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Geriatric Oncology

Relative Effectiveness and Safety of Chemotherapy in Elderly and Nonelderly Patients With Stage III Colon Cancer: A Systematic Review

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Colorectal neoplasms • Aged • Drug therapy • Comparative effectiveness research • Treatment outcome

CME Learning Objectives

Describe evidence of differential treatment response of chemotherapy in elderly versus nonelderly stage III colon cancer patients.

Synthesize differences in evidence of effectiveness and safety of chemotherapy between elderly and nonelderly stage III colon cancer patients to inform patient decision making and physician prescribing practices.

ABSTRACT

Background. **Chemotherapy effectiveness in clinical practice may differ from the efficacy demonstrated in clinical trials, particularly among populations underrepresented in clinical trials, such as elderly patients with cancer. This review aims to examine the relative effectiveness of chemotherapy for stage III colon cancer in elderly versus nonelderly patients.**

Methods. **A systematic literature review was conducted using the Agency for Healthcare Research and Quality approach. Literature searches were performed in Medline and Evidence-Based Medicine Reviews databases. Chemotherapy regimens approved for stage III colon cancer were reviewed. Four effectiveness and 15 safety outcomes were extracted.**

Results. **From 708 identified articles, 25 articles provided data on the relative effectiveness and safety of chemotherapy among elderly versus nonelderly patients. Four of 14 studies showed lower overall survival treatment effects, whereas one of five and one of four studies indicated more favorable treatment effects for time to progression and overall response rate. Grade 3 or 4 adverse events were higher among elderly patients for cardiac disorder (2/5 studies), leukopenia (1/5), neutropenia (4/16), thrombocytopenia (2/13), febrile neutropenia (1/4), infection (2/10), dehydration (2/6), diarrhea (6/20), and fatigue (6/13). Grade 3 or 4 adverse events were lower for neutropenia (2/16 studies), nausea/vomiting (1/16), and neuropathy (1/9).**

Conclusion. **The majority of the evidence suggests that chemotherapy has similar relative effectiveness and safety for patients >65 years of age versus younger patients with stage III colon cancer. When differences are reported, treatment effects are more often worse among the elderly. This review suggests that without other reasons for withholding treatment, elderly patients should receive chemotherapy as often as nonelderly patients.** ***The Oncologist*** 2013;18:54–63

Implications for Practice: The underrepresentation of elderly patients from clinical trials has led to uncertainty regarding the efficacy of chemotherapy agents among the elderly. This uncertainty has contributed to underuse in the elderly population. The evidence from this systematic review suggests that colon cancer chemotherapy effectiveness and safety generally are similar in elderly and nonelderly patients; however, there is some evidence of a higher incidence of adverse events in elderly versus nonelderly patients. This systematic review concludes that chemotherapy prescribing decisions for colon cancer should not be based upon age, but rather on other factors such as performance status. Overall, the evidence does not suggest lower chemotherapy effectiveness among elderly patients. Thus, this review does not support observed lower chemotherapy utilization in the elderly population. In the absence of other reasons for withholding treatment, elderly patients should be given chemotherapy as often as nonelderly patients.

INTRODUCTION

Comparative effectiveness research (CER) is defined as the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the deliv-

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ery of care" [1]. The purpose of CER is to provide consumers, clinicians, payers, and policy makers with information so they can make better health care decisions and use health care resources more effectively [1]. CER promotes personalized medicine and helps patients and their health care providers know if a treatment will work specifically for them. This is a challenge for elderly patients because much of this evidence comes from clinical trials, and elderly patients are often underrepresented in trials. A systematic approach to reviewing evidence may provide CER for a broad array of patients.

Systematic reviews assist in developing evidence-based treatment protocols and health care decision making. They are good tools that objectively gather and summarize all available evidence for decision makers. They can be used to develop practice guidelines, as well as risk assessments, economic analyses, and decision analyses [1–4]. They also point out the gaps in medical research [5, 6]. Thus, clinicians can read them to keep up with advancements in their fields, policy makers use them to decide what types of health care to provide, and granting agencies may require them to justify further research. Systematic reviews have been used to address the CER priorities set by the Institute of Medicine (IOM) [7]. Three of the IOM top 25 priorities for CER involve cancer. One priority is to compare the effectiveness of imaging techniques to help with diagnosing, staging, and monitoring the cancer [7]. For colorectal cancer (CRC), numerous systematic reviews answered this priority, looking at the use and quality of CRC screening, including symptom patterns and additional diagnostic tests, positron emission tomography and computed tomography (CT) screening, CT colonography and optical colonoscopy, and a diagnostic sentinel lymph node procedure [8–12].

A second IOM top 25 priority is to compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating cancer [7]. In response to this, a systematic review found that microsatellite instability can be used to predict nonresponse of adjuvant chemotherapy for CRC [13]. A third IOM top 25 priority is to compare the effectiveness of interventions to reduce health disparities in cancer outcomes [7]. Numerous systematic reviews have been conducted on the effectiveness of various interventions, including salvage surgery, intraoperative radiotherapy, neoadjuvant chemotherapy, perioperative chemotherapy, adjuvant chemotherapy, and specific chemotherapeutic drugs, such as irinotecan and bevacizumab [14–21].

