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Real-world evidence on adjuvant chemotherapy in older adults with stage II/III colon cancer

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Abstract

Colon cancer represents one of the most common cancers diagnosed in older adults worldwide. The standard of care in resected stage II and stage III colon cancer continues to evolve. While there is unequivocal evidence to suggest both disease free and overall survival benefits with the use of combination chemotherapy in patients with stage III colon cancer, data regarding its use in patients with stage II colon cancer are less clear. Further, although colon cancer is a disease that affects older adults, there is considerable debate on the value of adjuvant chemotherapy in the aging population. In particular, many older patients are undertreated when compared to their younger counterparts. In this review, we will describe the clinical trials that contributed to the current adjuvant chemotherapy approach in colon cancer, discuss representation of older adults in trials and the specific challenges associated with the management of this sub-population, and highlight the role of comprehensive geriatric assessments. We will also review how real-world evidence complements the data gaps from clinical trials of early stage colon cancer.

Key words: Colon cancer; Older adults; Adjuvant chemotherapy; Real-world evidence

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Core tip: Use of adjuvant chemotherapy consisting of fluoropyrimidines with/without oxaliplatin has improved survival outcomes for patients with resected colon cancer, especially in those with stage III disease. However, older adults are often not given the opportunity to benefit from chemotherapy after surgery because undertreatment may occur due to various patient and physician related factors. The issue is further compounded by the limited representation of older adults in clinical trials, resulting in underpowered subgroup analyses that do not provide conclusive answers regarding the

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utility of adjuvant chemotherapy in the advanced age group. We herein review the role of adjuvant chemotherapy in early stage colon cancer, specifically in the context of the older subpopulation, by focusing on both data from clinical trials and data from real-world evidence sources.

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INTRODUCTION

Colon cancer is the fourth most frequently diagnosed cancer in the world, with approximately 1.1 million new cases diagnosed annually^[1]. The median age at diagnosis is 67 years, making it the third most common cancer diagnosis in older patients^[1,2].

The definitive treatment for localized colon cancer is surgery, whereby the risk of recurrence increases as the local extent of disease increases^[3]. Adjuvant chemotherapy is targeted at occult metastasis and it is recommended in stage II disease with high-risk features, and stage III colon cancer^[4-6]. Available treatment options include single agent fluoropyrimidine (5-FU or capecitabine) and combination chemotherapy consisting of a fluoropyrimidine with oxaliplatin (FOLFOX or CAPOX) for 3 to 6 months. These guidelines are based on data from phase III randomized controlled trials^[7-11]. However, most of these clinical trials were limited by stringent inclusion and exclusion criteria, which precluded the broad participation of older adults^[12].

Apart from age related decline in organ functions, older adults are more likely to have comorbid conditions, which can potentially complicate the administration of adjuvant chemotherapy^[13,14]. However, age is not a robust surrogate marker for functional status and should not be used as a sole criterion to exclude patients from receiving treatment. A comprehensive geriatric assessment (CGA) can provide a better overall assessment of the functional status of older adults to guide the use of chemotherapy^[15].

Meanwhile, real-world evidence refers to the analysis of data collected from routine clinical practice, outside the context of trials^[16]. To date, real-world studies have also identified that older adults are less likely to receive adjuvant chemotherapy for colon cancer even though they stand to derive some benefit from treatment^[17-20].

In this review, we will discuss the standard of care for stage II and III colon cancer, participation of older adults in clinical trials, specific challenges in the management of this population, and summarize data from clinical trials and data from real-world evidence on the use of adjuvant chemotherapy in older adults.

CLINICAL TRIALS OF ADJUVANT CHEMOTHERAPY IN COLON CANCER

Evolution of fluoropyrimidines

The benefit of adjuvant chemotherapy with 5-FU and levamisole was first apparent in a small randomized trial from the late 1980s^[21,22]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) C-01 study and a subsequent meta-analysis further confirmed this disease free survival (DFS) benefit^[23,24]. This was followed by another study that observed a 40% reduction in recurrence and a 33% improvement in overall survival (OS) among patients with stage III colon cancer who were treated with 12 months of 5-FU and levamisole^[25], resulting in this being established as the standard adjuvant chemotherapy for colon cancer (Figure 1).

