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Review

Updates on the Management of Colorectal Cancer in Older Adults

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Simple Summary: The majority of cases of colorectal cancer occur in those above the age of 65. Treatment of colorectal cancer in older adults warrants specific considerations due to the effects of aging on comorbidities, functional and cognitive status and socioeconomic factors. Several recent advances have been made to improve oncological outcomes and reduce toxicities with colorectal cancer treatments in both localized and metastatic disease settings. This review highlights the importance comprehensive geriatric assessment and provides recommendations to guide management of older adults with colorectal cancer. It summarizes prospective data from recently reported clinical trials focused on older adults. Other recommendations must at times rely on extrapolations and post-hoc analyses due the underrepresentation of older adults in colorectal cancer trials. This review should also therefore serve as a call to action for the field to increase the representation of this substantial and often vulnerable group of patients in future colorectal cancer trials.

Abstract: Colorectal cancer (CRC) poses a significant global health challenge. Notably, the risk of CRC escalates with age, with the majority of cases occurring in those above the age of 65. Despite recent progress in tailoring treatments for early and advanced CRC, there is a lack of prospective data to guide the management of older patients, who are frequently underrepresented in clinical trials. This article reviews the contemporary landscape of managing older individuals with CRC, highlighting recent advancements and persisting challenges. The role of comprehensive geriatric assessment is explored. Opportunities for treatment escalation/de-escalation, with consideration of the older adult's fitness level are reviewed in the neoadjuvant, surgical, adjuvant and metastatic settings of colon and rectal cancers. Immunotherapy is shown as an effective option treatment in older adults that have CRC with microsatellite instability. Promising new technologies such as circulating tumor DNA and recent phase III trials adding later line systemic therapy options are discussed. Clinical recommendations based on the data available are summarized. We conclude that deliberate efforts to include older individuals in future colorectal cancer trials are essential to better guide the management of these patients in this rapidly evolving field.

Keywords: Colorectal cancer - 1; Geriatric Oncology - 2; Comprehensive Geriatric Assessment -3

Introduction

Colorectal cancer (CRC) is the second most deadly and third most commonly diagnosed cancer worldwide[1]. The risk of CRC increases with each decade of life. More than two thirds of CRC cases occur in those 65 years of age and older[2].

Important strides have been made in recent years to increase efficacy or reduce toxicity in the treatment of both early and advanced CRC. However, there often remains limited prospective data to guide the management of older patients with CRC[3]. Older patients are frequently underrepresented in or excluded from clinical trials. Under these circumstances, treating clinicians must often rely on the interpretation of pooled analyses. As the discipline of geriatric oncology has grown, there has been some emergence of prospective trials focusing specifically on older adults; however, these often include patients with a wide range of malignancies. Those trials looking

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specifically at interventions for older patients with CRC are few in number and often of smaller sample size.

When caring for the aging patient, additional complexities including age-related comorbidities, cognitive and functional impairments, and socioeconomic constraints may need to be considered. This article will highlight current advances and challenges in the management of older individuals with CRC. Specifically, we will examine the evidence that modern treatment approaches effectively improve quality of life and longevity in elderly patients with CRC. A focus will also be made to highlight strategies of treatment de-escalation that may be appropriately considered to minimize toxicity in older individuals who are less fit.

Geriatric Assessment

In geriatric oncology, functional rather than chronological age should determine management, as chronological age alone is poor predictor of cancer treatment tolerance[4]. A great deal of effort should be dedicated to evaluating functionality and maintaining it during the treatment of older adults. When the body is put under stress from disease or its treatments, functional limitations may be unmasked. This process of functional decline is expressed clinically as frailty: a state of increased vulnerability to stress, with increased risk of adverse outcomes during cancer treatment[5].

Various frailty scores have been developed and they clearly correlate with poorer overall survival[6,7]. These screening tools, such as the G8[8,9], may be used to identify patients in need of a more comprehensive geriatric assessment (CGA).

A CGA is a multidisciplinary diagnostic process focused on determining a frail older person's medical, psychological and functional capacity, with the goal of developing a coordinated and integrated plan for treatment and long-term follow up. The various assessment domains and common potential interventions are outlined (Table 1). CGA use is recommended in various guidelines[10,11]. Although the CGA calls for an individualized approach to patient care, for the purposes of discussion and recommendation of CRC therapies, we may consider patients on a spectrum: functionally independent (fit), those with vulnerability/frailty (medium-fit), and finally those with severe limitations, with no possibility of recovering functional reserves and limited life expectancy (unfit).

Table 1. Components of the Comprehensive Geriatric Assessment.

Domain	Deficit	Interventions
Functional Status	• Limitations in basic activities of daily living or instrumental activities of daily living • Timed Up and GO > 13s[12] • Falls history	• Home safety evaluation • Physiotherapy • Occupational therapy • Gait strengthening
Comorbidities	• Comorbid conditions • Hearing and visual impairments • Pre-existing neuropathy	• Co-management with primary care provider • Referrals to subspecialty services
Cognition	• Memory loss/impairment • Confusion	• Formal cognitive testing[13,14] • Delirium prevention • Capacity assessment • Involvement of caregivers
Nutrition	• Weight loss >5% • Iron deficiency or B12 deficiency anemia • Problems with eating	• Mini-Nutritional Assessment[15] • Dietician involvement • Supplementation • Medications (mirtazapine or olanzapine helpful in some circumstances) • Speech and language pathologist for swallowing assessment
Psychological Status	• Feeling sad or depressed • Anxiety	• Geriatric Depression Scale[16,17] • Psychiatry referral • Counseling • Chaplaincy referral

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Social Circumstances	• Patient lives alone • Lack of social support • Barriers to social activity	• Social work referral • Community resources • Meal/transportation programs
Polypharmacy	• ≥5 Prescribed medications • ≥ 1 Supplement	• Pharmacy review of medications for interactions • Discontinuation of unnecessary medications
Clinical Symptoms	• Pain • Nausea • Incontinence • Diarrhea or constipation • Neuropathy	• Supportive care/pain management referral • Single prescriber for opioids • Educational interventions

Adapted from Li et al.[18] - Geriatric Assessment-Driven Intervention (GAIN) study.

A growing body of evidence shows CGA effects oncological and non-oncological treatment decisions[19]. CGA is associated with improved communication and advanced care planning with patients[18,20,21]. CRASH[22] and CARG scores[23], which use various parameters determined during a CGA, may predict severe toxicity in older patients with cancer treated with systemic therapy. They have similar predictive performance[24].

The GAIN trial was one of the first randomized trials to show the benefit of geriatric intervention prior to initiation of chemotherapy for solid tumors in older adults[18]. Grade 3-5 adverse events were decreased by 10% (60.6%, in standard of care arm compared to 50.5% in intervention arm, p=0.02) by the addition of geriatric intervention. The finding that initial chemotherapy doses, rates of dose modification and discontinuation were not different between the two groups highlights that toxicities can be reduced through implementing geriatric interventions other than decreasing chemotherapy. The rates of emergency department visits, unplanned hospitalizations and survival did not differ during follow-up.

The GAP 70+ study similarly showed geriatric interventions can diminish the rate of grade 3-5 adverse events in elderly patients with advanced disease and at least one impaired geriatric assessment domain[25]. Grade 3-5 adverse events were reduced by 20% (71% in standard of care vs 51% in intervention arm). Unlike the GAIN trial, treatment intensity was reduced at cycle one (ie, primary dose reduction) in the geriatric intervention group more commonly. Importantly, reduced dose intensity in the intervention group did not compromise survival, which was similar between the study groups. Patients in the CGA group also had fewer falls and more medications discontinued, reducing polypharmacy.

The INTEGERATE study is another randomized trial investigating CGA in cancer patients[26]. They were able to show a benefit in quality-of-life scores, including better scores in functioning, mobility, burden of illness and future worries from integrating CGA into oncology care. A reduction in emergency department visits and hospital admissions was seen in this study. These results are in contrast to those of the Canadian 5C trial, where no quality-of-life benefit was identified from geriatric assessment and management intervention[27]. The lack of benefit in the 5C study could be because the geriatric assessment was not done until the day of or after first systemic therapy and only 1.7% of patients had their initial cancer treatment plan modified by geriatric assessment.

CGA has also been study in oncological surgery settings. A recently published trial randomized patients ≥ 65 years of age planning for gastrointestinal cancer surgeries to perioperative geriatric consultation, or usual standard of care[28]. The trial failed to meet its primary endpoint of reduction in post-operative length of stay in the intention to treat population. However, only 43% of patients in the experimental arm attended their pre-operative assessment. Geriatric intervention led to a significance reduction in post-operative length of stay (5.90 vs 8.21 days, P = 0.024) and a trend towards lower rates of postoperative intensive care use, 90-day readmissions, and major complications in the intervention group in the per protocol analysis. Similar to the 5C trial, these findings highlight the need for coordination of appointments when assessing geriatric interventions in future clinical trials. Consideration of telehealth and other measures to reduce the burden of additional clinical visits for older cancer patients should be explored.

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Other retrospective data has suggested decreased 90-day mortality from geriatric peri-operative co-management with surgeons in those undergoing surgery for cancer (odds ratio [OR], 0.43 [95% CI, 0.28-0.67]; $P < .001$)[29].

Despite the emerging data showing benefits of geriatric assessment in the management of older adults with cancer, uptake in clinical practice often remains somewhat limited. Several challenges persist in relation to the time and resources needed to complete a CGA, which takes approximately one hour initially and requires follow-up. There is a general and increasing shortage of geriatricians in the United States[30]. However, the implementation of comprehensive geriatric oncology care may provide a higher value (quality/cost) intervention compared to many more recently approved pharmaceutical interventions[31].

Examples of CRC-specific trials exploring geriatric interventions are highlighted within the text.

Localized Rectal Cancer with Microsatellite Stability

In recent years, evidence for several new approaches to manage stage I (T1-T2 without nodal involvement) and stage II-III (T3-T4, or any T with nodal involvement) rectal cancer has emerged. The inclusion of and sequencing of different treatment modalities (chemotherapy, radiation, and surgery) in management plans is often spiritedly debated at multidisciplinary tumor boards. Older, more frail patients can certainly add yet another layer of complexity to these decisions.

Early Stage

For early-stage rectal tumors, more minimally invasive procedures to avoid the morbidity associated with total mesorectal excision (TME) surgery are being explored. Current National Comprehensive Cancer Network (NCCN) guidelines suggest that transanal local excision may be appropriate for certain mobile T1 tumors[12]. If these criteria cannot be met, generally more extensive surgery with TME with or without radiation has been considered the standard of care. TME involves major surgery with either a lower anterior resection (LAR) or an abdominal perineal resection (APR), the latter of which always requires a permanent end colostomy. A systematic review including 36,315 patients found age > 65 was associated with a statistically significant increase in both anastomotic leak and post-operative death[32].

The GOSAFE study was a prospective observational study of cancer surgery in older patients (age ≥ 70) that assessed patient-reported outcomes post-operatively[33]. They were able to show that major colon and rectal surgery in older patients with CRC results in restoration of good quality of life following surgery in the majority of cases[34]. Furthermore, functional recovery to remain independent occurred in 78.6% (254/323) of patients with colon cancer and 70.6% (94/133) with rectal cancer post-operatively. The authors did note that an Eastern Collaborative Oncology Group (EGOG) score ≥ 2 preoperatively in patients with rectal cancer strongly predicted decline in quality of life post-operatively (OR 3.81, p = 0.006). These results should help inform shared decision making between patients and surgeons.

Surgery will have a role in many cases of early and locally advanced rectal disease, but the safe expansion of minimally invasive procedures in early disease is an appealing prospect, especially for older individuals with poor performance status.

Some phase II trials have assessed the feasibility of local excisions in T1-3 tumors. The TREC trial randomised 55 patients with cT1-T2, N0 rectal tumours to short-course radiation followed by transanal endoscopic microsurgery after 8-10 weeks (with TME reserved for those with high-risk histopathological features upon excision) versus upfront TME[35]. The study also included a cohort of 61 non-randomized patients considered to be high risk for conventional TME. These patients were older (median 74, oldest 89) and were more likely to have life-limiting comorbidities. 70% of the experimental group and 92% of the non-randomized group were able to avoid TME and complete pathological response was achieved in 26% and 31% respectively with short course radiation. An additional 4% of patients in the experimental group and 8% of patients in the non-randomized group achieved a complete clinical response without undergoing transanal endoscopic microsurgery. In the predominantly older non-randomized cohort, local recurrence free survival was excellent with a rate of 91% at 3 years. Extensive quality of life data suggested that organ-preserving therapy was well tolerated with slight worsening of fatigue, physical, social, role and bowel functions at three months, but with values largely returned to pre-treatment baseline by 6-12 months.