Management of elderly (>65 years old) cancer patients has been challenging because elderly patients are frequently excluded from clinical trials; therefore, clinicians are often unsure how elderly cancer patients will respond to treatments. For colorectal cancer, more than 40% of new cases occur in patients older than 75 years of age [22].

There is limited evidence regarding how chemotherapy impacts the prognosis of elderly patients compared to nonelderly patients. Chemotherapy could have a lower or higher effectiveness in elderly versus nonelderly patients. Chemotherapy could also result in a higher or lower incidence of specific adverse events in elderly versus nonelderly patients. The aim of this systematic review is to synthesize the available evidence and determine if there is a differential relative effectiveness in chemotherapy for stage III colon cancer between elderly and nonelderly patients.

Methods

This systematic review of clinical trials and effectiveness studies follows the approach recommended by the Agency for Healthcare Research and Quality [23]. These guidelines discuss topic refinement, analytic frameworks, study eligibility criteria, searching for relevant articles, when to select observational studies as evidence, data extraction, assessing the quality of individual studies, assessing applicability, presentation of findings, quantitative synthesis, grading strength of evidence, and reporting the review.

Search Strategy and Selection Criteria

Seven searches were performed in Medline and Evidence-Based Medicine Reviews (Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, National Health Service Economic Evaluation Database) databases on June 15–16, 2011. The searches used combinations of medical subject heading search terms: "colorectal neoplasms," "adenomatous polyposis coli," "colonic neoplasms," "colorectal neoplasms, hereditary nonpolyposis," "therapeutics," "efficacy," "effectiveness," "treatment outcome," "survival benefit," "surgery," "chemotherapy," "drug therapy," "elderly," "all aged (65 and over)," "age factors," "Medicare," "SEER Program," "cost," "cost analysis," "economics," and "health care economics and organizations." Articles were limited to studies written in English, pertaining to humans, and published from 2001 to 2011. The search strategies are provided as supplemental online data.

Reference sections of identified articles were scanned for additional relevant articles. Articles were kept if they met the following inclusion criteria: (a) Patients had stage III colon cancer, (b) treatment being studied was recommended chemotherapy for CRC as per National Comprehensive Cancer Network (NCCN) guidelines [24], (c) study looked at effectiveness of chemotherapy, (d) study included patients older than 65 years, and (e) study was a phase II, III, or IV trial or observational study with empirical analysis. Data were not extracted from reviews; instead, the studies reported in previous reviews were included in this study. Levels of evidence were not used in assessing the value of each publication selected for inclusion. Unpublished material was not included.

Data Extraction

Information regarding study characteristics (see supplemental online data) and study design were extracted. Point estimates, *p* values, and confidence intervals for effectiveness (overall survival, disease-free survival, time to progression, overall response rate, complete response, partial response, stable disease, progressive disease, tumor control rate) and safety outcomes (rate of adverse events) were extracted. It was decided *a priori* to accept age subgroups as presented in articles but to attempt to examine the effectiveness of chemotherapy among elderly (i.e., at least 65 years old) compared with nonelderly patients with stage III colon cancer. Authors were contacted for missing values if results were not broken down by age group.

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Statistical Analysis

Data were not combined using a meta-analysis due to the heterogeneity of population and setting. Instead, each effectiveness outcome was examined within each study to determine whether the results showed statistically significant differences between elderly versus nonelderly patients with stage III colon cancer. A χ^2 test for homogeneity was performed for safety outcome estimates if *p* values were not provided in the source article. Fisher's exact test was used if the χ^2 test could not be used.

Determining Differential Relative Effectiveness

Differential relative effectiveness between elderly and nonelderly patients was determined by comparing a reported estimate for elderly patients to a reported estimate for nonelderly patients for the same effectiveness or safety parameter. For instance, given overall survival values, if the overall survival value reported for elderly patients was not statistically significantly different from that reported for nonelderly patients, then that study was indicative of similar effectiveness between elderly and nonelderly patients based on overall survival values.

If there was a statistically significant difference, then there were two possible results. If the overall survival value reported for elderly patients was lower than that reported for nonelderly patients, then that study was demonstrative of less effectiveness in elderly versus nonelderly patients. On the contrary, if the overall survival value reported for elderly patients was higher than that reported for nonelderly patients, then the study was indicative of more effectiveness in elderly versus nonelderly patients. The same process was repeated for all reported values of all effectiveness and safety parameters.

Color Coding in Figures

When displaying summary results, figures were color-coded to demonstrate how many studies reported effectiveness parameters indicating higher, similar, or lower relative effectiveness in elderly versus nonelderly patients. Red indicates that chemotherapy was less effective in elderly versus nonelderly patients based on comparing the reported estimates for a specific effectiveness parameter between elderly and nonelderly patients. Blue means that chemotherapy was similarly effective in elderly versus nonelderly patients because there was no statistically significant difference between the reported estimates for a specific effectiveness parameter for elderly versus nonelderly patients. Green means that chemotherapy was more effective in elderly versus nonelderly patients based on comparing the reported estimates for a specific effectiveness parameter between elderly and nonelderly patients.

A similar coding scheme was used to show how many studies reporting safety outcomes indicated higher, similar, or lower rates of adverse events in elderly versus nonelderly patients. Red indicates that there was a higher incidence of a specific adverse event in elderly versus nonelderly patients for that study. Blue means that there was no statistically significant difference in incidence of the specific adverse event in elderly versus nonelderly patients for that study. Green means that there was a lower incidence of the specific adverse event in elderly versus nonelderly patients for that study.