The next decade of treatment was marked by the eventual omission of levamisole due to its inefficacy, and the modulation of 5-FU and leucovorin into different regimens, including the "Mayo" (bolus low-dose LV and 5-FU daily × 5), "Roswell Park" (weekly high-dose LV and bolus 5-FU), and "de Gramont's LV5FU2" (LV and bolus 5-FU plus infusion)^[26-29]. Although none of the three regimens proved to be superior, LV5FU2 became the most preferred regimen because it was significantly

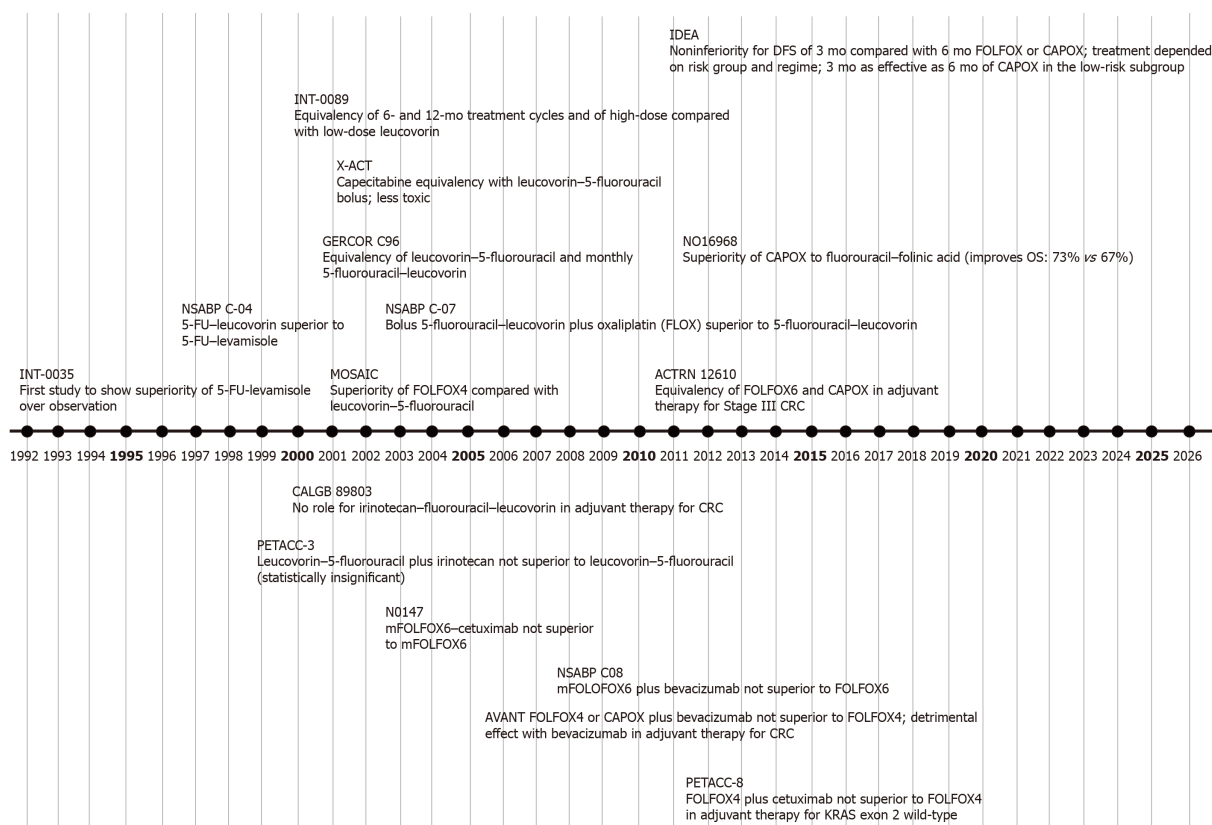


Figure 1 Timeline of evolution of adjuvant chemotherapy in colon cancer.

better tolerated than the bolus regimens^[28,29].

The standard duration of adjuvant chemotherapy was subsequently reduced from 12 to six months after the Intergroup-0089 and the GERCOR (French Oncology Research Group) C97-2 trials established non-inferiority of 6 months bolus 5FU regimens or LV5FU2, when compared to 12 months of 5FU/levamisole and 9 months of LV5FU2, respectively.

The X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) and NSABP C-06 studies evaluated the efficacy of oral fluoropyrimidines as compared to bolus 5-FU regimens. Both capecitabine and tegafur had similar DFS and OS, and they were also better tolerated than bolus 5-FU^[9,30].

