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Challenges in the Management of Older Patients with Colon Cancer

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Abstract

The majority of patients with colon cancer are over the age of 65. Their treatment poses multiple challenges to the oncologist, as these patients 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 anti-cancer therapy and the appropriate use of treatment modalities in the setting of comorbidity and concurrent frailty. The low number of older patients enrolled on large clinical trials results in a paucity of evidence to guide the oncologist 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 anti-cancer therapies and the role of combination therapy with possible increased toxicity in the non-curative setting. Overall, the available evidence demonstrates that fit older patients are able to tolerate treatment and derive similar clinical benefits as 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 will provide an overview of the available data regarding the management of older adults with colon cancer in the adjuvant and metastatic settings.

Keywords

Colon cancer; Elderly; Older Adults

Introduction

The field of geriatric oncology is rapidly growing as the average age of the US population steadily rises and the number of older patients diagnosed with cancer continues to increase. It is estimated that 20% of the US population will be older than 65 years of age 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 60-79 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 over the age of 75 [4]. The probability for developing colon cancer is 1 in 22 for men and 1 in 24 for women over the age of 70, compared with 1 in 67

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for men and 1 in 94 for women aged 60-69 [3]. Thus, oncologists should anticipate treating increasing numbers of older patients with colon cancer in the coming years.

Despite this large and growing patient population, older patients have traditionally been underrepresented in prospective randomized clinical trials, possibly due to eligibility criteria that specify performance status and comorbidity requirements. Hutchins et al. compared the proportion of patients with each type of cancer over the age of 65 enrolled on Southwest Oncology Group (SWOG) trials to the proportion of older patients with the same disease in the general US population [5]. Only 40% of patients with colon cancer enrolled on clinical trials were over the age of 65 while over 70% of patients with colon cancer in the general US population surpassed this age limit. More recently, similar results were demonstrated in evaluations of enrollment of older oncology patients in National Cancer Institute (NCI) sponsored phase II and III studies and in US Food and Drug Administration cancer drug registration studies [6-8]. These low rates make it difficult to practice evidence-based medicine while treating geriatric cancer patients.

Challenges in the Management of Older Oncology Patients

Predicting Life Expectancy and Benefit of Treatment

The management of older colon cancer patients 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 Centers for Disease Control (CDC) estimated the average life expectancy for a 65-year-old man and woman to be 17.0 and 19.7 years, respectively; and for a 75-year-old man or woman at 10.4 and 12.3 years, respectively [9]. Walter and Covinsky 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 three or more chronic conditions resulted in a decrease in life expectancy of approximately twelve 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 over 29,000 older patients with early stage colorectal cancer was examined for effect of comorbid conditions on survival [12]. The study confirmed the effect of comorbid conditions on 5 year survival of patients with early stage colorectal, whereby, the 5 year survival of a patient with stage 1 cancer with no chronic comorbidities was approximately 78% compared to 50% for patients with two 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 anti-cancer 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 with adequate supportive care [13]. Data from the prospective PACE study of 460 older cancer patients found that patients with a limited performance status (defined by Eastern Cooperative Group (ECOG) performance status 2-4, abnormal activity of daily living (ADL) and instrumental activities of daily living (IADL)) at baseline had a lower tolerance to surgery and chemotherapy and inferior clinical outcomes compared to younger patients [14]. A multivariate analysis revealed increased surgical morbidity among patients with an ECOG performance status 2-4, dependency IADL., or a high score in the Brief Fatigue Inventory (BFI).

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, the incorporation of the CGA into a busy oncology practice is hindered by the amount of time required for completion of this assessment. Given the need to simplify the geriatric assessment, research is ongoing to develop a simple screening tool to identify those older patients that would benefit from a more thorough geriatric assessment such as the CGA [15-19]. Such available tools include the Vulnerable Elders Survey (VES-13) which has been adopted as the official screening tool for older patients by the European Organization for Research and Treatment of Cancer (EORTC), with a sensitivity and specificity for detecting disabilities of 87% and 62% respectively [17, 20]. In comparison to the VES-13 scale, ECOG performance status evaluation was found to have similar ability to predict for abnormalities in CGA [21]. The development of simplified scales will enable oncologists to place the patient on a “Fitness” scale between: “Fit” (good performance status, limited comorbidities or geriatric syndromes) or “Frail” (poor performance status, multiple comorbidities or geriatric syndromes). ”Fit” patients are at increased risk of morbidity or mortality from their cancer. ”Frail” patients, with limited life expectancy due to other medical conditions, are more likely to experience morbidity and mortality from other comorbidities rather than their cancer. The treatment approach of patients in these two categories differs, with more aggressive treatment for “Fit” patients and more conservative therapies for “Frail” patients. Taking the differing outcomes of these two groups into account, the patient and the oncologist can develop a treatment plan in a shared decision process that incorporates physical and physiological considerations, cancer- and comorbidities-related outcomes, and the patient's health and treatment goals.