Only four studies reported overall survival hazard ratios indicating less relative chemotherapy effectiveness in elderly versus nonelderly patients. The majority of studies reporting overall survival (10/14 studies) indicate similar chemotherapy effectiveness in elderly versus nonelderly patients.

Results

The systematic literature search identified 708 articles (after removing duplicates). Figure 1 shows the selection process. Data were extracted from the 25 articles that met all inclusion and exclusion criteria. Within the 25 articles, there were 39 studies administering various chemotherapy regimens. These studies were either observational studies or trials. Each study reported estimates of various effectiveness and/or safety parameters. Of the 39 studies, 27 were trials and 12 were observational studies.

Chemotherapy Regimens

The NCCN-recommended chemotherapy regimens for stage III colon cancer were categorized into regimens including four of the following: 5-fluorouracil and leucovorin alone (5-FU/LV), 5-FU/LV and oxaliplatin (FOLFOX), capecitabine alone (Cap), or Cap and Ox (CapeOx) [25]. The fifth category of chemotherapy regimens consists of regimens using irinotecan (Iri) alone or with 5-FU/LV or Cap. The sixth category of chemotherapy regimens consists of regimens using bevacizumab (Bev) alone or with 5-FU/Ox. According to NCCN guidelines, irinotecan and bevacizumab are both recommended for metastasized colon cancer. However, in the studies that included both stage III and IV patients, it was unclear if irinotecan and bevacizumab were used for only stage IV or both stage III and IV cancer. The seventh category of chemotherapy regimens encompasses two studies that used multiple chemotherapy regimens. One study included 5-FU/Ox or 5-FU/Iri or 5-FU alone, or any one of the three options with bevacizumab or cetuximab. The second study included 5-FU/LV or CapeOx. Exact chemotherapy regimens for each of the 39 studies extracted are described in the supplemental online data along with other study characteristics, including author, year, study type, sample size, and age breakdown.

The number of studies producing estimates for various effectiveness parameters for each chemotherapy category is given in Table 1. Nine such studies provided effectiveness results for FOLFOX, four studies for CapeOx, three studies for Cap alone, and 14 studies for 5-FU/LV. Other regimens included irinotecan and bevacizumab. Five studies used Iri-based regimens, and two studies used regimens adding bevacizumab. Two studies used multiple regimens, as specified above. In total, 23 studies published effectiveness estimates and 28 studies published safety estimates (Table 1).

Overall Survival

Overall survival (OS) point estimates for different age groups were given in 20 studies. Figure 2 presents these values. The data from Figure 2 is presented in chart form in Figure 3. The six studies that did not directly compare OS estimates between elderly and nonelderly patients were omitted from Figure 3. Figure 3 shows the relative effectiveness of various chemotherapy regimens in elderly versus nonelderly patients based on reported overall survival values.

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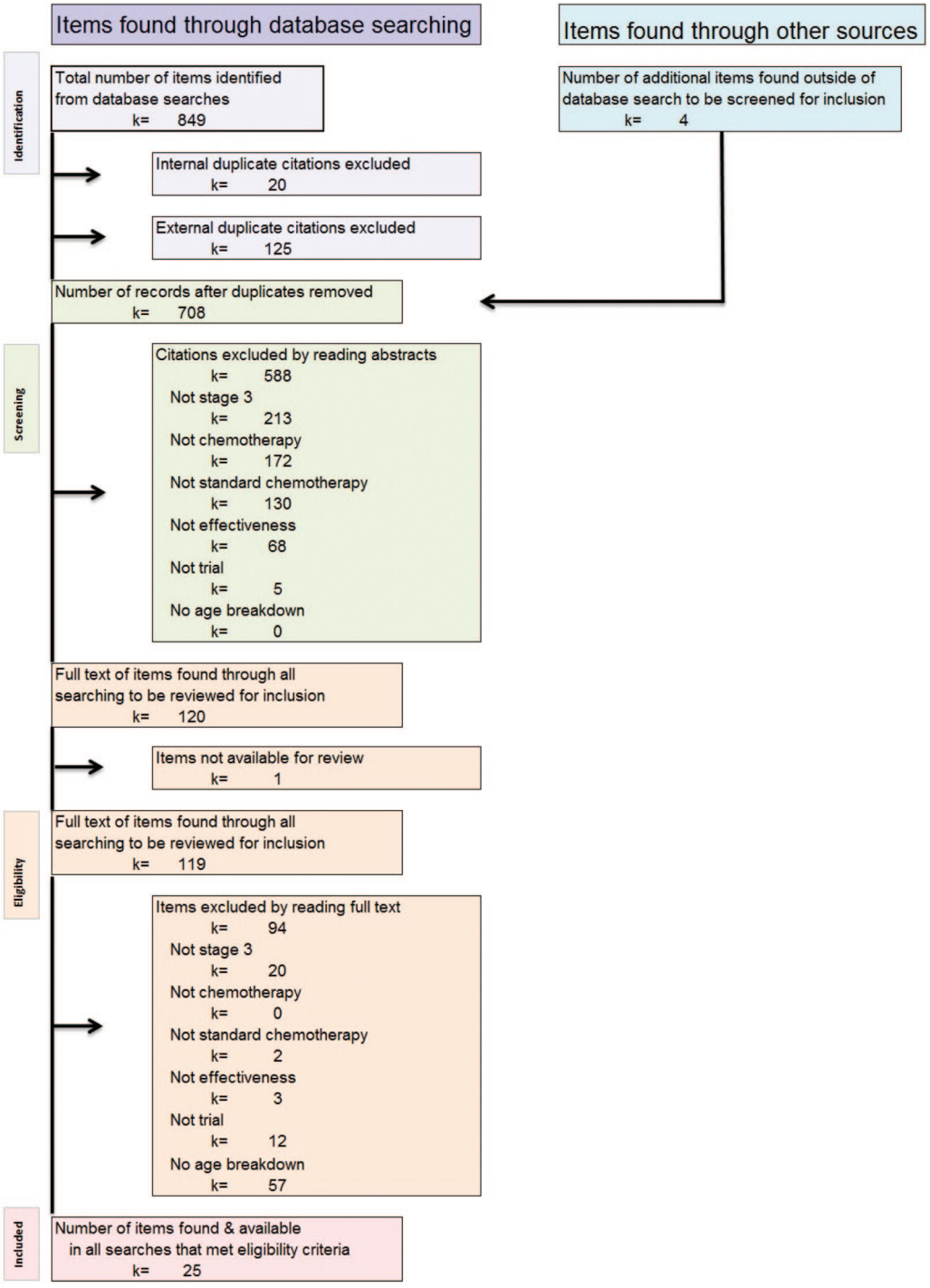