Combination chemotherapy with oxaliplatin

Three landmark trials established the role of combination chemotherapy with oxaliplatin and a fluoropyrimidine (Table 1)^[8,10,31]. The MOSAIC (Multicenter International Study of Oxaliplatin/5-FU/Leucovorin) study compared six months of adjuvant FOLFOX4 with LV5FU2 in patients with stage II and III colon cancer, and showed a 7.5% improvement in five-year DFS [hazard ratio (HR) = 0.78; $P = 0.005$], and 4.2% improvement in six-year OS (HR = 0.80; $P = 0.023$) with the addition of oxaliplatin in those with stage III disease^[32]. Although there was a modest benefit in DFS, there was no OS benefit in stage II colon cancer at six and ten years, respectively^[7,32]. Based on this trial, six months of adjuvant chemotherapy with FOLFOX became the new standard of care for patients with stage III colon cancer.

The NSABP C-07 and NO16968 trials demonstrated similar DFS and OS benefits with the addition of oxaliplatin to bolus 5-FU/leucovorin or capecitabine (CAPOX), when compared to bolus 5-FU/leucovorin^[8,10]. While the C-07 study included patients with stage II and III colon cancer, the latter study exclusively focused on those with stage III disease.

Although irinotecan is active in advanced settings, its addition to 5-FU/leucovorin as adjuvant treatment in stage II and III colon cancer did not show any incremental benefit across three different randomized trials^[33-36]. Furthermore, the addition of bevacizumab or cetuximab to FOLFOX was also not associated with any improvements in DFS or OS^[37-40].

Shorter duration of combination chemotherapy

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA)

Table 1 Landmark trials for the combination of adjuvant chemotherapy with oxaliplatin and fluoropyrimidines in resected colorectal cancer

Clinical Trial	Regimen	Patients (n/age)	Stage	DFS	OS
MOSAIC, 2004	FOLFOX4 <i>vs</i> LV5FU2	2246 Age 18-75 778, > 65 yr (34.6%)	II/III 40% Stage II	5-yr 73.3% <i>vs</i> 67.4%	6-yr 72.9% <i>vs</i> 68.7% For stage III No benefit for stage II at 6-yr and 10-yr
NSABP-C-07, 2007	Weekly bolus 5-FU/LV ± Oxaliplatin (FLOX)	2407 396, > 70 yr (16.4%)	II/III 695 Stage II (28.8%)	4-yr 73.2% <i>vs</i> 67.0%	5-yr N/A Unplanned subset analyses suggested no benefit for patients > 70 yr (71.6% <i>vs</i> 76.3%)
NO16968, 2015	CAPOX (XELOX) <i>vs</i> 5-FU/Leucovorin (C. Mayo/R. Park)	1886 409, > 70 yr (21.6%)	III	7-yr 63% <i>vs</i> 56% HR = 0.86 (95% CI: 0.64-1.16)	7-yr 73% <i>vs</i> 67% HR = 0.91 (95% CI: 0.66 TO 1.26)

DFS: Disease free survival; HR: Hazard ratio; OS: Overall survival.

collaboration performed a pooled analysis of 12834 patients enrolled across six randomized trials in order to evaluate the non-inferiority of three months of adjuvant CAPOX or FOLFOX therapy as compared to six months of treatment in stage III colon cancer^[11]. Although non-inferiority could not be confirmed in the overall population, three months of therapy was non-inferior to six months in lower risk patients (T1-3 and N1), particularly with CAPOX. Notably, in patients with T4 and/or N2 disease, six months of chemotherapy was superior to three months. Since these results were preliminary and OS data are not yet mature, both three and six months of adjuvant chemotherapy in low risk stage III colon cancer remain reasonable options. However, six months continues to be the standard duration when using single agent fluoropyrimidines.

