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## The Predictive and Prognostic Value of Sex in Early-Stage Colon Cancer: A Pooled Analysis of 33,345 Patients from the ACCENT Database

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### Abstract

Our study compares the outcomes of men and women with early stage colon cancer by analyzing the ACCENT database. Overall, men experienced inferior prognoses when compared with women for time to recurrence after adjusting for age, stage, and treatment. Sex was not a predictive factor of treatment efficacy. In exploratory analyses, worse outcomes in men were more prominent in older patients, but the stage of disease and type of adjuvant regimen did not modify the prognostic value of sex.

**Purpose**—To compare long-term outcomes between men and women in a large cohort of clinical trial participants with early-stage colon cancer, specifically by examining whether the prognostic effect of sex varies based on age, stage of disease, and type of adjuvant therapy received.

**Methods**—A pooled analysis of individual patient data from 33,345 patients with colon cancer enrolled in 24 phase III studies of various adjuvant systemic therapies was conducted. Chemotherapy consisted of (1) fluorouracil (5-FU), (2) 5-FU variations, (3) 5-FU plus oxaliplatin, (4) 5-FU plus irinotecan, or (5) oral fluoropyrimidine-based regimens. The primary endpoint was disease-free survival; secondary endpoints included overall survival and time to recurrence. Stratified Cox models were used to assess the effect of sex on outcomes. Multivariate models were used to assess adjusted effects and to explore the interaction among sex and other factors.

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#### Disclosure

The authors have stated that they have no conflicts of interest.

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**Results**—A total of 18,244 (55%) men and 15,101 (45%) women were included. In the entire cohort, the median age was 61 years; 91% (24,868) were white; 31% (10,347) and 69% (22,964) had stage I/II and III disease, respectively. Overall, men had inferior prognoses when compared with women for time to recurrence (hazard ratio [HR] 1.05 [95% CI, 1.01–1.09]) and other endpoints after adjusting for age, stage, and treatment. Sex was not a predictive factor of treatment efficacy ( $P$  for interaction between sex and treatment when adjusting for age and stage were .40, .67, and .77 for disease-free survival, overall survival, and time to recurrence, respectively). In exploratory analyses, worse outcomes in men were more prominent in the older patients when adjusting for stage and treatment (HR 1.08 in age  $\leq$  65 years vs. HR 1.18 in age  $>$  65 years; interaction  $P = .016$  for disease-free survival). The stage of disease and type of adjuvant regimen did not modify the prognostic value of sex.

**Conclusions**—Sex is a modest independent prognostic marker for patients with early-stage colon cancer, particularly in older patients.

### Keywords

Sex; Colon cancer; Survival; Outcomes

### Introduction

Despite preventive health measures and advances in diagnostic strategies, colon cancer continues to be a serious global health problem and remains one of the leading causes of cancer-related mortality worldwide.<sup>1,2</sup> In the United States alone, there are an estimated 150,000 incident cases of colon cancer per year and approximately one-third of these patients are expected to die of their disease.<sup>1,2</sup> The introduction of novel cytotoxic chemotherapy agents as well as the incorporation of molecularly targeted drugs into the treatment paradigms for colon cancer has contributed to significant improvements in patient outcomes.<sup>3–7</sup> Recent research efforts have examined new predictive and prognostic markers that can better enrich patient selection and further optimize the treatment success. To this end, sex has been identified as an independent prognostic factor for survival from colon cancer, with women surviving longer than men, although the results have been inconsistent and focused primarily on surgical outcomes.<sup>8–13</sup> It also is currently unclear if any potential sex differences in outcomes are due to specific lifestyle patterns among the female population, possible genetic and molecular mechanisms that predispose women to more favorable outcomes, or differential efficacy of adjuvant treatment between the sexes.

Because many of these prior studies were limited to either small sample sizes or single institutions, such sex differences have not been consistently observed. Importantly, most of these analyses were conducted before the widespread use of contemporary agents, eg, oxaliplatin, in the treatment of colon cancer. Analysis of emerging data highlights the existence of sex-specific pharmacokinetics for both fluoropyrimidines and platinum agents, which are frequently used in colon cancer management.<sup>14–18</sup> To our knowledge, the role of sex on outcomes has not been examined in detail within the context of oxaliplatin-based therapies. On the basis of these observations, we performed a prospectively planned, pooled analysis of patients participating in randomized phase III clinical trials based on the Adjuvant Colon Cancer Endpoint (ACCENT) group database. The main purpose of this analysis was to evaluate the prognostic effect of sex for survival in early-stage colon cancer. We also examined whether the effect of sex on outcomes varies based on age, stage of disease, study time period, and type of adjuvant therapy received. It is our hope that the findings from this analysis will be useful for improving therapy of colon cancer between men and women as well as for designing future clinical trials that involve new cytotoxic and molecularly targeted agents.