Figure 1. Flow diagram of systematic review article selection process, showing how articles were selected for inclusion in this review.

In addition to overall survival values, 1-year, 2-year, and 5-year survival percentage, and overall survival hazard ratio values are given. Only four studies (in red) reported overall survival hazard ratios indicating less relative chemotherapy effectiveness in elderly versus nonelderly patients. The majority of studies reporting overall survival (10/14 studies) indicate similar chemotherapy effectiveness (in blue) in elderly versus nonelderly patients.

There were four studies indicating less relative chemotherapy effectiveness in elderly versus nonelderly patients: two studies in which patients used 5-FU/LV chemotherapy and two studies in which patients used multiple chemotherapies. The two studies in which patients were given 5-FU/LV chemotherapy came from the same article by Zuckerman et al. [26]. The first study used the adjusted overall sample and the second study used the adjusted propensity score matched sample. In both studies, OS hazard ratios between various age groups (65–69, 70–74, 75–79, 80–84, and 85–89 years) were analyzed and *p* values were reported as $<.001$ for each age group (except for a reported *p* value of .006 for ages 65–69). In the first study, the OS hazard ratios were 0.47 (65–69), 0.32 (70–74), 0.41 (75–79), 0.59 (80–84), and 0.54 (85–89). In the

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Table 1. Number of studies reporting effectiveness and safety outcomes by chemotherapy type

Chemotherapy	Number of studies from articles	Number of studies reporting effectiveness outcomes	Number of studies reporting safety outcomes
FOLFOX	9	4	7
CapeOx	4	3	3
Cap	3	2	3
5-FU/LV	14	8	8
Iri-based	5	4	5
Bev-based	2	0	2
Multiple[a]	2	2	0
Total	39	23	28

[a]Combination of various chemotherapy regimens not broken down by agent.
Abbreviations: 5-FU/LV, 5-fluorouracil and leucovorin; Bev, bevacizumab; Cap, capecitabine; CapeOx, capecitabine and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; Iri, irinotecan; LV, leucovorin.

second study, the OS hazard ratios were 0.54 (65–69), 0.36 (70–74), 0.36 (75–79), 0.65 (80–84), and 0.51 (85–89).

The third study by McKibbin et al. used multiple chemotherapies (either 5-FU/Ox or 5-FU/Iri or 5-FU alone, or any one of the three options with bevacizumab or cetuximab) [27]. McKibbin et al. compared OS adjusted hazard ratios between patients aged >65 (1.19 with a 95% confidence interval of 1.02–1.39) and ≤65 (reference value) and determined a *p* value of .03. The fourth study by Haller et al. used multiple chemotherapies (either CapeOx or 5-FU/LV given as a Mayo Clinic or Roswell Park regimen) [28]. Haller et al. found that age was associated with less chemotherapy benefit according to an overall survival hazard ratio (1.17, 95% confidence interval = 1.06–1.28, $p = .0016$).

Other Effectiveness Outcomes

The other effectiveness outcomes extracted in this systematic review included progression-free survival (PFS) or disease-free survival (DFS), time to progression (TTP), and overall response rate (ORR). Figure 4 gives a summary of effectiveness results and uses the color coding described earlier. PFS/DFS values were similar between elderly and nonelderly patients in all four studies. Most TTP (4/5 studies) and ORR (3/4 studies) values were similar between elderly and nonelderly patients.

One study by Jensen et al. indicated that capecitabine chemotherapy was more effective in elderly (≥75) than nonelderly (<75) patients according to both TTP and ORR values [22]. TTP values were reported as 8.4 and 4.1 months for elderly and nonelderly patients, respectively, with a *p* value of .001, hazard ratio of 0.35, and confidence interval of 0.29–0.80. ORR values were reported as 72% and 31% for elderly and nonelderly patients, respectively, with a *p* value of .0006.