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The CARTS study was a similar single arm trial where cT1-T3, N0 rectal cancer patients were treated with long course chemoradiation (CRT) followed by transanal endoscopic microsurgery in the case of good response. The majority of patients were able to avoid major surgery with recurrence rates similar to those historically seen with TME. However, a major burden of low anterior resection syndrome (LARS) characterized by clustering of stools, soiling, and fecal incontinence was present in 50% of patients at two years.

In phase II NEO study, cT1-3abN0 low- or mid-rectal tumors were treated with 3 months of chemotherapy followed by transanal endoscopic surgery[36]. 57% achieved favorable response to chemotherapy allowing for organ preservation per protocol. At one year, the rate of major LARS was 14%, with minimal changes in quality of life.

On the whole, this data suggests there may be a role for more limited local excisions to treat CRC in older patient with poor performance status and early stage rectal cancers. This does not guarantee less morbidity, as particularly seen in those treated with CRT.

Locally Advanced

For more locally advanced rectal cancers, until recently, the standard of care was neoadjuvant radiation (short or long course CRT) followed by TME surgery, followed by adjuvant chemotherapy for an additional 4 months. In a retrospective Canadian study, patients 70 years or older with locally advanced rectal cancer seemed to have similar disease-free survival (DFS) and overall survival (OS) outcomes compared to those younger than 70[37]. This was the case despite older patients being less likely to complete neoadjuvant CRT and less likely to receive adjuvant chemotherapy.

The PRODIGE 42/GERICO 12 study provides some prospective randomized phase III data specific to individuals ≥ 75 years of age with resectable rectal tumors that were T3-T4 (with or without nodal involvement), or very low T2 tumors[38]. Patients were randomized to neoadjuvant short course radiation or CRT, followed by surgery. The primary endpoints were R0 resection rate (non-inferiority design) and maintenance of autonomy in instrumental activities of daily living (IADLS) scores. The study only accrued 105 of a planned 420 participants. 95.6% patients in the CRT arm versus 88.0% of patients in the SCRT arm had R0 resections, failing to meet non-inferiority for SCRT. Overall, there was a significant difference in the degradation rate of IADLS at month 3 (deterioration in 44% of CRT versus 14.8% in SCRT); however, this difference did not persist at 6 months. Secondary outcomes of OS (HR 0.28, p=0.05) and Cancer Specific survival (HR 0.21, p=0.027) appeared to be improved with short course radiation. We cannot conclude short-course radiation is superior to long-course CRT in older patients based on this limited data, although a larger trial to properly assess OS is warranted given these intriguing results.

Guidelines are however shifting to reflect a preference towards total neoadjuvant treatment (TNT) approaches for most patients with locally advanced rectal cancer[12]. TNT has several potential benefits including higher rates of treatment completion, reduction in rates of distant metastases and emerging data to suggest improvements in overall survival for at least one TNT regimen[39–43]. Conversely, there is simultaneously a push for novel approaches focused on omitting some potentially morbid treatment components without compromising outcomes. This may be especially prudent for older individuals and this population deserves specific attention in future trials.

Earlier trials showed neoadjuvant radiation improved local recurrences rates in locally advanced rectal cancer from 25-40% down to 5-9%[44,45]. However, the treatments are associated with grade 3-4 acute (any 27%, diarrhea 12%) and long-term (any 14%, strictures 4%, bladder problems 2%, gastrointestinal effects 9%) toxicities[46]. In the modern era of magnetic resonance imaging (MRI) staging and TME surgery, radiation may not be necessary for all locally advanced patients. The recently published PROSPECT trial asked the question whether radiation could be avoided in carefully selected patients in favour of perioperative chemotherapy and surgery alone[47]. Patients with cT2N1, or T3N0-1 without compromised mesorectal fascia eligible for sphincter-sparing surgery were enrolled. The median age was 57 with the oldest enrolled patient being 91 years of age. In the experimental arm, those that responded to neoadjuvant fluoropyrimidine and oxaliplatin (FOLFOX) chemotherapy could proceed to surgery without radiation. Non-inferiority of disease-free survival (80.8% at 5-years) compared to the tradition CRT approach was reached. 5-year OS rate of 90% was similar between arms and less than 2% had local recurrence. Importantly, at 12 months, patient

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reported outcomes suggested significantly lower rates of fatigue, neuropathy, better bowel function and better sexual function in the chemotherapy alone group. Although, this represents a good potential option for fitter older adults to avoid radiation complications, the full 12 cycles of FOLFOX recommended in this trial may still represent overtreatment for some patients.

In the OCUM study, cT2 tumors, or cT3 tumors of the mid-high rectum were treated with upfront surgery if there was >1mm distance between the tumor, tumor deposits or suspicious lymph nodes and the mesorectal fascia[48]. Only 35.7% of these patients went on to receive adjuvant therapy. The local recurrence rate of only 2.9% and distant metastases rate of 15.9% at 5-years show excellent outcomes are possible with upfront surgery and limited chemotherapy/radiation use in selective patients. We do not have comparison of study results based on age for the PROSPECT or OCUM trials[47,48].

Observational cohorts provided some evidence that those with complete clinical response to neo-adjuvant treatments had promising results despite omission of upfront surgery. The incidence of regrowth at 2 years was 25.2%, with a rate of distant metastases of 8% and disease-specific survival of 94% in one such cohort of 1009 patients[47]. These findings prompted the Organ Preservation for Rectal Adenocarcinoma (OPRA) study, which randomized patients with low-lying stage II and III rectal cancer to chemotherapy followed by CRT, or CRT followed by chemotherapy[43]. The results suggest that 53% of patients treated with CRT followed by 4-months of oxaliplatin-based chemotherapy may be able to avoid surgery without compromising DFS compared to historical norms. The recently published OPERA study looked to further improve the rates of organ preservation for T2-3bN0 (or N1 node <8mm) low-mid rectal tumors by incorporating radiation dose escalation[49]. Reported 3-year organ preservation rates achieved by combining standard chemoradiation with local brachytherapy or external beam boost were 81% and 59% respectively. Although, these approach seem enticing for older people with low rectal tumors, it should be noted that the oldest patients enrolled in these trials were 68 (OPRA) and 79 (OPERA). Furthermore, the social context of each patient should be considered as close monitoring and frequent assessment following TNT is essential for at least the first 2-3 years after therapy to identify regrowth requiring surgical intervention.

The PRODIGE 23 trial has shown benefit of neoadjuvant triplet chemotherapy in a highly selective patient population[40,42]. Patients > 75 years of age or with a history of ischemic coronary disease, or grade 2 or worse neuropathy were excluded. The trial randomized patients to 6 cycles of fluoropyrimidine plus oxaliplatin plus irinotecan (FOLFIRINOX), followed by long-course CRT, followed by surgery. The protocol also included adjuvant treatment. Compared to the standard of care arm (CRT, surgery, adjuvant chemotherapy), the pathological complete response rate was more than doubled (27.8% vs 12.1%). A recent update shows a 7-year metastasis-free survival of 73.6% vs 65.4% and an overall survival of 81.9% vs 76.1% in favour of the TNT arm. Grade 3-5 adverse were 47% in the FOLFIRINOX arm[42]. This regimen can be considered for older individuals who meet the inclusion criteria described.

Finally, the RAPIDO trial compared an approach involving short-course radiation followed by neoadjuvant chemotherapy (FOLFOX for 9 cycles or capecitabine plus oxaliplatin (CAPOX) for 6 cycles) only in those patients with locally advanced rectal cancer with high risk features[39]. Around 40% of patients were above 65 years of age in this trial. At 5-years, disease-related treatment failure was 27.8% (HR 0.79 compared to the standard of care arm). Distant metastases at 3 years was improved by about 8% (HR 0.69)[41]. These findings were achieved without affecting quality of life. However, adoption in some countries has been slow given the concern for an increased rate of locoregional failure (11.7% vs 8.1% at 5 years).

Although, the results of these recent total neoadjuvant approaches are promising, an individualized discussion is warranted. There is potential for overtreatment of certain patients. Clear expectations for potential benefits and harms must be laid out. It bears mentioning that modern adjuvant trials in rectal cancer largely failed to accrue and have not yielded consistent benefits from systemic therapy in terms of DFS and OS[50]. The ADORE trial is one example where the potential benefit was seen for adjuvant FOLFOX compared to a bolus fluoropyrimidine regimen in those with residual disease after CRT[51]. The DFS advantage appeared to hold up in an exploratory subgroup analysis of patients aged > 65. In general, neoadjuvant is favoured over adjuvant chemotherapy on the basis of the studies mentioned above.

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Localized Colon Cancer with Microsatellite Stability

Adjuvant chemotherapy is considered standard of care for resected stage III colon cancer. Older individuals are less likely to receive adjuvant treatment[52]. However, databases suggest older individuals with CRC who do receive adjuvant therapy do have a survival benefit, with longer treatment duration being associated with decreased mortality[53,54].

Sargent et al. performed a pooled analysis of 7 phase III randomized controlled trials evaluating 5-fluorouracil-based chemotherapy in patients with stage II and III colon cancer[55]. The results demonstrated a clear DFS benefit across all age groups. There similarly was no interaction between age and treatment effect for OS. There was some slight convergence of survival curves at 5-years in the group of patients older than 70 years of age, probably owing to deaths from other causes. Tolerance and toxicity were similar for older and younger adults.

Single Capecitabine and 5-fluorouracil (5-FU) are generally thought to have comparable efficacy, including in older adults[56,57]. The choice between the two can be individualized. 5-FU requires a central line (port-a-cath or peripherally inserted central catheter) for a pump infusion over 46 hours. This may present challenges to ambulatory older patients. Capecitabine is administered orally. Although oral administration presents some advantages, oral drugs may be subject to higher copayments depending on the health plan coverage and may be more prone to compliance issues and medication dosing errors. Given its renal excretion, capecitabine may be contra-indicated or require dose adjustment in those with chronic kidney disease. In the MRC FOCUS2 trial of older and frailer adults with metastatic colorectal cancer deemed unfit for upfront full dose therapy, grade 3-4 toxicities were higher with capecitabine than 5-fluorouracil[58]. Quality of life scores did not differ significantly between the two agents. Capecitabine was associated with higher rates of diarrhea, nausea and hand-foot syndrome, while 5-fluorouracil causes more stomatitis. Dihydropyrimidine dehydrogenase (DPD) testing can be considered prior to initiation of either agent[10]. Deficiency is estimated in 8% of Caucasians, warranting dose adjustment. Potential for life-threatening toxicities to 5-fluorouracil or capecitabine may result from treatment in those with severe DPD deficiency.

FOLFOX became a new standard of care for stage III colon cancer in 2004[59]. At 10-year follow-up of the MOSAIC trial, the absolute decrease in the risk of death from stage III colon cancer was 8.1% (67.1% alive with FOLFOX versus 59.0% with 5-FU). Absolute recurrence-free survival was also improved 8.4% (62.2% with FOLFOX recurrence-free versus 53.8% with 5-FU)[60]. The data regarding the use of oxaliplatin in older patients remains mixed however.

Subgroup analyses within this MOSAIC trial did not show a significant DFS benefit with the addition of oxaliplatin for patients age >70[59]. NSABP C-07 trial which investigated a FLOX regimen (not commonly used in practice nowadays) similarly did not demonstrate a benefit in those over 70 years of age[61,62]. The XELOXA trial comparing 5-FU to a combination of CAPOX showed a trend toward benefit from the addition of oxaliplatin in terms of DFS and OS in elderly patients, although this was diminished compared to younger patients and was not statically significant[63,64].

