

A POOLED ANALYSIS OF ADJUVANT CHEMOTHERAPY FOR RESECTED COLON CANCER IN ELDERLY PATIENTS

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ABSTRACT

Background Adjuvant chemotherapy is standard treatment for patients with resected colon cancer who are at high risk for recurrence, but the efficacy and toxicity of such treatment in patients more than 70 years of age are controversial.

Methods We performed a pooled analysis, based on the intention to treat, of individual patient data from seven phase 3 randomized trials (involving 3351 patients) in which the effects of postoperative fluorouracil plus leucovorin (five trials) or fluorouracil plus levamisole (two trials) were compared with the effects of surgery alone in patients with stage II or III colon cancer. The patients were grouped into four age categories of equal size, and analyses were repeated with 10-year age ranges (≤ 50 , 51 to 60, 61 to 70, and > 70 years), with the same conclusions. The toxic effects measured in all trials were nausea or vomiting, diarrhea, stomatitis, and leukopenia. Patients in the fluorouracil-plus-leucovorin and fluorouracil-plus-levamisole groups were combined for the efficacy analysis but kept separate for toxicity analyses.

Results Adjuvant treatment had a significant positive effect on both overall survival and time to tumor recurrence ($P < 0.001$ for each, with hazard ratios of death and recurrence of 0.76 [95 percent confidence interval, 0.68 to 0.85] and 0.68 [95 percent confidence interval, 0.60 to 0.76], respectively). The five-year overall survival was 71 percent for those who received adjuvant therapy, as compared with 64 percent for those untreated. No significant interaction was observed between age and the efficacy of treatment. The incidence of toxic effects was not increased among the elderly (age > 70 years), except for leukopenia in one study.

Conclusions Selected elderly patients with colon cancer can receive the same benefit from fluorouracil-based adjuvant therapy as their younger counterparts, without a significant increase in toxic effects. (N Engl J Med 2001;345:1091-7.)

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BY 2030, one in five Americans will be over 65 years of age.^{1,2} Physicians will be seeing increasing numbers of elderly patients with colorectal cancer and other cancers whose incidence increases with age. Currently, 60 percent of malignant disease occurs in persons over 65 years of age. More than half of these patients are over 70 years old, and one fourth of them are over 80 years old.³⁻⁷ In some clinical trials, the elderly have been excluded by design. More often, their outcomes have been pooled in results that have not been analyzed accord-

ing to age. Consequently, only limited data are available on the risks and benefits of specific cancer-treatment regimens in the elderly.⁸⁻¹¹ Moreover, elderly patients with cancer receive chemotherapy or radiotherapy less often than younger patients, regardless of the disease site or stage at diagnosis,¹²⁻¹⁵ and many elderly patients do not receive what is considered standard chemotherapy.^{14,15}

In colon cancer, the need for postsurgical treatment is dictated primarily by the stage of the cancer. For patients with node-positive (stage III) disease, adjuvant treatment with fluorouracil and levamisole reduces the risk of death by one third, as compared with surgery alone.^{16,17} According to a 1990 consensus statement by the National Cancer Institute, patients with stage III disease who are unable to enter a clinical trial should be offered adjuvant fluorouracil plus levamisole unless there are medical or psychosocial contraindications.¹⁸ Later studies demonstrated similar benefits from adjuvant treatment with fluorouracil plus leucovorin.¹⁹⁻²¹ Currently, fluorouracil plus leucovorin for six to eight months is standard adjuvant treatment for stage III colon cancer. The benefits of fluorouracil-based therapy for stage II colon cancer are unclear, although many trials permit the enrollment of patients after resection of either stage II or stage III disease.^{22,23}

Older patients with stage II or III colon cancer are both offered and receive adjuvant chemotherapy less frequently than younger patients.²⁴ For example, according to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program, which includes data on approximately 11 percent of the population, in 1992, only 48 percent of patients 65 to 74 years of age, and 24 percent of those 80 to 84 years of age, received adjuvant therapy for node-positive colorectal cancer.²⁵ Elderly patients do not receive adjuvant chemotherapy for a variety of reasons, including coexisting conditions, fear of toxic effects, declining functional and mental status, and lack of social support. However, most people older than 75 are independent, and their life expectancy without cancer is 10 to 12 years.^{1,26} Because colorectal cancer typically

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recurs within five years after diagnosis, it is reasonable to consider adjuvant chemotherapy to prevent recurrence in selected septuagenarians and octogenarians.