Considerations in the Treatment of Early Stage Colon Cancer

Curative Surgery in the Older Population

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 over 34,000 patients found that older patients are less likely to be offered curative surgery for colon cancer compared to their younger counterparts [24]. This disparity in treatment occurs despite multiple retrospective studies demonstrating the safety and tolerability of surgery in older adults, even those over 80 years of age [22, 23, 25]. The risk of increased post-surgical 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 pre-operative assessment using tools such as the PACE scale [14] and performing surgery on an elective (rather than emergent) basis can optimize treatment outcomes.

Adjuvant 5-Fluorouracil (5FU) chemotherapy

The percentage of older patients receiving chemotherapy in the adjuvant setting for stage II/III colon cancer is lower compared with their younger counterparts. One report found that 78% of patients under 55 years of age, 47% of patients aged 75-79 years and 24% of patients older than 80 years with stage III colon cancer received adjuvant chemotherapy [27]. Similar percentages were seen in a Surveillance, Epidemiology and End Result (SEER) Medicare population-based analysis of stage III colon cancer patients [28]. In this analysis,

the documented survival of patients aged 75-84 years with early stage disease was sufficient to warrant consideration for adjuvant chemotherapy. Since 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 colon cancer patients might be a result of a diminished desire in 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., a slight increase in rates of hospitalization for adjuvant 5FU-related adverse events was seen with advanced age (7% for 65-74 year old patient; 9% for 75-79 year old patients; 13% for 85-89 year old patients) [28]. Sargent and colleagues performed a pooled analysis of over 3,000 patients from 3 large randomized trials assessing the benefit of 5FU-based adjuvant chemotherapy over observation [29]. In a sub-analysis of 500 patients over the age of 70, an improvement in overall survival (OS) (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., no significant increase in adverse events was noted among older patients compared to their younger counterparts except for increased leukopenia.

Benefit from 5FU-based adjuvant chemotherapy for older patients has also been demonstrated by other groups [30-32]. Jessup and colleagues studied the use of adjuvant chemotherapy for octogenarians with stage III colon cancer through data from the National Cancer Database between 1990 and 2002 [33]. Despite a lower rate of chemotherapy use, the group that received adjuvant therapy derived similar benefit to that seen among younger patients in the cohort. Neugut et al. studied the optimal duration of adjuvant chemotherapy among over 1,700 older patients with stage III colon cancer [34]. The study demonstrated a benefit of 5-7 months of adjuvant therapy with 5FU (over 1-4 months). Colon cancer-specific mortality nearly doubled for patients treated for 1-4 months compared with those treated for 5-7 months.

The appropriate modality for administering 5FU in the adjuvant setting is not clear. In metastatic disease, infusional 5FU results in higher response rates, longer survival, and less toxicity compared to bolus dosing [35, 36]. Capecitabine has been shown to be as effective as bolus dose 5FU in the adjuvant setting in a phase III trial [37]. However, the trend towards 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 >70 years of age.

Older colon cancer patients with stage II disease pose an even greater treatment dilemma, due to the limited data available to guide the management of these patients and the general questionable benefit of adjuvant therapy in this setting. The QUASAR group's prospective study of adjuvant bolus dose 5FU in stage II colon cancer evaluated the benefit of single agent 5FU in stage II disease. The absolute benefit of adjuvant 5FU in addition to surgery on overall survival was 3.6% (95% CI: 1.0-6.0). A subgroup analysis suggested a trend towards reduced benefit of therapy in patients over the age of 70 (HR 1.13, 95% CI: 0.74-1.75) [38]. With this limited overall benefit, adjuvant 5FU 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 in Older Adults

