who underwent surgical resection of liver metastases between 2001 and 2004. Rates of 30- and 90-day postoperative mortality were 4.0% and 8.2%, respectively, whereas the 5-year survival rate was 25.5%. Advanced age (≥ 80 years), comorbidities, and synchronous colon and hepatic resection were associated with a worse 90-day mortality rate and decreased overall survival. Based on these data, advanced age should not be viewed as a contraindication for surgical procedures in the metastatic setting, although consideration should be given to patient selection and fitness for surgery.

Chemotherapy in the Metastatic Setting

As with all other treatment modalities, the use of chemotherapy in the metastatic setting must be tailored for each patient and the overall functional status. The use of combination therapy versus monotherapy is an issue of active debate in the management of older patients with metastatic colon cancer. Three phase III studies failed to show any survival benefit from the use of combination chemotherapy as first-line treatment compared with 5-FU monotherapy.^{54–56} With these data in mind, one must carefully weigh the risks and benefits of initiating a potentially toxic combination chemotherapy regimen for the treatment of a noncurative condition. Figer et al.⁵⁷ showed similar toxicity between young and old patients using the OPTIMOX-1 approach of combination chemotherapy treatments alternating with 5-FU monotherapy as maintenance, and suggested this may be a reasonable strategy in some older patients to minimize tox-

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Table 1 Treatment of Early-Stage Colon Cancer Among Older Patients: Summary of Available Data

Treatment	Available Data	Conclusion
Surgery	Older patients are less likely to be offered curative surgeries. Risk of perioperative mortality is dependent on surgical expertise and patient selection. ^{22,24} Laparoscopic approaches may offer a less-invasive treatment with fewer adverse events. ²⁶	Consideration of the biologic rather than the chronologic age is warranted when considering curative surgery for older patients with colon cancer.
Chemotherapy with single-agent 5-fluorouracil (5-FU)	Older patients with early-stage colon cancer are less likely to receive adjuvant chemotherapy despite sufficient long-term survival benefit. ²⁸ Adjuvant single-agent 5-FU has been shown to improve clinical outcomes of older adults with colon cancer, despite increase in hematologic adverse events compared with younger patients. ^{28–33} Stage II: Lack of benefit from adjuvant 5-FU among patients older than 70 years in the QUASAR study. ³⁸	Older patients with a good performance status and adequate life expectancy can benefit from adjuvant therapy with single-agent 5-FU. The benefit for older patients with stage II disease may be more limited.
Chemotherapy with 5-FU + oxaliplatin	Subgroup analyses and large retrospective studies show limited benefit for the addition of oxaliplatin to adjuvant 5-FU for older patients with early-stage colon cancer. ^{39–41}	The addition of oxaliplatin to adjuvant 5-FU is likely to increase toxicity among older patients. The clinical benefit of this approach remains controversial.
Long-term surveillance	Meta-analyses of randomized clinical trials showed improved survival for patients undergoing intensive surveillance after curative treatment for early-stage colon cancer. ^{45–48} Older patients are less-often offered the recommended monitoring schedule after treatment completion. ⁴⁹	Fit older patients with adequate life expectancy should undergo the recommended surveillance schedule after curative treatment of early-stage colon cancer.

icity without compromising benefit.⁵⁷ Quality of life of older patients may also be preserved using the OPTIMOX-2 approach, alternating between treatment and chemotherapy-free intervals, although cancer-related survival outcomes may be lower.⁵⁸

The use of 5-FU-based chemotherapy in the meta-static setting was studied in an analysis of older patients who participated in 22 clinical trials, showing similar benefits in overall survival, overall response rate, and progression-free survival to those seen in younger patients.³⁶ This analysis also showed improvement among

older patients in all these measures with the use of infusional versus bolus 5-FU among older patients. Recently, results of the MRC FOCUS2 (Chemotherapy Options in Elderly and Frail Patients With Metastatic Colorectal Cancer) trial were published, the largest randomized clinical trial reported to date in older patients with metastatic colon cancer.⁵⁹ This study randomized frail and/or older patients with untreated metastatic colon cancer to capecitabine or 5-FU, with or without oxaliplatin, with an initial empiric 20% dose reduction. This study did not show a difference in efficacy

Table 2 Take Home Messages Regarding Management of Older Patients With Early-Stage Colon Cancer