## Patients and Methods

### The ACCENT Database

ACCENT is an international collaboration of colon cancer researchers who have assembled a large database that consists of individual patient-level data from 24 large randomized phase III clinical trials that enrolled, between 1978 and 2003, patients with resected stage I to III colon cancer. The investigated adjuvant treatments included the following: (1) fluorouracil (5-FU) based regimens, (2) variations of 5-FU-based regimens, (3) combinations of 5-FU with oxaliplatin, (4) combinations of 5-FU with irinotecan, and (5) oral fluoropyrimidine chemotherapy. Data from a total of 55 treatment arms (46 active treatment arms and 9 surgery-only arms) and more than 33,000 patients with colon cancer have been collected. All clinical trials included in this data set were performed after obtaining approval from local institutional review committees, in accordance with the Declaration of Helsinki. Clinical trial participants also were required to provide written informed consent at the time that the studies were initially conducted. This sex-based, pooled analysis was approved by the Mayo Clinic Institutional Review Board.

### Clinical Trials and Data Included

For this analysis, we included all clinical trials from the ACCENT database. In addition to sex information, we collected demographic, clinical, and pathologic factors, such as age, race, performance status, stage, grade of disease, and number of lymph nodes examined. Long-term clinical endpoints included the following: overall survival (OS), defined as the time from randomization to death due to all causes; disease-free survival (DFS), defined as the time from randomization to the first occurrence of disease recurrence or death due to all causes; and time to recurrence (TTR), defined as the time from randomization to the first documented disease recurrence in which deaths without recurrence are censored for the TTR endpoint at the time of death. Data on subsequent treatment in the event of recurrent disease and on salvage therapy were beyond the scope of these studies and were not collected by the study protocols. Data on treatment toxicities and comorbid conditions also were largely unavailable in this database. We analyzed data from 33,345 individual patients who participated in 24 adjuvant phase III randomized controlled clinical trials for early-stage colon cancer. Details about the adjuvant ACCENT trials included in this analysis are summarized in Table 1.

### Statistical Methods

Baseline characteristics were summarized with descriptive statistics, such as medians (ranges) and frequencies (percentages). The distributions of demographic and clinical characteristics between men and women were compared with the 2-sample *t* test (or Wilcoxon rank sum test) and the  $\chi^2$  test for continuous and categorical factors, respectively. The distributions of time-to-event endpoints were estimated by Kaplan-Meier methods. The log-rank test, stratified by study, was used to compare these endpoints between men and women. Multivariate Cox proportional hazards models that stratified by study and controlled for potential confounding variables (eg, age, stage, and treatment) were constructed to estimate hazard ratios (HR) and associated 95% confidence intervals (CI) for the risk of recurrence and/or death between men and women. In addition to evaluating the prognostic value of sex, we assessed its predictive value on treatment outcomes. For trials that demonstrated a significant difference in treatment effect between the study arms in the original primary efficacy analysis, the interaction between sex and treatment on outcomes was tested by including an interaction term in the multivariate Cox models. Finally, we carried out exploratory analyses stratified by age (< 65 vs. > 65 years) and stage (II vs. III) to determine whether the prognostic impact of sex was modified by these parameters. SAS version 9.2 (SAS Institute, Cary, NC) was used for all statistical analyses.

## Results

### Characteristics of the Patient Population

Of the 33,345 patients with early-stage colon cancer included in this analysis, 18,244 (55%) were men and 15,101 (45%) were women. Distributions of patient and tumor characteristics by sex are detailed in Table 2. Overall, men were slightly older than women (median age, 62 years [range, 15–91 years] vs. 61 years [range, 15–90 years], respectively;  $P < .01$ ) and more likely to be white (91% vs. 90%, respectively;  $P < .01$ ) but less likely to have stage III disease (68% vs. 70%, respectively;  $P < .01$ ) and right-sided cancers (43% vs. 45%, respectively;  $P < .01$ ). In general, slightly higher percentages of male patients were enrolled across the different clinical trials that examined various types of adjuvant chemotherapy regimens because of the consistently lower rates of female study participation. However, treatments were well balanced between men and women within the individual clinical trials that were included in this analysis.