An earlier publication from the ACCENT database pooled these trials and failed to find evidence of improved DFS and had a trend towards detrimental effect for OS with addition of oxaliplatin to adjuvant stage II/III colon cancer treatment in patients over 70 years of age [65]. The most recent meta-analysis to address this question comprised of five publications, including eight studies with a total of close to 2,000 patients[66]. They did not find a statistically significant improvement in DFS or OS by the addition of oxaliplatin to adjuvant therapy in those ≥ 70 years of age with resected high-risk CRC.

A more recent pooled analysis of 12 trials from the ACCENT/IDEA databases did not investigate directly the additional benefit of oxaliplatin in stage III colon cancer, but rather compared toxicity patterns, treatment adherence and outcomes between patients ≥ 70 or <70 years of age receiving oxaliplatin-based regimens[67]. The rates of grade ≥ 3 toxicities were similar with FOLFOX between the two groups; however, CAPOX led to more diarrhea, mucositis and neutropenia, and less neuropathy in older compared to younger patients. There were higher rates of early treatment discontinuation amongst the older patients (22.0% vs 15.5%). While traditional outcomes such as DFS and OS were shorter for older patients, the authors highlighted that time to recurrence (TTR) was not statistically different based on age group in multivariable analysis. TTR allows for the direct impact of adjuvant chemotherapy on the recurrence rate to be assessed, by excluding background noise from

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non-cancer related deaths. The authors concluded that in older patients fit for clinical trial, oxaliplatin seems safe and effective to reduce recurrence rates.

The ongoing phase III ADAGE trial (ClinicalTrials.gov identifier: NCT02355379) specifically involves patients ≥ 70 years of age with resected stage III colon cancer and may provide the prospective data needed to settle the debate about adjuvant oxaliplatin in this setting.

"Real-world" experience is captured in the Surveillance, Epidemiology and End Results–Medicare registry. 814 patients older than 65 years of age who received adjuvant oxaliplatin-based therapy for stage III colon cancer were compared to 3581 patients who received fluoropyrimidine alone therapy[54]. Oxaliplatin-based therapy was associated with improved OS (HR 0.73, *P*<.001) and CRC-specific survival (HR 0.39, *P*<.001) when compared with 5-FU alone. The benefit did not extend to those 80 years of age and older. These results, which suggest older adults may benefit from oxaliplatin should be interpreted with some caution, as there is likely a selection bias in non-randomized data where fitter patients may be more likely to receive combination therapy. Other studies have shown only about 14% of stage III colon cancer patients 75 years of age or above receive oxaliplatin-based adjuvant therapy[52].

A major step forwarded to potentially limit the toxicity of oxaliplatin-based adjuvant therapy for stage III colon cancer came with the publication of the IDEA trial [68]. A preplanned prospective pooling of 6 trials compared the outcomes of 3 versus 6 months of CAPOX/FOLFOX[69]. For the OS analysis, there was no difference between 3 versus 6 months for those ≥ 70 years of age (HR 1·00, 0·88–1·14). Grade 2 or higher neuropathy rates were reduced to roughly 15% from 45% by treating for 3 months versus 6 months. Persistent neuropathy at longer follow-up is also decreased[70]. Guideline recommendations are largely based on an exploratory subgroup analysis of the IDEA trial. For patients with "low risk" disease, 3-months of CAPOX is statistically non-inferior to 6 months. For those with "high risk disease" (classified by T4 and/or N2), non-inferiority was not achieved statistically, but the absolute difference in OS at 5-years was 1% between 3 and 6 months of CAPOX and 2.8% between 3 and 6 months of FOLFOX[71,72]. Other data suggests that oxaliplatin can be dropped after 3 months while continuing the 5-FU/capecitabine component without compromising outcomes[73,74]. Based on the above data, particularly for older patients, if adjuvant oxaliplatin is considered, the potential diminishing returns of therapy beyond 3 months should be discussed.

Prospective data does exist incorporating the CGA into adjuvant treatment decisions specifically for patients with high-risk stage II and III CRC. A single institution study enrolled 195 patients ≥ 75 years of age and classified patients as "fit", "medium-fit", or "unfit"[75]. In multivariable analysis, they found that this geriatric classification was the only independent factor predictive of overall survival. The "unfit" population was nearly twice as likely to die from non-cancer related causes compared to cancer related causes, providing support for the therapeutic decision to not treat with adjuvant therapy in this population.

Stage II Disease

There is less data to support an OS benefit from adjuvant chemotherapy for stage II colon cancer [76,77]. Generally, in those with high risk clinical/histopathological features chemotherapy is considered, but observation is also considered an acceptable option[12]. Not all high risk features are considered equal and it should be noted that T4 disease (stage IIB) actually has poorer prognosis than stage IIIA disease on SEER data; although, increased risk does not necessarily translate to increased benefit from adjuvant therapy. The addition of oxaliplatin to fluorouracil did not show a statistically significant DFS or OS benefit for high-risk stage II disease in a post-hoc exploratory analysis of the MOSAIC trial[59,60]. This may appropriately lead to further hesitation to prescribe oxaliplatin in older patients with high-risk stage II disease.

Emerging technology of circulating tumour DNA (ctDNA) has the potential to aid decision making in this space. There is potential to spare both younger and older patients from chemotherapy without significantly impacting their chance of disease recurrence. ctDNA may be the most significant prognostic factor associated with recurrence for stage II and III CRC[78].

In the phase II DYNAMIC study, patients with stage II colon cancer (patients over 70 years of age comprised 27% of the study population) were randomized to either ctDNA-guided management or standard adjuvant management [79]. The ctDNA-guided management group received less

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chemotherapy than the standard arm (15% versus 28%; RR, 1.82), with non-inferior two-year DFS (93.5% versus 92.4%, respectively).

In older patients potentially at higher risk of morbidity from adjuvant chemotherapy for high-risk stage II disease, it is reasonable to consider ctDNA testing if available, to help support a decision to omit therapy. It must be noted however that early knowledge of cancer recurrence as predicted by ctDNA positivity in the absence of clear effective interventions has the potential to cause significant distress to patients. The use of these tests is currently not yet endorsed by NCCN or ESMO[12,80] guidelines and requires a nuanced discussion with patients before ordering.

Localized Colorectal Cancers with Microsatellite Instability

Arguably, one of the most exciting areas of clinical research for CRC in recent years involves the management of patients with deficient mismatch repair (dMMR) or microsatellite instability (MSI-high) CRC. Late-onset colorectal cancer (occurring in those 80 years of age or older) compared to earlier onset is more likely to be right-sided (82% vs 35%) and dMMR (35% vs 8%) – particularly driven by harbouring of BRAF V600E mutation (35% vs 8%)[81]. Testing for dMMR is essential to identify this subset of older patients with CRC as positive results provide prognostic information and are potentially predictive of benefit from immunotherapy.

Generally, dMMR is associated with lower recurrence risks in stage II disease CRC and adjuvant therapy is not recommended for these patients.

For stage III disease in the adjuvant setting, single agent 5-FU has generally not been shown to be beneficial for patients with dMMR CRCl[82,83]. Two recent meta-analyses have however suggested an overall survival benefit from the addition of adjuvant chemotherapy in the stage III dMMR colon cancer[84,85]. The addition of oxaliplatin to treatment in this overall population of dMMR patients appears beneficial. As previously discussed, the use of adjuvant oxaliplatin remains debated in elderly patients. In an ACCENT pooled analysis, only 37 patients over the age 70 with dMMR colon cancer were found to be randomly assigned to fluoropyrimidine versus fluoropyrimidine-oxaliplatin combination adjuvant therapy. Although these small numbers prevent addressing this important question for older adults, they did not identify a significant interaction between age and adjuvant oxaliplatin benefit in patients with dMMR disease[84]. Trials are ongoing to assess the role for immunotherapy in the adjuvant setting for these patients[86,87].

Rectal cancer will less commonly be dMMR, being found in approximately 2.7% of cases[88]. The rates may be lower for older adults[89]. In June 2023, Cercek et al. published a phase II single arm study of patients with dMMR stage II/III rectal cancer treated with dostarlimab (a PD-1 inhibitor) for 6 months. Remarkably, at initial publication 12 of 12 patients had a clinical complete response to immunotherapy alone[90]. At latest update, with 23 patients studied, a 100% clinical response rate still held. The oldest patient enrolled was 78 years-of-age. These results will require further follow-up, but the potential that the morbidity of cytotoxic chemotherapy, radiation and surgery may be avoided in this select group of patients is very encouraging for both younger and older adults. This treatment strategy is reflected in recent guidelines and should not be restricted based on age[12].

Results from the use of immunotherapy in localized colon cancer with dMMR seem similarly impressive[91]. In the NICHE2 study, 112 patients (age 20-82) with cT3-4 and/or node positive colon cancer were treated with 2 cycles of nivolumab and a single cycle of ipilimumab prior to surgery. A pathological complete response rate of 67% and major pathological response rate (<10% residual tumor volume) of 95% was reported. There is currently insufficient data to recommend neoadjuvant immunotherapy or surgery avoidance for majority of patients with dMMR colon cancer. However, for advanced local disease, or cases where surgery may be associated with higher risks of morbidity (as can be seen more frequently in less fit older adults) consideration of upfront immunotherapy may be reasonable[12,92].

Advanced/Metastatic Disease in Older Adults

22% of patients with CRC present with distant metastases[93] and many more will develop metastases during the course of their disease. Pathological evaluation of microsatellite status and next generation sequencing for RAS, BRAF, HER2 gives important information for both prognostication and treatment decisions.

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Colorectal cancer in the setting of limited metastases can often be treated with more aggressive approaches to potentially result in long-term survival or cure. The status of a patient's metastatic disease falls into 3 categories determined by a multidisciplinary team of surgeons, radiologists, medical oncologists, and radiation oncologists: resectable, borderline resectable, and unresectable/palliative. As with all patients, establishing treatment goals is essential to making management decisions with older adults. Shared decision making and CGA are key. It should be noted that older patients may hold quality of life as the highest priority[94] and the majority may not choose treatment if it would result in severe functional limitation[95].

Resectable disease involves situations where both the primary lesion and/or metastatic disease are amenable to curative intent resection. The 5-year survival rates following resection are generally between 20-45% for liver metastases and 25-35% for lung metastases[10]. Peritoneal resections are also possible in selected patients, leading to some long-term survivors[96,97]. Upfront surgery is a reasonable option for those with favorable disease features such as metachronous lesions, fewer metastases and only unilobar liver disease [10]. Neoadjuvant chemotherapy for 3 months prior to surgical resection may offer a test of time and biology in those with less favorable disease characteristics. Generally, this involves fluoropyrimidine and oxaliplatin doublet chemotherapy. Due to the curative intent of this approach, higher toxicity risk may be appropriate. It should be noted that despite the high risk of recurrence, neither perioperative FOLFOX [98,99] nor adjuvant FOLFOX[100] has been shown to increase overall survival in the setting of liver resection in randomized trials.

Borderline resectable in this context means that the metastatic disease and primary tumor (if still present) are potentially resectable in the setting of adequate response to systemic therapy. This is sometimes referred to as conversion therapy[10]. Selection of agents in this setting has generally been chosen based on regimens associated with the highest response rates. However, the recently published CAIRO-5 trial in patients with unresectable liver metastases gives some randomized data in this setting[101]. For left-sided, RAS/BRAF wild-type colorectal cancers, they found no difference in the rate of liver resection or progression-free survival when combining doublet chemotherapy with anti-epidermal growth factor receptor (EGFR) antibody or anti-vascular endothelial growth factor antibody (VEGF). This is despite marked difference in response rate: 80% for panitumumab versus 53% for bevacizumab combinations. There was higher toxicity with anti-EGFR antibody to consider. For right-sided or RAS/BRAF mutated disease, FOLFOXIRI and bevacizumab led to a higher rate of liver resection, and higher PFS than 5-FU and irinotecan (FOLFIRI) and bevacizumab/FOLFOX and bevacizumab (10.6 months versus 9.0 months, HR 0.76, p=0.032). In the TRIBE2 trial described below, similarly 17% of patients treated with FOLFOXIRI and bevacizumab underwent resection of metastases with negative margin versus 12% treated with FOLFOX and bevacizumab (p=0.047)[102]. The decision to be aggressive with an approach to borderline resectable disease in older adults must weigh factors including the overall health of the patient, functional status and social support that they may have. Unfortunately, there is a lack of specific data on older adults treated in this setting.