- Age alone should not be a contraindication for curative surgery for early-stage colon cancer. Careful preoperative patient assessment and planning will result in optimal clinical outcomes.
- Relative benefit from adjuvant treatment is similar across age groups; however, absolute benefit of chemotherapy may be smaller because of competing causes of death.
- Older adults derive a relative benefit from 5-fluorouracil-based adjuvant therapy similar to younger patients, with only a slight increase in toxicity, mainly in hematologic toxicities.
- The benefit of oxaliplatin-based therapy in adults older than 70 years is questionable and should be considered on an individual basis.

between capecitabine and 5-FU (progression-free survival: HR, 0.99; 95% CI, 0.82–1.2; $P = .93$; overall survival: HR, 0.96; 95% CI, 0.79–1.17; $P = .71$). In stark contrast to the common perception of capecitabine being a “gentler” therapy option, capecitabine was not associated with improved quality of life compared with 5-FU. Furthermore, treatment with capecitabine was associated with increased adverse events compared with 5-FU. The addition of oxaliplatin at 80% of standard dose to 5-FU or capecitabine resulted in improved response rates (13% vs. 35%; $P < .0001$), a trend toward improvement in progression-free survival that was not statistically significant (HR, 0.84; 95% CI, 0.69–1.01; $P = .07$), and no improvement in overall survival (HR, 0.99; 95% CI, 0.81–1.18; $P = .91$). The rate of grade 3 or higher toxicity was not increased with the addition of oxaliplatin at this lower dose.

Standard-dose FOLFOX in the treatment of older patients with metastatic colon cancer was evaluated in a pooled analysis of more than 3000 patients. Patients older than 70 years constituted only 16% of the study population ($n = 614$) and were found to experience increased rates of hematologic toxicity but similar rates of other toxicities, including neurologic and gastrointestinal adverse events, compared with the younger cohort.⁶⁰ In contrast to the results in the adjuvant setting, the relative benefit of the combination of oxaliplatin and 5-FU or capecitabine did not differ between older and younger patients.^{61,62}

The combination of irinotecan and 5-FU was evaluated in a retrospective analysis of large phase III clinical trials and in phase II studies, which all showed a clinical benefit associated with this combination among older patients.^{63,64} Mild increases in the rates of hematologic and gastrointestinal adverse events were noted among the older patient population. The ongoing phase III FFCD 2001-02 trial is evaluating this combination formally in patients aged 75 years or older. A preliminary report of the study verified that the combination is safe in older adults with manageable toxicities.⁶⁵ Table 3 summarizes important information on the management of older patients with metastatic colon cancer.

The Use of Biologic Agents in the Older Population

Bevacizumab

The addition of the vascular endothelial growth factor antibody bevacizumab has been shown to improve progression-free and overall survivals among patients with metastatic colon cancer in large phase III randomized clinical trials.^{66,67} Two large observational studies performed after the drug’s approval have reported data on the use of bevacizumab in older patients. The Bevacizumab Expanded Access Trial (BEAT) showed similar clinical outcomes between

Table 3 Take Home Messages Regarding Management of Older Patients With Metastatic Colon Cancer

- Age alone should not be a contraindication for surgical resection of solitary liver metastasis from colon cancer, yet the risk of perioperative morbidity is higher among older patients.
- The use of an OPTIMOX-1 or -2 strategy (combination chemotherapy alternating with 5-fluorouracil monotherapy treatment or chemotherapy-free intervals, respectively) is a preferred treatment strategy among older patients.
- Older adults, compared with younger adults, derive a similar relative benefit from the approved agents for treatment of metastatic colon cancer, with potentially increased rates of adverse events.

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young and old patients.⁶⁸ The BRiTE (Bevacizumab Regimens Investigation of Treatment Effects) study included 1953 patients with metastatic colon cancer, of which 45% were older than 65 years and 18% were older than 75 years.⁶⁹ Progression-free survival in the older patients was found to be similar to that reported for younger patients in the phase III registration trials. Two pooled analyses of phase II and III randomized clinical trials reported improved progression-free survival (HR, 0.58; 95% CI, 0.49–0.68 and HR, 0.52; 95% CI, 0.40–0.67, respectively) and overall survival (HR, 0.85; 95% CI, 0.74–0.97, and HR, 0.70; 95% CI, 0.55–0.90, respectively) with the addition of bevacizumab to standard chemotherapy in patients older than 65 and 70 years, similar to results seen in younger patients.^{70,71} One prospective phase II study evaluated the use of 5-FU with or without bevacizumab among 168 frail patients older than 65 years who were not candidates for combination chemotherapy. The addition of bevacizumab to 5-FU resulted in a statistically significant increase in progression-free survival (5.5 vs. 9.2 months; $P = .0002$) and a nonsignificant improvement in median overall survival (12.9 vs. 16.6 months; $P = .16$).⁷²