### Association of Sex with Outcomes

Men consistently had shorter event-free times for DFS, OS, and TTR when compared with women (Table 3). The unadjusted 5-year DFS, OS, and recurrence-free rates were 62% vs. 65% ( $P < .01$ ), 70% vs. 73% ( $P < .01$ ), and 66% vs. 67% ( $P = .04$ ) for men vs. women, respectively (Figure 1). When adjusting for age, overall stage, and treatment, sex differences in colon cancer outcomes persisted and continued to favor women. This effect was more pronounced for DFS (adjusted HR 1.12 [95% CI, 1.08–1.16];  $P < .0001$ ) and OS (adjusted HR 1.13 [95% CI, 1.09–1.17];  $P < .0001$ ) and less apparent for TTR in which the effect size was smaller (adjusted HR 1.05 [95% CI, 1.01–1.09];  $P = .0073$ ). A similar effect was observed in a separate model in which T and N stages were controlled separately (adjusted HR for DFS 1.13 [95% CI, 1.08–1.17],  $P < .0001$ ; adjusted HR for OS 1.15 [95% CI, 1.10–1.20],  $P < .0001$ ; and adjusted HR for TTR 1.06 [95% CI, 1.01–1.10],  $P = .0183$ ). The prognostic value of sex was seen across all treatment types and patient subgroups for DFS (Figure 2) as well as for OS and TTR (data not shown).

### Effect Modification

Among studies with significant treatment differences between the experimental arm and the control arm, the prognostic impact of sex on clinical outcomes was not modified by treatment assignment ( $P_{\text{interaction}} = .41, .67, \text{ and } .77$  for DFS, OS, and TTR, respectively). Furthermore, subset analyses stratified by age and stage of disease were conducted to determine if the prognostic effect of sex was modified by these variables (Table 4). Our findings showed that age was an effect modifier of DFS because sex disparities in outcomes were significantly different between younger and older patients (Figure 3). Although the favorable prognostic impact of female sex persisted across age groups, it was more evident in the elderly subset of the population, whereby the adjusted HR was 1.08 (95% CI, 1.04–1.13) in patients aged  $\leq 65$  years, whereas the adjusted HR was 1.18 (95% CI, 1.12–1.25) in patients aged  $> 65$  years ( $P_{\text{interaction}} = .02$ ). Age also modified the effect of sex on OS, albeit less strongly ( $P_{\text{interaction}} = .09$ ), but it did not consistently modify the effect of sex on TTR ( $P_{\text{interactions}} = .36$ ). In contrast, the stage of disease did not alter the prognostic influence of sex on DFS, OS, and TTR (all  $P_{\text{interaction}} > .05$ ).

## Discussion

Female sex as a favorable prognostic factor in colon cancer has previously been described, but the results have been very inconsistent.<sup>8–13</sup> Moreover, the majority of this research involved small numbers of patients, recruited subjects from only several local institutions, and almost all were conducted before the widespread use of oxaliplatin in the adjuvant

treatment of colon cancer. Consistent with some of these prior studies, our analysis of a large representative cohort of more than 30,000 clinical trial participants from 24 studies who received various adjuvant treatments after their curative resections, indicated that women with early-stage colon cancer experienced a statistically significant but very modest survival advantage when compared with men. This pattern was observed for DFS, OS, and TTR. Furthermore, we demonstrated that this survival benefit for women persisted across all ages, stages, and treatment types.

Of note, the sex differences in colon cancer survival seen in this study were less pronounced than those reported in previous series. For example, Watanabe et al<sup>13</sup> reported in a study of adjuvant 5-FU-based chemotherapy in colon cancer that the 5-year OS rate among women was 10% higher than that for men. In contrast, we only showed a 3% difference in 5-year OS rates between sexes that favored women. A potential factor for why the survival benefit for women was lower in this analysis may be related to our primary focus on clinical trial participants, most of whom were highly functional, with a good performance status at the time of study entry (99% of patients were Eastern Cooperative Oncology Group Performance Status Scale 0 or 1). This could have minimized any sex differences that would otherwise be evident in routine practice settings in which functional status may be more disparate. Results of some studies also indicate that there may be differences in colorectal screening uptake between sexes that lead to earlier disease detection among women and hence better outcomes.<sup>19,20</sup> In our cohort of patients, however, men were slightly more likely to be diagnosed with earlier-stage colon cancer, which may have further minimized any sex differences in survival. Nonetheless, the men included in this analysis were slightly older than the women, which may have contributed in part to the differences observed in specific survival endpoints, such as DFS and OS.