The MOSAIC trial evaluated the combination of oxaliplatin and infusional 5FU (FOLFOX) versus single agent infusional 5FU in the adjuvant setting, establishing FOLFOX as the standard of care for the adjuvant treatment of stage III colon cancer [39]. A pre-specified subgroup analysis of patients > 65 years of age (30% of enrolled patients) did not

demonstrate a reduction in recurrence risk. The ACCENT 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 (> 70 years). No benefit in disease free or overall survival was seen among older patients with the addition of oxaliplatin to 5FU for the whole cohort or among patients with stage III disease [40]. The NO16968 study evaluated the combination of capecitabine and oxaliplatin compared to 5FU and leucovorin in the adjuvant setting, and showed a non-statistically significant trend towards benefit with the addition of oxaliplatin in patients over the age of 70 (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 5FU appears to provide benefit for older patients in the adjuvant setting, mainly those with stage III disease, whereas the benefit from combination chemotherapy with 5FU and oxaliplatin in the adjuvant setting remains controversial.

Surveillance of Older Patients with Early Stage Colon Cancer

The NCCN guidelines define a surveillance schedule for patients with early stage colon cancer who have completed their curative surgery and chemotherapy treatments [44]. This schedule includes periodic physical examination, serial CEA monitoring, use of radiographic evaluation in high-risk patients, and surveillance colonoscopy following treatment completion. Four meta-analyses were performed, all demonstrating an improvement in overall survival among patients undergoing intense surveillance [45-48]. In addition, these analyses demonstrated 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 found that only 17.2 % of patients above age 66 received follow up testing at the recommended intervals while 60.2% of patients in this age group received testing less frequently than the recommended intervals [49]. Lack of adherence to guidelines was associated with advancing age and increasing number of comorbidities. Given the improvement in outcomes with the early detection of recurrence in colon cancer, fit older patients with should undergo the same surveillance schedule as younger patients with early stage colon cancer.

Early Stage Colon Cancer in the Older Patient – Summary

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

Issues in the Treatment of Metastatic Disease

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 survival and disease free survival in older patients compared favorably to their younger counterparts [50, 51]. Recently, outcomes of over 7,000 liver resections for colorectal metastasis in patients over the age of 70 were reported from a large international multicenter cohort [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% versus 1.6%; p<0.001) while the 3 year overall survival rate was lower (57.1% versus 60.2%; p<0.001) among older patients compared to younger patients. No difference in overall survival was seen between the subcategories of ages (70-75 years, 75-80 years, >80 years). Predictors for decreased survival were more than three hepatic metastases, presence of extra-hepatic disease, and lack of postoperative chemotherapy. Robertson et al. performed a similar analysis on 3,957 Medicare enrollees who underwent surgical resection of liver metastases between 2001-2004 [53]. Thirty and 90-day postoperative mortality rates were 4.0 and 8.2 percent respectively, while the five year survival rate was 25.5%. Advanced age (>80), comorbidities, and synchronous colon and hepatic resection were associated with 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 to the patient and his or her 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 5FU 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 non-curative condition. Figer et al. demonstrated similar toxicity between young and old patients using the OPTIMOX-1 approach of combination chemotherapy treatments alternating with 5FU monotherapy as maintenance, and suggested this may be a reasonable strategy in some older patients to minimize toxicity without compromising benefit [57]. Quality of life of older patients may also be preserved by applying the OPTIMOX-2 approach, alternating between treatment and chemotherapy-free intervals, although cancer-related survival outcomes may be lower with this strategy [58].

The use of 5FU-based chemotherapy in the metastatic setting was studied in an analysis of older patients who participated in 22 clinical trials, demonstrating similar benefit in overall survival (OS), overall response rate (RR), and progression free survival (PFS) to that seen in younger patients [36]. This analysis also demonstrated improvement in all the above measures with the use of infusional versus bolus 5FU among older patients. Recently, results of the FOCUS2 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 5FU, with or without oxaliplatin with an initial empiric 20% dose reduction. This study did not show a difference in efficacy between capecitabine and 5FU (PFS HR 0.99, 95% CI: 0.82-1.2, p=0.93; OS HR 0.96, 95%CI: 0.79-1.17, p=0.71). In stark contrast to the common perception of capecitabine being a “gentler” therapy option, capecitabine was not associated with improved quality of life in comparison to 5FU. Furthermore, treatment with capecitabine was associated with increased adverse events compared with 5FU. The addition of oxaliplatin at 80% of standard dose to 5FU or capecitabine resulted in improved response rates (13% versus 35%, p<0.0001), a trend toward improvement in PFS that was not statistically significant (HR 0.84, 95%CI: 0.69-1.01, p=0.07), and no improvement in OS (HR 0.99, 95%CI: 0.81-1.18, p=0.91). The rate of grade 3 or higher toxicity was not increased with the addition of oxaliplatin at this lower dose.