To investigate the effects of chemotherapy in the elderly, we conducted an age-based, pooled analysis of data from randomized trials that compared fluorouracil-based regimens with no adjuvant chemotherapy for patients with resected stage II or III colon cancer.

METHODS

Identification of Studies

We attempted to identify all reported studies comparing postoperative fluorouracil plus leucovorin or fluorouracil plus levamisole with surgery alone through a Medline search, a search of bibliographies, and discussions with the leaders of each identified trial. Data from one 250-patient trial were unavailable because the file containing the source data had been lost as a result of a computer malfunction.²⁷ Three trials that had not yet completed follow-up (the QUASAR trial,²⁸ a study of the Stockholm Colorectal Cancer Study Group, and the Netherlands Adjuvant Colorectal Cancer Study) were not included in this pooled analysis.

Trial Designs

Seven studies met the predetermined criteria for inclusion in this pooled analysis (Table 1).^{16,17,19-21} In all seven trials, patients were randomly assigned to either chemotherapy or no treatment after surgical resection. Five studies tested fluorouracil plus leucovorin, and two tested fluorouracil plus levamisole. Eligibility criteria included stage II (T3 or T4, N0, M0) or stage III (T1, 2, 3, or 4, N1, 2, or 3, M0) adenocarcinoma of the colon. Treatment began between 21 and 56 days after surgery. The trials of fluorouracil plus leucovorin used fluorouracil in doses ranging from 370 to 425 mg per square meter of body-surface area and leucovorin in doses ranging from 20 to 200 mg per square meter daily for five

days, repeated every four to five weeks. The trials of fluorouracil plus levamisole administered fluorouracil by rapid intravenous injection at a dose of 450 mg per square meter on five consecutive days. On day 28, patients began weekly injections of 450 mg of fluorouracil per square meter. Throughout treatment, levamisole was administered orally at a dose of 50 mg three times daily on days 1 through 3, repeated every two weeks.

The duration of treatment in both trials of fluorouracil plus levamisole was one year. The duration of treatment in the trials of fluorouracil plus leucovorin was 6 cycles in four of the trials and 12 cycles in the fifth (the Siena trial²⁰). The two studies of fluorouracil plus levamisole also included a group that received levamisole alone; patients assigned to levamisole alone were not included in our pooled analysis. No age-related eligibility criteria were specified for six of the seven studies; the Fondation Française de Cancérologie Digestive study²¹ excluded patients older than 75 years.

Adverse events were graded according to either the National Cancer Institute common toxicity criteria scale or the World Health Organization toxicity scale. In all trials, the patients were examined and the toxicity data, including the frequency and severity of nausea or vomiting, diarrhea, stomatitis, and leukopenia, were documented at least monthly by physicians or oncology nurses. Our analysis of toxicity focused on severe adverse reactions, those judged as grade 3 or higher on either scale.

Statistical Analysis

The outcome and toxic effects recorded for each patient were obtained from all seven trials. The primary end points were overall survival and time to recurrence. Overall survival was defined as the time from study entry to death. The time to recurrence was defined as the time from study entry to the first confirmed relapse. Data on patients who died without recurrence were censored at the time of death for time-to-recurrence analyses. Data on overall survival and time to recurrence were analyzed up to eight years from the date of randomization. Because information on the cause of death was not available for all patients, we classified deaths as occurring with or without known recurrence of disease.