To date, the causes for these sex differences in colon cancer outcomes have remained unclear. However, similar differences have been noted in both small- and non-small-cell lung cancers whereby women consistently fared better than men,<sup>21-23</sup> which suggests that there may be broad underlying hormonal, genetic, or molecular mechanisms that predispose women in general to more favorable prognoses that span across cancer sites. It is also possible that the survival advantage among women that is described for these cancers is purely a consequence of the longer natural life expectancy of women, as supported by recently published data that confirmed a reduced 10-year risk of death from all causes for women.<sup>1</sup> The lesser difference between men and women in the disease-specific endpoint TTR than DFS or OS could be partly explained by the higher mortality from non-colon cancer causes in men than in women. A possible contributor to the difference in TTR between men and women is the higher proportion of women than men with good prognostic features, such as defects in the DNA mismatch repair gene.<sup>24</sup>

One of the strengths of the current analysis is its reliable ascertainment of 3 outcome measurements: DFS, OS, and TTR. This is possible because of the standard, uniform follow-up protocols mandated by most clinical trials. Given that the primary aim of adjuvant therapy for colon cancer is to prolong patient survival by delaying or preventing recurrence, TTR is the most-sensitive measurement of the intended effect of adjuvant therapy. Unlike DFS and OS, TTR is less affected by disparities in treatment of recurrent disease, management of comorbid conditions, and differential rates of death from competing causes that are unrelated to colon cancer. In this study, the magnitude of the sex effect was lowest for TTR (HR 1.05, a 5-year difference of 1% between men and women), which suggests that any differential response to adjuvant therapy must be small. This is supported by our analysis of the predictive value of sex in which there was no evidence of significant interaction between sex and adjuvant treatment on any of the outcomes (all  $P_{\text{interactions}} > .05$ ). Conversely, the effect sizes for DFS and OS were larger than that for TTR, which

highlights that the observed sex disparities in colon cancer outcomes were less likely to be related to adjuvant treatment and more likely to be reflections of the wider phenomenon of differences in comorbidities and life expectancies between men and women.

An interesting study result was that the survival benefit for women was more apparent in patients aged > 65 years (HR 1.18 for DFS in men [95% CI, 1.12–1.25]) than in patients aged ≤ 65 years (HR 1.08 for DFS in men [95% CI, 1.04–1.13]) ( $P_{\text{interaction}} < .01$ ). Previous studies have proposed estrogen as a putative mechanism for the better cancer outcomes in women through its protective effect on carcinogenesis and metastases,<sup>25,26</sup> but our finding of a larger survival advantage in older (postmenopausal) women, in whom estrogen levels would be lower than younger women, cannot be easily explained by this postulate. Rather, there likely are a number of possible alternative reasons for the sex differences, including later stage at diagnosis in men, differences in access to and delivery of treatment, and the possibility that men may have a biologically more-aggressive disease or a poorer response to adjuvant therapies. By using the ACCENT clinical trial database, we attempted to begin exploring these hypotheses and found that stage of disease neither explained nor modified the sex effect on colon cancer outcomes ( $P_{\text{interactions}} > .05$ ). Further studies are warranted to investigate some of the remaining alternative hypotheses.

Despite its large size, this study has several limitations. First, treatment data that consist of chemotherapy dose intensities, delays, and toxicities were not available for analyses even though these treatment parameters could have a significant impact on survival. Future studies should try to account for such treatment-related data, especially because results of early research show that there may be sex differences in the metabolism of commonly used chemotherapy agents as well as sex differences in toxicity.<sup>14–18</sup> Second, although we were able to collect performance status data for the majority of individuals, other important baseline prognostic factors, such as pretreatment laboratory values and comorbid conditions, were not considered. Likewise, data about certain lifestyle patterns and behaviors, including concurrent medications as well as smoking and alcohol history, that can also affect outcomes were not captured. Concomitant medications may differ between sexes, and the potential influence of these drugs on chemotherapy efficacy and the measured outcomes is unknown.<sup>27</sup> The interplay among patient's sex, lifestyle, and behavioral factors, and outcomes is clearly an area that requires further research. Third, this was a pooled analysis of a very heterogeneous group of clinical trials that span 2 decades. However, it would seem unlikely that any tumor biology differences between men and women would vary significantly over time. Finally, the role of predictive and prognostic biomarkers and how they are differentially distributed between sexes are beyond the scope of this analysis, and remain to be studied.