Palliative treatment aims to help the older patient with metastatic CRC that is not amenable to resection achieve the best quality of life possible. Systemic therapy has significant potential benefit in this setting. With supportive care alone, the median survival from metastatic CRC is around 5 months [103]. In common circumstances, this may improve more than 7-fold with systemic therapy in the fit older patients[104]. Like other settings, the patient's fitness/frailty levels greatly influence treatment decisions and expected benefits.

Most commonly, treatment in the palliative setting involves combination chemotherapy (eg FOLFOX or FOLFIRI) combined with a biologic agent.

Traditional Chemotherapy Backbones in Palliative Setting

FOLFOX

In the pre-biologics era, the addition of oxaliplatin to 5-FU has shown clear benefit in terms of overall survival in those > 70 years old in pooled analyses of patients fit for clinical trials[105,106]. In elderly specific prospective phase II trials, this combination has similarly been shown to be safe and effective[107,108].

In vulnerable or frail older adults, there are a series of prospective elderly-specific trials and analyses showing that treatment intensification is not beneficial for these patients. The FOCUS-2

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study specifically enrolled patients with unresectable or metastatic CRC deemed "unfit" for full dose chemotherapy by their medical oncologist[58]. Patients were randomized to receive capecitabine or 5-FU with or without oxaliplatin at a decreased dose (20% reduction). The addition of oxaliplatin did not lead to a statistically significant improvement in progression-free survival (PFS) or OS in this population. Oxaliplatin use was associated with a detrimental effect on quality of life. In the single agent chemotherapy arms, Capecitabine and 5-FU had similar efficacy; however, as mentioned above, capecitabine led to increased toxicity without improvement in quality of life compared to 5-FU.

FOLFIRI

Data suggest in general treating with FOLFIRI chemotherapy followed by FOLFOX at progression has similar outcomes to the reverse sequence[109]. A 2008 pooled analysis of 4 phase III trials comparing fluoropyrimidine alone to its combination with irinotecan in the first line setting showed no relationship between age and treatment effect[109]. There was a trend towards improved overall survival with the addition of irinotecan, but this did not reach significance. Regression analysis suggested more diarrhea side-effects with increasing age.

The FFCD 2001-02 trial was a randomized phase III study that evaluated irinotecan combined with 5-FU versus 5-FU alone in patients with metastatic CRC age 75 years or older. PFS and OS were not improved by the addition of irinotecan in this trial, nor for any subgroup analysed[110]. Grade 3-4 toxicity were higher with the addition of irinotecan (76.3%) than 5-FU alone (52.2%). They incorporated assessment of geriatric factors for a subset of patients and found that in addition to irinotecan use, a mini-mental state examination score of <27/30 or a baseline impairment in IADLs had an OR of 5.43 (range, 2.09 to 14.11; $P < .001$) for grade 3-4 toxicity[111]. Baseline independence of IADLs was predictive of better OS, but not benefit from irinotecan[112]. Thus, similar to combination therapy with FOLFOX, less fit older patients may not be appropriate candidates for combination irinotecan plus 5-FU. In fit older adults, there may be benefit from FOLFIRI, but there remains some uncertainty.

Anti-VEGF Antibody

Pooled analyses of randomized trials have found evidence that the addition of anti-vascular endothelial growth factor antibody, bevacizumab, leads to increased survival in older patients[113,114]. The AVEX trial was a randomized trial in elderly patients >70 years of age deemed not to be candidates for doublet chemotherapy[115]. The addition of bevacizumab to single agent capecitabine met the primary endpoint of PFS (9.1 versus 5.1 months, HR 0.53, $p < 0.001$). The trial was not sufficiently powered for OS assessment (20.7 versus 16.8 months, HR 0.79, $p = 0.182$). A review concluded that bevacizumab has a similar safety profile in younger and older adults, with the exception of a slight increase in arterial thrombotic risk with age[116].

The phase III JCOG1018 RESPECT trial randomized elderly patients with unresectable metastatic CRC to FOLFOX/CAPOX plus bevacizumab versus capecitabine or 5-FU plus bevacizumab[117]. 93% of patients were > 75 years of age with a performance status of 0-1. In the preliminary results, they found no difference in median PFS or OS from the addition of oxaliplatin to fluoropyrimidine and bevacizumab. The rates of grade 2-4 neutropenia, nausea, diarrhea, fatigue, and neuropathy were higher with oxaliplatin. Certainly, these results seem to further support omitting oxaliplatin in more frail older adults and may lower the threshold to drop oxaliplatin at onset of toxicity in fit older adults receiving 5-FU and bevacizumab. These preliminary results are not sufficient to warrant the omission of oxaliplatin for all older patients in the front-line setting in light of previous data.

Trifluridine-tipiracil in combination with bevacizumab was not superior to capecitabine-bevacizumab for patients poor candidates for doublet chemotherapy. PFS was similar with 9.4 months for trifluridine-tipiracil plus bevacizumab versus 9.3 months for capecitabine plus bevacizumab[118]. Post-hoc analysis in patients 70 years of age and older did suggest favourable results with trifluridine-tipiracil plus bevacizumab in this population. This combination may be reasonably considered in older adults with contraindications to fluorouracil or capecitabine[118,119].

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Anti-EGFR Antibody

Anti-EGFR therapy is associated with an improvement in progression-free and overall survival in metastatic colorectal cancer in those with left-sided primary tumor without RAS, BRAF or HER2 alterations[104,120]. A recent pooled analysis of 7 randomized trials compared doublet chemotherapy (117 patients) to doublet chemotherapy with the addition anti-EGFR therapy (123 patients) in those > 70 years of age[121]. Older patients had inferior PFS and OS compared to younger patients. The analysis showed a non-statistically significant improvement in OS (24.7 vs 17.6 months; HR 0.77 p=0.092) and PFS (9.1 vs 8.7 months; HR 0.85, p=0.287) from the addition of anti-EGFR therapy to the treatment of adults > 70, after adjusting for key confounders. They however found no evidence that treatment effect was based on age. Older patients did not have statistically higher rates of grade 3+ neutropenia, diarrhea, nausea/vomiting, or neuropathy, suggesting doublet chemotherapy and anti-EGFR therapy can be safely administered.

The phase II PANDA study enrolled patients > 70 years of age with unresectable metastatic RAS-BRAF wild-type colorectal cancer[122]. All patients underwent initial G8 screening, and this was a stratification factor for randomization. 185 patients were randomized to 5-FU and panitumumab with or without oxaliplatin for 12 cycles, followed by panitumumab maintenance. Although, this trial was not designed to directly compare between the two arms, there was a notable reduction in rates of grade 3-4 toxicities: FOLFOX-panitumumab/5-FU-panitumumab: neutropenia 10%/1%; diarrhea 16%/1%; stomatitis 10%/4%; neurotoxicity 3%/0%; fatigue 8%/4%. Grade 3-4 hypomagnesemia was higher in the arm without oxaliplatin surprisingly (3%/8%) and skin toxicities were similar (25%/24%) between the two groups. PFS appeared similar in both groups: 9.6 months for FOLFOX-panitumumab and 9.0 months for 5-FU-panitumumab. Median OS was 23.5 months in FOLFOX-panitumumab arm and 22.0 months in the 5-FU-panitumumab arm (HR 1.0, p=.986). There was a significant interaction between age subgroups (70-75 versus >75 years) and OS, with better outcomes in younger patients treated with FOLFOX-panitumumab versus 5-FU-panitumumab. Similar to the results from the RESPECT trial, these findings may give some comfort that oxaliplatin can be omitted to reduce toxicity without major compromise to efficacy in older patients treated with biologic therapy in combination with fluoropyrimidine.

Triplet Chemotherapy and Biologic

The use of triplet (5-FU, irinotecan and oxaliplatin) chemotherapy and bevacizumab in the first line metastatic setting is popular in certain countries. The FOLFOXIRI plus bevacizumab was compared to over FOLFIRI plus bevacizumab in the original phase III TRIBE study[123]. They did show a benefit in OS (29.8 months with FOLFOXIRI plus bevacizumab vs 25.8 months in the control, HR 0.8, p=0.03), which was a secondary endpoint of the study[102]. The TRIBE2 study is a similar comparison between FOLFOXIRI plus bevacizumab versus FOLFOX plus bevacizumab[124]. Patients were treated for 8 cycles followed by 5-FU and bevacizumab maintenance. At first progression, the experimental arm was rechallenged with FOLFOXIRI and bevacizumab; whereas, the control arm was transitioned to FOLFIRI and bevacizumab at progression. The study showed an improvement in the PFS2 primary endpoint (defined as time until progression on any treatment given after first disease progression) of 19.2 months in the FOLFOXIRI plus bevacizumab arm versus 16.2 months in the control (HR 0.74, p=0.0005). Median overall survival also favored FOLFOXIRI plus bevacizumab arm (27.4 vs 22.5 months, HR 0.82, p=0.032). . The TRIBE studies included patients up to the age of 70 that had ECOG 0-2, but only those with ECOG 0 were eligible between the ages of 71-75. A pooled analysis of the two trials showed no difference in response rates or PFS between patients older and younger than 70 years of age and no interaction between treatment and age[125]. However, older patients had higher rates of grade ≥ 3 adverse events (73% versus 60% in those <70 years of age, p<0.01) including, 27% diarrhea and 16% febrile neutropenia. These increased toxicities likely should lead to caution using this regimen in older adults, and should it be reserved for the fittest patients under 75 years of age[10].

The combination of anti-EGFR therapy with triplet chemotherapy is not recommended in guidelines[10,126,127].

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Immunotherapy

Pembrolizumab has become the standard first-line therapy for dMMR metastatic CRC based on the results of the Keynote 177 trial[128]. PFS was doubled when compared to first line chemotherapy (16.5 months versus 8.2 months, HR 0.59). Due to a 60% rate of crossover, no overall survival benefit was established at final analysis[129]. However, given that treatment-related adverse events were 3 times higher in the chemotherapy group, immunotherapy is clearly justified in the frontline setting for the majority of these patients.

There were 90 patients over 70 years of age included in the trial, with the forest plot for PFS suggesting some attenuation of the benefit from pembrolizumab over chemotherapy in this age group (HR 0.52 for <70 years of age; HR 0.77 for those >70 years of age). There were similar findings for OS results. However, a growing body of literature has suggested that advanced age does not preclude, and may even increase benefit from immunotherapy in a variety of cancers[130]. In a recently published retrospective cohort study of mostly older adults with sporadic dMMR metastatic CRC (n=41 patients, median age 81, 22% with ECOG 2-3) treated with first-line pembrolizumab, the response rate was 49%, median PFS was 21 months and median OS was 36 months[131]. These results are on par with those of the Keynote 177 population as a whole. Immunotherapy should be considered in the front-line setting for metastatic disease in older patients with dMMR colorectal cancer.

Combination treatment with nivolumab and ipilimumab shows promising results in metastatic dMMR CRC from the phase III CheckMate 8HW study with an HR of 0.21 compared to standard chemotherapy[132]. Although data from other cancers suggest combination immunotherapy treatment has a similar safety profile in older and younger patients[133], we have yet to clearly establish superiority of combination therapy compared single agent immunotherapy in metastatic dMMR CRC.

Later Line Options

More therapeutic options beyond fluoropyrimidine-based chemotherapy combinations (and pembrolizumab for the patients with dMMR CRC) have been added to the colorectal cancer landscape in recent years.

The BEACON trial established encorafenib plus cetuximab as a preferred second or third line option for BRAF-mutated CRC due to improvement in overall survival and time until decline in quality of life[134,135]. The benefit was present in the subgroup of patients 65 years of age and older [136]. Dose interruptions did not differ significantly between those above and below 70 years of age; although, nausea/vomiting, abdominal pain, and fatigue/asthenia were more common in older patients[137].

The RECOURSE trial showed a modest benefit in overall survival for trifluridine-tipiracil over placebo after exposure to standard chemotherapy and antibody therapies[138]. Subgroup analysis suggested the benefits were similar for patients aged ≥65 and ≥70 years[139]. The recently published SUNLIGHT trial, showed additional benefit of adding bevacizumab to trifluridine-tipiracil[140]. The primary endpoint of the trial was OS, with the median being 10.8 months for the trifluridine-tipiracil plus bevacizumab group compared to 7.5 months with trifluridine-tipiracil alone. 44% of participants were 65 years of age or older and survival benefit was present irrespective of age.