TABLE 1. TRIAL CHARACTERISTICS.*

CHARACTERISTIC	GIVIO	NCIC-CTG	FFCD	NCCTG/INT	SIENA	NCCTG†	INT 0035‡
Recruitment							
Date of first randomization	January 1989	May 1987	October 1982	February 1988	January 1985	May 1978	January 1985
Total no. randomized	888	370	268§	428	239	276	968
Eligibility criteria							
Age	None	None	≤75 yr	None	None	None	None
ECOG performance status¶	≤2	≤2	≤2	NA	NA	NA	NA
Day chemotherapy began by	35	56	35	35	21	35	35
Treatment							
Fluorouracil (mg/m ²)	370	370	400	425	400	450	450
Leucovorin (mg/m ²)	200	200	200	20	200	—	—
Levamisole (mg)	—	—	—	—	—	50	50
Duration of therapy (mo)	6	6	6	6	12	12	12
Toxicity assessment scale	WHO	WHO	WHO	CTC	WHO	CTC	CTC
Median follow-up (yr)	5.29	5.89	5.17	6.41	8.54	7.75	—

*Modified from the International Multicentre Pooled Analysis of Colon Cancer Trials Investigators,²¹ with the permission of the publisher. GIVIO denotes Gruppo Interdisciplinare di Valutazione Interventi in Oncologia,²¹ NCIC-CTG National Cancer Institute of Canada Clinical Trials Group,²¹ FFCD Fondation Française de Cancérologie Digestive,²¹ NCCTG North Central Cancer Treatment Group,^{16,19} INT U.S. Gastrointestinal Intergroup,¹⁷ Siena University of Siena,²⁰ ECOG Eastern Cooperative Oncology Group, NA not applicable, WHO World Health Organization, and CTC common toxicity criteria.

†Of 408 patients randomized, 276 were in the control group or receiving fluorouracil-based regimens.

‡Of 1296 patients randomized, 968 were in the control group or receiving fluorouracil-based regimens.

§Of 361 patients randomized, 268 had colon cancer.

¶ECOG performance status is graded on a scale from 0 to 5, with 0 denoting fully active and 5 death. A score of 2 indicates that the patient is ambulatory more than 50 percent of the time.

The primary statistical goal of the analysis was to test for an age-by-treatment interaction. The formal statistical power depended on the number of patients ultimately included and was thus not fixed in advance. Post hoc calculations (by the method of Peterson and George²⁹) based strictly on the number of deaths observed in each age group (that is, ignoring the effect of treatment) indicated that the sample size we obtained provided 80 percent power to detect an interaction represented by a hazard ratio of 1.4. Specifically, this pooled analysis had an 80 percent chance of detecting a significant interaction if treatment conferred a 40 percent reduction in risk of death in younger patients but provided no benefit in the elderly.

For all analyses, the patients were initially divided into age groups of equal size. To simplify the presentation, analyses were repeated with the following age groups: 50 years or less, 51 to 60 years, 61 to 70 years, and more than 70 years. Since both analyses produced the same conclusions, we present the results using the 10-year age groups. For clinical outcomes, we first tested for heterogeneity between studies using the log-rank test stratified according to the patient's original study for analyses of efficacy³⁰ and the χ^2 test for analyses of toxicity. The primary efficacy analysis consisted of a Cox proportional-hazards regression model,³¹ stratified according to study, including terms for age, treatment, and an age-by-treatment interaction. Age-based analyses were repeated with age as a dichotomous variable (≤ 70 or > 70 years) and a continuous variable. The validity of the proportional-hazards assumption was investigated by graphical methods.³²

Multivariate models were used to adjust for base-line performance status and stage. Relations between rates of adverse events and age were analyzed with Pearson's χ^2 statistic. Time-to-event curves were calculated by the method of Kaplan and Meier.³³ All P values were two-sided, with P values of less than 0.05 considered to indicate statistical significance. Hazard ratios with accompanying 95 percent confidence intervals were reported for comparisons of patients who received chemotherapy and those who did not.

RESULTS

Characteristics of the Patients and Follow-up

We identified seven randomized studies with a total enrollment of 3437 patients. After review by each original study team, 86 (2.5 percent) of these patients were deemed ineligible. Of the remaining 3351 patients, 1446 (43 percent) had stage II disease and 1905 (57 percent) had stage III disease.