Stage II colon cancer

Although the benefit of adjuvant chemotherapy has been proven in clinical trials of patients with stage III colon cancer, the more modest DFS and OS benefits seen in stage II disease has prompted the need to categorize patients into low and high risk groups based on clinico-pathological factors^[23,41]. The four randomized clinical trials that included predominantly stage II colon cancer patients failed to show consistent benefits of adjuvant chemotherapy^[42-45]. A detailed description of the role of adjuvant chemotherapy for stage II colon cancer is beyond the scope of this review. However, there is general agreement that adjuvant treatment with a fluoropyrimidine may benefit some patients with resected stage II colon cancer when specific high features are present. These high-risk features typically include, but are not limited to, colonic obstruction or localized perforation at presentation, poorly differentiated histology, T4 lesion, fewer than 12 nodes sampled, perineural, vascular or lymphatic invasion, and close/indeterminate or positive margins^[4-6]. The role of microsatellite instability (MSI) in decision-making for adjuvant chemotherapy is still emerging; however, data suggest a high risk of treatment resistance to single agent fluoropyrimidines in MSI-high tumors^[46-48]. While additional benefit of oxaliplatin has not been proven in patients with stage II colon cancer, this is likely to overcome fluoropyrimidine resistance in those with MSI-high status, based on a small exploratory analysis from the MOSAIC trial^[7].

CLINICAL TRIAL PARTICIPATION OF OLDER ADULTS

Despite cancer being a disease of advanced age, older patients are under-represented in the majority of clinical trials^[49-52]. A paradox exists whereby patients aged greater than 65 years constitute approximately 70% of the overall population with colorectal cancer, but this age group represents only 30% of clinical trial participants^[52]. The main reasons that many older patients with colorectal cancer are excluded from studies include: previous or concomitant cancer treatments, comorbid conditions or

medications, and poor performance status^[53]. Interestingly, one-third of “eligible” older patients are still not invited to participate in trials, driven by the observation that physicians are less likely to discuss and/or offer clinical trials to older patients with cancer^[53,54].

There has been little change in this regard over last two decades, even though representation of other marginalized sub-groups such as women and ethnic minorities has improved^[55-58]. An upper numerical age limit continues to be a common exclusion factor across contemporary clinical trials, despite recommendations by many major international societies that encourage the recruitment of older patients and the adoption of criteria based on physiological age rather than chronological age^[59,60].

OLDER ADULTS: SPECIFIC ISSUES

Age-related decline in organ function

There are well described age-related deteriorations in organ function including in the hepatic, renal, cardiovascular, central nervous, and hematopoietic systems^[61,62]. This leads to loss of physiologic reserve, which decreases the threshold for decompensation when faced with stressors, such as chemotherapy. Declining hepatic and renal function can potentially expose older patients to oxaliplatin and capecitabine at higher peak concentrations for a longer duration, respectively^[62]. Moreover, due to potential muscle loss associated with aging, serum creatinine is a less reliable marker to assess renal function^[63,64]. Similar deteriorations in bone marrow reserve that come with aging can potentiate chemotherapy dose reductions and delays, and also exacerbate the risk of febrile neutropenia in older adults^[61].

Comorbid medical conditions

Patients older than 75 years have a median of five comorbid medical conditions. These may include anemia, cardiovascular disease, chronic obstructive airway disease, diabetes, previous cancer, and renal disease^[13,14]. Charlson’s comorbidity index is one of the available tools to quantify these comorbidities, and a score of more than 2 has been independently associated with an increase in mortality among patients with colorectal cancer^[65,66]. The interaction of comorbid conditions with the administration of adjuvant chemotherapy is rather complex. While the presence of severe comorbid conditions may outweigh the risk associated with adjuvant chemotherapy, patients with multiple well-control medical conditions are still likely to benefit from cancer treatment^[67]. The presence of comorbid conditions can also increase the toxicity due to chemotherapy. Capecitabine, for example, can cause severe side effects in the presence of renal dysfunction, as it is excreted by the kidneys^[68]. Moreover, capecitabine and 5-FU can lead to life-threatening coronary vasospasms that can result in further deterioration of cardiac function in those with pre-existing cardiovascular disease^[69,70].

Pharmacokinetics of chemotherapeutic drugs

There are significant age-based alterations in pharmacokinetics of chemotherapeutic drugs. For example, the absorption of capecitabine may be affected due to worsening splanchnic blood flow, secretion of digestive enzymes, and gut motility among older patients^[71]. The distribution of drugs is also affected by an increase in fat content and a decrease in intracellular water with advanced age, leading to a reduction in the peak concentration and contributing to longer half-lives of drugs^[72]. Further, declining hepatic and renal function can affect the metabolism and excretion of chemotherapeutic drugs^[61,62].