The CORRECT trial showed a 1.4 month survival benefit for regorafenib (160mg daily for three weeks on, one week off) in a later line setting over best supportive care[141]. This small benefit seemed to be independent of age [142]. Alternative, dosing schedules have been explored to reduce toxicity[143]. A small prospective trial of 23 patients over 75 years of age who were not frail by G8 screening/CGA suggested reasonable safety and efficacy when using a dose-escalation strategy and scheduling of 2 weeks on, 1 week off of regorafenib[144].

A new oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors, fruquintinib has shown efficacy in patients exposed or intolerant to the above-mentioned therapies where appropriate. In the FRESCO-2 trial, there was a 2.6 month OS benefit compared to placebo established (7.4 months for fruquintinib versus 4.8 months for placebo)[145]. The benefit appeared to be present in the patients older than 65 years of age. Overall, this appears to be well tolerated medication although there were some increased rates of hypertension, asthenia and hand-and-foot syndrome compared to placebo. Food and Drug Administration approval was granted on November 8, 2023.

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Conclusions

A summary of treatment recommendations is provided in Table 2. Where available, these recommendations are derived from elderly-specific prospective data. Unfortunately, many recommendations are ultimately derived from trials of mostly younger populations that have rapidly changed the standard of care for patients with CRC.

Table 2. Summary of Recommendations for treating Older Adults with Colorectal Cancer.

Clinical Scenario	Recommendations
All Stages of Disease	
	• Geriatric Screening tools such as the G8 should be used to identify patients who will benefit from Comprehensive Geriatric Assessment • Comprehensive Geriatric Assessment should be performed when possible in all older adults who score < 14 on G8 screening or have other clear health, functional or social limitations • Multidisciplinary discussion between oncology (surgeon, radiation oncologist, medical oncologist) and geriatric specialists • Enrollment in clinical trials whenever possible • Unfit patients with limited life expectancy or other more life-limiting conditions should be managed with best supportive interventions
Localized Disease, Microsatellite Stable	
Early Stage Rectal Cancer (T1-2, N0)	
FIT	• Transanal excision for feasible T1 tumors
MEDIUM FIT	• Transanal excision for feasible T1 tumors • Short-course radiation followed by transanal endoscopic microsurgery is a reasonable initial approach for T2 tumors
Locally Advanced Rectal Cancer (T3-4,N0-2, or TxN+), Neoadjuvant Therapy	
FIT	• TNT approaches are generally favored over adjuvant treatments. cT3 mid-high tumors or cT2 tumors without compromised mesorectal fascia however may be candidates for upfront surgery • cT2N1, or T3N0-1 without compromised mesorectal fascia – omission of radiation prior to surgery in those responding to FOLFOX does not compromise outcomes • Sequential FOLFIRINOX, CRT, surgery and adjuvant chemotherapy can be considered only for very fit patients <75 years of age • Short-course radiation followed by FOLFOX prior to surgery can be considered for those with high-risk features • Discuss watch and wait approaches for those with low tumors and complete clinical response to neoadjuvant therapy. If goal is to avoid surgery, success rates are higher when CRT is given before chemotherapy • CRT followed by transanal endoscopic microsurgery may be a reasonable initial approach for T3N0 tumors with ECOG 2. There are high risks of lower anterior resection syndrome with this approach
MEDIUM FIT	• TNT approaches are generally favored over adjuvant treatments. cT3 mid-high tumors or cT2 tumors without compromised mesorectal fascia however may be candidates for upfront surgery • Short-course radiation followed by total mesorectal excision may have short-term quality of life benefits over CRT followed by TME • Discuss watch and wait approaches for those with low tumors and complete clinical response to neoadjuvant therapy

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Colon Cancer, Adjuvant Therapy		
Stage II with high-risk features		
	FIT or MEDIUM FIT	• Consider 6 months of single agent capecitabine/5-FU • Omission of chemotherapy may be reasonable. Negative ct-DNA may further support decision to omit chemotherapy, particular in those without T4 disease
Stage III		
	FIT	• Low risk: 6 months of capecitabine/5-FU or 3 months of CAPOX or 6 months of capecitabine/5-FU • High risk (T4 or N2): Consider 3-6 months of CAPOX or 6 months of FOLFOX. The threshold to drop oxaliplatin beyond 3 months may be low • Shared decision making as benefit from adjuvant oxaliplatin is unclear in older adults
	MEDIUM FIT	• 6 months of capecitabine/5-FU
Localized Disease, Microsatellite Instability		
Rectal Cancer, Neoadjuvant Setting		
	FIT or MEDIUM FIT	• Upfront immunotherapy with consideration of surgical avoidance in setting of complete response
Colon Cancer, Adjuvant Setting		
Stage II		
	FIT or MEDIUM FIT	• Adjuvant chemotherapy generally is not recommended due to good prognosis and lack of benefit
Stage III		
	FIT	• Consider CAPOX or FOLFOX for 3-6 months
	MEDIUM FIT	• Benefit of adjuvant chemotherapy is unclear in those not fit for oxaliplatin, given potential harm from single agent capecitabine/5-FU
Metastatic Disease		
Resectable		
	FIT	• 6 months of perioperative FOLFOX, or proceed directly to resection • Perioperative/adjuvant chemotherapy has not shown survival benefit
	MEDIUM FIT	• Proceed directly to surgical, or consideration of single agent 5-FU or capecitabine • Perioperative/adjuvant chemotherapy has not shown survival benefit
Borderline Resectable		
	FIT	• Consider FOLFOXIRI plus bevacizumab for very fit patients <75 years of age • Doublet chemotherapy plus biologic is reasonable
	MEDIUM FIT	• Doublet chemotherapy and plus biologic with initial dose reduction, or single agent 5-FU with biologic
Palliative Setting, First Line		
	FIT	• Left sided primary, RAS/BRAF/HER2 wt: Doublet chemotherapy with anti-EGFR therapy. Discussion about unclear benefit of oxaliplatin/irinotecan with anti-EGFR-fluoropyrimidine in older patients • Right sided primary, or RAS/BRAF/HER mutant: Doublet chemotherapy with bevacizumab. Discussion about unclear benefit of oxaliplatin/irinotecan with bevacizumab-fluoropyrimidine in older patients • FOLFOXIRI with bevacizumab can only be considered for the fittest patients < 75 years of age after discussion of increased toxicity risk • Pembrolizumab for dMMR disease

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	MEDIUM FIT	• Left sided primary, RAS/BRAF/HER2 wt: 5-FU/capecitabine with anti-EGFR therapy • Right sided primary, or RAS/BRAF/HER mutant: 5-FU/capecitabine +/- bevacizumab • Trifluridine/tipiracil + bevacizumab in setting of 5-FU/capecitabine contraindication • Pembrolizumab for dMMR disease
Palliative Setting, Later Lines	FIT or MEDIUM FIT	• BRAF mutated: encorafenib-cetuximab is as a second or third line option • Trifluridine/tipiracil with bevacizumab is an effective option • Regorafenib may be appropriate for fit patients, but only after weighing the minimal survival benefit with the toxicity profile. Alternative dosing strategies should be employed • Fruqintinib is an appropriate option, preferably after trifluridine/tipiracil or regorafenib

Chronological age alone is not a reason to withhold potentially effective therapy. Geriatric assessment is more useful in helping with treatment decisions and limiting toxicity for older individuals with CRC. CGA should become routinely used in this setting.

Future Directions

In the future, expansion of minimally invasive techniques, prognostic tools such as ctDNA and refinement of immunotherapy use in dMMR disease may further reduce the morbidity associated with CRC management. A significant portion of CRC cases involve patients with advanced age and they warrant specific attention and inclusion in the design of future clinical trials. Further prospective validation of geriatric assessment tools to guide treatment selection, specifically in the context of CRC is needed. Obtaining robust quality of life and toxicity data in future studies is essential. This is especially true given the priorities of older adults with CRC, to better inform shared decision making.

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References

1. H. Sung *et al.*, "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries," *CA: A Cancer Journal for Clinicians,* vol. 71, no. 3, pp. 209-249, 2021, doi: https://doi.org/10.3322/caac.21660.
2. "National Cancer Institute: Surveillance, Epidemilology, and End Results Program: SEER Fact Sheets-Colon and Rectum Cancer. https://seer.cancer.gov/statfacts/html/colorect.html. Accessed July 31, 2023.."
3. D. Ioffe and E. Dotan, "Guidance for Treating the Older Adults with Colorectal Cancer," *Curr Treat Options Oncol,* vol. 24, no. 6, pp. 644-666, Jun 2023, doi: 10.1007/s11864-023-01071-6.
4. E. Quoix *et al.*, "Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial," *Lancet,* vol. 378, no. 9796, pp. 1079-88, Sep 17 2011, doi: 10.1016/S0140-6736(11)60780-0.
5. A. Clegg, J. Young, S. Iliffe, M. O. Rikkert, and K. Rockwood, "Frailty in elderly people," (in eng), *Lancet,* vol. 381, no. 9868, pp. 752-62, Mar 2 2013, doi: 10.1016/s0140-6736(12)62167-9.
6. C. Kenis *et al.*, "Performance of two geriatric screening tools in older patients with cancer," *J Clin Oncol,* vol. 32, no. 1, pp. 19-26, Jan 1 2014, doi: 10.1200/JCO.2013.51.1345.
7. M. C. Shinall, Jr. *et al.*, "Association of Preoperative Patient Frailty and Operative Stress With Postoperative Mortality," *JAMA Surg,* vol. 155, no. 1, p. e194620, Jan 1 2020, doi: 10.1001/jamasurg.2019.4620.