Death without the Recurrence of Cancer

The probability of death without recurrence of cancer was strongly associated with age. Patients 50 years old or younger had a 2 percent chance of death without detectable cancer, whereas those older than 70 years had a 13 percent chance (Table 2). Thirty-two percent of deaths among the oldest patients, but only 5 percent of deaths among the youngest patients, were due to causes other than cancer. Approximately 30 percent of the patients in each age group died with recurrence of cancer over the eight-year follow-up period.

Effect of Chemotherapy

No significant between-study heterogeneity in the effect of treatment was observed for overall survival or time to recurrence ($P=0.71$ and $P=0.98$, respectively). When data from all age groups were pooled, each trial showed a beneficial effect of treatment on overall survival and time to recurrence, although this benefit

TABLE 2. DEATHS WITH AND WITHOUT THE RECURRENCE OF CANCER, ACCORDING TO AGE GROUP.

AGE GROUP	NO. OF PATIENTS	no. of deaths (percent)	
		WITH RECURRENCE	WITHOUT RECURRENCE
≤ 50 yr	564	183 (32)	10 (2)
51–60 yr	1012	311 (31)	37 (4)
61–70 yr	1269	416 (33)	86 (7)
> 70 yr	506	147 (29)	68 (13)
Total	3351	1057 (32)	201 (6)

was not statistically significant in each individual trial (Fig. 1). In the pooled analysis, overall survival was significantly longer for patients treated with fluorouracil-based therapy than for patients who did not receive adjuvant treatment ($P<0.001$). The five-year survival rate was 71 percent in treated patients and 64 percent in untreated patients (hazard ratio for death from any cause, 0.76; 95 percent confidence interval, 0.68 to 0.85). The time to tumor recurrence was also significantly longer in treated patients ($P<0.001$), with a five-year recurrence-free rate of 69 percent in treated patients as compared with 58 percent in untreated patients (hazard ratio for recurrence, 0.68; 95 percent confidence interval, 0.60 to 0.76).

Efficacy of Chemotherapy According to Age Group

No significant interaction was observed between age and treatment effect for overall survival or freedom from tumor recurrence, regardless of how age was included in the analysis. The P values for the test of interaction in which age was divided into four categories were 0.61 for overall survival and 0.33 for the time to tumor recurrence. The curves for overall survival (Fig. 2A and 2B) and freedom from recurrence (Fig. 2C and 2D) comparing adjuvant treatment with no adjuvant treatment according to age group were very similar for the first five years of follow-up. The survival curves for the patients who were older than 70 years of age converged slightly after five years, probably because of deaths from other causes.

Adverse Events According to Age Group

Significant between-study heterogeneity was observed in the rates of adverse events. Although it was not a randomized comparison, patients treated with fluorouracil plus levamisole had significantly more leukopenia and nausea or vomiting ($P=0.001$ and $P=0.05$, respectively), whereas those treated with fluorouracil plus leucovorin had significantly more stomatitis and diarrhea ($P=0.001$ for both comparisons). Therefore, we performed separate analyses of toxicity according to age for the two treatment regimens (Ta-