Pharmacodynamics of chemotherapeutic agents

Cancer in older individuals develops from senescent cells, which are unable to undergo apoptosis, and hence, these cells are more likely to be resistant to chemotherapeutic agents that act by apoptosis^[73]. Decreased angiogenesis in tumors of older adults may also lead to decreased delivery of drugs to the neoplastic cells^[74]. Moreover, reduced levels of dehydropyrimidine dehydrogenase in older patients may cause delayed clearance of fluoropyrimidines, subsequently leading to increased adverse events with the use of capecitabine or 5-FU^[75].

Polypharmacy

While 90% of the older population uses at least one medication, the average number of drugs is four per patient^[76]. This predisposes older patients to potentially harmful drug interactions, which can negatively impact adherence to additional chemotherapy pills (capecitabine), as well as oral supportive medications that combat chemotherapy

related adverse effects^[77,78].

Quality of life

Quality of life should always be considered in treatment decision making, but it is particularly prioritized in older patients since aggressive use of chemotherapy may compromise their daily activities and overall wellbeing. There are limited data that accurately describe the effect of chemotherapy on the quality of life of older patients with colorectal cancer^[79]. However, there is recognition that older adults are less willing to endure the side-effects of chemotherapy, as compared to younger patients^[80]. This should not be presumed for all older patients with cancer and individual preferences must be considered when discussing the benefits and risks of chemotherapy. Further, increased anxiety and depression have been reported in older individuals at diagnosis of cancer^[81]. However, older adults who know about the diagnosis and prognosis of cancer are able to better cope with the anxiety compared with those who do not know the details^[82]. Therefore, a well-informed decision-making process with older adults is likely to improve the psychosocial aspects and better maintain quality of life.

ASSESSMENT OF FUNCTIONAL STATUS IN OLDER ADULTS

Performance status

Chronological age is a poor surrogate of physiologic and functional status of older patients^[83]. Performance status (PS) as assessed by physicians is commonly employed in oncology to ascertain the functional status of patients; the most validated scales include the Eastern Cooperative Oncology Group PS (ECOG PS), and Karnofsky PS (KPS)^[84,85]. In general, patients with ECOG PS > 2 and KPS < 60 are considered to be poor candidates for chemotherapy. However, data suggest that clinician assessments of functional status tend to underestimate the true functional status of older patients^[86].

CGA

A CGA involves a multidimensional evaluation of older patients, including their functional status, comorbid medical conditions, cognition, nutritional status, psychological state, socio-economic condition, and a record of the patient's medications^[87]. The purpose of a CGA is to identify frail older patients who may be able to tolerate chemotherapy, as well as fit older patients who may have a higher likelihood of developing chemotherapy related side effects. Several studies have demonstrated how CGA can add information to the conventional ECOG PS in older patients^[15,88,89], help in cancer treatment decision making^[15,90], predict complications and adverse events from chemotherapy^[91-94], and improve pain control, mental health, and well-being^[95]. Although there is no uniform CGA tool, various models have been implemented in different settings that encompass the core domains of the assessment^[96]. A combination of a self-administered questionnaire and a healthcare provider assessment is most often utilized. There is considerable debate as to which older patients actually benefit from the resource intensive CGA. In response to this, pre-CGA screening tools have also been developed^[97-99]. However, a systematic review concluded that there is limited sensitivity and specificity of these tools^[100]. The consensus guidelines by the American Society of Clinical Oncology (ASCO) and the International Society of Geriatric Oncology (SIOG) recommend the routine use of CGA in patients aged more than 65 years with cancer, but to date there has been variable adoption of CGA in busy routine clinical practices^[101,102].

CLINICAL TRIAL AND REAL-WORLD DATA OF OLDER ADULTS WITH STAGE II AND III COLON CANCER

Fluoropyrimidines

Due to poor representation in clinical trials, evidence for the efficacy of fluoropyrimidines as adjuvant chemotherapy in stage III colon cancer among older adults is derived mainly from pooled analysis of individual patient-level data from randomized trials, and data from population-based real-world studies. In particular, there was a large pooled analysis that included information from 3351 patients with stage II or III colon cancer from seven randomized phase III clinical trials evaluating the role of 5-FU (five with leucovorin, and two with levamisole), which categorized