Symptoms and Safety Outcomes

Symptoms and safety outcomes were extracted based on those reported in the studies. They include grade 3 or 4 cardiac disorder, anemia, leukopenia, neutropenia, thrombocytopenia, febrile neutropenia, infection, pain, hand-foot syndrome,

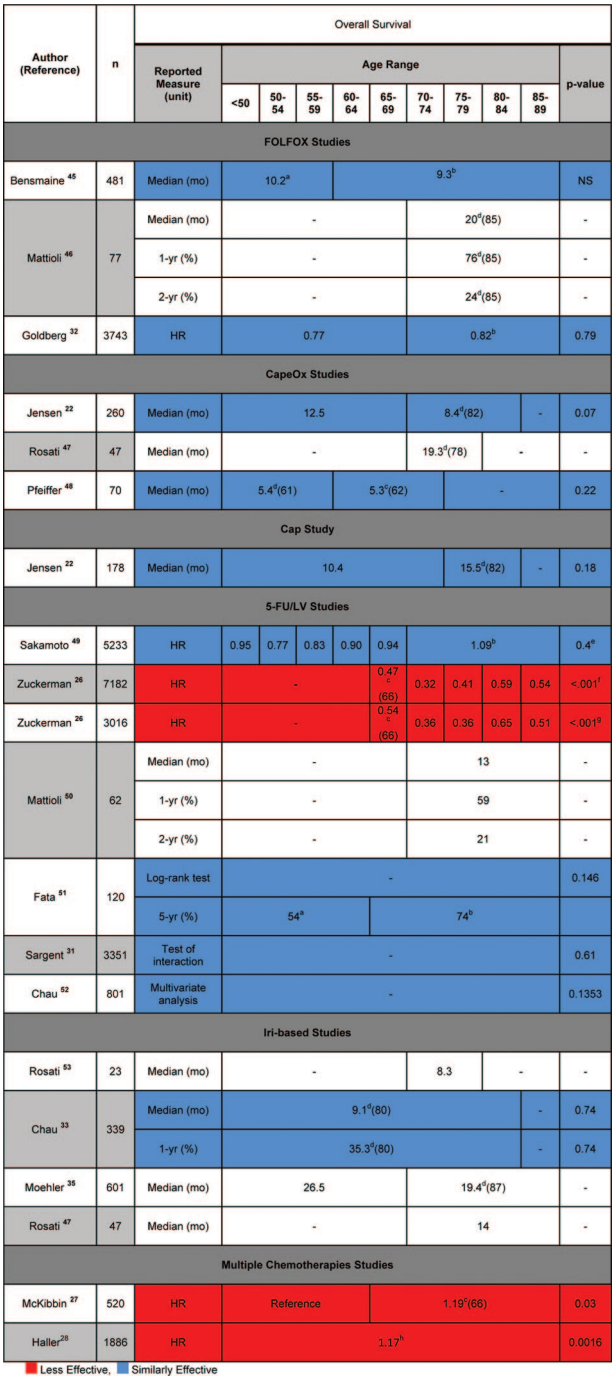

Figure 2. Reported estimates of overall survival for various chemotherapies by age group.
[a]Lowest age unknown.
[b]Highest age unknown.
[c]Minimum age of subgroup given in parentheses following superscript.
[d]Maximum age of subgroup given in parentheses following superscript.
[e]*p* value for overall trend.
[f]*p* value for each age group.
[g]*p* value for each age group was reported as <.001, except for .006 for ages 65–69.
[h]Hazard ratio of age using 10-year increments.
Abbreviations: 5-FU/LV, 5-fluorouracil and leucovorin; Bev, bevacizumab; Cap, capecitabine; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; Iri, irinotecan; LV, leucovorin; NS, not significant.

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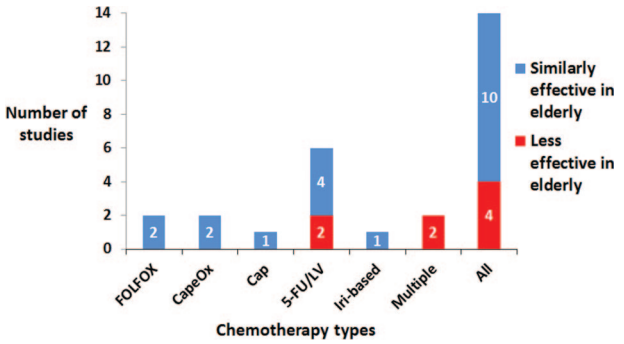

Figure 3. Relative overall survival impact of chemotherapies in elderly versus nonelderly patients with stage III colon cancer. The number of studies indicating differential relative effectiveness according to overall survival values for various chemotherapy regimens when comparing elderly and nonelderly patients with stage III colon cancer are shown.

Abbreviations: 5-FU/LV, 5-fluorouracil and leucovorin; Cap, capecitabine; CapeOx, capecitabine and oxaliplatin; FOLFOX, 5-fluorouracil, leucovorin, and oxaliplatin; Iri, irinotecan.

stomatitis, dehydration, diarrhea, nausea/vomiting, fatigue, and neuropathy. Figure 5 gives a summary of the results, showing how many studies demonstrated chemotherapy having lower (in green), similar (in blue), or higher (in red) incidences of adverse events in the elderly versus nonelderly patients.