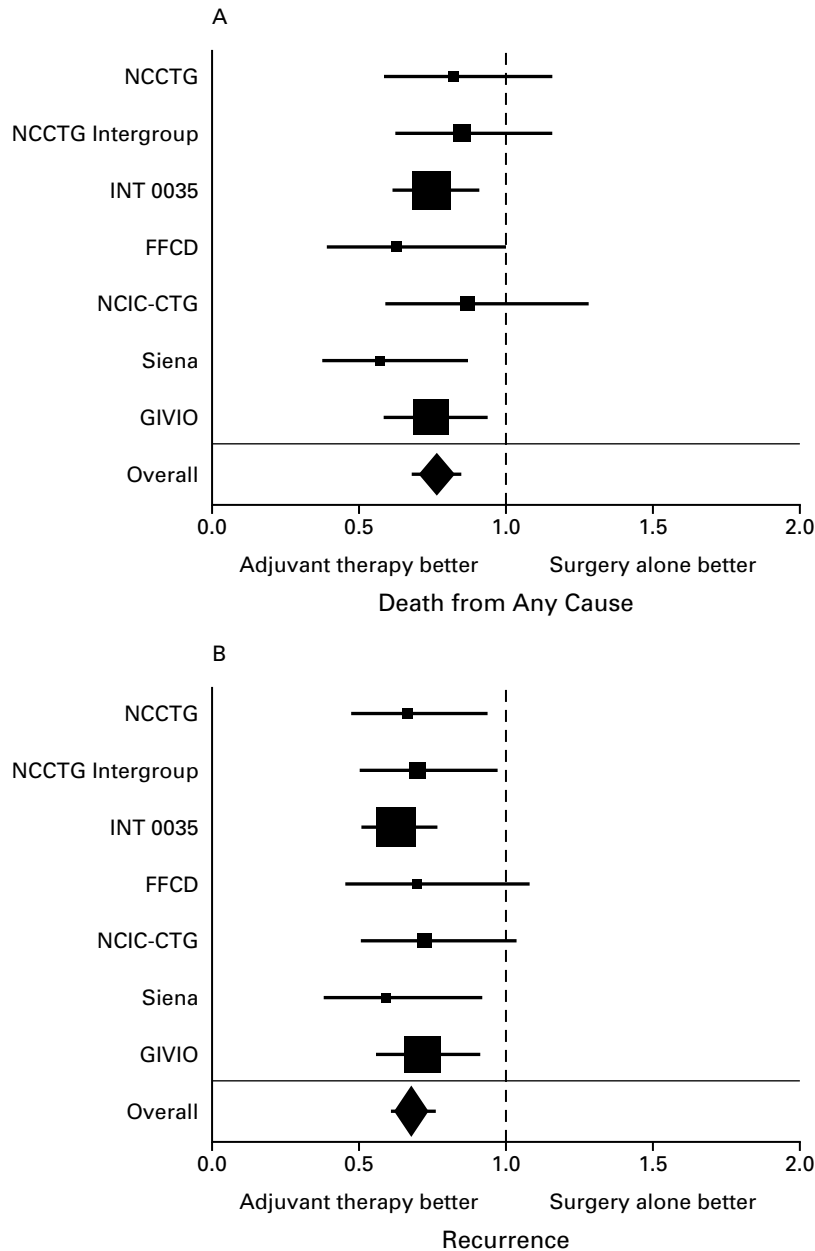


Figure 1. Hazard Ratios (and 95 Percent Confidence Intervals) for Death from Any Cause (Panel A) and Recurrence (Panel B) in the Adjuvant-Therapy and Surgery-Only Groups, According to Study. The size of the square is proportional to the sample size. NCCTG denotes North Central Cancer Treatment Group, INT U.S. Gastrointestinal Intergroup, FFCD Fondation Française de Cancérologie Digestive, NCIC-CTG National Cancer Institute Canada Clinical Trials Group, Siena University of Siena, and GIVIO Gruppo Interdisciplinare di Valutazione Interventi in Oncologia.

ble 3). Age was not significantly related to the rate of grade 3 or higher nausea or vomiting, stomatitis, or diarrhea among patients treated with either fluorouracil plus leucovorin or fluorouracil plus levamisole. Increased age was associated with higher rates of severe leukopenia in patients treated with fluorouracil plus levamisole ($P < 0.001$); this relation was of borderline

significance in patients who received fluorouracil plus leucovorin ($P = 0.05$).

DISCUSSION

This analysis included data on the largest population available to date for comparison of the benefits and toxic effects of adjuvant fluorouracil-based therapy for