## Conclusion

This analysis of an extensive cohort of clinical trial patients demonstrates only modest differences in outcomes, including DFS, OS, and TTR, between men and women who received various adjuvant chemotherapies for resected colon cancer, particularly among patients aged > 65 years. Additional studies are needed to better elucidate the processes that contribute to these sex-specific effects and to understand the interplay between such demographic determinants and novel molecular biomarkers. Of note, sex did not predict for adjuvant treatment benefit, which indicates that both men and women derived a similar magnitude of benefit from chemotherapy. Thus, future clinical trials of colon cancer in the adjuvant setting may not need to be stratified by sex and decisions regarding adjuvant chemotherapy should not be altered based on the sex of the patient alone.

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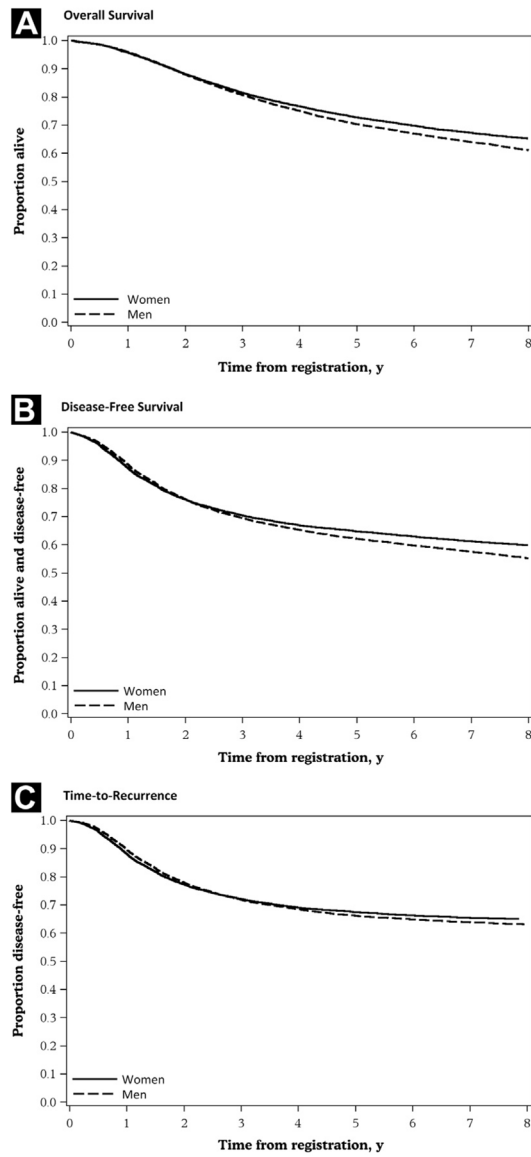
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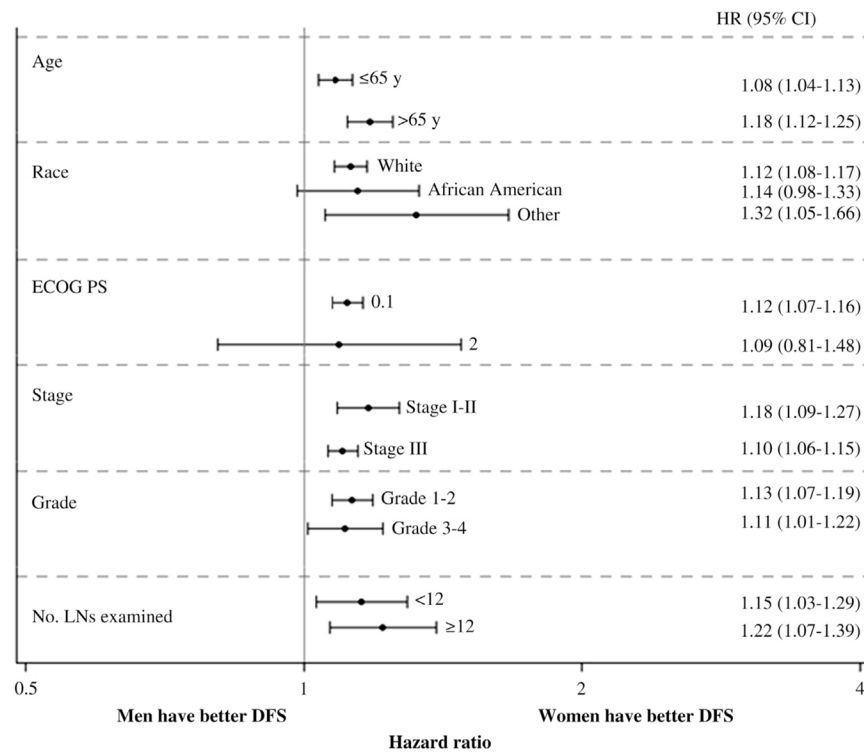