An evaluation of standard dose FOLFOX in the treatment of older patients with metastatic colon cancer was performed in a pooled analysis of over 3,000 patients. Patients over the age of 70 comprised only 16% of the study population (n=614) and experienced increased

rates of hematologic toxicity, with similar rates of other toxicities including neurologic and gastrointestinal adverse events compared to the younger cohort [60]. In contrast to the results in the adjuvant setting, the relative benefit of the combination of oxaliplatin and 5FU or capecitabine did not differ between older and younger patients [61, 62].

The combination of irinotecan and 5FU was evaluated in a retrospective analysis of large phase III clinical trials and in phase II studies, all demonstrating a clinical benefit 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 age 75 or older. A preliminary report of the study verified that the combination is safe in older adults with manageable toxicities [65].

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 survival among patients with metastatic colon cancer in large phase III randomized clinical trials [66, 67]. Two large observational studies following the drug's approval have reported data regarding the use of bevacizumab in older patients. The BEAT (Bevacizumab Expanded Access Trial) study demonstrated similar clinical outcomes between young and old patients [68]. The BRiTE (Bevacizumab Regimens Investigation of Treatment Effects) study included 1,953 patients with metastatic colon cancer, of which 45% were over the age of 65 and 18% over the age of 75 [69]. PFS 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 PFS [HR 0.58 (95%CI: 0.49-0.68) and 0.52 (95%CI: 0.40-0.67) in the two studies respectively] and OS [HR 0.85 (95%CI: 0.74-0.97) and 0.70 (95%CI: 0.55-0.90) in the two studies respectively] with the addition of bevacizumab to standard chemotherapy in patients over 65 and 70 years of age, similar to that seen in younger patients [70, 71]. One prospective phase II study evaluated the use of 5FU with or without bevacizumab among 168 frail patients over the age of 65 who were not candidates for combination chemotherapy. The addition of bevacizumab to 5FU resulted in a statistically significant increase in PFS (5.5 vs 9.2 months; p=0.0002) and a non-significant improvement in median OS (12.9 vs 16.6 months p=0.16) [72].

Despite these data, bevacizumab is utilized in only approximately one third of the older patient population [73]. This finding is likely related to concerns for increased adverse events with bevacizumab in this high-risk population. The above mentioned studies report an overall increase in arterial thromboembolic events among older patients [68, 70, 74, 75]. This increase was most pronounced in patients over the age of 75, 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 over the age of 65. For example, the PRIME study, which demonstrated improved clinical outcomes with the combination of FOLFOX and panitumumab, failed to demonstrate this same benefit in the subgroup of patients over the age of 65 (n=261) (PFS: HR=1.02 (95% CI: 0.75-1.38); OS: HR=0.81 (95% CI: 0.59-1.11)) [76]. In contrast, a retrospective report by Bouchahada

et al. 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 as that seen in younger patients [77]. 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 5FU compared to their younger counterparts [78]. The group led by Gravalos did not find any increase in toxicity rates with the combination of cetuximab and capecitabine used for treatment of 66 patients with metastatic colon cancer aged 70 and over [79]. Additional studies are needed to clarify the utility of these agents among older patients with metastatic colorectal cancer.

Metastatic Colon Cancer in the Older Patient–Summary

Treatment of older patients with metastatic colon cancer requires careful consideration and an informed discussion between the patient and their oncologist. Overall, the data demonstrate 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 non-curative setting must be considered prior to treatment initiation. Table 2 summarizes the available evidence for use of approved therapies for metastatic colon cancer in the older population.

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 setting. Careful evaluation, with the use geriatric assessment tools, will enable the oncologist to identify patients with comorbidities or functional decline. Ongoing studies are seeking how to utilize these tools to specifically tailor therapy to the patient's overall condition. Despite the large number of older patients with colon cancer, older patients represent a minority of patients enrolled on clinical trials. The recently published results of the FOCUS2 study has demonstrated 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 5FU/capecitabine and bevacizumab with or without oxaliplatin for management of older (≥70 years) metastatic colon cancer patients. It also incorporates a geriatric assessment to identify those older adults at risk for toxicity. Additional clinical trials targeting the older patient population are desperately needed to enhance our understanding of the optimal management of the older patient with colon cancer.