patients into four groups according to age (< or = 50, 51 to 60, 61 to 70, and > 70 years)^[103]. Adjuvant treatment was associated with improved OS (HR = 0.76; 95% CI: 0.68-0.85, $P < 0.001$), superior time to recurrence (HR = 0.68; 95% CI: 0.60-0.76; $P < 0.001$), and better 5-year OS (64% *vs* 71%). There were 506 patients aged more than 70 years, and no significant interaction was observed between age and treatment efficacy. Moreover, the incidence of adverse events was similar in the four age groups, except there was a higher incidence of leukopenia in patients older than 70 years. Although this analysis suggests similar benefits of chemotherapy in older patients as compared to their younger counterparts, findings were limited by the representation of only *fit* older patients who met the stringent inclusion criteria of clinical trials^[22,25,41,104,105].

Population-based studies complement clinical trials by providing information regarding the efficacy of adjuvant chemotherapy with 5FU in unselected patients in the real-world setting (Table 2). One such study analyzed data of patients aged more than 65 years diagnosed with stage III colon cancer from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and Medicare^[47]. Of the 4738 patients included in that analysis, 52% received adjuvant chemotherapy, and there was a 34% (HR = 0.66; 95% CI: 0.60-0.73) relative reduction in mortality with 5-FU based treatment. In a subsequent published study that used the same database, 51% (3672 out of 7182) patients aged more than 65 years received 5FU based adjuvant chemotherapy within 6 months of surgery^[106]. In that study, patients were categorized into five age groups (66-69, 70-74, 75-79, 80-84, and > 85 years) to analyze the effect of increasing age. While patients in all age groups derived benefit from adjuvant chemotherapy, the magnitude was not uniform across all ages whereby patients aged 70-74 years experienced 14% greater survival when compared to 8% in patients aged 80 to 84 years.

Another study that analyzed the use and efficacy of adjuvant chemotherapy in 85,934 patients across all ages with stage III colon cancer residing in community settings concluded that the benefit of adjuvant chemotherapy was similar in patients aged more than 80 years^[107].

Data from similar studies that examined the proportion of patients who completed the planned duration of chemotherapy suggest that one-third of older patients discontinued adjuvant treatment prematurely^[108,109]. Apart from advanced age, other factors associated with early termination of chemotherapy include physical frailty, treatment complications, and lack of social and psychological support.

In the previously described X-ACT trial that randomized stage III colon cancer patients to either capecitabine or 5-FU/leucovorin, 396 of 1987 enrolled patients were older than 70 years. Although older patients required more frequent dose modifications of capecitabine when compared to younger patients (65% *vs* 55%), capecitabine was non-inferior to 5-FU/leucovorin in the subgroup analysis involving patients aged more than 70 years [5-year OS, 68.8% and 65.0% (HR = 0.91, 95% CI: 0.65-1.26)]^[9]. However, capecitabine should still be used with caution in very old patients because of the increased toxicity associated with declining renal function^[110]. The efficacy and safety data for UFT in older adults are very limited. A small trial of 63 patients aged greater than 70 years suggests a favorable toxicity profile^[111].

Combination chemotherapy with oxaliplatin

Unlike fluoropyrimidines, the benefit of adding oxaliplatin in the adjuvant treatment of older patients with resected colon cancer is more controversial. The main driver for this is the under-representation of the older population in the landmark MOSAIC and NSABP C-07 trials^[112,113]. The MOSAIC trial excluded those older than 75 years, and only 14% (315 of 2246) of patients were aged 70 to 75 years so the subgroup analysis was underpowered to show any benefit of FOLFOX as compared to 5FU/leucovorin. The HRs for DFS and OS were 0.93 (95% CI: 0.64 to 1.35) and 1.10 (95% CI: 0.73 to 1.65), respectively^[112]. While the NSABP C-07 study did not apply an upper age limit to enrollment, only 14% of the participants were aged more than 70 years. Similar to MOSAIC's subgroup analysis, there was no observed DFS and OS advantage with the addition of oxaliplatin among patients older than 70 years^[113]. Moreover, the Adjuvant Colon Cancer End Points (ACCENT) group analyzed the pooled data of 14528 patients from seven randomized trials. Of these, 2575 patients were older than 70 years. Although there was a 3-year DFS benefit with combination chemotherapy, no incremental OS benefit was seen in older patients^[12]. Likewise, a systematic review published by Cancer Care Ontario concluded little additional benefit of oxaliplatin in patients older than 70 years of age^[114].