### Clinical Practice Points

- Female sex as a favorable prognostic factor in colon cancer has been previously described, but the results have been very inconsistent.
- The majority of this research involved small numbers of patients, recruited subjects from only several local institutions, and almost all were conducted before the widespread use of oxaliplatin in the adjuvant treatment of colon cancer.
- Our analysis of a large representative cohort of more than 30,000 clinical trial participants from 24 studies who received various adjuvant treatments after their curative resections indicated that women with early-stage colon cancer experienced a statistically significant but a very modest survival advantage when compared with men.
- This pattern was observed for disease-free survival, overall survival, and time to tumor recurrence.
- We also demonstrated that this survival benefit for women, albeit minor, persisted across all ages, stages, and adjuvant treatment types.
- Given the modest survival difference between sexes, future clinical trials of colon cancer in the adjuvant setting may not need to be stratified by sex and decisions regarding adjuvant chemotherapy should not be altered based on the sex of the patient alone.



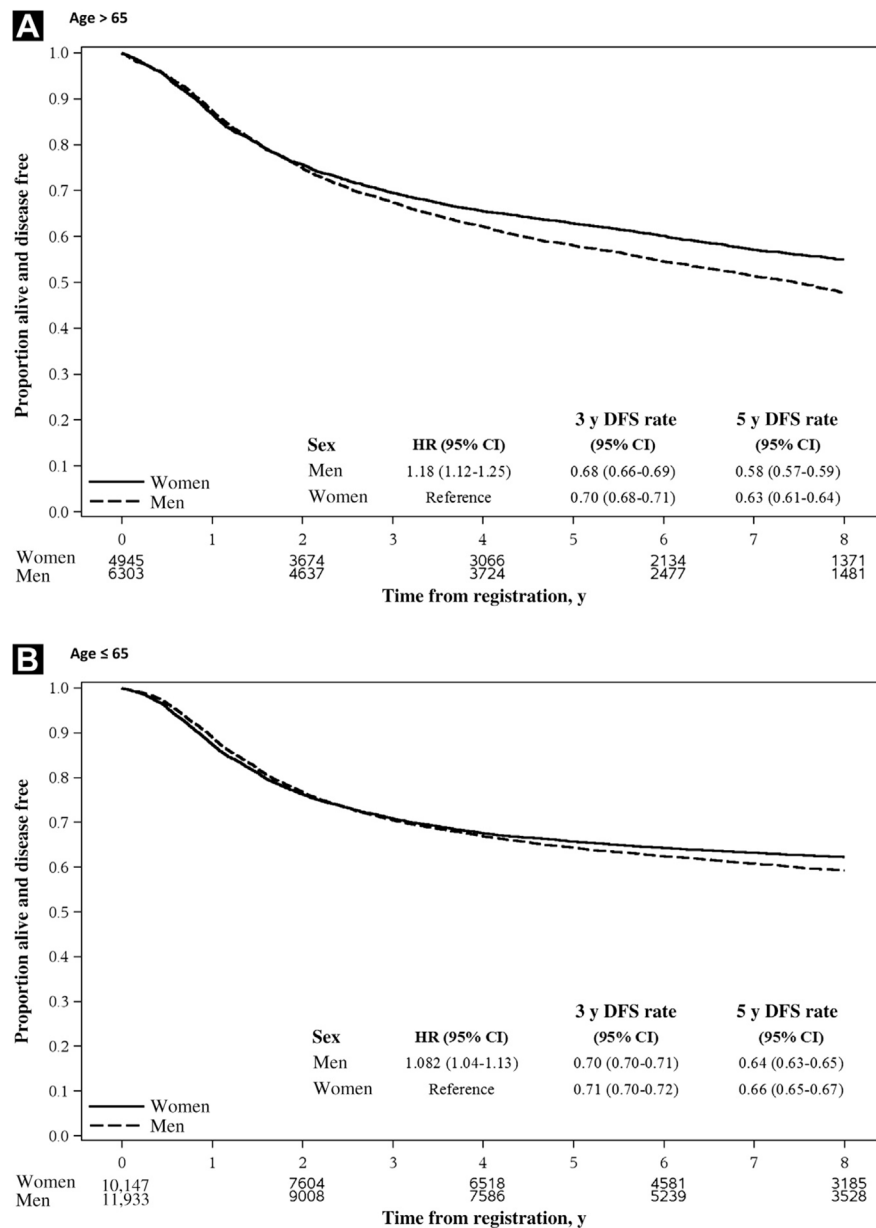
**Figure 1.** Kaplan-Meier Curves for Outcomes. (A) Overall Survival. (B) Disease-Free Survival. (C) Time to Recurrence



**Figure 2. Prognostic Impacts of Sex on DFS Stratified by Patient Characteristics**

HRs (95% CI) (which compared DFS in men with women) were estimated by Cox model adjusted for age, stage, and treatment when it was applicable and stratified by the study. HRs for subgroups classified by the number of LNs examined were only based on patients with stage II disease.