Maculopapular rash, anorexia, constipation, dyspnea, anxiety, depression, insomnia, and psychological distress are also common symptoms of colon cancer chemotherapy. However, no studies reported these symptoms, so they were not reported in this review.

Adverse Events More Frequently Seen in Elderly Patients

The majority of all adverse events occurred at a similar rate in elderly versus nonelderly patients. However, there were studies reporting higher incidences of adverse events in 9 out of 15 grade 3 or 4 adverse events: cardiac disorder (2/5 studies) [29, 30], leukopenia (1/5) [31], neutropenia (4/16) [32–34], thrombocytopenia (2/13) [32, 34], febrile neutropenia (1/4) [34], infection (2/10) [29, 32], dehydration (2/6) [29, 34], diarrhea (6/20) [22, 27, 29, 34–35], and fatigue (6/13) [27, 32, 34–35].

Fatigue was seen more frequently in elderly versus nonelderly patients according to six studies. Goldberg et al. reported values of fatigue incidence from three different trials indicating higher incidence of fatigue in elderly (≥70 years) versus nonelderly (<70 years) patients receiving FOLFOX [32]. Reported incidences of fatigue were 7% and 4% ($p = .08$ or .003 when age modeled as a continuous variable), 19% and 9% ($p = .04$), and 19% and 9% ($p = .03$) in elderly and nonelderly patients, respectively.

Moehler et al. reported fatigue as 5.0% and 1.3% ($p = 0.03$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving Iri/5-FU/LV chemotherapy, respectively [35]. McKibbin et al. reported fatigue (grade unspecified) as 36% and 17% ($p < .01$) in elderly (>65 years) and nonelderly (≤65 years) patients receiving Iri/5-FU chemotherapy, respectively [27]. Allegra et al. reported fatigue (grade 3) as 15.2% and 6.9% ($p < .001$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving 5-FU/Ox with or without bevacizumab as chemotherapy [34].

Diarrhea had a higher incidence in elderly versus nonelderly patients according to six studies. McKibbin et al. reported higher incidences of diarrhea (grade unspecified) in elderly (>65 years) versus nonelderly (≤65 years) patients twice [27]. In one study, patients were given 5-FU/Ox chemotherapy. The incidence of diarrhea was 32% and 19% ($p < .01$) in elderly and nonelderly patients respectively. In a second study, patients were given 5-FU/Iri chemotherapy. The incidence of diarrhea was 56% and 31% ($p = .001$) in elderly and nonelderly patients, respectively.

Jensen et al. reported diarrhea as 18% and 6% ($p = .01$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving CapeOx chemotherapy [22]. Schmoll et al reported diarrhea as 23% and 17% ($p < .05$) in elderly (≥65 years) and nonelderly (<65 years) patients receiving CapeOx chemotherapy [29]. Moehler et al. reported late-onset diarrhea as 16% and 7.1% in elderly (≥70 years) and nonelderly (<70 years) patients receiving Iri/5-FU/LV chemotherapy [35]. Allegra et al reported diarrhea (grade 3) as 16.4% and 9.5% ($p < .001$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving 5-FU/Ox with or without bevacizumab chemotherapy [34].

Neutropenia was seen more often in elderly versus nonelderly patients according to four studies. Goldberg et al. reported a higher rate of neutropenia in elderly (≥70 years) versus nonelderly (<70 years) patients receiving FOLFOX chemotherapy in two separate trials [32]. Rates of neutropenia were reported as 49% and 43% ($p = .04$ or $p < .001$ when age was modeled as a continuous variable) and 60% and 43% ($p = .02$) in elderly and nonelderly patients, respectively. Chau et al. reported neutropenia as 35% and 22% ($p = .0228$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving irinotecan chemotherapy [33]. Allegra et al. reported grade 3 neutropenia as 42.2% and 28.8% ($p < .001$) and grade 4 neutropenia as 13% and 6% ($p < .001$) in elderly (≥70 years) and nonelderly (<70 years) patients receiving 5-FU/Ox with or without bevacizumab as chemotherapy [34].

Adverse Events Less Frequently Seen in Elderly Patients

Only neutropenia, nausea/vomiting, and neuropathy were seen less frequently in elderly versus nonelderly patients in 2/16 [35], 1/16 [32], and 1/9 [27] of all studies. A lower incidence of neutropenia was reported in patients receiving Iri/5-FU/LV chemotherapy by Moehler et al. [35]. Of the elderly patients (≥70 years), 0.6% experienced neutropenia, whereas 4.1% of the nonelderly patients (<70 years) experienced neutropenia. The p value was not provided, so it was calculated to be .02 by the χ^2 test for homogeneity. McKibbin et al. reported the incidence of neutropenia (grade unspecified) as 18% and 28% in elderly and nonelderly patients, respectively, with a reported p value of 0.03 [27].