In contrast, the NO16968 trial randomized 1886 patients with stage III colon cancer to CAPOX or 5-FU/leucovorin. There was a preplanned subgroup analysis which demonstrated a similar magnitude of benefit in younger and older patients^[10]. Furthermore, a pooled analysis of four clinical trials evaluated the role of oxaliplatin

Table 2 Real word data of older adults with stage II and III colon cancer

Ref.	Study design	n/stage	Age selection	Treatment arms/parameters	Conclusion
Sargent <i>et al</i> ^[103] , 2001	Pooled analysis 7 trials	3351, stage II/III	≤ 50, 51- 60, 61-70, and > 70 yr	Fluorouracil plus leucovorin or levamisole <i>vs</i> surgery alone	Same benefit from fluorouracil-based adjuvant therapy as their younger counterparts
Sundararajan <i>et al</i> ^[117] , 2002	Retrospective cohort	4768, node-positive	65 years of age or older	Association of 5-FU adjuvant therapy with survival	5-FU therapy is significantly associated with reduced mortality in older patients
Zuckerman <i>et al</i> ^[106] , 2009	Observational, retrospective cohort	3016, stage III	aged 66 and older	5-FU or leucovorin within 6 mo after surgery	Elderly patients had a significant survival benefit associated with adjuvant chemotherapy
Jessup <i>et al</i> ^[107] , 2005	Prospective data	85934, stage III	< 60, 60-69, 70-79, > 80 yr	Adjuvant chemotherapy usage and 5-yr survival	Elderly patients have the same benefit as younger patients but are less frequently treated
Neugut <i>et al</i> ^[108] , 2006	Retrospective database	1722, stage III	≥ 65 years of age	Early discontinuation of FU-based chemotherapy	High percentage of early treatment discontinuation in the elderly population
Dobie <i>et al</i> ^[109] , 2006	Retrospective SEER analysis	3193, stage III	65 years and older	Adjuvant chemotherapy completion and its relation to 3-year cancer mortality	Incomplete adjuvant chemotherapy associated to physical frailty and treatment complications
McCleary <i>et al</i> ^[112] , 2013	Pooled analysis, ACCENT group	14528, stage II/III	age < 70 and age ≥ 70 years	Impact of age on colon cancer recurrence and mortality after adjuvant therapy	Reduced benefit from adding oxaliplatin to fluoropyrimidines in the adjuvant setting for patients > 70 years
Meyers <i>et al</i> ^[114] , 2017	Systematic review	Stage II and III	age < 70 and age ≥ 70 years	Benefit from adjuvant chemotherapy (5-fluorouracil /leucovorin/ oxaliplatin or capecitabine/ oxaliplatin)	Patients with high-risk stage II disease may benefit from adjuvant chemotherapy
Green <i>et al</i> ^[117] , 2019	Retrospective SEER-Medicare database analysis	31990, stage II/III	Aged 66-69, 70-74, 75-79, 80-84, 85-89 and 90+	Use and outcomes of adjuvant chemotherapy	Administration of adjuvant chemotherapy for colon cancer decreases with advancing age, but improved outcomes are seen in stage III patients under 90years of age
Sanoff <i>et al</i> ^[121] , 2012	Retrospective data source analysis	4060, stage III	< 50, 50-64, 65-69, 70-74 yr	Oxaliplatin <i>vs</i> non-oxaliplatin-containing adjuvant chemotherapy	The addition of oxaliplatin to 5-FU appears to be associated with better survival among patients receiving adjuvant colon cancer treatment in the community

5-FU: 5-fluorouracil; SEER: Surveillance, Epidemiology, and End Results; ACCENT: Adjuvant Colon Cancer End Points.

in patients aged more than 70 years^[115]. This particular analysis excluded the MOSAIC study because of inaccessibility to patient level data and the NSABP C-07 study due to its use of an outdated regimen. A total of 4819 patients from four randomized trials were examined of whom 904 patients were more than 70 years old^[9,10,37,38]. It concluded that the addition of oxaliplatin improved DFS and OS in both younger and older patients, although there was a modest attenuation in the survival benefit (DFS, < 70 years: HR = 0.68; 95%CI: 0.61-0.76; *P* < 0.0001; > 70 years: HR = 0.77; 95%CI: 0.62-0.95; *P* = 0.014).