Abbreviations: DFS = disease-free survival; HR = hazard ratio; LN = lymph node.



**Figure 3. Kaplan-Meier Curves for DFS Stratified by Sex and Age Group. (A) Age > 65 y. (B) Age ≤ 65 y**

HRs (95% CI) were estimated by Cox model adjusted for stage and treatment and were stratified by study. The numbers under the graph are the number of patients at risk at randomization, 2, 4, and 8 y after randomization.

Abbreviations: DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group Performance Status Scale; HR = hazard ratio; LN = lymph node.

Table 1

## Treatment and Total Sample Size of Clinical Trials Included

Study Group	Clinical Trial	Control Arm	Experimental Arm	Total Sample Size
5-FU vs. surgery	NCCTG-78-48-52 <sup>a</sup>	Surgery	5-FU + LEV	247
	NCCTG-87-46-51 <sup>a</sup>	Surgery	5-FU + LV	408
	INT-0035 <sup>a</sup>	Surgery	5-FU + LEV	926
	FFCD <sup>a</sup>	Surgery	5-FU + CF	256
	NCIC <sup>a</sup>	Surgery	5-FU + CF	359
	SIENA <sup>a</sup>	Surgery	5-FU + CF	239
	GIVIO <sup>a</sup>	Surgery	5-FU + CF	846
	C01	Surgery	MOF	724
5-FU vs. 5-FU variations	C02	Surgery	PVI of 5-FU	896
	NCCTG-89-46-51	5-FU + LV × 1 y	5-FU + LEV × 6 mo; 5-FU + LEV + LV × 1 y; 5-FU + LEV + LV × 6 mo	915
	NCCTG-91-46-53	Standard dose; LEV + 5-FU + CF	High dose; LEV + 5-FU + CF	878
	S9415	5-FU + LV + LEV	CI 5-FU + LV	939
	C03	MOF	5-FU + LV	1042
	C04	5-FU + LV	5-FU + LV + LEV; 5-FU + LEV	2083
	C05	5-FU + LV	5-FU + LV + interferon	2136
	GERCOR	LV5FU2	FUFOL	902
	INT-0089	LEV	HDLV; LDLV; LEV + LDLV	3363
	QUASAR	5-FU + 175 mg L-folinic acid + placebo	5-FU + 25 mg L-folinic acid + placebo; 5-FU + 25 mg L-folinic acid + levamisole; 5-FU + 175 mg L-folinic acid + levamisole	3517
5-FU vs. 5-FU + oxaliplatin	MOSAIC <sup>a</sup>	5-FU + LV	FOLFOX4	2241
	C07 <sup>a</sup>	5-FU + LV	FOLFOX	2434
5-FU vs. 5-FU + irinotecan	C89803	5-FU + LV	IFL	1264
	PETACC3	5-FU + LV	FOLFIRI	3188
5-FU vs. oral	XACT	5-FU + LV	Capecitabine	1986
	C06	5-FU + LV	Uracil/tegafur	1557

Abbreviations: 5-FU = fluorouracil; CF = cisplatin/5-FU; CI 5-FU = continuous infusion 5-FU; FOLFOX = 5-FU infusion/oxaliplatin/leucovorin; FUFOL = 5-FU bolus plus leucovorin; HDLV = high-dose leucovorin; IFL = 5-FU bolus/oxaliplatin/leucovorin; LDLV = low-dose leucovorin; LEV = levamisole; LV = leucovorin; MOF = semustine/vincristine/5-FU; PVI = protracted venous infusion.

<sup>a</sup>The significant treatment effect differences were shown among the arms in original publications based on individual trial data.