8. C. Kenis *et al.*, "Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study," *Ann Oncol,* vol. 24, no. 5, pp. 1306-12, May 2013, doi: 10.1093/annonc/mds619.
9. M. Takahashi *et al.*, "The G8 screening tool enhances prognostic value to ECOG performance status in elderly cancer patients: A retrospective, single institutional study," *PLoS One,* vol. 12, no. 6, p. e0179694, 2017, doi: 10.1371/journal.pone.0179694.
10. A. Cervantes *et al.*, "Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up," *Ann Oncol,* vol. 34, no. 1, pp. 10-32, Jan 2023, doi: 10.1016/j.annonc.2022.10.003.
11. W. Dale *et al.*, "Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy: ASCO Guideline Update," *J Clin Oncol,* p. JCO2300933, Jul 17 2023, doi: 10.1200/JCO.23.00933.
12. "National Comprehensive Cancer Network: Colon Cancer. Version 2.2023 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed August 9, 2023.."
13. M. F. Folstein, S. E. Folstein, and P. R. McHugh, ""Mini-mental state". A practical method for grading the cognitive state of patients for the clinician," *J Psychiatr Res,* vol. 12, no. 3, pp. 189-98, Nov 1975, doi: 10.1016/0022-3956(75)90026-6.
14. Z. S. Nasreddine *et al.*, "The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment," *J Am Geriatr Soc,* vol. 53, no. 4, pp. 695-9, Apr 2005, doi: 10.1111/j.1532-5415.2005.53221.x.
15. M. J. Kaiser *et al.*, "Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status," *J Nutr Health Aging,* vol. 13, no. 9, pp. 782-8, Nov 2009, doi: 10.1007/s12603-009-0214-7.
16. O. P. Almeida and S. A. Almeida, "Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV," *Int J Geriatr Psychiatry,* vol. 14, no. 10, pp. 858-65, Oct 1999, doi: 10.1002/(sici)1099-1166(199910)14:10<858::aid-gps35>3.0.co;2-8.
17. J. I. Sheikh and J. A. Yesavage, "Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version," *Clinical Gerontologist: The Journal of Aging and Mental Health,* vol. 5, no. 1-2, pp. 165-173, 1986, doi: 10.1300/J018v05n01_09.
18. D. Li *et al.*, "Geriatric Assessment-Driven Intervention (GAIN) on Chemotherapy-Related Toxic Effects in Older Adults With Cancer: A Randomized Clinical Trial," *JAMA Oncol,* vol. 7, no. 11, p. e214158, Nov 1 2021, doi: 10.1001/jamaoncol.2021.4158.
19. M. Hamaker *et al.*, "Geriatric assessment in the management of older patients with cancer - A systematic review (update)," *J Geriatr Oncol,* vol. 13, no. 6, pp. 761-777, Jul 2022, doi: 10.1016/j.jgo.2022.04.008.
20. C. DuMontier *et al.*, "Randomized controlled trial of geriatric consultation versus standard care in older adults with hematologic malignancies," *Haematologica,* vol. 107, no. 5, pp. 1172-1180, May 1 2022, doi: 10.3324/haematol.2021.278802.
21. S. G. Mohile *et al.*, "Communication With Older Patients With Cancer Using Geriatric Assessment: A Cluster-Randomized Clinical Trial From the National Cancer Institute Community Oncology Research Program," *JAMA Oncol,* vol. 6, no. 2, pp. 196-204, Feb 1 2020, doi: 10.1001/jamaoncol.2019.4728.
22. M. Extermann *et al.*, "Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score," *Cancer,* vol. 118, no. 13, pp. 3377-86, Jul 1 2012, doi: 10.1002/cncr.26646.
23. A. Hurria *et al.*, "Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study," *J Clin Oncol,* vol. 29, no. 25, pp. 3457-65, Sep 1 2011, doi: 10.1200/JCO.2011.34.7625.
24. I. Ortland *et al.*, "Comparing the performance of the CARG and the CRASH score for predicting toxicity in older patients with cancer," *J Geriatr Oncol,* vol. 11, no. 6, pp. 997-1005, Jul 2020, doi: 10.1016/j.jgo.2019.12.016.
25. S. G. Mohile *et al.*, "Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study," *Lancet,* vol. 398, no. 10314, pp. 1894-1904, Nov 20 2021, doi: 10.1016/S0140-6736(21)01789-X.
26. W. K. Soo, M. T. King, A. Pope, P. Parente, P. Darzins, and I. D. Davis, "Integrated Geriatric Assessment and Treatment Effectiveness (INTEGERATE) in older people with cancer starting systemic anticancer treatment in Australia: a multicentre, open-label, randomised controlled trial," *Lancet Healthy Longev,* vol. 3, no. 9, pp. e617-e627, Sep 2022, doi: 10.1016/S2666-7568(22)00169-6.
27. M. Puts *et al.*, "Impact of Geriatric Assessment and Management on Quality of Life, Unplanned Hospitalizations, Toxicity, and Survival for Older Adults With Cancer: The Randomized 5C Trial," *J Clin Oncol,* vol. 41, no. 4, pp. 847-858, Feb 1 2023, doi: 10.1200/JCO.22.01007.
28. R. D. Nipp *et al.*, "Effects of a perioperative geriatric intervention for older adults with Cancer: A randomized clinical trial," *J Geriatr Oncol,* vol. 13, no. 4, pp. 410-415, May 2022, doi: 10.1016/j.jgo.2022.01.001.

 doi:10.20944/preprints202404.0689.v1

29. A. Shahrokni *et al.*, "Association of Geriatric Comanagement and 90-Day Postoperative Mortality Among Patients Aged 75 Years and Older With Cancer," *JAMA Netw Open,* vol. 3, no. 8, p. e209265, Aug 3 2020, doi: 10.1001/jamanetworkopen.2020.9265.
30. P. E. Lester, T. S. Dharmarajan, and E. Weinstein, "The Looming Geriatrician Shortage: Ramifications and Solutions," *J Aging Health,* vol. 32, no. 9, pp. 1052-1062, Oct 2020, doi: 10.1177/0898264319879325.
31. N. B. Leighl, S. Nirmalakumar, D. A. Ezeife, and B. Gyawali, "An Arm and a Leg: The Rising Cost of Cancer Drugs and Impact on Access," *American Society of Clinical Oncology Educational Book,* no. 41, pp. e1-e12, 2021, doi: 10.1200/edbk_100028.
32. B. C. Paun, S. Cassie, A. R. MacLean, E. Dixon, and W. D. Buie, "Postoperative complications following surgery for rectal cancer," *Ann Surg,* vol. 251, no. 5, pp. 807-18, May 2010, doi: 10.1097/SLA.0b013e3181dae4ed.
33. I. Montroni *et al.*, "Quality of Life in Older Adults After Major Cancer Surgery: The GOSAFE International Study," *J Natl Cancer Inst,* vol. 114, no. 7, pp. 969-978, Jul 11 2022, doi: 10.1093/jnci/djac071.
34. I. Montroni *et al.*, "Predicting Functional Recovery and Quality of Life in Older Patients Undergoing Colorectal Cancer Surgery: Real-World Data From the International GOSAFE Study," (in eng), *J Clin Oncol,* p. Jco2202195, Jun 30 2023, doi: 10.1200/jco.22.02195.
35. S. P. Bach *et al.*, "Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study," *Lancet Gastroenterol Hepatol,* vol. 6, no. 2, pp. 92-105, Feb 2021, doi: 10.1016/S2468-1253(20)30333-2.
36. H. F. Kennecke *et al.*, "Neoadjuvant Chemotherapy, Excision, and Observation for Early Rectal Cancer: The Phase II NEO Trial (CCTG CO.28) Primary End Point Results," *J Clin Oncol,* vol. 41, no. 2, pp. 233-242, Jan 10 2023, doi: 10.1200/JCO.22.00184.
37. D. M. Jiang *et al.*, "Clinical outcomes of elderly patients receiving neoadjuvant chemoradiation for locally advanced rectal cancer," *Ann Oncol,* vol. 26, no. 10, pp. 2102-6, Oct 2015, doi: 10.1093/annonc/mdv331.
38. E. Francois *et al.*, "Comparison of short course radiotherapy with chemoradiotherapy for locally advanced rectal cancers in the elderly: A multicentre, randomised, non-blinded, phase 3 trial," *Eur J Cancer,* vol. 180, pp. 62-70, Feb 2023, doi: 10.1016/j.ejca.2022.11.020.
39. R. R. Bahadoer *et al.*, "Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial," *Lancet Oncol,* vol. 22, no. 1, pp. 29-42, Jan 2021, doi: 10.1016/S1470-2045(20)30555-6.
40. T. Conroy *et al.*, "Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial," *Lancet Oncol,* vol. 22, no. 5, pp. 702-715, May 2021, doi: 10.1016/S1470-2045(21)00079-6.
41. E. A. Dijkstra *et al.*, "Locoregional Failure During and After Short-course Radiotherapy followed by Chemotherapy and Surgery Compared to Long-course Chemoradiotherapy and Surgery - A Five-year Follow-up of the RAPIDO Trial," *Ann Surg,* Jan 20 2023, doi: 10.1097/SLA.0000000000005799.
42. E. P. Conroy T, Rio E, Evesque L, Mesgouez-Nebout N, Vendrely V, Artignan X, Bouche O, Boileve A, Delaye M, Gargot D, Boige V, Bonichon-Lamichhane V, Louvet C, De La Fouchardiere C, Morand C, Pezzella V, Rullier E, Castan F, Borg C, "Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial.," *ASCO General Meeting* 2023.
43. J. Garcia-Aguilar *et al.*, "Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy," *J Clin Oncol,* vol. 40, no. 23, pp. 2546-2556, Aug 10 2022, doi: 10.1200/JCO.22.00032.
44. J. F. Bosset *et al.*, "Chemotherapy with preoperative radiotherapy in rectal cancer," *N Engl J Med,* vol. 355, no. 11, pp. 1114-23, Sep 14 2006, doi: 10.1056/NEJMoa060829.
45. M. Braendengen *et al.*, "Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer," *J Clin Oncol,* vol. 26, no. 22, pp. 3687-94, Aug 1 2008, doi: 10.1200/JCO.2007.15.3858.
46. R. Sauer *et al.*, "Preoperative versus postoperative chemoradiotherapy for rectal cancer," *N Engl J Med,* vol. 351, no. 17, pp. 1731-40, Oct 21 2004, doi: 10.1056/NEJMoa040694.
47. D. Schrag *et al.*, "Preoperative Treatment of Locally Advanced Rectal Cancer," *N Engl J Med,* vol. 389, no. 4, pp. 322-334, Jul 27 2023, doi: 10.1056/NEJMoa2303269.
48. R. Ruppert *et al.*, "Risk-Adapted Neoadjuvant Chemoradiotherapy in Rectal Cancer: Final Report of the OCUM Study," *J Clin Oncol,* vol. 41, no. 24, pp. 4025-4034, Aug 20 2023, doi: 10.1200/JCO.22.02166.
49. J. P. Gerard *et al.*, "Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3 rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial," *Lancet Gastroenterol Hepatol,* vol. 8, no. 4, pp. 356-367, Apr 2023, doi: 10.1016/S2468-1253(22)00392-2.

50. A. J. Breugom *et al.*, "Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data," *Lancet Oncol,* vol. 16, no. 2, pp. 200-7, Feb 2015, doi: 10.1016/S1470-2045(14)71199-4.
51. Y. S. Hong *et al.*, "Oxaliplatin-Based Adjuvant Chemotherapy for Rectal Cancer After Preoperative Chemoradiotherapy (ADORE): Long-Term Results of a Randomized Controlled Trial," *J Clin Oncol,* vol. 37, no. 33, pp. 3111-3123, Nov 20 2019, doi: 10.1200/JCO.19.00016.
52. K. L. Kahn *et al.*, "Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer," *JAMA,* vol. 303, no. 11, pp. 1037-45, Mar 17 2010, doi: 10.1001/jama.2010.272.
53. A. I. Neugut *et al.*, "Duration of adjuvant chemotherapy for colon cancer and survival among the elderly," *J Clin Oncol,* vol. 24, no. 15, pp. 2368-75, May 20 2006, doi: 10.1200/JCO.2005.04.5005.
54. H. K. Sanoff *et al.*, "Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years," *J Clin Oncol,* vol. 30, no. 21, pp. 2624-34, Jul 20 2012, doi: 10.1200/JCO.2011.41.1140.
55. D. J. Sargent *et al.*, "A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients," *N Engl J Med,* vol. 345, no. 15, pp. 1091-7, Oct 11 2001, doi: 10.1056/NEJMoa010957.
56. W. Scheithauer *et al.*, "Oral capecitabine as an alternative to i.v. 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial," *Ann Oncol,* vol. 14, no. 12, pp. 1735-43, Dec 2003, doi: 10.1093/annonc/mdg500.
57. C. Twelves *et al.*, "Capecitabine as adjuvant treatment for stage III colon cancer," *N Engl J Med,* vol. 352, no. 26, pp. 2696-704, Jun 30 2005, doi: 10.1056/NEJMoa043116.
58. M. T. Seymour *et al.*, "Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial," *Lancet,* vol. 377, no. 9779, pp. 1749-59, May 21 2011, doi: 10.1016/S0140-6736(11)60399-1.
59. T. Andre *et al.*, "Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer," *N Engl J Med,* vol. 350, no. 23, pp. 2343-51, Jun 3 2004, doi: 10.1056/NEJMoa032709.
60. T. Andre *et al.*, "Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study," *J Clin Oncol,* vol. 33, no. 35, pp. 4176-87, Dec 10 2015, doi: 10.1200/JCO.2015.63.4238.
61. J. P. Kuebler *et al.*, "Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07," *J Clin Oncol,* vol. 25, no. 16, pp. 2198-204, Jun 1 2007, doi: 10.1200/JCO.2006.08.2974.
62. G. Yothers *et al.*, "Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses," *J Clin Oncol,* vol. 29, no. 28, pp. 3768-74, Oct 1 2011, doi: 10.1200/JCO.2011.36.4539.
63. D. G. Haller *et al.*, "Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer," *J Clin Oncol,* vol. 29, no. 11, pp. 1465-71, Apr 10 2011, doi: 10.1200/JCO.2010.33.6297.
64. H. J. Schmoll *et al.*, "Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial," *J Clin Oncol,* vol. 33, no. 32, pp. 3733-40, Nov 10 2015, doi: 10.1200/JCO.2015.60.9107.
65. N. J. McCleary *et al.*, "Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database," *J Clin Oncol,* vol. 31, no. 20, pp. 2600-6, Jul 10 2013, doi: 10.1200/JCO.2013.49.6638.
66. L. Dottorini *et al.*, "Oxaliplatin in Adjuvant Colorectal Cancer: Is There a Role in Older Patients?," *J Clin Oncol,* vol. 41, no. 18, pp. 3300-3303, Jun 20 2023, doi: 10.1200/JCO.23.00354.
67. C. Gallois *et al.*, "Oxaliplatin-Based Adjuvant Chemotherapy in Older Patients With Stage III Colon Cancer: An ACCENT/IDEA Pooled Analysis of 12 Trials," *Journal of Clinical Oncology,* vol. 0, no. 0, p. JCO.23.01326, doi: 10.1200/jco.23.01326.
68. A. Grothey *et al.*, "Duration of Adjuvant Chemotherapy for Stage III Colon Cancer," *N Engl J Med,* vol. 378, no. 13, pp. 1177-1188, Mar 29 2018, doi: 10.1056/NEJMoa1713709.
69. T. Andre *et al.*, "Effect of duration of adjuvant chemotherapy for patients with stage III colon cancer (IDEA collaboration): final results from a prospective, pooled analysis of six randomised, phase 3 trials," *Lancet Oncol,* vol. 21, no. 12, pp. 1620-1629, Dec 2020, doi: 10.1016/S1470-2045(20)30527-1.
70. T. Yoshino *et al.*, "Final Analysis of 3 Versus 6 Months of Adjuvant Oxaliplatin and Fluoropyrimidine-Based Therapy in Patients With Stage III Colon Cancer: The Randomized Phase III ACHIEVE Trial," *J Clin Oncol,* vol. 40, no. 29, pp. 3419-3429, Oct 10 2022, doi: 10.1200/JCO.21.02628.
71. C. Lieu *et al.*, "Duration of Oxaliplatin-Containing Adjuvant Therapy for Stage III Colon Cancer: ASCO Clinical Practice Guideline," *J Clin Oncol,* vol. 37, no. 16, pp. 1436-1447, Jun 1 2019, doi: 10.1200/JCO.19.00281.
72. M. Koopman and C. J. A. Punt, "Duration of adjuvant treatment for patients with stage III colon cancer," *Lancet Oncol,* vol. 21, no. 12, pp. 1545-1547, Dec 2020, doi: 10.1016/S1470-2045(20)30618-5.