In Goldberg et al., the incidence of nausea/vomiting in patients receiving FOLFOX chemotherapy was reported as 7% in elderly patients (≥70 years) and 9% in nonelderly patients (<70 years) [32]. The reported p value in a model with age as a continuous variable was <.001, whereas the reported p value from a logistic regression model for age as a dichotomous vari-

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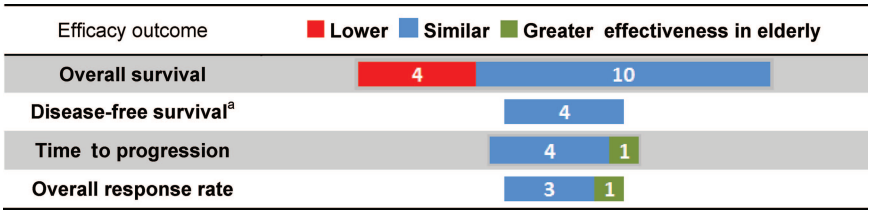

Figure 4. Relative effectiveness of chemotherapies in elderly versus nonelderly patients with stage III colon cancer. The number of studies indicating differential relative effectiveness between elderly and nonelderly patients with stage III colon cancer is shown according to reported overall survival, disease-free survival, time to progression, and overall response rates.

[a]One study provided progression-free survival estimates.

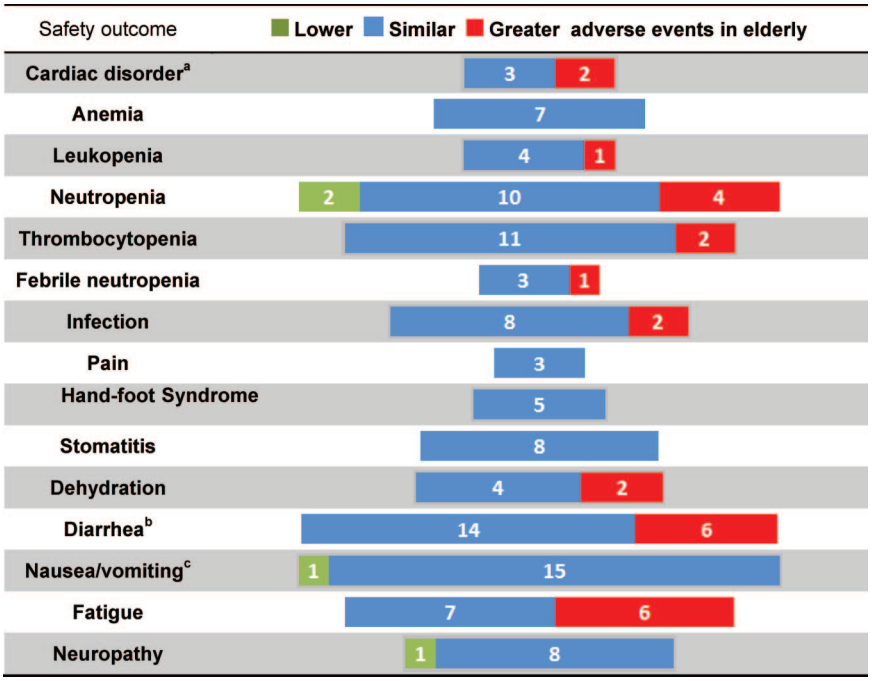

Figure 5. Relative reporting of grade 3 or 4 adverse events from chemotherapies in elderly versus nonelderly patients with stage III colon cancer. The number of studies indicating a difference in the relative incidence of grade 3 or 4 adverse events between elderly and nonelderly patients with stage III colon cancer is shown.

[a]Cardiac disorders consist of cardiac disorders, myocardial infarction, arterial thrombosis, and venous thrombosis. One study represented by red indicated higher incidence of arterial thrombosis, but similar incidence of venous thrombosis in the elderly. Another study represented by red indicated the opposite.

[b]One study represented by red indicated higher incidence of late-onset diarrhea but similar incidence of early-onset diarrhea in the elderly.

[c]Four studies reported nausea only.

able (age <70 vs. ≥ 70) in a model adjusted for study, sex, and performance status was .38.

In McKibbin et al., the incidence of neuropathy (grade unspecified) in patients receiving 5-FU/Ox chemotherapy was reported as 15% in elderly patients (>65 years) and 26% in nonelderly patients (≤ 65 years), with a reported p value of .02 [27].

Discussion

Previous literature has indicated that colon cancer survival is better in nonelderly versus elderly patients [36]. However, it is unknown whether this is due to differential relative effect of chemotherapy among elderly versus nonelderly colon cancer patients or other factors. Elderly patients are less likely to receive chemotherapy and more likely to have other risks for reduced survival. Therefore, patients and their medical oncologists benefit from evidence that separates out the chemotherapy benefits and harms from confounding factors that affect relative survival and adverse events among elderly patients compared to nonelderly patients. This systematic review compares the relative effectiveness and incidence of adverse events of chemotherapy in elderly versus nonelderly stage III patients.

The vast majority of evidence in this review suggests that chemotherapy has similar relative effectiveness and safety outcomes in patients in their sixties, seventies, and eighties compared to younger patients. However, when looking at the evidence suggesting a difference, higher adverse event rates in elderly versus nonelderly patients are most observed. Fatigue, diarrhea, and neutropenia have the most reported differences in incidence when comparing elderly and nonelderly patients.