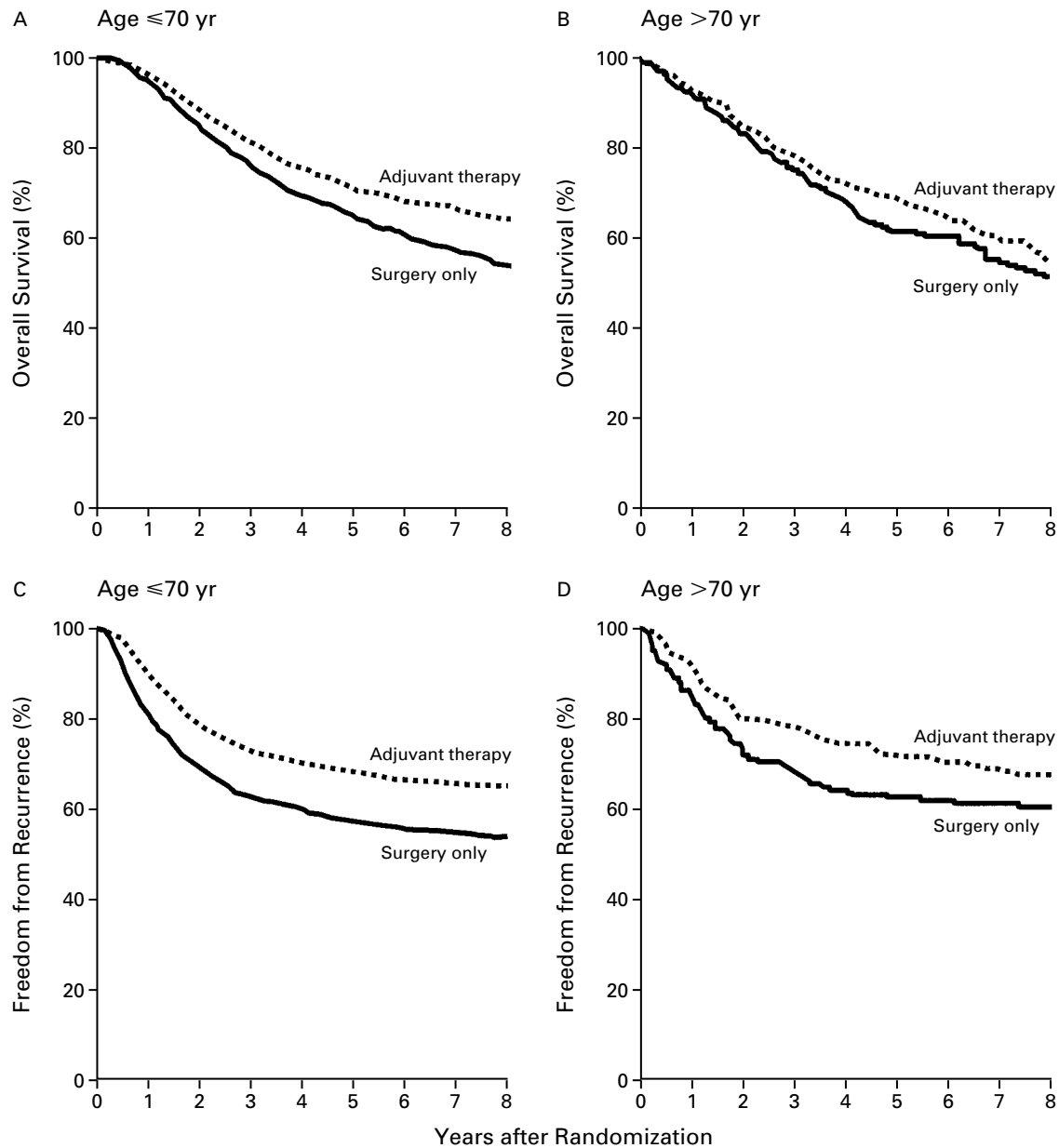


Figure 2. Kaplan-Meier Estimates of Overall Survival (Panels A and B) and Freedom from Recurrence (Panels C and D), According to Age Group and Treatment Assignment.

resected stages II and III colon cancer with those of no adjuvant therapy. Patients treated with fluorouracil plus leucovorin or levamisole had a 7 percent absolute increase in five-year overall survival and a five-year recurrence-free rate of 69 percent, as compared with 58 percent in untreated patients. This pooled analysis confirms the results of numerous individual adjuvant trials that showed a benefit of fluorouracil-based therapy in stage III colon carcinoma.^{16,17,19-21}

Some drugs, including chemotherapeutic agents used in cancer, have different absorption, distribution,

metabolism, and toxicity in elderly patients and in younger patients.³⁴⁻⁴¹ There is no evidence that the susceptibility of colon cancer to chemotherapy differs in younger and older patients.