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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 due to competing causes of death.
- Older adults derive a relative benefit from 5-FU based adjuvant therapy similar to younger patients with only a slight increase in toxicity, mainly in hematological toxicities.
- The benefit of oxaliplatin based therapy in adults > 70 years of age is questionable and should be considered on an individual patient basis.

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 strategies (combination chemotherapy alternating with 5FU monotherapy treatment or chemotherapy free intervals respectively) is a preferred treatment strategy among older patients.
- Older adults, in comparison to younger adults, derive a similar relative benefit from the approved agents for treatment of metastatic colon cancer with potentially increased rates of adverse events.

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-EGFR therapy among older patients are limited; retrospective analyses demonstrate acceptable toxicity profile.

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 peri-operative mortality is dependent upon surgical expertise and patient selection [22, 24]. Laparoscopic approaches may offer a less invasive treatment with less 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 Single agent 5Fluorouracil (5FU)	Older patients with early stage colon cancer are less likely to receive adjuvant chemotherapy despite sufficient long-term survival benefit [28]. Adjuvant single agent 5FU has been shown to improve clinical outcomes of older adults with colon cancer, despite increase in hematologic adverse events compared to younger patients [28-33]. **Stage II** – Lack of benefit from adjuvant 5FU among patient over the age of 70 in the QUASAR study [38].	Older patients with a good performance status and adequate life expectancy can benefit from adjuvant therapy with single agent 5FU. The benefit for older patients with stage II disease may be more limited.
Chemotherapy 5FU + Oxaliplatin	Subgroup analyses and large retrospective studies show limited benefit for the addition of oxaliplatin to adjuvant 5FU for older patients with early stage colon cancer. [39-41].	The addition of oxaliplatin to adjuvant 5FU 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 demonstrated improved survival for patients undergoing intensive surveillance following curative treatment for early stage colon cancer [45-48]. Older patients are less often offered the recommended monitoring schedule upon their treatment completion [49].	Fit older patients with adequate life expectancy should undergo the recommended surveillance schedule following curative treatment of early colon cancer.

5FU – 5-Fluorouracil;

Table 2

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 post operative morbidity and mortality among older patients undergoing hepatic resection. Increased risk was seen among patients with >3 liver lesions, extra hepatic disease, co-morbidities and lack of postoperative chemotherapy [52, 53].	Surgical resection of liver metastasis can be considered as a therapeutic option for fit older patients with limited co-morbidities.
Systemic Metastatic disease	**Concurrent vs sequential therapy**	Large randomized clinical trial 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 patient with mCRC. OPTIMOX-1 or 2 strategies may be a reasonable strategy among older patients.
	Single agent chemotherapy (5FU)	Retrospective analysis demonstrates benefit in terms of OS, RR and PFS among older patient with metastatic disease treated with single agent 5FU similar to those seen among younger patients [36]. The use of capecitabine is associated with increased toxicity when used in frail older patients [59].	Single agent 5FU can improve clinical outcomes of older patients with mCRC.
	Combination Chemotherapy	The addition of oxaliplatin or irinotecan to 5FU for the treatment of older mCRC patients results in increased frequency of adverse events [60, 63]. Most reports demonstrate 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 due to 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 thrombolic events among older patients, mainly in those over 75 years old [68, 70-72, 75]	Bevacizumab should be offered to appropriate older patients with mCRC with combination chemotherapy or single agent 5FU. Cardiac evaluation of patients at high risk may be warranted.
	Cetuximab/Panitumimab - Anti EGFR Ab	Subgroup analyses from large randomized clinical trials fail to demonstrate a benefit to the addition of these agents to combination chemotherapy among older patients [76] The limited data that is available reports good tolerance of these agents among older patients [77-79].	Limited data is available regarding the efficacy of anti-EGFR antibody for older mCRC patients.

mCRC- metastatic colorectal cancer; PFS- progression free survival; OS- overall survival; RR – response rate; 5FU- 5-fluorouracil; VEGF- Vascular endothelial growth factor; EGFR-Epidermal Growth Factor Receptor.