The higher incidence of fatigue, diarrhea, and neutropenia among elderly patients was seen for a wide variety of chemo-

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therapy regimens, so no associations between a specific chemotherapy regimen and higher incidence of adverse event can be anticipated. This was also true for the higher incidences seen in elderly patients for other adverse events. In addition, when looking at the evidence suggesting a difference in outcomes in elderly versus nonelderly patients, a few studies reported lower incidence of adverse events, as well as lower and higher effectiveness of chemotherapy in elderly patients. However, these studies were even fewer in comparison to the number of studies reporting a higher incidence of adverse events in elderly versus nonelderly patients. A plausible explanation for the studies reporting lower incidence of adverse events in elderly patients is that these patients received lower doses or less aggressive chemotherapy treatment than nonelderly patients.

Any differences in safety outcomes when comparing elderly and nonelderly patients may be partially due to inherent discrepancies between the two populations. Because no major difference in treatment effects between elderly and nonelderly patients was found, this systematic review suggests that in the absence of other reasons for withholding treatment, elderly patients should receive chemotherapy as often as nonelderly patients.

Any differences in safety outcomes when comparing elderly and nonelderly patients may be partially due to inherent discrepancies between the two populations. Because no major difference in treatment effects between elderly and nonelderly patients was found, this systematic review suggests that in the absence of other reasons for withholding treatment, elderly patients should receive chemotherapy as often as nonelderly patients. Our systematic review does not support the lower treatment rates seen in patients in their sixties, seventies, and eighties.

Previous reviews have found similar effectiveness results. A review by Au et al. found that chemotherapy offered a similar benefit to elderly and nonelderly patients, but more data were needed regarding the toxicity of therapy [37]. Similarly, a review by Kohne et al. concluded that fit elderly patients could be given aggressive chemotherapy just as it would be given to nonelderly patients [38]. A review by Power et al. came to similar findings and added that older patients are more willing to take chemotherapy if they are fully informed of its potential toxicities and benefits [39].

Chemotherapy use among elderly patients has risen over time. Whereas approximately 22% of patients 80 years and older received treatment in 1990–1991, nearly 40% of patients in this age group received treatment a decade later [40]. However, treatment rates are still considered low [22, 40–41]. Elderly patients are less likely to receive treatment due to a variety of reasons including decreased functional and cognitive ability, financial barriers, lack of social support, comorbidities, patient preference, and clinician knowledge and attitudes [22, 41, 42]. Clinicians are often concerned with treating elderly patients because of the lack of generalizability of trial results [22].

There are likely other factors that affect the relative effectiveness of chemotherapy, some of which could be correlated with age. For instance, the likelihood of a poorer performance status is greater in an elderly than nonelderly patient. Future research should try to disentangle factors like performance status, comorbidities, and organ function from age alone when determining patient-centered outcomes associated with chemotherapy. It should be noted that there is a difference between performance status, functional status, and problems discovered in geriatric assessment in older patients with cancer [43]. Furthermore, even if elderly patients receive treatment, they are more likely to receive substandard treatment or discontinue treatment, often due to the higher incidence of specific treatment-related toxicities [22, 40]. It is important for clinicians to be aware of these specific toxicities so they can warn their elderly patients ahead of time.

Adjuvant chemotherapy is recommended for stage III colon cancer per NCCN guidelines; however, it remains controversial and underused in the elderly population. Recent studies have shown that older patients with stage III colon cancer, often with pre-existing comorbidities, were less likely to receive adjuvant chemotherapy, when the survival benefit was comparable across age groups [44, 45].

This systematic review is limited by the heterogeneity of the study populations and the quality of the articles studied. Ideally, a systematic review would uncover sufficient evidence to perform a meta-analysis or weighted average of estimates. Due to the paucity of studies that address this topic and the inconsistency in metrics used to report benefits of chemotherapy, such a synthesis was unfeasible.

Additionally, the lower age limit for an elderly patient varied between 60 and 75 years amongst different trials. However, most elderly patients were younger than 80 years and considered fit. The studied effects of older patients in these articles may not be applicable to all older patients because those who received treatment may reflect a selective and small subset of the total elderly population. A recent trial was designed to include frail and elderly patients with metastatic colorectal cancer by using reduced-dose chemotherapy options [46]. However, it is one of the only trials that includes this population of patients, so CER is still very important in helping determine the evidence for this population of patients. The CER movement is aimed at not only providing information on the relative effectiveness of one chemotherapeutic agent versus another, but also on providing evidence on subpopulations of patients, including the elderly. This systematic review presents various effectiveness and safety outcomes in a way that is applicable for elderly patients.

Conclusion

The vast majority of the evidence from this systematic review indicates that the relative treatment effect of chemotherapy for stage III cancer in terms of both effectiveness and safety is similar among older patients compared to younger patients. When differences in the relative treatment effect between elderly and nonelderly patients are reported, the prognosis is worse for the elderly. Furthermore, the reported chemotherapy effects on grade 3 or 4 adverse event rates are more often higher among elderly versus nonelderly patients. Nonetheless, because no major difference in treatment effects between elderly and nonelderly

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patients was found, this systematic review suggests that in the absence of other reasons for withholding treatment, elderly patients should receive chemotherapy as often as nonelderly patients. Our systematic review does not support the lower treatment rates seen in older patients. Comparative effectiveness research should continue to provide additional evidence for populations historically underrepresented in clinical trials, such as the elderly population.

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Disclosures

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