Elderly patients may not be offered chemotherapy or may choose not to be treated with chemotherapy because of a perception that they will have greater toxic effects or tolerate the treatment poorly. Elderly patients have greater morbidity and mortality with aggressive regimens for leukemia or lymphoma.^{35,37,39} Reports concerning the toxicity of fluorouracil-based

TABLE 3. PERCENTAGE OF PATIENTS WITH TOXIC EFFECTS OF GRADE 3 OR HIGHER, ACCORDING TO AGE GROUP.

TREATMENT AND EFFECT	AGE		P VALUE
	≤70 YR	>70 YR	
	%		
Fluorouracil plus leucovorin*			
Nausea or vomiting	5	2	0.15
Diarrhea	15	15	0.99
Stomatitis	11	15	0.21
Leukopenia	4	8	0.05
Fluorouracil plus levamisole†			
Nausea or vomiting	7	9	0.37
Diarrhea	9	11	0.44
Stomatitis	5	9	0.09
Leukopenia	17	31	0.001

*There were 987 patients 70 years old or younger and 130 patients over 70 years old who received this treatment.

†There were 470 patients 70 years old or younger and 128 patients over 70 years old who received this treatment.

chemotherapy for colorectal cancer in the elderly are conflicting; increased rates of stomatitis, nausea, vomiting, leukopenia, or hospitalization have been observed in some studies,⁴²⁻⁴⁵ whereas others report no excess toxicity.⁴⁶⁻⁴⁸ In a randomized trial involving 1014 patients that compared different schedules of fluorouracil plus levamisole, with or without leucovorin, the incidence of gastrointestinal toxic effects, leukopenia, and dermatitis was not significantly different among age groups.⁴⁸

We found that elderly patients did not have higher rates of nausea or vomiting, stomatitis, or diarrhea than younger patients when treated with fluorouracil plus either leucovorin or levamisole. The incidence of leukopenia was significantly higher among elderly patients who received fluorouracil plus levamisole, but among those who received fluorouracil plus leucovorin the increase was of borderline significance. These findings are consistent with other reports of no increase in myelotoxicity in healthy elderly patients treated with chemotherapeutic regimens that are considered moderately toxic in younger patients.^{37,39,49-53}

No initial reductions in the dose of fluorouracil are recommended for patients with altered renal or hepatic function.⁵⁴ In other studies, fluorouracil clearance has not been associated with age.⁵⁵ Nevertheless, doses are commonly reduced empirically in elderly patients, ostensibly to prevent serious side effects. In some instances, this action may decrease efficacy.^{35,56-58}

The principal limitation of this study concerns its potential applicability to the general population of elderly patients. As a result of exclusion criteria and screening, elderly patients who enter clinical trials are a select group, with good performance status and cognition, access to transportation, and limited numbers of coexisting conditions. Although many elderly pa-

tients in the community have similar characteristics, others have multiple coexisting conditions, malnutrition, and poor social support. How these factors might affect the efficacy and tolerability of fluorouracil-based chemotherapy is unknown. Until further studies are performed, the decision to treat an elderly patient who has several other problems should involve the physicians, patient, and family.

Only 23 of the 3351 patients (0.7 percent) in the trials we analyzed were over the age of 80 years. Caution is therefore advised in extrapolating these findings to octogenarians. However, in the subgroup of octogenarians who are robust enough to meet typical protocol-eligibility requirements, the data offer no clear contraindications to therapy and support the assertion that treatment should be considered for selected persons among even the oldest patients with colon cancer. In addition, the data support the notion that these patients should be considered appropriate candidates for clinical trials of chemotherapy.

In this study, as expected, the oldest patients had a higher probability of dying without evidence of recurrence (13 percent) than the youngest patients (2 percent). In addition, 32 percent of deaths among the oldest patients, but only 5 percent of deaths among the youngest patients, were due to causes other than cancer. Nevertheless, most deaths in all age groups were due to colon cancer. Thus, it is reasonable to consider chemotherapy in nearly all patients with resected stage II and stage III colon cancer.

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