**Table 2**

Baseline Patient Characteristics by Sex

Characteristics	No. Trials	Overall (n = 33,345)	Men (n = 18,244)	Women (n = 15,101)	P Value
Age, years	24				<.0001 <sup>a</sup>
n		33,345	18,244	15,101	
Median (range) age, years		61.0 (15.0–91.0)	62.0 (15.0–90.0)	61.0 (15.0–91.0)	
Total no. age group					.0006 <sup>b</sup>
65 years		22,092 (66.3)	11,939 (65.4)	10,153 (67.2)	
>65 years		11,253 (33.7)	6305 (34.6)	4948 (32.8)	
Total no. race	20				<.0001 <sup>b</sup>
n		27,282	14,832	12,450	
White		24,868 (91.2)	13,621 (91.8)	11,247 (90.3)	
African American		1546 (5.7)	729 (4.9)	817 (6.6)	
Asian		294 (1.1)	161 (1.1)	133 (1.1)	
Other		574 (2.1)	321 (2.2)	253 (2.0)	
Total no. ECOG PS	20				.3081 <sup>b</sup>
n		27,221	14,805	12,416	
0–1		26,928 (98.9)	14,637 (98.9)	12,291 (99.0)	
2		293 (1.1)	168 (1.1)	125 (1.0)	
Total no. stage	24				.0011 <sup>b</sup>
n		33,311	18,226	15,085	
I–II		10,347 (31.1)	5798 (31.8)	4549 (30.2)	
III		22,964 (68.9)	12,428 (68.2)	10,536 (69.8)	
Total no. tumor grade	16				.2988 <sup>b</sup>
n		19,531	10,625	8906	
1/2		15,782 (80.8)	8614 (81.1)	7168 (80.5)	
3/4		3749 (19.2)	2011 (18.9)	1738 (19.5)	
LN <sub>s</sub> examined	21				
n		26,511	14,436	12,075	

Characteristics	No. Trials	Overall (n = 33,345)	Men (n = 18,244)	Women (n = 15,101)	P Value
No. LN assessed, median (range)		12.0 (0.0–116.0)	12.0 (0.0–116.0)	12.0 (0.0–99.0)	.0036 <sup>c</sup>
LN assessed, binary, no. (%)					.0039 <sup>b</sup>
<12		13,031 (49.1)	7213 (50.0)	5818 (48.2)	
12		13,483 (50.9)	7225 (50.0)	6258 (51.8)	
Positive LN, counts <sup>d</sup>	21				.0030 <sup>c</sup>
n		26,820	14,608	12,212	
Median (range)		1.0 (0.0–44.0)	1.0 (0.0–42.0)	1.0 (0.0–44.0)	

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status Score; LN = lymph node.

<sup>a</sup>Two-sample *t* test.

<sup>b</sup>The  $\chi^2$  test.

<sup>c</sup>The Wilcoxon rank sum test.

<sup>d</sup>Among patients with stage III disease.

Table 3

Comparing Clinical Outcomes Between Men and Women<sup>a</sup>

Sex	No. Patients	No. Events	5-Y Event rate (95% CI)	Adjusted Hazard Ratio (95% CI) <sup>b</sup>	P Value <sup>c</sup>
DFS					
Men	18,237	7634	0.62 (0.61–0.63)	1.12 (1.08–1.16)	<.0001
Women	15,092	5735	0.65 (0.64–0.66)	Reference	
OS					
Men	18,245	6550	0.70 (0.70–0.71)	1.13 (1.09–1.17)	<.0001
Women	15,101	4893	0.73 (0.72–0.73)	Reference	
TTR					
Men	18,225	6271	0.66 (0.65–0.67)	1.05 (1.01–1.09)	.0073
Women	15,085	5005	0.67 (0.67–0.68)	Reference	

Abbreviations: DFS = disease-free survival; OS = overall survival; TTR = time to recurrence.

<sup>a</sup>All analyses were stratified by study.<sup>b</sup>Adjusting for age, stage, and treatment.<sup>c</sup>Likelihood ratio test of Cox proportional hazard model.



**Table 4**Testing Interaction Effects Between Sex and Key Factors on Outcomes<sup>a</sup>

Key Factor	Disease-free Survival	Overall Survival	Time to Recurrence
Treatment (experimental arm vs. control arm) <sup>b</sup>	.41	.67	.77
Stage (I/II vs. III)	.13	.20	.94
Age (>65 vs. ≤65 y)	.016	.086	.36

<sup>a</sup>The table presents *P* values based on the likelihood-ratio test for testing the interaction terms included in the Cox models, stratified by study; all the models were adjusted for treatment, stage, and age when it was applicable.

<sup>b</sup>Only studies with significant treatment effects were included for assessing the interaction effect between sex and treatment.