Despite these data, bevacizumab is used in only approximately one-third of the older patient population.⁷³ This finding is likely related to concerns about increased adverse events with bevacizumab in this high-risk population. The studies mentioned earlier report an overall increase in arterial thromboembolic events among older patients.^{68,70,74,75} This increase was most pronounced in patients older than 75 years, for whom the risk was increased by 2.5- to 3-fold. Conversely, the incidence of other adverse events, such as gastrointestinal perforation, venous thromboembolic events, hypertension, and bleeding, did not increase with increasing age in these analyses.^{68,70,71,74}

Cetuximab/Panitumumab

The data regarding the use of anti-epidermal growth factor receptor (EGFR) therapy in older patients are limited. Studies conducted with anti-EGFR agents (cetuximab and panitumumab) report mixed efficacy results in subgroup analyses of patients older than 65 years. For example, the PRIME study (Panitumumab Randomized Trial in Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy), which showed improved clinical outcomes with the combination of FOLFOX

and panitumumab, failed to show this same benefit in the subgroup of patients older than 65 years ($n = 261$; progression-free survival: HR, 1.02; 95% CI, 0.75–1.38; and overall survival: HR, 0.81; 95% CI, 0.59–1.11).⁷⁶ In contrast, a retrospective report by Bouchahda et al.⁷⁷ evaluated a small number ($n = 56$) of older patients (median age, 76 years) treated with cetuximab and reported no increased incidence of adverse events and similar efficacy compared with younger patients. The same group reported slightly higher toxicity and similar clinical outcomes among older patients (age > 70 years) treated with cetuximab alone or in combination with irinotecan or 5-FU compared with their younger counterparts.⁷⁸ Conversely, Gravalos et al.⁷⁹ did not find any increase in toxicity rates with the combination of cetuximab and capecitabine in 66 patients aged 70 years and older with metastatic colon cancer. Additional studies are needed to clarify the efficacy of these agents in this patient population.

Summary

Treatment of older patients with metastatic colon cancer requires careful consideration and an informed discussion between the patient and the oncologist. Overall, the data show clinical benefit at the expense of increased toxicities when the approved agents are used in the older population. The risk/benefit ratio of therapy in this noncurative setting must be considered before treatment initiation. Table 4 summarizes the available evidence for using approved therapies for metastatic colon cancer in the older population. Table 5 summarizes important information on the use of targeted therapy in the management of older patients with metastatic colon cancer.

Conclusions

The treatment of older patients with colon cancer is challenging and requires careful consideration of multiple factors by the treating oncologist. Overall, fit older patients should be offered all appropriate treatment modalities for the management of colon cancer in the early and advanced settings. Careful evaluation, with the use of geriatric assessment tools, will enable the oncologist to identify patients with comorbidities or functional decline. Ongoing stud-

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Table 4 Treatment of Metastatic Colorectal Cancer Among Older Patients: Summary of Available Data

Setting	Treatment	Available Data	Conclusion
Solitary metastasis	Surgery	Retrospective analyses showed increased rates of postoperative morbidity and mortality among older patients undergoing hepatic resection. Increased risk was seen among patients with > 3 liver lesions, extrahepatic disease, comorbidities, and lack of postoperative chemotherapy. ^{52,53}	Surgical resection of liver metastasis can be considered a therapeutic option for fit older patients with limited comorbidities.
Systemic metastatic disease	Concurrent vs. sequential therapy	Large randomized clinical trials failed to report a survival advantage from the use of combination chemotherapy compared with single-agent treatment. ^{54–56} Intermittent use of combination therapy (OPTIMOX strategy) has been shown to be favorable among older patients. ^{57,58}	Careful assessment of the risk/benefit ratio for using combination chemotherapy in the treatment of older patients with mCRC. OPTIMOX-1 or -2 may be a reasonable strategy among older patients.
	Single-agent chemotherapy (5-FU)	Retrospective analysis demonstrates similar benefit in terms of OS, RR, and PFS among older patients with metastatic disease treated with single-agent 5-FU to that seen among younger patients. ³⁶ The use of capecitabine is associated with increased toxicity when used in frail older patients. ⁵⁹	Single-agent 5-FU can improve clinical outcomes of older patients with mCRC.
	Combination chemotherapy	The addition of oxaliplatin or irinotecan to 5-FU for the treatment of older patients with mCRC results in increased frequency of adverse events. ^{60,63} Most reports show clinical improvement, similar to that seen in younger patients, with the use of combination chemotherapy in the metastatic setting. ^{59,61,62,64}	Fit older patients with metastatic colon cancer can be considered for combination chemotherapy. Close monitoring is required because of increased risk for adverse events.
	Bevacizumab (anti-VEGF antibody)	Improved PFS and OS among older patients with mCRC treated with bevacizumab. Increased incidence of arterial thrombotic events among older patients, mainly in those older than 75 years. ^{68,70–72,75}	Bevacizumab should be offered to appropriate older patients with mCRC with combination chemotherapy or single-agent 5-FU. Cardiac evaluation of patients at high risk may be warranted.
	Cetuximab/panitumumab (anti-EGFR antibody)	Subgroup analyses from large randomized clinical trials fail to show a benefit to the addition of these agents to combination chemotherapy among older patients. ⁷⁶ The limited data available report good tolerance of these agents among older patients. ^{77–79}	Limited data are available regarding the efficacy of anti-EGFR antibody for older patients with mCRC.