73. S. T. Kim *et al.*, "Oxaliplatin (3 months v 6 months) With 6 Months of Fluoropyrimidine as Adjuvant Therapy in Patients With Stage II/III Colon Cancer: KCSG CO09-07," *J Clin Oncol,* vol. 40, no. 33, pp. 3868-3877, Nov 20 2022, doi: 10.1200/JCO.21.02962.
74. C. Gallois *et al.*, "Prognostic Impact of Early Treatment and Oxaliplatin Discontinuation in Patients With Stage III Colon Cancer: An ACCENT/IDEA Pooled Analysis of 11 Adjuvant Trials," *J Clin Oncol,* vol. 41, no. 4, pp. 803-815, Feb 1 2023, doi: 10.1200/JCO.21.02726.
75. M. Antonio *et al.*, "Geriatric Assessment Predicts Survival and Competing Mortality in Elderly Patients with Early Colorectal Cancer: Can It Help in Adjuvant Therapy Decision-Making?," *Oncologist,* vol. 22, no. 8, pp. 934-943, Aug 2017, doi: 10.1634/theoncologist.2016-0462.
76. J. Kannarkatt, J. Joseph, P. C. Kurniali, A. Al-Janadi, and B. Hrinczenko, "Adjuvant Chemotherapy for Stage II Colon Cancer: A Clinical Dilemma," *J Oncol Pract,* vol. 13, no. 4, pp. 233-241, Apr 2017, doi: 10.1200/JOP.2016.017210.
77. B. M. Meyers, R. Cosby, F. Quereshy, and D. Jonker, "Adjuvant Chemotherapy for Stage II and III Colon Cancer Following Complete Resection: A Cancer Care Ontario Systematic Review," *Clin Oncol (R Coll Radiol),* vol. 29, no. 7, pp. 459-465, Jul 2017, doi: 10.1016/j.clon.2017.03.001.
78. D. Kotani *et al.*, "Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer," *Nat Med,* vol. 29, no. 1, pp. 127-134, Jan 2023, doi: 10.1038/s41591-022-02115-4.
79. J. Tie *et al.*, "Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer," *N Engl J Med,* vol. 386, no. 24, pp. 2261-2272, Jun 16 2022, doi: 10.1056/NEJMoa2200075.
80. G. Argiles *et al.*, "Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up," *Ann Oncol,* vol. 31, no. 10, pp. 1291-1305, Oct 2020, doi: 10.1016/j.annonc.2020.06.022.
81. E. S. Christenson *et al.*, "Colorectal cancer in patients of advanced age is associated with increased incidence of BRAF p.V600E mutation and mismatch repair deficiency," *Front Oncol,* vol. 13, p. 1193259, 2023, doi: 10.3389/fonc.2023.1193259.
82. F. Battaglin, M. Naseem, H. J. Lenz, and M. E. Salem, "Microsatellite instability in colorectal cancer: overview of its clinical significance and novel perspectives," *Clin Adv Hematol Oncol,* vol. 16, no. 11, pp. 735-745, Nov 2018. [Online]. Available: https://www.ncbi.nlm.nih.gov/pubmed/30543589.
83. C. M. Ribic *et al.*, "Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer," *N Engl J Med,* vol. 349, no. 3, pp. 247-57, Jul 17 2003, doi: 10.1056/NEJMoa022289.
84. R. Cohen *et al.*, "Microsatellite Instability in Patients With Stage III Colon Cancer Receiving Fluoropyrimidine With or Without Oxaliplatin: An ACCENT Pooled Analysis of 12 Adjuvant Trials," *J Clin Oncol,* vol. 39, no. 6, pp. 642-651, Feb 20 2021, doi: 10.1200/JCO.20.01600.
85. G. Tomasello, M. Ghidini, B. Galassi, F. Grossi, A. Luciani, and F. Petrelli, "Survival benefit with adjuvant chemotherapy in stage III microsatellite-high/deficient mismatch repair colon cancer: a systematic review and meta-analysis," *Sci Rep,* vol. 12, no. 1, p. 1055, Jan 20 2022, doi: 10.1038/s41598-022-05065-6.
86. F. A. Sinicrope *et al.*, "Randomized trial of standard chemotherapy alone or combined with atezolizumab as adjuvant therapy for patients with stage III colon cancer and deficient mismatch repair (ATOMIC, Alliance A021502)," *Journal of Clinical Oncology,* vol. 37, no. 15_suppl, pp. e15169-e15169, 2019, doi: 10.1200/JCO.2019.37.15_suppl.e15169.
87. D. Lau *et al.*, "Rationale and design of the POLEM trial: avelumab plus fluoropyrimidine-based chemotherapy as adjuvant treatment for stage III mismatch repair deficient or POLE exonuclease domain mutant colon cancer: a phase III randomised study," *ESMO Open,* vol. 5, no. 1, Feb 2020, doi: 10.1136/esmoopen-2019-000638.
88. D. J. Papke, Jr., M. B. Yurgelun, A. E. Noffsinger, K. O. Turner, R. M. Genta, and M. Redston, "Prevalence of Mismatch-Repair Deficiency in Rectal Adenocarcinomas," *N Engl J Med,* vol. 387, no. 18, pp. 1714-1716, Nov 3 2022, doi: 10.1056/NEJMc2210175.
89. A. Puccini *et al.*, "Impact of Patient Age on Molecular Alterations of Left-Sided Colorectal Tumors," *Oncologist,* vol. 24, no. 3, pp. 319-326, Mar 2019, doi: 10.1634/theoncologist.2018-0117.
90. A. Cercek *et al.*, "PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer," *N Engl J Med,* vol. 386, no. 25, pp. 2363-2376, Jun 23 2022, doi: 10.1056/NEJMoa2201445.
91. V. Y. L. Chalabi M, van den Berg J, Sikorska K, Beets G, Lent A.V, Grootscholten M.C., Aalbers A, Buller N., Marsman H., Hendriks E, Burger P.W.A, Aukema T, Oosterling S, Beets-Tan R, Schumacher T.N, van Leerdam M, Voest E.E, Haanen J.B.A.G., "Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study," *Annals of Oncology,* vol. 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089, 2022.
92. K. Ludford *et al.*, "Neoadjuvant Pembrolizumab in Localized Microsatellite Instability High/Deficient Mismatch Repair Solid Tumors," *J Clin Oncol,* vol. 41, no. 12, pp. 2181-2190, Apr 20 2023, doi: 10.1200/JCO.22.01351.
93. R. L. Siegel, N. S. Wagle, A. Cercek, R. A. Smith, and A. Jemal, "Colorectal cancer statistics, 2023," *CA Cancer J Clin,* vol. 73, no. 3, pp. 233-254, May-Jun 2023, doi: 10.3322/caac.21772.

94. P. Seghers *et al.*, "Patient Preferences for Treatment Outcomes in Oncology with a Focus on the Older Patient-A Systematic Review," *Cancers (Basel)*, vol. 14, no. 5, Feb 23 2022, doi: 10.3390/cancers14051147.
95. T. R. Fried, E. H. Bradley, V. R. Towle, and H. Allore, "Understanding the treatment preferences of seriously ill patients," *N Engl J Med*, vol. 346, no. 14, pp. 1061-6, Apr 4 2002, doi: 10.1056/NEJMsa012528.
96. F. Quenet *et al.*, "Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial," *Lancet Oncol*, vol. 22, no. 2, pp. 256-266, Feb 2021, doi: 10.1016/S1470-2045(20)30599-4.
97. V. J. Verwaal, S. Bruin, H. Boot, G. van Slooten, and H. van Tinteren, "8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer," *Ann Surg Oncol*, vol. 15, no. 9, pp. 2426-32, Sep 2008, doi: 10.1245/s10434-008-9966-2.
98. B. Nordlinger *et al.*, "Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial," *Lancet*, vol. 371, no. 9617, pp. 1007-16, Mar 22 2008, doi: 10.1016/S0140-6736(08)60455-9.
99. B. Nordlinger *et al.*, "Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial," *Lancet Oncol*, vol. 14, no. 12, pp. 1208-15, Nov 2013, doi: 10.1016/S1470-2045(13)70447-9.
100. Y. Kanemitsu *et al.*, "Hepatectomy Followed by mFOLFOX6 Versus Hepatectomy Alone for Liver-Only Metastatic Colorectal Cancer (JCOG0603): A Phase II or III Randomized Controlled Trial," *J Clin Oncol*, vol. 39, no. 34, pp. 3789-3799, Dec 1 2021, doi: 10.1200/JCO.21.01032.
101. M. J. G. Bond *et al.*, "First-line systemic treatment strategies in patients with initially unresectable colorectal cancer liver metastases (CAIRO5): an open-label, multicentre, randomised, controlled, phase 3 study from the Dutch Colorectal Cancer Group," *Lancet Oncol*, vol. 24, no. 7, pp. 757-771, Jul 2023, doi: 10.1016/S1470-2045(23)00219-X.
102. C. Cremolini *et al.*, "FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study," *Lancet Oncol*, vol. 16, no. 13, pp. 1306-15, Oct 2015, doi: 10.1016/S1470-2045(15)00122-9.
103. W. Scheithauer, H. Rosen, G. V. Kornek, C. Sebesta, and D. Depisch, "Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer," *BMJ*, vol. 306, no. 6880, pp. 752-5, Mar 20 1993, doi: 10.1136/bmj.306.6880.752.
104. J. Watanabe *et al.*, "Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With RAS Wild-type, Left-Sided Metastatic Colorectal Cancer: A Randomized Clinical Trial," *JAMA*, vol. 329, no. 15, pp. 1271-1282, Apr 18 2023, doi: 10.1001/jama.2023.4428.
105. G. Folprecht *et al.*, "Efficacy of 5-fluorouracil-based chemotherapy in elderly patients with metastatic colorectal cancer: a pooled analysis of clinical trials," *Ann Oncol*, vol. 15, no. 9, pp. 1330-8, Sep 2004, doi: 10.1093/annonc/mdh344.
106. R. M. Goldberg *et al.*, "Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer," *J Clin Oncol*, vol. 24, no. 25, pp. 4085-91, Sep 1 2006, doi: 10.1200/JCO.2006.06.9039.
107. M. Berretta *et al.*, "FOLFOX4 in the treatment of metastatic colorectal cancer in elderly patients: a prospective study," *Arch Gerontol Geriatr*, vol. 52, no. 1, pp. 89-93, Jan-Feb 2011, doi: 10.1016/j.archger.2010.02.006.
108. G. Rosati *et al.*, "Phase II trial of oxaliplatin and tegafur/uracil and oral folinic acid for advanced or metastatic colorectal cancer in elderly patients," *Oncology*, vol. 69, no. 2, pp. 122-9, 2005, doi: 10.1159/000087814.
109. C. Tournigand *et al.*, "FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study," *J Clin Oncol*, vol. 22, no. 2, pp. 229-37, Jan 15 2004, doi: 10.1200/JCO.2004.05.113.
110. T. Aparicio *et al.*, "Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02)," *Ann Oncol*, vol. 27, no. 1, pp. 121-7, Jan 2016, doi: 10.1093/annonc/mdv491.
111. T. Aparicio *et al.*, "Geriatric factors predict chemotherapy feasibility: ancillary results of FFCD 2001-02 phase III study in first-line chemotherapy for metastatic colorectal cancer in elderly patients," *J Clin Oncol*, vol. 31, no. 11, pp. 1464-70, Apr 10 2013, doi: 10.1200/JCO.2012.42.9894.
112. T. Aparicio *et al.*, "Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderly metastatic colorectal cancer patients," *Eur J Cancer*, vol. 74, pp. 98-108, Mar 2017, doi: 10.1016/j.ejca.2016.09.029.