With the increasing number of patients that are considered “older”, the significance of real-world evidence and its capacity to complement randomized trials are

increasingly being recognized^[116]. However, similar to the case with clinical trial data, results from real-world evidence studies that analyzed the outcomes of oxaliplatin in older patients are conflicting. The largest contemporary real world study of patients older than 65 years included 31990 patients with stage II/III colon cancer from the SEER/Medicare database and grouped patients by age at five year intervals^[117]. Overall, there was a gradual decline in the use of adjuvant chemotherapy, ranging from 57% in 66-69 years old to 1% in those aged more than 90 years. While the benefit of adjuvant chemotherapy was seen in all patients less than 90 years, those with stage II disease had increased mortality with adjuvant chemotherapy. Of note, the SEER/Medicare does not include data on high risk features of stage II colon cancer, so this finding should be interpreted with caution. Likewise, the authors did not perform an analysis based on type of chemotherapy because there was poor sensitivity in identifying specific chemotherapeutic agents^[118]. In other studies that linked with SEER/Medicare database, oxaliplatin in stage III colon cancer demonstrated OS benefit in the age group of 70-74 years old (HR = 0.66; 95%CI: 0.52-0.84)^[119]. However, there was no significant incremental benefit of oxaliplatin in patients older than 75 years (HR = 0.84; 95%CI: 0.69-1.04)^[120].

While there is no clear consensus regarding the impact of combination chemotherapy in older adults, data on its safety are reassuring in that there were no increases in emergency department use, hospitalizations, and early deaths^[121]. In patients older than 75 years, the odds of developing chemotherapy induced nausea and vomiting [odds ratio (OR) = 2.14; 95%CI: 1.73-2.65], as well as neutropenia (OR = 17.3; 95%CI: 9.80-30.42) were higher in patients receiving FOLFOX as compared to 5FU alone. However, no differences were observed in rates of diarrhea, dehydration, infection, or acute coronary events.

Stage II colon cancer in older patients

The benefit of adjuvant chemotherapy in resected stage II colon cancer is debatable, with most guidelines recommending that it be considered only in patients with high risk features. Moreover, data of older patients with stage II colon cancer are scarce, with the majority of current treatment recommendations extrapolated from those in younger patients. A SEER/Medicare database study identified 24847 patients aged more than 65 years with stage II colon cancer, of whom 75% had at least one high risk feature, and 20% of these received adjuvant chemotherapy. There was no difference in 5-year OS in treated and untreated patients (HR = 1.03; 95%CI: 0.94-1.13; $P = 0.47$)^[122]. This raises the question of benefit of adjuvant chemotherapy in older adults with stage II colon cancer. The SIOG recommendations on treatment of older adults with stage II colon cancer acknowledge the limited data in this clinical situation^[123]. However, older age by itself should not be a sole exclusion criterion to offer adjuvant chemotherapy in stage II colon cancer with high-risk features. Thus, a discussion with older patients with high-risk stage II colon cancer regarding a small potential benefit and possible toxicities must be conducted while considering the patients' preferences.

CONCLUSION

Underrepresentation of older patients in clinical trials of adjuvant chemotherapy for stage II and III colon cancer has contributed to significant gaps in our understanding of the true benefit of such therapy. However, real-world evidence and pooled analysis from these clinical trials have allowed oncologists to arrive at some agreement. In older patients with stage II colon cancer, there are limited data to suggest efficacy of adjuvant chemotherapy, even among those with high-risk features. In contrast, single agent fluoropyrimidine appears to provide similar benefit in older patients as younger patients. There are contradicting data on the incremental value of adding oxaliplatin to fluoropyrimidines in stage III colon cancer. This is largely because most of the analyses were either *post hoc* (exploratory) in design or underpowered to reach definitive conclusions. Likewise, available data from real-world evidence are limited by inherent selection bias and confounding by indication. However, further real-world evidence using novel statistical methods eliminating such confounding and biases is likely to shine further light on controversies which are unlikely to be resolved by future clinical trials. As we move forward, the integration of CGAs of older adults may represent a more useful and reliable method to select appropriate older patients for adjuvant chemotherapy. This is due to the observation that chronological age is a poor proxy for functional status and should not be used as a standalone factor for treatment decision-making since it may unintentionally deny older patients the potential benefits of adjuvant chemotherapy.

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