Abbreviations: 5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression-free survival; RR, response rate; VEGF, vascular endothelial growth factor.

Table 5 Take Home Messages Regarding the Use of Targeted Therapy in the Management of Older Patients With Metastatic Colon Cancer

- Older patients derive similar clinical benefit from the use of bevacizumab in the metastatic setting as younger patients, with higher rate of toxicities, mainly arterial thromboembolic events.
- Data regarding the use of anti-epidermal growth factor receptor therapy among older patients are limited; retrospective analyses show an acceptable toxicity profile.

ies are evaluating how to use these tools to specifically tailor therapy to the patient's overall condition. Despite the large number of older patients with colon cancer, they represent a minority of patients enrolled in clinical trials. The recently published results of the MRC FOCUS2 study have shown that studies targeting older frail patients are feasible and provide clinically relevant information.⁵⁹ The ongoing NCCTG (North Central Cancer Treatment Group) N0949 trial is evaluating the use of 5-FU/capecitabine and bevacizumab with or without oxaliplatin for the management of older patients (age $\geq$ 70 years) with metastatic colon cancer. It also incorporates a geriatric assessment to identify older adults at risk for toxicity. Additional clinical trials targeting the older patient population are desperately needed to enhance understanding of the optimal management of older patients with colon cancer.

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- Your patient is a 75-year-old, otherwise healthy woman who was recently diagnosed with stage III colon cancer. On the basis of the current review by Dotan and colleagues, what can you tell this patient regarding her treatment and prognosis?
 - Older adults with colon cancer have no difference in life expectancy compared with younger adults
 - Chronic disease has no effect on the risk for mortality related to colon cancer**
 - In general, patient functional status should not be part of the decision about how to treat colon cancer
 - She is less likely to receive adjuvant chemotherapy for her cancer compared with a younger patient
- The patient undergoes surgical resection. What should you consider regarding adjuvant treatment with 5-fluorouracil for this patient?
 - Adjuvant treatment with 5-fluorouracil promotes a dramatic increase in the risk for adverse events in older vs. younger adults
 - Treatment for 5–7 months may improve cancer-specific mortality compared with treatment for 1–2 months**
 - 5-fluorouracil improves survival to a higher degree among older vs younger adults
 - 5-fluorouracil is associated with a lower risk for leukopenia among older vs younger adults
- What else should you consider regarding adjuvant treatment for this patient?**
 - Bevacizumab can improve survival outcomes
 - Oxaliplatin has emerged as the adjuvant treatment of choice
 - Older adults should not receive intermittent combination chemotherapy**
 - Biologic agents are generally unsafe to use among older adults
- The patient enters remission after treatment. What should you consider regarding cancer surveillance for this patient?
 - Older age has no effect on the rate of intensive surveillance
 - A higher number of comorbidities has no effect on the rate of intensive surveillance
 - She should receive intensive surveillance, even if she develops other major medical illness
 - Intensive surveillance can improve overall survival

Activity Evaluation

1. The activity supported the learning objectives. Strongly Disagree Strongly Agree 1 2 3 4 5	3. The content learned from this activity will impact my practice. Strongly Disagree Strongly Agree 1 2 3 4 5
2. The material was organized clearly for learning to occur. Strongly Disagree Strongly Agree 1 2 3 4 5	4. The activity was presented objectively and free of commercial bias. Strongly Disagree Strongly Agree 1 2 3 4 5

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