113. J. Cassidy, L. B. Saltz, B. J. Giantonio, F. F. Kabbinavar, H. I. Hurwitz, and U. P. Rohr, "Effect of bevacizumab in older patients with metastatic colorectal cancer: pooled analysis of four randomized studies," *J Cancer Res Clin Oncol,* vol. 136, no. 5, pp. 737-43, May 2010, doi: 10.1007/s00432-009-0712-3.
114. F. F. Kabbinavar, H. I. Hurwitz, J. Yi, S. Sarkar, and O. Rosen, "Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials," *J Clin Oncol,* vol. 27, no. 2, pp. 199-205, Jan 10 2009, doi: 10.1200/JCO.2008.17.7931.
115. D. Cunningham *et al.*, "Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer (AVEX): an open-label, randomised phase 3 trial," *Lancet Oncol,* vol. 14, no. 11, pp. 1077-1085, Oct 2013, doi: 10.1016/S1470-2045(13)70154-2.
116. F. Sclafani and D. Cunningham, "Bevacizumab in elderly patients with metastatic colorectal cancer," *J Geriatr Oncol,* vol. 5, no. 1, pp. 78-88, Jan 2014, doi: 10.1016/j.jgo.2013.08.006.
117. T. Hamaguchi *et al.*, "A randomized phase III trial of mFOLFOX7 or CapeOX plus bevacizumab versus 5-FU/l-LV or capecitabine plus bevacizumab as initial therapy in elderly patients with metastatic colorectal cancer: JCOG1018 study (RESPECT)," *Journal of Clinical Oncology,* vol. 40, no. 4_suppl, pp. 10-10, 2022, doi: 10.1200/JCO.2022.40.4_suppl.010.
118. T. Andre *et al.*, "Trifluridine-tipiracil plus bevacizumab versus capecitabine plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer ineligible for intensive therapy (SOLSTICE): a randomised, open-label phase 3 study," *Lancet Gastroenterol Hepatol,* vol. 8, no. 2, pp. 133-144, Feb 2023, doi: 10.1016/S2468-1253(22)00334-X.
119. E. Van Cutsem *et al.*, "Trifluridine/tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study," *Ann Oncol,* vol. 31, no. 9, pp. 1160-1168, Sep 2020, doi: 10.1016/j.annonc.2020.05.024.
120. S. Tejpar *et al.*, "Prognostic and Predictive Relevance of Primary Tumor Location in Patients With RAS Wild-Type Metastatic Colorectal Cancer: Retrospective Analyses of the CRYSTAL and FIRE-3 Trials," *JAMA Oncol,* vol. 3, no. 2, pp. 194-201, Feb 1 2017, doi: 10.1001/jamaoncol.2016.3797.
121. D. Papamichael *et al.*, "Efficacy of anti-epidermal growth factor receptor agents in patients with RAS wild-type metastatic colorectal cancer >/= 70 years," *Eur J Cancer,* vol. 163, pp. 1-15, Mar 2022, doi: 10.1016/j.ejca.2021.12.007.
122. S. Lonardi *et al.*, "Initial Panitumumab Plus Fluorouracil, Leucovorin, and Oxaliplatin or Plus Fluorouracil and Leucovorin in Elderly Patients With RAS and BRAF Wild-Type Metastatic Colorectal Cancer: The PANDA Trial by GONO Foundation," *J Clin Oncol,* p. JCO2300506, Aug 3 2023, doi: 10.1200/JCO.23.00506.
123. F. Loupakis *et al.*, "Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer," *N Engl J Med,* vol. 371, no. 17, pp. 1609-18, Oct 23 2014, doi: 10.1056/NEJMoa1403108.
124. C. Cremolini *et al.*, "Upfront FOLFOXIRI plus bevacizumab and reintroduction after progression versus mFOLFOX6 plus bevacizumab followed by FOLFIRI plus bevacizumab in the treatment of patients with metastatic colorectal cancer (TRIBE2): a multicentre, open-label, phase 3, randomised, controlled trial," *Lancet Oncol,* vol. 21, no. 4, pp. 497-507, Apr 2020, doi: 10.1016/S1470-2045(19)30862-9.
125. F. Marmorino *et al.*, "Impact of age and gender on the safety and efficacy of chemotherapy plus bevacizumab in metastatic colorectal cancer: a pooled analysis of TRIBE and TRIBE2 studies," *Ann Oncol,* vol. 30, no. 12, pp. 1969-1977, Dec 1 2019, doi: 10.1093/annonc/mdz403.
126. D. P. Modest *et al.*, "FOLFOXIRI Plus Panitumumab As First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer: The Randomized, Open-Label, Phase II VOLFI Study (AIO KRK0109)," *J Clin Oncol,* vol. 37, no. 35, pp. 3401-3411, Dec 10 2019, doi: 10.1200/JCO.19.01340.
127. D. Rossini *et al.*, "Upfront Modified Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan Plus Panitumumab Versus Fluorouracil, Leucovorin, and Oxaliplatin Plus Panitumumab for Patients With RAS/BRAF Wild-Type Metastatic Colorectal Cancer: The Phase III TRIPLETE Study by GONO," *J Clin Oncol,* vol. 40, no. 25, pp. 2878-2888, Sep 1 2022, doi: 10.1200/JCO.22.00839.
128. T. André *et al.*, "Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer," *New England Journal of Medicine,* vol. 383, no. 23, pp. 2207-2218, 2020, doi: 10.1056/NEJMoa2017699.
129. L. A. Diaz, Jr. *et al.*, "Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study," *Lancet Oncol,* vol. 23, no. 5, pp. 659-670, May 2022, doi: 10.1016/S1470-2045(22)00197-8.
130. Q. Wu *et al.*, "Correlation between patients' age and cancer immunotherapy efficacy," *Oncoimmunology,* vol. 8, no. 4, p. e1568810, 2019, doi: 10.1080/2162402X.2019.1568810.
131. B. Saberzadeh-Ardestani *et al.*, "Association Between Survival and Metastatic Site in Mismatch Repair–Deficient Metastatic Colorectal Cancer Treated With First-line Pembrolizumab," *JAMA Network Open,* vol. 6, no. 2, pp. e230400-e230400, 2023, doi: 10.1001/jamanetworkopen.2023.0400.
132. T. Andre *et al.*, "Nivolumab (NIVO) plus ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic

 doi:10.20944/preprints202404.0689.v1

colorectal cancer (mCRC): First results of the CheckMate 8HW study," *Journal of Clinical Oncology,* vol. 42, no. 3_suppl, pp. LBA768-LBA768, 2024, doi: 10.1200/JCO.2024.42.3_suppl.LBA768.

133. L. G. Paz-Ares *et al.*, "Safety of First-Line Nivolumab Plus Ipilimumab in Patients With Metastatic NSCLC: A Pooled Analysis of CheckMate 227, CheckMate 568, and CheckMate 817," *Journal of Thoracic Oncology,* vol. 18, no. 1, pp. 79-92, 2023/01/01/ 2023, doi: https://doi.org/10.1016/j.jtho.2022.08.014.
134. S. Kopetz *et al.*, "Quality of life with encorafenib plus cetuximab with or without binimetinib treatment in patients with BRAF V600E-mutant metastatic colorectal cancer: patient-reported outcomes from BEACON CRC," *ESMO Open,* vol. 7, no. 3, p. 100477, Jun 2022, doi: 10.1016/j.esmoop.2022.100477.
135. S. Kopetz *et al.*, "Encorafenib, Binimetinib, and Cetuximab in BRAF V600E–Mutated Colorectal Cancer," *New England Journal of Medicine,* vol. 381, no. 17, pp. 1632-1643, 2019, doi: 10.1056/NEJMoa1908075.
136. J. Tabernero *et al.*, "Encorafenib Plus Cetuximab as a New Standard of Care for Previously Treated BRAF V600E-Mutant Metastatic Colorectal Cancer: Updated Survival Results and Subgroup Analyses from the BEACON Study," *J Clin Oncol,* vol. 39, no. 4, pp. 273-284, Feb 1 2021, doi: 10.1200/JCO.20.02088.
137. J. Taieb *et al.*, "Adverse Events Associated with Encorafenib Plus Cetuximab in Patients with BRAFV600E-mutant Metastatic Colorectal Cancer: An in-depth Analysis of the BEACON CRC Study," *Clin Colorectal Cancer,* vol. 22, no. 1, pp. 59-66, Mar 2023, doi: 10.1016/j.clcc.2022.12.003.
138. R. J. Mayer *et al.*, "Randomized trial of TAS-102 for refractory metastatic colorectal cancer," *N Engl J Med,* vol. 372, no. 20, pp. 1909-19, May 14 2015, doi: 10.1056/NEJMoa1414325.
139. E. Van Cutsem *et al.*, "The subgroups of the phase III RECOURSE trial of trifluridine/tipiracil (TAS-102) versus placebo with best supportive care in patients with metastatic colorectal cancer," *Eur J Cancer,* vol. 90, pp. 63-72, Feb 2018, doi: 10.1016/j.ejca.2017.10.009.
140. G. W. Prager *et al.*, "Trifluridine-Tipiracil and Bevacizumab in Refractory Metastatic Colorectal Cancer," *N Engl J Med,* vol. 388, no. 18, pp. 1657-1667, May 4 2023, doi: 10.1056/NEJMoa2214963.
141. A. Grothey *et al.*, "Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial," *Lancet,* vol. 381, no. 9863, pp. 303-12, Jan 26 2013, doi: 10.1016/S0140-6736(12)61900-X.
142. E. v. Cutsem *et al.*, "Regorafenib (REG) in progressive metastatic colorectal cancer (mCRC): Analysis of age subgroups in the phase III CORRECT trial," *Journal of Clinical Oncology,* vol. 31, no. 15_suppl, pp. 3636-3636, 2013, doi: 10.1200/jco.2013.31.15_suppl.3636.
143. T. S. Bekaii-Saab *et al.*, "Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study," *Lancet Oncol,* vol. 20, no. 8, pp. 1070-1082, Aug 2019, doi: 10.1016/S1470-2045(19)30272-4.
144. R. Petrioli *et al.*, "Efficacy and Safety of Regorafenib With 2/1 Schedule for Patients >/= 75 Years With Metastatic Colorectal Cancer (mCRC) After Failure of 2 Lines of Chemotherapy," *Clin Colorectal Cancer,* vol. 17, no. 4, pp. 307-312, Dec 2018, doi: 10.1016/j.clcc.2018.02.005.
145. A. Dasari *et al.*, "Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study," *Lancet,* vol. 402, no. 10395, pp. 41-53, Jul 1 2023, doi: 10.1016/S0140-6736(23)00772-9.